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Drosophila melanogaster

Scientists have uncovered that 2-way signaling from 2 different sets of cells is necessary for blood cell regulation in Drosophila.

The researchers knew that blood progenitor cells receive signals from cells that live in a nearby niche. And these signals keep the progenitors in a stem cell-like state so, when needed, they can begin differentiating into blood cells.

But the team's new discovery shows that the blood progenitor cells receive critical signals back from the daughter blood cells they create. And these signals tell the progenitor cells when enough blood cells have been made and it's time to stop differentiating.

"The cells in the niche provide a safe environment to support blood progenitor cells," said study author Julian A. Martinez-Agosto, MD, PhD, of the University of California, Los Angeles. "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, Dr Martinez-Agosto said.

But his team's research identified additional signals not coming from the niche cells. The new signals were coming from the daughter blood cells the progenitors were making.

The researchers noted that, once the progenitor cells had begun differentiating and the blood cells they were creating became mature, the progenitors became quiescent and did not proliferate. The team theorized there must be a signal coming from the daughter cells that told the progenitors to stop proliferating 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," said Utpal Banerjee, PhD, also of UCLA.

"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 researchers showed that the daughter cells are sending back a signal to the progenitors that is mediated by adenosine deaminase growth factor A. The signal regulates extracellular levels of adenosine, which counters the effects of Hedgehog signaling coming from the niche cells.

"We've shown that adenosine as a molecule is really important for regulating the proliferation of progenitor cells in blood," Dr Martinez-Agosto said.

"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. Maybe other progenitors or stem cells are using the same signaling to determine when

to differentiate or not."

Going forward, the researchers plan to determine 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.

This research was published December 23 in Cell.

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