

Advance in regenerative medicine could make reprogrammed cells safer while improving their function

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The enormous promise of regenerative medicine is matched by equally enormous challenges. But a new finding by a team of researchers led by Weill Cornell Medical College has the potential to improve both the safety and performance of reprogrammed cells.

The researchers' study, published in today's issue of the journal *Nature*, found that an enzyme, activation-induced cytidine deaminase (AID), helps in the process that changes an adult human cell into an induced [pluripotent stem cell](#) (iPS cell). These iPS [cells](#) can then be developed into any kind of cell needed to therapeutically restore tissues and organs.

The finding settles an ongoing controversy regarding use of AID to reprogram cells, says the study's senior investigator, Dr. Todd Evans, vice chair for research and professor of cell and [developmental biology](#) in the Department of Surgery at Weill Cornell Medical College.

"The dispute was whether AID is required to make iPS cells, and we found that the enzyme does make reprogramming very efficient, although it is not absolutely necessary," says Dr. Evans, an internationally-recognized authority on [regenerative medicine](#). "In fact, we plan to test if reprogramming iPS cells without AID may even be helpful."

One reason is that AID can cause [genetic mutations](#) that can lead to

cancer. AID is best known as a master regulator of antibody diversity in B cells, and in order to create varied types of beneficial antibodies, it routinely mutates [antibody genes](#). But sometimes the process goes awry, resulting in development of B cell lymphoma, Dr. Evans says. "That leads us to believe that if you can reprogram cells without AID, it could reduce risk of potential mutations, and thus be safer."

iPS Cells Without AID Remember What They Once Were

In order to push a cell, such as a fibroblast, to revert to an iPS cell, the epigenetic "markers" that define an adult cell must be removed. "All cells of the body have the same genes, but they are used differently in different tissues," Dr. Evans explains. "If an undifferentiated cell becomes a heart cell, somehow it has to lock in and stabilize that particular adult phenotype and not forget what it is."

One way that function is accomplished is by placing a methylation group on top of certain genes that activate other cell destinations—such as to become a liver cell—usually switching those genes off. "We have known how these marks are put on genes, but we didn't know how they were taken off in the process of pushing an adult cell to revert back to a stem-cell-like state," Dr. Evans says.

Dr. Evans and his colleagues found that the AID enzyme removed those epigenetic markers.

They then created a mouse that did not produce AID to see if the animal's adult fibroblast cells could be pushed back to iPS cells. "If you need AID to reprogram the cells, you shouldn't be able to do it, or do it well."

Surprisingly, they found that the cells at first seemed to want to reprogram even faster than normal cells, but most never fully reverted to a stem-cell-like state. "They eventually crashed and differentiated back into a fibroblast," Dr. Evans says. "What that meant is that they never cleared their memory of being a fibroblast cell. AID efficiently removes that epigenetic memory, smoothing the way for a cell to morph into an undifferentiated state."

But some of the mouse adult fibroblasts lacking AID—those that Dr. Evans says they "babysat"—did become iPS cells.

Despite the fact that reprogramming adult cells without AID is inefficient, the researchers say that the method may offer another advantage besides increased safety.

"It might be useful to allow epigenetic memory to be retained," Dr. Evans says. "If you want to make new [cardiac cells](#) to repair a patient's heart, it might be better to start with a cardiac cell and push it to become an iPS cell, from which other cardiac cells could be made. If these cells remember they were cardiac cells, they might make a better heart cell than if they came from reprogrammed fibroblasts."

Provided by Weill Cornell Medical College

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