Protein primes mouse stem cells to quickly repair injury, study finds

April 18 2017

Credit: martha sexton/public domain

Like drag car racers revving their engines at the starting line, stem cells respond more quickly to injury when they've been previously primed

with one dose of a single protein, according to a study from the Stanford University School of Medicine.

Mice given the priming protein recover muscle function more quickly after damage, their skin heals more rapidly and even the shaved area around the injury regrows hair more quickly, the study found. Harnessing the power of this protein may one day help people recover more quickly from surgery or restore youthful vigor to aging stem cells.

"We're trying to better understand wound healing in response to trauma and aging," said Thomas Rando, MD, PhD, professor of neurology and neurological sciences. "We've shown that muscle and bone marrow stem cells enter a stage of alertness in response to distant injury that allows them to spring into action more quickly. Now we've pinpointed the protein responsible for priming them to do what they do better and faster."

Rando, who also directs Stanford's Glenn Center for the Biology of Aging, is the senior author of the study, which will be published April 18 in *Cell Reports*. Former postdoctoral scholar Joseph Rodgers, PhD, is the lead author. Rodgers is now an assistant professor of stem cell biology and regenerative medicine at the University of Southern California.

Potential therapy

"Our research shows that by priming the body before an injury you can speed the process of tissue repair and recovery, similar to how a vaccine prepares the body to a fight infection," Rodgers said. "We believe this could be a therapeutic approach to improve recovery in situations where injuries can be anticipated, such as surgery, combat or sports."

Normally, adult, tissue-specific stem cells are held in a kind of cellular deep freeze called quiescence to avoid unnecessary cell division in the

absence of injury. In a 2014 paper published in *Nature*, Rodgers and Rando showed in laboratory mice that an injury to the muscle of one leg caused a change in the muscle stem cells of the other leg. These cells entered what the researchers called an "alert" phase of the cell cycle that is distinct from either fully resting or fully active stem cells.

The fact that muscle stem cells distant from the injury were alerted indicated that the damaged muscle must release a soluble factor that can travel throughout the body to wake up quiescent stem cells. Rodgers and his colleagues found that a protein called hepatocyte growth factor, which exists in a latent form in the spaces between muscle cells and tissue, can activate a critical signaling pathway in the cells by binding to their surfaces. This pathway stimulates the production of proteins important in alerting the stem cells. But it wasn't known how HGF itself became activated.

In the new study, Rodgers and his colleagues identified the activating factor by injecting uninjured animals with blood serum isolated from animals with an induced muscle injury. (Mice were anesthetized prior to a local injection of muscle-damaging toxin; they were given pain relief and antibiotics during the recovery period.) After 2.5 days, the researchers found that muscle stem cells from the recipient animals were in an alert state and completed their first cell division much more quickly than occurred in animals that had received blood serum from uninjured mice.

"Clearly, blood from the injured animal contains a factor that alerts the stem cells," said Rando. "We wanted to know, what is it in the blood that is doing this?"

Increased levels of a protein

The researchers found that the serum from the injured animals had the

same levels of HGF as the control serum. However, it did have increased levels of a protein called HGFA that activates HGF by snipping it into two pieces. Treating the serum with an antibody that blocked the activity of HGFA eliminated the recovery benefit of pretreatment, the researchers found.

In a related experiment, exposing the animals to a single intravenous dose of HGFA alone two days prior to injury helped the mice recover more quickly. They scampered around on their wheels sooner and their skin healed more quickly than mice that received a control injection. They also regrew their hair around the shaved surgical site more completely than did the control animals.

"Just like in the muscles, we saw the responses in the skin were dramatically improved when the stem cells were alerted," Rando said.

In addition to pinpointing possible ways to prepare people for surgeries or other situations in which they might sustain wounds, the researchers are intrigued by the role HGF and HGFA might play in aging. It's known that the pathway activated by these proteins is less active in older people and animals.

"Stem cell activity diminishes with advancing age, and older people heal more slowly and less effectively than younger people. Might it be possible to restore youthful healing by activating this pathway?" said Rando. "We'd love to find out."

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Provided by Stanford University Medical Center