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Mutation Plays Key Role in Hypertension

A gene mutation of a key enzyme that regulates smooth muscle contraction and blood pressure in rats has been identified by researchers at the University of Illinois at Chicago. The finding, the first genetic link to muscle contraction and high blood pressure, may lead to improved treatments for hypertension.

The study appears in the September issue of *Molecular Biology of the Cell*.

When myosin, a protein that is abundant in muscle and is necessary for muscle contraction, is activated, smooth muscle cells in blood vessel walls contract and raise blood pressure. The cells also proliferate, thickening the walls and narrowing the channel, further increasing blood pressure.

Together, this results in hypertension, according to Dr. Primal de Lanerolle, professor of physiology and biophysics and senior author of the study. The current crop of drugs used to treat hypertension mainly targets contraction of the smooth muscle cells. They do not affect the proliferation of the cells, and the thickening of the walls of blood vessels is presently irreversible.

In the new study, the researchers were able to confirm the increased levels of the activated form of myosin in hypertensive rats, a widely used animal model of hypertension. More importantly, they established why myosin activation is elevated and linked the mechanism to a gene mutation.

The researchers found there was more of a protein called smooth muscle myosin light chain kinase, which activates myosin, in their hypertensive rats than in closely related rats that do not develop hypertension. They also found that there was more of the kinase's messenger RNA, the genetic message the cell uses to make the kinase.

"This told us that whatever was happening to raise levels of the kinase was happening at a genetic level," de Lanerolle said.

Although secondary hypertension may result from another disorder or from some medications, essential hypertension -- the most common form of high blood pressure -- has no known cause. Genetic, environmental and behavioral factors, such as diet, are believed to play a role, but no gene mutations have been identified in proteins that regulate smooth muscle contraction in essential hypertension.

Dr. Yoo-Jeong Han, research associate in physiology and biophysics and lead author of the study, determined the DNA sequence of the stretch of the kinase gene that controls how often it is copied, and thus controls the level of kinase in the cell. She found a mutation in the hypertensive animals -- an insertion of a small extra piece of DNA.

The insertion changes the shape of the gene slightly, Han said, making it easier for a transcription factor (another protein that is essentially an on/off switch for genes) to bind and turn on the kinase gene.

"The result is more copies of the gene, more of the kinase in the cell, and, ultimately, more contraction and proliferation of smooth muscle cells," she said.

The transcription factor that binds the mutated gene more easily is part of a cell signalling pathway. This pathway is activated by a protein called Ras, and mutations in Ras have been previously implicated in numerous human cancers.

"When we blocked Ras signalling in the hypertensive rats, we were able to block the proliferation of the smooth muscle cells in the vessel walls and the development of hypertension," said de Lanerolle.

The next question, according to de Lanerolle, is whether a similar mechanism operates in humans to cause essential hypertension.

"If we find a similar mutation in the equivalent human gene, it will make it easier to identify people at risk for developing hypertension," de Lanerolle said. "People with a genetic predisposition to hypertension would be able to lower their risk through behavioral change or, someday, perhaps, drug therapy."

We-Yang Hu, Olga Chernaya, Nenad Antic, Lianzhi Gu and Mariann Piano of UIC and Mahesh Gupta of the University of Chicago also collaborated on the study, which was supported in part by grants from the National Institutes of Health. Yoo-Jeong Han and Wen-Yang Hu are supported by the American Heart Association.

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