

Dr. Larissa Shimoda to discuss mechanisms of hypoxic pulmonary hypertension

EurekAlert

WASHINGTON, DC When muscles and organs are deprived of an adequate supply of oxygen--a condition called hypoxia--the body's usual responses include increased circulation and a slight drop in blood pressure in the blood vessels serving the affected tissue. However, the blood vessels in the lungs react differently: blood pressure in the lungs rises, often with deleterious effects on the lungs' tissue and the heart. Larissa A. Shimoda, PhD, Associate Professor of Medicine at the Johns Hopkins University School of Medicine in Baltimore, Md., has dedicated her research to learning why this happens and whether it's possible to treat the condition using drugs that are already on the market.

Dr. Shimoda has focused on the mechanisms that control pulmonary circulation, and she has identified a number of key changes that occur in pulmonary vascular smooth muscle cells that contribute to the development of hypoxic pulmonary hypertension. Understanding these changes and how they occur has implications for the treatment of hypoxic pulmonary hypertension in patients with chronic lung diseases such as emphysema, chronic bronchitis and cystic fibrosis.

The American Physiological Society (APS) has recognized the importance of Dr. Shimoda's work by awarding her the Henry Pickering Bowditch Award Lecture. This award is given to select scientists younger than 42 whose accomplishments are original and outstanding and is the Society's second-highest award.

Dr. Shimoda will present her lecture during the meeting Experimental Biology 2011 (EB 2011) being held April 9-13, 2011 at the Walter E. Washington Convention Center, Washington, DC.

HIF-1 and the Lungs

All cells have a transcription factor called hypoxia-inducible factor 1 (HIF-1). Transcription factors are proteins that bind to specific DNA sequences and help regulate genetic expression. Depriving cells of adequate oxygen activates HIF-1, which regulates oxygen homeostasis, or the tissue's ability to maintain equilibrium in oxygen metabolism.

However, according to Dr. Shimoda, that activation in the muscle cells surrounding the lung's blood vessels causes the arteries to constrict. When the hypoxia is chronic, over time the blood vessel walls also get thicker, thus reducing the space through which blood can flow. The mechanism by which HIF-1 is activated in the muscle cells lining the lung blood vessels is missing in the muscle around blood vessels from other parts of the body.

"This may be one reason that the effects of prolonged hypoxia on blood pressure are restricted to the pulmonary circulation," Dr. Shimoda says.

Old Drugs, New Tricks

People who have chronic lung diseases have an increased risk of developing pulmonary hypertension, which, when severe, can be fatal. The potentially lethal impact of hypoxic pulmonary hypertension motivates Dr. Shimoda in her quest to find a treatment. She is collaborating with Gregg Semenza, MD, PhD, Professor at Johns Hopkins' Department of Pediatrics, Medicine, Oncology, and Radiation Oncology, who discovered HIF-1 in 1992. He reviewed information in the Johns Hopkins Drug Library and found several drugs that may function as HIF-1 inhibitors. These drugs include digoxin (also known as digitalis), which is used to treat congestive heart failure and slow the heart rate in people with atrial fibrillation, and acroflavin, an antibiotic antifungal.

"The good thing about these drugs is that because they are older, already on the market and have been used clinically for decades, they do not have to go through all of the requirements new drugs need in terms of development and testing for safety," says Dr. Shimoda. Her team is now studying the use of these drugs in treating hypoxic pulmonary hypertension in animal models, and if all goes well, she hopes to move the drugs into clinical trials in humans in the future.

Dr. Shimoda will discuss her research when she presents this year's Bowditch Lecture, "Effects of chronic hypoxia on the pulmonary circulation: Role of HIF-1," on Sunday, April 10, 5:45 pm, during the meeting at the Walter E. Washington Convention Center, Washington, DC.

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