

New approach to pulmonary hypertension shows promise

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Researchers at the University of Alberta have identified a "central command system" for pulmonary hypertension, a disease that currently has no cure and kills thousands each year.

"We believe this finding opens the door to a new strategy and the development of a new stream of drugs to treat this complex and lethal disease," said Dr. Evangelos Michelakis, director of the U of A pulmonary hypertension program and senior author of the study, which appears today in the *Proceedings of the National Academy of Sciences*.

Much like cancer, pulmonary hypertension is caused by the uncontrolled proliferation of cells. In the case of pulmonary hypertension, these cells build up in the pulmonary arteries, block blood flow and cause perpetual high-blood pressure in the lungs and, eventually, heart failure.

Pulmonary hypertension is especially dangerous because it is difficult to diagnose, Michelakis said, adding that it can appear in anyone at any age but is most commonly found in females in their 30s. The prime symptom is shortness of breath.

"The current treatments for pulmonary hypertension do not work. At best they might somewhat prolong and improve quality of life, but nothing cures it—it usually kills patients within four to five years from diagnosis," said Sebastien Bonnet, a post-doctoral fellow in the U of A Department of Medicine and first author of the paper.

However, the U of A researchers believe they've made a breakthrough in their discovery of the role that nuclear-factor-of-activated-T-lymphocytes (NFAT) play in the cause of the disease. The researchers have identified NFAT as a potential controlling element of pulmonary hypertension in both human tissues and animal models.

When it is working properly, NFAT co-ordinates several cellular functions by regulating the expression of multiple genes. It is normally activated in important health-maintaining functions, such as the regulation of immune cells and the development of the heart. However, it causes havoc when it is activated "inappropriately", such as in the case of pulmonary hypertension.

"You can think of NFAT as a rogue air traffic controller that keeps planes in the air that need to land or sends them to the wrong destinations and causes them to attack places they shouldn't," explained Michelakis, the Canada Research Chair in Pulmonary Hypertension.

Multiple abnormalities have been described in pulmonary hypertension, making the treatment difficult. Most current therapies are designed to attack one abnormality at a time, Michelakis said, adding that this work shows for the first time that several of these abnormalities, so far considered to be unrelated to each other, may in fact be the result of a single problem—activation of NFAT.

"Therefore, by attacking NFAT, the 'common denominator' of these abnormalities, you might be able to treat them all at once," he said.

In January this year, the same U of A research team published a paper announcing a possible new treatment for various types of cancer using a molecule called dichloroacetate (DCA). In that study, the team showed that NFAT is also activated in cancer. The team has previously shown that DCA also reverses pulmonary hypertension in animal models.

Michelakis believes that this new approach—looking at pulmonary hypertension through a "cancer window"—will facilitate the development of effective therapies.

"In both cases, we're taking a novel approach by determining the 'central command centers' for these diseases—like NFAT—and then trying to come up with ways to attack them at their root causes," he added.

"The development of multidisciplinary programs that focus on pulmonary hypertension all over the world is significantly improving the diagnosis and care of patients with pulmonary hypertension," said Linda Webster, a co-author of the study and manager of the U of A pulmonary hypertension program.

Source: University of Alberta

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