Researchers discover pathway that eliminates genetic defects in red blood cells

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Researchers at the University of Pennsylvania School of Medicine have discovered a unique molecular pathway that detects and selectively eliminates defective messenger RNAs from red blood cells. Other such pathways – known as surveillance pathways – operate in a more general way, in many cell types. Knowing how this specific surveillance system works can help researchers better understand hereditary diseases, in this case, thalassemia, a form of anemia, which is the most common genetic disorder worldwide.

The results appear in the most recent issue of *Nature Structural and Molecular Biology*.

Cells have developed surveillance mechanisms that identify and destroy abnormal RNAs. Mistakes in a cell's reading of RNA into protein can lead to the production of an abnormal protein, and this can result in abnormal cell function or death.

The form of thalassemia studied by the Penn group is caused by a mutation that allows the cell's ribosome to read too far, making a protein that is too long. Thalassemias result from an underproduction of hemoglobin proteins – the oxygen carrying molecule in blood – hence the anemia. The particular mutation they study is carried by millions of people in Southeast Asia and is a major a cause of fetal loss and disease in adults. Specifically in this study they show how far the ribosome has to read into the RNA to trigger destabilization of the protein.

Several surveillance pathways have been identified over the last few years that recognize specific types of mutations in RNAs. For example, the most well-described pathway is one that recognizes nonsense mutations that result in an RNA that makes a protein that is too short. Duchene's muscular dystrophy and cystic fibrosis are examples of hereditary diseases that result from nonsense mutations.

"We describe a surveillance pathway that targets RNA that is only found in red blood cells," says senior author Stephen A. Liebhaber, MD, Professor of Genetics and Medicine. "More general surveillance pathways are in all cells. The specificity of this particular surveillance pathway has not been previously observed and predicts that there's something quite unusual about how RNAs are handled in red blood cells. We're interested in how this specific surveillance system works in red blood cells because such understanding will increase our knowledge of how these cells make high levels of hemoglobin and how defects in this system could contribute to genetic disorders and possibly be reversed."

"This type of surveillance pathway that is regulated at the tissue level could also exist in other highly specialized cells," says first author Jian Kong, PhD, Senior Research Investigator. "Investigating the mechanism of this pathway may help in understanding a wider range of genetic disorders."

Liebhaber is looking forward to further analysis of this surveillance pathway in order to determine why it is specific to red cells and to define the corresponding steps in gene expression in the red cell that are so unusual. Such information should lead to new ideas on how to manipulate this system in a variety of blood diseases.

Source: University of Pennsylvania