The Yin and Yang of stem cell quiescence and proliferation

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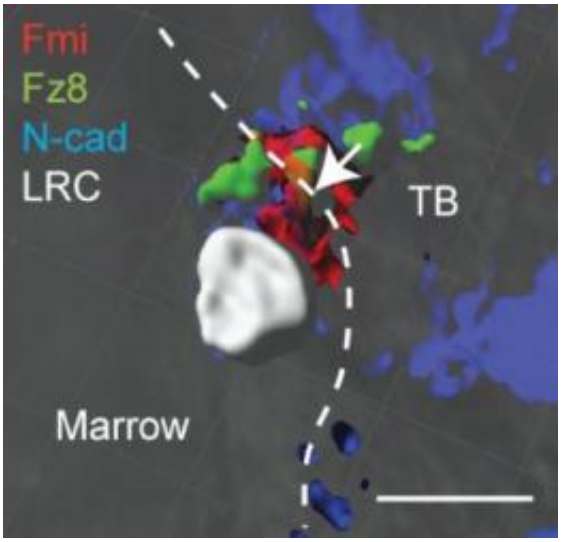

A quiescent hematopoietic stem cell (white) engages in a molecular dialog with a preosteoblast (blue). The communication takes place via Flamingo (shown in red) and Frizzled (green), which are found at the interface between the two. Credit: Courtesy of Ryohichi Sugimura, Stowers Institute for Medical Research

Not all adult stem cells are created equal. Some are busy regenerating worn out or damaged tissues, while their quieter brethren serve as a strategic back-up crew that only steps in when demand shoots up. Now, researchers at the Stowers Institute for Medical Research have identified an important molecular cue that keeps quiescent mouse hematopoietic (or blood-forming) stem cells from proliferating when their services are not needed.

Publishing in the July 20, 2012 issue of *Cell*, the team led by Stowers Investigator Linheng Li, Ph.D., report that Flamingo and Frizzled 8, a tag team best known for its role in establishing cell polarity, are crucial for maintaining a quiescent reserve pool of hematopoietic stem cells in mouse bone marrow. Their finding adds new insight into the mechanism that controls the delicate balance between long-term maintenance of stem cells and the requirements of ongoing tissue maintenance and regeneration.

"Hematopoietic stem cells daily produce billions of blood cells via a strict hierarchy of lineage-specific progenitors," says Li. "Identifying the molecular signals that allow hematopoietic stem cell populations to sustain this level of output over a lifetime is fundamental to understanding the development of different cell types, the nature of tumor formation, and the aging process. My hope is that these insights will help scientists make meaningful progress towards new therapies for diseases of the blood."

The current working model, which grew out of earlier work by Li and others, postulates that hematopoietic stem cells (HSC), which are part of the reserve pool sit quietly and only divide a few times a year. They jump into action only when needed to replace active HSCs damaged by daily wear and tear or to increase their numbers in response to injury or disease. But how quiescent and active hematopoietic stem cell subpopulations are maintained and regulated *in vivo* is largely unknown.

What is known is that both populations of cells reside in adjacent specialized microenvironments, which provide many of the molecular cues that guide stem cell activity. Frequently cycling HSCs constitute around 90 percent of all hematopoietic stem cells and are found in the central marrow, where they seek the company of endothelial and perivascular cells. The main home base of quiescent hematopoietic stem cells is trabecular bone, the spongy part typically found at the end of

long bones. Here, these cells engage in a constant molecular dialog with preosteoblasts, the precursors of bone-forming osteoblasts, which are characterized by the expression of N-cadherin.

Trying to decode the nature of the conversation graduate student and first author Ryohichi Sugimura focused on Flamingo (Fmi), a surface-based adhesion molecule, and Frizzled 8 (Fz8), a membrane-based receptor. Both molecules are part of the non-canonical arm of the so-called Wnt signaling pathway, a large network of secreted signaling molecules and their receptors. The canonical arm of the Wnt-signaling pathway exerts its influence through beta-catenin and helps regulate stem cell self-renewal in the intestine and hair follicles.

After *in vitro* experiments had revealed that Fmi and Fz8 accumulate at the interface between co-cultured quiescent hematopoietic stem cells and preosteoblasts, Sugimura and his colleagues were able to show that Fmi also regulates Fz8 distribution *in vivo*. This observation provided the first hint that these cooperation partners may carry at least part of the conversation that instructs hematopoietic stem cells to sit still. It also confirmed the previous finding by Li's team that a portion of HSCs resides in the N-cadherin+ osteoblastic niche.

When Sugimura examined the expression patterns of individual members of the Wnt signaling network within quiescent HSCs' microenvironment he found that levels of canonical Wnt ligands where low. Levels of non-canonical Wnt ligands and inhibitors of the canonical arm of the Wnt signaling network, on the other hand, were high.

"These observations indicated that the osteoblast niche provides a microenvironment in which non-canonical Wnt signaling prevails over canonical Wnt-signaling under normal conditions," says Sugimura. "It also suggested that Fmi and Fz8 may play a direct role in maintaining the pool of quiescent hematopoietic stem cells."

Mice that had been genetically engineered to lack either Fmi or Fz8 provided the crucial clue: Not only had the number of quiescent hematopoietic stem cells plummeted in these mice, their hematopoietic stem cell function was reduced by more than 70 percent as well.

Treatment with the cell-cycle specific cytotoxic drug 5-flourouracil, which wipes out actively dividing hematopoietic stem cells, confirmed the role of non-canonical Wnt-family members Flamingo and Frizzled 8. Under stress the previously observed expression patterns were reversed and canonical Wnt-signaling dominated over non-canonical signaling, enabling quiescent HSCs to proliferate and replenish the diminished supply of actively cycling HSCs.

"A better understanding of how the balance shifts between the two will provide the necessary mechanistic insight that allows us to reduce non-canonical Wnt-signaling and dial up canonical Wnt-signaling in order to activate quiescent hematopoietic stem cells during aging," says Li. "But the knob will have to be turned carefully. If the balance shifts to far in favor of canonical Wnt-signaling, it may well increase the risk of leukemia."

Provided by Stowers Institute for Medical Research

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