MedicalXpress

Scientists discover enzyme that keeps blood stem cells functional to prevent anemia

March 23 2015

Stem cells can generate any type of cell in the body, but they are inactive most of the time—and for good reason. When stem cells become too active and divide too often, they risk acquiring cell damage and mutations. In the case of blood stem cells (also called hematopoietic stem cells or HSCs), this can lead to blood cancers, a loss of blood cells and an impaired ability to fight disease.

Now scientists at The Scripps Research Institute (TSRI) have found that a particular enzyme in HSCs is key to maintaining healthy periods of inactivity. Their findings, published recently in the journal *Blood*, show that animal models without this enzyme experience dangerous HSC activation and ultimately succumb to lethal anemia.

"These HSCs remain active too long and then disappear," said TSRI Associate Professor Karsten Sauer, senior author of the new study. "As a consequence, the mice lose their red blood cells and die."

With this new understanding of the enzyme, called Inositol trisphosphate 3-kinase B (ItpkB), scientists are closer to improving therapies for diseases such as bone marrow failure syndrome, anemia, leukemia, lymphoma and immunodeficiencies.

Stem Cells Need Rest

HSCs are a type of adult stem cell that lives in little niches in the bone

marrow. They are normally inactive, or "quiescent," and only divide to self-renew about every two months.

However, when mature blood cells are lost, for example through severe bleeding or during infections, HSCs become activated to generate new "progenitor" cells—the cells that replenish the blood supply and produce immune cells to fight disease. Once the blood cells have been replenished, the HSC become quiescent again.

The balance between inactivity and activity is important because HSC activation generates side products that harm HSC. In addition, every division introduces a risk of mutation, sometimes leading to cancer. "It's like a car wearing down its own engine while it is doing its work," said Sauer. "Like people, HSCs need long periods of rest to remain healthy and work well."

This means normal HSCs only ramp up production during times of need. Disease strikes when HSCs either stop regenerating or become hyperactive. For example, chronic myelogenous leukemia is caused by overproduction of certain white blood cells in the bone marrow.

New Role for Enzyme

Sauer and his colleagues set out to better understand the mechanisms that activate and deactivate HSCs. "Despite the importance of a proper 'work-rest balance' for HSCs, we know amazingly little about the molecular mechanisms controlling this," said Sauer.

They focused on ItpkB because it is produced in HSCs, and the Sauer lab and others had previously shown that ItpkB controls a major signaling pathway in other cells that had been implicated in activating HSC.

"What made ItpkB an attractive protein to study is that it can dampen

activating signaling in other cells. We hypothesized that ItpkB might do the same in HSCs to keep them at rest. Moreover, ItpkB is an enzyme whose function can be controlled by small molecules. This might facilitate drug development if our hypothesis were true," said Sauer.

The researchers started with a strain of mice that lacked the gene to produce ItpkB. The team found that these mice indeed developed hyperactive HSCs. Eventually, the mutant HSCs exhausted themselves and stopped producing progenitor cells. The mice without ItpkB experienced severe anemia as they ran out of red blood cells.

"It's like a car—you need to hit the gas pedal to get some activity, but if you hit it too hard, you can crash into a wall," said Sauer. "ItpkB is that spring that prevents you from pushing the pedal all the way through."

The researchers linked the abnormal behavior of mutant HSCs to a dangerous chain of events at the molecular level.

ItpkB's job is to attach phosphates to molecules called inositols, which then send messages to other parts of the cell. Sauer and his colleagues had found that ItpkB can turn one inositol, called IP3, into an inositol called IP4.

This is significant because IP4 controls cell proliferation, cellular metabolism and aspects of the immune system. The new study shows that IP4 also protects HSCs by dampening certain haywire signals. These go unchecked without ItpkB, and HSCs skip the healthy periods of inactivity.

The researchers then treated animal models with rapamycin, an approved anti-cancer drug, and found it halted the abnormal signaling process and prevented the excessive division of HSCs lacking ItpkB. This supported the notion that ItpkB maintains HSCs quiescence by dampening the

major activating signaling pathway mentioned above.

Sauer said future studies in his lab will focus on studying whether ItpkB has a similar function in human HSCs. "A major question is whether we can translate our findings into innovative therapies," said Sauer. "If we can show that ItpkB also keeps human HSCs healthy, this could open avenues to target ItpkB to improve HSC function in bone marrow failure syndromes and immunodeficiencies or to increase the success rates of HSC transplantation therapies for leukemias and lymphomas."

More information: IP3 3-Kinase B Controls Hematopoietic Stem Cell Homeostasis and Prevents Lethal Hematopoietic Failure in Mice, www.bloodjournal.org/content/e … blood-2014-06-583187

Provided by The Scripps Research Institute