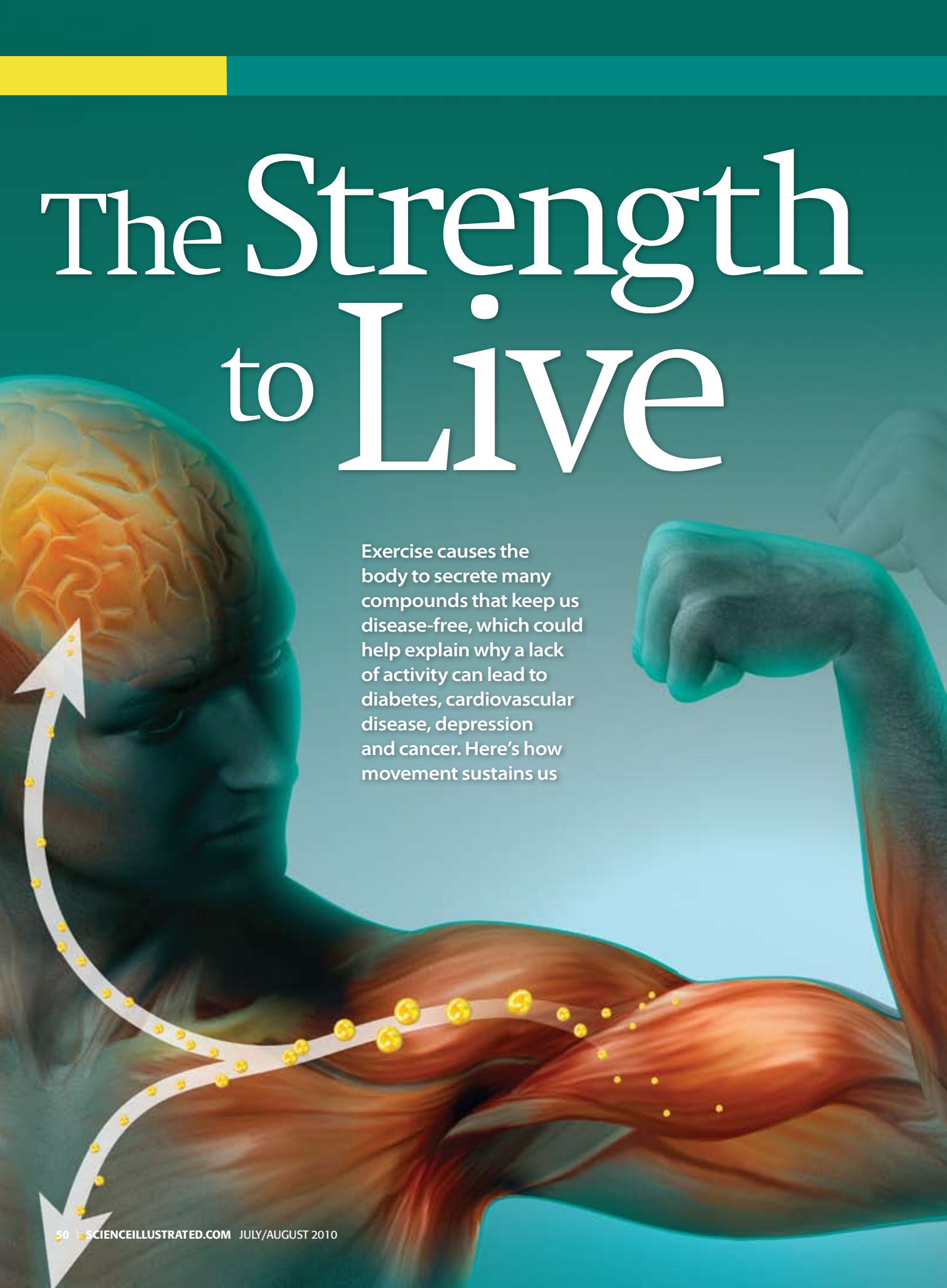
The Strength to Live



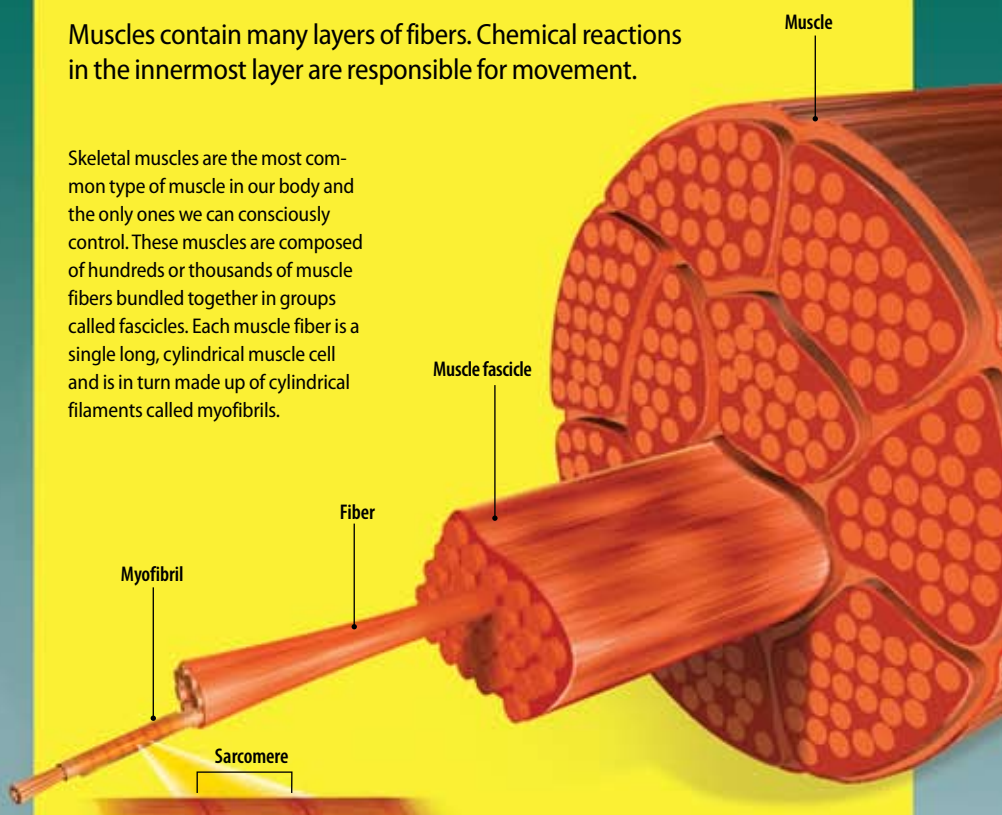
Exercise causes the body to secrete many compounds that keep us disease-free, which could help explain why a lack of activity can lead to diabetes, cardiovascular disease, depression and cancer. Here's how movement sustains us

BACKGROUND

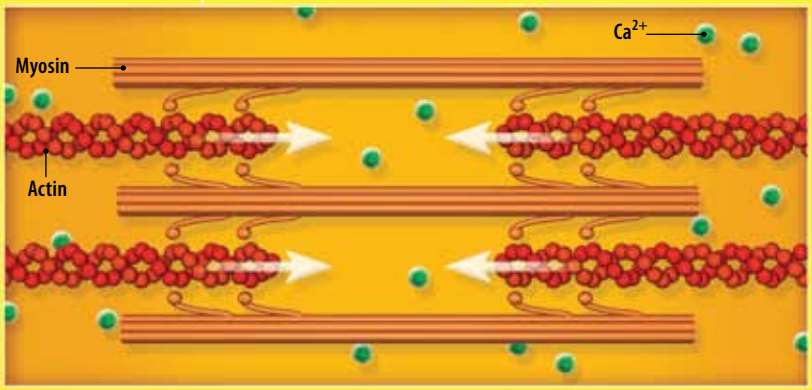
Calcium Ions Make Us Move

Muscles contain many layers of fibers. Chemical reactions in the innermost layer are responsible for movement.

Skeletal muscles are the most common type of muscle in our body and the only ones we can consciously control. These muscles are composed of hundreds or thousands of muscle fibers bundled together in groups called fascicles. Each muscle fiber is a single long, cylindrical muscle cell and is in turn made up of cylindrical filaments called myofibrils.



Each myofibril contains thin and thick filaments, with dark bands where both types of filament overlap. The area between the bands is called the sarcomere, which forms the primary unit responsible for muscle contraction.



When a nerve impulse activates a muscle, calcium ions (Ca^{2+}) stream out into the muscle cell. The calcium allows actin (thin) and myosin (thick) filaments within the myofibril to bind, pulling the filaments toward each other. The sliding filaments cause each sarcomere to contract a bit. This process occurs simultaneously across all the sarcomeres, so that the entire fiber contracts at once.

> "Our identification of the muscle secretome will set a new agenda for the scientific community which is likely to dominate the coming decade."
>
> –Bente Klarlund Pedersen
> Centre of Inflammation and Metabolism at Rigshospitalet, Copenhagen

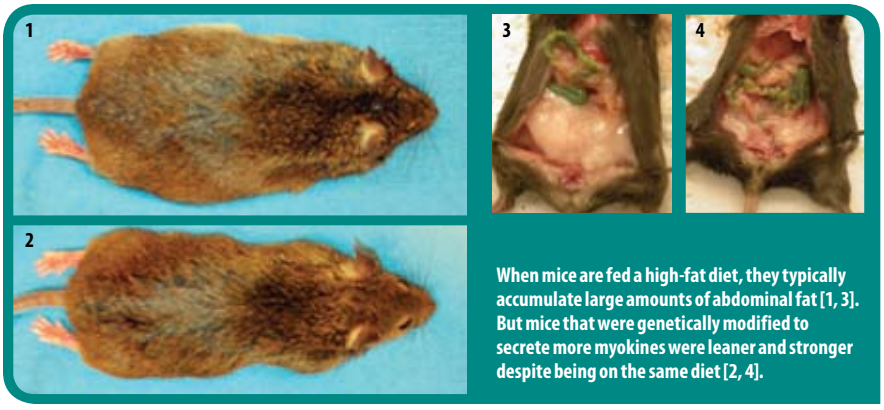
Exercise is the cornerstone of good health—it strengthens the heart and lungs and helps us keep our weight under control. Staying active also benefits the body in more-subtle ways, reducing the risk of obesity, diabetes and cardiovascular disease. For example, physical activity seems to ward off insulin resistance, which occurs when cells become less sensitive to the ability of the hormone insulin to decrease blood glucose levels. This resistance can cause a buildup of blood sugar, which may lead to several illnesses, including cardiovascular disease. Sedentary adults are more likely to suffer insulin resistance, a condition that could eventually lead to Type 2 diabetes. And people who don't exercise are more likely to suffer atherosclerosis, a condition in which plaques form on the walls of arteries. The deposits can become so thick that blood cannot flow through.

A common factor in all diseases associated with a lack of exercise is constant, low-level inflammation in the body. This inflammation manifests as a slight increase in the number of immune-signaling molecules, called cytokines, circulating in the blood. But although researchers have known about the interplay between exercise and inflammation for some time, it is only in the past decade that they have begun to understand the biological underpinnings of the phenomenon.

How Exercise Bestows Its Benefits

Scientists had been looking for half a century for a conclusive link between exercise and the changes it induces. The skeletal muscles that help us move our limbs were obvious targets for studying exercise-related physiological and biochemical changes. Many of the effects muscles have on metabolism and systemic inflammation were thought to be indirect—somehow muscle movement affected the nervous system, researchers believed, which in turn reduced inflammation in the body. But experiments in patients with spinal-cord injuries, who could no longer voluntarily move their muscles, suggested that muscles reduced inflammation directly, rather than being mediated solely by the nervous system. When these patients' paralyzed muscles were electrically stimulated, the researchers noticed metabolic and hormonal responses despite no involvement of the nervous system.

As a result, scientists hunted for an "exercise factor," the exact process or chemical released by contracting skeletal muscles that might account for some of the exercise-induced changes in other parts of the body. "It was while looking for a mechanistic explanation for exercise-induced immune changes that I came across interleukin (IL)-6," says Bente Klarlund Pedersen, the director of the Centre



When mice are fed a high-fat diet, they typically accumulate large amounts of abdominal fat [1, 3]. But mice that were genetically modified to secrete more myokines were leaner and stronger despite being on the same diet [2, 4].

CLOCKWISE FROM TOP: M. ESKESTAD/POLFOTO; CENTRE OF INFLAMMATION AND METABOLISM (2); COURTESY ELSEVIER; PRECEDING PAGES: CLAUS LUNAU

of Inflammation and Metabolism at Rigshospitalet in Copenhagen. "Our identification of muscle as a cytokine-producing organ was a breakthrough."

In 2000, Pedersen found that contracting muscles released significant amounts of IL-6 into the circulation during prolonged exercise. Such muscle-secreted cytokines and hormones were dubbed myokines. Further experiments also showed that this muscle-derived IL-6 has played an important role in metabolism.

The First Piece of the Puzzle

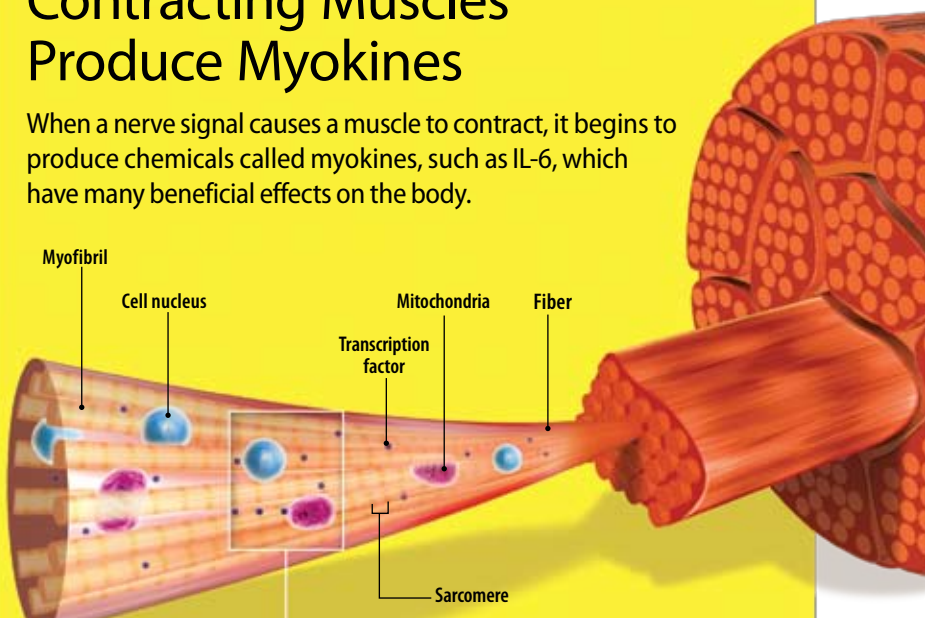
IL-6 is a classic pro-inflammatory cytokine, normally secreted as a signaling molecule to cause inflammation that helps the body fight off infection by microorganisms. IL-6 is also the first and most abundant myokine produced during exercise, and its concentration increases exponentially during strenuous activity, peaking at the end before falling back shortly after. Pedersen and her colleagues initially thought that muscle damage from exercise induced immune cells to secrete IL-6. One of Pedersen's key discoveries was that contracting muscles produce IL-6 themselves and secrete it into the blood. She also found that exercise-induced IL-6 actually reduces inflammation rather than causing it.

Because IL-6 is mainly produced in immune cells, researchers tried to figure out why muscles released it during moderate exercise. One explanation is that calcium secreted within muscle cells during a contraction could cause intermediate proteins, known as transcription factors, to stimulate IL-6 production. Another theory is that reactive oxygen species (ROS)—chemical waste products created in muscles during exercise that react with and alter other compounds in the cell—could act on other transcription factors to raise levels of IL-6.

"Some of the benefits of regular exercise may be due to its anti-inflammatory effects, which may be mediated in part by IL-6," says

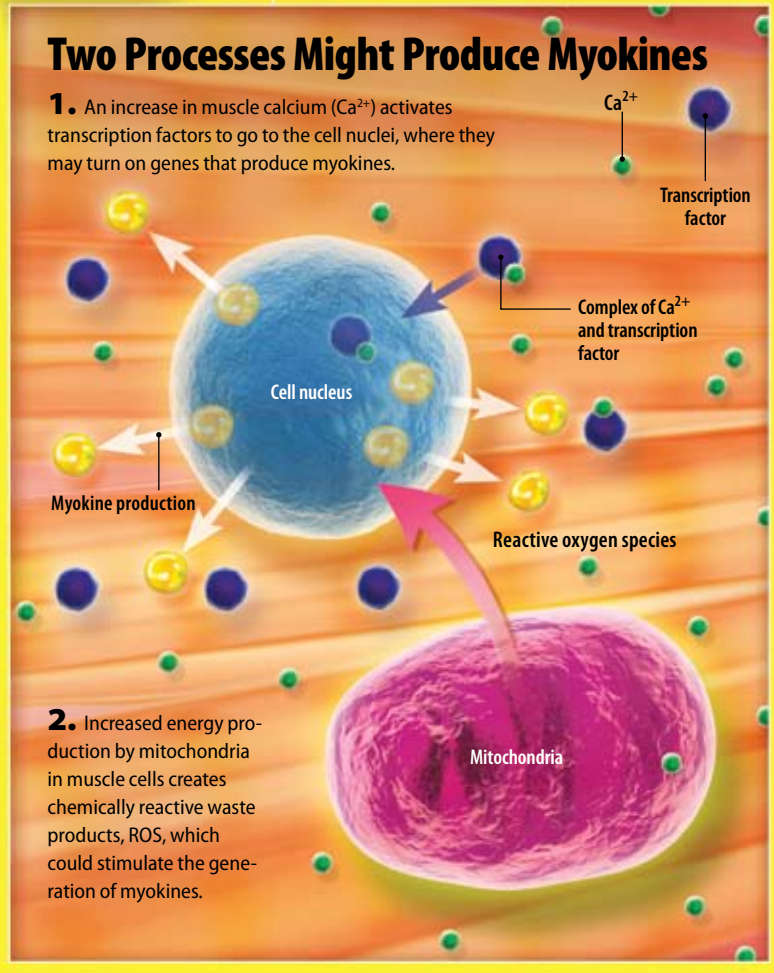
Contracting Muscles Produce Myokines

When a nerve signal causes a muscle to contract, it begins to produce chemicals called myokines, such as IL-6, which have many beneficial effects on the body.



Two Processes Might Produce Myokines

1. An increase in muscle calcium (Ca^{2+}) activates transcription factors to go to the cell nuclei, where they may turn on genes that produce myokines.



2. Increased energy production by mitochondria in muscle cells creates chemically reactive waste products, ROS, which could stimulate the generation of myokines.

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A Sedentary Lifestyle Causes Disease

Part of the benefit of exercise stems from the anti-inflammatory effects of myokines. Without them, abdominal fat promotes mild inflammation in the body, which is associated with a number of chronic diseases

Dementia and depression: Exercise helps guard against depression, possibly by increasing production of a myokine, BDNF. This myokine helps the cells of our nervous system grow and survive, and reduced levels have been associated with depression and impaired memory and cognition.

Cardiovascular disease: Chronic inflammation can activate immune cells, and these cells can influence plaque formation in arteries. These deposits cause a narrowing of the arteries, leading to high blood pressure and increasing the risk of blood clots, heart attacks and strokes.

Breast and colon cancer: Inflammation can cause the pancreas to secrete more insulin, which can increase cell growth, especially in the colon, and may ultimately lead to cancer. It is also possible that lack of exercise could prevent the secretion of a myokine with anticancer properties, but such a myokine hasn't yet been identified.

Type 2 diabetes and obesity: Low-grade inflammation and insulin resistance are also known to lead to Type 2 diabetes. In addition, without exercise-induced secretion of IL-15, we accumulate abdominal fat, which can contribute to obesity.

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Pedersen. This finding was initially confusing, since IL-6 causes inflammation when secreted by immune cells. The key to this conundrum seems to be other pro-inflammatory molecules, such as tumor necrosis factor alpha (TNF-alpha), which determines whether IL-6 will increase or decrease inflammation. When TNF-alpha is present, IL-6 promotes inflammation. But exercise appears to inhibit TNF-alpha, and the IL-6 molecules suppress inflammation instead. Whether IL-6 has a pro- or anti-inflammatory role thus depends on when, in which cells and with which other molecules it's released.

Using Myokines to Boost Metabolism and Prevent Diseases

After IL-6, other myokines were discovered, each with a specific effect on body composition and physiology. A myokine expressed in skeletal muscle called IL-15 promotes muscle formation and may also reduce accumulation of fat, especially in the abdomen. Belly fat is particularly harmful because it is associated with insulin resistance and diabetes. Mice that expressed high levels of IL-15 have significantly reduced body fat; and the results are similar in people. Humans with higher IL-15 gene expression levels, which can be achieved through strength training, also tend to have lower levels of body fat. Further, researchers believe that IL-15 promotes muscle growth both

Exercise Pills

Chronic inflammation is associated with aging and long-term medical conditions, but exercise can alleviate the inflammation because of the secretion of anti-inflammatory myokines during physical activity. To mimic the effects of exercise in those who cannot

by increasing protein production and inhibiting protein breakdown. Another kind of myokine, IL-8, helps the body form new blood vessels.

The brain is not immune to the effects of myokines, either. One myokine, brain-derived neurotrophic factor (BDNF), helps regulate the survival, growth and maintenance of nerve cells. Decreased levels of this protein are associated with major depression, impaired memory and cognitive function, and Alzheimer's disease. Although this protein increases in muscles after exercise, it is not released into the bloodstream, so BDNF's direct effect may be only on fat metabolism in the muscle. Its other effects may be indirect.

To understand myokine regulation and its effects on body composition, biologist Kenneth Walsh of Boston University bred mice that expressed a protein that increases the secretion of fibroblast growth factor-21 (FGF21), another myokine. These mice became leaner and stronger than others despite being fed the same diet and getting less physical activity.

Myokines' influence on inflammation, obesity and insulin resistance has implications for cardiovascular diseases and even cancer. Low-grade inflammation and insulin resistance can lead to hypertension, stroke and heart disease, partly through atherosclerosis. The increased insulin secretion that occurs as a result of insulin resistance can also promote cell proliferation that could result in cancer. Pedersen speculates that some myokines may have anticancer properties, and her efforts to find more myokines will undoubtedly uncover more of these proteins' positive effects.

Researchers analyze a patient's metabolism to try to understand the beneficial effects of exercise.

FROM TOP: CENTRE OF INFLAMMATION AND METABOLISM; CLAUS LUNAU

Next Step: Put It in a Pill

Exercise plays a central part in regulating metabolism and protecting us from chronic diseases, but just how it improves our health involves a complex interaction between cells and signaling molecules, such as myokines. As the roster of known myokines increases, it has opened up the study of muscles as hormone-secreting organs, like any other gland. This knowledge should provide rich territory for scientists to mine and could lead to drugs that could alter myokines' activity. For people who are bedridden because of illness or infirmity, drugs that mimic beneficial myokines could help reduce the incidence of chronic-inflammation-related disease. "Our identification of the muscle secretome [the entire map of all the proteins that muscles secrete]," Pedersen says, "will set a new agenda for the scientific community which is likely to dominate the coming decade." ■

physically do it, researchers are investigating whether these myokines could be given as a supplement. This could prove particularly beneficial for those with limited mobility.

Both aging and getting too little exercise also result in muscle wasting, which leads to a vicious cycle of further inactivity and insufficient myokine secretion. In this situation, treatment with IL-15 could help ameliorate Type 2 diabetes and build muscle, and IL-6 supplements may protect healthy individuals against insulin resistance.

Anti-inflammatory drugs could also restore protein synthesis and thus prevent muscle wasting. Researchers treated age-related muscle atrophy in mice with ibuprofen, an anti-inflammatory agent. Unfortunately, high doses of these medications can cause serious side effects in humans. But some drugs, like salsalate, have shown promising results against inflammation-induced insulin resistance, and similar treatments could one day be used to protect against chronic diseases and muscle loss.