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Gamma interferon a wake-up call for stem cell response to infection

HOUSTON -- (June 10, 2010) – Most of the time, the body's blood-forming (hematopoietic) stem cells remain dormant, with just a few producing blood cells and maintaining a balance among the different types.

However, invading bacteria can be a call-to-arms, awaking the sleeping stem cells and prompting them to produce immune system cells that fight the foreign organisms. The "bugler" that awakes the stem cells in this battle is gamma interferon, a front-line protein defender against bacterial infection, said researchers from Baylor College of Medicine (www.bcm.edu) in a report that appears in the current issue of the journal *Nature* (www.nature.com).

"We are looking at the normal function of stem cells," said Dr. Margaret Goodell (www.bcm.edu/star/index.cfm?pmid=2947), professor of molecular and human genetics at BCM and director of the Stem Cells and Regenerative Medicine (STaR) (www.bcm.edu/star/index.cfm?PMID=0) Center. She is the report's senior author. "One of those is to respond to an infection."

Goodell and her colleagues knew that cells farther along in the differentiation process responded to infection, increasing the production of immune cells.

"We were sure there was a mechanism by which hematopoietic stem cells respond to infection, but it was not obvious," she said. They started their work with gamma interferon because they knew it played an important role in bacterial infection.

The collaboration and talents of two researchers in her laboratory – first co-authors Drs. Megan T. Baldridge and Katherine Y. King – facilitated the work with mice that led to this finding, said Goodell. Both are at BCM.

"I think our findings represent an exciting new avenue for studying hematopoiesis," said King. "By viewing the hematopoietic stem cell as the source of the immune system, we are finding fundamental ways in which the immune response affects bone marrow. This is the first time that anyone has

extensively studied hematopoietic stem cells in the context of an in vivo model (a living organism) of infection."

"As a specialist in infectious diseases, I see many patients whose bone marrow no longer produces sufficient blood cells as a consequence of their infection. This is particularly relevant in chronic infections such as mycobacterial diseases (that include tuberculosis) and AIDS," said King. "Our studies lend insight into the causes of this decrease in bone marrow function during such infections, and I hope the work will someday lead to new therapies."

Studies in mice with a chronic or long-term infection called Mycobacterium avium show that a greater proportion of a particular subset of their cells called long-term hematopoietic (blood-forming) stem cells are active. Gamma interferon prompts this activity. Mice that lack gamma interferon have fewer of these stem cells active during infection.

These findings show that gamma interferon not only activates stem cells during infection, but also regulate stem cells in normal times, enabling them to maintain the types of blood cells that exist in proportion or homeostasis.

"Our model predicts that bacterial infection detected by sentinel immune cells stimulates the increased release of gamma interferon, which then travels through the blood stream to activate HSCs (hematopoietic stem cells) in the bone marrow, leading to expansion and mobilization of the immune progenitor pool (the cells that ultimately produce immune system cells)," the researchers wrote.

They found that sustained activity by the hematopoietic stem cells can lead to at least transient problems with the quality of the stem cells and their abilities to stimulate production of more immune system cells.

"One of the most important things we found is the chronic infections (such as tuberculosis or HIV/AIDS) may be lead to bone marrow exhaustion," said Baldridge. "We knew that a condition called anemia of chronic disease exists, and this could be one of the contributing factors."

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