Study identifies cell-cycle phase that primes stem cells for action

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Resting, adult stem cells of many types of tissues enter a reversible "alert" phase in response to a distant injury, according to a study in mice by researchers at the Stanford University School of Medicine.

The study describes for the first time a new phase in the resting portion of the cell cycle. It also explains how stem cells prime themselves to rapidly respond to tissue damage without prematurely committing to energetically expensive (and possibly unnecessary) cell division. These alert cells are distinct from fully resting or fully activated stem cells, and they divide and repair subsequent tissue damage much more quickly than do fully resting stem cells.

The findings imply that nearly any type of injury may put stem cells throughout the body on notice for possible future regenerative needs.

"These alert stem cells changed markedly in response to a distant muscle injury," said Thomas Rando, MD, PhD, professor of neurobiology and neurological sciences. "They are partially awake and are poised to respond to additional challenges and make new tissue as needed. This is a systemic, or whole-body, response to injury that has never been seen before."

The researchers suggest the alert phase represents a novel form of cellular memory similar to that displayed by the immune system, which relies upon prior experiences to drive future responses.

Rando, who also directs Stanford's Glenn Laboratories for the Biology of Aging, is the senior author of the study, published online May 25 in *Nature*. Postdoctoral scholar Joseph Rodgers, PhD, is the lead author.

Resting state?

The researchers were studying the response of mouse muscle stem cells, or satellite cells, to muscle injury. Conventional wisdom holds that adult stem cells are by nature quiescent—a term that indicates a profound resting state characterized by small size and no cell division. It's a kind of cellular deep freeze. In contrast, most other cells cycle through rounds of DNA replication and cell division in discrete, well-defined phases. A quiescent stem cell can "wake up" and enter the cell cycle in response to local signals of damage or other regeneration needs.

Rando and his colleagues were studying this activation process in laboratory mice by watching how muscle stem cells in one leg respond to a nearby muscle injury in the same leg. (Mice were anesthetized prior to a local injection of muscle-damaging toxin; they were given pain relief and antibiotics during the recovery period.) The researchers had planned to observe the quiescent muscle stem cells in the uninjured leg as a control for their experiment. However, they instead saw something unexpected.

"The muscle stem cells in the uninjured leg had definitely changed," said Rando, who is director of the Rehabilitation Research & Development Center of Excellence at the Veterans Affairs Palo Alto Health Care System. "They were very clearly biochemically different from completely dormant, quiescent cells, and from fully activated stem cells. We termed this state an 'alert' state of quiescence."

These alert cells were larger than their quiescent peers in uninjured mice. They also entered the cell cycle more readily when stimulated, and

they exhibited increased activity of their mitochondria—cellular structures that serve as energy factories. Despite these changes, however, the alert cells were not yet actively moving on their own through the cell cycle. The condition was reversible: The differences persisted for about 28 days after a distant injury, after which the alert cells again displayed normal features of full quiescence.

Power of 'alert' cells

The researchers wondered whether these "alert" stem cells could repair subsequent tissue damage more quickly than resting stem cells. They found that mice that had first undergone an alerting injury in one leg were able, three days later, to more quickly and efficiently repair muscle damage in the other leg than control mice. In particular, during 24 days of recovery, the damaged muscle fibers in mice with the alerting injury were larger at every time point than those of the control animals.

Surprisingly, the muscle stem cells also became alert in response to bone or minor skin injuries—injuries in which the cells are not known to play any regenerative role.

Conversely, other non-muscle adult stem cells, including hematopoietic stem cells in the bone marrow and mesenchymal stem cells in the muscle, became alert in response to muscle damage.

"It is clear that this alert state is a systemic response," said Rando.

Although it's not clear exactly how the body's stem cells are receiving the message to alert, the researchers did identify some key signaling pathways, including one governed by a protein called mTORC1. The mTORC1 pathway activates the production of proteins needed for cell division and is known to play a critical role in stem cell proliferation.

Another protein, hepatocyte growth factor, or HGF, exists in a latent form in the spaces between muscle stem cells and other cells in the tissue, making it well-placed to respond to body-wide circulatory signals. When activated, HGF binds to the surface of stem cells and activates the mTORC1 pathway. Although Rando and his colleagues found that blocking HGF's ability to bind to the cells also inhibited their ability to become alert in response to a distant injury, it's not yet known what activates HGF.

Possible boost for healing

"Can we begin to identify the molecules released into the circulation upon injury that go to these tissues and alert the stem cells?" said Rando. "If we could learn more about these factors, it's possible we could artificially alert stem cells in someone about to go into surgery, for example, to speed healing after the procedure."

The study's findings also address some long-standing questions about cells' quiescent state.

"Researchers studying cellular quiescence in the laboratory decades ago noticed that, when you withdraw growth factors, cells stop dividing," said Rando. "They observed that there were different ways a cell could exist in that state. But until now, no one has described this phenomenon in detail or investigated its physiological consequences. They were seeing what we have now explained on a molecular level and in stem cells in the body—the first real evidence of a second state of quiescence that allows much more rapid and effective tissue repair."

More information: Paper: mTORC1 controls the adaptive transition of quiescent stem cells from G0 to GAlert, DOI: 10.1038/nature13255