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Adult stem cells are touchy-feely, need environmental clues

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A certain type of adult stem cell can turn into bone, muscle, neurons or other types of tissue depending on the "feel" of its physical environment, according to researchers at the University of Pennsylvania.

The researchers discovered that mesenchymal stem cells, which regularly reside in the bone marrow as part of the body's natural regenerative mechanism, depend on physical clues from their local environment in order to transform into different types of tissue. The researchers were even able to manipulate stem cells by changing the firmness of the gel on which they were grown.

The researchers believe that their findings, which appear in the Aug. 25 issue of the journal *Cell*, could change the way in which people work with stem cells.

"Basically, mesenchymal stem cells feel where they're at and become what they feel," said Dennis Discher, a professor in Penn's School of Engineering and Applied Science. "The results begin to establish a physical basis for both stem-cell use against diseases and for stem-cell behavior in embryonic development,"

Much of the work in stem-cell science has involved the study of the chemical microenvironment, the soup of chemical messenger signals that are generally thought to guide stem cells through the process of differentiation, where relatively "blank" stem cells turn into specific cell types. For the first time, the Penn researchers have proven that the

physical microenvironment is also crucial for guiding the cells through differentiation. According to Adam Engler, the first author on the study and a graduate student in the School of Engineering and Applied Science, soft microenvironments, that mimic the brain, guide the cells toward becoming neurons, stiffer microenvironments, that mimic muscle, guide the cells toward becoming muscle cells and comparatively rigid microenvironments guide the cells toward becoming bone.

"While I anticipated that the physical environment might limit the fate of stem cells, I never really thought that it would be sufficient to direct cell fate," said Lee Sweeney, a coauthor of the study and chairman of Physiology in Penn's School of Medicine. "When I saw Adam's first images, I was stunned to see that the physical environment alone was telling the stem cells to become neurons or muscle or bone. "

Mesenchymal stem cells sense their environment through the force it takes them to push against surrounding objects. Each cell has its own skeleton and molecular motors that it uses as muscles. According to the researchers, the amount of force the stem cell needs to move its cellular muscles triggers an internal chemical signal that, in turn, directs the cell to differentiate.

"The cytoskeleton uses motors that, like our muscles, are based on the mechanical tension created by molecules of actin and myosin," Engler said. "When we deprive these stem cells of myosin, the cells do not respond to their physical environment, only their chemical environment."

But, the physical microenvironment can change due to injury and also in disease, which would make it difficult to use these stem cells in certain types of therapy. After a heart attack, for example, the heart becomes so scarred that stem cells seem ineffective in fixing the damage by turning into replacement cardiac muscle.

"The cardiac tissue may have been so damaged during the heart attack that the stem cells do not recognize the microenvironment as a guide for turning into heart muscle," Discher said; "however, our studies show that it might be possible to 'prime' stem cells for therapy in the lab, before implanting them in the heart, spine or whatever damaged environment you want to place them."

Source: University of Pennsylvania