MedicalXpress

'Different kind of stem cell' possesses attributes favoring regenerative medicine

November 19 2012

A research team at Georgetown Lombardi Comprehensive Cancer Center say the new and powerful cells they first created in the laboratory a year ago constitute a new stem-like state of adult epithelial cells. They say these cells have attributes that may make regenerative medicine truly possible.

In the November 19 online early edition of the Proceedings of the National Academy of Sciences (*PNAS*), they report that these new stem-like cells do not express the same genes as embryonic stem cells and induced pluripotent stem cells (iPSCs) do. That explains why they don't produce tumors when they grow in the laboratory, as the other stem cells do, and why they are stable, producing the kind of cells researchers want them to.

"These seem to be exactly the kind of cells that we need to make regenerative medicine a reality," says the study's senior investigator, chairman of the department of pathology at Georgetown Lombardi, a part of Georgetown University Medical Center.

This study is a continuation of work that led to a breakthrough in December 2011 when Schlegel and his colleagues demonstrated that he and his team had designed a laboratory technique that keep both normal as well as cancer cells alive indefinitely—which previously had not been possible.

They had discovered that adding two different substances to these cells

(a Rho kinase inhibitor and fibroblast feeder cells) pushes them to morph into stem-like cells that stay alive indefinitely. When the two substances are withdrawn from the cells, they revert back to the type of cell that they once were. They dubbed these cells conditionally reprogrammed cells (CRCs).

The advance was seen as an exciting demonstration of personalized cancer medicine. In fact, a case study authored by Schlegel and his team, reported in the September 27 issue of the New England Journal of Medicine (NEJM), demonstrated how CRCs derived from normal and tumor cells of a 24-year-old man with a rare type of lung tumor allowed physicians to identify an effective cancer therapy. These cells were used to screen potential treatments and in this way, the scientists were able to see which therapies were active against the tumor cells and less harmful to the normal cells.

"Our first clinical application utilizing this technique represents a powerful example of individualized medicine," Schlegel said in September. But he cautioned, "It will take an army of researchers and solid science to figure out if this technique will be the advance we need to usher in a new era of personalized medicine."

This study was designed to see how the CRCs compared to known properties of embryonic stem cells and iPSCs, which are adult cells that have been manipulated by addition of genes to make them capable of differentiating (morphing into new adult cell types). Both embryonic stem cells and iPSCs have been investigated for use in regenerative medicine, but each can form tumors when injected into mice and "it is difficult to control what kind of cells these cells differentiate into," Schlegel says. "You may want them to be a lung cell, but they could form a skin cell instead."

In contrast, cells derived from the lung will develop stem-like properties

when the conditions are added, allowing expansion of the lung cell population. However, when the conditions are withdrawn, they will revert to differentiated lung cells, he says. Schlegel added that they do this rapidly—within three days of adding the inhibitor and feeder cells, they efficiently generated large numbers of stem-like cells. It is also completely reversible: when the conditions are taken away, the cells lose their stem-like properties and potentially can be safely implanted into tissue.

The researchers compared gene expression between the three cell types and found that while some of the same genes are expressed in all the cells, CRCs don't over express the same critical genes that embryonic stem cells and iPSCs do. "Because they don't express those genes, they don't form tumors and they are lineage committed, unlike the other cells," Schlegel says. "That shows us that CRCs are a different kind of stem-like cell."

As part of the study, the research team showed that when cervical cells are conditioned and placed on a three-dimensional platform, they start to form cells that "look like the cervix," Schlegel says. The same is true from cells in the trachea—on a 3-D platform, they begin to look like a trachea, he says.

If and when use of CRCs are perfected for the clinic—and that will take considerable work, Schlegel says—they potential could be used in a wide variety of novel ways.

"Perhaps they could be used more broadly for chemosensitivity, as we demonstrated in the NEJM study, for regenerative medicine to replace organ tissue that is damaged, for diabetes—we could remove remaining islet ells in the pancreas, expand them, and implant them back into the pancreas —and to treat the many storage diseases caused by lack of liver enzymes. In those cases, we can take liver cells out, expand them and

insert normal genes in them, and put them back in patients," Schlegel says.

"The potential of these cells are vast, and exciting research to help define their ability is ongoing," he says.

Provided by Georgetown University Medical Center