How stem cells can combat age-related muscle loss
By Harnoor Gill

Age is more than just a number—it is a collection of numbers. For instance, people over the age of 30 begin to lose as much as three to five percent of their muscle mass per decade (3). This progressive loss of muscle mass due to the aging process is known as sarcopenia and it can be debilitating. Sarcopenia, which eerily means "lack of flesh", is accompanied by a number of different health risks (7).

Muscle is undoubtedly an important part of our body and daily life. Besides supporting our skeleton, it has the vital role of allowing us to move and do fun things like rollerblade or bake cupcakes. When we lose muscle mass and strength, it can inhibit our daily activities and increase our risk of accidents, such as falls and fractures (1). Sarcopenia can lengthen our hospital stays as well, which leads to prolonged stagnancy and even more muscle decline (4). In addition, sarcopenia can increase risk for chronic diseases such as obesity and diabetes (2).

On a molecular level, the causes of sarcopenia are complex. Figure 1 shows muscle fibers and the various factors that contribute to the pathophysiology of sarcopenia, which include altered levels of inflammatory factors, insulin, and sex hormones (8). Dehydroepiandrosterone (DHEA) is a hormone produced by the adrenal gland; it helps produce other hormones, including testosterone and estrogen. DHEA levels fall as an individual ages —declines in DHEA and testosterone may be related to the loss of muscle strength in sarcopenia (9). Free radicals, which are oxygen-containing molecules that can cause damage to your DNA, proteins and lipids when present in excess, have also been implicated in aging muscle (11). Loss of motor neurons, which are cells that transmit signals from the brain and spinal cord to muscles, leads to weakness of the muscle and furthers disease progression.

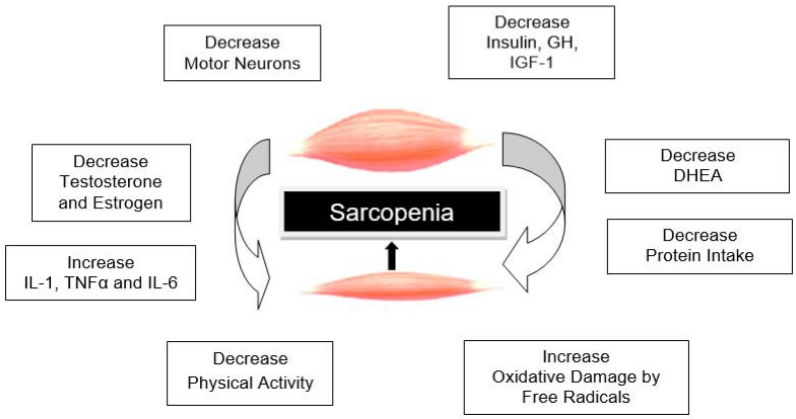

Figure 1 Cellular changes in aging muscle fibers in sarcopenia

Though muscle loss can feel as inevitable as, well, aging, all hope is not lost. Clinical trials testing exercise, nutritional supplements, physiological intervention and drugs

have been conducted. Exercise was found to be most effective in reducing sarcopenia (2). In fact, individuals that are more active in their lifetimes tend to experience less muscle loss as they age, making exercise an appealing preventative treatment. One way in which exercise, particularly resistance or strength training, benefits sarcopenia patients is by increasing muscle regeneration (4). Exercise also reduces inflammation, which tends to increase with age and exaggerates the harmful effects of sarcopenia, causing additional harm to muscles (2).

However, exercise is not a viable option for patients who are bedridden or otherwise immobile. In these patients, stem cell therapy holds immense potential (2). Induced pluripotent stem cells (iPSCs), which can conveniently turn into any human cell type needed for therapeutic purposes, are being explored as a treatment option. The patient's own cells are genetically reprogrammed and turned into a "blank canvas," or an iPSC. These iPSCs are ready to be painted again into a new type of cell that the patient may need.

Sometimes, this repainting needs a little "nudge". This nudge can come in the form of a small molecule called givinostat, which is a histone deacetylase inhibitor (6). Givinostat can guide the iPSCs to become muscle progenitor cells (MPCs) by blocking enzymes called histone deacetylases, which make DNA less accessible for gene expression. In this way, givinostat is able to "turn on" specific genes that are necessary for muscle specialization. MPCs can then specialize and become myocytes, or muscle cells. The myocytes also make extracellular vesicles that aid in muscle repair (4). You can think of these vesicles as small bubbles that carry materials that facilitate muscle regeneration—the vesicles deliver their contents to cells by fusing with cell membranes.

The clinical concern with administering iPSCs is that they rapidly and indefinitely divide, which can lead to tumor formation inside of the body. Stem cell biologists, such as Dr. Wanling Xuan at the Vascular Biology Center at the Medical College of Georgia, are instead actively investigating the benefits of either administering the MPCs induced from iPSCs with givinostat or by introducing the vesicles that they secrete (4).

The therapeutic strategies being investigated can be personalized to fit the profile of the patient. For patients with age-related muscle loss, delivering the vesicles alone is a good option for regenerating and revitalizing aged stem cells (4). For sarcopenia patients with a muscle injury, administering the MPCs would be more appropriate (4). One of the challenges with administering MPCs is determining whether or not they will integrate or "fit in" with the aged or diseased environment, making this an active area of research.

Stem cell therapy is promising because it can combat the detriments of aging, an innate yet variable biological process, on our muscles. For patients with sarcopenia, this regenerative therapy can mean the difference between a sedentary life and a life full of movement.

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