MedicalXpress

Epigenetic gene silencing may hold key to fatal lung vascular disease

June 7 2010

A rare but fatal disease of blood vessels in the lung may be caused in part by aberrant silencing of genes rather than genetic mutation, new research reports.

Pulmonary arterial hypertension, a syndrome characterized by gradual blockage of blood vessels in the lungs, has been linked to genetic causes in a small percentage of patients. But University of Chicago researchers have now found that a form of epigenetics - the modification of gene expression - causes the disease in an animal model and could contribute to the disease in humans.

Published in the American Heart Association journal *Circulation*, the finding opens a promising avenue for research into the origins of vascular disorders.

"This introduces a new concept: DNA methylation, a form of epigenetics, may play a role in pulmonary arterial hypertension," said Jalees Rehman, MD, Assistant Professor of Medicine and an author of the paper. "We think this is going to be a big part of cardiovascular research in the next decade to come."

Pulmonary arterial hypertension, or PAH, has a 15 percent mortality rate at one year following diagnosis and causes tens of thousands of U.S. hospitalizations each year. The disease is known to run in families and has been traced to a mutation in the BMPR2 gene, but only 1 in 4 people with that mutation develop PAH.

So a team of researchers, led by Stephen Archer, MD, Professor of Medicine and Chief of the Section of Cardiology at the University of Chicago Medical Center, looked for other inheritable causes of PAH. The hunt led them to a gene that encodes an important mitochondria protein called superoxide dismutase 2 (SOD2). SOD2 is expressed at lower levels in the lungs of PAH patients but the gene itself is not mutated.

Experiments conducted in fawn-hooded rats, a breed that spontaneously develops PAH, found that the SOD2 gene is hypermethylated, an epigenetic modification that silences gene expression.

"Picture the reading of DNA (gene transcription) as the opening of a zipper. Transcription factors must run along this DNA zipper to allow the DNA to open so the gene can be read. Methylation blocks this reading, much like having a thread stuck in the zipper prevents its opening. This way, methylation silences a perfectly normal gene" Archer said.

Using an inhibitor of the cell's methylating enzymes, Archer's team was able to reduce SOD2 methylation and increase the gene's expression in fawn-hooded rats. Treatment of the rats with a SOD2 analog also reversed the PAH-like symptoms of the rats, increasing their ability to exercise on a treadmill - the same test used in patients with this disease.

"That's an exciting aspect of epigenetics," Archer said. "Unlike a mutation that might be hard to fix, if a gene were silenced by methylation and you wanted to turn it back on there are drugs that do that, and you might be able to reactivate it."

Other promising therapeutic implications stem from crossover between PAH and cancer. The SOD2 protein is involved in oxidative stress, the natural response of cells to harmful reactive oxygen species. When the

gene is down-regulated, cells become resistant to the programmed cell death of apoptosis and grow unabated, similar to what is seen in cancer. Indeed, a research group at the University of Iowa recently published data supporting a role for epigenetic SOD2 silencing in tumor growth, Archer said.

"It makes you think diseases of excess cell proliferation may have a commonality that's bigger than the specialty of cardiology or pulmonary medicine or oncology," Archer said. "I think there is going to be a lot of interest in the next few years in cancer drugs being applied to vascular diseases, and vascular drugs being applied to malignant diseases."

Additional studies will be required to determine if lower SOD2 levels in PAH patients are due to the same mechanism of epigenetic silencing observed in rats, Archer said. If the gene is indeed hypermethylated in humans, that mechanism may be a promising therapeutic target to reverse or limit disease in PAH patients, particularly as some demethylating drugs are already used for blood disorders.

Similarly, proof of methylation would be valuable for diagnostics, enabling epigenetic screens that would allow doctors to quickly assess a person's susceptibility to PAH. Researchers are also looking at the possibility that other vascular diseases, such as atherosclerosis and coronary heart disease have epigenetic origins as well.

"What would be a very interesting question to ask is whether this same thing happens in other blood vessels, where smooth muscle cells also cause disease," Rehman said. "We're hoping that in other vascular diseases we will find similar epigenetic modifiers. It's really a conceptual innovation in vascular research."

More information: The paper, "Epigenetic attenuation of mitochondrial superoxide dismutase 2 (SOD2) in pulmonary arterial

hypertension: A basis for excessive cell proliferation and a new therapeutic target," appears June 7, 2010 in Circulation.

Provided by University of Chicago Medical Center