Promoting healing by keeping skeletal stem cells 'young'

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Scientists seeking new ways to fight maladies ranging from arthritis and osteoporosis to broken bones that won't heal have cleared a formidable hurdle, pinpointing and controlling a key molecular player to keep stem cells in a sort of extended infancy. It's a step that makes treatment with the cells in the future more likely for patients.

Controlling and delaying development of the cells, known as mesenchymal (pronounced meh-ZINK-a-mill) stem cells, is a long-sought goal for researchers. It's a necessary step for doctors who would like to expand the number of true skeletal stem cells available for a procedure before the cells start becoming specific types of cells that may - or may not - be needed in a patient with, say, weak bones from osteoporosis, or an old knee injury.

"A big problem has been that these stem cells like to differentiate rapidly - oftentimes too rapidly to make them very useful," said Matthew J. Hilton, Ph.D., the leader of the team at the University of Rochester Medical Center. "It's been very hard to get a useful number of stem cells that can still become any one of several types of tissue a patient might need. Having a large population of true skeletal stem cells available is a key consideration for new therapies, and that's been a real roadblock thus far."

In a study published online in the journal *Development*, Hilton's team discussed how it was able to increase the number and delay the development of stem cells that create bones, cartilage, muscle and fat.

The first authors of the paper are Yufeng Dong, Ph.D., senior instructor, and technician Alana Jesse, who worked in Hilton's laboratory at the Center for Musculoskeletal Research.

Hilton's team showed in mice that a molecule called Notch, which is well known for the influence it wields on stem cells that form the blood and the nervous system, is a key factor in the development of mesenchymal stem cells, which make up a tiny fraction of the cells in the bone marrow and other tissues.

The team showed that Notch prevents stem cells from maturing. When the scientists activated the Notch pathway, the stem cells didn't progress as usual. Instead, they remained indefinitely in an immature state and did not go on to become bone cells, cartilage cells, or cells for connective tissue.

The team also settled a long-standing question, fingering the molecule RBPJ-kappa as the molecule through which Notch works in mesenchymal stem cells. That knowledge is crucial for scientists trying to understand precisely how Notch works in bone and cartilage development. A few years ago, Hilton was part of a team that showed that Notch is a critical regulator of the development of bone and cartilage. The latest study extends those observations, providing important details that suggest appropriate activation and manipulation of the Notch pathway may provide doctors with a tool to maintain and expand mesenchymal stem cells for use in treating disease.

The work is part of ongoing research around the world aimed at harnessing the promise of stem cells for human health. Unfortunately, stem cell therapy has been slow to actually make a difference in the lives of patients with problems of the bones and cartilage, Hilton notes, largely because so many questions are currently unanswered.

"To really make stem-cell medicine work, we need to understand where the stem cells have come from and how to get them to become the cell you want, when and where you want it. We are definitely in the infancy of learning how to manipulate stem cells and use them in treatment," said Hilton, assistant professor of Orthopaedics and Rehabilitation.

"This research helps set the foundation for ultimately trying new therapies in patients," he added. "For instance, let's say a patient has a fracture that simply won't heal. The patient comes in and has a sample of bone marrow drawn. Their skeletal stem cells are isolated and expanded in the laboratory via controlled Notch activation, then put back into the patient to create new bone in numbers great enough to heal the fracture. That's the hope."

Work in Hilton's laboratory was initially funded through start-up funds from the medical center. The early findings have helped him attract two grants from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, part of the National Institutes of Health, and the University has filed a patent on the Notch technology.

Provided by University of Rochester Medical Center