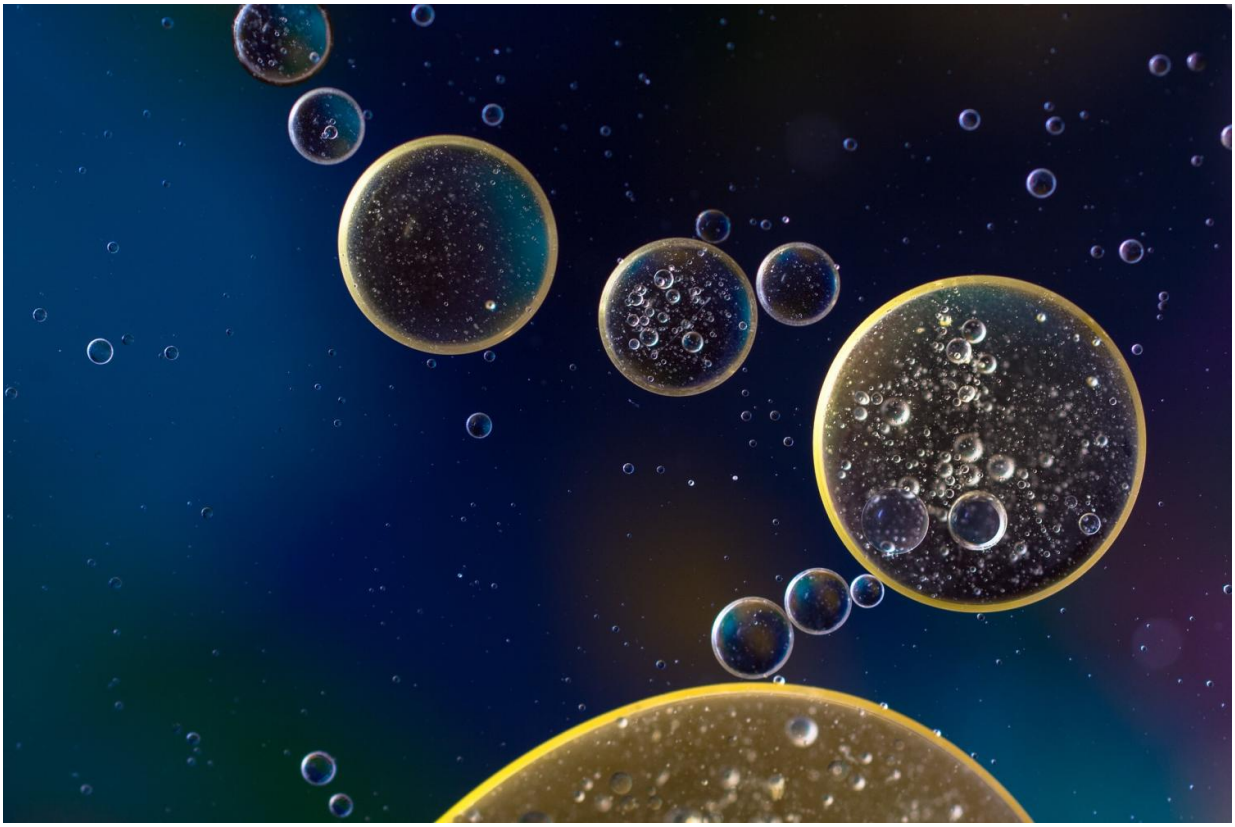
MedicalXpress

Study identifies stem cell that gives rise to new bone and cartilage in humans

September 20 2018



Credit: CC0 Public Domain

A decade-long effort led by Stanford University School of Medicine scientists has been rewarded with the identification of the human skeletal stem cell.

The cell, which can be isolated from human bone or generated from specialized cells in fat, gives rise to progenitor cells that can make new bone, the spongy stroma of the bone's interior and the cartilage that helps our knees and other joints function smoothly and painlessly.

The discovery allowed the researchers to create a kind of family tree of stem cells important to the development and maintenance of the human skeleton. It could also pave the way to treatments for regenerating bone and cartilage in people.

"Every day children and adults need normal bone, cartilage and stromal tissue," said Michael Longaker, MD, professor of plastic and reconstructive surgery. "There are 75 million Americans with arthritis, for example. Imagine if we could turn readily available fat cells from liposuction into stem cells that could be injected into their joints to make new cartilage, or if we could stimulate the formation of new bone to repair fractures in older people."

A paper describing the finding, which follows the discovery by the same group of the mouse skeletal stem cell in 2015, will be published online Sept. 20 in *Cell*.

Longaker, the Deane P. and Louise Mitchell Professor in the School of Medicine and the co-director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine, is the senior author. The lead authors are Charles K.F. Chan, Ph.D., assistant professor of surgery; medical student Gunsagar Gulati, MD; Rahul Sinha, Ph.D., instructor of stem cell biology and regenerative medicine; and research assistant Justin Vincent Tompkins.

'True, multipotential, self-renewing'

The skeletal stem cells are distinct from another cell type called the

mesenchymal stem cell, which can generate skeletal tissues, fat and muscle. Mesenchymal stem cells, which can be isolated from blood, bone marrow or fat, are considered by some clinicians to function as all-purpose stem cells. They have been tested, with limited success, in clinical trials and as unproven experimental treatments for their ability to regenerate a variety of tissues. Recently, three elderly patients in Florida were blinded or lost most of their sight after mesenchymal stem cells from fat were injected into their eyes as an experimental treatment for macular degeneration.

"Mesenchymal stem cells are loosely characterized and likely to include many populations of cells, each of which may respond differently and unpredictably to differentiation signals," Chan said. "In contrast, the skeletal stem cell we've identified possesses all of the hallmark qualities of true, multipotential, self-renewing, tissue-specific stem cells. They are restricted in terms of their fate potential to just skeletal tissues, which is likely to make them much more clinically useful."

Skeletal regeneration is an important capability for any bony animal evolving in a rough-and-tumble world where only the most fit, or the fastest-healing, are likely to survive very long into adulthood. Some vertebrates, such as newts, are able to regenerate entire limbs if necessary, but the healing ability of other animals, such as mice and humans, is more modest. Although humans can usually heal a bone fracture fairly well, they begin to lose some of that ability with age. And they are completely unable to regenerate the cartilage that wears away with age or repetitive use. Researchers have wondered whether the skeletal stem cell could be used clinically to help replace damaged or missing bone or cartilage, but it's been very difficult to identify.

Adult stem cells lineage-restricted

Unlike embryonic stem cells, which are present only in the earliest stages

of development, adult stem cells are thought to be found in all major tissue types, where they bide their time until needed to repair damage or trauma. Each adult stem cell is lineage-restricted—that is, it makes progenitor cells that give rise only to the types of cells that naturally occur in that tissue. For our skeleton, that means cells that make bone, cartilage and stroma.

Chan, Longaker and their colleagues had hoped to use what they learned from identifying the mouse skeletal stem cell to quickly isolate its human counterpart. But the quest turned out to be more difficult than they had anticipated. Most cell isolation efforts focus on using a technology called fluorescence activated cell sorting to separate cells based on the expression of proteins on their surface. Often, similar cell types from different species share some key cell surface markers.

But the human skeletal stem cell turned out to share few markers with its mouse counterpart. Instead, the researchers had to compare the gene expression profiles of the mouse skeletal stem cell with those of several human cell types found at the growing ends of developing human bone. Doing so, they were able to identify a cell population that made many of the same proteins as the mouse skeletal stem cell. They then worked backward to identify markers on the surface of the human cells that could be used to isolate and study them as a pure population.

"This was quite a bioinformatics challenge, and it required a big team of interdisciplinary researchers, but eventually Chuck and his colleagues were able to identify a series of markers that we felt had great potential," Longaker said. "Then they had to prove two things: Can these cells self-renew, or make more of themselves indefinitely, and can they make the three main lineages that comprise the human skeleton?"

The researchers showed that the human skeletal stem cell they identified is both self-renewing and capable of making bone, cartilage and stroma

progenitors. It is found at the end of developing bone, as well as in increased numbers near the site of healing fractures. Not only can it be isolated from fracture sites, it can also be generated by reprogramming human fat cells or induced pluripotent stem cells to assume a skeletal fate.

'The perfect niche'

Intriguingly, the skeletal stem cell also provided a nurturing environment for the growth of human hematopoietic stem cells—or the cells in our bone marrow that give rise to our blood and immune system—without the need for additional growth factors found in serum.

"Blood-forming stem cells love the interior of spongy bone," Chan said. "It's the perfect niche for them. We found that the stromal population that arises from the skeletal stem cell can keep hematopoietic stem cells alive for two weeks without serum."

By studying the differentiation potential of the human skeletal stem cell, the researchers were able to construct a family tree of stem cells to serve as a foundation for further studies into potential clinical applications. Understanding the similarities and differences between the mouse and human skeletal stem cell may also unravel mysteries about skeletal formation and intrinsic properties that differentiate mouse and human skeletons.

"Now we can begin to understand why human bone is denser than that of mice, or why human bones grow to be so much larger," Longaker said.

In particular, the researchers found that the human skeletal stem cell expresses genes active in the Wnt signaling pathway known to modulate bone formation, whereas the mouse skeletal stem cell does not.

The ultimate goal of the researchers, however, is to find a way to use the human skeletal stem cell in the clinic. Longaker envisions a future in which arthroscopy—a minimally invasive procedure in which a tiny camera or surgical instruments, or both, are inserted into a joint to visualize and treat damaged cartilage—could include the injection of a skeletal stem cell specifically restricted to generate new cartilage, for example.

"I would hope that, within the next decade or so, this cell source will be a game-changer in the field of arthroscopic and regenerative medicine," Longaker said. "The United States has a rapidly aging population that undergoes almost 2 million joint replacements each year. If we can use this stem cell for relatively noninvasive therapies, it could be a dream come true."

Provided by Stanford University Medical Center