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‘Back talk’ from blood cells to their progenitors is critical to balancing blood supply

When it comes to the body’s blood supply, maintaining the right balance is crucial. UCLA stem cell scientists have now discovered that in the common fruit fly, this balancing act requires a complex “conversation” involving more parties than originally thought.

In a new study, they show that two-way signaling from two different sets of cells is necessary for bloody-supply balance, both to ensure that enough blood cells are produced to respond to injury and infection and that blood progenitor cells remain available for future needs.

In one of these signaling conversations, the stem cell–like blood progenitor cells, which contribute to the cells of the blood in the fruit fly Drosophila, receive signals from other cells that live in a nearby safe zone, known as a “niche.” These signals keep the progenitors in a stem cell–like state so that, when needed, they can begin differentiating into blood cells.

And in a startling discovery, the scientists found that the progenitor cells also receive critical signals back from the daughter blood cells they create, telling the progenitors when enough cells have been made and it’s time to stop differentiating.

The discovery of this “back talk” from the daughter blood cells was published Dec. 23 in the peer-reviewed journal Cell.

“The cells in the niche provide a safe environment to support blood progenitor cells,” said 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 niche cells are removed, blood progenitor cells differentiate unchecked. Ultimately, the fruit fly runs out of progenitor cells and is not able to make new cells to mount an immune response to infection or injury, Martinez-Agosto said.

Martinez-Agosto and 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 the UCLA Division of Life Sciences, identified the additional signals coming from the daughter blood cells — 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 and did not multiply. They theorized that there must be a signal coming from the daughter cells telling 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. The scientists showed that the daughter cells send a signal back 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 contact with the cells of the niche.”

The Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research: UCLA’s stem cell center was launched in 2005 with a UCLA commitment of $20 million over five years. A $20 million gift from the Eli and Edythe Broad Foundation in 2007 resulted in the renaming of the

center. With more than 200 members, the Broad Stem Cell Research Center is committed to a multidisciplinary, integrated collaboration among scientific, academic and medical disciplines for the purpose of understanding adult and human embryonic stem cells. The center supports innovation, excellence and the highest ethical standards focused on stem cell research with the intent of facilitating basic scientific inquiry directed toward future clinical applications to treat disease. The center is a collaboration of the David Geffen School of Medicine at UCLA, UCLA's Jonsson Cancer Center, the UCLA Henry Samueli School of Engineering and Applied Science and the UCLA College of Letters and Science.

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