Blood progenitor cells receive signals from niche cells and the daughter blood cells they create

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Maintaining balance is crucial. In Drosophila, the common fruit fly, the creation and maintenance of the blood supply requires such balance.

UCLA stem cell scientists have now uncovered that two-way signaling from two different sets of cells is necessary for that balance, both to ensure enough blood cells are made to respond to injury and infection and that the blood progenitor cell population remains available for future needs.

The stem cell-like blood progenitor cells – which contribute to the cells of the adult fruit fly's blood supply – receive signals from cells that live in a nearby safe zone, or niche. These signals keep the progenitors in the same stem cell-like state so, when needed, they can begin differentiating into blood cells.

And in a new discovery, the UCLA stem cell scientists found that the blood progenitor cells receive critical signals back from the daughter blood cells they create, telling the progenitor cells when enough blood cells have been made and it's time to stop differentiating.

The new discovery of the "back talk" from the daughter blood cells appears Dec. 23, 2011 in the peer-reviewed journal *Cell*.

"The cells in the niche provide a safe environment to support blood progenitor cells," said study co-senior author Dr. Julian A. Martinez-Agosto, an assistant professor of human genetics and pediatrics and a researcher with the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA. "When the blood progenitor cells receive signals from the niche cells it creates an environment for those cells to maintain their potential and not differentiate."

Previous studies have shown that when you remove the niche cells, the blood progenitor cells differentiate unchecked. Ultimately, the fruit fly runs out of blood progenitor cells and is not able to make new blood cells to mount an immune response to infection or injury, Martinez-Agosto said.

The new findings by Martinez-Agosto and study co-senior author Utpal Banerjee, a Broad center researcher and the Irving and Jean Stone Professor and chairman of molecular, cell and developmental biology in Life Sciences, identified additional signals not coming from the niche cells. The new signals were coming from the daughter blood cells the progenitors were making, a surprising discovery, Banerjee said.

Martinez-Agosto and Banerjee noted in the four-year study that once the progenitors cells had begun differentiating and the blood cells they were creating became mature, the progenitors became very quiescent, or quiet, and did not multiply. They theorized that there must be a signal coming from the daughter cells that told the progenitors to stop multiplying and differentiating.

"It was a very surprising finding, because there was no reason to suspect that the differentiating cells had any role at all in the process," Banerjee said. "It's always been the paradigm in stem cell biology that all that was needed was the signaling from the niche cells to maintain the progenitor population. Now, we've shown that you also need the signals from the daughter cells to help maintain the progenitor cell population."

The signaling from the niche cells that maintains the progenitor population is called Hedgehog. In this study, the scientists showed that the daughter cells are sending back a signal to the progenitors that is mediated by Adenosine deaminase growth factor A (Adgf-A). The signal regulates extracellular levels of adenosine, which opposes or counters the effects of Hedgehog signaling.

"We've shown that adenosine as a molecule is really important for regulating the proliferation of progenitor cells in blood. And it requires a delicate balance – just enough signaling to give you more blood cells, but not so much that all the progenitor cells are lost," Martinez-Agosto said. "Maybe other progenitors or stem cells are using the same signaling to determine when to differentiate or not."

The team used the fruit fly because it is a very accessible model organism in which genes can be easily manipulated and their effects on cells monitored, Martinez-Agosto said. They dissected the fly lymph gland, where blood cells are made, and used green florescence to label progenitors and their daughter cells to determine when they were differentiating.

Going forward, the team will try to understand if the progenitor cells can sense the adenosine in their microenvironment under stress and injury conditions and how cell division biologically counters the niche signaling to promote formation of blood cells.

The study was funded in part by the National Heart, Lung and Blood Institute.

"Our findings reveal signals arising from differentiating cells that are required for maintaining progenitor cell quiescence and that function with the niche-derived signal in maintaining the progenitor state," the study states. "Similar homeostatic mechanisms are likely to be utilized in other systems that maintain relatively large numbers of progenitors that are not all in direct

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