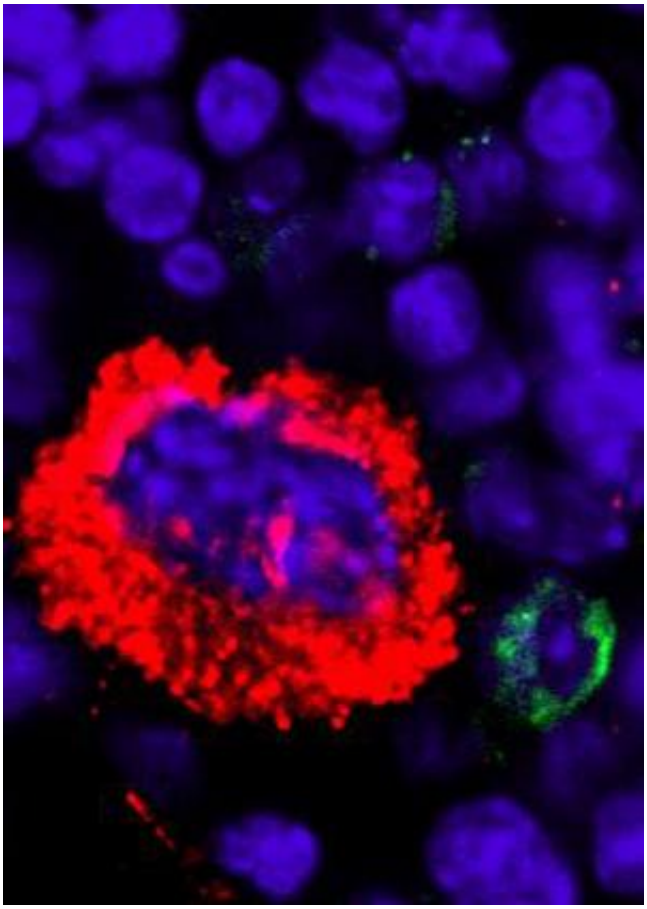
New insight that 'mega' cells control the growth of blood-producing cells

October 19 2014



In this image, a hematopoietic stem cell (green) attaches to a megakaryocyte (red) in bone marrow. Credit: Meng Zhao, Ph.D., Linheng Li Lab, Stowers Institute for Medical Research

While megakaryocytes are best known for producing platelets that heal

wounds, these "mega" cells found in bone marrow also play a critical role in regulating stem cells according to new research from the Stowers Institute for Medical Research. In fact, hematopoietic stem cells differentiate to generate megakaryocytes in bone marrow. The Stowers study is the first to show that hematopoietic stem cells (the parent cells) can be directly controlled by their own progeny (megakaryocytes).

The findings from the lab Stowers Investigator Linheng Li, Ph.D., described in the Oct. 19 issue of the journal *Nature Medicine*, could cause researchers to rethink what they know about the workings of megakaryocytes and potentially lead to new treatments for patients recovering from chemotherapy or organ transplantation.

"Our results suggest that megakaryocytes might be used clinically to facilitate adult stem cell regeneration and to expand cultured cells for adult stem cell transplants," says Meng Zhao, Ph.D., a postdoctoral fellow at Stowers and lead author on the study.

Stowers researchers discovered that megakaryocytes directly regulate the function of murine hematopoietic stem cells—adult stem cells that form blood and immune cells and that constantly renew the body's blood supply. These cells can also develop into all types of blood cells, including white blood cells, red blood cells, and platelets.

Because of their remarkable ability to renew themselves and differentiate into other cells, hematopoietic stems cells are the focus of intense research and have been used to treat many diseases and conditions. The transplantation of isolated human hematopoietic stem cells is used in the treatment of anemia, immune deficiencies and other diseases, including cancer.

Basic research has centered on identifying and characterizing hematopoietic stem cells, however, it is still not clear how hematopoietic

stem cells actually work, and how they are regulated because of the complexity of the bone marrow microenvironment. Zhao and his colleagues discovered that as a terminally differentiated progeny, megakaryocytes regulate hematopoietic stem cells by performing two previously unknown functions.

"Megakaryocytes can directly regulate the amount of hematopoietic stem cells by telling the cells when they need to keep in the quiescent stage, and when they need to start proliferating to meet increased demand," Maintaining that delicate balance is important, he adds. "You don't want to have too many or too few hematopoietic stem cells."

These findings are supported by similar research from the laboratory of Paul S. Frenette, Ph.D., at the Albert Einstein College of Medicine, also reported in the Oct. 19 issue of *Nature Medicine*.

Employing the advanced technology of the Institute's Cytometry, Imaging and Histology centers, the researchers examined the relationship between megakaryocytes and hematopoietic stem cells in mouse bone marrow. In the course of their research, they found that the protein transforming growth factor B1 (TGF-B1), contained in megakaryocytes, signaled quiescence of hematopoietic stem cells. They also found that when under stress from chemotherapy, megakaryocytes signaled fibroblast growth factor 1 (FGF1), to stimulate the proliferation of hematopoietic stem cells.

"Our findings suggest that megakaryocytes are required for the recovery of hematopoietic stem cells post chemotherapy," explains Li. The discovery could provide insight for using megakaryocyte-derived factors, such as TGF-B1 and FGF1, clinically to facilitate regeneration of hematopoietic stem cells, he adds.

Engineering a megakaryocyte niche (a special environment in which

stem cells live and renew) that supports the growth of hematopoietic stem cells in culture, is the next step for the researchers. Zhao and his colleagues are also investigating whether a megakaryocyte niche can be used to help expand human hematopoietic stem cells in vitro and stem cell transplantation for patients.

More information: *Nature Medicine*. DOI: 10.1038/nm.3706

Provided by Stowers Institute for Medical Research