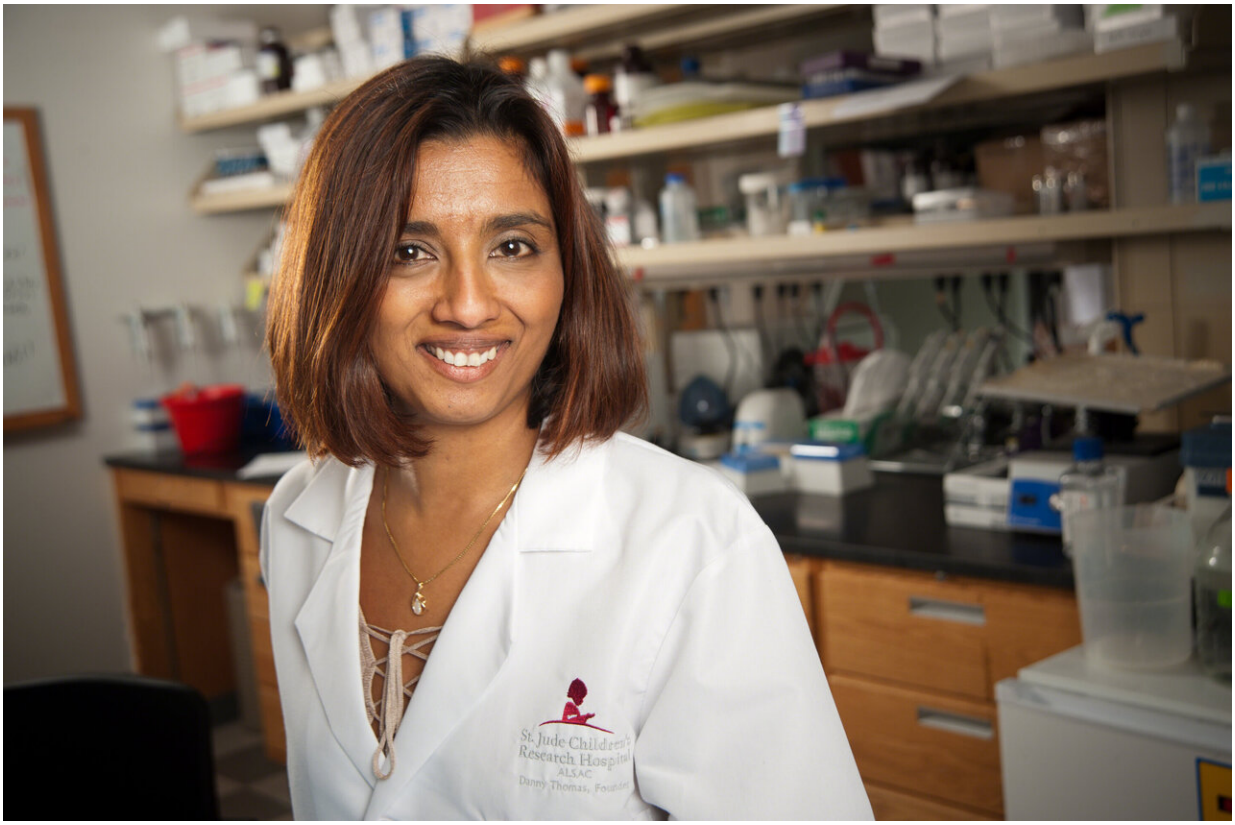
Rapamycin may reduce accumulation of a toxic β-thalassemia protein

August 22 2019



Mondira Kundu, MD, PhD, Associate Member, St. Jude Children's Research Hospital departments of Pathology and Cell & Molecular Biology. Credit: St. Jude Children's Research Hospital

Rapamycin, a drug widely used to protect organ transplant patients, eased symptoms of β-thalassemia in mice and showed promise for

treatment of humans with the inherited disorder, researchers reported. St. Jude Children's Research Hospital investigators led the study, which appears online today in the journal *Science Translational Medicine*.

Researchers showed that rapamycin worked by activating a protein quality-control pathway—the autophagy pathway—in cells. That reduced the accumulation of the toxic proteins that destroy red blood cells in individuals with β-thalassemia. Untreated, the buildup leads to fewer red blood cells, anemia, fatigue and other symptoms, including an enlarged spleen, heart and liver, and fragile bones.

"There is an urgent need for better drugs to treat the many thousands of people born worldwide each year with β-thalassemia," said Mitchell Weiss, M.D., Ph.D., chair of the St. Jude Department of Hematology. He and Mondira Kundu, M.D., Ph.D., of the St. Jude Department of Pathology and Department of Cell and Molecular Biology, are the corresponding authors.

"Rapamycin won regulatory approval almost 20 years ago," Weiss said. "The drug can be safely administered and is relatively inexpensive. Given that, and the findings from this study, our next objective is to design a small clinical trial to test the safety and efficacy of rapamycin for treatment of β-thalassemia."

Research is also underway to identify additional drugs that regulate autophagy.

β-thalassemia

β-thalassemia is one of the most common blood disorders in the world. The standard treatment, blood transfusion, is not universally available and requires medication to prevent iron overload that is a side effect of treatment. While many patients with β-thalassemia are living longer and

enjoying a better quality of life, disease-related morbidity and mortality is still substantial.

β-thalassemia is caused by mutations in the HBB gene that disrupts production of the protein hemoglobin, which red blood cells use to ferry oxygen throughout the body. Hemoglobin has four protein chains—two α-globin and two β-globin. β-thalassemia patients make lower than normal levels of β-globin, in some cases none. The free α-globin accumulates and disrupts red blood cell production.

Reducing free α-globin

Researchers knew rapamycin inhibited mTOR, a protein that inactivates the enzyme ULK1. In this study, the scientists reported that β-thalassemic mice lacking the Ulk1 gene had an approximately two-fold increase in α-globin accumulation compared to mice with the Ulk1 gene.

"Rapamycin inhibition of mTOR can activate ULK1," said first author Christophe Lechauve, Ph.D., of the Weiss laboratory. "β-thalassemic mice treated with rapamycin showed a significant reduction in α-globin accumulation and ineffective erythropoiesis along with a longer life span for red blood cells."

Rapamycin also reduced levels of free α-globin in immature red blood cells, erythroblasts, in individuals with β-thalassemia.

More information: Christophe Lechauve et al. The autophagy-activating kinase ULK1 mediates clearance of free α-globin in β-thalassemia, *Science Translational Medicine* (2019). DOI: 10.1126/scitranslmed.aav4881

Provided by St. Jude Children's Research Hospital