Mature B cells reprogrammed to stem-cell-like state

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Fully mature, differentiated B cells can be reprogrammed to an embryonic-stem-cell-like state, without the use of an egg according to a study published in the April 18 issue of *Cell*.

In previous research, induced pluripotent stem (IPS) cells have been created from fibroblasts, a specific type of skin cells that may differentiate into other types of skin cells. Because there is no way to tell if the fibroblasts were fully differentiated, the cells used in earlier experiments may have been less differentiated and therefore easier to convert to the embryonic-stem-cell-like state of IPS cells.

B cells are immune cells that can bind to specific antigens, such as proteins from bacteria, viruses or microorganisms. Unlike fibroblasts, mature B cells have a specific part of their DNA cut out as a final maturation step. “Once that piece of DNA is cut out, it can’t come back,” says Jacob Hanna, first author on the paper and a postdoctoral fellow in Whitehead Member Rudolf Jaenisch’s lab. “Checking the genome give us a way to make sure the resulting IPS cells were not from immature cells.”

Hanna and his colleagues began the experiment by generating IPS cells from immature B cells. Similar to the process used to create IPS cells from fibroblast cells, Hanna successfully reprogrammed the immature B cells into IPS cells by using retroviruses to transfer four genes (Oct4, Sox2, c-Myc and Klf4) into the cells’ DNA.

However, an additional factor, CCAAT/enhancer-binding-protein-α (C/EBPα), was needed to nudge mature B cells to be reprogrammed as IPS cells.

Like IPS cells from earlier fibroblast studies, the IPS cells from both the mature and immature B cells could be used to create mice. The mice grown from the reprogrammed mature B cells were missing the same part of their DNA as the mature B cells, demonstrating that Hanna and his colleagues had successfully reprogrammed fully differentiated cells.

In addition to demonstrating the power of reprogramming, this work offers the promise of powerful new mouse models for autoimmune diseases such as multiple sclerosis and type 1 diabetes, in which the body attacks certain types of its own cells. For example, mature B or T cells specific for nerve cells called glia could be reprogrammed to IPS cells and then used to create mice with an entire immune system that is primed to only attack the glia cells, thereby creating a mouse model for studying multiple sclerosis.

Eventually, researchers will be able to study diseases by following a similar process with human cells, predicts Jaenisch, who is also a professor of biology at Massachusetts Institute of Technology. “In principle, this will allow you to transfer a complex genetic human disease into a Petri dish, and study it,” he says. “That could be the first step to analyze the disease and to define a therapy.”

Source: Whitehead Institute for Biomedical Research