Team isolates stem cell that gives rise to bones, cartilage in mice

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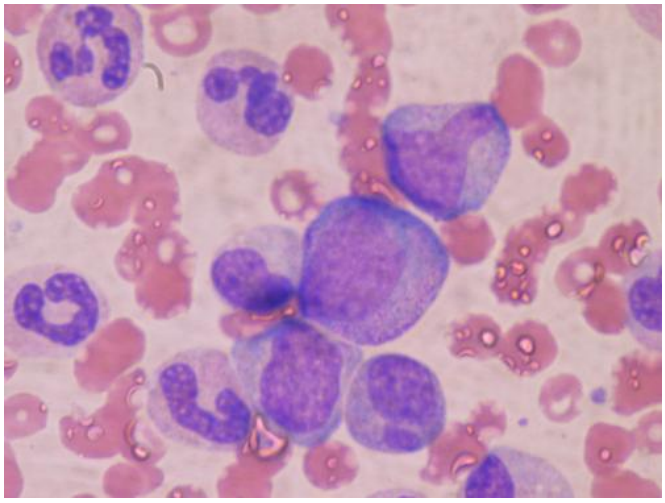

Hematopoietic precursor cells: promyelocyte in the center, two metamyelocytes next to it and band cells from a bone marrow aspirate. Credit: Bobjgalindo/Wikipedia

Researchers at the Stanford University School of Medicine have discovered the stem cell in mice that gives rise to bone, cartilage and a key part of bone marrow called the stroma.

In addition, the researchers have charted the chemical signals that can create skeletal stem cells and steer their development into each of these specific tissues. The discovery sets the stage for a wide range of potential therapies for skeletal disorders such as bone fractures, brittle bones, osteosarcoma or damaged cartilage.

A paper describing the findings will be published Jan. 15 in *Cell*.

"Millions of times a year, orthopedic surgeons see torn cartilage in a joint and have to take it out because cartilage doesn't heal well, but that lack of cartilage predisposes the patient to arthritis down the road," said Michael Longaker, MD, a professor of plastic and reconstructive surgery at Stanford and a senior author of the paper. "This research raises the possibility that we can create new skeletal stem cells from patients' own tissues and use them to grow new cartilage." Longaker is also co-director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine.

An intensive search

The researchers started by focusing on groups of cells that divide rapidly at the ends of mouse bones, and then showed that these collections of cells could form all parts of bone: the bone itself, cartilage and the stroma—the spongy tissue at the center of bones that helps hematopoietic stem cells turn into blood and immune cells. Through extensive effort, they then identified a single type of cell that could, by itself, form all these elements of the skeleton.

The scientists then went much further, mapping the developmental tree of skeletal stem cells to track exactly how they changed into intermediate progenitor cells and eventually each type of skeletal tissue.

"Mapping the tree led to an in-depth understanding of all the genetic switches that have to be flipped in order to give rise to more specific progenitors and eventually highly specialized cells," said postdoctoral scholar Charles Chan, PhD, who shares lead authorship of the paper with postdoctoral scholar David Lo, MD, graduate student James Chen and research assistant Elly Eun Young Seo. With that information, the researchers were able to find factors that, when provided in the right amount and at the right time, would steer the development of skeletal stem cells into bone, cartilage or stromal cells.

"If this is translated into humans, we then have a way to isolate skeletal stem cells and rescue

cartilage from wear and tear or aging, repair bones that have nonhealing fractures and renew the bone marrow niche in those who have had it damaged in one way or another," said Irving Weissman, MD, professor of pathology and of developmental biology, who directs the Stanford Institute for Stem Cell Biology and Regenerative Medicine. Weissman, the other senior author of the paper, also holds the Virginia and Daniel K. Ludwig Professorship in Clinical Investigation in Cancer Research.

Reprogramming fat cells

In addition to learning how to create bone, cartilage and stromal cells out of skeletal stem cells, the researchers found out how to create skeletal stem cells themselves out of fat or muscle cells. The ability to reprogram mature fat cells directly into skeletal stem cells through the application of specific signals "was really interesting and quite unexpected," Longaker said.

It raises fascinating possibilities for future therapies, he added. "Right now, if you have lost a significant portion of your leg or jaw bones, you have to borrow from Peter to pay Paul in that you have to cut another bone like the fibula into the shape you need, move it and attach it to the blood supply," said Longaker, who is also the Deane P. and Louise Mitchell Professor in the School of Medicine. "But if your existing bone is not available or not sufficient, using this research you might be able to put some of your own fat into a biomimetic scaffold, let it grow into the bone you want in a muscle or fat pocket, and then move that new bone to where it's needed."

Other therapies might be deployed in one surgical session, Chan said. "The number of skeletal stem cells decreases dramatically with age, so bone fractures or dental implants don't heal very well in the elderly because new bone doesn't grow easily," he said. "But perhaps you will be able to take fat from the patient's body during surgery, combine it with these reprogramming factors right there in the operating room and immediately transplant new skeletal stem cells back into the patient."

Now that the researchers have successfully mapped the skeletal stem cell system in mice, they are confident that they will be able to do the same in humans. "In this research we now have a Rosetta stone that should help find the human skeletal stem cells and decode the chemical language they use to steer their development," Chan said. "The pathways in humans should be very similar and share many of the major genes used in the mouse skeletal system."

More information: Identification and Specification of the Mouse Skeletal Stem Cell, Volume 160, Issues 1-2, p285–298, 15 January 2015. www.cell.com/cell/abstract/S0092-8674(14)01572-4

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