MedicalXpress

Why a hereditary anemia is caused by genetic mutation in mechanically sensitive ion channel

March 8 2013, by Ellen Goldbaum

A genetic mutation that alters the kinetics of an ion channel in red blood cells has been identified as the cause behind a hereditary anemia, according to a paper published this month in the *Proceedings of the National Academy of Sciences* by University at Buffalo scientists and colleagues.

The research team was led by Frederick Sachs, PhD, SUNY Distinguished Professor in the UB Department of Physiology and Biophysics, who discovered in the 1980s that some ion channels are mechanosensitive, that is, they convert mechanical stress into electrical or biochemical signals.

The findings of the new study are significant, Sachs says, because it is the first time defects in a mechanosensitive ion channel have been implicated as the cause of a disease.

"We found that the mutations in the gene that codes for the ion channel called PIEZO1 causes the channel to stay open too long, causing an ion leak in red cells," explains Sachs. "Calcium and sodium enter, and potassium leaves, and that affects the ability of the red cell to regulate its volume. The cells become dehydrated and can break open, releasing their hemoglobin into the blood, and causing symptoms, such as the shortness of breath seen in anemic patients."

The anemia that results from the mutations in PIEZO1 is called familial xerocytosis, a mild to moderate form of anemia. The ion channel, PIEZO1, is about 10 nanometers across, and it increases its dimensions significantly upon opening; that change in dimensions is what is responsible for its mechanical sensitivity.

Mechanosensitive ion channels are likely to play a role in many diseases, since all cells are mechanically sensitive. Sachs and his colleagues have worked on activation of these channels in Duchenne muscular dystrophy, which is caused by errors in a gene coding for a fibrous protein that reinforces the cell membrane. The increased stress caused by this loss of reinforcement causes the channels to open and the leak of calcium is likely what causes the muscles to atrophy, Sachs explains.

Sachs and colleagues at UB founded a biotech company in Buffalo, Tonus Therapeutics to create a therapy for muscular dystrophy based on a peptide they discovered that inhibits the channels involved in that disease. They originally discovered the peptide in a tarantula venom but now it is synthesized chemically. The peptide has received orphan drug designation from the FDA.

"We were pleased to find that our spider venom peptide also inhibits the PIEZO1 channel," says Sachs.

"This means our peptide could be a potential therapy in blood diseases, where there are defects in the ways that red blood cells regulate cell volume," he says.

In normal cells, he says, the mechanosensitive ion channels usually remain closed.

"I think the cells use them as emergency valves so the only time they open is when cells are under extreme stress," he explains. "Consequently,

our peptide doesn't bother healthy cells, so it's nontoxic. It only affects unhealthy cells, cells which are mechanically stressed."

More information: Study: http://bit.ly/13LgCzc

Provided by University at Buffalo