PHYSIOLOGY 28: 330–358, 2013; doi:10.1152/physiol.00019.2013

Exercise is the Real Polypill

Carmen Fiuza-Luces,[1,2] Nuria Garatachea,[3] Nathan A. Berger,[4] and Alejandro Lucia[1,2]

[1]Universidad Europea Madrid, Madrid, Spain; [2]Instituto de Investigación, Hospital 12 de Octubre, Madrid, Spain; [3]Facultad de Ciencias de la Salud y del Deporte, Universidad de Zaragoza, Huesca, Spain; and [4]Center for Science, Health and Society, Case Western Reserve University, School of Medicine, Cleveland, Ohio
alejandro.lucia@uem.es

The concept of a "polypill" is receiving growing attention to prevent cardiovascular disease. Yet similar if not overall higher benefits are achievable with regular exercise, a drug-free intervention for which our genome has been haped over evolution. Compared with drugs, exercise is available at low cost and relatively free of adverse effects. We summarize epidemiological evidence on the preventive/therapeutic benefits of exercise and on the main biological mediators involved.

An Evolutionary Perspective

Despite recent strong selection pressure (495), our genetic makeup is largely shaped to support the physical activity (PA) patterns of hunter-gatherer societies living in the Paleolithic era, for which food/fluid procurement (and thus survival) was obligatorily linked to PA (71, 347). The energy expenditure of hunter-gatherers during PA (~1,000–1,500 kcal/day) can be reached with 3–4 h/day of moderate-to-vigorous PA (MVPA), e.g., brisk/very brisk walking (71, 346). Yet technological improvements over just ~350 generations (agricultural followed by industrial and, most recently, digital revolution) have led to dramatic reductions in human PA levels (26, 475): ~1/3 of adults worldwide are currently inactive, and the endemic inactivity trend starts in early life (166).

Physical inactivity in contemporary obesogenic environments initiates maladaptations that cause chronic disease and is becoming a major public health problem (36). In contrast, regular PA has a profound effect on the expression of a substantial proportion of our genome (474), which has been selected for optimizing aerobic metabolism to conserve energy in an environment of food scarcity (40, 41), resulting in numerous beneficial adaptations and decreased risk of chronic diseases, as discussed below.

Epidemiological Evidence I: Exercise Benefits–How Protective is Exercise per se Against Conventional Cardiovascular Risk Factors Compared With Drugs?

The main outcome of regular PA[1], achieving moderate-to-high peak cardiorespiratory fitness (>8 METs[2]), reduces the risk of cardiovascular events and all-cause mortality (234). There is strong epidemiological evidence indicating that regular PA is associated with reduced rates of all-cause mortality, cardiovascular disease (CVD), hypertension, stroke, metabolic syndrome, Type 2 diabetes, breast and colon cancer, depression, and falling (see Ref. 255 for a review). Especially provocative are recent findings showing a positive and negative association between leisure time spent sitting or doing PA, respectively, and mortality risk among survivors of colorectal cancer (55). Furthermore, the benefits of PA are such that a dose response is usually observed in the general population. Higher MVPA levels [≥450 min/wk, clearly above the minimum international recommendations of 150 min/wk of MVPA (515)] are associated with longer life expectancy (317). And athletes, who are those humans sustaining the highest possible PA levels, live longer than their nonathletic counterparts (415). Most epidemiological research up to date has focused on exercise and CVD risk factors or cardiovascular outcomes. For instance, the benefits of regular exercise on all-cause mortality and CVD are well above those of a nutritional intervention, supplementation with marine-derived omega-3 polyunsaturated fatty acids (PUFAs), which has gained considerable popularity owing to the potential ability of omega-3 PUFAs to lower triglyceride levels, prevent serious arrhythmias, or decrease platelet aggregation and blood pressure (BP) (423). These protective roles of omega-3 PUFAs are, however, controversial since a recent meta-analysis showed that omega-3 PUFAs are not significantly associated with decreased risk of all-cause mortality and major CVD outcomes (405).

Exercise training has a restoring/improving effect on endothelial function (103, 158, 500). This is an important consideration because endothelial dysfunction is a risk factor for CVD, whereas normal or enhanced endothelial function has a protective

[1]The terms "PA" (physical activity) and "exercise" are used interchangeably in this review to make reading more fluent.

[2]1 MET equals an oxygen consumption of 3.5 ml·kg^{-1}·min^{-1}.

1548-9213/13 ©2013 Int. Union Physiol. Sci./Am. Physiol. Soc.

effect (158–160). In previously sedentary middle-aged and older healthy men, regular aerobic exercise can prevent the age-associated loss in endothelium-dependent vasodilation (as assessed by vasodilatory response to acetylcholine) and restore this variable to levels similar to those of young adults (103). Exercise also reduces more "traditional" CVD risk factors, albeit probably its effects are modest compared with the impact of medications, with the possible exception of (pre-) diabetes. This is illustrated in the paragraphs below, where we compare the effects of exercise interventions alone to those of common drugs on conventional CVD risk factors. There is scant biomedical literature containing direct comparison of exercise to pharmacological intervention. Therefore, the comparisons presented herein are based on the results of recent meta-analyses (independently searched by two authors, C. Fiuza-Luces and N. Garatachea) of *1*) randomized controlled trials (RCTs) of drugs or drug combinations and *2*) RCTs of exercise training alone.

Exercise vs. Drugs: Glucose Intolerance

A recent meta-analysis has reported that exercise training is associated with an overall 0.67% decline in glycosylated hemoglobin (HbA1c) levels [95% confidence intervals (CI), −0.84 to −0.49] (479). Separate analyses showed that each of aerobic (−0.73%; 95% CI, −1.06 to −0.40), resistance (−0.57%; 95% CI, −1.14 to −0.01), or combined aerobic and resistance training modes were associated with declines in HbA1c levels compared with control participants (−0.51%; 95% CI, −0.79 to −0.23). The overall reduction in HbA1c of −0.67% brought about by exercise compares relatively well with the recently reported reductions achieved by commonly used oral antidiabetic medications such as metformin monotheraphy and dipeptidyl peptidase inhibitors (sitagliptin, saxagliptin, vildagliptin, linagliptin), which can lower HbA1c levels by 1.12% (95% CI, −0.92 to −1.32) (182) and 0.76% (95% CI, −0.83 to −0.68), respectively (362). On the other hand, a recent meta-analysis has shown that non-drug approaches (diet, exercise) are superior to drug interventions in diabetes prevention [risk ratio of 0.52 (95% CI, 0.46–0.58) vs. 0.70 (95% CI, 0.58–0.85), respectively ($P < 0.05$)] (191).

Exercise vs. Drugs: Blood Lipids

A recent meta-analysis of RTCs (223) has shown a significant decrease in triglycerides after exercise interventions (−6.0 mg/dl; 95% CI, −11.8 to −0.2) but not in total cholesterol (0.9 mg/dl; 95% CI, −3.2 to 5.0), high-density lipoprotein (HDL) cholesterol (1.0 mg/dl; 95% CI, −0.2 to 2.1), or low-density lipoprotein (LDL) cholesterol (2.1 mg/dl; 95% CI, −1.5 to 5.7). Relative to baseline values, changes were equivalent to 0.4%, 2.1%, 1.5%, and −5.7% for total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides, respectively. Statins, especially simvastatin and atorvastatin, are the most widely prescribed cholesterol-lowering drugs (113). A meta-analysis of 21 trials testing statin regimens reported a weighted mean difference after 1 year of treatment of 1.07 mM (−29%) for LDL cholesterol (18). A more recent meta-analysis of the effects of atorvastatin on blood lipids showed decreases of 36–53% for LDL cholesterol (2).

Exercise vs. Drugs: Blood Pressure

A recent meta-analysis reported BP reductions with aerobic exercise in healthy subjects [−2.4 mmHg (95% CI, −4.2 to −0.6) for systolic BP (SBP) and −1.6 mmHg (95% CI, −2.4 to 0.74) for diastolic BP (DBP)] and in hypertensive people [−6.9 mmHg (95% CI, −9.1 to −4.6) for SBP and −4.9 mmHg (95% CI, −6.5 to −3.3)] for DBP (73). Resistance training, including either dynamic (72, 74, 222) or static exercises (74, 221, 358), also has a BP-lowering effect in people with normal pressure or prehypertension, overall, −3.87 mmHg (95% CI, −6.19 to −1.54) for SBP and −3.6 mmHg (95% CI, −5.0 to −2.1) for DBP. Of note, it is difficult to compare the effects of exercise and drugs since we are not aware of a meta-analysis comparing the effects of BP-lowering drugs vs. no drug administration. Nevertheless, the effects of exercise on BP are probably of higher magnitude than those obtained with any single BP-lowering drug, e.g., aliskiren, a renin inhibitor that induces an overall BP reduction of −0.18 mmHg (95% CI, −1.07 to 0.71) or angiotensin receptor blockers, which induce an overall BP reduction of −0.15 mmHg (95% CI, −1.38 to 1.69) (138). Exercise effects on BP are, however, likely to be similar or slightly lower than those of drug combinations, as suggested by the fact that drug combinations are substantially more efficacious than monotherapy in lowering BP. For instance, aliskiren combined with angiotensin receptor blockers would be superior to aliskiren monotherapy at the maximum recommended dose on SBP (−4.80 mmHg; 95% CI, −6.22 to −3.39) and DBP reduction (−2.96 mmHg; 95% CI, −4.63 to −1.28). Similar results can be found for aliskiren combined with angiotensin receptor blockers vs. angiotensin receptor blockers monotherapy (SBP: −4.43 mmHg, 95% CI: −5.91 to −2.96; DBP: −2.40 mmHg, 95% CI: −3.41 to −1.39) (531).

Exercise vs. Drugs: Thrombosis

Longitudinal studies have shown that increased levels of PA reduce thrombosis-related cardiovascular events, e.g., nonfatal myocardial infarctions, strokes, and mortality, in people with (252, 376,

504) or without a history of CVD (279, 330, 496). A recent meta-analysis has concluded that moderate exercise training after successful coronary stenting, compared with control group, does not significantly change the incidence of stent thrombosis and major adverse cardiovascular events (death, myocardial infarction, stroke) for up to 3 years (1.8% vs. 2.0%, $P = 0.73$; and 14.9% vs. 15.0%, $P = 0.97$, respectively) but is effective in reducing unscheduled hospital visits for worsening angina (20.2% vs. 27.2%, $P < 0.0001$) (451). Comparisons with drugs are also difficult here, but pharmacological interventions would seem to outweigh exercise benefits. For instance, in a meta-analysis with 5,821 patients undergoing coronary stenting, the use of cilostazol-based triple antiplatelet therapy (TAT) was associated with a significant reduction in the risk of major adverse cardiovascular events compared with dual antiplatelet therapy (DAT) (9.2% vs. 13.4%; odds ratio of 0.59; 95% CI, 0.46 to 0.76) (142).

Thus, although regular exercise and cardiorespiratory fitness are associated with a significant reduction in cardiac events (165, 329, 442), it seems that the benefits of regular exercise go beyond reducing traditional CVD risk factors. This is consistent with classic (see Ref. 213 for a review) and recent reports showing that high cardiorespiratory fitness can reduce morbidity and mortality independent of standard CVD risk factors (254, 354, 445). Notably, Mora et al. evaluated 27,055 apparently healthy women and found that ~59% of the risk reduction for all forms of CVD associated with higher levels of PA could be attributed to the effects of exercise on known risk factors, with inflammatory/hemostatic biomarkers (e.g., C-reactive protein, fibrinogen) making the largest contribution to PA reduction of CVD, followed by BP, lipids, and body mass index (319). So, where is the "risk factor gap" explaining the remaining variance (~40%) in CVD risk reduction achieved by regular exercise?

Epidemiological Evidence II: Exercise Attenuates Aging Autonomic Dysfunction

Besides improving endothelial function (see above), regular exercise contributes to attenuate aging autonomic dysfunction; thus autonomic dysfunction could be one of the missing or nonconventional risk factors that is altered by exercise, as elegantly hypothesized by Joyner and Green in a recent review (213) and summarized below.

Aging is associated with marked increases in sympathetic nervous system (SNS) activity to several peripheral tissues, possibly to stimulate thermogenesis to prevent increasing adiposity (436). This tonic activation of the peripheral SNS has, however, deleterious consequences on the structure and function of the cardiovascular system, e.g., chronically reduced leg blood flow, increased arterial BP, impaired baroreflex function, or hypertrophy of large arteries, which in turn can increase CVD risk (436). Chronically augmented SNS-mediated reductions in peripheral blood flow and vascular conductance can also contribute to the etiology of the metabolic syndrome, by increasing glucose intolerance and insulin resistance (23, 270). Heart rate variability (HRV) is a noninvasive measure of the autonomic nervous system function and a surrogate index for clinical outcome in trials of CVD prevention (344), with high values reflecting a survival advantage, whereas reduced HRV is a marker of autonomic dysfunction that may be associated with poorer cardiovascular health and outcomes (412), including also a substantial increase in the incidence of coronary heart disease, myocardial infarction, fatal coronary disease, and total mortality in diabetic individuals (269). A recent study has shown that a simpler marker of SNS, elevated resting heart rate, is a risk factor for mortality (16% risk increase per 10 beats/min) independent of conventional CVD risk factors (208). Furthermore, high levels of sympathetic outflow in conjunction with endothelial dysfunction may have a synergistic and detrimental effect in terms of CVD risk (89). On the other hand, there is evidence that exercise training can keep the autonomic nervous system healthy, including in old people.

Moderate aerobic exercise (brisk walking) for 3 mo attenuates age-related reductions in baroreflex function, and there appears to be an exercise "dose-response" with regard to the exercise benefits, with endurance-trained older individuals showing similar baroreflex function than their moderately active younger peers (316). A recent meta-analysis has shown that HRV increases with exercise training (344), with this effect being reported in middle-aged or old people who are either healthy (106, 134, 374) or have myocardial infarction (51, 65, 108, 245, 262, 288, 289, 295, 359, 421), chronic heart failure (227, 288, 375, 440), transluminal coronary angioplasty, coronary artery bypass grafting (197, 281, 464, 477), or diabetes (123, 277, 535). Although angiotensin II and nitric oxide ($NO^{\cdot}$) may play a mediating role and more research is needed, to date, it seems that exercise may influence HRV in humans via increasing vagal modulation and decreasing sympathetic tone (412).

Autonomic dysfunction can also contribute significantly to the risk for sudden death due to ventricular fibrillation, which is the leading cause of death in most industrially developed countries (33). Alterations in cardiac parasympathetic control are

indeed associated with an increased risk for sudden death (34, 56, 90, 413), and there is a particularly strong association between reductions in HRV or baroreceptor reflex sensitivity and increased incidence of sudden cardiac death in patients recovering from myocardial infarction (14, 31, 112, 187, 244, 246, 466). This provides evidence supporting the probability that myocardial infarction reduces cardiac parasympathetic regulation and enhances β2-adrenoceptor expression sensitivity, leading to intracellular calcium dysregulation and arrhythmias (33). Thus not only β-adrenoceptor antagonists but also aerobic exercise interventions, which favorably improve cardiac autonomic balance by increasing parasympathetic or decreasing sympathetic activity (114, 290, 353, 370, 450), could reduce the incidence of lethal ventricular arrhythmias (32, 33). Evidence from canine models indicates that exercise training improves cardiac parasympathetic regulation (as reflected by increased HRV), restores a more normal β-adrenoceptor balance (i.e., reducing β2-adrenoceptor sensitivity and expression), and protects against ventricular fibrillation induced by acute myocardial ischemia (see Ref. 33 for a review).

Epidemiological Evidence III in the Context of the 21st Century's Medicine: Exercise Has "Polypill-Like" Effects

Paradoxically, the pandemic spread of cardio-metabolic diseases has paralleled the ground-breaking advances in pharmacology, and CVD remains the leading cause of death worldwide (307). Further complicating the problem, therapeutic strategies designed to control several CVD risk factors simultaneously in people without evidence of CVD are expensive and difficult to implement. The development of fixed-dose drug combinations originally designed for the treatment of myocardial infarction such as statins, diuretics, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, or aspirin in one pill could help to potentially overcome these limitations and is gaining attention as a promising preventive strategy in the 21st century (335, 422).

Wald and Law first described a combination pill for CVD prevention (498), which they called a "polypill" (499). In 2001, a World Health Organization and Wellcome Trust meeting of experts concluded that a fixed-dose polypill containing aspirin, statin, and two BP-lowering agents may improve adherence to treatment as well as substantially reduce the cost of the drugs, particularly for low- and middle-income countries (516). And, in 2003, Wald and Law claimed that CVD could be reduced by 88% and strokes by 80% if all those over 55 years of age were given a polypill containing three low-dose BP-lowering medications: a statin, low-dose aspirin, and folic acid (499). This controversial and provocative approach of "medicalizing" the population has been followed by more targeted approaches. For instance, a large clinical trial is being conducted in five countries to investigate the effects of a polypill (aspirin, an ACE inhibitor, and a statin) on ischemic heart disease recurrence (137). Yet polypill-like benefits are achievable with a drug-free intervention, regular PA.

Elley et al. recently conducted a meta-analysis (the only one we are aware of) on both the efficacy and tolerability of polypills (115). They reviewed data on six RCTs, including a total of 2,218 subjects (1,116 in a polypill group and 1,102 in a comparison group) who were mostly middle-aged adults (men/women, 50–60 yr) with no previous CVD but with ≥1 risk factors. The polypill consisted of one to three antihypertensive drugs (calcium channel blocker, thiazide, ACE inhibitor or angiotensin receptor blocker, or combinations of the above) and one lipid-lowering medication (atorvastatin or simvastatin) with or without aspirin for primary CVD prevention, and treatment lasted 6–56 wk. In FIGURE 1, we compare the results of the above-mentioned meta-analysis on important outcomes related to CVD risk factors (BP, total and LDL cholesterol), with those reported in two recent meta-analyses of the effects of regular exercise in middle-aged adults: a study by Pattyn et al. in 272 middle-aged men/women with the metabolic syndrome but with no other CVD (median age 52 yr, 82 sedentary controls, and 190 individuals exercising during 8–52 wk) (364) and a report by Cornelissen and Smart in 5,223 middle-aged men/women without CVD (1,822 controls and 3,401 people who were exercise training for 4–52 wk) (75). Comparable and in fact slightly higher benefits on total and LDL cholesterol can be obtained with endurance exercise compared with polypills. Whereas isometric exercise and polypills have an overall similar BP-lowering effect, as FIGURE 1 shows, the other exercise modes have a more modest effect. Of note, additional and important health benefits of exercise interventions that are unlikely to be achieved by polypills are significant decreases and increases in adiposity and cardiorespiratory fitness, respectively (364). Rates of tolerability/adherence to the intervention also seem to favor exercise interventions, with an average drop out from the exercise programs of 10% (364), whereas those taking polypills are more likely to discontinue medication compared with placebo or one drug component (20% vs. 14%) (115).

Despite provocative reports in the literature, e.g., orally active drugs such as the AMPK-activator 5-amino-1-β-D-ribofuranosyl-imidazole-4-carboxamide (AICAR) can increase endurance without exercise

training (331), it would be unrealistic to think that the multi-systemic benefits of regular PA can be replaced by ingesting daily an "exercise-like" polypill (95, 155). Nonetheless, identification of the bioactive molecules and biological mechanisms that are candidates for mediating exercise benefits through biological pathways that are largely different from those targeted by common drugs, is of medical interest, since it might help to improve our knowledge of the pathophysiology of diseases of modern civilization as well as to maximize the efficacy of PA interventions by implementing the best possible exercise dosage, resulting in optimal circulating levels of "beneficial" molecules.

Although describing in detail all the biological mechanisms/mediators (including complex molecular-signaling pathways) that can potentially respond and adapt to exercise stimuli is beyond our scope, the intent of the subsequent part of this review is to summarize the current body of knowledge on the main biological mediators (ingredients) of the preventive/therapeutic effects of regular PA against most prevalent chronic diseases, cardiometabolic disorders, and cancer, and of its anti-aging effects.

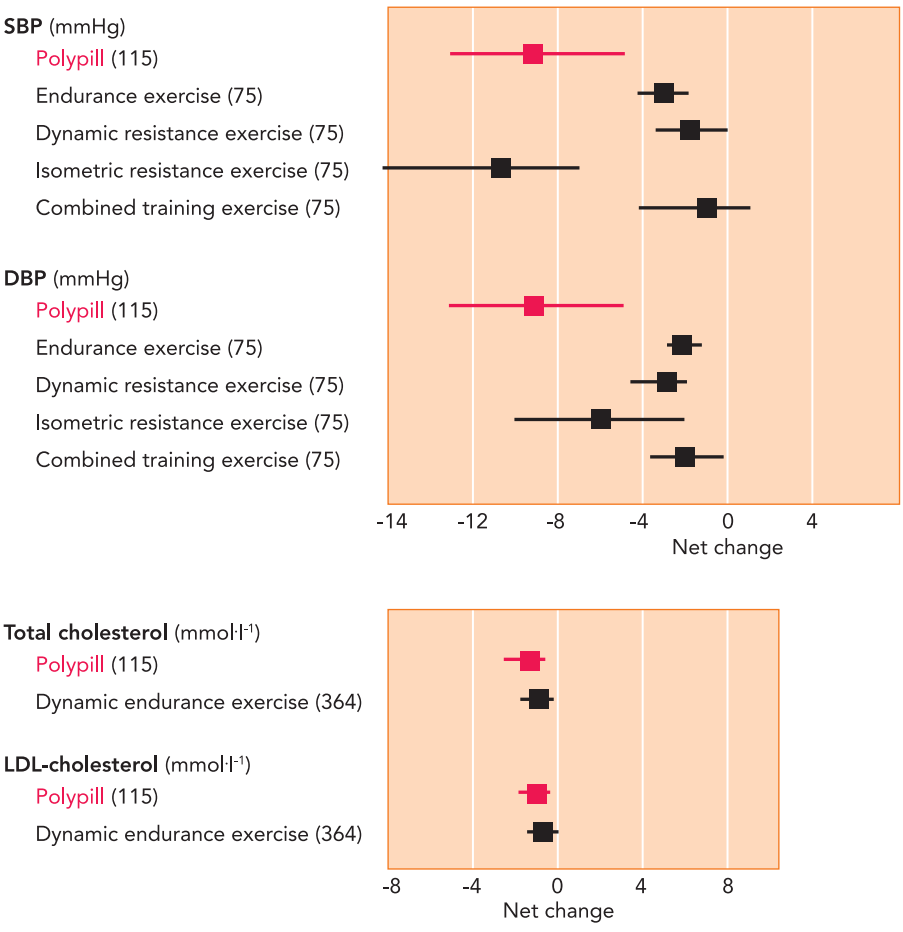

FIGURE 1. **Comparison on the effects of the polypill vs. exercise interventions on outcomes related to CVD risk using data from meta-analyses (see text for more details)**
Data of mean change in the outcomes are expressed in mean and 95% confidence intervals.

Skeletal-Muscle Manufactures the Pill

Skeletal-muscle fibers can produce several hundred secreted factors, including proteins, growth factors, cytokines, and metallopeptidases (42, 178, 345, 407, 527), with such secretory capacity increasing during muscle contractions (13, 94, 163, 190, 286, 357, 367), myogenesis (85, 87, 178), and muscle remodeling (529), or after exercise training (102, 345, 407). Muscle-derived molecules exerting either paracrine or endocrine effects are termed "myokines" (367) and are strong candidates to make up a substantial fraction of the exercise polypill. Here, we focus on the main myokines and their putative protective role against disease phenotypes (see also FIGURE 2 and Table 1).

Myostatin, the first described secreted muscle factor to fulfil the criteria of a myokine, is a potent muscle-growth inhibitor (302) that acts via SMAD signaling (398) or mammalian target-of-rapamycin (mTOR) inhibition (12, 249, 271, 301, 403, 426, 476). Acute endurance (170, 278) or resistance (228, 397) and chronic endurance exercise reduce myostatin expression (170, 184, 236, 237, 292). Although myostatin increases might contribute to insulin resistance (184, 360), obesity (185), muscle wasting (63, 70, 97, 154), or aging-sarcopenia (523), its loss/inhibition decreases adiposity (164, 303, 521, 530), induces browning of the white adipose tissue [through AMPK-peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α)-iriscin pathway] (443), and ameliorates muscle weakness (29, 38, 241, 256, 272, 323, 328, 386, 448, 478, 497, 532).

IL-6 is probably the myokine prototype (366); its release by working muscles explains the consistently reported increase in blood IL-6 with exercise (118, 183, 212, 220, 278, 369, 411, 457, 458). Muscle release of IL-6 increases with exercise intensity (356) and duration (125), with muscle-mass recruitment (368), and when muscle glycogen stores are low (220, 456), but decreases with muscle damage (285, 509) or with carbohydrate ingestion (179, 248, 265–267, 339–341). Endogenous nitric oxide ($NO^{\cdot}$), interaction between Ca^{2+}/nuclear factor of activated T-cell (NFAT), and glycogen/p38 MAPK pathways are putative upstream signals leading to muscle-IL-6 secretion (368). More controversial are the effects of chronic exercise on muscle-derived IL-6 (81, 126), yet a training increase in the sensitivity of its receptor IL-6Rα has been reported (219). This myokine exerts its action locally (within muscles) or peripherally (in a

hormone-like fashion) to mediate, among others, important metabolic and anti-inflammatory/immune modulatory effects. IL-6 has "leptin-like" actions: through AMPK activation in both skeletal-muscle and adipose tissue (6, 61, 145, 224), it increases glucose uptake (126) and intra-muscle (50, 61, 373) or whole-body (486) lipid oxidation (61, 214). Systemic low-level inflammation is a cardinal feature of aging, cardio-metabolic diseases, and some types of cancer that can be attenuated by the cumulative effect of regular exercise bouts, during which the muscle can release myokines such as IL-6; this creates a healthy milieu by inducing the production of the anti-inflammatory cytokines
IL-1Ra, IL-10, or sTNF-R, and inhibiting the pro-inflammatory cytokine TNF-α (122, 294, 312, 355, 356). Other potential roles of IL-6 are stimulation of muscle growth (7, 441) and angiogenesis (172).

Another prototype of contraction-induced myokine is IL-15, with resistance exercise stimulating its secretion (338, 402). In addition to its local anabolic/anti-catabolic effects (59, 60, 135, 338, 390, 391), IL-15 plays an anti-obesogenic effect (337, 388), mainly by inhibiting lipid deposition (8–10, 24, 59, 136, 389). Thus muscle-derived IL-15 is advocated as one of the mediators of the anti-obesity effects of exercise (520). Although leukemia inhibitory factor (LIF) can be released by many tissues and have multiple effects, the functional role of contraction-induced LIF (e.g., after resistance exercise) would be restricted to skeletal muscles, where it stimulates hypertrophy/regeneration, mainly through satellite cell proliferation (47–49, 161, 216, 217, 243, 418, 452, 453, 506). Contraction-induced myokines IL-7 (174) and IL-8 (86, 278, 341) also work mainly at the local level, where they modulate muscle development (174) or promote angiogenesis through

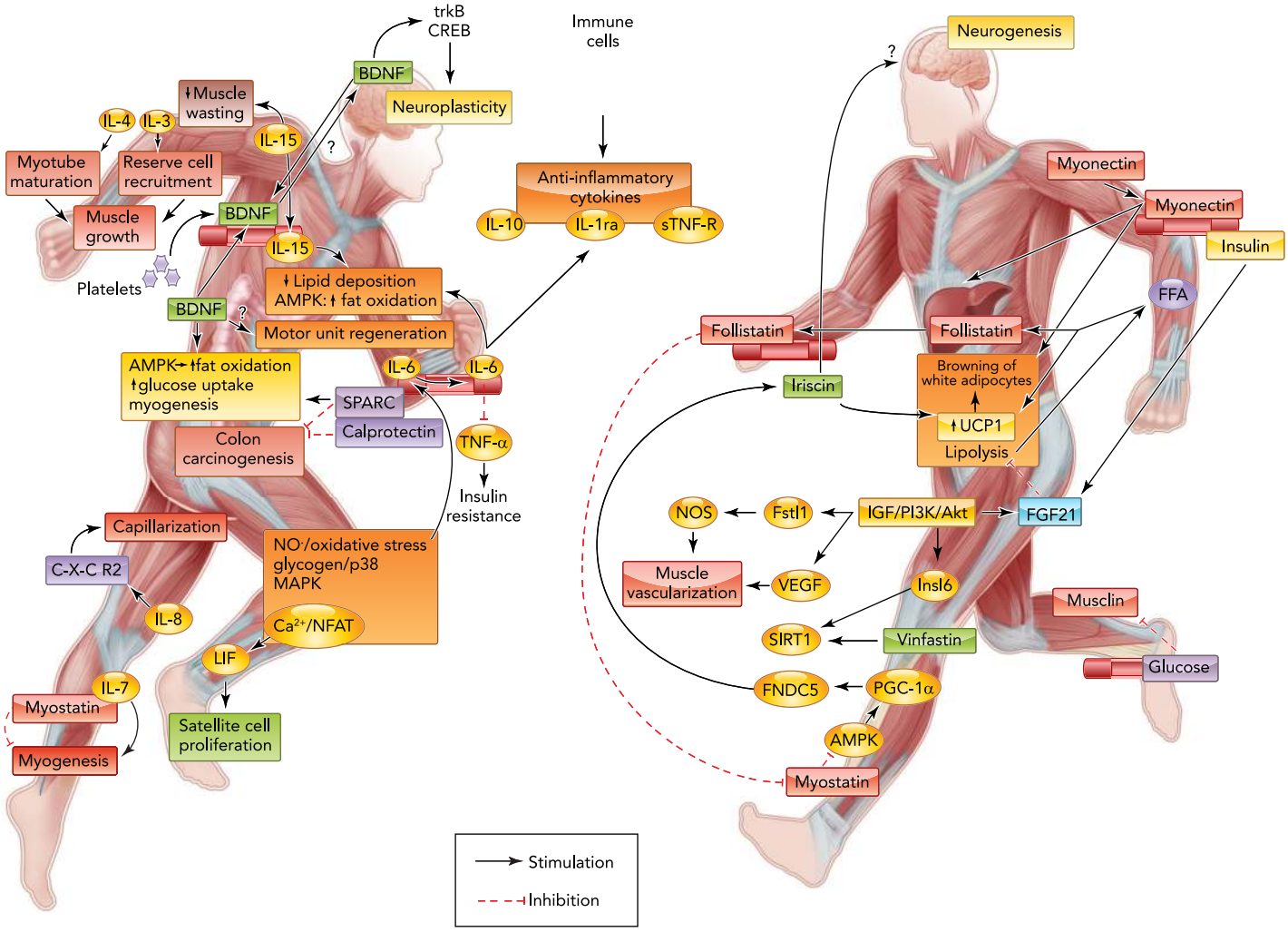

FIGURE 2. **Summary of the main myokines, their putative effects, and the molecular signals/pathways involved**
AMPK, AMP-activated protein kinase; BDNF, brain-derived neurotrophic factor; CREB, cAMP response-element-binding protein; C-X-C R2, C-X-C receptor 2; FFA, free-fatty acid; FGF21, fibroblast growth factor 21; Fndc5, fibronectin type III domain-containing 5 protein; Fstl1, follistatin-like 1; IGF, insulin-like growth factor; IL-1ra, IL-1 receptor antagonist; Insl6, insulin-like 6; LIF, leukemia inhibitory factor; NO·, nitric oxide; NOS, nitric oxide synthase; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator 1α; PI3K, phosphatidylinositol 3-kinase; SIRT1, sirtuin 1; SPARC, secreted protein acidic and rich in cysteine; sTNF-R, soluble TNF receptors; trkB, tropomyosin receptor kinase; UCP1, uncoupling protein 1.

Table 1. ***The exercise "vademecum": characteristics of the main myokines that are candidates to be ingredients of the exercise polypill (stem cells are also listed)***

Name of Molecule or Cell	Structure (If Molecule) or Cell Type	Main Tissue(s) of Origin	Main Type of Exercise Probably Maximizing its Release/Secretion	Main Target Tissue(s) Associated With Exercise-Induced Release/Secretion	Main Biological Effect(s) Associated With Exercise-Induced Release/Secretion	Main Putative Health Benefit(s) Associated With Exercise-Induced Released/Secretion	Potential Future Medical Application(s)/ Target Diseases	Dietary Considerations
BDNF (brain-derived neurotrophic factor)	Similar to other neurotrophins; is initially synthesized as a precursor (pro-BDNF, of 32 kDa), which is subsequently cleaved to generate the mature BDNF (mBDNF, 14 kDa)	Neuronal tissues: brain (e.g., hippocampus) and rest of central nervous system	Moderate-intensity aerobic exercise	Skeletal muscle	↑ Muscle fat oxidation	↑ Capillarization of ischemic tissues	Enhancing anti-depressant/ anxiolytic treatment; protection against neurodegeneration (including possibly dementia)	Caloric restriction might maximize exercise effects (at least in diabetic murine models)
		Nonneuronal tissues: vascular endothelial cells, platelets, lymphocytes, eosinophils, monocytes, pituitary gland, working skeletal muscle (possibly mainly type II fibers and satellite cells or neurons within muscle beds)		Brain	↑ Neuroplasticity	↑ Brain maintenance/ function and promotes neuroplasticity		
				Motoneurons	↑ Motor unit regeneration	↑ Motor neuron maintenance/repair		
CAC [circulating angiogenic cells including EPCs (endothelial progenitor cells)*]	Any circulating mononuclear cell supporting vascular repair and re-endothelialization	Bone marrow	Vigorous aerobic exercise (e.g., bicycling, running), especially if inducing transient ischemia in cardiac patients	Damaged endothelium (although actual CAC engraftment remains to be clearly shown in humans)	↑ Endothelial repair and vasculogenesis	↓ CVD risk	Use of exercise preconditioning to increase the efficacy of regenerative therapies with stem-cells (by increasing circulating levels of CAC), especially in cardiovascular medicine	
	Bone marrow-derived stem/progenitor cells (i.e., mainly EPCs) Non bone marrow-derived (pro-angiogenic macrophages and T-cells, circulating cells originating from the vessel itself)	Bloodstream and vessels (but to a lower extent)				↓ Disease progression once CVD is already established		
FGF21 (fibroblast growth factor 21)	Member of the fibroblast growth factor (FGF) super family	Mainly liver	Not clearly known yet (increased secretion shown with both aerobic and resistance exercise)	Adipose tissue	↓ Lipolysis	↓ Lipotoxicity of chronically elevated FFA	Use of exercise in obese people as a coadjuvant therapy to decrease insulin resistance and diabetes risk	
		Skeletal muscle				↓ FFA-induced insulin resistance		
		Other tissues (pancreas, adipose tissue, thymus)						
Fst1 [follistatin-like 1, also known as TSC-36 (TGF-beta-stimulated clone 36)]	Extracellular glycoprotein that, despite limited homology, has been grouped into the follistatin family of proteins	Myocardium	Not known yet	Skeletal muscle	↑ Endothelial function and revascularization	Coadjuvant in muscle regeneration	To be determined (yet likely muscle atrophy conditions)	
		Skeletal muscle						

Table 1. (continued)

Name of Molecule or Cell	Structure (If Molecule) or Cell Type	Main Tissue(s) of Origin	Main Type of Exercise Probably Maximizing its Release/Secretion	Main Target Tissue(s) Associated With Exercise-Induced Release/Secretion	Main Biological Effect(s) Associated With Exercise-Induced Release/Secretion	Main Putative Health Benefit(s) Associated With Exercise-Induced Released/Secretion	Potential Future Medical Application(s)/Target Diseases	Dietary Considerations
IL-4 and IL-13	Share substantial structure homology and redundant functions	Lymphocytes (TH2 CD4+ helper cells),mast cells and neutrophils Various origins (brain, cancer cells, liver, fibroblasts, and muscle cells) Working muscles	Intense strength exercise	Skeletal muscle	↑ Muscle growth	↓ Muscle atrophy ↑ Muscle repair following damage	Muscle atrophy (e.g., IL-4 co-injection with transplanted myoblasts might be an approach to enhance the migration of transplanted cells for the treatment of Duchenne dystrophy)	
IL-6 (also termed interferon, beta 2)	Belongs to the IL-6 cytokine superfamily (LIF, IL-11, CNF, cardiotrophin-1, oncostatin) that share structural similarities and the gp130 receptor subunit Low-weight protein like all cytokines (pro-peptide of 212 amino acids is cleaved into a mature IL-6 peptide (184 amino acids)	Working muscles [type I and II fibers, satellite cells (rodents)] Immune cells Adipocytes	Intense aerobic exercise involving large muscle mass but non-damaging (e.g., running in trained athletes or brisk/very brisk walking in general)	Skeletal muscle Adipose tissue Pituitary gland-liver Immune cells	↑ Muscle lipolysis ↑ Muscle growth ↑ Adipocyte lipolysis ↑ Liver-glucose release to blood ↓ Inflammation Immunomodulation	Protection against cardio-metabolic diseases ↓ Inflammation	Cardio-metabolic diseases	Carbohydrate ingestion during exercise (e.g., brisk walking) inhibits the release of muscle-IL-6 and, unless in highly performing athletes, is probably not necessary or justified
IL-7	Predicted molecular mass of 17 kDa and ~25 kDa for non-glycosylated and glycosylated protein, respectively	Lymphoid organs (spleen) Epithelial cells Skeletal muscle	Strength exercise	Skeletal muscle	Regulation of muscle development	?	?	
IL-8	Belongs to the C-X-C chemokine family, low-molecular protein of ~8 kDa, which has an amino acid sequence Glu-Leu-Arg preceding the first conserved cysteine amino acid residue in the primary protein structure	Monocytes and macrophages Endothelial cells Working skeletal muscle	Probably exhaustive endurance exercise (e.g., distance running)	Skeletal muscle	Muscle angiogenesis, i.e., contributes to the exercise training effect on muscle capillarization	?	?	Like for IL-6, low glycogen stores increase muscle secretion of this myokine
IL-15	Belongs to the IL-2 superfamily (14–15 kDa, four-helix configuration)	Working muscles (type I and mainly type II fibers)	Mainly strength exercise	Skeletal muscle	Promotes muscle anabolism/inhibits catabolism	Protection against muscle wasting caused by aging or chronic disease	IL-15 and IL-15Rα are potential pharmacological targets against: muscle wasting and its end-points associated with disease or aging (sarcopenia and cancer-cachexia)	Anti-obesogenic effects are likely independent of diet

Table 1. (continued)

Name of Molecule or Cell	Structure (If Molecule) or Cell Type	Main Tissue(s) of Origin	Main Type of Exercise Probably Maximizing its Release/Secretion	Main Target Tissue(s) Associated With Exercise-Induced Release/Secretion	Main Biological Effect(s) Associated With Exercise-Induced Release/Secretion	Main Putative Health Benefit(s) Associated With Exercise-Induced Released/Secretion	Potential Future Medical Application(s)/Target Diseases	Dietary Considerations
	Two IL-15 isoforms exist: a long signaling secreted peptide (48 amino acids) and a short signaling peptide (21 amino acids)	Various origins (lymphoid tissues, kidney, brain, cardiac muscle, lung, pancreas, testis, liver, placenta, epithelial cells, and activated macrophages, and maybe adipocytes)		Adipose tissue	Anti-obesogenic (↓ mainly visceral fat) effect	Protection against obesity	Obesity	
				(Skeletal muscle-adipose tissue cross talk)	Insulin-sensitizing effect			
Insl6 (insulin-like 6)	Member of the insulin-like/relaxin family	Male germ cells	Unknown	Skeletal muscle	Muscle regenerative factor (↑ activation of satellite cells in injured muscles)	↑ Muscle regeneration	Strategies to enhance Insl6-mediated signalling could be a useful treatment for skeletal muscle myopathies or trauma-induced muscle injuries	
Irisin	112-amino acid glycoprotein that is derived from the cleavage and secretion to circulation of the type I membrane protein Fndc5 (209 amino acids)	Skeletal muscle Working skeletal-muscle (muscle is the main tissue where *FNDC5* gene is expressed) Muscle-related tissues (e.g., pericardium, heart) To a minor extent, kidney, liver, lung, or adipose tissue	To be clearly determined	White adipose tissue	"Browning" of white adipose tissue through ↑ UCP1 and thus ↑ thermogenesis	Protection against diabetes and obesity	Exercise as a coadjuvant for anti-obesogenic/ and anti-diabetic therapies targeting iriscin	
LIF (leukemia inhibiting factor)	Belongs to the IL-6 cytokine superfamily Long-chain four α-helix bundle protein, which is highly glycosylated (38–67 kDa, which can be deglycosylated to ~20 kDa)	Working muscles (type I fibers, satellite cells) Central nervous system (hypothalamus, hippocampus, amygdala, cerebellum, cerebral cortex, and basal forebrain nuclei)	Mainly strength exercise	Skeletal muscle	Mainly local (autocrine/ paracrine effect): ↑ Muscle growth (satellite cell proliferation) ↑ Muscle regeneration	Protection against muscle wasting	Muscle wasting	
MSCs (mesenchymal stem cells)	Mononuclear cell population that, when cultured ex vivo, adheres to plastic with a fibroblast-like morphology. In vivo characteristics include adherence to plastic, specific surface antigen expression pattern and differentiation potential	Bone marrow	Eccentric exercise inducing muscle damage	Skeletal muscle	Tissue repair and vasculogenesis in damaged skeletal muscle	↑ Muscle repair (complementing the effects of muscle satellite cells)	Muscle atrophy	

Table 1. (continued)

Name of Molecule or Cell	Structure (If Molecule) or Cell Type	Main Tissue(s) of Origin	Main Type of Exercise Probably Maximizing its Release/Secretion	Main Target Tissue(s) Associated With Exercise-Induced Release/Secretion	Main Biological Effect(s) Associated With Exercise-Induced Release/Secretion	Main Putative Health Benefit(s) Associated With Exercise-Induced Released/Secretion	Potential Future Medical Application(s)/Target Diseases	Dietary Considerations
		Adipose tissue	Vigorous aerobic exercise inducing no muscle damage but transient myocardial ischemia in case of CVD patients	Myocardium?	Same effect in damages in myocardium?	↑ Myocardium repair?	Peripheral arterial disease	
		Others sources: dental pulp, cord blood, and a variety of MSCs (mMSCs) residing in skeletal muscles			Note: tissue engraftment of exercise-released nonresident MSCs remains to be demonstrated in humans		Same as with CAC: use of exercise to increase the efficacy of regenerative therapies with stem cells (by increasing circulating levels of MSCs)	
Myonectin [also termed CTRP5 (C1q/TNF-related protein 5)]	340-amino acid-protein. Tends to form heteromeric complexes with other proteins of the CTRP family, possibly to expand its function	Skeletal muscle (especially in type I fibers, at least in animals)	Remains to be determined in humans	Liver	↑ FFA uptake in liver and adipocytes	Control of whole body metabolism (muscle-liver-adipose tissue cross talk)	?	
Musclin (also termed osteocrin)	20-kDa protein, contains a region homologous to members of the natriuretic peptide family, i.e., it can share related functions or receptors	Skeletal muscle (mainly type II fibers)	Remains to be determined whether exercise actually induces musclin expression in humans	Adipose tissue Skeletal muscle	↓ Glucose uptake in muscle	?	?	Musclin expression increases with obesity and with feeding
		Non-muscle sources (osteocytes, osteoblasts)						
Myostatin [also termed, GDF8 (growth differentiation factor 8)]	378-amino acid protein, belongs to the TGB family	Skeletal muscle	Acute endurance and resistance exercise decrease myostatin expression, but decreased expression has been more consistently shown with aerobic training than with resistance training	Skeletal muscle	Main effects associated to myostatin inhibition which can be partly achieved by exercise are: ↑ Muscle growth ↓ Adiposity ↑ Insulin sensitivity	Attenuation of disease/age muscle wasting	Use of exercise as a coadjuvant of myostatin-inhibition therapies for muscle wasting	
$NO^{\cdot}$ (nitric oxide)		Contracting muscles (with the main NOS isozyme expressed in muscles being nNOSμ)	Vigorous aerobic exercise (e.g., bicycling)	Adipose tissue? Skeletal muscles	↑ Glucose uptake	Obesity/diabetes prevention ↑ Glucose control in Type 2 diabetes Duchenne muscular dystrophy? (Disease associated with decreased nNOSμ) ↑ Myogenesis and muscle repair	Therapeutics that mimic the muscle-NO pathway (e.g., Type 2 diabetes)?	

Table 1. (continued)

Name of Molecule or Cell	Structure (If Molecule) or Cell Type	Main Tissue(s) of Origin	Main Type of Exercise Probably Maximizing its Release/Secretion	Main Target Tissue(s) Associated With Exercise-Induced Release/Secretion	Main Biological Effect(s) Associated With Exercise-Induced Release/Secretion	Main Putative Health Benefit(s) Associated With Exercise-Induced Released/Secretion	Potential Future Medical Application(s)/Target Diseases	Dietary Considerations
NSCs (neural stem cells, also termed neural progenitor cells)	Stem cells that, at least in embryonic state, can differentiate into neurons, astrocytes, and oligodendrocytes	Central nervous system	Aerobic exercise (only shown in rodent models)	Central nervous system	Increased neurogenesis	↑ Neural plasticity ↑ Brain function (included cognitive capacity)	Using exercise as a co-adjuvant therapy against aging neuro-degeneration	
NT4 (neurotrophin-4, also known as NT4/5)	Member of the nerve growth factor family, which also includes BDNF. The mature peptide has a predicted molecular mass of approximately 14 kDa, and is 130 amino acid in length	Working muscles (type I fibers)	?	Motoneurons	Growth and remodeling of adult motoneuron innervation	↑ Neuromuscular performance	Using exercise to attenuate age loss of neuromuscular performance or as a coadjuvant treatment against neuromuscular disorders?	
S100A8-S100A9 complex (calprotectin)	S100 family proteins MRP-8 (S100A8) and MRP-14 (S100A9) are small (10–14 kDa) calcium-binding proteins that form a heterodimer	Neutrophils, monocytes, acute-phase macrophages Secretory epithelia Working muscles	Exhausting endurance exercise (e.g., marathon running)	Remains to be clearly elucidated	Among other effects (including cytokine-like action), anti-tumor effect	↑ Protection against cancer (e.g., colon)?	Using exercise as a coadjuvant treatment against colon cancer (not only for prevention)	
SPARC [secreted protein acidic and rich in cysteine, also known as basement membrane protein (BM)-40]	Multifunctional nonstructural, matricellular glycoprotein (43 kDa) associated with the extracellular matrix that is expressed abundantly in basal lamina	Skeletal muscles (progenitors cells, fibers, endothelial cells) Tumors (ovarian, colorectal, melanomas) Adipocytes, fibroblasts, endothelial cells, cardiac myocytes (at low levels), α-smooth muscle actin-positive myofibroblasts, CD45-positive leukocytes	Strength exercise?		Regulation of glucose metabolism Inhibits proliferation of colon cancer cells	Prevents tumorigenesis of colon cancer	Same as above	
Visfatin [also known as NAMPT (nicotinamide phosphoribosyltransferase) or PBEF (pre-B cell enhancing factor)]	Multifunctional protein. Polypeptide of 491 amino acids with a molecular mass of 52 kDa	Ubiquitous expression in human tissues, including adipose and skeletal muscle tissue (i.e., it is both an adipokine and a myokine) Liver Bone marrow Lymphocytes Beta-cells and human islets Heart	Endurance exercise	Skeletal muscle and adipose tissue	AMPK activation →↑ SIRT1 → PGC-1α It provides NAD^+	Might mediate major exercise-induced health/anti-aging effects involving SIRT1-pathways: anti-oxidant defense, macromolecular damage repair, or mitochondriogenesis	Exercise as a major component of anti-aging medicine	

AMPK, adenosine monophosphate-activated protein kinase; CVD, cardiovascular disease; FFA, free-fatty acids; Fndc5, fibronectin type III domain-containing 5 protein; IL-15Rα, interleukin-15 receptor; NOS, nitric oxide synthase; PPAR-α, peroxisome proliferator-activated receptor α; SIRT1, sirtuin 1; TGB, transforming growth factor; UCP1: uncoupling protein 1. *Research is growing fast in the field since the original paper by Asahara et al. (15) where the term endothelial progenitor cell (EPC) was first introduced, and caution is needed with nomenclature. The difficulty of identifying cells with a unique EPC phenotype (based on cell membrane antigens) as originally defined by Asahara et al. and the fact that a variety of hematopoietic cells (including stem and progenitors) participate in initiating and modulating neo-angiogenesis make the issue complicated and the term EPC too restrictive (see Ref. 181 for a review). As such, the broader term circulating angiogenic cells (CAC) is being used in the literature instead of EPC.

C-X-C receptor 2 receptor signaling (131). IL-4 and IL-13, which share a substantial fraction of their sequence structure and biological roles, are upregulated by resistance training (385), with IL-4 mediating NFATc2-induced muscle growth (192) and myotube maturation (247) and IL-3 stimulating additional recruitment of reserve cells during IGF-I-induced hypertrophy (204).

Among all neurotrophins (molecules that stimulate neuronal survival, differentiation, or growth), brain-derived neurotrophic factor (BDNF) is the most affected by exercise (231). Circulating BDNF increases with aerobic exercise (121, 147, 409, 437, 465, 510), especially with high-intensity exercise (121, 431, 510), and rapidly decreases to basal levels shortly after exertion (431), suggesting its clearance is mediated by target-tissue uptake (284). Less clear is its response to acute resistance exercise (76, 146, 429) or resistance exercise training (66, 146, 263, 429, 435, 437, 524, 534). Several tissues, such as contracting muscles (111, 152, 293) or platelets (465), can express BDNF. Yet the main origin of exercise-induced blood BDNF is likely the brain before this molecule crosses the blood-brain barrier (284). Increased BDNF transcripts in exercised rodents' brains are well documented, providing mechanistic support for a beneficial exercise effect in cognitive function (4, 5, 30, 153, 193, 275, 315, 333, 334, 352, 396, 417, 425, 460, 488, 507), e.g., through the downstream signals tropomyosin receptor kinase (trkB), cAMP response-element-binding protein (CREB), or synapsin I (488). Exercise-induced BDNF in rodents is also likely to contribute to the anticancer effect of PA (57). Muscle-produced BDNF could act locally, enhancing muscle lipid oxidation via AMPK-activation (293), whereas exercise-induced BDNF coming from different sources might improve depression (526) or anxiety symptoms through MAPK signaling pathways (110), maintain brain function and promote neuroplasticity (78, 153), or enhance the efficacy of antidepressant treatment (416). BDNF can also help maintain/repair motoneurons (327) like other muscle-derived neurotrophins such as neurotrophin 4 (133, 162) or could regulate satellite-cell function/regeneration (69, 326).

Secreted protein acidic and rich in cysteine (SPARC), is a matricellular protein that regulates cell proliferation/migration and is implicated in numerous biological processes (45). It was recently identified as a myokine (13, 345) whose expression increases with resistance training (345). SPARC, which is in fact a potential target in cancer immunotherapy (198), might mediate the preventive effects of exercise on colon cancer by suppressing the formation of aberrant crypt foci, probably through stimulation of apoptosis via caspase-3 and -8 (13). Circulating (117, 318, 324, 365) and muscle-transcript levels of S100A8-S100A9 complex (calprotectin) increase with acute endurance exercise (324). Potential beneficial effects (yet to be demonstrated) of muscle-derived calprotectin might also be cancer protection for its ability to induce apoptosis in certain tumor lines (528), including colon cancer lines (143), or to inhibit matrix metalloproteinases associated with cancer invasion and metastasis (200).

Although there is controversy (473), recent research has identified a novel PGC-1α-induced myokine called iriscin (43). In white adipocytes, iriscin induces expression of uncoupling protein 1 and other brown adipose tissue-associated genes [partly via increased peroxisome proliferator-activated receptor α (PPAR-α)] and thus increases thermogenesis and switching of these cells toward a brown, fat-like phenotype (43). These provocative findings have led to the postulation that iriscin may be a therapeutic agent against cardiometabolic disorders and a major component of the exercise polypill (420). Iriscin is linked with improved aerobic fitness in cardiac patients (253), muscle mass, and metabolic factors in healthy people (195), and neurogenesis in animal models (171).

IGF-phosphatidylinositol 3-kinase (PI3K)-Akt signaling plays a central role in muscle regeneration (88, 372), inducing myokines with an essentially local action: insulin-like 6, which activates satellite cell activation (529); follistatin-like 1, which promotes endothelial function and revascularization in response to ischemic insult through endothelial $NO^{\cdot}$ synthase (eNOS) signaling (357); and VEGF, which stimulates angiogenesis (463). The Akt pathway also upregulates muscle fibroblast growth factor 21 (FGF21) (201), an insulin-regulated myokine (188) that is released to the blood during exercise (84), although there exists controversy on the effects of regular exercise in its basal levels (83, 287, 522). By inhibiting lipolysis in adipocytes, exercise-released FGF21 could play a protective role against lipotoxicity, i.e., ectopic deposition of lipids in the liver or muscle (84).

Other myokines and their putative roles (awaiting more human research) include myonectin, a metabolic regulator that stimulates uptake of free-fatty acids in liver and adipocytes (439); musclin (343, 525), an inhibitor of muscle-glucose uptake (274); and visfatin (503), a NAD+ biosynthetic enzyme whose expression and circulating levels increase (77) and decrease, respectively, with exercise training (93). By virtue of its activating effect on NAD+-dependent sirtuin 1 (SIRT1), visfatin might mediate major exercise-induced health/anti-aging effects involving SIRT1-pathways (235): anti-oxidant defense, macromolecular damage repair, or mitochondriogenesis. Of note, visfatin is also an adipokine with rather different

functions, i.e., pro-inflammatory (410) and anti-apoptotic effects (91, 268).

Exercise and Regenerative Medicine

Pluripotent stem cells (SCs) able to differentiate into many cell types are proposed as a valuable therapeutic source, notably in ischemic tissues with low self-repair capacity. Because using embryonic SCs has ethical and immune-related limitations (401), researchers have explored other means of obtaining SCs, e.g., isolating them from extracorporeal sources (placenta, umbilical cord) or reprogramming of mature cells. Yet another strategy is stimulating adult SC proliferation and migration from their home tissue (e.g., bone marrow) to target damaged tissue for subsequent engraftment and cell regeneration by applying specific physiological stimuli, of which exercise is a good example (284) (FIGURE 3).

Together with macrophage-mediated reverse cholesterol transport[3] the capacity for vessel wall regeneration and angiogenesis is the main mechanism responsible for maintaining cardiovascular health (321). The lower CVD risk associated with regular exercise is largely mediated by an improvement in such capacity (511). Endothelial regeneration and neovascularization not only depends on cells residing within the vessel wall but also on circulating SCs coming from other sources, notably the bone marrow. A specific SC subset, originally identified as endothelial progenitor cells (15) or now more broadly referred to as circulating angiogenic cells

[3]Although there is some recent controversy (305), regular exercise seems to stimulate macrophage-reverse cholesterol transport RCT in vitro (351) and in vivo (408), with exercise-triggered activation of peroxisome proliferator-activated receptor gamma (abbreviated as PPARγ or NR1C, according to the unified nomenclature system for the nuclear receptor superfamily) within these cells being advocated as a putative involved mechanism (52, 472).

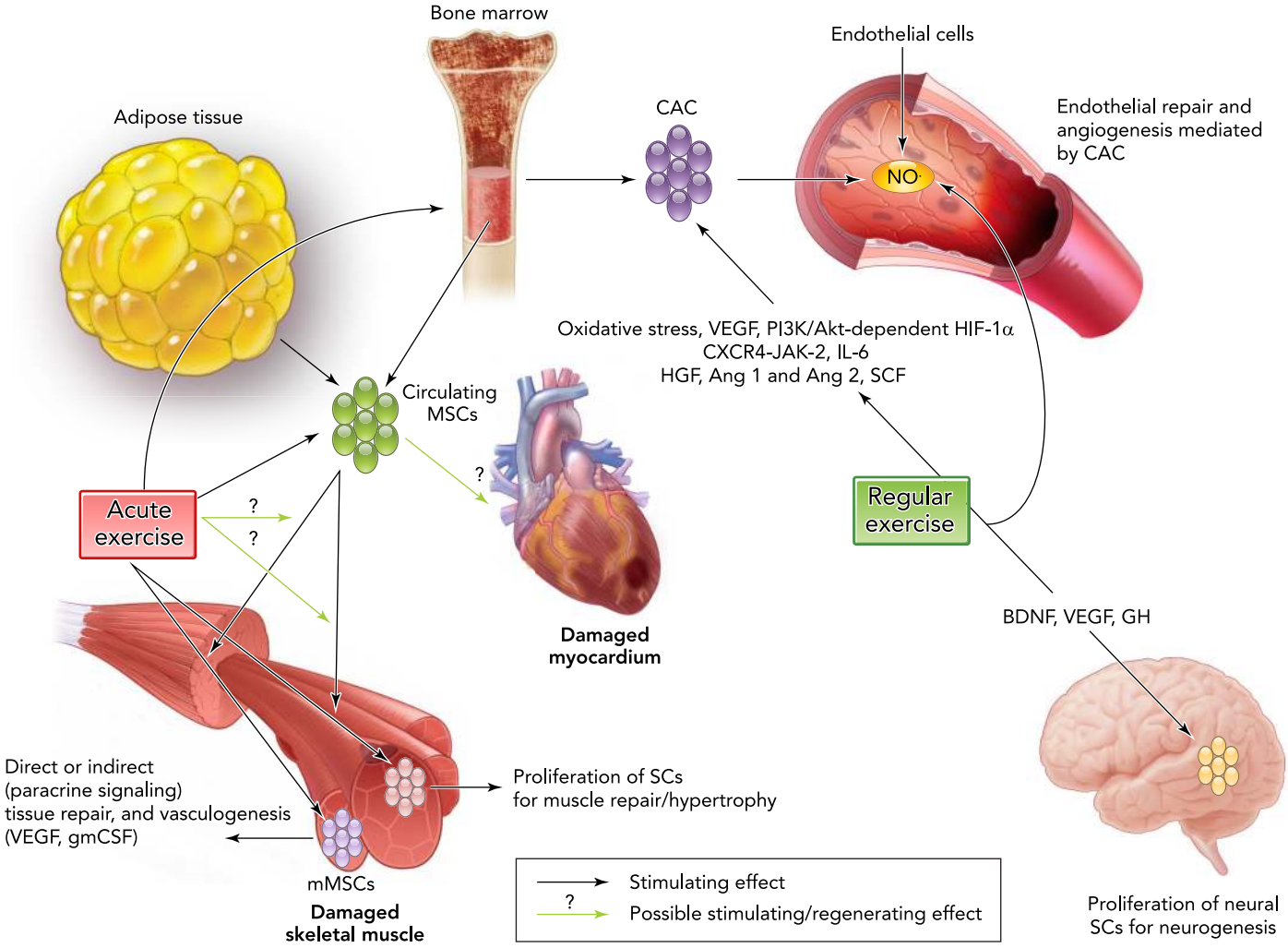

FIGURE 3. **Summary of the main types of stem cells associated with exercise, their main putative effects, and the molecular signals/pathways involved**
Ang, angiopoietin; CAC, circulating angiogenic cells; C-X-C R4, C-X-C motif receptor 4; GH, growth hormone; HGF, hepatocyte growth factor; HIF-1α, hypoxia-inducible factor 1-α; JAK-2, janus kinase-2; mMSC, muscle-derived mesenchymal stem cells; SC, stem cell; SCF, stem cell factor.

(CAC), target the vascular endothelium, where they can engraft and promote repair and angiogenesis (82, 505). Low CAC counts/function is correlated with risk of CVD (19) or diabetes complications (308) and decreases with senescence (480, 508), whereas high CAC (see below) represents a link between regular exercise and decreased CVD risk (250), with such exercise benefits starting early in life (501). CAC increases could also provide mechanistic support for the training-induced improvement in myocardial perfusion and lower disease progression in CVD patients (167, 173, 336, 434); they also could complement the exercise benefits in endothelial $NO^{\cdot}$ production and thus in vascular tone regulation, with regular bouts of exercise-increased laminar flow increasing the expression/activation (through phosphorylation via Akt) of eNOS while attenuating $NO^{\cdot}$ degradation into reactive oxygen species (ROS) or reactive nitrogen species (RNS) (144).

Circulating CAC increase with acute exercise in healthy individuals (39, 157, 313, 322, 485), people at risk for CVD (399), and CVD patients (3), although this effect is blunted with age (276, 471). Intense exercise, especially if inducing transient myocardial ischemia, seems the most potent stimulus for CAC release and subsequent vasculogenesis in CVD patients (3). Acute exercise also appears to reverse CAC dysfunction in CVD patients (483, 484). Regular exercise increases CAC number (250, 282, 424) or function in people with CVD (44, 141, 459, 484), metabolic syndrome (120), peripheral artery disease (430), or obesity/overweight (68), and in the elderly (519). However, this effect has not been corroborated in some healthy cohorts (394, 471, 512), and data from animal studies showing actual CAC engraftment in injured tissues (92) remains to be validated in humans. Postulated biological mediators of exercise-induced CAC proliferation and release to the bloodstream are reduced CAC apoptosis (250), oxidative stress (511), thrombin (276), VEGF (3, 250), stimulation of PI3K/Akt-dependent hypoxia-induced factor-1α (92) or C-X-C motif receptor 4-janus kinase-2 signaling pathways (519), IL-6 (39), pro-angiogenic factors (hepatocyte growth factor, angiopoietin 1 and 2 or stem cell factor) (39), endothelial-derived $NO^{\cdot}$ (512) or maybe $NO^{\cdot}$ produced locally in the bone marrow (511), and $NO^{\cdot}$/oxidative stress interaction (314, 511). Increases in $NO^{\cdot}$ produced inside CAC might mediate the improvement in the function of these cells with exercise (206).

Research on another type of SC, mesenchymal stem cells (MSCs) (129), has grown fast in the last decade (139). Regardless of their origin (mainly, but not only, bone marrow and adipose tissue), they represent pluripotent progenitors of mesoderm- or even non-mesoderm-derived tissues with a wide variety of therapeutic potential (graft vs. host or Crohn's disease, wound healing or as vehicles of anticancer genes) (139, 536). Intense exercise, whether inducing (395) or not inducing eccentric muscle damage, is a potent stimulus for MSC release to the bloodstream (280, 432). Vigorous exertion also increases the migratory capacity of MSCs, an effect potentially mediated by the myokine IL-6 (432). Similar to what occurs with CAC, intense exercise-inducing transient ischemia can increase circulating MSCs in CVD patients (280), which is a potentially promising finding because, together with the few cardiac-resident SCs, MSCs have the potential to repair damaged myocardium (518). However, actual engraftment of migratory MSCs in damaged tissue (muscle, myocardium) remains to be demonstrated.

SCs can also reside within the perivascular niche of a variety of tissues, directly repairing injury or indirectly facilitating regeneration by excreting cytokines/growth factors that can stimulate other resident SCs (58, 304). This seems to be the case for skeletal muscles, where not only satellite cells but also a variety of resident MSCs (mMSCs) can repair damage (16, 100, 325, 419, 482). Proliferation of mMSCs is stimulated by the muscle protein α7 integrin or by eccentric exercise (482), and these cells can secrete angiogenic factors (VEGF, granulocyte-macrophage colony-stimulating factor), contributing to vessel remodeling in skeletal muscles following eccentric damage (196).

Proliferation of neural SCs might also contribute to improve brain regenerative capacity and cognitive ability, with some rodent models showing training increases in hippocampal (242, 514) or periventricular progenitors (35). Current candidate neutrophins mediating exercise-induced neurogenesis are above-mentioned BDNF (231, 533), growth hormone (35), or VEGF (79, 116).

The ROS Paradox

As first reported 35 years ago (105), acute exercise generates ROS (see Ref. 384 for a review) and does so in an intensity- (209, 387, 428) and duration-dependent manner (37). Exercise-generated ROS come from many sources (384) and include hydrogen peroxide (H_2O_2) (28, 297, 487, 492), superoxide anion ($O_2^{-}\cdot$) (22, 296, 400), or hydroxyl radicals (OH^{-}) (104, 124, 348, 381) (FIGURE 4). However, strong evidence showing that regular exercise upregulates endogenous antioxidants not only in muscles (1, 27, 80, 148, 149, 156, 169, 177, 180, 189, 207, 211, 225, 251, 259, 260, 264, 296, 297, 299, 309, 349, 377–379, 381, 404, 428, 446, 470, 490, 493, 494), where the effect can be evident after just five consecutive training days (493, 494), but also in liver

(194, 211, 491), blood (17, 21, 46, 53, 62, 64, 96, 98, 107, 127, 128, 140, 151, 215, 229, 232, 238, 239, 258, 264, 291, 306, 311, 342, 350, 404, 406, 433, 438, 444, 449, 461, 467, 469, 470), or other tissues (brain, heart, kidney, stomach, intestine, vessels) (27, 96, 132, 186, 264, 332, 404, 468, 490) has changed the old view of exercise as a potential source of harmful oxidative damage. In fact, muscle-derived ROS occurring during prolonged inactivity contribute to disuse muscle atrophy (382, 383), whereas the same stimulus coming from working fibers is required for training adaptations to occur (149, 150, 168, 404). This apparent paradox could be explained by the hormesis theory (54, 210, 392, 393): chemicals and toxic substances that are deleterious at high doses can have a low-dose beneficial effect. Thus increases in ROS elicited by moderate-intensity exercise could lead to beneficial adaptations, especially increased muscle oxidative capacity (109, 202). Yet, if ROS levels are increased many-fold above basal levels and antioxidant defense capacity, muscle atrophy can occur, e.g., Duchenne muscular dystrophy (383, 393). A second potential factor is differences in the ROS origin between contracting and resting muscle fibers, with mitochondria being the primary source in the latter (218) but not in the former (380).

ROS might play an important signaling role in angiogenesis (67), improved vascular distensibility (261), PGC-1α upregulation (404, 447), PGC-1α/nuclear

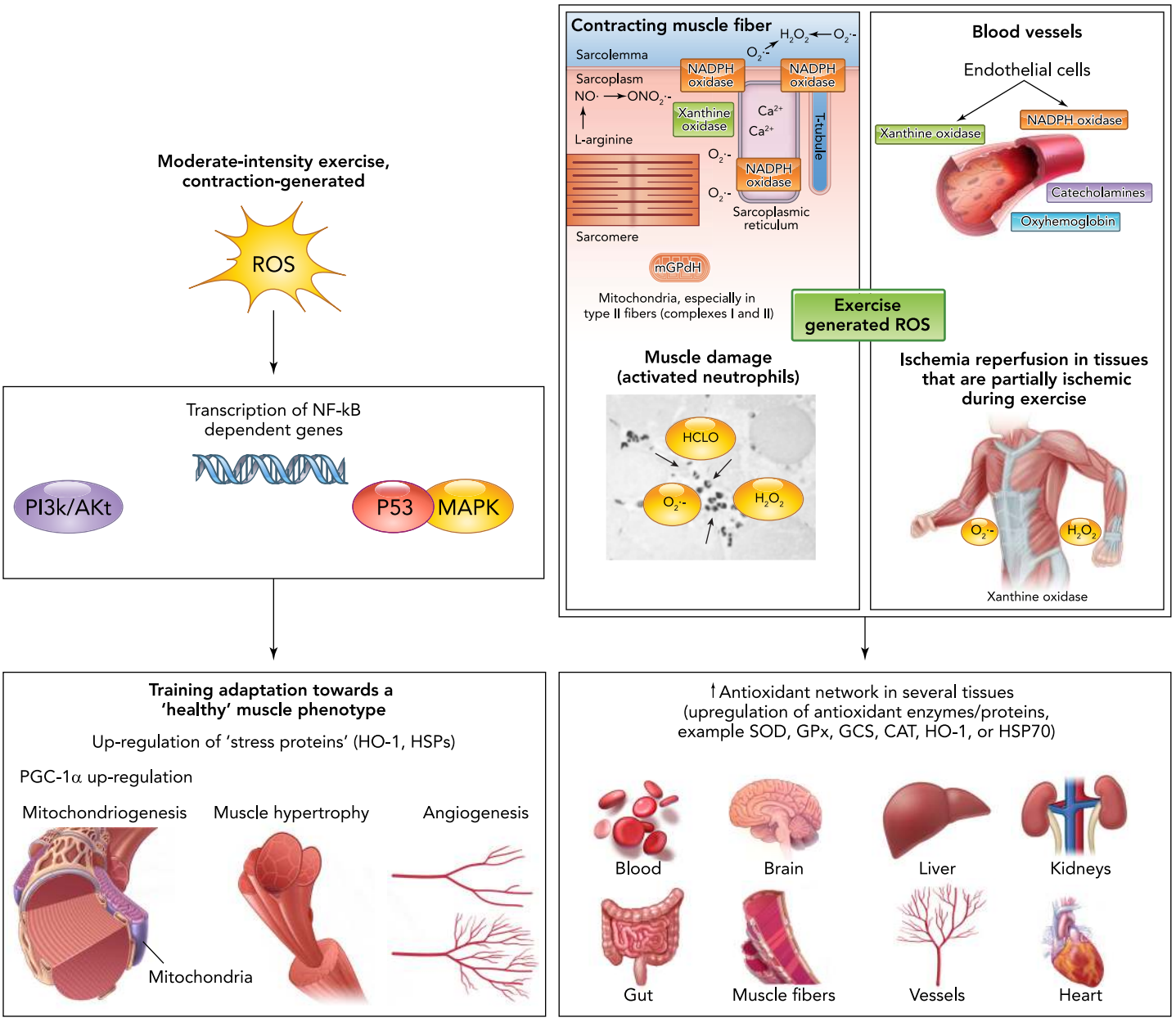

FIGURE 4. **Summary of exercise-generated ROS, their main putative effects, and the molecular signals/pathways involved**
CAT, catalase; GCS, γ-glutamylcysteine synthetase; GPx, glutathione peroxidase; H_2O_2, hydrogen peroxide; HO-1, heme oxygenase-1; HSP: heat shock proteins; NADPH, nicotinamide adenine dinucleotide phosphate; $O_2^{-}\cdot$, superoxide anion radical; SOD, super oxide dismutase.

respiratory factor 1-stimulated mitochondriogenesis (199, 371, 517), upregulation of cytoprotective "stress proteins" (heme oxygenase 1, heat shock proteins like HSP60 and HSP70) in muscle (25, 101, 119, 273, 298, 363, 454, 455), or skeletal muscle hypertrophy (203, 427). An important signaling link between contraction-induced ROS production and exercise adaptations involves the redox regulation of NF-κB, a family of transcriptional activators controlling the expression of genes involved in inflammation, cell growth, stress responses, or apoptosis (109, 210, 240, 310, 481). Other pathways are MAPK, PI3K/Akt, or p53 activation (11, 203, 361). Interestingly, despite its popularity among westerners for its hypothetical anti-disease/rejuvenating effects, antioxidant supplementation does not mimic, and in fact can reverse, beneficial exercise adaptations (127, 148, 149, 226, 404).

Skeletal muscle also generates RNS including $NO^{\cdot}$ (20, 99, 233, 462, 502) or nitrite ion (NO_2^-) (489), which at high doses may cause nitrosative stress and tissue damage but at low doses has beneficial regulatory effects in vasodilation, glucose uptake, or immune function (300).

Autophagy

Autophagy, a cellular quality control mechanism of degradation and recycling of damaged macromolecules and organelles, is gaining attention for its potential involvement in longevity promotion (414) and defense against chronic diseases (320). It could also mediate some of the exercise benefits (FIGURE 5), as suggested by recent data from rodent models.

In normal mice, acute exercise increases autophagy activity in skeletal/cardiac muscles and tissues involved in glucose/energy homeostasis (pancreas, liver, adipose tissue), whereas transgenic mice deficient in stimulus-induced autophagy show decreased endurance and altered glucose metabolism (175). Exercise also induces autophagy in mouse brain, supporting its potential to promote elimination of damaging proteins causing aging

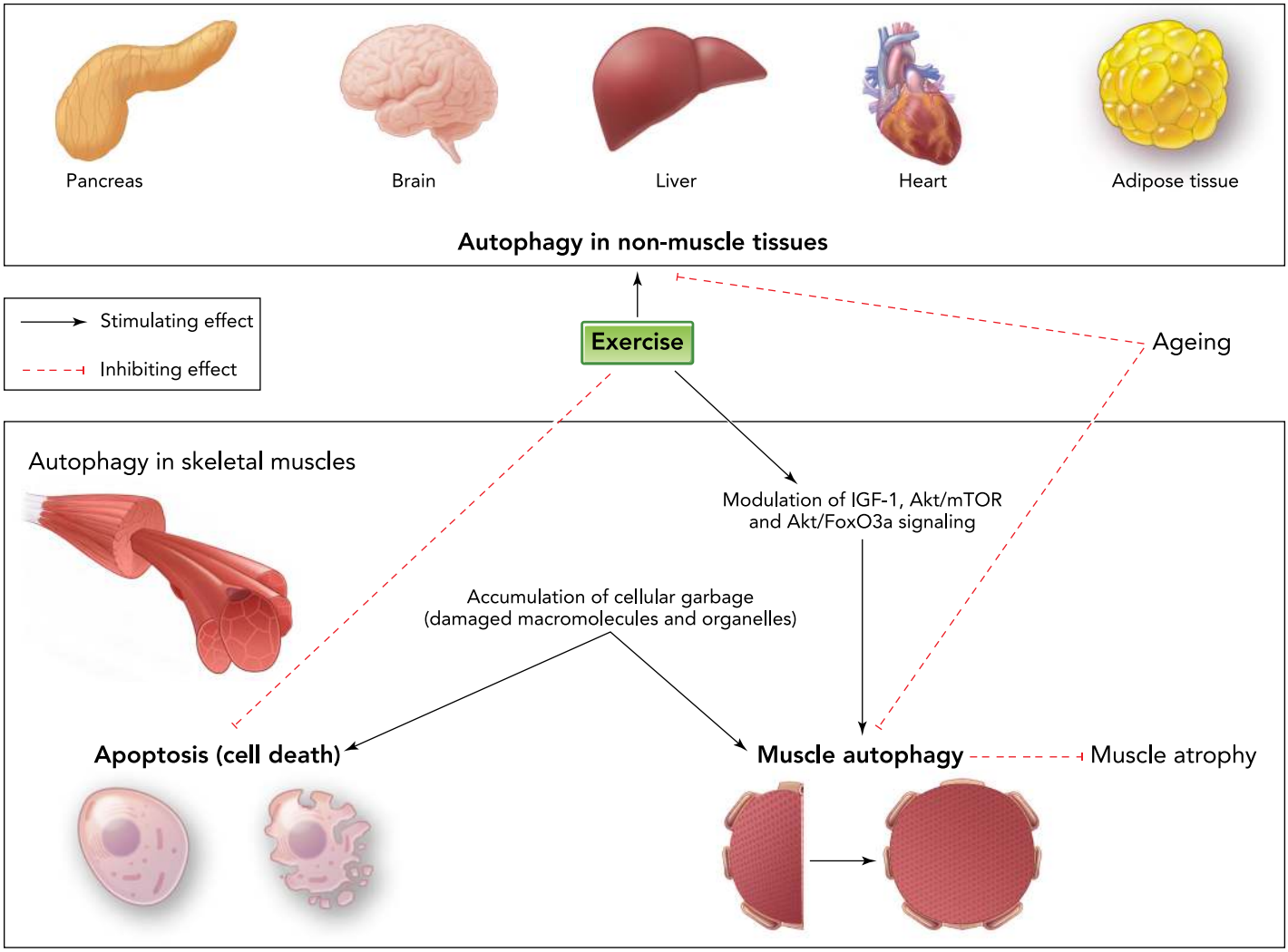

FIGURE 5. **Exercise and autophagy**
FoxO3a, FOXO transcription factor; mTOR, mammalian target-of-rapamycin.

neurodegeneration (176). Chronic exercise increases autophagy activity and reduces apoptosis in aging muscle (230, 283) by modulating IGF-I, Akt/mTOR, and Akt/FoxO3a signaling, thereby preventing loss of muscle mass/strength (283). Others, however, found the protective effect of chronic exercise on diabetes-induced muscle atrophy was probably due to decreased muscle autophagy (257). Taken together, these apparently controversial data would suggest an optimal balance is obtained in the trained muscle between "healthy" autophagy-induced turnover of damaged cellular components (which attenuates/prevents muscle atrophy), and "excessive" autophagy-mediated protein degradation (which eventually leads to muscle atrophy).

Data is still scarce in humans, yet recent preliminary reports suggest upregulation of muscle markers of autophagy after strenuous acute endurance (205) or resistance exercise (130), or after a combined weight loss and moderate-intensity exercise program in old obese women (513).

Summary and Perspective

There is strong epidemiological evidence on the beneficial effects of regular exercise, which are likely to go well beyond reducing CVD risk factors. Furthermore, exercise benefits can overcome those of common drugs when one considers that the exercise polypill combines preventive, multi-systemic effects with little adverse consequences and at lower cost. Exercise, and especially the contracting muscle, is indeed a source of numerous drug-like molecules with beneficial effects across all ages. Furthermore, regular exercise is probably the lifestyle intervention with the most profound upregulating effect on hundreds of genes involved in tissue maintenance and homeostasis, implying a complex cross talk between muscles and other tissues. Progress in proteomics and other techniques is allowing identification of a myriad of novel myokines and also is unraveling the fact that many molecules can have a quite different effect depending on their tissue of origin, as well as on the metabolic state (rest vs. exercise) during which they are secreted to the bloodstream.

Identification of exercise adaptations is helping to improve our understanding of the pathophysiology of chronic diseases and changing old views, which could help investigate new therapeutic targets and approaches. For instance, ROS signals are increasingly viewed as mediators of the health-promoting, lifespan-extending capabilities of exercise, even questioning the classic Harman's Free Radical Theory of Aging. With regard to aging, the "oldest old" are the most rapidly growing population segment among westerners. As opposed to exercise, no drug intervention has proven efficient to maintain muscle fitness, a key factor to ensure independent living throughout all stages of life. ■

No conflicts of interest, financial or otherwise, are declared by the author(s).

Author contributions: C.F.-L. and A.L. conception and design of research; C.F.-L., N.G., and A.L. drafted manuscript; C.F.-L., N.G., N.B., and A.L. edited and revised manuscript; C.F.-L., N.G., N.B., and A.L. approved final version of manuscript; N.G. and A.L. prepared figures.

References

1. Abruzzo PM, Esposito F, Marchionni C, di Tullio S, Belia S, Fulle S, Veicsteinas A, Marini M. Moderate exercise training induces ROS-related adaptations to skeletal muscles. *Int J Sports Med*. In press.
2. Adams SP, Tsang M, Wright JM. Lipid lowering efficacy of atorvastatin. *Cochrane Database Syst Rev* 12: CD008226, 2012.
3. Adams V, Lenk K, Linke A, Lenz D, Erbs S, Sandri M, Tarnok A, Gielen S, Emmrich F, Schuler G, Hambrecht R. Increase of circulating endothelial progenitor cells in patients with coronary artery disease after exercise-induced ischemia. *Arterioscler Thromb Vasc Biol* 24: 684–690, 2004.
4. Adlard PA, Perreau VM, Engesser-Cesar C, Cotman CW. The timecourse of induction of brain-derived neurotrophic factor mRNA and protein in the rat hippocampus following voluntary exercise. *Neurosci Lett* 363: 43–48, 2004.
5. Aguiar AS Jr, Speck AE, Prediger RD, Kapczinski F, Pinho RA. Downhill training upregulates mice hippocampal and striatal brain-derived neurotrophic factor levels. *J Neural Transm* 115: 1251–1255, 2008.
6. Al-Khalili L, Bouzakri K, Glund S, Lonnqvist F, Koistinen HA, Krook A. Signaling specificity of interleukin-6 action on glucose and lipid metabolism in skeletal muscle. *Mol Endocrinol* 20: 3364–3375, 2006.
7. Al-Shanti N, Saini A, Faulkner SH, Stewart CE. Beneficial synergistic interactions of TNF-alpha and IL-6 in C2 skeletal myoblasts–potential cross-talk with IGF system. *Growth Factors* 26: 61–73, 2008.
8. Almendro V, Busquets S, Ametller E, Carbo N, Figueras M, Fuster G, Argiles JM, Lopez-Soriano FJ. Effects of interleukin-15 on lipid oxidation: disposal of an oral [^{14}C]-triolein load. *Biochim Biophys Acta* 1761: 37–42, 2006.
9. Almendro V, Fuster G, Ametller E, Costelli P, Pilla F, Busquets S, Figueras M, Argiles JM, Lopez-Soriano FJ. Interleukin-15 increases calcineurin expression in 3T3–L1 cells: possible involvement on in vivo adipocyte differentiation. *Int J Mol Med* 24: 453–458, 2009.
10. Alvarez B, Carbo N, Lopez-Soriano J, Drivdahl RH, Busquets S, Lopez-Soriano FJ, Argiles JM, Quinn LS. Effects of interleukin-15 (IL-15) on adipose tissue mass in rodent obesity models: evidence for direct IL-15 action on adipose tissue. *Biochim Biophys Acta* 1570: 33–37, 2002.
11. Allen RG, Tresini M. Oxidative stress and gene regulation. *Free Radic Biol Med* 28: 463–499, 2000.
12. Amirouche A, Durieux AC, Banzet S, Koulmann N, Bonnefoy R, Mouret C, Bigard X, Peinnequin A, Freyssenet D. Down-regulation of Akt/mammalian target of rapamycin signaling pathway in response to myostatin overexpression in skeletal muscle. *Endocrinology* 150: 286–294, 2009.
13. Aoi W, Naito Y, Takagi T, Tanimura Y, Takanami Y, Kawai Y, Sakuma K, Hang LP, Mizushima K, Hirai Y, Koyama R, Wada S, Higashi A, Kokura S, Ichikawa H, Yoshikawa T. A novel myokine, secreted protein acidic and rich in cysteine (SPARC), suppresses colon tumorigenesis via regular exercise. *Gut* 62: 882–889, 2013.
14. Appel ML, Berger RD, Saul JP, Smith JM, Cohen RJ. Beat to beat variability in cardiovascular variables: noise or music? *J Am Coll Cardiol* 14: 1139–1148, 1989.
15. Asahara T, Murohara T, Sullivan A, Silver M, van der Zee R, Li T, Witzenbichler B, Schatteman G, Isner JM. Isolation of putative progenitor endothelial cells for angiogenesis. *Science* 275: 964–967, 1997.

16. Asakura A, Seale P, Girgis-Gabardo A, Rudnicki MA. Myogenic specification of side population cells in skeletal muscle. *J Cell Biol* 159: 123–134, 2002.

17. Azizbeigi K, Azarbayjani MA, Peeri M, Agha-Alinejad H, Stannard S. The effect of progressive resistance training on oxidative stress and erythrocyte antioxidant enzymes activity in untrained men. *Int J Sport Nutr Exerc Metab* 23: 230–238, 2013.

18. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 376: 1670–1681, 2010.

19. Bakogiannis C, Tousoulis D, Androulakis E, Briasoulis A, Papageorgiou N, Vogiatzi G, Kampoli AM, Charakida M, Siasos G, Latsios G, Antoniades C, Stefanadis C. Circulating endothelial progenitor cells as biomarkers for prediction of cardiovascular outcomes. *Curr Med Chem* 19: 2597–2604, 2012.

20. Balon TW, Nadler JL. Nitric oxide release is present from incubated skeletal muscle preparations. *J Appl Physiol* 77: 2519–2521, 1994.

21. Banfi G, Malavazos A, Iorio E, Dolci A, Doneda L, Verna R, Corsi MM. Plasma oxidative stress biomarkers, nitric oxide and heat shock protein 70 in trained elite soccer players. *Eur J Appl Physiol* 96: 483–486, 2006.

22. Barclay JK, Reading SA, Murrant CL, Woodley NE. Inotropic effects on mammalian skeletal muscle change with contraction frequency. *Can J Physiol Pharmacol* 81: 753–758, 2003.

23. Baron AD, Laakso M, Brechtel G, Hoit B, Watt C, Edelman SV. Reduced postprandial skeletal muscle blood flow contributes to glucose intolerance in human obesity. *J Clin Endocrinol Metab* 70: 1525–1533, 1990.

24. Barra NG, Reid S, MacKenzie R, Werstuck G, Trigatti BL, Richards C, Holloway AC, Ashkar AA. Interleukin-15 contributes to the regulation of murine adipose tissue and human adipocytes. *Obesity (Silver Spring)* 18: 1601–1607, 2010.

25. Barreiro E, Comtois AS, Mohammed S, Lands LC, Hussain SN. Role of heme oxygenases in sepsis-induced diaphragmatic contractile dysfunction and oxidative stress. *Am J Physiol Lung Cell Mol Physiol* 283: L476–L484, 2002.

26. Bassett DR. Physical activity of Canadian and American children: a focus on youth in Amish, Mennonite, and modern cultures. *Appl Physiol Nutr Metab* 33: 831–835, 2008.

27. Bayod S, Del Valle J, Lalanza JF, Sanchez-Roige S, de Luxan-Delgado B, Coto-Montes A, Canudas AM, Camins A, Escorihuela RM, Pallas M. Long-term physical exercise induces changes in sirtuin 1 pathway and oxidative parameters in adult rat tissues. *Exp Gerontol* 47: 925–935, 2012.

28. Bejma J, Ramires P, Ji LL. Free radical generation and oxidative stress with ageing and exercise: differential effects in the myocardium and liver. *Acta Physiol Scand* 169: 343–351, 2000.

29. Benny Klimek ME, Aydogdu T, Link MJ, Pons M, Koniaris LG, Zimmers TA. Acute inhibition of myostatin-family proteins preserves skeletal muscle in mouse models of cancer cachexia. *Biochem Biophys Res Commun* 391: 1548–1554, 2010.

30. Berchtold NC, Chinn G, Chou M, Kesslak JP, Cotman CW. Exercise primes a molecular memory for brain-derived neurotrophic factor protein induction in the rat hippocampus. *Neuroscience* 133: 853–861, 2005.

31. Bigger JTJ. The predictive value of RR variability and baroreflex sensitivity in coronary heart disease. *Cardiac Electrophysiol Rev* 1/2: 198–204, 1997.

32. Billman GE. Aerobic exercise conditioning: a non-pharmacological antiarrhythmic intervention. *J Appl Physiol* 92: 446–454, 2002.

33. Billman GE. Cardiac autonomic neural remodeling and susceptibility to sudden cardiac death: effect of endurance exercise training. *Am J Physiol Heart Circ Physiol* 297: H1171–H1193, 2009.

34. Billman GE. A comprehensive review and analysis of 25 years of data from an in vivo canine model of sudden cardiac death: implications for future anti-arrhythmic drug development. *Pharmacol Ther* 111: 808–835, 2006.

35. Blackmore DG, Golmohammadi MG, Large B, Waters MJ, Rietze RL. Exercise increases neural stem cell number in a growth hormone-dependent manner, augmenting the regenerative response in aged mice. *Stem Cells* 27: 2044–2052, 2009.

36. Blair SN. Physical inactivity: the biggest public health problem of the 21st century. *Br J Sports Med* 43: 1–2, 2009.

37. Bloomer RJ, Davis PG, Consitt LA, Wideman L. Plasma protein carbonyl response to increasing exercise duration in aerobically trained men and women. *Int J Sports Med* 28: 21–25, 2007.

38. Bogdanovich S, Krag TO, Barton ER, Morris LD, Whittemore LA, Ahima RS, Khurana TS. Functional improvement of dystrophic muscle by myostatin blockade. *Nature* 420: 418–421, 2002.

39. Bonsignore MR, Morici G, Riccioni R, Huertas A, Petrucci E, Veca M, Mariani G, Bonanno A, Chimenti L, Gioia M, Palange P, Testa U. Hemopoietic and angiogenetic progenitors in healthy athletes: different responses to endurance and maximal exercise. *J Appl Physiol* 109: 60–67, 2010.

40. Booth FW, Laye MJ, Lees SJ, Rector RS, Thyfault JP. Reduced physical activity and risk of chronic disease: the biology behind the consequences. *Eur J Appl Physiol* 102: 381–390, 2008.

41. Booth FW, Lees SJ. Fundamental questions about genes, inactivity, and chronic diseases. *Physiol Genomics* 28: 146–157, 2007.

42. Bortoluzzi S, Scannapieco P, Cestaro A, Danieli GA, Schiaffino S. Computational reconstruction of the human skeletal muscle secretome. *Proteins* 62: 776–792, 2006.

43. Bostrom P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, Rasbach KA, Bostrom EA, Choi JH, Long JZ, Kajimura S, Zingaretti MC, Vind BF, Tu H, Cinti S, Hojlund K, Gygi SP, Spiegelman BM. A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature* 481: 463–468, 2012.

44. Brehm M, Picard F, Ebner P, Turan G, Bolke E, Kostering M, Schuller P, Fleissner T, Ilousis D, Augusta K, Peiper M, Schannwell C, Strauer BE. Effects of exercise training on mobilization and functional activity of blood-derived progenitor cells in patients with acute myocardial infarction. *Eur J Med Res* 14: 393–405, 2009.

45. Brekken RA, Sage EH. SPARC, a matricellular protein: at the crossroads of cell-matrix communication. *Matrix Biol* 19: 816–827, 2001.

46. Brites FD, Evelson PA, Christiansen MG, Nicol MF, Basilico MJ, Wikinski RW, Llesuy SF. Soccer players under regular training show oxidative stress but an improved plasma antioxidant status. *Clin Sci (Lond)* 96: 381–385, 1999.

47. Broholm C, Laye MJ, Brandt C, Vadalasetty R, Pilegaard H, Pedersen BK, Scheele C. LIF is a contraction-induced myokine stimulating human myocyte proliferation. *J Appl Physiol* 111: 251–259, 2011.

48. Broholm C, Mortensen OH, Nielsen S, Akerstrom T, Zankari A, Dahl B, Pedersen BK. Exercise induces expression of leukaemia inhibitory factor in human skeletal muscle. *J Physiol* 586: 2195–2201, 2008.

49. Broholm C, Pedersen BK. Leukaemia inhibitory factor: an exercise-induced myokine. *Exerc Immunol Rev* 16: 77–85, 2010.

50. Bruce CR, Dyck DJ. Cytokine regulation of skeletal muscle fatty acid metabolism: effect of interleukin-6 and tumor necrosis factor-alpha. *Am J Physiol Endocrinol Metab* 287: E616–E621, 2004.

51. Bryniarski L, Kawecka-Jaszcz K, Bacior B, Grodecki J, Rajzer M. Effect of exercise rehabilitation on heart rate variability in hypertensives after myocardial infarction. *J Hypertens* 15: 1739–1743, 1997.

52. Butcher LR, Thomas A, Backx K, Roberts A, Webb R, Morris K. Low-intensity exercise exerts beneficial effects on plasma lipids via PPARgamma. *Med Sci Sports Exerc* 40: 1263–1270, 2008.

53. Cakir-Atabek H, Demir S, PinarbaSili RD, Gunduz N. Effects of different resistance training intensity on indices of oxidative stress. *J Strength Cond Res* 24: 2491–2497, 2010.

54. Calabrese LH, Nieman DC. Exercise, immunity, infection. *J Am Osteopath Assoc* 96: 166–176, 1996.

55. Campbell PT, Patel AV, Newton CC, Jacobs EJ, Gapstur SM. Associations of recreational physical activity and leisure time spent sitting with colorectal cancer survival. *J Clin Oncol* 31: 876–885, 2013.

56. Cao JM, Chen LS, KenKnight BH, Ohara T, Lee MH, Tsai J, Lai WW, Karagueuzian HS, Wolf PL, Fishbein MC, Chen PS. Nerve sprouting and sudden cardiac death. *Circ Res* 86: 816–821, 2000.

57. Cao L, Liu X, Lin EJ, Wang C, Choi EY, Riban V, Lin B, During MJ. Environmental and genetic activation of a brain-adipocyte BDNF/leptin axis causes cancer remission and inhibition. *Cell* 142: 52–64, 2010.

58. Caplan AI. Why are MSCs therapeutic? New data: new insight. *J Pathol* 217: 318–324, 2009.

59. Carbo N, Lopez-Soriano J, Costelli P, Alvarez B, Busquets S, Baccino FM, Quinn LS, Lopez-Soriano FJ, Argiles JM. Interleukin-15 mediates reciprocal regulation of adipose and muscle mass: a potential role in body weight control. *Biochim Biophys Acta* 1526: 17–24, 2001.

60. Carbo N, Lopez-Soriano J, Costelli P, Busquets S, Alvarez B, Baccino FM, Quinn LS, Lopez-Soriano FJ, Argiles JM. Interleukin-15 antagonizes muscle protein waste in tumour-bearing rats. *Br J Cancer* 83: 526–531, 2000.

61. Carey AL, Steinberg GR, Macaulay SL, Thomas WG, Holmes AG, Ramm G, Prelovsek O, Hohnen-Behrens C, Watt MJ, James DE, Kemp BE, Pedersen BK, Febbraio MA. Interleukin-6 increases insulin-stimulated glucose disposal in humans and glucose uptake and fatty acid oxidation in vitro via AMP-activated protein kinase. *Diabetes* 55: 2688–2697, 2006.

62. Carlsohn A, Rohn S, Bittmann F, Raila J, Mayer F, Schweigert FJ. Exercise increases the plasma antioxidant capacity of adolescent athletes. *Ann Nutr Metab* 53: 96–103, 2008.

63. Carlson CJ, Booth FW, Gordon SE. Skeletal muscle myostatin mRNA expression is fiber-type specific and increases during hindlimb unloading. *Am J Physiol Regul Integr Comp Physiol* 277: R601–R606, 1999.

64. Cases N, Aguilo A, Tauler P, Sureda A, Llompart I, Pons A, Tur JA. Differential response of plasma and immune cell's vitamin E levels to physical activity and antioxidant vitamin supplementation. *Eur J Clin Nutr* 59: 781–788, 2005.

65. Casolo G, Balli E, Taddei T, Amuhasi J, Gori C. Decreased spontaneous heart rate variability in congestive heart failure. *Am J Cardiol* 64: 1162–1167, 1989.

66. Castellano V, White LJ. Serum brain-derived neurotrophic factor response to aerobic exercise in multiple sclerosis. *J Neurol Sci* 269: 85–91, 2008.

67. Castier Y, Brandes RP, Leseche G, Tedgui A, Lehoux S. p47phox-dependent NADPH oxidase regulates flow-induced vascular remodeling. *Circ Res* 97: 533–540, 2005.

68. Cesari F, Sofi F, Gori AM, Corsani I, Capalbo A, Caporale R, Abbate R, Gensini GF, Casini A. Physical activity and circulating endothelial progenitor cells: an intervention study. *Eur J Clin Invest* 42: 927–932, 2012.

69. Clow C, Jasmin BJ. Brain-derived neurotrophic factor regulates satellite cell differentiation and skeltal muscle regeneration. *Mol Biol Cell* 21: 2182–2190, 2010.

70. Constantin D, McCullough J, Mahajan RP, Greenhaff PL. Novel events in the molecular regulation of muscle mass in critically ill patients. *J Physiol* 589: 3883–3895, 2011.

71. Cordain L, Gotshall RW, Eaton SB, Eaton SB, 3rd. Physical activity, energy expenditure and fitness: an evolutionary perspective. *Int J Sports Med* 19: 328–335, 1998.

72. Cornelissen VA, Fagard RH. Effect of resistance training on resting blood pressure: a meta-analysis of randomized controlled trials. *J Hypertens* 23: 251–259, 2005.

73. Cornelissen VA, Fagard RH. Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. *Hypertension* 46: 667–675, 2005.

74. Cornelissen VA, Fagard RH, Coeckelberghs E, Vanhees L. Impact of resistance training on blood pressure and other cardiovascular risk factors: a meta-analysis of randomized, controlled trials. *Hypertension* 58: 950–958, 2011.

75. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. *J Am Heart Assoc* 2: e004473, 2013.

76. Correia PR, Pansani A, Machado F, Andrade M, Silva AC, Scorza FA, Cavalheiro EA, Arida RM. Acute strength exercise and the involvement of small or large muscle mass on plasma brain-derived neurotrophic factor levels. *Clinics* 65: 1123–1126, 2010.

77. Costford SR, Bajpeyi S, Pasarica M, Albarado DC, Thomas SC, Xie H, Church TS, Jubrias SA, Conley KE, Smith SR. Skeletal muscle NAMPT is induced by exercise in humans. *Am J Physiol Endocrinol Metab* 298: E117–E126, 2010.

78. Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends Neurosci* 25: 295–301, 2002.

79. Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health: key roles of growth factor cascades and inflammation. *Trends Neurosci* 30: 464–472, 2007.

80. Criswell D, Powers S, Dodd S, Lawler J, Edwards W, Renshler K, Grinton S. High intensity training-induced changes in skeletal muscle antioxidant enzyme activity. *Med Sci Sports Exerc* 25: 1135–1140, 1993.

81. Croft L, Bartlett JD, MacLaren DP, Reilly T, Evans L, Mattey DL, Nixon NB, Drust B, Morton JP. High-intensity interval training attenuates the exercise-induced increase in plasma IL-6 in response to acute exercise. *Appl Physiol Nutr Metab* 34: 1098–1107, 2009.

82. Crosby JR, Kaminski WE, Schatteman G, Martin PJ, Raines EW, Seifert RA, Bowen-Pope DF. Endothelial cells of hematopoietic origin make a significant contribution to adult blood vessel formation. *Circ Res* 87: 728–730, 2000.

83. Cuevas-Ramos D, Almeda-Valdes P, Gomez-Perez FJ, Meza-Arana CE, Cruz-Bautista I, Arellano-Campos O, Navarrete-Lopez M, Aguilar-Salinas CA. Daily physical activity, fasting glucose, uric acid, and body mass index are independent factors associated with serum fibroblast growth factor 21 levels. *Eur J Endocrinol* 163: 469–477, 2010.

84. Cuevas-Ramos D, Almeda-Valdes P, Meza-Arana CE, Brito-Cordova G, Gomez-Perez FJ, Mehta R, Oseguera-Moguel J, Aguilar-Salinas CA. Exercise increases serum fibroblast growth factor 21 (FGF21) levels. *PLos One* 7: e38022, 2012.

85. Chan CY, Masui O, Krakovska O, Belozerov VE, Voisin S, Ghanny S, Chen J, Moyez D, Zhu P, Evans KR, McDermott JC, Siu KW. Identification of differentially regulated secretome components during skeletal myogenesis. *Mol Cell Proteomic* 10: M110004804, 2011.

86. Chan MH, Carey AL, Watt MJ, Febbraio MA. Cytokine gene expression in human skeletal muscle during concentric contraction: evidence that IL-8, like IL-6, is influenced by glycogen availability. *Am J Physiol Regul Integr Comp Physiol* 287: R322–R327, 2004.

87. Chan XC, McDermott JC, Siu KW. Identification of secreted proteins during skeletal muscle development. *J Proteome Res* 6: 698–710, 2007.

88. Charge SB, Rudnicki MA. Cellular and molecular regulation of muscle regeneration. *Physiol Rev* 84: 209–238, 2004.

89. Charkoudian N, Joyner MJ, Barnes SA, Johnson CP, Eisenach JH, Dietz NM, Wallin BG. Relationship between muscle sympathetic nerve activity and systemic hemodynamics during nitric oxide synthase inhibition in humans. *Am J Physiol Heart Circ Physiol* 291: H1378–H1383, 2006.

90. Chen PS, Chen LS, Cao JM, Sharifi B, Karagueuzian HS, Fishbein MC. Sympathetic nerve sprouting, electrical remodeling and the mechanisms of sudden cardiac death. *Cardiovasc Res* 50: 409–416, 2001.

91. Cheng Q, Dong W, Qian L, Wu J, Peng Y. Visfatin inhibits apoptosis of pancreatic beta-cell line, MIN6, via the mitogen-activated protein kinase/phosphoinositide 3-kinase pathway. *Mol Endocrinol* 47: 13–21, 2011.

92. Cheng XW, Kuzuya M, Kim W, Song H, Hu L, Inoue A, Nakamura K, Di Q, Sasaki T, Tsuzuki M, Shi GP, Okumura K, Murohara T. Exercise training stimulates ischemia-induced neovascularization via phosphatidylinositol 3-kinase/Akt-dependent hypoxia-induced factor-1 alpha reactivation in mice of advanced age. *Circulation* 122: 707–716, 2010.

93. Choi KM, Kim JH, Cho GJ, Baik SH, Park HS, Kim SM. Effect of exercise training on plasma visfatin and eotaxin levels. *Eur J Endocrinol* 157: 437–442, 2007.

94. Choi S, Liu X, Li P, Akimoto T, Lee SY, Zhang M, Yan Z. Transcriptional profiling in mouse skeletal muscle following a single bout of voluntary running: evidence of increased cell proliferation. *J Appl Physiol* 99: 2406–2415, 2005.

95. Church TS, Blair SN. When will we treat physical activity as a legitimate medical therapy . . . even though it does not come in a pill? *Br J Sports Med* 43: 80–81, 2009.

96. da Rocha RF, de Oliveira MR, Pasquali MA, Andrades ME, Oliveira MW, Behr GA, Moreira JC. Vascular redox imbalance in rats submitted to chronic exercise. *Cell Biochem Funct* 28: 190–196, 2010.

97. Dasarathy S, Dodig M, Muc SM, Kalhan SC, McCullough AJ. Skeletal muscle atrophy is associated with an increased expression of myostatin and impaired satellite cell function in the portacaval anastamosis rat. *Am J Physiol Gastrointest Liver Physiol* 287: G1124–G1130, 2004.

98. Dekany M, Nemeskeri V, Gyore I, Harbula I, Malomsoki J, Pucsok J. Antioxidant status of interval-trained athletes in various sports. *Int J Sports Med* 27: 112–116, 2006.

99. Delp MD, Laughlin MH. Time course of enhanced endothelium-mediated dilation in aorta of trained rats. *Med Sci Sports Exerc* 29: 1454–1461, 1997.

100. Dellavalle A, Sampaolesi M, Tonlorenzi R, Tagliafico E, Sacchetti B, Perani L, Innocenzi A, Galvez BG, Messina G, Morosetti R, Li S, Belicchi M, Peretti G, Chamberlain JS, Wright WE, Torrente Y, Ferrari S, Bianco P, Cossu G. Pericytes of human skeletal muscle are myogenic precursors distinct from satellite cells. *Nat Cell Biol* 9: 255–267, 2007.

101. Demirel HA, Hamilton KL, Shanely RA, Tumer N, Koroly MJ, Powers SK. Age and attenuation of exercise-induced myocardial HSP72 accumulation. *Am J Physiol Heart Circ Physiol* 285: H1609–H1615, 2003.

102. Dennis RA, Zhu H, Kortebein PM, Bush HM, Harvey JF, Sullivan DH, Peterson CA. Muscle expression of genes associated with inflammation, growth, and remodeling is strongly correlated in older adults with resistance training outcomes. *Physiol Genomics* 38: 169–175, 2009.

103. DeSouza CA, Shapiro LF, Clevenger CM, Dinenno FA, Monahan KD, Tanaka H, Seals DR. Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men. *Circulation* 102: 1351–1357, 2000.

104. Diaz PT, She ZW, Davis WB, Clanton TL. Hydroxylation of salicylate by the in vitro diaphragm: evidence for hydroxyl radical production during fatigue. *J Appl Physiol* 75: 540–545, 1993.

105. Dillard CJ, Litov RE, Savin WM, Dumelin EE, Tappel AL. Effects of exercise, vitamin E, and ozone on pulmonary function and lipid peroxidation. *J Appl Physiol* 45: 927–932, 1978.

106. Dixon EM, Kamath MV, McCartney N, Fallen EL. Neural regulation of heart rate variability in endurance athletes and sedentary controls. *Cardiovasc Res* 26: 713–719, 1992.

107. Djordjevic D, Cubrilo D, Macura M, Barudzic N, Djuric D, Jakovljevic V. The influence of training status on oxidative stress in young male handball players. *Mol Cell Biochem* 351: 251–259, 2011.

108. Drexler H, Coats AJ. Explaining fatigue in congestive heart failure. *Annu Rev Med* 47: 241–256, 1996.

109. Droge W. Free radicals in the physiological control of cell function. *Physiol Rev* 82: 47–95, 2002.

110. Duman CH, Schlesinger L, Russell DS, Duman RS. Voluntary exercise produces antidepressant and anxiolytic behavioral effects in mice. *Brain Res* 1199: 148–158, 2008.

111. Dupont-Versteegden EE, Houle JD, Dennis RA, Zhang J, Knox M, Wagoner G, Peterson CA. Exercise-induced gene expression in soleus muscle is dependent on time after spinal cord injury in rats. *Muscle Nerve* 29: 73–81, 2004.

112. Eckberg DL. Sympathovagal balance: a critical appraisal. *Circulation* 98: 2643–2644, 1998.

113. Edwards JE, Moore RA. Statins in hypercholesterolaemia: a dose-specific meta-analysis of lipid changes in randomised, double blind trials. *BMC Fam Pract* 4: 18, 2003.

114. Ekblom B, Kilbom A, Soltysiak J. Physical training, bradycardia, and autonomic nervous system. *Scand J Clin Lab Invest* 32: 251–256, 1973.

115. Elley CR, Gupta AK, Webster R, Selak V, Jun M, Patel A, Rodgers A, Thom S. The efficacy and tolerability of 'polypills': meta-analysis of randomised controlled trials. *PLos One* 7: e52145, 2012.

116. Fabel K, Fabel K, Tam B, Kaufer D, Baiker A, Simmons N, Kuo CJ, Palmer TD. VEGF is necessary for exercise-induced adult hippocampal neurogenesis. *Eur J Neurosci* 18: 2803–2812, 2003.

117. Fagerhol MK, Nielsen HG, Vetlesen A, Sandvik K, Lyberg T. Increase in plasma calprotectin during long-distance running. *Scand J Clin Lab Invest* 65: 211–220, 2005.

118. Farmawati A, Kitajima Y, Nedachi T, Sato M, Kanzaki M, Nagatomi R. Characterization of contraction-induced IL-6 up-regulation using contractile C2C12 myotubes. *Endocr J* 60: 137–147, 2013.

119. Febbraio MA, Koukoulas I. HSP72 gene expression progressively increases in human skeletal muscle during prolonged, exhaustive exercise. *J Appl Physiol* 89: 1055–1060, 2000.

120. Fernandez JM, Rosado-Alvarez D, Da Silva Grigoletto M.E, Rangel-Zuniga OA, Landaeta-Diaz LL, Caballero-Villarraso J, Lopez-Miranda J, Perez-Jimenez F, Fuentes-Jimenez F. Moderate-to-high-intensity training and a hypocaloric Mediterranean diet enhance endothelial progenitor cells and fitness in subjects with the metabolic syndrome. *Clin Sci (Lond)* 123: 361–373, 2012.

121. Ferris LT, Williams JS, Shen CL. The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. *Med Sci Sports Exerc* 39: 728–734, 2007.

122. Fiers W. Tumor necrosis factor. Characterization at the molecular, cellular and in vivo level. *FEBS Lett* 285: 199–212, 1991.

123. Figueroa A, Baynard T, Fernhall B, Carhart R, Kanaley JA. Endurance training improves post-exercise cardiac autonomic modulation in obese women with and without Type 2 diabetes. *Eur J Appl Physiol* 100: 437–444, 2007.

124. Finaud J, Lac G, Filaire E. Oxidative stress: relationship with exercise and training. *Sports Med* 36: 327–358, 2006.

125. Fischer CP. Interleukin-6 in acute exercise and training: what is the biological relevance? *Exerc Immunol Rev* 12: 6–33, 2006.

126. Fischer CP, Plomgaard P, Hansen AK, Pilegaard H, Saltin B, Pedersen BK. Endurance training reduces the contraction-induced interleukin-6 mRNA expression in human skeletal muscle. *Am J Physiol Endocrinol Metab* 287: E1189–E1194, 2004.

127. Fisher G, Schwartz DD, Quindry J, Barberio MD, Foster EB, Jones KW, Pascoe DD. Lymphocyte enzymatic antioxidant responses to oxidative stress following high-intensity interval exercise. *J Appl Physiol* 110: 730–737, 2011.

128. Franzoni F, Ghiadoni L, Galetta F, Plantinga Y, Lubrano V, Huang Y, Salvetti G, Regoli F, Taddei S, Santoro G, Salvetti A. Physical activity, plasma antioxidant capacity, and endothelium-dependent vasodilation in young and older men. *Am J Hypertens* 18: 510–516, 2005.

129. Friedenstein AJ, Chailakhjan RK, Lalykina KS. The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells. *Cell Tissue Kinet* 3: 393–403, 1970.

130. Fry CS, Drummond MJ, Glynn EL, Dickinson JM, Gundermann DM, Timmerman KL, Walker DK, Volpi E, Rasmussen BB. Skeletal muscle autophagy and protein breakdown following resistance exercise are similar in younger and older adults. *J Gerontol A Biol Sci Med Sci* 68: 599–607, 2013.

131. Frydelund-Larsen L, Penkowa M, Akerstrom T, Zankari A, Nielsen S, Pedersen BK. Exercise induces interleukin-8 receptor (CXCR2) expression in human skeletal muscle. *Exp Physiol* 92: 233–240, 2007.

132. Fukai T, Siegfried MR, Ushio-Fukai M, Cheng Y, Kojda G, Harrison DG. Regulation of the vascular extracellular superoxide dismutase by nitric oxide and exercise training. *J Clin Invest* 105: 1631–1639, 2000.

133. Funakoshi H, Belluardo N, Arenas E, Yamamoto Y, Casabona A, Persson H, Ibanez CF. Muscle-derived neurotrophin-4 as an activity-dependent trophic signal for adult motor neurons. *Science* 268: 1495–1499, 1995.

134. Furlan R, Piazza S, Dell'Orto S, Gentile E, Cerutti S, Pagani M, Malliani A. Early and late effects of exercise and athletic training on neural mechanisms controlling heart rate. *Cardiovasc Res* 27: 482–488, 1993.

135. Furmanczyk PS, Quinn LS. Interleukin-15 increases myosin accretion in human skeletal myogenic cultures. *Cell Biol Int* 27: 845–851, 2003.

136. Fuster G, Almendro V, Fontes-Oliveira CC, Toledo M, Costelli P, Busquets S, Lopez-Soriano FJ, Argiles JM. Interleukin-15 affects differentiation and apoptosis in adipocytes: implications in obesity. *Lipids* 46: 1033–1042, 2011.

137. Fuster V, Sanz G. Fixed-dose compounds and the secondary prevention of ischemic heart disease. *Rev Esp Cardiol* 64, *Suppl* 2: 3–9, 2011.

138. Gao D, Ning N, Niu X, Wei J, Sun P, Hao Aliskiren vs G. angiotensin receptor blockers in hypertension: meta-analysis of randomized controlled trials. *Am J Hypertens* 24: 613–621, 2011.

139. Garcia-Gomez I, Elvira G, Zapata AG, Lamana ML, Ramirez M, Castro JG, Arranz MG, Vicente A, Bueren J, Garcia-Olmo D. Mesenchymal stem cells: biological properties and clinical applications. *Expert Opin Biol Ther* 10: 1453–1468, 2010.

140. Garcia-Lopez D, Cuevas MJ, Almar M, Lima E, De Paz JA, Gonzalez-Gallego J. Effects of eccentric exercise on NF-kappaB activation in blood mononuclear cells. *Med Sci Sports Exerc* 39: 653–664, 2007.

141. Gatta L, Armani A, Iellamo F, Consoli C, Molinari F, Caminiti G, Volterrani M, Rosano GM. Effects of a short-term exercise training on serum factors involved in ventricular remodelling in chronic heart failure patients. *Int J Cardiol* 155: 409–413, 2012.

142. Geng DF, Liu M, Jin DM, Wu W, Deng J, Wang JF. Cilostazol-based triple antiplatelet therapy compared to dual antiplatelet therapy in patients with coronary stent implantation: a meta-analysis of 5,821 patients. *Cardiology* 122: 148–157, 2012.

143. Ghavami S, Kerkhoff C, Los M, Hashemi M, Sorg C, Karami-Tehrani F. Mechanism of apoptosis induced by S100A8/A9 in colon cancer cell lines: the role of ROS and the effect of metal ions. *J Leukoc Biol* 76: 169–175, 2004.

144. Gielen S, Sandri M, Erbs S, Adams V. Exercise-induced modulation of endothelial nitric oxide production. *Curr Pharm Biotechnol* 12: 1375–1384, 2011.

145. Glund S, Deshmukh A, Long YC, Moller T, Koistinen HA, Caidahl K, Zierath JR, Krook A. Interleukin-6 directly increases glucose metabolism in resting human skeletal muscle. *Diabetes* 56: 1630–1637, 2007.

146. Goekint M, De Pauw K, Roelands B, Njemini R, Bautmans I, Mets T, Meeusen R. Strength training does not influence serum brain-derived neurotrophic factor. *Eur J Appl Physiol* 110: 285–293, 2010.

147. Gold SM, Schulz KH, Hartmann S, Mladek M, Lang UE, Hellweg R, Reer R, Braumann KM, Heesen C. Basal serum levels and reactivity of nerve growth factor and brain-derived neurotrophic factor to standardized acute exercise in multiple sclerosis and controls. *J Neuroimmunol* 138: 99–105, 2003.

148. Gomez-Cabrera MC, Borras C, Pallardo FV, Sastre J, Ji LL, Vina J. Decreasing xanthine oxidase-mediated oxidative stress prevents useful cellular adaptations to exercise in rats. *J Physiol* 567: 113–120, 2005.

149. Gomez-Cabrera MC, Domenech E, Romagnoli M, Arduini A, Borras C, Pallardo FV, Sastre J, Vina J. Oral administration of vitamin C decreases muscle mitochondrial biogenesis and hampers training-induced adaptations in endurance performance. *Am J Clin Nutr* 87: 142–149, 2008.

150. Gomez-Cabrera MC, Domenech E, Vina J. Moderate exercise is an antioxidant: upregulation of antioxidant genes by training. *Free Radic Biol Med* 44: 126–131, 2008.

151. Gomez-Cabrera MC, Martinez A, Santangelo G, Pallardo FV, Sastre J, Vina J. Oxidative stress in marathon runners: interest of antioxidant supplementation. *Br J Nutr* 96, *Suppl* 1: S31–S33, 2006.

152. Gomez-Pinilla F, Ying Z, Opazo P, Roy RR, Edgerton VR. Differential regulation by exercise of BDNF and NT-3 in rat spinal cord and skeletal muscle. *Eur J Neurosci* 13: 1078–1084, 2001.

153. Gomez-Pinilla F, Ying Z, Roy RR, Molteni R, Edgerton VR. Voluntary exercise induces a BDNF-mediated mechanism that promotes neuroplasticity. *J Neurophysiol* 88: 2187–2195, 2002.

154. Gonzalez-Cadavid NF, Taylor WE, Yarasheski K, Sinha-Hikim I, Ma K, Ezzat S, Shen R, Lalani R, Asa S, Mamita M, Nair G, Arver S, Bhasin S. Organization of the human myostatin gene and expression in healthy men and HIV-infected men with muscle wasting. *Proc Natl Acad Sci USA* 95: 14938–14943, 1998.

155. Goodyear LJ. The exercise pill: too good to be true? *N Engl J Med* 359: 1842–1844, 2008.

156. Gore M, Fiebig R, Hollander J, Leeuwenburgh C, Ohno H, Ji LL. Endurance training alters antioxidant enzyme gene expression in rat skeletal muscle. *Can J Physiol Pharmacol* 76: 1139–1145, 1998.

157. Goussetis E, Spiropoulos A, Tsironi M, Skenderi K, Margeli A, Graphakos S, Baltopoulos P, Papassotiriou I. Spartathlon, a 246 kilometer foot race: effects of acute inflammation induced by prolonged exercise on circulating progenitor reparative cells. *Blood Cells Mol Dis* 42: 294–299, 2009.

158. Green DJ, Maiorana A, O'Driscoll G, Taylor R. Effect of exercise training on endothelium-derived nitric oxide function in humans. *J Physiol* 561: 1–25, 2004.

159. Green DJ, O'Driscoll G, Joyner MJ, Cable NT. Exercise and cardiovascular risk reduction: time to update the rationale for exercise? *J Appl Physiol* 105: 766–768, 2008.

160. Green DJ, Walsh JH, Maiorana A, Best MJ, Taylor RR, O'Driscoll JG. Exercise-induced improvement in endothelial dysfunction is not mediated by changes in CV risk factors: pooled analysis of diverse patient populations. *Am J Physiol Heart Circ Physiol* 285: H2679–H2687, 2003.

161. Gregorevic P, Williams DA, Lynch GS. Effects of leukemia inhibitory factor on rat skeletal muscles are modulated by clenbuterol. *Muscle Nerve* 25: 194–201, 2002.

162. Griesbeck O, Parsadanian AS, Sendtner M, Thoenen H. Expression of neurotrophins in skeletal muscle: quantitative comparison and significance for motoneuron survival and maintenance of function. *J Neurosci Res* 42: 21–33, 1995.

163. Guelfi KJ, Casey TM, Giles JJ, Fournier PA, Arthur PG. A proteomic analysis of the acute effects of high-intensity exercise on skeletal muscle proteins in fasted rats. *Clin Exp Pharmacol Physiol* 33: 952–957, 2006.

164. Guo T, Jou W, Chanturiya T, Portas J, Gavrilova O, McPherron AC. Myostatin inhibition in muscle, but not adipose tissue, decreases fat mass and improves insulin sensitivity. *PLos One* 4: e4937, 2009.

165. Hakim AA, Curb JD, Petrovitch H, Rodriguez BL, Yano K, Ross GW, White LR, Abbott RD. Effects of walking on coronary heart disease in elderly men: the Honolulu Heart Program. *Circulation* 100: 9–13, 1999.

166. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U, and Lancet Physical Activity Series Working G. Global physical activity levels: surveillance progress, pitfalls, and prospects. *Lancet* 380: 247–257, 2012.

167. Hambrecht R, Walther C, Mobius-Winkler S, Gielen S, Linke A, Conradi K, Erbs S, Kluge R, Kendziorra K, Sabri O, Sick P, Schuler G. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial. *Circulation* 109: 1371–1378, 2004.

168. Hamilton KL, Staib JL, Phillips T, Hess A, Lennon SL, Powers SK. Exercise, antioxidants, and HSP72: protection against myocardial ischemia/reperfusion. *Free Radic Biol Med* 34: 800–809, 2003.

169. Hammeren J, Powers S, Lawler J, Criswell D, Martin D, Lowenthal D, Pollock M. Exercise training-induced alterations in skeletal muscle oxidative and antioxidant enzyme activity in senescent rats. *Int J Sports Med* 13: 412–416, 1992.

170. Harber MP, Crane JD, Dickinson JM, Jemiolo B, Raue U, Trappe TA, Trappe SW. Protein synthesis and the expression of growth-related genes are altered by running in human vastus lateralis and soleus muscles. *Am J Physiol Regul Integr Comp Physiol* 296: R708–R714, 2009.

171. Hashemi MS, Ghaedi K, Salamian A, Karbalaie K, Emadi-Baygi M, Tanhaei S, Nasr-Esfahani MH, Baharvand H. Fndc5 knockdown significantly decreased neural differentiation rate of mouse embryonic stem cells. *Neuroscience* 231: 296–304, 2013.

172. Hashizume M, Hayakawa N, Suzuki M, Mihara M. IL-6/sIL-6R trans-signalling, but not TNF-alpha induced angiogenesis in a HUVEC and synovial cell co-culture system. *Rheumatol Int* 29: 1449–1454, 2009.

173. Haskell WL, Alderman EL, Fair JM, Maron DJ, Mackey SF, Superko HR, Williams PT, Johnstone IM, Champagne MA, Krauss RM. Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease. The Stanford Coronary Risk Intervention Project (SCRIP). *Circulation* 89: 975–990, 1994.

174. Haugen F, Norheim F, Lian H, Wensaas AJ, Dueland S, Berg O, Funderud A, Skalhegg BS, Raastad T, Drevon CA. IL-7 is expressed and secreted by human skeletal muscle cells. *Am J Physiol Cell Physiol* 298: C807–C816, 2010.

175. He C, Bassik MC, Moresi V, Sun K, Wei Y, Zou Z, An Z, Loh J, Fisher J, Sun Q, Korsmeyer S, Packer M, May HI, Hill JA, Virgin HW, Gilpin C, Xiao G, Bassel-Duby R, Scherer PE, Levine B. Exercise-induced BCL2-regulated autophagy is required for muscle glucose homeostasis. *Nature* 481: 511–515, 2012.

176. He C, Sumpter R Jr, Levine B. Exercise induces autophagy in peripheral tissues and in the brain. *Autophagy* 8: 1548–1551, 2012.

177. Hellsten Y, Apple FS, Sjodin B. Effect of sprint cycle training on activities of antioxidant enzymes in human skeletal muscle. *J Appl Physiol* 81: 1484–1487, 1996.

178. Henningsen J, Rigbolt KT, Blagoev B, Pedersen BK, Kratchmarova I. Dynamics of the skeletal muscle secretome during myoblast differentiation. *Mol Cell Proteomic* 9: 2482–2496, 2010.

179. Henson DA, Nieman DC, Nehlsen-Cannarella SL, Fagoaga OR, Shannon M, Bolton MR, Davis JM, Gaffney CT, Kelln WJ, Austin MD, Hjertman JM, Schilling BK. Influence of carbohydrate on cytokine and phagocytic responses to 2 h of rowing. *Med Sci Sports Exerc* 32: 1384–1389, 2000.

180. Higuchi M, Cartier LJ, Chen M, Holloszy JO. Superoxide dismutase and catalase in skeletal muscle: adaptive response to exercise. *J Gerontol* 40: 281–286, 1985.

181. Hirschi KK, Ingram DA, Yoder MC. Assessing identity, phenotype, and fate of endothelial progenitor cells. *Arterioscler Thromb Vasc Biol* 28: 1584–1595, 2008.

182. Hirst JA, Farmer AJ, Ali R, Roberts NW, Stevens RJ. Quantifying the effect of metformin treatment and dose on glycemic control. *Diabetes Care* 35: 446–454, 2012.

183. Hiscock N, Chan MH, Bisucci T, Darby IA, Febbraio MA. Skeletal myocytes are a source of interleukin-6 mRNA expression and protein release during contraction: evidence of fiber type specificity. *FASEB J* 18: 992–994, 2004.

184. Hittel DS, Axelson M, Sarna N, Shearer J, Huffman KM, Kraus WE. Myostatin decreases with aerobic exercise and associates with insulin resistance. *Med Sci Sports Exerc* 42: 2023–2029, 2010.

185. Hittel DS, Berggren JR, Shearer J, Boyle K, Houmard JA. Increased secretion and expression of myostatin in skeletal muscle from extremely obese women. *Diabetes* 58: 30–38, 2009.

186. Hoffman-Goetz L, Pervaiz N, Guan J. Voluntary exercise training in mice increases the expression of antioxidant enzymes and decreases the expression of TNF-alpha in intestinal lymphocytes. *Brain Behav Immun* 23: 498–506, 2009.

187. Hohnloser SH, Klingenheben T, Zabel M, Li YG. Heart rate variability used as an arrhythmia risk stratifier after myocardial infarction. *Pacing Clin Electrophysiol* 20: 2594–2601, 1997.

188. Hojman P, Pedersen M, Nielsen AR, Krogh-Madsen R, Yfanti C, Akerstrom T, Nielsen S, Pedersen BK. Fibroblast growth factor-21 is induced in human skeletal muscles by hyperinsulinemia. *Diabetes* 58: 2797–2801, 2009.

189. Hollander J, Fiebig R, Gore M, Bejma J, Ookawara T, Ohno H, Ji LL. Superoxide dismutase gene expression in skeletal muscle: fiber-specific adaptation to endurance training. *Am J Physiol Regul Integr Comp Physiol* 277: R856–R862, 1999.

190. Holloway KV, O'Gorman M, Woods P, Morton JP, Evans L, Cable NT, Goldspink DF, Burniston JG. Proteomic investigation of changes in human vastus lateralis muscle in response to interval-exercise training. *Proteomics* 9: 5155–5174, 2009.

191. Hopper I, Billah B, Skiba M, Krum H. Prevention of diabetes and reduction in major cardiovascular events in studies of subjects with prediabetes: meta-analysis of randomised controlled clinical trials. *Eur J Cardiovasc Prev Rehabil* 18: 813–823, 2011.

192. Horsley V, Jansen KM, Mills ST, Pavlath GK. IL-4 acts as a myoblast recruitment factor during mammalian muscle growth. *Cell* 113: 483–494, 2003.

193. Huang AM, Jen CJ, Chen HF, Yu L, Kuo YM, Chen HI. Compulsive exercise acutely upregulates rat hippocampal brain-derived neurotrophic factor. *J Neural Transm* 113: 803–811, 2006.

194. Huang CC, Lin WT, Hsu FL, Tsai PW, Hou CC. Metabolomics investigation of exercise-modulated changes in metabolism in rat liver after exhaustive and endurance exercises. *Eur J Appl Physiol* 108: 557–566, 2010.

195. Huh JY, Panagiotou G, Mougios V, Brinkoetter M, Vamvini MT, Schneider BE, Mantzoros CS. FNDC5 and irisin in humans: I. Predictors of circulating concentrations in serum and plasma and II. mRNA expression and circulating concentrations in response to weight loss and exercise. *Metabolism* 61: 1725–1738, 2012.

196. Huntsman HD, Zachwieja N, Zou K, Ripchik P, Valero MC, De Lisio M, Boppart MD. Mesenchymal stem cells contribute to vascular growth in skeletal muscle in response to eccentric exercise. *Am J Physiol Heart Circ Physiol* 304: H72–H81, 2013.

197. Iellamo F, Legramante JM, Massaro M, Raimondi G, Galante A. Effects of a residential exercise training on baroreflex sensitivity and heart rate variability in patients with coronary artery disease: A randomized, controlled study. *Circulation* 102: 2588–2592, 2000.

198. Inoue M, Senju S, Hirata S, Ikuta Y, Hayashida Y, Irie A, Harao M, Imai K, Tomita Y, Tsunoda T, Furukawa Y, Ito T, Nakamura Y, Baba H, Nishimura Y. Identification of SPARC as a candidate target antigen for immunotherapy of various cancers. *Int J Cancer* 127: 1393–1403, 2010.

199. Irrcher I, Ljubicic V, Hood DA. Interactions between ROS and AMP kinase activity in the regulation of PGC-1alpha transcription in skeletal muscle cells. *Am J Physiol Cell Physiol* 296: C116–C123, 2009.

200. Isaksen B, Fagerhol MK. Calprotectin inhibits matrix metalloproteinases by sequestration of zinc. *Mol Pathol* 54: 289–292, 2001.

201. Izumiya Y, Bina HA, Ouchi N, Akasaki Y, Kharitonenkov A, Walsh K. FGF21 is an Akt-regulated myokine. *FEBS Lett* 582: 3805–3810, 2008.

202. Jackson MJ. Free radicals generated by contracting muscle: by-products of metabolism or key regulators of muscle function? *Free Radic Biol Med* 44: 132–141, 2008.

203. Jackson MJ, Papa S, Bolanos J, Bruckdorfer R, Carlsen H, Elliott RM, Flier J, Griffiths HR, Heales S, Holst B, Lorusso M, Lund E, Oivind Moskaug J, Moser U, Di Paola M, Polidori MC, Signorile A, Stahl W, Vina-Ribes J, Astley SB. Antioxidants, reactive oxygen and nitrogen species, gene induction and mitochondrial function. *Mol Aspects Med* 23: 209–285, 2002.

204. Jacquemin V, Butler-Browne GS, Furling D, Mouly V. IL-13 mediates the recruitment of reserve cells for fusion during IGF-1-induced hypertrophy of human myotubes. *J Cell Sci* 120: 670–681, 2007.

205. Jamart C, Francaux M, Millet GY, Deldicque L, Frere D, Feasson L. Modulation of autophagy and ubiquitin-proteasome pathways during ultra-endurance running. *J Appl Physiol* 112: 1529–1537, 2012.

206. Jenkins NT, Witkowski S, Spangenburg EE, Hagberg JM. Effects of acute and chronic endurance exercise on intracellular nitric oxide in putative endothelial progenitor cells: role of NAPDH oxidase. *Am J Physiol Heart Circ Physiol* 297: H1798–H1805, 2009.

207. Jenkins RR, Friedland R, Howald H. The relationship of oxygen uptake to superoxide dismutase and catalase activity in human skeletal muscle. *Int J Sports Med* 5: 11–14, 1984.

208. Jensen MT, Suadicani P, Hein HO, Gyntelberg F. Elevated resting heart rate, physical fitness and all-cause mortality: a 16-year follow-up in the Copenhagen Male Study. *Heart* 99: 882–887, 2013.

209. Ji LL, Fu R, Mitchell EW. Glutathione and antioxidant enzymes in skeletal muscle: effects of fiber type and exercise intensity. *J Appl Physiol* 73: 1854–1859, 1992.

210. Ji LL, Gomez-Cabrera MC, Vina J. Exercise and hormesis: activation of cellular antioxidant signaling pathway. *Ann NY Acad Sci* 1067: 425–435, 2006.

211. Ji LL, Stratman FW, Lardy HA. Antioxidant enzyme systems in rat liver and skeletal muscle. Influences of selenium deficiency, chronic training, and acute exercise. *Arch Biochem Biophys* 263: 150–160, 1988.

212. Jonsdottir IH, Schjerling P, Ostrowski K, Asp S, Richter EA, Pedersen BK. Muscle contractions induce interleukin-6 mRNA production in rat skeletal muscles. *J Physiol* 528: 157–163, 2000.

213. Joyner MJ, Green DJ. Exercise protects the cardiovascular system: effects beyond traditional risk factors. *J Physiol* 587: 5551–5558, 2009.

214. Kahn BB, Alquier T, Carling D, Hardie DG. AMP-activated protein kinase: ancient energy gauge provides clues to modern understanding of metabolism. *Cell Metab* 1: 15–25, 2005.

215. Kalani R, Judge S, Carter C, Pahor M, Leeuwenburgh C. Effects of caloric restriction and exercise on age-related, chronic inflammation assessed by C-reactive protein and interleukin-6. *J Gerontol A Biol Sci Med Sci* 61: 211–217, 2006.

216. Kami K, Morikawa Y, Sekimoto M, Senba E. Gene expression of receptors for IL-6, LIF, and CNTF in regenerating skeletal muscles. *J Histochem Cytochem* 48: 1203–1213, 2000.

217. Kami K, Senba E. Localization of leukemia inhibitory factor and interleukin-6 messenger ribonucleic acids in regenerating rat skeletal muscle. *Muscle Nerve* 21: 819–822, 1998.

218. Kavazis AN, Talbert EE, Smuder AJ, Hudson MB, Nelson WB, Powers SK. Mechanical ventilation induces diaphragmatic mitochondrial dysfunction and increased oxidant production. *Free Radic Biol Med* 46: 842–850, 2009.

219. Keller C, Steensberg A, Hansen AK, Fischer CP, Plomgaard P, Pedersen BK. Effect of exercise, training, and glycogen availability on IL-6 receptor expression in human skeletal muscle. *J Appl Physiol* 99: 2075–2079, 2005.

220. Keller C, Steensberg A, Pilegaard H, Osada T, Saltin B, Pedersen BK, Neufer PD. Transcriptional activation of the IL-6 gene in human contracting skeletal muscle: influence of muscle glycogen content. *FASEB J* 15: 2748–2750, 2001.

221. Kelley GA, Kelley KS. Isometric handgrip exercise and resting blood pressure: a meta-analysis of randomized controlled trials. *J Hypertens* 28: 411–418, 2010.

222. Kelley GA, Kelley KS. Progressive resistance exercise and resting blood pressure: a meta-analysis of randomized controlled trials. *Hypertension* 35: 838–843, 2000.

223. Kelley GA, Kelley KS, Roberts S, Haskell W. Comparison of aerobic exercise, diet or both on lipids and lipoproteins in adults: a meta-analysis of randomized controlled trials. *Clin Nutr* 31: 156–167, 2012.

224. Kelly M, Keller C, Avilucea PR, Keller P, Luo Z, Xiang X, Giralt M, Hidalgo J, Saha AK, Pedersen BK, Ruderman NB. AMPK activity is diminished in tissues of IL-6 knockout mice: the effect of exercise. *Biochem Biophys Res Commun* 320: 449–454, 2004.

225. Khassaf M, Child RB, McArdle A, Brodie DA, Esanu C, Jackson MJ. Time course of responses of human skeletal muscle to oxidative stress induced by nondamaging exercise. *J Appl Physiol* 90: 1031–1035, 2001.

226. Khassaf M, McArdle A, Esanu C, Vasilaki A, McArdle F, Griffiths RD, Brodie DA, Jackson MJ. Effect of vitamin C supplements on antioxidant defence and stress proteins in human lymphocytes and skeletal muscle. *J Physiol* 549: 645–652, 2003.

227. Kiilavuori K, Toivonen L, Naveri H, Leinonen H. Reversal of autonomic derangements by physical training in chronic heart failure assessed by heart rate variability. *Eur Heart J* 16: 490–495, 1995.

228. Kim JS, Cross JM, Bamman MM. Impact of resistance loading on myostatin expression and cell cycle regulation in young and older men and women. *Am J Physiol Endocrinol Metab* 288: E1110–E1119, 2005.

229. Kim KS, Paik IY, Woo JH, Kang BY. The effect of training type on oxidative DNA damage and antioxidant capacity during three-dimensional space exercise. *Med Princ Pract* 19: 133–141, 2010.

230. Kim YA, Kim YS, Oh SL, Kim HJ, Song W. Autophagic response to exercise training in skeletal muscle with age. *J Physiol Biochem.* In press.

231. Knaepen K, Goekint M, Heyman EM, Meeusen R. Neuroplasticity: exercise-induced response of peripheral brain-derived neurotrophic factor: a systematic review of experimental studies in human subjects. *Sports Med* 40: 765–801, 2010.

232. Knez WL, Jenkins DG, Coombes JS. Oxidative stress in half and full Ironman triathletes. *Med Sci Sports Exerc* 39: 283–288, 2007.

233. Kobzik L, Reid MB, Bredt DS, Stamler JS. Nitric oxide in skeletal muscle. *Nature* 372: 546–548, 1994.

234. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, Sugawara A, Totsuka K, Shimano H, Ohashi Y, Yamada N, Sone H. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA* 301: 2024–2035, 2009.

235. Koltai E, Szabo Z, Atalay M, Boldogh I, Naito H, Goto S, Nyakas C, Radak Z. Exercise alters SIRT1, SIRT6, NAD and NAMPT levels in skeletal muscle of aged rats. *Mech Ageing Dev* 131: 21–28, 2010.

236. Konopka AR, Douglass MD, Kaminsky LA, Jemiolo B, Trappe TA, Trappe S, Harber MP. Molecular adaptations to aerobic exercise training in skeletal muscle of older women. *J Gerontol A Biol Sci Med Sci* 65: 1201–1207, 2010.

237. Kopple JD, Cohen AH, Wang H, Qing D, Tang Z, Fournier M, Lewis M, Casaburi R, Storer T. Effect of exercise on mRNA levels for growth factors in skeletal muscle of hemodialysis patients. *J Ren Nutr* 16: 312–324, 2006.

238. Kostaropoulos IA, Nikolaidis MG, Jamurtas AZ, Ikonomou GV, Makrygiannis V, Papadopoulos G, Kouretas D. Comparison of the blood redox status between long-distance and short-distance runners. *Physiol Res* 55: 611–616, 2006.

239. Koury JC, de Olilveria AV Jr, Portella ES, de Olilveria CF, Lopes GC, Donangelo CM. Zinc and copper biochemical indices of antioxidant status in elite athletes of different modalities. *Int J Sport Nutr Exerc Metab* 14: 358–372, 2004.

240. Kramer HF, Goodyear LJ. Exercise, MAPK, and NF-kappaB signaling in skeletal muscle. *J Appl Physiol* 103: 388–395, 2007.

241. Krivickas LS, Walsh R, Amato AA. Single muscle fiber contractile properties in adults with muscular dystrophy treated with MYO-029. *Muscle Nerve* 39: 3–9, 2009.

242. Kronenberg G, Bick-Sander A, Bunk E, Wolf C, Ehninger D, Kempermann G. Physical exercise prevents age-related decline in precursor cell activity in the mouse dentate gyrus. *Neurobiol Aging* 27: 1505–1513, 2006.

243. Kurek J, Bower J, Romanella M, Austin L. Leukaemia inhibitory factor treatment stimulates muscle regeneration in the mdx mouse. *Neurosci Lett* 212: 167–170, 1996.

244. La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet* 351: 478–484, 1998.

245. La Rovere MT, Mortara A, Sandrone G, Lombardi F. Autonomic nervous system adaptations to short-term exercise training. *Chest* 101: 299–303, 1992.

246. La Rovere MT, Specchia G, Mortara A, Schwartz PJ. Baroreflex sensitivity, clinical correlates, and cardiovascular mortality among patients with a first myocardial infarction. A prospective study. *Circulation* 78: 816–824, 1988.

247. Lafreniere JF, Mills P, Bouchentouf M, Tremblay JP. Interleukin-4 improves the migration of human myogenic precursor cells in vitro and in vivo. *Exp Cell Res* 312: 1127–1141, 2006.

248. Lancaster GI, Jentjens RL, Moseley L, Jeukendrup AE, Gleeson M. Effect of pre-exercise carbohydrate ingestion on plasma cytokine, stress hormone, and neutrophil degranulation responses to continuous, high-intensity exercise. *Int J Sport Nutr Exerc Metab* 13: 436–453, 2003.

249. Langley B, Thomas M, Bishop A, Sharma M, Gilmour S, Kambadur R. Myostatin inhibits myoblast differentiation by down-regulating MyoD expression. *J Biol Chem* 277: 49831–49840, 2002.

250. Laufs U, Werner N, Link A, Endres M, Wassmann S, Jurgens K, Miche E, Bohm M, Nickenig G. Physical training increases endothelial progenitor cells, inhibits neointima formation, and enhances angiogenesis. *Circulation* 109: 220–226, 2004.

251. Laughlin MH, Simpson T, Sexton WL, Brown OR, Smith JK, Korthuis RJ. Skeletal muscle oxidative capacity, antioxidant enzymes, and exercise training. *J Appl Physiol* 68: 2337–2343, 1990.

252. Laukkanen JA, Kurl S, Salonen R, Rauramaa R, Salonen JT. The predictive value of cardiorespiratory fitness for cardiovascular events in men with various risk profiles: a prospective population-based cohort study. *Eur Heart J* 25: 1428–1437, 2004.

253. Lecker SH, Zavin A, Cao P, Arena R, Allsup K, Daniels KM, Joseph J, Schulze PC, Forman DE. Expression of the irisin precursor FNDC5 in skeletal muscle correlates with aerobic exercise performance in patients with heart failure. *Circ Heart Fail* 5: 812–818, 2012.

254. Lee DC, Sui X, Ortega FB, Kim YS, Church TS, Winett RA, Ekelund U, Katzmarzyk PT, Blair SN. Comparisons of leisure-time physical activity and cardiorespiratory fitness as predictors of all-cause mortality in men and women. *Br J Sports Med* 45: 504–510, 2011.

255. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Lancet Physical Activity Series Working G. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet* 380: 219–229, 2012.

256. Lee SJ, McPherron AC. Regulation of myostatin activity and muscle growth. *Proc Natl Acad Sci USA* 98: 9306–9311, 2001.

257. Lee Y, Kim JH, Hong Y, Lee SR, Chang KT, Hong Y. Prophylactic effects of swimming exercise on autophagy-induced muscle atrophy in diabetic rats. *Lab Anim Res* 28: 171–179, 2012.

258. Leelarungrayub D, Saidee K, Pothongsunun P, Pratanaphon S, YanKai A, Bloomer RJ. Six weeks of aerobic dance exercise improves blood oxidative stress status and increases interleukin-2 in previously sedentary women. *J Bodyw Mov Ther* 15: 355–362, 2011.

259. Leeuwenburgh C, Fiebig R, Chandwaney R, Ji LL. Aging and exercise training in skeletal muscle: responses of glutathione and antioxidant enzyme systems. *Am J Physiol Regul Integr Comp Physiol* 267: R439–R445, 1994.

260. Leeuwenburgh C, Hollander J, Leichtweis S, Griffiths M, Gore M, Ji LL. Adaptations of glutathione antioxidant system to endurance training are tissue and muscle fiber specific. *Am J Physiol Regul Integr Comp Physiol* 272: R363–R369, 1997.

261. Lehoux S. Redox signalling in vascular responses to shear and stretch. *Cardiovasc Res* 71: 269–279, 2006.

262. Leitch JW, Newling RP, Basta M, Inder K, Dear K, Fletcher PJ. Randomized trial of a hospital-based exercise training program after acute myocardial infarction: cardiac autonomic effects. *J Am Coll Cardiol* 29: 1263–1268, 1997.

263. Levinger I, Goodman C, Matthews V, Hare DL, Jerums G, Garnham A, Selig S. BDNF, metabolic risk factors, and resistance training in middle-aged individuals. *Med Sci Sports Exerc* 40: 535–541, 2008.

264. Lew H, Quintanilha A. Effects of endurance training and exercise on tissue antioxidative capacity and acetaminophen detoxification. *Eur J Drug Metab Pharmacokinet* 16: 59–68, 1991.

265. Li TL, Gleeson M. The effect of single and repeated bouts of prolonged cycling on leukocyte redistribution, neutrophil degranulation, IL-6, and plasma stress hormone responses. *Int J Sport Nutr Exerc Metab* 14: 501–516, 2004.

266. Li TL, Gleeson M. The effects of carbohydrate supplementation during the second of two prolonged cycling bouts on immunoendocrine responses. *Eur J Appl Physiol* 95: 391–399, 2005.

267. Li TL, Wu CL, Gleeson M, Williams C. The effects of pre-exercise high carbohydrate meals with different glycemic indices on blood leukocyte redistribution, IL-6, and hormonal responses during a subsequent prolonged exercise. *Int J Sport Nutr Exerc Metab* 14: 647–656, 2004.

268. Li Y, Zhang Y, Dorweiler B, Cui D, Wang T, Woo CW, Brunkan CS, Wolberger C, Imai S, Tabas I. Extracellular Nampt promotes macrophage survival via a nonenzymatic interleukin-6/STAT3 signaling mechanism. *J Biol Chem* 283: 34833–34843, 2008.

269. Liao D, Carnethon M, Evans GW, Cascio WE, Heiss G. Lower heart rate variability is associated with the development of coronary heart disease in individuals with diabetes: the atherosclerosis risk in communities (ARIC) study. *Diabetes* 51: 3524–3531, 2002.

270. Lind L, Lithell H. Decreased peripheral blood flow in the pathogenesis of the metabolic syndrome comprising hypertension, hyperlipidemia, and hyperinsulinemia. *Am Heart J* 125: 1494–1497, 1993.

271. Lipina C, Kendall H, McPherron AC, Taylor PM, Hundal HS. Mechanisms involved in the enhancement of mammalian target of rapamycin signalling and hypertrophy in skeletal muscle of myostatin-deficient mice. *FEBS Lett* 584: 2403–2408, 2010.

272. Liu CM, Yang Z, Liu CW, Wang R, Tien P, Dale R, Sun LQ. Myostatin antisense RNA-mediated muscle growth in normal and cancer cachexia mice. *Gene Ther* 15: 155–160, 2008.

273. Liu Y, Gampert L, Nething K, Steinacker JM. Response and function of skeletal muscle heat shock protein 70. *Front Biosci* 11: 2802–2827, 2006.

274. Liu Y, Huo X, Pang XF, Zong ZH, Meng X, Liu GL. Musclin inhibits insulin activation of Akt/protein kinase B in rat skeletal muscle. *J Int Med Res* 36: 496–504, 2008.

275. Liu YF, Chen HI, Wu CL, Kuo YM, Yu L, Huang AM, Wu FS, Chuang JI, Jen CJ. Differential effects of treadmill running and wheel running on spatial or aversive learning and memory: roles of amygdalar brain-derived neurotrophic factor and synaptotagmin I. *J Physiol* 587: 3221–3231, 2009.

276. Lockard MM, Witkowski S, Jenkins NT, Spangenburg EE, Obisesan TO, Hagberg JM. Thrombin and exercise similarly influence expression of cell cycle genes in cultured putative endothelial progenitor cells. *J Appl Physiol* 108: 1682–1690, 2010.

277. Loimaala A, Huikuri HV, Koobi T, Rinne M, Nenonen A, Vuori I. Exercise training improves baroreflex sensitivity in type 2 diabetes. *Diabetes* 52: 1837–1842, 2003.

278. Louis E, Raue U, Yang Y, Jemiolo B, Trappe S. Time course of proteolytic, cytokine, and myostatin gene expression after acute exercise in human skeletal muscle. *J Appl Physiol* 103: 1744–1751, 2007.

279. Lovasi GS, Lemaitre RN, Siscovick DS, Dublin S, Bis JC, Lumley T, Heckbert SR, Smith NL, Psaty BM. Amount of leisure-time physical activity and risk of nonfatal myocardial infarction. *Ann Epidemiol* 17: 410–416, 2007.

280. Lucia A, De La Rosa A, Silvan MA, Lopez-Mojares LM, Boraita A, Perez M, Foster C, Garcia-Castro J, Ramirez M. Mobilisation of mesenchymal cells in cardiac patients: is intense exercise necessary? *Br J Sports Med* 43: 221–223, 2009.

281. Lucini D, Milani RV, Costantino G, Lavie CJ, Porta A, Pagani M. Effects of cardiac rehabilitation and exercise training on autonomic regulation in patients with coronary artery disease. *Am Heart J* 143: 977–983, 2002.

282. Luk TH, Dai YL, Siu CW, Yiu KH, Chan HT, Fong DY, Lee SW, Li SW, Tam S, Lau CP, Tse HF. Habitual physical activity is associated with endothelial function and endothelial progenitor cells in patients with stable coronary artery disease. *Eur J Cardiovasc Prev Rehabil* 16: 464–471, 2009.

283. Luo L, Lu AM, Wang Y, Hong A, Chen Y, Hu J, Li X, Qin ZH. Chronic resistance training activates autophagy and reduces apoptosis of muscle cells by modulating IGF-1 and its receptors, Akt/mTOR and Akt/FOXO3a signaling in aged rats. *Exp Gerontol* 48: 427–436, 2013.

284. Macaluso F, Myburgh KH. Current evidence that exercise can increase the number of adult stem cells. *J Muscle Res Cell Motil* 33: 187–198, 2012.

285. MacIntyre DL, Sorichter S, Mair J, Berg A, McKenzie DC. Markers of inflammation and myofibrillar proteins following eccentric exercise in humans. *Eur J Appl Physiol* 84: 180–186, 2001.

286. Mahoney DJ, Parise G, Melov S, Safdar A, Tarnopolsky MA. Analysis of global mRNA expression in human skeletal muscle during recovery from endurance exercise. *FASEB J* 19: 1498–1500, 2005.

287. Mai K, Schwarz F, Bobbert T, Andres J, Assmann A, Pfeiffer AF, Spranger J. Relation between fibroblast growth factor-21, adiposity, metabolism, and weight reduction. *Metabolism* 60: 306–311, 2011.

288. Malfatto G, Branzi G, Riva B, Sala L, Leonetti G, Facchini M. Recovery of cardiac autonomic responsiveness with low-intensity physical training in patients with chronic heart failure. *Eur J Heart Fail* 4: 159–166, 2002.

289. Malfatto G, Facchini M, Bragato R, Branzi G, Sala L, Leonetti G. Short and long term effects of exercise training on the tonic autonomic modulation of heart rate variability after myocardial infarction. *Eur Heart J* 17: 532–538, 1996.

290. Manzi V, Castagna C, Padua E, Lombardo M, D'Ottavio S, Massaro M, Volterrani M, Iellamo F. Dose-response relationship of autonomic nervous system responses to individualized training impulse in marathon runners. *Am J Physiol Heart Circ Physiol* 296: H1733–H1740, 2009.

291. Martinovic J, Dopsaj V, Dopsaj MJ, Kotur-Stevuljevic J, Vujovic A, Stefanovic A, Nesic G. Long-term effects of oxidative stress in volleyball players. *Int J Sports Med* 30: 851–856, 2009.

292. Matsakas A, Friedel A, Hertrampf T, Diel P. Short-term endurance training results in a muscle-specific decrease of myostatin mRNA content in the rat. *Acta Physiol Scand* 183: 299–307, 2005.

293. Matthews VB, Astrom MB, Chan MH, Bruce CR, Krabbe KS, Prelovsek O, Akerstrom T, Yfanti C, Broholm C, Mortensen OH, Penkowa M, Hojman P, Zankari A, Watt MJ, Bruunsgaard H, Pedersen BK, Febbraio MA. Brain-derived neurotrophic factor is produced by skeletal muscle cells in response to contraction and enhances fat oxidation via activation of AMP-activated protein kinase. *Diabetologia* 52: 1409–1418, 2009.

294. Matthys P, Mitera T, Heremans H, Van Damme J, Billiau A. Anti-gamma interferon and anti-interleukin-6 antibodies affect staphylococcal enterotoxin B-induced weight loss, hypoglycemia, and cytokine release in D-galactosamine-sensitized and unsensitized mice. *Infect Immun* 63: 1158–1164, 1995.

295. Mazzuero G, Lanfranchi P, Colombo R, Giannuzzi P, Giordano A. Long-term adaptation of 24-h heart rate variability after myocardial infarction. The EAMI Study Group Exercise Training in Anterior Myocardial Infarction. *Chest* 101: 304–308, 1992.

296. McArdle A, Pattwell D, Vasilaki A, Griffiths RD, Jackson MJ. Contractile activity-induced oxidative stress: cellular origin and adaptive responses. *Am J Physiol Cell Physiol* 280: C621–C627, 2001.

297. McArdle A, van der Meulen J, Close GL, Pattwell D, Van Remmen H, Huang TT, Richardson AG, Epstein CJ, Faulkner JA, Jackson MJ. Role of mitochondrial superoxide dismutase in contraction-induced generation of reactive oxygen species in skeletal muscle extracellular space. *Am J Physiol Cell Physiol* 286: C1152–C1158, 2004.

298. McArdle A, Vasilaki A, Jackson M. Exercise and skeletal muscle ageing: cellular and molecular mechanisms. *Ageing Res Rev* 1: 79–93, 2002.

299. McArdle F, Spiers S, Aldemir H, Vasilaki A, Beaver A, Iwanejko L, McArdle A, Jackson MJ. Preconditioning of skeletal muscle against contraction-induced damage: the role of adaptations to oxidants in mice. *J Physiol* 561: 233–244, 2004.

300. McConell GK, Rattigan S, Lee-Young RS, Wadley GD, Merry TL. Skeletal muscle nitric oxide signaling and exercise: a focus on glucose metabolism. *Am J Physiol Endocrinol Metab* 303: E301–E307, 2012.

301. McFarlane C, Plummer E, Thomas M, Hennebry A, Ashby M, Ling N, Smith H, Sharma M, Kambadur R. Myostatin induces cachexia by activating the ubiquitin proteolytic system through an NF-kappaB-independent, FoxO1-dependent mechanism. *J Cell Physiol* 209: 501–514, 2006.

302. McPherron AC, Lawler AM, Lee SJ. Regulation of skeletal muscle mass in mice by a new TGF-beta superfamily member. *Nature* 387: 83–90, 1997.

303. McPherron AC, Lee SJ. Suppression of body fat accumulation in myostatin-deficient mice. *J Clin Invest* 109: 595–601, 2002.

304. Meirelles Lda S, Fontes AM, Covas DT, Caplan AI. Mechanisms involved in the therapeutic properties of mesenchymal stem cells. *Cytokine Growth Factor Rev* 20: 419–427, 2009.

305. Meissner M, Nijstad N, Kuipers F, Tietge UJ. Voluntary exercise increases cholesterol efflux but not macrophage reverse cholesterol transport in vivo in mice. *Nutr Metab (Lond)* 7: 54, 2010.

306. Melikoglu MA, Kaldirimci M, Katkat D, Sen I, Kaplan I, Senel K. The effect of regular long term training on antioxidant enzymatic activities. *J Sports Med Phys Fitness* 48: 388–390, 2008.

307. Mendis S, Lindholm LH, Anderson SG, Alwan A, Koju R, Onwubere BJ, Kayani AM, Abeysinghe N, Duneas A, Tabagari S, Fan W, Sarraf-Zadegan N, Nordet P, Whitworth J, Heagerty A. Total cardiovascular risk approach to improve efficiency of cardiovascular prevention in resource constrain settings. *J Clin Epidemiol* 64: 1451–1462, 2011.

308. Menegazzo L, Albiero M, Avogaro A, Fadini GP. Endothelial progenitor cells in diabetes mellitus. *Biofactors* 38: 194–202, 2012.

309. Mercken EM, Hageman GJ, Langen RC, Wouters EF, Schols AM. Decreased exercise-induced expression of nuclear factor-kappaB-regulated genes in muscle of patients with COPD. *Chest* 139: 337–346, 2011.

310. Meyer M, Pahl HL, Baeuerle PA. Regulation of the transcription factors NF-kappa B and AP-1 by redox changes. *Chem Biol Interact* 91: 91–100, 1994.

311. Miyazaki H, Oh-ishi S, Ookawara T, Kizaki T, Toshinai K, Ha S, Haga S, Ji LL, Ohno H. Strenuous endurance training in humans reduces oxidative stress following exhausting exercise. *Eur J Appl Physiol* 84: 1–6, 2001.

312. Mizuhara H, O'Neill E, Seki N, Ogawa T, Kusunoki C, Otsuka K, Satoh S, Niwa M, Senoh H, Fujiwara H. T cell activation-associated hepatic injury: mediation by tumor necrosis factors and protection by interleukin 6. *J Exp Med* 179: 1529–1537, 1994.

313. Mobius-Winkler S, Hilberg T, Menzel K, Golla E, Burman A, Schuler G, Adams V. Time-dependent mobilization of circulating progenitor cells during strenuous exercise in healthy individuals. *J Appl Physiol* 107: 1943–1950, 2009.

314. Moebius-Winkler S, Schuler G, Adams V. Endothelial progenitor cells and exercise-induced redox regulation. *Antioxid Redox Signal* 15: 997–1011, 2011.

315. Molteni R, Wu A, Vaynman S, Ying Z, Barnard RJ, Gomez-Pinilla F. Exercise reverses the harmful effects of consumption of a high-fat diet on synaptic and behavioral plasticity associated to the action of brain-derived neurotrophic factor. *Neuroscience* 123: 429–440, 2004.

316. Monahan KD, Dinenno FA, Tanaka H, Clevenger CM, DeSouza CA, Seals DR. Regular aerobic exercise modulates age-associated declines in cardiovagal baroreflex sensitivity in healthy men. *J Physiol* 529: 263–271, 2000.

317. Moore SC, Patel AV, Matthews CE, Berrington de Gonzalez A, Park Y, Katki HA, Linet MS, Weiderpass E, Visvanathan K, Helzlsouer KJ, Thun M, Gapstur SM, Hartge P, Lee IM. Leisure time physical activity of moderate to vigorous intensity and mortality: a large pooled cohort analysis. *PLos Med* 9: e1001335, 2012.

318. Mooren FC, Lechtermann A, Fobker M, Brandt B, Sorg C, Volker K, Nacken W. The response of the novel pro-inflammatory molecules S100A8/A9 to exercise. *Int J Sports Med* 27: 751–758, 2006.

319. Mora S, Cook N, Buring JE, Ridker PM, Lee IM. Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms. *Circulation* 116: 2110–2118, 2007.

320. Moran M, Moreno-Lastres D, Marin-Buera L, Arenas J, Martin MA, Ugalde C. Mitochondrial respiratory chain dysfunction: implications in neurodegeneration. *Free Radic Biol Med* 53: 595–609, 2012.

321. Moreno PR, Sanz J, Fuster V. Promoting mechanisms of vascular health: circulating progenitor cells, angiogenesis, and reverse cholesterol transport. *J Am Coll Cardiol* 53: 2315–2323, 2009.

322. Morici G, Zangla D, Santoro A, Pelosi E, Petrucci E, Gioia M, Bonanno A, Profita M, Bellia V, Testa U, Bonsignore MR. Supramaximal exercise mobilizes hematopoietic progenitors and reticulocytes in athletes. *Am J Physiol Regul Integr Comp Physiol* 289: R1496–R1503, 2005.

323. Morrison BM, Lachey JL, Warsing LC, Ting BL, Pullen AE, Underwood KW, Kumar R, Sako D, Grinberg A, Wong V, Colantuoni E, Seehra JS, Wagner KR. A soluble activin type IIB receptor improves function in a mouse model of amyotrophic lateral sclerosis. *Exp Neurol* 217: 258–268, 2009.

324. Mortensen OH, Andersen K, Fischer C, Nielsen AR, Nielsen S, Akerstrom T, Aastrom MB, Borup R, Pedersen BK. Calprotectin is released from human skeletal muscle tissue during exercise. *J Physiol* 586: 3551–3562, 2008.

325. Motohashi N, Uezumi A, Yada E, Fukada S, Fukushima K, Imaizumi K, Miyagoe-Suzuki Y, Takeda S. Muscle CD31$^-$ CD45$^-$ side population cells promote muscle regeneration by stimulating proliferation and migration of myoblasts. *Am J Pathol* 173: 781–791, 2008.

326. Mousavi K, Jasmin BJ. BDNF is expressed in skeletal muscle satellite cells and inhibits myogenic differentiation. *J Neurosci* 26: 5739–5749, 2006.

327. Mousavi K, Parry DJ, Jasmin BJ. BDNF rescues myosin heavy chain IIB muscle fibers after neonatal nerve injury. *Am J Physiol Cell Physiol* 287: C22–C29, 2004.

328. Murphy KT, Ryall JG, Snell SM, Nair L, Koopman R, Krasney PA, Ibebunjo C, Holden KS, Loria PM, Salatto CT, Lynch GS. Antibody-directed myostatin inhibition improves diaphragm pathology in young but not adult dystrophic mdx mice. *Am J Pathol* 176: 2425–2434, 2010.

329. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 346: 793–801, 2002.

330. Myint PK, Luben RN, Wareham NJ, Welch AA, Bingham SA, Day NE, Khaw KT. Combined work and leisure physical activity and risk of stroke in men and women in the European prospective investigation into Cancer-Norfolk Prospective Population Study. *Neuroepidemiology* 27: 122–129, 2006.

331. Narkar VA, Downes M, Yu RT, Embler E, Wang YX, Banayo E, Mihaylova MM, Nelson MC, Zou Y, Juguilon H, Kang H, Shaw RJ, Evans RM. AMPK and PPARdelta agonists are exercise mimetics. *Cell* 134: 405–415, 2008.

332. Navarro A, Gomez C, Lopez-Cepero JM, Boveris A. Beneficial effects of moderate exercise on mice aging: survival, behavior, oxidative stress, and mitochondrial electron transfer. *Am J Physiol Regul Integr Comp Physiol* 286: R505–R511, 2004.

333. Neeper SA, Gomez-Pinilla F, Choi J, Cotman C. Exercise and brain neurotrophins. *Nature* 373: 109, 1995.

334. Neeper SA, Gomez-Pinilla F, Choi J, Cotman CW. Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain. *Brain Res* 726: 49–56, 1996.

335. Nguyen C, Cheng-Lai A. The polypill: a potential global solution to cardiovascular disease. *Cardiol Rev* 21: 49–54, 2013.

336. Niebauer J, Hambrecht R, Velich T, Hauer K, Marburger C, Kalberer B, Weiss C, von Hodenberg E, Schlierf G, Schuler G, Zimmermann R, Kubler W. Attenuated progression of coronary artery disease after 6 years of multifactorial risk intervention: role of physical exercise. *Circulation* 96: 2534–2541, 1997.

337. Nielsen AR, Hojman P, Erikstrup C, Fischer CP, Plomgaard P, Mounier R, Mortensen OH, Broholm C, Taudorf S, Krogh-Madsen R, Lindegaard B, Petersen AM, Gehl J, Pedersen BK. Association between interleukin-15 and obesity: interleukin-15 as a potential regulator of fat mass. *J Clin Endocrinol Metab* 93: 4486–4493, 2008.

338. Nielsen AR, Mounier R, Plomgaard P, Mortensen OH, Penkowa M, Speerschneider T, Pilegaard H, Pedersen BK. Expression of interleukin-15 in human skeletal muscle effect of exercise and muscle fibre type composition. *J Physiol* 584: 305–312, 2007.

339. Nieman DC, Davis JM, Brown VA, Henson DA, Dumke CL, Utter AC, Vinci DM, Downs MF, Smith JC, Carson J, Brown A, McAnulty SR, McAnulty LS. Influence of carbohydrate ingestion on immune changes after 2 h of intensive resistance training. *J Appl Physiol* 96: 1292–1298, 2004.

340. Nieman DC, Davis JM, Henson DA, Gross SJ, Dumke CL, Utter AC, Vinci DM, Carson JA, Brown A, McAnulty SR, McAnulty LS, Triplett NT. Muscle cytokine mRNA changes after 2.5 h of cycling: influence of carbohydrate. *Med Sci Sports Exerc* 37: 1283–1290, 2005.

341. Nieman DC, Davis JM, Henson DA, Walberg-Rankin J, Shute M, Dumke CL, Utter AC, Vinci DM, Carson JA, Brown A, Lee WJ, McAnulty SR, McAnulty LS. Carbohydrate ingestion influences skeletal muscle cytokine mRNA and plasma cytokine levels after a 3-h run. *J Appl Physiol* 94: 1917–1925, 2003.

342. Niess AM, Hartmann A, Grunert-Fuchs M, Poch B, Speit G. DNA damage after exhaustive treadmill running in trained and untrained men. *Int J Sports Med* 17: 397–403, 1996.

343. Nishizawa H, Matsuda M, Yamada Y, Kawai K, Suzuki E, Makishima M, Kitamura T, Shimomura I. Musclin, a novel skeletal muscle-derived secretory factor. *J Biol Chem* 279: 19391–19395, 2004.

344. Nolan RP, Jong P, Barry-Bianchi SM, Tanaka TH, Floras JS. Effects of drug, biobehavioral and exercise therapies on heart rate variability in coronary artery disease: a systematic review. *Eur J Cardiovasc Prev Rehabil* 15: 386–396, 2008.

345. Norheim F, Raastad T, Thiede B, Rustan AC, Drevon CA, Haugen F. Proteomic identification of secreted proteins from human skeletal muscle cells and expression in response to strength training. *Am J Physiol Endocrinol Metab* 301: E1013–E1021, 2011.

346. O'Keefe JH, Vogel R, Lavie CJ, Cordain L. Achieving hunter-gatherer fitness in the 21(st) century: back to the future. *Am J Med* 123: 1082–1086, 2010.

347. O'Keefe JH, Vogel R, Lavie CJ, Cordain L. Exercise like a hunter-gatherer: a prescription for organic physical fitness. *Prog Cardiovasc Dis* 53: 471–479, 2011.

348. O'Neill CA, Stebbins CL, Bonigut S, Halliwell B, Longhurst JC. Production of hydroxyl radicals in contracting skeletal muscle of cats. *J Appl Physiol* 81: 1197–1206, 1996.

349. Oh-ishi S, Kizaki T, Ookawara T, Sakurai T, Izawa T, Nagata N, Ohno H. Endurance training improves the resistance of rat diaphragm to exercise-induced oxidative stress. *Am J Respir Crit Care Med* 156: 1579–1585, 1997.

350. Ohno H, Yahata T, Sato Y, Yamamura K, Taniguchi N. Physical training and fasting erythrocyte activities of free radical scavenging enzyme systems in sedentary men. *Eur J Appl Physiol Occup Physiol* 57: 173–176, 1988.

351. Olchawa B, Kingwell BA, Hoang A, Schneider L, Miyazaki O, Nestel P, Sviridov D. Physical fitness and reverse cholesterol transport. *Arterioscler Thromb Vasc Biol* 24: 1087–1091, 2004.

352. Oliff HS, Berchtold NC, Isackson P, Cotman CW. Exercise-induced regulation of brain-derived neurotrophic factor (BDNF) transcripts in the rat hippocampus. *Brain Res Mol Brain Res* 61: 147–153, 1998.

353. Ordway GA, Charles JB, Randall DC, Billman GE, Wekstein DR. Heart rate adaptation to exercise training in cardiac-denervated dogs. *J Appl Physiol* 52: 1586–1590, 1982.

354. Ortega FB, Lee DC, Katzmarzyk PT, Ruiz JR, Sui X, Church TS, Blair SN. The intriguing metabolically healthy but obese phenotype: cardiovascular prognosis and role of fitness. *Eur Heart J* 34: 389–397, 2013.

355. Ostrowski K, Rohde T, Zacho M, Asp S, Pedersen BK. Evidence that interleukin-6 is produced in human skeletal muscle during prolonged running. *J Physiol* 508: 949–953, 1998.

356. Ostrowski K, Schjerling P, Pedersen BK. Physical activity and plasma interleukin-6 in humans: effect of intensity of exercise. *Eur J Appl Physiol* 83: 512–515, 2000.

357. Ouchi N, Oshima Y, Ohashi K, Higuchi A, Ikegami C, Izumiya Y, Walsh K. Follistatin-like 1, a secreted muscle protein, promotes endothelial cell function and revascularization in ischemic tissue through a nitric-oxide synthase-dependent mechanism. *J Biol Chem* 283: 32802–32811, 2008.

358. Owen A, Wiles J, Swaine I. Effect of isometric exercise on resting blood pressure: a meta analysis. *J Hum Hypertens* 24: 796–800, 2010.

359. Oya M, Itoh H, Kato K, Tanabe K, Murayama M. Effects of exercise training on the recovery of the autonomic nervous system and exercise capacity after acute myocardial infarction. *Jpn Circ J* 63: 843–848, 1999.

360. Palsgaard J, Brons C, Friedrichsen M, Dominguez H, Jensen M, Storgaard H, Spohr C, Torp-Pedersen C, Borup R, De Meyts P, Vaag A. Gene expression in skeletal muscle biopsies from people with type 2 diabetes and relatives: differential regulation of insulin signaling pathways. *PLos One* 4: e6575, 2009.

361. Pantano C, Reynaert NL, van der Vliet A, Janssen-Heininger YM. Redox-sensitive kinases of the nuclear factor-kappaB signaling pathway. *Antioxid Redox Signal* 8: 1791–1806, 2006.

362. Park H, Park C, Kim Y, Rascati KL. Efficacy and safety of dipeptidyl peptidase-4 inhibitors in type 2 diabetes: meta-analysis. *Ann Pharmacother* 46: 1453–1469, 2012.

363. Pattwell DM, McArdle A, Morgan JE, Patridge TA, Jackson MJ. Release of reactive oxygen and nitrogen species from contracting skeletal muscle cells. *Free Radic Biol Med* 37: 1064–1072, 2004.

364. Pattyn N, Cornelissen VA, Eshghi SR, Vanhees L. The effect of exercise on the cardiovascular risk factors constituting the metabolic syndrome: a meta-analysis of controlled trials. *Sports Med* 43: 121–133, 2013.

365. Peake J, Peiffer JJ, Abbiss CR, Nosaka K, Okutsu M, Laursen PB, Suzuki K. Body temperature and its effect on leukocyte mobilization, cytokines and markers of neutrophil activation during and after exercise. *Eur J Appl Physiol* 102: 391–401, 2008.

366. Pedersen BK. Muscular interleukin-6 and its role as an energy sensor. *Med Sci Sports Exerc* 44: 392–396, 2012.

367. Pedersen BK, Akerstrom TC, Nielsen AR, Fischer CP. Role of myokines in exercise and metabolism. *J Appl Physiol* 103: 1093–1098, 2007.

368. Pedersen BK, Febbraio MA. Muscle as an endocrine organ: focus on muscle-derived interleukin-6. *Physiol Rev* 88: 1379–1406, 2008.

369. Penkowa M, Keller C, Keller P, Jauffred S, Pedersen BK. Immunohistochemical detection of interleukin-6 in human skeletal muscle fibers following exercise. *FASEB J* 17: 2166–2168, 2003.

370. Perhonen MA, Haapalahti P, Kivisto S, Hekkala AM, Vaananen H, Swan H, Toivonen L. Effect of physical training on ventricular repolarization in type 1 long QT syndrome: a pilot study in asymptomatic carriers of the G589D KCNQ1 mutation. *Europace* 8: 894–898, 2006.

371. Pesce V, Cormio A, Fracasso F, Lezza AM, Cantatore P, Gadaleta MN. Age-related changes of mitochondrial DNA content and mitochondrial genotypic and phenotypic alterations in rat hindlimb skeletal muscles. *J Gerontol A Biol Sci Med Sci* 60: 715–723, 2005.

372. Peter AK, Ko CY, Kim MH, Hsu N, Ouchi N, Rhie S, Izumiya Y, Zeng L, Walsh K, Crosbie RH. Myogenic Akt signaling upregulates the utrophin-glycoprotein complex and promotes sarcolemma stability in muscular dystrophy. *Hum Mol Genet* 18: 318–327, 2009.

373. Petersen EW, Carey AL, Sacchetti M, Steinberg GR, Macaulay SL, Febbraio MA, Pedersen BK. Acute IL-6 treatment increases fatty acid turnover in elderly humans in vivo and in tissue culture in vitro. *Am J Physiol Endocrinol Metab* 288: E155–E162, 2005.

374. Pichot V, Roche F, Denis C, Garet M, Duverney D, Costes F, Barthelemy JC. Interval training in elderly men increases both heart rate variability and baroreflex activity. *Clin Auton Res* 15: 107–115, 2005.

375. Pietila M, Malminiemi K, Vesalainen R, Jartti T, Teras M, Nagren K, Lehikoinen P, Voipio-Pulkki LM. Exercise training in chronic heart failure: beneficial effects on cardiac ^{11}C-hydroxyephedrine PET, autonomic nervous control, and ventricular repolarization. *J Nucl Med* 43: 773–779, 2002.

376. Pitsavos C, Kavouras SA, Panagiotakos DB, Arapi S, Anastasiou CA, Zombolos S, Stravopodis P, Mantas Y, Kogias Y, Antonoulas A, Stefanadis C, Investigators GS. Physical activity status and acute coronary syndromes survival The GREECS (Greek Study of Acute Coronary Syndromes) study. *J Am Coll Cardiol* 51: 2034–2039, 2008.

377. Powers SK, Criswell D, Lawler J, Ji LL, Martin D, Herb RA, Dudley G. Influence of exercise and fiber type on antioxidant enzyme activity in rat skeletal muscle. *Am J Physiol Regul Integr Comp Physiol* 266: R375–R380, 1994.

378. Powers SK, Criswell D, Lieu FK, Dodd S, Silverman H. Exercise-induced cellular alterations in the diaphragm. *Am J Physiol Regul Integr Comp Physiol* 263: R1093–R1098, 1992.

379. Powers SK, Farkas GA, Criswell D, Herb RA, Zambito K, Dodd S. Metabolic characteristics of primary inspiratory and expiratory muscles in the dog. *J Appl Physiol* 77: 2188–2193, 1994.

380. Powers SK, Jackson MJ. Exercise-induced oxidative stress: cellular mechanisms and impact on muscle force production. *Physiol Rev* 88: 1243–1276, 2008.

381. Powers SK, Ji LL, Leeuwenburgh C. Exercise training-induced alterations in skeletal muscle antioxidant capacity: a brief review. *Med Sci Sports Exerc* 31: 987–997, 1999.

382. Powers SK, Kavazis AN, DeRuisseau KC. Mechanisms of disuse muscle atrophy: role of oxidative stress. *Am J Physiol Regul Integr Comp Physiol* 288: R337–R344, 2005.

383. Powers SK, Kavazis AN, McClung JM. Oxidative stress and disuse muscle atrophy. *J Appl Physiol* 102: 2389–2397, 2007.

384. Powers SK, Talbert EE, Adhihetty PJ. Reactive oxygen and nitrogen species as intracellular signals in skeletal muscle. *J Physiol* 589: 2129–2138, 2011.

385. Prokopchuk O, Liu Y, Wang L, Wirth K, Schmidtbleicher D, Steinacker JM. Skeletal muscle IL-4, IL-4Ralpha, IL-13 and IL-13Ralpha1 expression and response to strength training. *Exerc Immunol Rev* 13: 67–75, 2007.

386. Qiao C, Li J, Zheng H, Bogan J, Yuan Z, Zhang C, Bogan D, Kornegay J, Xiao X. Hydrodynamic limb vein injection of adeno-associated virus serotype 8 vector carrying canine myostatin propeptide gene into normal dogs enhances muscle growth. *Hum Gene Ther* 20: 1–10, 2009.

387. Quindry JC, Stone WL, King J, Broeder CE. The effects of acute exercise on neutrophils and plasma oxidative stress. *Med Sci Sports Exerc* 35: 1139–1145, 2003.

388. Quinn LS, Anderson BG. Interleukin-15, IL-15 receptor-alpha, and obesity: concordance of laboratory animal and human genetic studies. *J Obes* 2011: 456347, 2011.

389. Quinn LS, Anderson BG, Strait-Bodey L, Stroud AM, Argiles JM. Oversecretion of interleukin-15 from skeletal muscle reduces adiposity. *Am J Physiol Endocrinol Metab* 296: E191–E202, 2009.

390. Quinn LS, Haugk KL, Grabstein KH. Interleukin-15: a novel anabolic cytokine for skeletal muscle. *Endocrinology* 136: 3669–3672, 1995.

391. Quinn LS, Strait-Bodey L, Anderson BG, Argiles JM, Havel PJ. Interleukin-15 stimulates adiponectin secretion by 3T3-L1 adipocytes: evidence for a skeletal muscle-to-fat signaling pathway. *Cell Biol Int* 29: 449–457, 2005.

392. Radak Z, Chung HY, Goto S. Exercise and hormesis: oxidative stress-related adaptation for successful aging. *Biogerontology* 6: 71–75, 2005.

393. Radak Z, Chung HY, Koltai E, Taylor AW, Goto S. Exercise, oxidative stress and hormesis. *Ageing Res Rev* 7: 34–42, 2008.

394. Rakobowchuk M, Harris E, Taylor A, Baliga V, Cubbon RM, Rossiter HB, Birch KM. Heavy and moderate interval exercise training alters low-flow-mediated constriction but does not increase circulating progenitor cells in healthy humans. *Exp Physiol* 97: 375–385, 2012.

395. Ramirez M, Lucia A, Gomez-Gallego F, Esteve-Lanao J, Perez-Martinez A, Foster C, Andreu AL, Martin MA, Madero L, Arenas J, Garcia-Castro J. Mobilisation of mesenchymal cells into blood in response to skeletal muscle injury. *Br J Sports Med* 40: 719–722, 2006.

396. Rasmussen P, Brassard P, Adser H, Pedersen MV, Leick L, Hart E, Secher NH, Pedersen BK, Pilegaard H. Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. *Exp Physiol* 94: 1062–1069, 2009.

397. Raue U, Slivka D, Jemiolo B, Hollon C, Trappe S. Myogenic gene expression at rest and after a bout of resistance exercise in young (18–30 yr) and old (80–89 yr) women. *J Appl Physiol* 101: 53–59, 2006.

398. Rebbapragada A, Benchabane H, Wrana JL, Celeste AJ, Attisano L. Myostatin signals through a transforming growth factor beta-like signaling pathway to block adipogenesis. *Mol Cell Biol* 23: 7230–7242, 2003.

399. Rehman J, Li J, Parvathaneni L, Karlsson G, Panchal VR, Temm CJ, Mahenthiran J, March KL. Exercise acutely increases circulating endothelial progenitor cells and monocyte-/macrophage-derived angiogenic cells. *J Am Coll Cardiol* 43: 2314–2318, 2004.

400. Reid MB, Shoji T, Moody MR, Entman ML. Reactive oxygen in skeletal muscle. II. Extracellular release of free radicals. *J Appl Physiol* 73: 1805–1809, 1992.

401. Rezanejad H, Matin MM. Induced pluripotent stem cells: progress and future perspectives in the stem cell world. *Cell Reprogram* 14: 459–470, 2012.

402. Riechman SE, Balasekaran G, Roth SM, Ferrell RE. Association of interleukin-15 protein and interleukin-15 receptor genetic variation with resistance exercise training responses. *J Appl Physiol* 97: 2214–2219, 2004.

403. Rios R, Fernandez-Nocelos S, Carneiro I, Arce VM, Devesa J. Differential response to exogenous and endogenous myostatin in myoblasts suggests that myostatin acts as an autocrine factor in vivo. *Endocrinology* 145: 2795–2803, 2004.

404. Ristow M, Zarse K, Oberbach A, Kloting N, Birringer M, Kiehntopf M, Stumvoll M, Kahn CR, Bluher M. Antioxidants prevent health-promoting effects of physical exercise in humans. *Proc Natl Acad Sci USA* 106: 8665–8670, 2009.

405. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. *JAMA* 308: 1024–1033, 2012.

406. Robertson JD, Maughan RJ, Duthie GG, Morrice PC. Increased blood antioxidant systems of runners in response to training load. *Clin Sci (Lond)* 80: 611–618, 1991.

407. Roca-Rivada A, Al-Massadi O, Castelao C, Senin LL, Alonso J, Seoane LM, Garcia-Caballero T, Casanueva FF, Pardo M. Muscle tissue as an endocrine organ: comparative secretome profiling of slow-oxidative and fast-glycolytic rat muscle explants and its variation with exercise. *J Proteomics* 75: 5414–5425, 2012.

408. Rocco DD, Okuda LS, Pinto RS, Ferreira FD, Kubo SK, Nakandakare ER, Quintao EC, Catanozi S, Passarelli M. Aerobic exercise improves reverse cholesterol transport in cholesteryl ester transfer protein transgenic mice. *Lipids* 46: 617–625, 2011.

409. Rojas Vega S, Struder HK, Vera Wahrmann B, Schmidt A, Bloch W, Hollmann W. Acute BDNF and cortisol response to low intensity exercise and following ramp incremental exercise to exhaustion in humans. *Brain Res* 1121: 59–65, 2006.

410. Romacho T, Azcutia V, Vazquez-Bella M, Matesanz N, Cercas E, Nevado J, Carraro R, Rodriguez-Manas L, Sanchez-Ferrer CF, Peiro C. Extracellular PBEF/NAMPT/visfatin activates pro-inflammatory signalling in human vascular smooth muscle cells through nicotinamide phosphoribosyltransferase activity. *Diabetologia* 52: 2455–2463, 2009.

411. Rosendal L, Sogaard K, Kjaer M, Sjogaard G, Langberg H, Kristiansen J. Increase in interstitial interleukin-6 of human skeletal muscle with repetitive low-force exercise. *J Appl Physiol* 98: 477–481, 2005.

412. Routledge FS, Campbell TS, McFetridge-Durdle JA, Bacon SL. Improvements in heart rate variability with exercise therapy. *Can J Cardiol* 26: 303–312, 2010.

413. Rubart M, Zipes DP. Mechanisms of sudden cardiac death. *J Clin Invest* 115: 2305–2315, 2005.

414. Rubinsztein DC, Marino G, Kroemer G. Autophagy and aging. *Cell* 146: 682–695, 2011.

415. Ruiz JR, Moran M, Arenas J, Lucia A. Strenuous endurance exercise improves life expectancy: it's in our genes. *Br J Sports Med* 45: 159–161, 2011.

416. Russo-Neustadt AA, Alejandre H, Garcia C, Ivy AS, Chen MJ. Hippocampal brain-derived neurotrophic factor expression following treatment with reboxetine, citalopram, and physical exercise. *Neuropsychopharmacology* 29: 2189–2199, 2004.

417. Russo-Neustadt AA, Beard RC, Huang YM, Cotman CW. Physical activity and antidepressant treatment potentiate the expression of specific brain-derived neurotrophic factor transcripts in the rat hippocampus. *Neuroscience* 101: 305–312, 2000.

418. Sakuma K, Watanabe K, Sano M, Uramoto I, Totsuka T. Differential adaptation of growth and differentiation factor 8/myostatin, fibroblast growth factor 6 and leukemia inhibitory factor in overloaded, regenerating and denervated rat muscles. *Biochim Biophys Acta* 1497: 77–88, 2000.

419. Sampaolesi M, Blot S, D'Antona G, Granger N, Tonlorenzi R, Innocenzi A, Mognol P, Thibaud JL, Galvez BG, Barthelemy I, Perani L, Mantero S, Guttinger M, Pansarasa O, Rinaldi C, Cusella De Angelis MG, Torrente Y, Bordignon C, Bottinelli R, Cossu G. Mesoangioblast stem cells ameliorate muscle function in dystrophic dogs. *Nature* 444: 574–579, 2006.

420. Sanchis-Gomar F, Lippi G, Mayero S, Perez-Quilis C, Garcia-Gimenez JL. Irisin: a new potential hormonal target for the treatment of obesity and type 2 diabetes. *J Diabetes* 4: 196, 2012.

421. Sandercock GR, Grocott-Mason R, Brodie DA. Changes in short-term measures of heart rate variability after eight weeks of cardiac rehabilitation. *Clin Auton Res* 17: 39–45, 2007.

422. Sanz G, Fuster V. Maximizing therapeutic envelope for prevention of cardiovascular disease: role of polypill. *Mt Sinai J Med* 79: 683–688, 2012.

423. Saravanan P, Davidson NC, Schmidt EB, Calder PC. Cardiovascular effects of marine omega-3 fatty acids. *Lancet* 376: 540–550, 2010.

424. Sarto P, Balducci E, Balconi G, Fiordaliso F, Merlo L, Tuzzato G, Pappagallo GL, Frigato N, Zanocco A, Forestieri C, Azzarello G, Mazzucco A, Valenti MT, Alborino F, Noventa D, Vinante O, Pascotto P, Sartore S, Dejana E, Latini R. Effects of exercise training on endothelial progenitor cells in patients with chronic heart failure. *J Card Fail* 13: 701–708, 2007.

425. Sartori CR, Vieira AS, Ferrari EM, Langone F, Tongiorgi E, Parada CA. The antidepressive effect of the physical exercise correlates with increased levels of mature BDNF, and proBDNF proteolytic cleavage-related genes, p11 and tPA. *Neuroscience* 180: 9–18, 2011.

426. Sartori R, Milan G, Patron M, Mammucari C, Blaauw B, Abraham R, Sandri M. Smad2 and 3 transcription factors control muscle mass in adulthood. *Am J Physiol Cell Physiol* 296: C1248–C1257, 2009.

427. Scheele C, Nielsen S, Pedersen BK. ROS and myokines promote muscle adaptation to exercise. *Trends Endocrinol Metab* 20: 95–99, 2009.

428. Scheffer DL, Silva LA, Tromm CB, da Rosa GL, Silveira PC, de Souza CT, Latini A, Pinho RA. Impact of different resistance training protocols on muscular oxidative stress parameters. *Appl Physiol Nutr Metab* 37: 1239–1246, 2012.

429. Schiffer T, Schulte S, Hollmann W, Bloch W, Struder HK. Effects of strength and endurance training on brain-derived neurotrophic factor and insulin-like growth factor 1 in humans. *Horm Metab Res* 41: 250–254, 2009.

430. Schlager O, Giurgea A, Schuhfried O, Seidinger D, Hammer A, Groger M, Fialka-Moser V, Gschwandtner M, Koppensteiner R, Steiner S. Exercise training increases endothelial progenitor cells and decreases asymmetric dimethylarginine in peripheral arterial disease: a randomized controlled trial. *Atherosclerosis* 217: 240–248, 2011.

431. Schmidt-Kassow M, Schadle S, Otterbein S, Thiel C, Doehring A, Lotsch J, Kaiser J. Kinetics of serum brain-derived neurotrophic factor following low-intensity versus high-intensity exercise in men and women. *Neuroreport* 23: 889–893, 2012.

432. Schmidt A, Bierwirth S, Weber S, Platen P, Schinkothe T, Bloch W. Short intensive exercise increases the migratory activity of mesenchymal stem cells. *Br J Sports Med* 43: 195–198, 2009.

433. Schneider CD, Barp J, Ribeiro JL, Bello-Klein A, Oliveira AR. Oxidative stress after three different intensities of running. *Can J Appl Physiol* 30: 723–734, 2005.

434. Schuler G, Hambrecht R, Schlierf G, Niebauer J, Hauer K, Neumann J, Hoberg E, Drinkmann A, Bacher F, Grunze M. Regular physical exercise and low-fat diet. Effects on progression of coronary artery disease. *Circulation* 86: 1–11, 1992.

435. Schulz KH, Gold SM, Witte J, Bartsch K, Lang UE, Hellweg R, Reer R, Braumann KM, Heesen C. Impact of aerobic training on immune-endocrine parameters, neurotrophic factors, quality of life and coordinative function in multiple sclerosis. *J Neurol Sci* 225: 11–18, 2004.

436. Seals DR, Dinenno FA. Collateral damage: cardiovascular consequences of chronic sympathetic activation with human aging. *Am J Physiol Heart Circ Physiol* 287: H1895–H1905, 2004.

437. Seifert T, Brassard P, Wissenberg M, Rasmussen P, Nordby P, Stallknecht B, Adser H, Jakobsen AH, Pilegaard H, Nielsen HB, Secher NH. Endurance training enhances BDNF release from the human brain. *Am J Physiol Regul Integr Comp Physiol* 298: R372–R377, 2010.

438. Selamoglu S, Turgay F, Kayatekin BM, Gonenc S, Yslegen C. Aerobic and anaerobic training effects on the antioxidant enzymes of the blood. *Acta Physiol Hung* 87: 267–273, 2000.

439. Seldin MM, Peterson JM, Byerly MS, Wei Z, Wong GW. Myonectin (CTRP15), a novel myokine that links skeletal muscle to systemic lipid homeostasis. *J Biol Chem* 287: 11968–11980, 2012.

440. Selig SE, Carey MF, Menzies DG, Patterson J, Geerling RH, Williams AD, Bamroongsuk V, Toia D, Krum H, Hare DL. Moderate-intensity resistance exercise training in patients with chronic heart failure improves strength, endurance, heart rate variability, and forearm blood flow. *J Card Fail* 10: 21–30, 2004.

441. Serrano AL, Baeza-Raja B, Perdiguero E, Jardi M, Munoz-Canoves P. Interleukin-6 is an essential regulator of satellite cell-mediated skeletal muscle hypertrophy. *Cell Metab* 7: 33–44, 2008.

442. Sesso HD, Paffenbarger RS Jr, Lee IM. Physical activity and coronary heart disease in men: The Harvard Alumni Health Study. *Circulation* 102: 975–980, 2000.

443. Shan T, Liang X, Bi P, Kuang S. Myostatin knockout drives browning of white adipose tissue through activating the AMPK-PGC1alpha-Fndc5 pathway in muscle. *FASEB J* 27: 1981–1989, 2013.

444. Shin YA, Lee JH, Song W, Jun TW. Exercise training improves the antioxidant enzyme activity with no changes of telomere length. *Mech Ageing Dev* 129: 254–260, 2008.

445. Shook RP, Lee DC, Sui X, Prasad V, Hooker SP, Church TS, Blair SN. Cardiorespiratory fitness reduces the risk of incident hypertension associated with a parental history of hypertension. *Hypertension* 59: 1220–1224, 2012.

446. Silva LA, Pinho CA, Scarabelot KS, Fraga DB, Volpato AM, Boeck CR, De Souza CT, Streck EL, Pinho RA. Physical exercise increases mitochondrial function and reduces oxidative damage in skeletal muscle. *Eur J Appl Physiol* 105: 861–867, 2009.

447. Silveira LR, Pereira-Da-Silva L, Juel C, Hellsten Y. Formation of hydrogen peroxide and nitric oxide in rat skeletal muscle cells during contractions. *Free Radic Biol Med* 35: 455–464, 2003.

448. Siriett V, Platt L, Salerno MS, Ling N, Kambadur R, Sharma M. Prolonged absence of myostatin reduces sarcopenia. *J Cell Physiol* 209: 866–873, 2006.

449. Skenderi KP, Tsironi M, Lazaropoulou C, Anastasiou CA, Matalas AL, Kanavaki I, Thalmann M, Goussetis E, Papassotiriou I, Chrousos GP. Changes in free radical generation and antioxidant capacity during ultramarathon foot race. *Eur J Clin Invest* 38: 159–165, 2008.

450. Sloan RP, Shapiro PA, DeMeersman RE, Bagiella E, Brondolo EN, McKinley PS, Slavov I, Fang Y, Myers MM. The effect of aerobic training and cardiac autonomic regulation in young adults. *Am J Public Health* 99: 921–928, 2009.

451. Soga Y, Yokoi H, Amemiya K, Iwabuchi M, Nobuyoshi M. Safety and efficacy of exercise training after coronary stenting in patients with stable coronary artery disease. *Circ J* 75: 2379–2386, 2011.

452. Spangenburg EE, Booth FW. Leukemia inhibitory factor restores the hypertrophic response to increased loading in the LIF(−/−) mouse. *Cytokine* 34: 125–130, 2006.

453. Spangenburg EE, Booth FW. Multiple signaling pathways mediate LIF-induced skeletal muscle satellite cell proliferation. *Am J Physiol Cell Physiol* 283: C204–C211, 2002.

454. Staib JL, Quindry JC, French JP, Criswell DS, Powers SK. Increased temperature, not cardiac load, activates heat shock transcription factor 1 and heat shock protein 72 expression in the heart. *Am J Physiol Regul Integr Comp Physiol* 292: R432–R439, 2007.

455. Staib JL, Tumer N, Powers SK. Increased temperature and protein oxidation lead to HSP72 mRNA and protein accumulation in the in vivo exercised rat heart. *Exp Physiol* 94: 71–80, 2009.

456. Steensberg A, Febbraio MA, Osada T, Schjerling P, van Hall G, Saltin B, Pedersen BK. Interleukin-6 production in contracting human skeletal muscle is influenced by pre-exercise muscle glycogen content. *J Physiol* 537: 633–639, 2001.

457. Steensberg A, Keller C, Starkie RL, Osada T, Febbraio MA, Pedersen BK. IL-6 and TNF-alpha expression in, and release from, contracting human skeletal muscle. *Am J Physiol Endocrinol Metab* 283: E1272–E1278, 2002.

458. Steensberg A, van Hall G, Osada T, Sacchetti M, Saltin B, Klarlund Pedersen B. Production of interleukin-6 in contracting human skeletal muscles can account for the exercise-induced increase in plasma interleukin-6. *J Physiol* 529: 237–242, 2000.

459. Steiner S, Niessner A, Ziegler S, Richter B, Seidinger D, Pleiner J, Penka M, Wolzt M, Huber K, Wojta J, Minar E, Kopp CW. Endurance training increases the number of endothelial progenitor cells in patients with cardiovascular risk and coronary artery disease. *Atherosclerosis* 181: 305–310, 2005.

460. Stranahan AM, Lee K, Martin B, Maudsley S, Golden E, Cutler RG, Mattson MP. Voluntary exercise and caloric restriction enhance hippocampal dendritic spine density and BDNF levels in diabetic mice. *Hippocampus* 19: 951–961, 2009.

461. Subudhi AW, Davis SL, Kipp RW, Askew EW. Antioxidant status and oxidative stress in elite alpine ski racers. *Int J Sport Nutr Exerc Metab* 11: 32–41, 2001.

462. Sureda A, Tauler P, Aguilo A, Cases N, Fuentespina E, Cordova A, Tur JA, Pons A. Relation between oxidative stress markers and antioxidant endogenous defences during exhaustive exercise. *Free Radic Res* 39: 1317–1324, 2005.

463. Takahashi A, Kureishi Y, Yang J, Luo Z, Guo K, Mukhopadhyay D, Ivashchenko Y, Branellec D, Walsh K. Myogenic Akt signaling regulates blood vessel recruitment during myofiber growth. *Mol Cell Biol* 22: 4803–4814, 2002.

464. Takeyama J, Itoh H, Kato M, Koike A, Aoki K, Fu LT, Watanabe H, Nagayama M, Katagiri T. Effects of physical training on the recovery of the autonomic nervous activity during exercise after coronary artery bypass grafting: effects of physical training after CABG. *Jpn Circ J* 64: 809–813, 2000.

465. Tang SW, Chu E, Hui T, Helmeste D, Law C. Influence of exercise on serum brain-derived neurotrophic factor concentrations in healthy human subjects. *Neurosci Lett* 431: 62–65, 2008.

466. Task Force of the European Society of Cardiology, and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* 93: 1043–1065, 1996.

467. Tauler P, Aguilo A, Gimeno I, Fuentespina E, Tur JA, Pons A. Response of blood cell antioxidant enzyme defences to antioxidant diet supplementation and to intense exercise. *Eur J Nutr* 45: 187–195, 2006.

468. Terblanche SE. The effects of exhaustive exercise on the activity levels of catalase in various tissues of male and female rats. *Cell Biol Int* 23: 749–753, 2000.

469. Tessier F, Margaritis I, Richard MJ, Moynot C, Marconnet P. Selenium and training effects on the glutathione system and aerobic performance. *Med Sci Sports Exerc* 27: 390–396, 1995.

470. Theodorou AA, Nikolaidis MG, Paschalis V, Koutsias S, Panayiotou G, Fatouros IG, Koutedakis Y, Jamurtas AZ. No effect of antioxidant supplementation on muscle performance and blood redox status adaptations to eccentric training. *Am J Clin Nutr* 93: 1373–1383, 2011.

471. Thijssen DH, Vos JB, Verseyden C, van Zonneveld AJ, Smits P, Sweep FC, Hopman MT, de Boer HC. Haematopoietic stem cells and endothelial progenitor cells in healthy men: effect of aging and training. *Aging Cell* 5: 495–503, 2006.

472. Thomas AW, Davies NA, Moir H, Watkeys L, Ruffino JS, Isa SA, Butcher LR, Hughes MG, Morris K, Webb R. Exercise-associated generation of PPARgamma ligands activates PPARgamma signaling events and upregulates genes related to lipid metabolism. *J Appl Physiol* 112: 806–815, 2012.

473. Timmons JA, Baar K, Davidsen PK, Atherton PJ. Is irisin a human exercise gene? *Nature* 488: E9–E10; discussion E10–E11, 2012.

474. Timmons JA, Knudsen S, Rankinen T, Koch LG, Sarzynski M, Jensen T, Keller P, Scheele C, Vollaard NB, Nielsen S, Akerstrom T, MacDougald OA, Jansson E, Greenhaff PL, Tarnopolsky MA, van Loon LJ, Pedersen BK, Sundberg CJ, Wahlestedt C, Britton SL, Bouchard C. Using molecular classification to predict gains in maximal aerobic capacity following endurance exercise training in humans. *J Appl Physiol* 108: 1487–1496, 2010.

475. Tremblay MS, Esliger DW, Copeland JL, Barnes JD, Bassett DR. Moving forward by looking back: lessons learned from long-lost lifestyles. *Appl Physiol Nutr Metab* 33: 836–842, 2008.

476. Trendelenburg AU, Meyer A, Rohner D, Boyle J, Hatakeyama S, Glass DJ. Myostatin reduces Akt/TORC1/p70S6K signaling, inhibiting myoblast differentiation and myotube size. *Am J Physiol Cell Physiol* 296: C1258–C1270, 2009.

477. Tsai MW, Chie WC, Kuo TB, Chen MF, Liu JP, Chen TT, Wu YT. Effects of exercise training on heart rate variability after coronary angioplasty. *Phys Ther* 86: 626–635, 2006.

478. Tsuchida K. Myostatin inhibition by a follistatin-derived peptide ameliorates the pathophysiology of muscular dystrophy model mice. *Acta Myol* 27: 14–18, 2008.

479. Umpierre D, Ribeiro PA, Kramer CK, Leitao CB, Zucatti AT, Azevedo MJ, Gross JL, Ribeiro JP, Schaan BD. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. *JAMA* 305: 1790–1799, 2011.

480. Ungvari Z, Kaley G, de Cabo R, Sonntag WE, Csiszar A. Mechanisms of vascular aging: new perspectives. *J Gerontol A Biol Sci Med Sci* 65: 1028–1041, 2010.

481. Upham BL, Trosko JE. Oxidative-dependent integration of signal transduction with intercellular gap junctional communication in the control of gene expression. *Antioxid Redox Signal* 11: 297–307, 2009.

482. Valero MC, Huntsman HD, Liu J, Zou K, Boppart MD. Eccentric exercise facilitates mesenchymal stem cell appearance in skeletal muscle. *PLos One* 7: e29760, 2012.

483. Van Craenenbroeck EM, Beckers PJ, Possemiers NM, Wuyts K, Frederix G, Hoymans VY, Wuyts F, Paelinck BP, Vrints CJ, Conraads VM. Exercise acutely reverses dysfunction of circulating angiogenic cells in chronic heart failure. *Eur Heart J* 31: 1924–1934, 2010.

484. Van Craenenbroeck EM, Hoymans VY, Beckers PJ, Possemiers NM, Wuyts K, Paelinck BP, Vrints CJ, Conraads VM. Exercise training improves function of circulating angiogenic cells in patients with chronic heart failure. *Basic Res Cardiol* 105: 665–676, 2010.

485. Van Craenenbroeck EM, Vrints CJ, Haine SE, Vermeulen K, Goovaerts I, Van Tendeloo VF, Hoymans VY, Conraads VM. A maximal exercise bout increases the number of circulating CD34+/KDR+ endothelial progenitor cells in healthy subjects. Relation with lipid profile. *J Appl Physiol* 104: 1006–1013, 2008.

486. van Hall G, Steensberg A, Sacchetti M, Fischer C, Keller C, Schjerling P, Hiscock N, Moller K, Saltin B, Febbraio MA, Pedersen BK. Interleukin-6 stimulates lipolysis and fat oxidation in humans. *J Clin Endocrinol Metab* 88: 3005–3010, 2003.

487. Vasilaki A, Mansouri A, Remmen H, van der Meulen JH, Larkin L, Richardson AG, McArdle A, Faulkner JA, Jackson MJ. Free radical generation by skeletal muscle of adult and old mice: effect of contractile activity. *Aging Cell* 5: 109–117, 2006.

488. Vaynman S, Ying Z, Gomez-Pinilla F. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *Eur J Neurosci* 20: 2580–2590, 2004.

489. Veal EA, Day AM, Morgan BA. Hydrogen peroxide sensing and signaling. *Mol Cell* 26: 1–14, 2007.

490. Venditti P, Di Meo S. Effect of training on antioxidant capacity, tissue damage, and endurance of adult male rats. *Int J Sports Med* 18: 497–502, 1997.

491. Venditti P, Masullo P, Meo SD. Effect of exercise duration on characteristics of mitochondrial population from rat liver. *Arch Biochem Biophys* 368: 112–120, 1999.

492. Vina J, Gimeno A, Sastre J, Desco C, Asensi M, Pallardo FV, Cuesta A, Ferrero JA, Terada LS, Repine JE. Mechanism of free radical production in exhaustive exercise in humans and rats; role of xanthine oxidase and protection by allopurinol. *IUBMB Life* 49: 539–544, 2000.

493. Vincent HK, Powers SK, Demirel HA, Coombes JS, Naito H. Exercise training protects against contraction-induced lipid peroxidation in the diaphragm. *Eur J Appl Physiol Occup Physiol* 79: 268–273, 1999.

494. Vincent HK, Powers SK, Stewart DJ, Demirel HA, Shanely RA, Naito H. Short-term exercise training improves diaphragm antioxidant capacity and endurance. *Eur J Appl Physiol* 81: 67–74, 2000.

495. Voight BF, Kudaravalli S, Wen X, Pritchard JK. A map of recent positive selection in the human genome. *PLoS Biol* 4: e72, 2006.

496. Wagner A, Simon C, Evans A, Ferrieres J, Montaye M, Ducimetiere P, Arveiler D. Physical activity and coronary event incidence in Northern Ireland and France: the Prospective Epidemiological Study of Myocardial Infarction (PRIME). *Circulation* 105: 2247–2252, 2002.

497. Wagner KR, Fleckenstein JL, Amato AA, Barohn RJ, Bushby K, Escolar DM, Flanigan KM, Pestronk A, Tawil R, Wolfe GI, Eagle M, Florence JM, King WM, Pandya S, Straub V, Juneau P, Meyers K, Csimma C, Araujo T, Allen R, Parsons SA, Wozney JM, Lavallie ER, Mendell JR. A phase I/IItrial of MYO-029 in adult subjects with muscular dystrophy. *Ann Neurol* 63: 561–571, 2008.

498. Wald NJ, Law MR. *Formulation for the Prevention of Cardiovascular Disease*. United Kingdom, Patents GB008791 and GB0100548, 2000.

499. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 326: 1419, 2003.

500. Walsh JH, Yong G, Cheetham C, Watts GF, O'Driscoll GJ, Taylor RR, Green DJ. Effects of exercise training on conduit and resistance vessel function in treated and untreated hypercholesterolaemic subjects. *Eur Heart J* 24: 1681–1689, 2003.

501. Walther C, Gaede L, Adams V, Gelbrich G, Leichtle A, Erbs S, Sonnabend M, Fikenzer K, Korner A, Kiess W, Bruegel M, Thiery J, Schuler G. Effect of increased exercise in school children on physical fitness and endothelial progenitor cells: a prospective randomized trial. *Circulation* 120: 2251–2259, 2009.

502. Wang JS, Chow SE, Chen JK. Strenuous, acute exercise affects reciprocal modulation of platelet and polymorphonuclear leukocyte activities under shear flow in men. *J Thromb Haemost* 1: 2031–2037, 2003.

503. Wang P, Du H, Zhang RY, Guan YF, Xu TY, Xu QY, Su DF, Miao CY. Circulating and local visfatin/Nampt/PBEF levels in spontaneously hypertensive rats, stroke-prone spontaneously hypertensive rats and Wistar-Kyoto rats. *J Physiol Sci* 60: 317–324, 2010.

504. Wannamethee SG, Shaper AG, Walker M. Physical activity and mortality in older men with diagnosed coronary heart disease. *Circulation* 102: 1358–1363, 2000.

505. Werner N, Junk S, Laufs U, Link A, Walenta K, Bohm M, Nickenig G. Intravenous transfusion of endothelial progenitor cells reduces neointima formation after vascular injury. *Circ Res* 93: e17–24, 2003.

506. White JD, Bower JJ, Kurek JB, Austin L. Leukemia inhibitory factor enhances regeneration in skeletal muscles after myoblast transplantation. *Muscle Nerve* 24: 695–697, 2001.

507. Widenfalk J, Olson L, Thoren P. Deprived of habitual running, rats downregulate BDNF and TrkB messages in the brain. *Neurosci Res* 34: 125–132, 1999.

508. Williamson K, Stringer SE, Alexander MY. Endothelial progenitor cells enter the aging arena. *Front Physiol* 3: 30, 2012.

509. Willoughby DS, McFarlin B, Bois C. Interleukin-6 expression after repeated bouts of eccentric exercise. *Int J Sports Med* 24: 15–21, 2003.

510. Winter B, Breitenstein C, Mooren FC, Voelker K, Fobker M, Lechtermann A, Krueger K, Fromme A, Korsukewitz C, Floel A, Knecht S. High impact running improves learning. *Neurobiol Learn Mem* 87: 597–609, 2007.

511. Witkowski S, Jenkins NT, Hagberg JM. Enhancing treatment for cardiovascular disease: exercise and circulating angiogenic cells. *Exerc Sport Sci Rev* 39: 93–101, 2011.

512. Witkowski S, Lockard MM, Jenkins NT, Obisesan TO, Spangenburg EE, Hagberg JM. Relationship between circulating progenitor cells, vascular function and oxidative stress with long-term training and short-term detraining in older men. *Clin Sci (Lond)* 118: 303–311, 2010.

513. Wohlgemuth SE, Lees HA, Marzetti E, Manini TM, Aranda JM, Daniels MJ, Pahor M, Perri MG, Leeuwenburgh C, Anton SD. An exploratory analysis of the effects of a weight loss plus exercise program on cellular quality control mechanisms in older overweight women. *Rejuvenation Res* 14: 315–324, 2011.

514. Wolf SA, Melnik A, Kempermann G. Physical exercise increases adult neurogenesis and telomerase activity, and improves behavioral deficits in a mouse model of schizophrenia. *Brain Behav Immun* 25: 971–980, 2011.

515. World Health Organization. *Global Recommendations on Physical Activity For Health*. Geneva, Switzerland: WHO Press, 2010.

516. World Health Organization. *Secondary Prevention of Non-communicable Disease in Low and Middle Income Countries Through Community-Based and Health Service Interventions*. Geneva, Switzerland: WHO Press, 2002.

517. Wright DC, Han DH, Garcia-Roves PM, Geiger PC, Jones TE, Holloszy JO. Exercise-induced mitochondrial biogenesis begins before the increase in muscle PGC-1alpha expression. *J Biol Chem* 282: 194–199, 2007.

518. Wu J, Li J, Zhang N, Zhang C. Stem cell-based therapies in ischemic heart diseases: a focus on aspects of microcirculation and inflammation. *Basic Res Cardiol* 106: 317–324, 2011.

519. Xia WH, Li J, Su C, Yang Z, Chen L, Wu F, Zhang YY, Yu BB, Qiu YX, Wang SM, Tao J. Physical exercise attenuates age-associated reduction in endothelium-reparative capacity of endothelial progenitor cells by increasing CXCR4/JAK-2 signaling in healthy men. *Aging Cell* 11: 111–119, 2012.

520. Yang H, Chang J, Chen W, Zhao L, Qu B, Tang C, Qi Y, Zhang J. Treadmill exercise promotes interleukin 15 expression in skeletal muscle and interleukin 15 receptor alpha expression in adipose tissue of high-fat diet rats. *Endocrine* 43: 579–585, 2013.

521. Yang J, Zhao B. Postnatal expression of myostatin propeptide cDNA maintained high muscle growth and normal adipose tissue mass in transgenic mice fed a high-fat diet. *Mol Reprod Dev* 73: 462–469, 2006.

522. Yang SJ, Hong HC, Choi HY, Yoo HJ, Cho GJ, Hwang TG, Baik SH, Choi DS, Kim SM, Choi KM. Effects of a three-month combined exercise programme on fibroblast growth factor 21 and fetuin-A levels and arterial stiffness in obese women. *Clin Endocrinol (Oxf)* 75: 464–469, 2011.

523. Yarasheski KE, Bhasin S, Sinha-Hikim I, Pak-Loduca J, Gonzalez-Cadavid NF. Serum myostatin-immunoreactive protein is increased in 60–92 year old women and men with muscle wasting. *J Nutr Health Aging* 6: 343–348, 2002.

524. Yarrow JF, White LJ, McCoy SC, Borst SE. Training augments resistance exercise induced elevation of circulating brain derived neurotrophic factor (BDNF). *Neurosci Lett* 479: 161–165, 2010.

525. Yasui A, Nishizawa H, Okuno Y, Morita K, Kobayashi H, Kawai K, Matsuda M, Kishida K, Kihara S, Kamei Y, Ogawa Y, Funahashi T, Shimomura I. Foxo1 represses expression of musclin, a skeletal muscle-derived secretory factor. *Biochem Biophys Res Commun* 364: 358–365, 2007.

526. Yau SY, Lau BW, Tong JB, Wong R, Ching YP, Qiu G, Tang SW, Lee TM, So KF. Hippocampal neurogenesis and dendritic plasticity support running-improved spatial learning and depression-like behaviour in stressed rats. *PLos One* 6: e24263, 2011.

527. Yoon JH, Yea K, Kim J, Choi YS, Park S, Lee H, Lee CS, Suh PG, Ryu SH. Comparative proteomic analysis of the insulin-induced L6 myotube secretome. *Proteomics* 9: 51–60, 2009.

528. Yui S, Mikami M, Yamazaki M. Purification and characterization of the cytotoxic factor in rat peritoneal exudate cells: its identification as the calcium binding protein complex, calprotectin. *J Leukoc Biol* 58: 307–316, 1995.

529. Zeng L, Akasaki Y, Sato K, Ouchi N, Izumiya Y, Walsh K. Insulin-like 6 is induced by muscle injury and functions as a regenerative factor. *J Biol Chem* 285: 36060–36069, 2010.

530. Zhao B, Wall RJ, Yang J. Transgenic expression of myostatin propeptide prevents diet-induced obesity and insulin resistance. *Biochem Biophys Res Commun* 337: 248–255, 2005.

531. Zhenfeng Z, Huilan S, Junya J, Dong L, Shan L. A systematic review and meta-analysis of aliskiren and angiotension receptor blockers in the management of essential hypertension. *J Renin Angiotensin Aldosterone Syst* 12: 102–112, 2011.

532. Zhu J, Li Y, Shen W, Qiao C, Ambrosio F, Lavasani M, Nozaki M, Branca MF, Huard J. Relationships between transforming growth factor-beta1, myostatin, and decorin: implications for skeletal muscle fibrosis. *J Biol Chem* 282: 25852–25863, 2007.

533. Zoladz JA, Pilc A. The effect of physical activity on the brain derived neurotrophic factor: from animal to human studies. *J Physiol Pharmacol* 61: 533–541, 2010.

534. Zoladz JA, Pilc A, Majerczak J, Grandys M, Zapart-Bukowska J, Duda K. Endurance training increases plasma brain-derived neurotrophic factor concentration in young healthy men. *J Physiol Pharmacol* 59, *Suppl* 7: 119–132, 2008.

535. Zoppini G, Cacciatori V, Gemma ML, Moghetti P, Targher G, Zamboni C, Thomaseth K, Bellavere F, Muggeo M. Effect of moderate aerobic exercise on sympatho-vagal balance in Type 2 diabetic patients. *Diabet Med* 24: 370–376, 2007.

536. Zuk PA, Zhu M, Ashjian P, De Ugarte DA, Huang JI, Mizuno H, Alfonso ZC, Fraser JK, Benhaim P, Hedrick MH. Human adipose tissue is a source of multipotent stem cells. *Mol Biol Cell* 13: 4279–4295, 2002.