Researchers find culprit in aging muscles that heal poorly

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Communication is critical. Garbled in, garbled out, so to (mis-)speak. Workers who get incomplete instructions produce an incomplete product, and that's exactly what happens with the stem cells in our aging muscles, according to researchers from the Stanford University School of Medicine.

Their study found that, as we age, the lines of communication to the stem cells of our muscles deteriorate and, without the full instructions, it takes longer for injured muscles to heal. Even then, the repairs aren't as good. But now that the researchers have uncovered the conduit that conveys the work orders to muscle stem cells, that knowledge could open the door to new therapies for injuries in a host of different tissues.

The key to the whole process is Wnt, a protein traditionally thought to help promote maintenance and proliferation of stem cells in many tissues. But in this instance, Wnt appears to block proper communication.

"That was a total surprise," said Thomas Rando, MD, PhD, associate professor of neurology and neurological sciences. "We had no idea that the Wnt signaling pathway would have a negative effect on stem cell function." Rando, who also does research and clinical work at the Veterans Affairs Palo Alto Health Care System, is senior author of the research that will be published in the Aug. 10 issue of *Science*.

Rando said many drugs can block Wnt signaling. "Theoretically, given

the number of ways to block Wnt and Wnt signaling, one could envision this becoming a therapeutic," he said. "You could potentially enhance the healing of aged tissues by reducing this effect of Wnt signaling on the resident stem cells."

In addition to helping the elderly heal faster and better from muscle injuries, Rando said, the potential benefits could include tissues such as skin, gut and bone marrow, or for that matter, potentially any tissue, such as liver and brain, in which stem cells contribute to normal cellular turnover.

Rando and his colleagues made the discovery while studying the effect of environment on muscle stem cell activity in mice. Rando had already discovered that old muscle stem cells, if placed in a youthful environment, had just as great a capacity for repairing acutely damaged tissue as do young cells.

It was while the researchers were testing the opposite situation - how the repair capabilities of young muscle stem cells were affected by being placed in an aged environment - that the Wnt pathway came to light. The work was done with live mice whose circulatory systems were joined, and in lab dishes with young cells immersed in serum from old blood.

As expected, the young muscle stem cells were influenced negatively by the aged environment, repairing damaged muscle tissue just as slowly and poorly as old stem cells in the same surroundings. This confirmed their earlier research showing that the ability of muscle stem cells to regenerate tissue depends on the age of the cells' environment (including the age of the blood supplying the tissue), not the age of the stem cell.

Although Rando's research focused on the repair of acute trauma to muscles, he suspects that the same sort of problem arises on a lesser scale in repairing damage that results from the normal wear and tear of

aging.

Rando also found that the misdirected stem cells - the ones that failed to generate new muscle cells in the old environment - were instead differentiating into scar-tissue-producing cells called fibroblasts. The stem cells weren't just failing to respond to the garbled instructions, they were actually giving rise to daughter cells that turned into the wrong thing. The consequence of muscle stem cells producing fewer muscle cells (myoblasts) and more fibroblasts is that the healing muscle had more scar tissue, also known as fibrosis.

"That says something about how cells decide who they're going to be. Even if they start off knowing they're supposed to be a muscle cell, they can change," said Rando. "If you're exposed to the wrong environment, it will change your fate."

Rando said the type of fibrosis that occurs in the aging muscle tissue is the same type seen in muscular dystrophy. He is already exploring how inhibiting Wnt signaling might help provide therapy for that disease.

Wnt has also popped up unexpectedly in work by researchers at the National Institutes of Health, published in the same issue of *Science*, who were studying the effects of a deficiency of a hormone called klotho. Klotho deficiency causes a syndrome that resembles extremely rapid aging in mice, which end up dying very young compared with normal mice. In seeking to understand why that happens, the NIH researchers discovered that klotho inhibits Wnt activity. The hypothesis is that klotho production declines with age, and thus its effectiveness against Wnt decreases, allowing Wnt activity to pick up and disrupt the normal signaling to the stem cells in a variety of tissues studied.

Rando said that, although the work of his team and the NIH researchers is different in terms of the techniques used and the questions being

studied, "what's surprising is how supportive of each other the fundamental conclusions (of the two papers) are about Wnt signaling and aging."

Source: Stanford University Medical Center