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Mouse study suggests genomic screening before cancer treatment may prevent anemia

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Many types of leukemia are caused by loss of enzymes such as Pten, which normally keeps cell growth in check, or conversely, the over-activation of enzymes that normally enhance cell proliferation, such as Shp2. Some anti-leukemia treatments work by inhibiting Shp2 or other enzymes involved in the same cellular systems, but researchers at University of California, San Diego School of Medicine have now found that mice lacking both of these enzymes—Pten and Shp2—can't produce and sustain enough red blood cells. The study, published October 12 by *Proceedings of the National Academy of Sciences*, helps explain why anemia is a common side effect of anti-cancer drugs that target enzymes involved in tumor growth.

"Based on this unexpected finding, we might want to think about screening cancer patients' genetic backgrounds for loss of Pten or Pten-regulated signals before prescribing anti-cancer drugs that might do more harm than good," said senior author Gen-Sheng Feng, PhD, professor of pathology at UC San Diego School of Medicine. "In addition, this information could help guide better design of pharmaceuticals for leukemia and other types of cancer in the era of precision medicine."

Feng and his team genetically engineered mice to lack either Pten, Shp2 or both enzymes. The Pten-deficient mice had elevated white blood cells counts, consistent with leukemia. The Shp2-deficient mice experienced the opposite—lower white blood cell counts. Mice lacking both Pten and Shp2 had relatively normal white blood cell counts.

Yet the researchers were surprised to find that despite the apparent reversal of leukemia, the mice lacking both enzymes had shorter lifespans than normal mice or mice lacking just one of these enzymes. It turns out that combined deficiency of Shp2 and Pten induces lethal anemia. The researchers determined that the anemia they observed was due to two factors—red blood cells failed to develop properly from bone marrow and red blood cells that did form didn't last as long as they should. Without red blood cells, the body's organs and tissues don't receive the oxygen they need.

To confirm these genetic studies, the researchers also treated the Pten-deficient leukemic mice with a Shp2 inhibitor or trametinib, a drug that inhibits another enzyme in the same cellular communication network as Shp2. Trametinib is widely used to treat pancreatic and other types of cancer, and it's known for frequently causing anemia in patients who receive the drug. Feng's team found that trametinib treatment had an effect similar to removing the Shp2 gene or chemical inhibition of Shp2—the mice were severely anemic.

"What we've learned is that even if we know a lot about how individual molecules function in a cell, designing effective therapeutics that target them will require a more comprehensive understanding of the cross-talk between molecules in a particular cell type, and in the context of disease," said Feng, also a professor of biological sciences.

More information: "Shp2 and Pten have antagonistic roles in myeloproliferation but cooperate to promote erythropoiesis in mammals." *PNAS* 2015 ; published ahead of print October 12, 2015, DOI: 10.1073/pnas.1507599112

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