Cell cycle speed is key to making aging cells young again

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A fundamental axiom of biology used to be that cell fate is a one-way street—once a cell commits to becoming muscle, skin, or blood it always remains muscle, skin, or blood cell. That belief was upended in the past decade when a Japanese scientist introduced four simple factors into skin cells and returned them to an embryonic-like state, capable of becoming almost any cell type in the body.

Hopeful of revolutionary medical therapies using a patient's own cells, scientists rushed to capitalize on the discovery by 2012 Nobel Laureate Shinya Yamanaka. However, the process has remained slow and inefficient, and scientists have had a difficult time discovering a genetic explanation of why this should be.

In the Jan. 30 issue of the journal *Cell*, Yale School of Medicine researchers identified a major obstacle to converting cells back to their youthful state—the speed of the cell cycle, or the time required for a cell to divide.

When the cell cycle accelerates to a certain speed, the barriers that keep a cell's fate on one path diminish. In such a state, cells are easily persuaded to change their identity and become pluripotent, or capable of becoming multiple cell types

"One analogy may be that when temperature increases to sufficient degrees, even a very hard piece of steel can be malleable so that you can give it a new shape easily," said Shangqin Guo, assistant professor of cell

biology at the Yale Stem Cell Center and lead author of the paper. "Once cells are cycling extremely fast, they do not seem to face the same barriers to becoming pluripotent."

Guo's team studied blood-forming cells, which when dividing undergo specific changes in their cell cycle to produce new blood cells. Blood-forming progenitor cells normally produce only new blood cells. However, the introduction of Yamanaka factors sometimes—but not always—help these blood-forming cells become other types of cells. The new report finds that after this treatment blood-forming cells tend to become pluripotent when the cell cycle is completed in eight hours or less, an unusual speed for adult cells. Cells that cycle more slowly remain blood cells.

"This discovery changes the way people think about how to change cell fate and reveals that a basic 'house-keeping' function of a cell, such as its cell cycle length, can actually have a major impact on switching the fate of a cell," said Haifan Lin, director of the Yale Stem Cell Center.

The study has other implications than explaining the bottleneck in reprogramming that makes it difficult to produce individualized pluripotent stem cells for research and therapy. Shangqin Guo noted that many human diseases are associated with abnormalities in establishing proper cell identity as well as abnormalities in cell cycle behavior.

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