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Researchers find that two antagonistic proteins help keep leukemia at bay, pointing to new potential treatments

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Two proteins that scientists once thought carried out the same functions are actually antagonists of each other, and keeping them in balance is key to preventing diseases such as cancer, according to new findings published in the February 25 issue of *Developmental Cell* by scientists at Fox Chase Cancer Center. The results suggest that new compounds could fight cancer by targeting the pathways responsible for maintaining the proper balance between the proteins.

"It's our job now to understand how we can intervene therapeutically in this system, so we can restore balance when it's thrown off," says study author David L. Wiest, PhD, professor and deputy chief scientific officer at Fox Chase.

The two proteins—"Rpl22" and "Rpl22-like1", which contribute to the process by which additional cellular proteins are made—are created from two similar genes, leading researchers to previously believe they were performing identical functions in the body. "What we're finding is that is absolutely not true," says Wiest. "Not only are they performing different functions, they are antagonizing each other."

During the study, Wiest and his team knocked out Rpl22 in zebrafish—a common model of human disease. Without Rpl22, the zebrafish don't develop a type of T cells (a blood cell) that helps fight infections. The same developmental defect was observed when they knocked out

Rpl22-like1, indicating that both proteins are independently required to enable stem cells to give rise to T cells.

But when the researchers tried to restore T cells in zebrafish that lacked Rpl22 by adding back Rpl22-like1, it didn't work. The reverse was also true—Rpl22 was not enough to restore function after the researchers eliminated Rpl22-like1. These results led Wiest and his team to believe that, although the proteins are both involved in producing stem cells, they do not perform the same function.

To learn more about the proteins' individual functions, the researchers looked at the levels of different proteins involved in stem cell production when either Rpl22 or Rpl22-like1 was absent. Without Rpl22-like1, cells had lower levels of a protein known as Smad1—a critical driver of stem cell development. And when Rpl22 disappeared, levels of Smad1 increased dramatically.

Both proteins can bind directly to the cellular RNA from which Smad1 is produced, suggesting that they maintain balance in stem cell production via their antagonistic effects on Smad1 expression, explains Wiest.

"I like to think of Rpl22 as a brake, and Rpl22-like1 as a gas pedal – in order to drive stem cell production, both have to be employed properly. If one or the other is too high, this upsets the balance of forces that regulate stem cell production, with potentially deadly effects," says Wiest.

Specifically, too much Rpl22 (the "brake"), and stem cell production shuts off, decreasing the number of blood cells and leading to problems such as anemia. Too much Rpl22-like1 (the "gas pedal"), on the other hand, can create an over-production of stem cells, leading to leukemia.

Previous research has found that Rpl22-like1 is often elevated in cancer, including 80% of cases of acute myeloid leukemia (AML). Conversely, researchers have found that in other cancers, the gene that encodes Rpl22 is deleted. "Either one of these events is sufficient to alter the balance in stem cell production in a way that pushes towards cancer," says Wiest.

Provided by Fox Chase Cancer Center