The Elderly Muscle

Researchers untangle the multifarious nature of muscle aging. So far, the only reliable treatment is exercise.

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To you readers over age 30, we've got some bad news for you. Chances are good you've already begun losing muscle. And it only gets worse. Up to a quarter of adults over the age of 60 and half of those over 80 have thinner arms and legs than they did in their youth.

In 1988, Tufts University's Irwin Rosenberg coined the term "sarcopenia" from Greek roots to describe this age-related lack (*penia*) of flesh (*sarx*). Muscle aging likely has several underlying factors, including decreased numbers of muscle stem cells, mitochondrial dysfunction, a decline in protein quality and turnover, and hormonal deregulation. Loss of muscle mass is associated with—and possibly preceded by—muscle weakness, which can make carrying out daily activities, such as climbing stairs or even getting up from a chair, difficult for many seniors. This can lead to inactivity, which itself leads to muscle loss at any age. Thus, older people can enter a vicious cycle that will eventually lead to an increased risk of falls, a loss of independence, and even premature death.

The good news is that exercise can stave off and even reverse muscle loss and weakness. Recent research has demonstrated that physical activity can promote mitochondrial health, increase protein turnover, and restore levels of signaling molecules involved in muscle function. But while scientists know a lot about what goes wrong in aging, and know that exercise can slow the inevitable, the details of this relationship are just starting to come into focus.

The role of muscle stem cells

Skeletal muscle consists of multinucleated fibers formed by the fusion of muscle precursor cells, or myoblasts, during embryonic and fetal development and postnatally until the tissue reaches its adult size. Mature fibers are post-mitotic, meaning they do not divide anymore. As a result, in adulthood both muscle growth and repair are made possible only by the presence of muscle stem cells.

In 1961, Rockefeller University biophysicist Alexander Mauro, using electron microscopy, first described muscle stem cells, calling them "satellite cells" because of their position at the periphery of the muscle fiber.[1] Subsequently, researchers have demonstrated that satellite cells are the only cells able to repair muscle—which explains why recovery from muscle injuries among the elderly is slow and often incomplete: the number of satellite cells falls from 8 percent of total muscle nuclei in young adults to just 0.8 percent after about 70 to 75 years of age.

Of course, a decline of the satellite cells' ability to divide and repair could also be to blame, but research does not support this idea. In pioneering studies carried out in 1989, biologists Heather Carlson and John Faulkner at the University of Michigan showed that muscle iso-

lated from a two-year-old rat was repaired faster and better when grafted into two- to three-month-old rats.[2] More recently, we isolated these cells from young and old adults and were surprised to find that elderly human satellite cells grew in culture as well as those from young subjects did.[3] So it seems that declining function of satellite cells is not the problem; there are just fewer of them in muscle to do the job of repair and growth.

The elderly human satellite cells we examined did, however, show dramatic changes in their epigenetic fingerprint, with the repression of many genes by DNA methylation. One gene, called *sprouty 1*, is known to be an important regulator of cell quiescence. Reduced *sprouty 1* expression can limit satellite cell self-renewal and may partially explain the progressive decline in the number of satellite cells observed in human muscles during aging. Indeed, stimulation of *sprouty 1* expression prevents age-related loss of satellite cells and counteracts age-related degeneration of neuromuscular junctions in mice.[4]

Mitochondrial contributors

Other likely culprits of muscle aging are the mitochondria, the powerhouses of muscle. To work efficiently, skeletal muscle needs a sufficient number of fully functional mitochondria. These organelles represent around 5 percent to 12 percent of the volume of human muscle fibers, depending on activity and muscle specialization (fast-twitch versus slow-twitch). And research suggests that abnormalities in mitochondrial morphology, number, and function are closely related to the loss of muscle mass observed in the elderly.

In 2013, David Glass of Novartis and colleagues found that markers of mitochondrial metabolism pathways were significantly downregulated as rats aged, and this correlated with the onset of sarcopenia.[5] Although the findings are merely correlative, the timing and near-perfect relationship between decline in mitochondrial gene expression and the onset of sarcopenia provides strong evidence that mitochondrial dysfunction may be driving sarcopenia. The expression of genes and production of proteins that regulate mitochondrial fission and fusion—processes that maintain mitochondrial volume and function—also dropped, suggesting that mitochondrial dynamics are also perturbed during muscle aging.

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As with muscle stem cell decline, the underlying cause of poor mitochondrial health may be gene regulation. In 2016, Alice Pannérec and her colleagues from Nestlé Institute of Health Sciences and Manchester Metropolitan University in the UK examined the transcriptomes of rat and human muscle and found that susceptibility to sarcopenia in both species was closely linked to deregulation of gene networks involved in mitochondrial processes, regulation of the extracellular matrix, and fibrosis, the formation of excess connective tissue in a muscle caused by the accumulation of extracellular matrix proteins.[6]

Protein quality control

Even if they eat plenty of protein, older people often cannot maintain muscle mass, probably because their bodies cannot turn proteins into muscle fast enough to keep up with the natural rate of the tissue's breakdown. Moreover, the muscles of older people undergo lower levels of autophagy, a process that under healthy conditions recycles used and damaged proteins, organelles, and other cell structures. (See "Eat Yourself to Live: Autophagy's Role in Health and Disease," *The Scientist*, March 2018.) This can result in an imbalance between protein production and degradation that is likely linked to muscle aging.

There may also be other ways that reduced autophagy may contribute to both muscle loss and muscle weakness during aging. In order to maintain muscle strength, muscle cells must get rid of the intracellular garbage that accumulates over time. In the case of muscle cells, this garbage includes old organelles such as mitochondria and endoplasmic reticuli, clumps of damaged proteins, and free radicals, all of which can become cytotoxic over time. By recycling mitochondria, muscle fibers boost energy production and preserve muscle function. If muscle fibers fail to clear these potentially dangerous entities, they will become smaller and weaker. Sure enough, in a study from Marco Sandri's group at the University of Padova in Italy, mice whose skeletal muscles lacked one of the main genes that controls autophagy, *Atg7*, had profound muscle loss and age-dependant muscle weakness.[7]

Blood signals

In 2005, Stanford University stem cell biologist Thomas Rando and colleagues combined the circulation of young and old mice and found that factors in the blood of young mice were able to rejuvenate muscle repair in aged mice. (See "How old cells can regain youth," *The Scientist*, February 17, 2005.) It is now well known that the levels of circulating hormones and growth factors drastically decrease with age and that this has an effect on muscle aging. Indeed, hormone replacement therapy can efficiently reverse muscle aging, in part by activating pathways involved in protein synthesis.

Moreover, the muscle itself is a secretory endocrine organ. Proteins produced by the muscle when it contracts flow into the blood, either on their own or encased in membrane-bound vesicles that protect them from degradation by circulating enzymes. Bente Pedersen of the Centre of Inflammation and Metabolism and Centre for Physical Activity Research in Denmark was the first to use the term myokine to describe these proteins. Secreted myokines can act locally on muscle cells or other types of cells such as fibroblasts and inflammatory cells to coordinate mus-

HOW MUSCLES AGE

Sarcopenia, the loss of muscle mass with age, can start as early as one's 30s, and affects a large proportion of the elderly. Fortunately, exercise can combat muscle aging, likely by reversing many of the age-related physiological changes at the root of this decline.

YOUNG MUSCLE

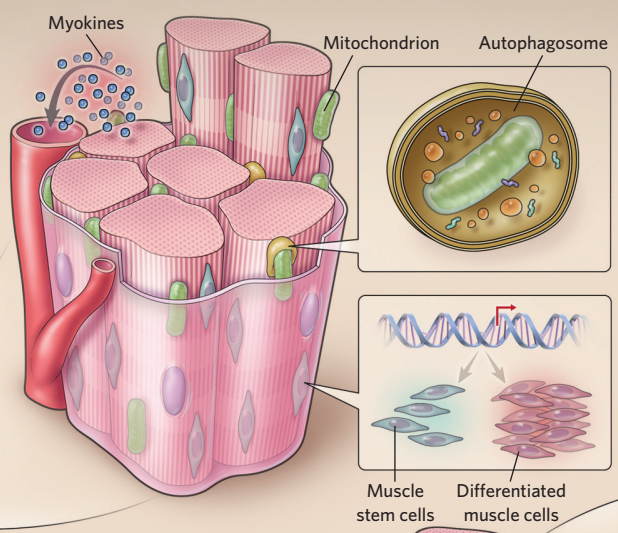
OLD MUSCLE

BLOOD-BORNE FACTORS

Signaling factors known as myokines can be released into the blood directly or through excreted vesicles, and travel through the circulatory system to coordinate muscle physiology and repair. For example, apelin, which decreases with age, boosts the formation of new mitochondria, stimulates protein synthesis and autophagy, and supports the function of muscle stem cells.

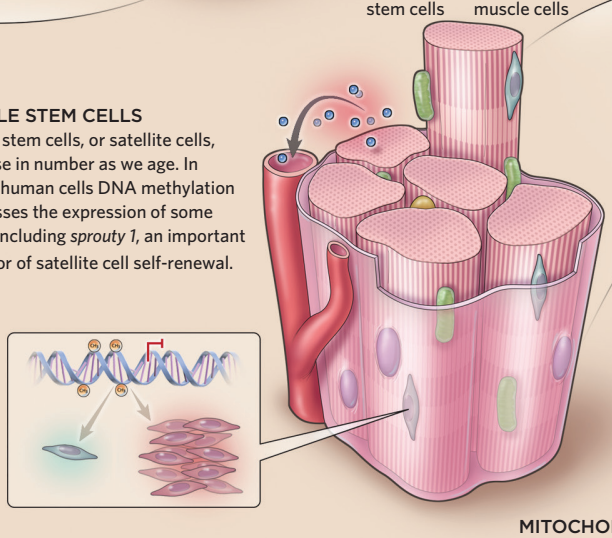
MAINTAINING PROTEIN BALANCE

Old muscles undergo lower levels of autophagy. Combined with lower protein production, this can result in an imbalance of proteins linked to muscle aging.



MUSCLE STEM CELLS

Muscle stem cells, or satellite cells, decrease in number as we age. In elderly-human cells DNA methylation suppresses the expression of some genes, including *sprouty 1*, an important regulator of satellite cell self-renewal.



MITOCHONDRIA

Muscles develop abnormalities in mitochondrial morphology, number, and function with age.

EXERCISE: A sedentary lifestyle can induce molecular processes of muscle aging, such as decreases in the efficiency and number of mitochondria. Conversely, exercise reverses a gene expression profile consistent with mitochondrial dysfunction and restores levels of mitochondrial proteins. Exercise also increases autophagy levels and restores levels of myokines involved in muscle function.

cle physiology and repair, or they can have effects in distant organs, such as the brain.

Although several of these myokines have been identified—in culture, human muscle fibers secrete up to 965 different proteins—researchers have only just begun to understand their role in muscle aging. The first myokine to be identified, interleukin-6 (IL-6), participates in muscle maintenance by decreasing levels of inflammatory cytokines in the muscle environment, while increasing insulin-stimulated glucose uptake and fatty-acid oxidation. Elderly people with high circulating levels of IL-6 are more prone to sarcopenia. Another myokine, insulin-like growth factor 1 (IGF-1), can trigger the swelling of muscle fibers, including after exercise. IGF-1 levels decrease with age, as do levels of the cell-surface receptor that IGF-1 binds to, and mice that overexpress IGF-1 are resistant to age-related sarcopenia.

Nathalie Viguerie and colleagues from the Institute of Metabolic and Cardiovascular Diseases at INSERM-Toulouse University in France recently discovered a novel myokine, which they termed apelin.[8] The researchers have demonstrated that this peptide can correct many of the pathways that are deregulated in aging muscle. When injected into old mice, apelin boosted the formation of new mitochondria, stimulated protein synthesis, autophagy, and other key metabolic pathways, and enhanced the regenerative capacity of aging muscle by increasing the number and function of satellite cells. As with IGF-1, levels of circulating apelin declined during aging in humans, suggesting that restoring apelin levels to those measured in young adults may ameliorate sarcopenia.

Exercise to combat muscle aging

Although the causes of muscle loss are numerous and complex, there is now copious evidence to suggest that exercise may prevent or reverse many of these age-related changes, whereas inactivity will accelerate muscle aging. Earlier this year, for example, Janet Lord of the University of Birmingham and Steven Harridge at King's College London examined the muscles of 125 male and female amateur cyclists and showed that a lifetime of regular exercise can slow down muscle aging: there were no losses in muscle mass or muscle strength among those who were older and exercised regularly. More surprisingly, the immune system had not aged much either.[9]

Exercise's influence on muscle health likely acts through as many mechanisms as those underlying age-related muscle loss and weakness. For example, the number of satellite cells can be increased by exercise, and active elderly people have more of these cells than more-sedentary individuals do. This is the reason why exercise prior to hip and knee surgery can speed up recovery in the elderly.

Physical activity also affects the muscle's mitochondria. A lack of exercise decreases the efficiency and number of mitochondria in skeletal muscle, while exercise promotes mitochondrial health. Last year, Caterina Tezze in Sandri's lab at the University of Padova identified a strong correlation between a decline in the levels of OPA1, a protein involved in shaping the mitochondria, and a decrease in muscle mass and force in elderly subjects, while OPA1 levels were maintained in the muscles of senior athletes who had exercised regularly throughout their lives.[10]

Exercise can even spur muscle cells to maintain more-youthful levels of gene transcripts and proteins. For example, Sreekumaran Nair from the Mayo Clinic in Rochester, Minnesota, and colleagues found that high-intensity aerobic interval training reversed many age-related differences in muscle composition, including restoring mitochondrial protein levels.[11] And Simon Melov at the Buck Institute for Research on Aging and Mark Tarnopolsky of McMaster University in Canada and their colleagues have found that while healthy older adults (average age 70) had a gene-expression profile that was consistent with mitochondrial dysfunction prior to a resistance exercise training program, in just six months this genetic fingerprint had completely reversed to expression lev-

AGE-RELATED MUSCLE DISEASES

Sarcopenia is part of the general process of aging, but it can be triggered prematurely in some late-onset muscle diseases. For example, oculopharyngeal muscular dystrophy (OPMD) is a rare genetic disease that primarily affects the eyelid (oculo) and throat (pharyngeal) muscles. Mutations in the *polyadenylate binding protein nuclear 1 (PABPN1)* gene lead to the production of an abnormal protein that forms aggregates only in nuclei of muscle fibers. The late onset of the disease, which generally appears between 50 and 60 years of age, suggests that the affected muscles successfully cope with the abnormal protein for many years. However, the ability to deal with abnormal proteins decreases with age, and an imbalance between elimination and aggregation could trigger the onset of OPMD.

OPMD shows mechanistic similarities with severe degenerative disorders in which perturbed RNA metabolism and pathological assemblies of RNA-binding proteins are involved in the formation of cytoplasmic or nuclear aggregates. In patients with spinocerebellar ataxias, ALS, Alzheimer's, Huntington's, or Parkinson's diseases, these aggregates form in the neurons. In the case of myotonic dystrophy and inclusion body myositis, they form in the muscle fibers. Defining the exact alteration in RNA metabolism is an interesting question facing researchers studying muscle aging. Of note, all of these diseases are also characterized by abnormal mitochondria, which are observed in aging muscle.

Research into these diseases should not only lead to specific treatments, but also to interventions for the generally healthy aging population. And the reverse is also true: understanding how to stall muscle aging may provide tools to ameliorate pathological conditions. Therefore, cooperation between the pathophysiology and aging fields to study these diseases, for which animal and cellular models exist, should be a focus of future research.

els comparable to those observed in young subjects. Additionally, exercise improved muscle function: the older adults were 59 percent weaker than the younger adults before training, and only 38 percent weaker afterward.[12] Different types of exercise can trigger variable but specific responses in the muscle. For example, whereas strength training is efficient at making muscle, high intensity interval training in aerobic exercises such as biking and walking had the greatest effect at the cellular level at combating age-related loss and weakness, according to Nair's work.

Exercise also appears to influence autophagy. In December 2011, Sandri and his colleagues were the first to report, in mice, that autophagy activity could be boosted by voluntary physical activity, in this case, running on a treadmill.[13] In January 2012, the team of Beth Levine at the University of Texas Southwestern Medical Center confirmed that exercise rapidly increased autophagy activity and that autophagy is required for exercise to have its beneficial effects: physically active mice that were unable to ramp up autophagy did not show any increase in muscle mass, mitochondrial content, or insulin sensitivity after running.[14]

Finally, exercise can also apparently restore levels of myokines that decline with age. For example, when elderly subjects followed a regular program of physical activity, there was a direct correlation between the improvement in their physical performance and the increase in the level of circulating apelin.[15] Similarly, Ivan Bautmans from Vrije Universiteit Brussel showed that increased circulating levels of inflammation markers correlate with muscle fatigue in geriatric patients, and that resistance training decreased inflammatory myokines in young adults.[16]

By these mechanisms and others we have yet to discover, exercise can improve overall strength in the elderly, and specifically, the metabolic vigor of skeletal muscle. Being the most abundant tissue in the average human body, accounting for 30 percent to 40 percent of its total mass, muscle is not only critical for locomotion and breathing, but also for glucose, lipid, and amino-acid homeostasis. The age-associated loss of muscle mass and quality thus contributes to the general metabolic dysfunction commonly seen in elderly patients. In older women, one hour of brisk walking produced elevated insulin sensitivity on the following day. Therefore, it is never too late to exercise to try to combat the consequences of muscle aging.

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A detailed understanding of the molecular and cellular pathways involved in muscle aging could pave the way for the development of therapeutic interventions to boost protein synthesis and increase muscle mass. For now, regular exercise combined with good nutrition is still the most effective way to fight sarcopenia, and possibly aging overall. In addition to detailing the underlying causes of muscle aging, future research should seek to define optimal physical exercise and nutritional programs to combat age-related muscle loss and weakness. It may not significantly increase human lifespan, but it will certainly help people reach the end of their lifespan in a healthier condition. ■

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