

HIGHLIGHTED TOPIC | *Signals Mediating Skeletal Muscle Remodeling by Activity*

## Variability in training-induced skeletal muscle adaptation

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**Timmons JA.** Variability in training-induced skeletal muscle adaptation. *J Appl Physiol* 110: 846–853, 2011. First published October 28, 2010; doi:10.1152/jappphysiol.00934.2010.—When human skeletal muscle is exposed to exercise training, the outcomes, in terms of physiological adaptation, are unpredictable. The significance of this fact has long been underappreciated, and only recently has progress been made in identifying some of the molecular bases for the heterogeneous response to exercise training. It is not only of great medical importance that some individuals do not substantially physiologically adapt to exercise training, but the study of the heterogeneity itself provides a powerful opportunity to dissect out the genetic and environmental factors that limit adaptation, directly in humans. In the following review I will discuss new developments linking genetic and transcript abundance variability to an individual's potential to improve their aerobic capacity or endurance performance or induce muscle hypertrophy. I will also comment on the idea that certain gene networks may be associated with muscle "adaptability" regardless the stimulus provided.

microarray; personalized medicine; aerobic fitness; transcriptomics; genomics

THERE IS A FAMILIAL contribution toward the ability for humans to adapt physiologically to regular, supervised physical activity (10), and much of this familial component may be due to variation in the DNA sequence of the genes inherited from our parents. Furthermore, for many of the major physiological outcomes derived from regular aerobic training, such as increased aerobic capacity, enhanced endurance performance, improved insulin sensitivity, and reduced blood pressure, there is a large range, within the population, of observed improvements (12). Thus no matter which training parameter is studied, "nonresponders" are readily observed. For some variables this equates to ~10% of the study population, while for others, such as "insulin sensitivity," it can exceed 20% of the population (11). This remarkable observation is one of the major legacies of the HERITAGE Family Study. It is also an observation that is largely ignored by the majority of researchers interested in the health benefits of exercise training, presumably because the focus has been on the "average" health benefits within a population and the desire to have a simple health promotion message.

Indeed, concern has been raised over the appropriateness of the "nonresponder" terminology (8). Yet the term is entirely valid when placed within context (11, 85, 91, 92, 100). Furthermore, while the intercorrelation between being a "nonresponder" for one physiological trait and another is very low ( $\sim r = 0.1$ – $0.05$ ), it is not zero. Thus, when scaled to the human population as a whole, there will be millions of humans

that cannot improve their aerobic capacity or their insulin sensitivity or reduce their blood pressure with supervised aerobic exercise training, and at this stage one cannot even rule out the existence of tens of thousands of global "nonresponders" (8). More importantly, there is a hierarchy of health benefits from exercise training, whereby improved aerobic fitness should have (based on current knowledge) a much greater bearing on future health outcome than, for example, modulating metabolism (6, 7, 40, 55, 69, 98). Thus "nonresponsiveness" to the major outcomes must be taken seriously from both a public health and a personalized medicine perspective (8, 86), regardless of whether the same individual gains benefit in other, arguably less important, ways from the exercise training. Molecular diagnosis of these "low responders" also offers the opportunity to trial nonconventional exercise and lifestyle interventions in an attempt to have a larger impact on their metabolic or cardiovascular health.

The variability in training-induced physiological adaptation also provides a unique opportunity to examine the relationship between molecular responses to exercise and the magnitude of physiological change in outbred humans (91–93). This provides a new research strategy for molecular physiology (91), as to date the majority of molecular mechanisms suggested to govern muscle adaptation to exercise, in humans, originate from the cell biology and murine transgenic/knockout literature. If the molecular response measured in the muscle (or bloodstream) of humans can be shown to be proportional (linear or otherwise) to the extent of physiological change in aerobic fitness, metabolic fitness, muscle hypertrophy, or exercise performance, then it is logical that there is more likely to be a cause-effect relationship between that molecular or cellular parameter and the physiological system being studied. As it

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is impractical (and arguably illogical) to modulate a “single gene” in vivo in humans and examine the relationship with a physiological outcome, greater effort must be taken to link the modulation of gene expression networks with the heterogeneous physiological change (91).

There is also a potential danger of studying acute molecular responses to exercise in humans and attempting to extrapolate to mechanisms driving chronic adaptation when no evidence of adaptive potential has been established in each subject. Indeed, it makes sense that if there is a consistent acute activation of a protein kinase in all subjects, yet great heterogeneity in chronic muscle adaptation, then that protein kinase is very unlikely to “determine” or “regulate” physiological adaptation. Indeed, so far little connection can be made between acute “gene” regulation and the molecular changes that characterize long-term adaptation (53). One cautionary note on this point would be that when such studies do address this relationship, the molecular marker [e.g., AMP-activated protein kinase (AMPK) activation] may simply reflect the proportion of muscle fiber recruitment during the endurance training stimulus (67) and thus simply indicate that ineffective standardization of muscle loading between subjects occurred, yielding a potentially false association. Indeed, one needs to be very careful when using the term “predict” as independent blinded validation is required to make such a claim. In the following sections I will discuss what is known about the molecules that influence the variability in training-induced skeletal muscle adaptations for aerobic, metabolic, and strength/hypertrophy-related fitness phenotypes and how one attempts to study such variables in humans.

#### AEROBIC AND ENDURANCE CAPACITY

Early during an endurance training program (e.g., 2 wk) there is a moderate inverse relationship between baseline aerobic fitness and improvements observed, and this physiological response is sensitive to the training modality (46). However, as the duration (weeks) of exercise training is extended to 6 wk and beyond, there is a very modest (9, 10) or no significant relationship (47, 61, 92) between baseline  $\dot{V}O_{2\max}$  and the improvement in  $\dot{V}O_{2\max}$  observed with endurance training. In older female subjects that undertook low-intensity, low-volume training, the incidence of nonresponders was much higher than typically observed and did reflect baseline fitness (81), suggesting that a minimum training stimulus is required to study the full potential of an individual’s aerobic-capacity system. Notably, the molecular markers that discriminate high responders from low responders do so regardless of whether those subjects undergo intensive interval training for 10 wk, moderately intense constant-load cycling for 6 wk, or 20 wk of incrementally load-adjusted moderately intense aerobic cycling (92). Maximal aerobic capacity is claimed to be limited by maximal delivery of oxygen to the periphery, and hence by cardiac function (78), at least in young muscular and physically active males. However, as baseline aerobic capacity neither positively nor negatively associates with the gains in exercise training-induced maximal aerobic power, and strength training can sometimes promote an improved  $\dot{V}O_{2\max}$ , when endurance training does not (46), it is more likely that  $\dot{V}O_{2\max}$  in sedentary adults is a capacity determined by the integration of multiple physiological systems, including macro and micro

cardiovascular function and skeletal muscle aerobic characteristics.

Regardless of which physiological systems “limit”  $\dot{V}O_{2\max}$  in vivo, insight into the molecular mechanisms determining training adaptation can still be obtained by studying skeletal muscle gene expression (54, 92). This idea has understandably caused a degree of confusion. The reason that this is possible reflects the fact that studying muscle gene expression provides a “window” into the regulation of an individual’s genome, quantifying responses to a variety of physiological stimuli, responses that will partly reflect variations in gene sequence, variations that will be equally relevant in the vascular, cardiac, and lung tissues (where repeated tissue sampling is not possible). Thus I am going to discuss how muscle gene expression responses to exercise have produced insight into the molecular basis for the heterogeneous training responses in human maximal aerobic capacity. The first examples are based on the candidate gene approach, a popular approach to link molecules to exercise-induced adaptation in aerobic function. For example, peroxisome proliferator-activated receptor  $\gamma$  coactivator 1 (PGC-1 $\alpha$ ) (60) and AMPK (51) are considered two major candidates for regulating skeletal muscle phenotype responses to endurance training (71) and have been extensively studied in both humans and mice.

Overexpression of PGC-1 $\alpha$  can modestly increase the percentage of slow-twitch fiber expression in mice (60) and was thus thought to influence insulin action on skeletal muscle as well as determining muscle endurance performance (41, 42). PGC-1 $\alpha$  was even thought to be specifically downregulated in the skeletal muscle of Type II diabetic patients (68), thus explaining insulin resistance. While this could have been due to physical inactivity (94), it is likely the finding was a reflection of the investigators utilizing biopsy samples following, and not before, a pharmacological hyperinsulinemic clamp (see 30). Indeed, PGC-1 $\alpha$  overexpression in skeletal muscle has yielded animals that are more prone to diet-induced insulin resistance (21) while the PGC-1 $\alpha$  knockout mouse can respond to endurance training and upregulate components of the mitochondrial proteome and improve their aerobic capacity (58). PGC-1 $\alpha$  therefore provides an excellent example of genetic redundancy, where PGC-1 $\alpha$  is able to regulate oxidative metabolism in simple cell models, yet when “deleted” in vivo compensation occurs by yet to be determined factors. Indeed, single-gene knockout murine models are not informative about complex polygenic in vivo human phenotypes, indeed a potentially self-evident point, and yet expenditure on manipulating single genes in mice for the benefit of understanding common human disease has never been greater, a genuinely worrying trend.

AMPK has been postulated as the key energy sensor during exercise, whereby alterations in [AMP] would activate AMPK, and AMPK would enact downstream transcriptional events that occur following exercise (51). Why, in response to an “energy crisis,” AMPK switches on lipid oxidation (by reducing malonyl-CoA inhibition of CPT1) in favor of the more economical fuel, carbohydrate, has been ignored and seems completely at odds with AMPK’s supposed “energy sensor” role. Ironically, during aerobic muscle contraction [AMP] is stable and only during reduced blood flow (97) or high-intensity contraction (38) do AMP levels change measurably, suggesting that during moderately intense aerobic exercise, AMP has little to do with AMPK activation. AMPK is claimed to regulate substrate

uptake and oxidation during muscle contraction; however, when genetically ablated, muscle glucose uptake during exercise is unaltered (64). Further, neither knockout of the  $\alpha 2$ -AMPK subunit or the  $\alpha 1$ -AMPK subunit alters the gene expression response to endurance running in mice (52), and the various knockout models have yielded marginal phenotypes completely inconsistent with the presentation that AMPK is a master regulator of skeletal muscle phenotype (44). Compellingly, no evidence has been presented that subject-to-subject variability in either PGC-1 $\alpha$  or AMPK activation correlates with muscle adaptation, raising the question as to why such focus has been placed on these molecules by the exercise physiology community over the last decade. Importantly, there are also no reproducible genetic associations between either PGC-1 $\alpha$  or AMPK sequence variation and gains in aerobic capacity or muscle metabolic capacity changes with endurance training (12).

An alternative to the candidate gene approach is to use genomic screening technologies that capture expression data for a large proportion of the genome and use informatics and robust statistics to link molecules to physiological change. Microarray technologies hold many advantages over qPCR especially regarding data normalization and statistical modeling of gene networks. For example, we recently demonstrated that the training-induced improvements in  $\dot{V}O_{2\max}$  following either intensive interval training for 10 wk, moderately intense constant-load cycling for 6 wk, or 20 wk of incrementally tailored aerobic cycling could be predicted by the preexercise resting muscle expression profile of 29 genes, or a number of genetic variants in a subgroup of the same genes. This was not a simple correlation but was a genuine blind prediction of training response across independent data sets. It was also particularly striking that the improvement in  $\dot{V}O_{2\max}$  was not at all related to the improvement in endurance performance (100), and this was also the case for males in the study by Lortie et al. (61), while for female subjects a modest relationship was found (61). It is therefore likely that the molecular responses that underpin improvements in aerobic exercise performance and aerobic exercise capacity are distinct.

For gains in  $\dot{V}O_{2\max}$ , do the 29 genes that make up the molecular “predictor” (pretraining) (92) shed any light on the molecular networks that determine cardiorespiratory and muscle aerobic capacity adaptation? The first notable point is that most of the 29 genes are not regulated (up or down) by exercise, while they form a network of interacting genes (based on literature data) that is described as being “developmental” in nature. There are some obvious members of this extended network that are known to be involved in cardiovascular adaptation. For example, *ID3* is a *TGF $\beta$ 1*- and superoxide-regulated gene, which interacts (70) with another “predictor gene,” Kruppel Like Factor 4, and is involved with angiogenesis (63). TGF- $\beta$  signaling also plays a central role in tissue remodeling. These molecules provide a link between aerobic capacity and developmental processes (33, 99), and it is plausible that the level of expression of the 29 genes is preset before birth. The broader network, connected to the 29 genes, was also populated by IGF2 and a number of interleukins, including IL-15, IL-32, and IL-8, but not IL-6 (92), and these may represent local endocrine signals between the myocytes, extracellular matrix, and vascular cells. The predictor genes also, based again on literature, appear to influence the expres-

sion of many of the genes more regulated by exercise in high-responder subjects (54).

However, to focus on the individual genes and their known biochemical functions is to partly miss the point. In genetic epidemiology too much importance has been placed on knowing the “function” of an individual gene and assessing how plausible it is for that function to be associated with the physiological or disease trait being studied, to judge the validity of an association. Such thinking makes two major assumptions: first, that we have sufficient knowledge to accurately define the biochemical repertoire of a given protein or functional RNA and, second, that the function of a protein or RNA can be defined without consideration of the context (e.g., gene network) it operates within, in a given tissue or cell. Thus further studies, looking at the simultaneous role of these 29 genes, in the various organ systems that can contribute to aerobic capacity in vivo will be required to understand in detail how they are able to predict the plasticity of the oxygen transport/consumption system in humans. Given that they are themselves not regulated (in muscle tissue at least) by exercise training, it may be their ability to either influence or inform about other “connected” genes that explains their predictive power. With that point in mind we have demonstrated that subjects who demonstrate a large increase in  $\dot{V}O_{2\max}$  also have a unique muscle transcriptional response 24 h following their last endurance exercise training session (91–93). In this particular study, cycle workload was held constant during the 6 wk of aerobic training, which meant that the highest responders actually had the least “relative” training intensity by the final week of training. Despite this, high responders were still characterized by a much larger gene expression response than low or nonresponders. In fact, ~800 mRNAs were differentially expressed in the training cohort as a whole, while at least 100 of these were more regulated in the high responders than the low responders (92).

Gene ontology analysis (1) of the regulated genes indicated that modulation of extracellular matrix, MHC, and calcium signaling genes were the transducers of aerobic adaptation in humans (92). Such genes, including integrins, appear to connect mechanical work to muscle tissue adaptation during endurance training. Analysis also indicated that calcium-regulated protein modulation, including the regulation of calcineurin, was a promising mechanism connecting endurance training and aerobic adaptation (19, 20, 72). The analysis of the human dataset is somewhat consistent therefore with the constitutively active calcineurin murine model. In that model, there is a switch of fiber type from fast to slow, a process that can be opposed by the administration of cyclosporin (CsA) (72) as well as the induction of mitochondrial gene expression. While the shift in the myosin heavy chain proteins is not relevant as this does not occur in humans (50), the accompanying metabolic adaptations represent a common feature of human muscle remodeling following endurance training (34). Indeed, using gene-set enrichment analysis (84) we have shown that the mitochondrial related gene family (~400 genes in this case) is the most regulated gene family in human skeletal muscle with endurance training (92), despite the fact that most only change by 15–20% in abundance. The link between calcium signaling (and CaMKII in particular) and molecular remodeling in response to endurance exercise is further supported by other observations (82), including human skeletal muscle studies



(66), as well as by informatic analysis in our lab (92, 93). Interestingly, high responders for  $\dot{V}O_{2\max}$  do not demonstrate a greater mitochondrial gene expression response than low responders. Furthermore, there is no relationship between changes in muscle energy metabolism during training and the magnitude of the improvement in  $\dot{V}O_{2\max}$  (100). These observations suggest that molecules regulated acutely by exercise are not regulating the aerobic capacity adaptive process. Rather, modulation of these molecules reflects short-term energy homeostasis within the muscle and/or deregulation of muscle molecular phenotype when the cell is exposed to an acute energy "crisis."

Thus, based on the available human data, aerobic capacity is an important predictor of human health (6, 7, 40, 55, 69); improvements in aerobic capacity can be predicted from the expression level of a group of non-exercise-responsive genes (in muscle) and that the molecular processes stimulated in the high responders (for aerobic capacity) involve calcium signaling, extracellular matrix signaling, and promotion of angiogenesis (91, 92). In contrast, improvements in aerobic performance relate more to alterations in muscle energy metabolism (100) and it would be expected that the genes that control the variable training-induced improvements in performance will be distinct from those that control the health-related gains in aerobic capacity. That is, it is a mistake to assume both of these parameters are always directly coupled. There is evidence that mitochondrial-related genes and metabolic control influence exercise performance. In fact, the only credible, non-training-related strategy, for improving human performance is manipulation of muscle energy metabolism, directly (15, 17, 35, 36, 87, 89, 90, 95, 96) and through enhanced oxygen delivery in the elite athlete or patient situation (31). Exercise performance improvements following endurance training are therefore plausibly linked to enhanced mitochondrial function, especially to modulation of energy metabolism during the rest-to-work transition period (95). Under these conditions the reduction in lactate production and phosphocreatine degradation are the "biomarkers" of improved mitochondrial function (100) and need not causally be related to the molecular basis for fatigue.

A survey of the genetic evidence for linkage between variation in energy metabolism genes and DNA sequence variation provides some interesting preliminary support for an important link (62). Eynon et al. (27) took the logical approach of examining a polygenic mitochondrial-related "gene profile" and its association with aerobic performance. They found that a combination of polymorphisms in NRF2, PGC-1 $\alpha$ , and PPAR $\alpha$ , assessed by a scaled combinatorial scoring system, associated with the attainment of a better record of competitive endurance performance. However, it is critical to emphasize that pure genetic association studies, examining the relationship between genetic variants and human performance, have been underpowered and few if any yield associations that have been universally replicated (12) while many negative studies will be missing from the literature, creating publication bias. For example, for the ACE gene insertion/deletion genotype (I/I, I/D, and D/D), medium-duration aerobic endurance performance is claimed to improve to a greater extent in those carrying the I/I genotype (16). Rather than figure out the connection between the ACE gene I/I genotype and, for example, metabolic control, it is more productive to put this observation into context. There have been over 60 articles examin-

ing the link between the ACE gene and human fitness and performance, and currently it is not possible to draw any conclusions as to the involvement of the ACE gene in human exercise capacity (12). Indeed, without numerous large (5,000 subject) intervention studies and/or the application of novel genomic strategies (92), information from genetic association studies will continue to be largely unreliable and insufficiently replicated in independent laboratories. For the time being, candidate molecules that demonstrate a heterogeneous response to acute exercise, rather than a consistent response, are more likely to represent genuine regulators of metabolic adaptation in human skeletal muscle and hence partly determine improvements in aerobic performance.

#### MUSCLE HYPERTROPHY AND STRENGTH

Gains in skeletal muscle mass with resistance training are also highly variable between individuals (5, 49), from no change to ~60% increases in muscle size. There are a number of factors that might affect the hypertrophic response, including nutritional support and genetic variation, and a few individual genetic polymorphisms have been identified that may explain a small degree of variability in the resistance training-induced hypertrophic or strength gain phenotype (22, 49, 73). Muscle hypertrophy, like the response of muscle to endurance training, is regulated by a complex series of partially redundant signaling molecules (23), including the mTORC1 complex. Molecular responses to acute resistance exercise appear to originate from cues within the muscle tissue (rather than in response to circulating factors) (101), and at some stage muscle hypertrophy is potentially limited by the availability of muscle satellite cells (74). What in turn determines a variable density of satellite cells, or a variable ability for them to proliferate and integrate in vivo, is unclear but could involve RNA as well as protein factors.

Non-protein-coding RNA has emerged in recent years (88) as being of relevance to skeletal muscle biology (30, 79). In particular, microRNAs (miRNAs) are accepted regulators of mammalian cell phenotype (4, 39, 80). miRNAs are ~22-nucleotide posttranscriptional regulators of gene product abundance able to block the translation of protein-coding genes (59). miRNAs regulate development and differentiation (26, 76), and brain and skeletal muscle tissue have the most tissue-specific miRNA species (57). miRNAs have also been implicated in the regulation of metabolism (25, 26), muscle disorders (24, 28), and recently insulin resistance in Type II diabetes (30). In vivo in humans miRNAs may impact on protein synthesis rather than mRNA stability (30) where they can be considered regulators of muscle protein expression. miRNAs are plausible candidate molecules for contributing to heterogeneous muscle hypertrophy because they have been shown to influence skeletal muscle satellite cell proliferation and differentiation. Indeed, recent data from our laboratory, in collaboration with Stuart Phillips, indicate that several highly expressed miRNAs are selectively regulated in subjects that represent the lowest 20% of responders in a longitudinal resistance training intervention study (45). Clearly this represents a fruitful area for further investigations and clearly genetic variance located in noncoding DNA regions will now be critical to map out.

Gains in muscle size and strength also reflect the capacity to form new myofibrils. Within the preexisting muscle, phosphorylation of the mTORC1 complex yields a signal transduction event resulting in ribosomal S6 kinase 1 (S6K1) and eukaryotic initiation factor 4E (eIF4E) binding protein phosphorylation ultimately leading to enhanced protein synthesis through reduced inhibition of eIF4E. Direct inhibition of mTORC1 signaling in humans blocks the mixed-muscle protein synthesis induced by acute high-intensity fatiguing muscle contractions (23). This acute intervention data would imply that genes regulating translation initiation signaling determine (or regulate) progressive skeletal muscle hypertrophy in response to resistance training. Variation in the hypertrophy derived from supervised strength training in humans (5) allowed Mayhew and colleagues (65) to explore the causal relationship between acute mTORC1 signaling and the gains in muscle mass observed after 16 wk of resistance training. Both protein synthesis and mTORC1-related signaling are elevated 24 h post acute resistance exercise and regulation of S6K1 was found to correlate with increased myofibrillar size after 16 wk of training (65) via prolonged autoinhibitory domain silencing. However, protein synthesis measured in response to an acute bout of unaccustomed exercise does not always agree with activation of the proposed causal signaling molecules and indeed acute synthesis was not predictive of chronic hypertrophy responses in a subset of subjects (65). This is somewhat analogous with the observations above, whereby short-term gains in  $\dot{V}O_{2\max}$  do not relate to the same parameters as longer-term changes.

Likewise, muscle anabolic responses to alternative stimuli, namely infused insulin and amino acids, do not relate in a linear manner to activation of mTORC1-regulated molecules (37) demonstrating that regulation of protein synthesis (and in this study also protein breakdown) is distributed across further unknown pathways. This is analogous to the observation that anabolic stimuli and hypertrophy of existing muscle fibers eventually appear limited by the further incorporation of nuclei from satellite cells (74), i.e., factors beyond the preexisting fibers add a new layer of regulation when one point of limitation is exceeded. Interactions between muscle protein metabolism and endurance exercise and cardiovascular conditioning exemplify additional considerations for potentially relevant genes. For example, insulin's ability to regulate muscle protein synthesis and mTORC1-related signaling appears dependent on an intact vascular response to insulin, and thus a bout of endurance exercise can overcome aged-related "insulin resistance" where insulin resistance is defined as impaired protein synthesis (rather than impaired glucose uptake) (29). It is also true that in the existing genetic association studies (12) there is some overlap between candidate genes for aerobic and strength phenotypes, suggesting that the idea that these two muscle traits are at either end of a molecular spectrum may be rather too simplistic (2, 48, 83). In fact, as will be briefly discussed below, the interaction between any two bouts of exercise may alter the molecular response observed to the initial period of contraction, and this may reflect the fact that the "recovery period" is also altered in nature or duration, and thus interactions are not really reflecting the differing physiological load.

In support of the idea that mechanical loading of human skeletal muscle, within the diversity experienced during voluntary exercise, will activate a number of overlapping path-

ways (which are not easily segregated into strength or endurance in nature) is the recent work by the Gibala laboratory (13, 14, 32). Here, high-intensity, short-duration sprint training yields endurance and metabolic adaptations synonymous with classic endurance training (3, 100). Likewise, as mentioned above, under certain circumstances strength training is more effective at improving  $\dot{V}O_{2\max}$  in an individual than a similar duration of aerobic training (46) presumably because some sedentary subjects have poor muscle conditioning limiting test performance and hence the strength training protocol has a more rapid impact on improving this factor. These data represent the only crossover-designed study that I am aware of. In a resistance training intervention study ( $n = 153$ ) Riechman et al. found that a polymorphism in the gene for interleukin 15 receptor explained a relatively large proportion of the variation in muscle hypertrophy (77). A similar association between IL-15 and muscle hypertrophy has also been recently reported in 748 subjects (75). Both studies are small for a genetic association study and would benefit from further replication. Intriguingly, IL-15 was also connected to the gene network that predicted variation in aerobic capacity changes to endurance training (92). This exemplifies the idea that "trainability" genes could in fact be defined as tissue or organ plasticity genes, and they should probably not be defined by the physiological stimuli they are first associated with.

## CONCLUSIONS

There are several preliminary conclusions that can be made. First, in the hunt for greater understanding of the molecular basis for skeletal muscle adaptation in humans, subject-to-subject variability is a very powerful aid to discovery. Second, it will become more and more apparent that the search for "single gene master regulators" of physiological adaptation is futile; genes work in complex, nonlinear, redundant networks, and thus we need to take a fresh approach to molecular physiology. Third, when considering the molecular basis and signals that regulate skeletal muscle adaptation to physical activity, it is too simplistic to consider that the strength and endurance phenotypes are placed at opposing ends of a molecular spectrum, at least in the context of voluntary human muscle activation. Probably the single most important philosophical question to raise at this point is why, given our apparent recent heritage as an "active" hunter gatherer (18, 56), do we have a significant number of humans unable to mount a strong physiological adaptive response to physical activity? Is it the case that for some subjects we provide an inappropriate pattern of stimulus for their particular genotype? We are far away from a scientific basis for tailored exercise prescription for the general public, and recent studies examining muscle adaptation using different intervals of recovery (43, 102) have not reproducibly demonstrated greater adaptation occurs with extended recovery, even though distinct molecular responses have been noted (43, 102). Likewise the genes that predict aerobic capacity changes with endurance training appear independent of duration and cycling intensity (92), at least above a certain minimum threshold. If one considers the idea that within the range of voluntary muscle contractions possible, the gene networks that are important for both endurance and strength adaptation will demonstrate significant overlap because they are "muscle plasticity networks," then there comes

a point when mounting a high protein synthesis response to any type of exercise (as we assume high responders do), from an energetic perspective, offsets the advantage of gaining a higher physiological capacity. There is in essence a cost for everything in life, yet without greater insight into the actual environmental conditions that shaped our genome, or how rapid genomic and epigenomic evolution really are, providing an explanation for the clear existence of physiological nonresponders is challenging.

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#### DISCLOSURES

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