

Newly identified genes impact how transplanted stem cells give rise to blood cells

February 16 2016

A team of researchers led by scientists at St. Jude Children's Research Hospital is looking at ways to improve how blood-forming stem cells can be used for therapeutic interventions. The work has uncovered a group of genes that regulate how hematopoietic stem cells start to grow and thrive in mice. The function of many of these genes was previously unknown. Reconstitution of a robust blood-forming system is essential for recovery from many catastrophic diseases as well as from chemotherapy treatments. A report on this study appears today in the *Journal of Experimental Medicine*.

Hematopoietic stem cell transplantation is the only therapy that cures many catastrophic malignancies linked to bone marrow or immune system failure. However, generating sufficient quantities of viable stem cells for this type of intervention is immensely challenging. Despite efforts to increase the yield of [blood-forming stem cells](#), the viability of these cells in culture remains a problem. As an alternative to this type of approach, St. Jude researchers are looking at ways to enhance how these rare but valuable stem cells take hold once transplanted into a new host.

"We recognized that one barrier to improving blood stem cell transplantation is a lack of understanding of how these blood-forming stem cells successfully grow in the challenged environment of transplant. So we set out to identify the genes that control this process," said Shannon McKinney-Freeman, Ph.D., assistant member in the St. Jude Department of Hematology and the study's corresponding author.

"Our hope is to decipher the critical molecular pathways that control the ability of these clinically valuable cells to transplant into a new host," added Per Holmfeldt, formerly a postdoctoral fellow at St. Jude and one of the study's authors.

According to the National Bone Marrow Registry, about 3,000 children require hematopoietic stem cell transplantation each year in the United States. Much of the mortality and morbidity linked to this type of transplantation is due to infection and other complications but could be addressed in some way by protocols that enhance the growth of new blood cells arising from [transplanted stem cells](#).

After four years of work, a new screening method developed in mouse model systems turned up 17 genes that are novel regulators of hematopoietic stem cell transplantation. Thirteen of these genes had never before been linked to the biology of engraftment of blood-forming stem cells. Engraftment is when new blood-forming stem cells start to grow and produce healthy, mature blood cells.

The scientists were also able to pinpoint the role of the Foxa3 gene, which was shown for the first time to play an important role in repopulating blood-forming stem cells in the experimental system used by the researchers. Investigators found that Foxa3 likely regulates the blood-cell-forming response that takes place under the conditions of stress experienced after transplantation.

"Our functional screen in mice is a first step to enhancing hematopoietic stem [cell transplantation](#). If we are to improve transplant outcomes in patients, we next need to study these identified genes and the molecules they specify in much more detail," McKinney-Freeman said. "The more we understand the full scope of the molecular mechanisms that regulate stable engraftment of blood [stem cells](#), the better equipped we will be to develop and clinically test novel therapies to improve health outcomes."

More information: Per Holmfeldt et al. Functional screen identifies regulators of murine hematopoietic stem cell repopulation, *The Journal of Experimental Medicine* (2016). [DOI: 10.1084/jem.20150806](https://doi.org/10.1084/jem.20150806)

Provided by St. Jude Children's Research Hospital

Citation: Newly identified genes impact how transplanted stem cells give rise to blood cells (2016, February 16) retrieved 20 November 2023 from <https://medicalxpress.com/news/2016-02-newly-genes-impact-transplanted-stem.html>

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