Fighting sickle cell disease using a medication for type 2 diabetes

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Sickle cell disease and the blood disorder beta thalassemia affect more than 180,000 Americans and millions more worldwide. Both diseases can be made milder or even cured by increasing fetal hemoglobin (HbF) levels, but current treatment to ramp up HbF is limited in its effectiveness. Researchers at Baylor College of Medicine and Texas Children's Cancer and Hematology Centers have discovered a gene, FOXO3, involved in controlling fetal hemoglobin production and were able to target the gene and "turn on" fetal hemoglobin levels in patient samples in the lab using the diabetes drug metformin. This offers promising new treatments – the first new drug treatment for sickle cell disease in 30 years and the first ever for beta thalassemia.

"It was a major breakthrough to show that a common drug already in use for type 2 diabetes could be a treatment for sickle cell disease by inducing fetal hemoglobin, a type of hemoglobin that doesn't become sickle shaped but is usually turned off in infancy," said Dr. Vivien Sheehan, assistant professor of pediatrics at Baylor and Texas Children's Cancer and Hematology Centers and lead investigator of the research. "This is an exciting example of collaborative, bench-to-bedside research that has now resulted in a clinical trial that is already enrolling patients."

Sheehan launched this research as a clinical fellow at Baylor College of Medicine in 2011 with the goal of identifying new drug targets to help sickle cell patients make more fetal hemoglobin. The only widely used drug to treat sickle cell disease, hydroxyurea, targets fetal hemoglobin by slowing red blood cells from maturing, but does not make enough HbF

to help up to half of sickle cell patients and generally does not work in beta thalassemia.

Fetal hemoglobin is present in newborns until about 6 months, and then is replaced by adult hemoglobin. Children with sickle cell disease produce a defective form of adult hemoglobin that causes red blood cells to become sickle shaped and get stuck in blood vessels, causing painful episodes and other symptoms. In beta thalassemia, patients simply do not produce enough hemoglobin, causing anemia, fatigue and other serious complications.

Starting with 171 patient blood samples and later expanding to 400 more, Sheehan and her research colleagues were looking for genetic differences in sickle cell patients who make a lot of fetal hemoglobin versus those who do not. Collaborating with Baylor's Human Genome Sequencing Center, they used whole exome sequencing and discovered that the FOXO3 gene seemed to control fetal hemoglobin. They found that patients with mutations in the FOXO3 gene made less fetal hemoglobin. Researchers proved this association in the lab by knocking out FOXO3 in human bone marrow cells, which resulted in less fetal hemoglobin, and then overexpressing the gene, which increased it.

Next, researchers used a well-studied diabetes medication, metformin, to increase FOXO3 levels in human bone marrow cells from sickle cell patients. It was already known that metformin induces FOXO3, Sheehan said. When they increased FOXO3, the cells made more fetal hemoglobin. When they treated bone marrow cells with hydroxyurea and metformin, they made even more, up to 67 percent.

"Patients who make this much fetal hemoglobin would, in theory, be cured of sickle cell disease, and act like a sickle cell trait patient clinically. Metformin may also be an effective therapy for beta thalassemia patients, as it can help them make more hemoglobin by

adding HbF, without slowing the production of red cells like hydroxyurea," she said.

With funding from Pfizer, a clinical trial has launched to further study the effectiveness of metformin in patients with sickle cell disease and beta thalassemia. The clinical trial will enroll patients ages 16 to 40 years old from Baylor College of Medicine clinics, Texas Children's Cancer and Hematology Centers and the University of Texas Health Science Center at Houston. It will include patients with sickle cell disease not on any treatment, sickle cell patients being treated with hydroxyurea, and patients with beta thalassemia. They will be treated with metformin orally for six months, enough time to see a response in fetal hemoglobin, Sheehan said.

Provided by Baylor College of Medicine