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Scientists identify potential drug target for treatment-resistant anemias

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Researchers at Whitehead Institute have identified a protein that is the target of glucocorticoids, the drugs that are used to increase red blood cell production in patients with certain types of anemia, including those resulting from trauma, sepsis, malaria, kidney dialysis, and chemotherapy. The discovery could spur development of drugs capable of increasing this protein's production without causing the severe side effects associated with glucocorticoids.

"This research is medically important, and we are using it to find a better way to increase the production of red blood cells for these patients," says Harvey Lodish, who is a Whitehead Institute Founding Member and a professor of biology at MIT. "It is also a new insight into how self-renewal in stem cells can be controlled, and a new way to think about how we can use an RNA binding protein to maintain stem and progenitor cells."

Anemia occurs due to a breakdown in erythropoiesis, the multi-step process that creates red blood cells. Some common anemias can be treated with a recombinant form of the hormone erythropoietin (EPO), which normally stimulates red blood-cell production at a fairly late stage of erythropoiesis.

However, certain anemias fail to respond to EPO, creating a large unmet medical need. In the case of Diamond Blackfan anemia (DBA), patients lack a sufficient number of EPO-responsive cells. Instead, glucocorticoids such as prednisone or prednisolone are used to treat

DBA and other anemias resistant to EPO by increasing the numbers of the later progenitor cells that respond to EPO. These drugs cause a host of negative side effects, including decreased bone density, immunosuppression, stunted growth, and cataracts, all of which are particularly burdensome for young patients.

Earlier work in the Lodish lab determined that glucocorticoids increase red blood cell production by acting on early progenitors of red blood cells, called burst forming unit-erythroids (BFU-Es). During erythropoiesis, BFU-Es produce later progenitors called colony forming unit-erythroids (CFU-Es), which are then stimulated by EPO to generate the pro-erythroblasts that eventually become red blood cells. By dividing numerous times before maturing, BFU-Es have a limited ability to self-renew. After exposure to glucocorticoids, BFU-Es divide more times than usual, which ultimately increases the total number of red blood cells they produce.

To determine how glucocorticoids prolong BFU-Es' self-renewing phase, Lingbo Zhang, a graduate student in the Lodish lab, studied the drugs' effects in mouse BFU-Es. His work is described online this week on the website of the journal *Nature*.

Zhang determined that glucocorticoids increase the expression of the protein Zfp36l2, which binds to messenger RNAs (mRNAs) that otherwise would push BFU-Es to differentiate. Under the sway of Zfp36l2, BFU-Es undergo additional rounds of self-renewing cell divisions, forming eventually more EPO- responsive CFU-Es and that can increase red blood cell production by up to 20-fold in vitro.

"It's amazing that the body can trigger this process using one essential gene," says Zhang. "But this is still the very beginning. What glucocorticoids are doing in these cells has been like a black box and now we have one piece of what's happening in that box. And that will

help us toward our goal to find a hormone or drug that could be used as a replacement for glucocorticoids."

More information: ZFP36L2 is required for self-renewal of early burst-forming unit erythroid progenitors, *Nature*, online on June 9, 2013. DOI: 10.1038/nature12215

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