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Research Highlights

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The innate debate over HSCs

Megan Scudellari¹

New evidence confirms the instructive role of cytokines in blood stem cell differentiation

Nature versus nurture isn't just a debate over child rearing anymore. Scientists are having the same argument about the commitment decisions of haematopoietic stem cells: do blood stem cells differentiate from the inside or outside? Two recent papers tip the scales firmly toward the latter.

There are two models for how regulatory molecules, like cytokines, might influence haematopoietic stem cell (HSC) differentiation. In the permissive model, cells independently commit to a lineage and then external cytokines permit certain lineages to live while the others die off. In the instructive model, cytokines directly cause HSCs to differentiate into specific lineages. The distinction is only straightforward conceptually, as many study results can be interpreted for either model. For example, if a pool of multipotent cells treated with granulocyte colony-stimulating factor (G-CSF) primarily differentiate into granulocytes, did the cytokine shepherd progenitors into a granulocytic lineage or permit cells precommitted to become granulocytes to survive as other lineages died off?

In a recent *Science* publication, [Timm Schroeder](#) and colleagues at the Institute for Stem Cell Research at the Helmholtz Center in Munich cultured almost 700 murine granulocyte-macrophage progenitors (GMPs) in either macrophage colony-stimulating factor (M-CSF) or G-CSF and observed the cells with continuous single-cell imaging technologies to track how the cells responded to the cytokines¹. They specifically watched for evidence of cell death, a sign of permissive regulation.

After counting colonies without any sign of apoptosis, the team found that GMPs cultured in M-CSF or G-CSF led to the respective production of exclusively monocytic (M) or neutrophil granulocytic (G) cells. "We've shown the signals that emanate from these cytokine receptors can influence the commitment machinery of these progenitor cells," says Schroeder, confirming the instructive model of regulation in the case of M-CSF and G-CSF on GMPs.

"This is the first direct evidence that apoptosis is not the mechanism for these two cytokines to affect the differentiation of [GMPs]," says [Chengcheng Zhang](#), an HSC researcher at the University of Texas Southwestern Medical Center. The instructive model, however, does not necessarily fit for all cell types, he adds. "I think the realistic situation is very complex. Maybe the instructive model works in some situations and the permissive model in others." Schroeder agrees: "We've shown simply that these cells can do this, but you have to look for every cytokine in every cell type separately. It's dangerous to generalize too much."

In a complementary study published in *Cell* on 24 July, researchers at the Center of Immunology of Marseille-Luminy in France chanced upon the same instructive effect in HSCs while examining the knockout of MafB, a transcription factor highly expressed in mature monocytes and macrophages². "We started out with a curious observation," says [Michael Sieweke](#), senior author on the paper: in bone marrow transplantations, MafB knockouts were more likely to become myeloid cells than lymphoid or erythroid cells. Further molecular analysis showed that MafB regulates the sensitivity of HSCs to M-CSF — when MafB levels are reduced, the cell is more sensitive to M-CSF, which activates a myeloid master regulator, PU.1, and instructs the cells to a myeloid fate.

Schroeder says it's quite nice to see his and Sieweke's group reach the same idea using different routes. "They [Sieweke's group] took a molecular approach and came to the same conclusion."

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Author affiliations

1. [Megan Scudellari](#) is a freelance writer based in Durham, North Carolina.

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