REVIEW
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The Importance of Resistance Exercise Training to Combat Neuromuscular Aging

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Older adults undergoing age-related decrements in muscle health can benefit substantially from resistance exercise training, a potent stimulus for whole muscle and myofiber hypertrophy, neuromuscular performance gains, and improved functional mobility. With the use of advancing technologies, research continues to elucidate the mechanisms of and heterogeneity in adaptations to resistance exercise training beyond differences in exercise prescription. This review highlights the current knowledge in these areas and emphasizes knowledge gaps that require future attention of the field.

Introduction

Skeletal muscle is a highly adaptable tissue that comprises ~30–40% of total body mass and is remarkably compromised by aging (74). Declines in muscle mass approach nearly 10% per decade and are accelerated with advancing age (51, 87, 88). Muscle-associated clinical pathologies, including sarcopenia and frailty, are more prevalent in individuals in the ninth decade of life (8, 102). Loss of muscle mass is particularly concerning, given its important roles in physiological processes including movement (92), metabolism (154), signaling (107), disease and infection resistance (25), independence (150), and quality of life (9). Furthermore, declines in muscle health have been associated with premature mortality among community-dwelling older adults (16). As a result, exercise training interventions that rescue muscle mass and function have enormous potential to improve the experience of aging and reduce the incidence of age-related conditions that deteriorate quality of life. Progressive resistance exercise training (RT) represents the most widely recognized strategy to combat age-related muscle atrophy and improve overall muscle health on multiple levels: *1*) muscle mass, *2*) neuromuscular performance (e.g., strength and power), and *3*) cellular and subcellular adaptations. The purpose of this review is to *1*) summarize the health benefits of RT in the aging neuromuscular system; *2*) overview known underlying mechanisms of RT adaptation in the older adult; *3*) outline an evidence-based RT prescription proven to promote these adaptations; and *4*) highlight key knowledge gaps ripe for future research.

Health Benefits of Resistance Exercise Training in the Aging Neuromuscular System

Muscle Mass

The etiology of age-related muscle atrophy is a multi-faceted degenerative process involving both atrophy of fast (type IIa and IIx) myofibers (78, 97, 108, 135) and a reduction in total myofiber number (85). RT is a potent hypertrophy stimulus for all myofiber types, particularly the type II fibers typically compromised by aging. With RT, older adults exhibit well-characterized shifts in myofiber type distribution (IIx to IIa shift) and concomitant myofiber hypertrophy across fiber types (preferential to type II myofibers) (13, 103, 142, 144). There is no definitive evidence of myofiber hyperplasia in adult humans (although we recognize current limitations in measurement tools). Furthermore, the limited evidence of hyperplasia in animal models is based on an extreme degree of physiological stress to induce myofiber splitting (148). Thus, to our knowledge, no human intervention can restore myofiber number: combating aging muscle atrophy with RT is likely fully dependent on the induction of myofiber hypertrophy. Still, many older adults respond to RT with myofiber hypertrophy sufficient to meet or exceed the type II myofiber size of sex-matched young adults (13, 78).

Neuromuscular Performance

Whereas muscle mass declines at a rate of ~1% per year, accompanying neuromuscular functional reductions (e.g., muscle strength and power) occur more rapidly (92). Longitudinal studies have demonstrated decreases in muscle strength of ~2–4% per year (54, 55), and another study found a reduction

of ~8–9% in muscle power over a 3-year period (132). Muscle power is the product of force and contractile velocity; thus age-related loss of muscle power is driven by reductions in the force-generating capacity of muscle, as well as slowing of the rate of force development (RFD) (93). Loss of muscle power is a strong predictor of physical impairment in older adults (26, 42, 98, 131). Contractile properties of single myofibers, when normalized for myofiber size, are not compromised with aging (55, 127, 130, 132), with some data suggesting that heightened fiber function may compensate for deficits at the whole muscle level (61). Although the notable reductions in lower extremity muscle power (27, 122, 130, 132) suggest that whole muscle atrophy is a major driver, muscle atrophy does not account for the entirety of power decline: relative muscle power (i.e., adjusted for muscle mass) is also reduced with advancing age (116, 121, 132, 135), suggesting that a neurological component is also involved. Indeed, older adults may have ~30–40% fewer motor units compared with young adults (76, 79, 108, 119–121), and there is evidence to suggest increased size of surviving motor units [as supported by electromyographic studies (95, 121, 141)] and motor unit remodeling via type I myofiber grouping (67, 77, 135). These findings combined suggest that neural activation of these larger type I motor units may play a role in reducing explosive force and thus power (89).

The effectiveness of RT in reversing age-related reductions in muscle function has been consistently demonstrated. A 25–35% increase in leg muscle strength, measured as one repetition maximum (1RM) (105, 106, 115, 144), and similar improvement in upper body strength (28, 46, 66, 124) occur in healthy older adults with at least 8–12 wk (28, 64, 105, 115, 144) of moderate to high-intensity RT (>70% 1RM) (13, 24, 33, 144). Interestingly, the increases in muscle strength and power with RT occur before and exceed the hypertrophic morphological response (34, 54). This is explained by the early physiological phase of neuroadaptation that normally follows the first weeks of training. These findings support the hypothesis that a main factor of muscle wasting is impaired neurological control—more so than an intrinsic inability of older muscle fibers to generate force—and confirm the effectiveness of RT to improve neuromuscular function in older adults. Moreover, an increase in lower extremity muscle power is accompanied by an improvement in balance (50, 69, 81, 82, 90) and reduced fall risk, which contributes to reduced mortality in older adults (43, 137).

The benefits of RT exceed improvements in skeletal muscle size and strength alone (FIGURE 1). Strength improvement and myofiber hypertrophy due to RT reduce the motor unit activation demand to perform a given submaximal movement, as we (115, 144) and others (71) have shown during a sit-to-stand task. The basis of this may be related to motor unit remodeling that accompanies sedentary aging as an apparent result of denervation-reinnervation events (67, 75, 77). Encouragingly, short-term RT appears to reverse this phenomenon, at least in those individuals with a higher degree of motor unit remodeling (76).

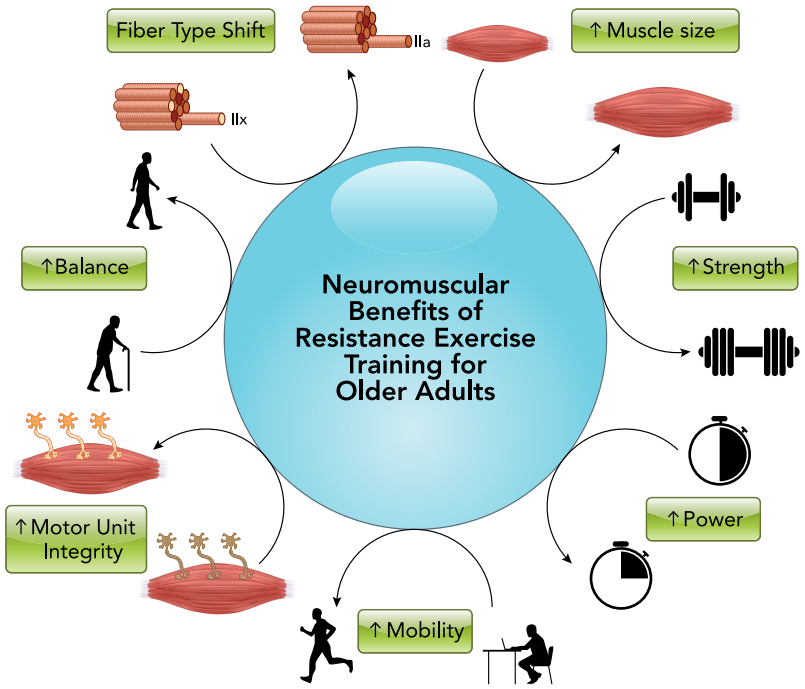

FIGURE 1. **Neuromuscular benefits for older adults undergoing resistance exercise training**
The neuromuscular benefits for older adults undergoing resistance exercise training (RT) extend beyond muscle mass and strength. For a summary of RT benefits on other organ systems, see text.

Mechanisms of Resistance Exercise Training Adaptation in the Older Adult

Muscle Protein Synthesis

Skeletal muscle mass is regulated by the fine balance between two cellular processes: protein synthesis and breakdown. A positive net balance is achieved when the rate of protein synthesis exceeds the rate of degradation. Several studies have found that muscle protein synthesis increases after an acute bout of RT (30, 31, 39, 56, 118), and the effect can last up to 48 h. However, more recent findings have also revealed that the acute response to exercise is not always predictive of a long-term adaptation (31, 101). Moreover, the magnitude of the response to RT is different between younger and older adults (40, 80), with aging affecting skeletal muscle tissue sensitivity to anabolic stimuli, such as physical activity and nutrition (104, 138).

Despite these caveats, chronic RT increases basal muscle protein synthesis in both young (133) and older adults (103), and this has been shown to correlate with increased skeletal muscle thickness (133) and myofiber cross-sectional area (CSA) (31). The perpetual repetition of training sessions stimulates the activation of the mechanistic target of rapamycin complex 1 (mTORC1), which directly promotes protein synthesis via phosphorylation of specific downstream effectors (S6K1, rpS6, eEF2, and 4EBP1). It is beyond the scope of this review to describe in detail the mechanisms that regulate hypertrophy through mTORC1; however, it is interesting to note that mTORC1 also plays a key role on ribosomal function and biogenesis (21), which are primary promoters of translational capacity. Recent studies have demonstrated that muscle levels of ribosomal RNAs (rRNAs) are highly elevated after resistance exercise in young subjects (49) but not in older adults (15, 143) and that basal levels of upstream mRNAs (ribosome regulators) are predictive of the myofiber hypertrophic response to RT (149). Furthermore, via cluster analysis, differential myofiber hypertrophy among older adults in response to short-term RT appears to be mediated at least in part by differential induction of ribosome biogenesis, enabling heightened capacity for protein synthesis (143).

Several studies have also shown that a single bout of RT can increase the muscle protein anabolic response to nutritional stimuli (17, 37, 41). Exercise, with an increased demand of blood flow and energy, increases the delivery of dietary nutrients and modulates the protein synthetic response to food ingestion (41, 111). Indeed, very old adults undergoing heavy RT benefitted further from the addition of a protein supplement, further highlighting the link between RT-induced demand and nutrient availability in aiding hypertrophy (10). However, it has been recently shown that regular RT increases basal muscle protein synthesis in healthy older adults but does not further improve the muscle protein anabolic response to amino acids (103).

Training also impacts muscle protein breakdown as a physiological response to the damage caused by muscular contraction. Protein breakdown increases following an acute bout of RT, and this response seems to be similar in young and older adults (57). Recently, Damas found that muscle protein breakdown is more pronounced in novice subjects, and this is reduced in favor of an enhanced protein synthetic response with subsequent training (29). These findings underpin the positive effect of RT on muscle repair and regeneration, leading to reinstatement and maintenance of muscle mass throughout life. Thus the primary effects of exercise on muscle protein balance, largely mediated through mTORC1 and ribosomal biogenesis, facilitate a shift to a positive net balance and lead to an increase in muscle mass.

Insights from Exercise -Omics

The recent advent of genome-wide and phenome-wide association studies (often termed the GWAS and PheWAS era) has created heightened potential for discovery, providing the opportunity to investigate all possible contributors to RT adaptations. The burgeoning -omics fields are interconnected through their influence on phenotype (FIGURE 2), as recently described in greater detail in the context of exercise physiology (14, 68, 157). These areas represent the new horizon for exercise biology, and the currently available literature has barely begun to scratch the surface of this enormous potential. The field as a whole will be able to leverage the amassed -omics data sets soon to be generated in the ground-breaking NIH Common Fund initiative, the Molecular Transducers of Physical Activity Consortium (MoTrPAC). Early explorations, along with studies targeted at investigating an isolated pathway or biological process, have provided considerable insight into potential mechanisms underlying RT adaptations in older adults. With the continual advancement of available technologies, studies are often not uniform with regard to the selected platform (e.g., targeted PCR to microarray to transcriptomics). However, these methodological differences (including disparities in exercise regimens, biopsy timing, etc.) present a strength, since several recurrent themes are still able to emerge, including mitochondrial health (96, 136), inflammation (128, 149), and regulation of protein metabolism (7, 117, 126, 136, 149).

A focal point of exercise and aging research has been the mechanistic investigation into response heterogeneity to exercise training in aging adults by comparing baseline muscle characteristics across a range of hypertrophic responses to resistance exercise. Targeted investigations into single nucleotide polymorphisms in inflammatory cytokines (35, 112) and upstream regulatory elements (112) have shed light on the potential impact of inflammation to blunt adaptive responses to RT (6, 97, 152). More comprehensive approaches using microarray (117, 149) elaborate on the impact of basal gene expression on the training response. For instance, we have found enormous differential gene expression (8,026 genes) between non-responders and extreme responders to RT, predominantly associated with regulation of transcription, muscle function and development, and inflammation (149). Another investigation found increased activity of the rapamycin pathway in individuals who responded best to RT training (117). Beyond this, microRNA (miRNA) abundances (32, 109, 155) and

transcript splice variants (156) have been implicated in contributing to the magnitude of RT adaptations, and additional regulatory mechanisms of gene expression (e.g., methylation, acetylation) are also likely involved.

Some studies have demonstrated limited plasticity to exercise training in older adults compared with young adults (59, 127, 139), and this may be the result of a generally less robust adaptive response in basal gene expression (128), gene silencing (via miRNA) (36, 134), and/or another yet unexplored facet of metabolism. Nonetheless, RT is more likely to reverse the expression of age-related genes than those unaffected by aging (96). Raue and colleagues provided early insight into the relationship between the exercise response and changes in gene expression, showing a basal increase in 144 genes after RT training in older women (128). In this study, two inflammation-related genes (TNFRSF12A and NFKBIA) demonstrated significant relationships with changes in skeletal muscle mass and strength throughout training. Likewise, studies have found relationships between RT-induced gains and changes in abundances of miRNAs (32, 134, 155), highlighting the dynamics of posttranscriptional gene expression regulation and interdependence of -omics tracks in adaptations to exercise. In a comparison across three modes of exercise, Robinson and colleagues found that RT increased basal expression of 33 unique genes, along with increased expression of angiogenic factors (e.g., targets of VEGFA) and growth signaling-associated genes across all training modes. In a concomitant proteomics analysis (136), the group found 185 proteins that increased in response to RT, mainly related to translation processes (e.g., tRNA aminoacylation) and ribosome function, highlighting the importance of enhanced translational capacity to support the heightened demands of RT.

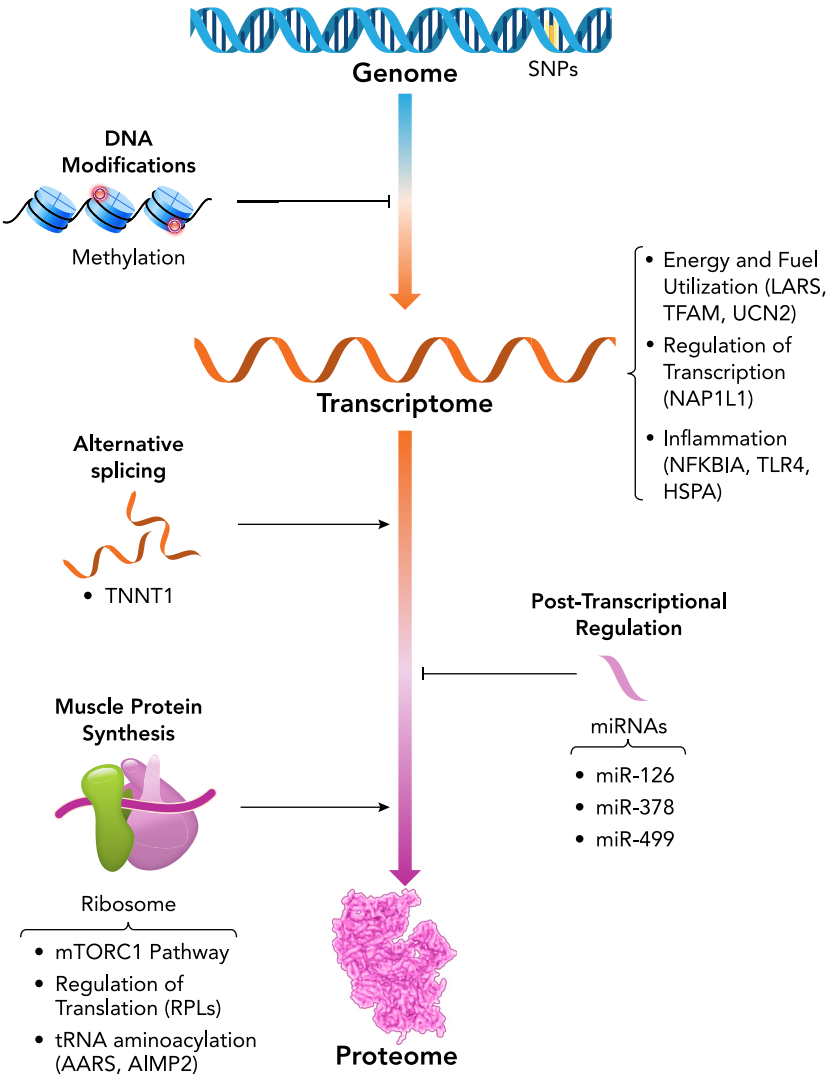

FIGURE 2. **Regulation of skeletal muscle gene expression and protein expression**
Regulation of skeletal muscle gene expression and, ultimately, protein expression, occurs at multiple levels, influencing both baseline phenotype and responsiveness to an RT. Molecular networks of interest, based on current knowledge (32, 36, 117, 128, 134, 136, 149, 155, 156), are highlighted in this diagram and provided in context in the text.

Resistance Training Prescription for the Older Adult

Exercise dosage underlies all potential physiological benefits of RT. Most RT intervention studies have only used one or two training doses, which provides little insight into a dose-response relationship. To our knowledge, only one study has employed four doses (144) in an attempt to titrate the optimal exercise regimen. Nevertheless, a collective agreement in the field is that progressively overloading the muscle through RT is necessary to create continuous adaptations (2). When familiarization to proper exercise technique and structured progression are components of the study design, RT is safe and effective for older adults, with rates of injuries extremely low and similar across all ages and intensities (48, 52). Furthermore, adherence and dropout rates do not differ by training intensity (129), but adherence may be slightly higher on a lower-frequency regimen (144). It is important to note that, even within a given prescription, response heterogeneity is still evident; thus the truly optimal exercise dose is likely variable by individual.

Frequency, Intensity, and Volume

Training dose is dependent on several factors, including number of sets and repetitions, frequency, and intensity. Each of these components is an important consideration in designing an RT regimen. For example, total weekly volume is equal in the

following two scenarios: *1*) 3 sets of 15 repetitions per set at a 45-kg load repeated 2 days/wk and *2*) 3 sets of 6 repetitionss per set at a 75-kg load repeated 3 days/wk. There is considerable variance across studies with regard to exercise programs, but the primary outcome of the study (e.g., hypertrophy, strength, functional mobility) likely dictates the optimal exercise prescription. Although the ACSM recommends that older adults participate in a minimum of two RT sessions per week (3), some researchers use a low frequency as a minimal effective dose (1 day/wk) to promote adaptations (38, 145), and others use a more aggressive approach to maximize changes (3 days/wk) (13, 45, 84, 86, 110). Several have found no difference across training frequencies for strength adaptations (19, 38, 145).

Frequency, however, is not the sole determinant of adaptation. In our recent four-arm, randomized dose-response RT trial among older adults, we noted substantially greater gains in total body lean mass, thigh muscle mass, and isometric strength when the 3 day/week prescription involved a lower intensity "light" day during the midweek session, as compared with high-intensity training all 3 days each week (144). This finding highlights that, in designing exercise prescriptions for older adults, recovery must be considered as carefully as intensity. However, there is no standardized definition of high, moderate, or low intensity in the literature. Two previous analyses have classified >70% 1RM as high intensity, 50–70% 1RM as moderate intensity, and <50% 1RM as low intensity (11, 129). High-intensity RT has been shown to improve lower body strength to a greater degree than moderate or lower intensity, if training volume is equivalent (129). High-intensity RT has also been shown to improve strength, anaerobic power, and mobility, and to increase bone mineral density more than low-intensity RT (47, 147). Outside of intensity, explosive training has also been an interest in the field due to its potential to maximize RFD, which could translate into better functional mobility and balance. One meta-analysis found that there was a similar effect between high-intensity strength training and explosive training (62), although gains in RFD and muscle strength did not always coincide.

Session volume (number of sets and repetitions per session) was found to be positively associated with lean body mass increases in a meta-analysis of 49 studies averaging 20 wk in duration (113). If intensity is held constant, short-term (6–10 wk) gains in muscle mass and strength are similar between high (3 sets) and low (1 set) session volume (18, 125), but a clear benefit appears for the higher session volume prescription by the 20th week of training (123). In a small, 20-wk study of community-dwelling older adults, a high session volume (3 sets vs. 1 set to failure) training program improved muscle strength, endurance, and 400-m walk time. However, both training programs improved functional movements (chair rise, 6-m backward walk, stair climb) and muscular endurance (58). These studies further support the well-accepted concept of progressive overload to continue to promote training adaptations over time (e.g., by manipulating session volume, frequency, and/or intensity).

Detraining

Following cessation of training, some evidence suggests older adults can maintain dynamic strength for several months (86). For example, after 24 wk of RT, only minor changes occurred with 3 wk of detraining, although improvements in walking speed remained elevated (63). Over longer periods, RT adaptations are gradually lost (83, 146). Maintenance of muscle strength and size can be preserved on a minimal dose (one set) after 12 wk of RT (151). In one study, both young and older adults were followed for 32 wk after 16 wk of 3 days/wk RT and were assigned to either no training, 1 day/wk at 1/3 the initial weekly exercise volume (3 sets), or 1 day/wk at 1/9 the initial weekly exercise volume (one set) (13). Without a maintenance dose, loss of RT-induced muscle mass gains was detected in both age groups after only 8 wk of detraining, whereas decrements in 1RM were not detected until 32 wk of detraining. The investigators also found that a maintenance dose of 1/3 or 1/9 the volume preserved strength in both age groups, but, among older adults, only the higher maintenance dose preserved the RT-induced increases in muscle mass, whereas young adults effectively preserved gains in mass on both doses (13). Exercise intensity may also play an important role in preventing detraining, with one study demonstrating that strength and mobility were preserved throughout 2 years of detraining following high-intensity RT (82% 1RM) but not after lower-intensity RT (55% 1RM) (47). Thus the minimal effective dose for increasing and then preserving muscle mass in older adults is likely a very manageable number of muscular contractions.

Response Heterogeneity

Although all individuals garner some degree of beneficial adaptations to RT, there is appreciable variability in responsiveness to RT when strictly defined as the magnitude of whole muscle or myofiber hypertrophy (1, 4, 23, 32, 44, 70) (FIGURE 3). One approach to classifying and studying response heterogeneity is to group responders using K-means clustering, a method introduced several decades ago (73) and first applied to exercise response heterogeneity in 2007 (7). We have

used this method to group subjects by myofiber hypertrophy after a training stimulus (7, 114, 149) and validated the method in subsequent trials (142, 144). Important considerations for clustering include exercise prescription (i.e., a given individual's response might be poor on a given RT prescription but very good on another) and baseline phenotype [i.e., individuals with poorer muscle mass at the outset may improve more by a regression to the mean phenomenon (22)]. A number of non-modifiable (e.g., sex, race, ethnicity, age, genotype) and modifiable (e.g., co-morbidities, functional capacity, diet, medications, sleep) factors may influence response heterogeneity, but each has yet to be fully explored. To our knowledge, no studies have demonstrated differences in response heterogeneity in response to RT as a direct influence of any of these factors in isolation. Once again, this highlights the potential impact of future GWAS-PheWAS applications to RT trials. Although the causes of response heterogeneity are not fully understood, strategies to attenuate the range of heterogeneity or reduce the number of non-responders may leverage optimization of exercise dose, nutrition, and possibly pharmaceutical adjuvants. For example, response heterogeneity to traditional 3 days/wk RT programs has been noted in older adults (142), but recent work using 2 days/wk of high-resistance concentric-eccentric training and 1 day/wk low-resistance, high-velocity, concentric-only training showed meaningful improvements in thigh muscle mass and myofiber CSA in a high proportion of older adult participants (144).

Another yet poorly understood component of variability in response to RT is an apparent result of advancing age. Although adults aged 60–75 yr still possess a robust, albeit attenuated, hypertrophic ability following 16 wk of RT (13, 78, 153), octogenarians and very old adults often display a limited or blunted hypertrophic capacity (59, 127, 139). Overall, although response heterogeneity presents a challenge for investigators, it also serves as an opportunity to explore its mechanistic basis, highlighting the importance of continued research into subcellular adaptations to exercise training.

Knowledge Gaps Ripe for Future Research

Mechanistic Knowledge Gaps

Discovery-oriented research may reveal previously unknown molecular transducers of adaptations to RT unique to the individual and perhaps common linkages among phenotypic groups (e.g., age, sex, disease status, or medication profile), creating opportunities to design prescriptions with greater precision. Numerous molecular mapping tools remain largely unexplored in the context of exercise

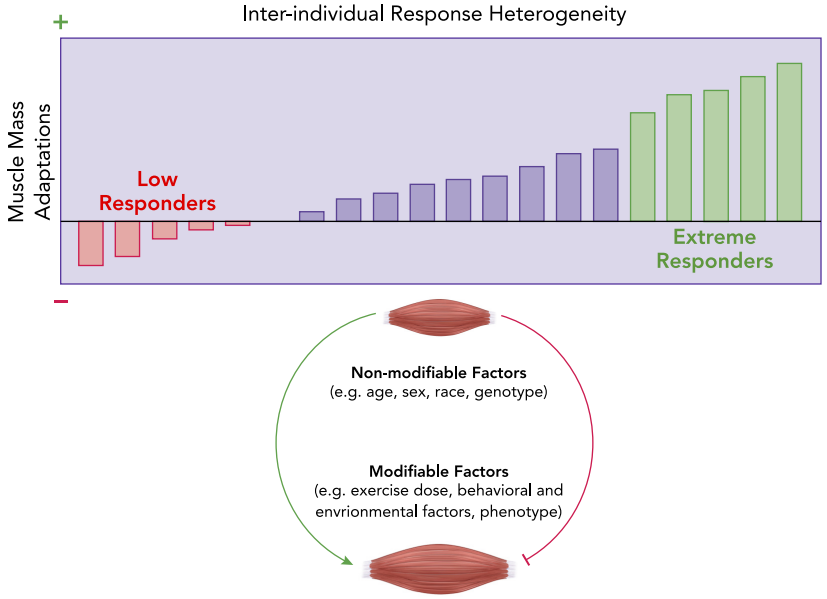

FIGURE 3. **Response heterogeneity to progressive resistance exercise training in older adults**
Potential causes of heterogeneity include both non-modifiable (e.g., age, sex, race, genotype) and modifiable (e.g., exercise dose, behavioral and environmental factors, phenotype) factors (5). Titrating the exercise dose has been effective in reducing the number of low responders (144).

in aging muscle, including but not limited to metabolomics, microbiomics, and ribosome biology. Still, the more commonly used platforms (e.g., RNA-Seq, miRNA-Seq) receive preferential attention in aerobic training study designs, leaving many questions to be answered through RT interventions. For example, the molecular basis of the range of adaptability to short-term RT remains incompletely understood. Examination of transient, exercise-induced changes in gene transcription, translation, and regulatory factors (e.g., methylation, histone modification, gene silencing, and alternative splicing) may provide insight into potential deficiencies in aging skeletal muscle in general or among individuals or subgroups that might be rescued by tailored exercise prescriptions with or without pharmaceutical adjuvant therapies.

Clinical Knowledge Gaps

The benefits of preserving muscle mass through RT during aging extend well beyond strength and power [e.g., heightened exercise tolerance (72); decreased difficulty in activities of daily living (65); enhanced cognition, memory, and mood (12, 91, 94); reduced disease susceptibility (25); improved surgical outcomes (53); and prolonged independence (150) and lifespan (140)], but several unknowns remain. Future studies should be designed to examine the benefits of long-term (i.e., lifelong) resistance exercise training, as has become a recent fascination in the endurance exercise and aging literature (20, 60, 99, 100). Since the popularity of RT as a structured exercise prescription is a

relatively recent phenomenon, lagging slightly behind the running boom and other aerobic training trends, individuals with a lifelong RT training background will soon begin to reach retirement age. It would provide considerable insight to investigate not only the skeletal muscle benefits but other health outcomes with lifelong RT. Short-term RT studies have previously demonstrated considerable success in inducing a range of non-muscle health benefits (12, 65, 72, 91, 94). It is attractive to speculate that lifelong RT may not only enhance the degree of these benefits but also prevent other age-related declines that show limited reversibility with short-term exercise training.

In addition to muscle- and performance-specific adaptations to long-term RT and acute responses to a single exposure, it is beneficial to continue to pursue an understanding of the behavioral determinants of participation in and adherence to an RT regimen. For example, aging athletes who are aerobically inclined may engage in RT to forestall overuse injuries, whereas others may be more motivated by non-muscle adaptations to RT (e.g., body composition changes, cognitive function, mobility difficulty, psychological well-being). Through continued pursuit into the molecular basis of RT adaptation, optimization of exercise prescription, and approaches to maximize awareness and adherence, we expect RT to strengthen its position as an effective tool for maximizing healthspan in the aging population. ■

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