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# Scientists reprogram mature blood cells from mice into blood-forming HSCs

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Researchers at Boston Children's Hospital have reprogrammed mature blood cells from mice into blood-forming hematopoietic stem cells (HSCs), using a cocktail of eight genetic switches called transcription factors. The reprogrammed cells, which the researchers have dubbed induced HSCs (iHSCs), have the functional hallmarks of HSCs, are able to self-renew like HSCs, and can give rise to all of the cellular components of the blood like HSCs.

The findings mark a significant step toward one of the most sought-after goals of regenerative medicine: the ability to produce HSCs suitable for hematopoietic stem cell transplantation (HSCT) from other cell types, in particular more mature or differentiated cells.

The research team, led by Derrick J. Rossi, PhD, of Boston Children's Program in Cellular and Molecular Medicine, reported their work today online in the journal *Cell*.

HSCs are the basic starting material for HSCTs, regardless of their source (bone marrow, umbilical cord blood, peripheral blood). The success of any individual patient's HSCT is tied to the number of HSCs available for transplant: the more cells, the more likely the transplant will take hold. However, HSCs are quite rare.

"HSCs only comprise about one in every 20,000 cells in the bone marrow," says Rossi. "If we could generate autologous HSCs from a patient's other cells, it could be transformative for transplant medicine and for our ability to model diseases of blood development."

In their study, Rossi and his collaborators, including lead author Jonah Riddell, PhD, screened gene expression in 40 different types of blood and blood progenitor cells from mice. From this screen they identified 36 transcription factors—genes that control when other genes are turned on and off—that are expressed exclusively in HSCs, not in cells that arise from them.

"Blood cell production invariably goes in one direction: from stem cells, to progenitors, to mature effector cells," Rossi explains. "We wanted to reverse the process and derive HSCs from differentiated blood cells using transcription factors that we found were specific to HSCs."

In a series of mouse transplantation experiments, Rossi's team found that six—Hlf, Runx1t1, Pbx1, Lmo2, Zfp37 and Prdm5—of the 36 factors, plus two additional factors not originally identified in their screen—Mycn and Meis1—were sufficient to robustly reprogram two kinds of blood progenitor cells (pro/pre B cells and common myeloid progenitor cells) into iHSCs.

Rossi's team reprogrammed their source cells by exposing them to viruses containing the genes for all eight factors and a molecular switch that turned the factor genes on in the presence of doxycycline. They then transplanted the exposed cells into recipient mice and activated the genes by giving the mice doxycycline.

The resulting iHSCs were capable of generating the entire blood cell repertoire in the transplanted mice, showing that they had gained the ability to differentiate into all blood lineages. Stem cells collected from those recipients were themselves capable of reconstituting the blood of secondary transplant recipients, proving that the eight-factor cocktail could instill the capacity for self-renewal—a hallmark property of HSCs.

Taking the work a step further, Rossi's team treated mature mouse myeloid cells with the same eight-factor cocktail. Again, when transplanted into mice, iHSCs were generated that produced all of the blood lineages and could regenerate the blood of secondary transplant recipients.

Stuart Orkin, MD, one of the leaders of Dana-Farber/Boston Children's Cancer and Blood Disorders Center and a co-author on the paper, notes that the use of mice as a kind of reactor for reprogramming marks a novel direction in HSC research.

"In the blood research field, no one has the conditions to expand HSCs in the tissue culture dish," he says. "Instead, by letting the reprogramming occur in mice, Rossi takes advantage of the signaling and environmental cues HSCs would normally experience."

Orkin adds that iHSCs are nearly indistinguishable from normal HSCs at the transcriptional level. "The iHSCs have a gene expression pattern remarkably similar to HSCs."

The current findings are far from translation to the transplantation clinic. Still to be answered are the precise contribution of each of the eight factors to the reprogramming process and whether approaches that do not rely on viruses and transcription factors can have similar success. It also is not yet known whether the same results can be achieved using human cells or whether other, non-blood cells can be reprogrammed to iHSCs.

But with these results Rossi's team has already succeeded where many other attempts have failed. And iHSCs in their current state constitute a promising springboard for better understanding of HSC biology and development.

"Our data show that the functional and molecular identity of HSCs can be tapped with relatively few factors using the paradigm of cellular reprogramming in a manner similar to the generation of induced pluripotent stem cells," Rossi says.

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Source:  
Boston Children's Hospital

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