Modulator of fetal hemoglobin switch may target sickle cell disease

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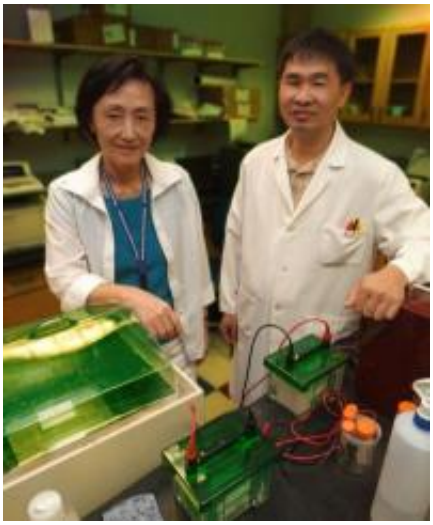

A retired but well-preserved mechanism for regulating viruses that has worked its way into the human genome appears to modulate a switch between adult and fetal hemoglobin production, Medical College of Georgia researchers report. That switch could be the key to more targeted therapies for sickle cell patients whose misshaped adult hemoglobin hinders its ability to deliver oxygen throughout the body. Fetal hemoglobin, on the other hand, can't take on the dysfunctional sickle shape Credit: Phil Jones, Campus Photographer

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That switch could be the key to more targeted therapies for sickle cell patients whose misshaped adult hemoglobin hinders its ability to deliver oxygen throughout the body. Fetal hemoglobin, on the other hand, can't take on the dysfunctional sickle shape.

After deleting the modulator, ERV-9, from laboratory mice that express human hemoglobin, MCG researchers found that red blood cells started producing dramatically more fetal hemoglobin, which would be ideal for sickle cell patients, said Dr. Dorothy Y.H. Tuan, molecular biologist in the MCG Schools of Medicine and Graduate Studies. She is corresponding author on the study published in PNAS; Dr. Wenhu Pi, assistant research scientist at MCG, is first author.

Fetal hemoglobin retrieves oxygen from the mother's blood. Shortly after birth, babies start producing adult hemoglobin, which gets oxygen from their own, newly functioning lungs.

It's a dramatic switch - close to 100 percent - and when researchers try to increase the level of either hemoglobin type, the other type goes down. "It's always a yo-yo. They must be competing for something," Tuan said.

She believes the competition is for transcription factors NF-Y and GATA-2, proteins that bind to and activate fetal and adult globin genes.

Tuan's lab has mounting evidence that ERV-9, currently viewed as junk DNA in the body, performs a critical function in ensuring adult hemoglobin production gets the lion's share of the transcription factors after birth.

Adult beta-globin gene expression in the genetically engineered mice went down 50 to 80 percent and fetal gamma-globin gene expression went up after removing ERV-9. "That is the ideal situation for patients with sickle cell disease," Tuan said. "I think we have put our fingers on a

key switching mechanism."

Without ERV-9, the adult hemoglobin gene is not as competitive for the transcription factors - NF-Y and GATA-2 - that it needs to be highly expressed. Still, it's a long-distance relationship: ERV-9 and the adult hemoglobin gene sit far apart on a stretch of DNA. One of Tuan's many follow-up studies is determining whether during development, ERV-9 favors the fetal hemoglobin gene, a much closer DNA neighbor.

"We want to study fetal red blood cells and see what ERV-9 is doing there," Tuan said. She also wants to better understand ERV-9's apparent ability to suppress globin genes by studying how, during development, its own DNA is chemically altered in a process called epigenetics.

DNA has four chemical bases - A, G, C and T - and ERV-9's DNA contains a lot of the C, or cytosine, which is easily chemically altered. The net effect of chemical alteration - part of normal development - is gene suppression.

If her hypothesis is correct and the fetal and adult genes are competing for NF-Y and GATA-2, what happens if there is a bigger supply of these transcription factors? "If you can increase NF-Y and GATA-2 so there is plenty around, maybe both the beta and gamma genes will be activated without one suppressing the other," Tuan said.

She has a $1.9 million grant from the National Heart, Lung and Blood Institute to further explore whether this natural mechanism she has identified might benefit sickle cell patients. There's plenty of proof that increasing fetal hemoglobin percentages helps patients. A small percentage of people with sickle cell disease, who for some unknown reason continue to express higher levels of fetal hemoglobin - about 25 percent instead of the 1-2 percent expressed by most - are asymptomatic, Tuan said. Typical sickle cell patients, on the other hand, suffer frequent

fatigue, pain and a myriad of other health problems resulting from their blood cells' impaired oxygen delivery.

Hydroxyurea, a drug used to treat sickle cell disease, increases the percentages of fetal hemoglobin in some patients but it's an indirect action that comes with a lot of side effects, she said. The new findings led her to speculate that if hydroxyurea activates the fetal gamma gene through increasing the supply of NF-Y and/or GATA-2 in red blood cells, then designing drugs to directly increase the amount of these transcription factors would yield the same benefit with fewer side effects.

She notes that the thousands of copies of ERV-9 found in human chromosomes likely help modulate the activity of other genes.

Provided by Medical College of Georgia

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