THE AGING PROCESS IS ASSOCIATED with a progressive decline in motor function attributable largely to sarcopenia, an age-associated loss of muscle mass and strength that occurs to varying degrees in all individuals (2). Although sarcopenia is not classified as a disease, it is a major contributing factor to increased frailty and loss of mobility in older adults (3) and contributes to an increase in mortality (9). Skeletal muscle is a dynamic tissue, responsive to multiple signals including mechanical load, nutrition, neural activity, hormones, and growth factors. However, the capacity to respond to these growth cues declines with age. An inability to respond to increased loading, especially following periods of atrophy, could accelerate the progression of sarcopenia and contribute to the loss of functional mobility, independence, and the onset of frailty. Therefore, it is of tremendous importance that we understand how muscles of older individuals respond to load to initiate growth. The mechanisms responsible for the decrease in muscle function and growth response with age are poorly understood and are likely the result of alterations in multiple interacting pathways involved in the “growth response,” which include transcriptional activation/repression of specific genes, increases in protein translation initiation, alterations in protein degradation, activation/proliferation/differentiation of satellite cells, and increases in oxidative metabolism to support an increase in ATP demand.

In this issue of the *Journal of Applied Physiology*, Raue et al. (7a) specifically examined the transcriptional response of the vastus lateralis muscle of young and old individuals to acute resistance exercise in both the untrained and trained state and identified the set of genes that are both responsive to resistance exercise and correlated to gains in muscle size and strength. These genes were termed the “transcriptome signature of resistance exercise adaptations.” Although previous gene array studies have investigated the difference between the transcriptional response of whole muscle from young and old adults to either acute or chronic resistance training, none have examined both the untrained and trained response to resistance exercise in the same subjects (5, 11, 12). Furthermore, no aging studies have examined a population of men and women that are more than 80 years old. The significance of the present study was in the design, which allowed for examination of the acute transcriptional response in both untrained and trained muscle, in addition to allowing for an analysis of changes in the basal transcriptional state of young and old muscle to 12 wk of non-damaging resistance training, providing for one of the most comprehensive gene array datasets collected to date. One novel aspect of this study was that transcriptional profiling was performed on individual muscle fibers identified as either slow (MHC I) or fast (MHC IIa), allowing for a direct comparison between the whole muscle, which is composed of multiple cell types, and the single muscle fiber. This approach revealed that MHC IIa fibers in young adults are more responsive transcriptionally than MHC I fibers to the resistance training protocol used in this study. Of particular significance was the lack of transcriptional response in the MHC IIa fibers of old (63 genes) vs. young (463 genes) muscle, which correlates with the attenuated hypertrophy observed in MHC IIa fibers of older adults following resistance training (7, 10).

The study by Raue et al. (7a) could be considered as yet another gene array study that has produced lists of differentially expressed genes of unclear physiological importance. It is true that it is unclear which of the transcriptionally expressed genes or gene sets is most important for eliciting the proper growth response to resistance exercise. Furthermore, it is unclear as to what differentially expressed genes are important in the attenuated growth response in old compared with young muscle. However, a major strength of the present study is the fact that the gene sets have been correlated to a physiological response, i.e., hypertrophy, and that the design allows for the ability to make multiple comparisons such as (1) changes in baseline expression to training; (2) changes in the acute response of untrained and trained muscles; and, probably the most novel, (3) changes occurring in the whole muscle vs. changes in a single cell type, i.e., the muscle fiber. These types of comparisons have not been possible in previous studies and could reveal interesting new insights into the response of skeletal muscle to aging. For example, comparison of the acute (4 h postexercise) transcriptional response of untrained (1st training session) and trained (36th training session) muscle shows a significantly greater response in young (24 yr) vs. old (84 yr) adults. Interestingly, the numbers of genes responding to acute exercise in untrained vs. trained muscle decreases in young adults (1,165 vs. 644 genes) but stays fairly constant in the old adults (595 vs. 569). This suggests a lack of a training response in the older adults. However, if one looks at the basal response to progressive resistance training, i.e., the genes that changed expression in the basal state after 12 wk of training, one finds that a greater number of genes changed expression in the old (144) vs. the young (12) adults. This suggests that at least some cell types in old muscle are capable of adapting to resistance training.

One highlighted gene family was the NF-κB pathway, which is usually associated with inflammation, increased proteolysis, and muscle atrophy; however, in this study, the expression of several genes within the pathway, including TNFRSF12A (Fn14 or the TWEAK receptor), MAP3K14 (NF-κB inducible kinase, NIK), NFKBIA (IkBα), and USP2 (ubiquitin specific peptidase 2), were changed in response to resistance exercise in...
such a way as to suggest an increase in the NF-κB pathway at the level of the muscle fiber (6). Another interesting observation was that FOXO1 was positively correlated with resistance exercise and hypertrophy, whereas FOXO3a was negatively correlated to growth. Furthermore, MuRF1 increased after acute exercise in both young and old adults, whereas MAFbx/atrogen-1 increased only in the old adults. These genes are most often associated with atrophy and have thus been called “atrogenes”(4). These findings call into question the use of the term atrogenes, because upregulation of these genes and pathways could be associated with remodeling and not necessarily a prelude to atrophy.

The study by Raue et al. (7a) is not the first to use gene arrays to study the differential transcriptional response of skeletal muscle from young and old adults to resistance training (5, 8, 11). Furthermore, the attenuation of growth in response to increased loading in older adults is in all likelihood not solely the result of changes in transcription but also involves alterations in cell signaling and protein translation. The present study, however, is noteworthy because it provides a unique and comprehensive microarray dataset on human muscle from octogenarians who have been shown to have an attenuated adaptation to resistance exercise (10). As with previous studies, this dataset represents a single time point; however, the choice of 4 h postexercise has captured a greater number of transcriptional changes associated with resistance exercise compared with previous studies that sampled later time points (8, 11). Furthermore, the present study is more comprehensive than most in that it examined both the acute transcriptional response to nondamaging resistance exercise and the response to progressive exercise training at both the whole muscle and single fiber level. This study does not answer the question of “why is growth in response to resistance exercise attenuated in older adults,” however, it does show that the transcriptional response to resistance exercise at both the whole muscle and single fiber level is significantly altered in older adults and provides insights into additional pathways that should be further examined. This study makes a significant and novel contribution to our understanding of the growth-associated transcriptional response of skeletal muscle to resistance exercise in both young and old adults.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES