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Repurposed anti-cholesterol drug could improve treatment-resistant anemias

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Each year, between 25 and 35 children in the United States and Canada are diagnosed with an inherited bone marrow failure syndrome called Diamond Blackfan anemia (DBA), according to the US Centers for Disease Control and Prevention. Although rare, this syndrome causes a deficiency in producing red blood cells that is devastating for patients and their families. The only treatment, other than blood transfusions, is glucocorticoids—steroids that cause unwanted and even dangerous side effects, including stunted growth, osteoporosis, cataracts, and glaucoma.

Whitehead Institute Founding Member Harvey Lodish first took an interest in DBA back in 2007 at a small meeting of researchers and patient families. When he learned that there was no clear understanding of why glucocorticoids seemed to help DBA patients, he decided to devote a portion of his lab's efforts to solving this mystery.

"We're not only trying to understand how to treat a rare disease, but we're also trying to understand a basic biological problem, which is how stem cells and certain other types of cells make a decision when they divide," says Lodish, who is also Professor of Biology and Professor of Biological Engineering at MIT. "What kind of cell does a blood- forming stem cell become, a stem cell like its parent, or a cell that begins the process of differentiation towards forming a red blood cell or a white blood cell?"

Now research in Lodish's lab has identified a cell receptor that, when stimulated by a currently approved cholesterol-lowering drug, and used

in combination with low amounts of glucocorticoids, causes a three- to five-fold increase in red blood cell production. The research, which is described online this week in the journal *Nature*, is serving as the foundation for an upcoming clinical trial.

Unlike some anemias, DBA cannot be treated by erythropoietin (EPO), a hormone that controls red blood cell production by causing red blood cell progenitors, called colony forming unit-erythroids (CFU-Es), to divide and differentiate into red blood cells. In DBA, the CFU-Es die before they can make red blood cells, and patients have too few CFU-Es to make EPO treatment effective.

In 2010, Lodish and his lab determined that glucocorticoids increase red blood cells in EPO-resistant anemias, including DBA, by acting on burst-forming unit-erythroids (BFU-Es), which are cells that, when they divide, can produce multiple CFU-Es. Glucocorticoids increase the likelihood that when BFU-Es divide, one or both of the resulting cells remains a BFU-E instead of differentiating into CFU-Es. Patients treated with glucocorticoids have more BFU-Es, which in turn produce more CFU-Es and, ultimately, more red blood cells.

Recently, Sherry Lee and Xiaofei Gao, both postdoctoral researchers in the Lodish lab, screened for drugs that could interact with and boost glucocorticoids' activity. Because glucocorticoids act by binding to a receptor in the cytoplasm that migrates into the nucleus and affects expression of multiple genes, the scientists screened for drugs that inhibit or activate other nuclear receptors. Two drugs used for lipid disorders worked with glucocorticoids to increase red blood cell production in vitro. Both of those drugs, including fenofibrate, activate the peroxisome proliferator-activated receptor (PPAR) alpha. Fenofibrate was approved by the FDA in 2001 and has been used to treat high cholesterol in adults and children.

When Lee and Gao studied the mechanism of action of glucocorticoids and fenofibrate, they determined that the glucocorticoid receptor binds to approximately 1000 sites in the DNA and turns on a large number of genes. Fenofibrate activates the PPAR alpha receptor, which subsequently binds adjacent to the glucocorticoid receptor on the DNA. The two receptors modulate a cohort of genes that are critical for BFU-E cell self-renewal and ultimately that produce more red blood cells.

Combined treatment of a glucocorticoid and fenofibrate significantly increased levels of red blood cell numbers in a mouse model of chronic anemia. In fact, the synergy between the two drugs was so powerful that the mice did not require treatment with glucocorticoids.

"The dosage of fenofibrate used in treating EPO-resistant anemia is lower than the treatment for high cholesterol," says Lee, who is a co-author of the *Nature* paper with Gao. "Given the well-documented safety profile of fenofibrate, we expect fewer side effects when using fenofibrate to treat anemia."

Lee and Gao's research was partially funded by the Diamond Blackfan Anemia Foundation (DBAF), an organization that strives to educate patients and the medical community and to advance research initiatives that promote a better understanding and treatment for DBA.

"DBAF, in partnership with DBA Canada (DBAC), is proud to support the hard work and commitment of Dr. Lodish and his entire lab," says Dawn Baumgardner, DBAF's Executive Director. "The prospects of a clinical trial and better treatment options are exciting and anxiously anticipated by the entire DBA community. This research gives our DBA patients and families hope and may also lead to significant progress and implications for other disorders. The DBAF and DBAC are grateful to Dr. Lodish's lab and our DBA families around the world for their tireless efforts."

The results from Lee and Gao's preliminary work are so promising that Shilpa Hattangadi, Assistant Professor of Pediatrics (Hematology/Oncology) and Pathology at Yale School of Medicine and a former researcher in the Lodish lab, is leading a clinical trial to test the effectiveness of a glucocorticoid/fenofibrate treatment in children with DBA.

"Four years ago, I was at an annual DBA meeting where I suggested doing a screen of FDA-approved drugs," says Dr. Hattangadi. "It's exciting to have four years later the Lodish lab publish the results of such a screen, and within six months, start designing the clinical trial and recruiting patients. I'm a physician/researcher, and this is what I trained to do."

Beyond the treatment of DBA, Gao is optimistic about the impact that glucocorticoids/fenofibrate treatment may have on seemingly unrelated conditions.

"Glucocorticoids represent one of the most prescribed classes of drugs," he says. "Basically, if PPAR alpha is important in a disease that is currently treated by glucocorticoids, we may have a new way to treat those diseases that reduces the harmful side effects of glucocorticoids. That could affect a lot of patients."

More information: "PPARα and glucocorticoid receptor synergize to promote erythroid progenitor self-renewal" *Nature*, online May 11, 2015. nature.com/articles/doi:10.1038/nature14326

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