Researchers coax human stem cells to rapidly generate bone, heart muscle

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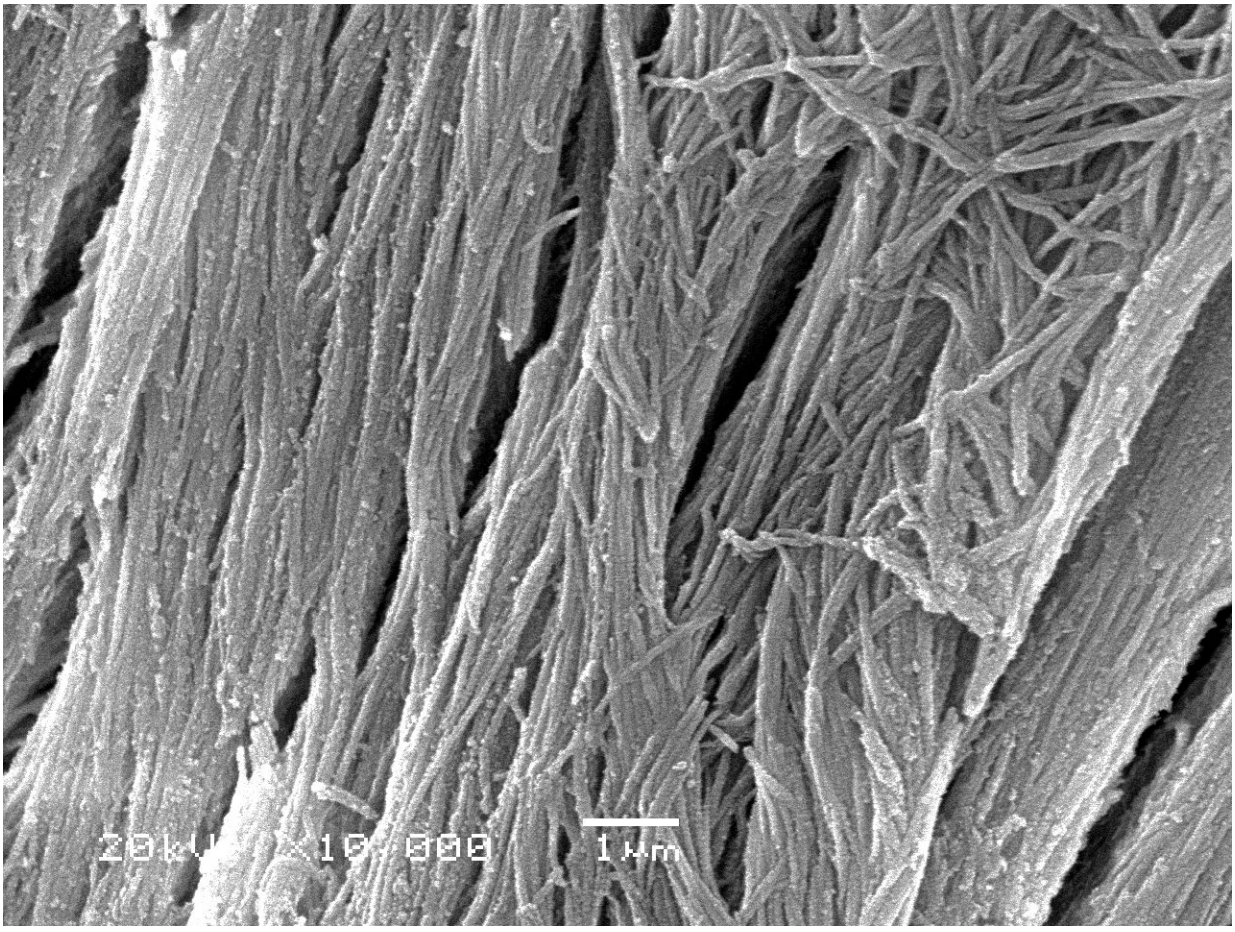

Electronic micrography 10000 magnification of mineralized collagen fibers in bone. Credit: Wikipedia/CC BY-SA 3.0

Researchers at the Stanford University School of Medicine have mapped out the sets of biological and chemical signals necessary to quickly and efficiently direct human embryonic stem cells to become pure populations of any of 12 cell types, including bone, heart muscle and cartilage.

The ability to make pure populations of these cells within days rather than the weeks or months previously required is a key step toward clinically useful regenerative medicine—potentially allowing researchers to generate new beating heart cells to repair damage after a heart attack or to create cartilage or bone to reinvigorate creaky joints or heal from trauma.

The study also highlights key, but short-lived, patterns of gene expression that occur during human embryo segmentation and confirms that human development appears to rely on processes that are evolutionarily conserved among many animals. These insights may also lead to a better understanding of how congenital defects occur.

"Regenerative medicine relies on the ability to turn pluripotent human stem cells into specialized tissue stem cells that can engraft and function in patients," said Irving Weissman, MD, the director of Stanford's Institute for Stem Cell Biology and Regenerative Medicine, and also of its Ludwig Cancer Center. "It took us years to be able to isolate blood-forming and brain-forming stem cells. Here we used our knowledge of the developmental biology of many other animal models to provide the positive and negative signaling factors to guide the developmental choices of these tissue and organ stem cells. Within five to nine days we can generate virtually all the pure cell populations that we need."

Weissman and Lay Teng Ang, of the Genome Institute of Singapore, are the senior authors of the study, which will be published July 14 in *Cell*. Graduate student Kyle Loh and research assistant Angela Chen, both at

Stanford, share lead authorship of the study.

Unraveling the mysteries

Embryonic stem cells are pluripotent, meaning they can become any type of cell in the body. They do so by responding to a variety of time- and location-specific cues within the developing embryo that direct them to become specific cell types. Researchers have learned a lot about how this process is controlled in animals, including fish, mice and frogs.

In contrast to many other animals, human embryonic development is a mysterious process, particularly in the first weeks after conception. This is because cultivating a human embryo for longer than 14 days is banned by many countries and scientific societies. But we do know that, like other animals, the human embryo in its earliest stages consists of three main components known as germ layers: the ectoderm, the endoderm and the mesoderm.

Each of these germ layers is responsible for generating certain cell types as the embryo develops. The mesoderm, for example, gives rise to key cell types, including cardiac and skeletal muscle, connective tissue, bone, blood vessels, blood cells, cartilage and portions of the kidneys and skin.

"The ability to generate pure populations of these cell types is very important for any kind of clinically important regenerative medicine," said Loh, "as well as to develop a basic road map of human embryonic development. Previously, making these cell types took weeks to months, primarily because it wasn't possible to accurately control cell fate. As a result, researchers would end up with a hodgepodge of cell types."

Loh and Chen wanted to know what signals drive the formation of each of the mesodermally derived cell types. To do so, they started with a human embryonic stem cell line, which they chemically nudged to

become cells that form what's known as the primitive streak on the hollow ball of cells of the early embryo. They then experimented with varying combinations of well-known signaling molecules, including WNT, BMP and Hedgehog, as a way to coax these cells to become ever-more-specialized precursor cells.

A yes-and-no strategy

They learned that often the cells progressed down the developmental path through a series of consecutive choices between two possible options. Think about the carnival game in which a disc is dropped down a slanted, peg-studded board to land in one of several cups at the bottom. The eventual destination is determined by whether the disc goes to the left or right of each consecutive peg.

The quickest, most efficient way to micromanage the cells' developmental decisions was to apply a simultaneous combination of factors that both encouraged the differentiation into one lineage while also actively blocking the cells from a different fate—a kind of "yes" and "no" strategy.

For example, cells in the primitive streak can become either endoderm or one of two types of mesoderm. Inhibiting the activity of a signaling molecule called TGF beta drives the cells to a mesodermal fate. Adding a signaling molecule called WNT, while also blocking the activity of another molecule known as BMP, promotes differentiation into one kind of mesoderm; conversely, adding BMP while blocking WNT drives the cells to instead become the other type of mesoderm.

"We learned during this process that it is equally important to understand how unwanted cell types develop and find a way to block that process while encouraging the developmental path we do want," said Loh.

By carefully guiding the cells' choices at each fork in the road, Loh and Chen were able to generate bone cell precursors that formed human bone when transplanted into laboratory mice and beating heart muscle cells, as well as 10 other mesodermal-derived cell lineages.

At each developmental stage, the researchers conducted single-cell RNA sequencing to identify unique gene expression patterns and assess the purity of individual cell populations. By looking at the gene expression profile in single cells, the researchers were able to identify previously unknown transient states that typified the progression from precursor to more-specialized cells.

Segmentation in embryo development

In particular they observed for the first time a transient pulse of gene expression that precedes the segmentation of the human embryo into discrete parts that will become the head, trunk and limbs of the body. The process mirrors what is known to occur in other animals, and confirms that the segmentation process in human development has been evolutionarily conserved.

"The segmentation of the embryo is a fundamental step in human development," said Loh. "Now we can see that, evolutionarily, it's a very conserved process." Understanding when and how segmentation and other key developmental steps occur could provide important clues as to how congenital birth defects arise when these steps go awry.

The ability to quickly generate purified populations of specialized precursor cells has opened new doors to further study.

"Next, we'd like to show that these different human progenitor cells can regenerate their respective tissues and perhaps even ameliorate disease in animal models," said Loh.

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