

Formation of plexiform lesions in experimental severe pulmonary arterial hypertension

EurekAlert

ATS 2010, NEW ORLEANS? A new preclinical model of pulmonary arterial hypertension (PAH) may lead to improved research and ultimately better therapies for this life-threatening problem, according to its developers, researchers at the University of South Alabama.

The researchers modified a recently developed rat model of severe PAH and found that the model can mimic the plexiform lesion, the signature lesion of PAH.

Their results will be presented at the ATS 2010 International Conference in New Orleans.

"This study provides convincing evidence for the first time that the plexiform lesion develops in an experimental rat model of severe PAH," said Kohtaro Abe, M.D., Ph.D., lead author of the study. "To date, no small animal model of pulmonary arterial hypertension exists that rigorously mimics the plexiform lesion, the hallmark lesion of severe PAH, found in human patients."

PAH is characterized by high blood pressure in the lung that leads to pressure overload and failure of the right side of the heart. Approximately 2,000 - 5,000 patients are newly diagnosed with PAH each year in the United States and, despite recent advances in the understanding and treatment of this disorder, PAH is still a progressive and fatal illness. One major barricade to better therapies is the lack of appropriate animal models. Although a number of rodent models of PAH are currently used, none of them develops the classic plexiform lesion.

"An animal model that closely mimics human PAH is needed for better understanding and treatment of this devastating pulmonary vascular disorder," said Dr. Abe.

Because plexiform lesions are found only in late and advanced stages of PAH patients, Dr. Abe and colleagues hypothesized that the lesion would also develop in later stages of experimental models of severe PAH.

"One report of a patient with PAH found it took five years to develop plexiform lesions after diagnosis of severe PAH. Assuming that the natural history of chronic disorders is proportional to the life span of the species, five years in humans translates into about 10 weeks in rats," explained Dr. Abe.

To determine whether they would be able to induce plexiform lesions in rats, the researchers injected rats with a vascular endothelial growth factor receptor blocker (SUGEN5416) and kept them in a hypoxic chamber for three weeks before returning

them to a normalized oxygen level for an additional 10-11 weeks.

They found that all of the rats developed the plexiform lesions. "We found in these late stages of severe PAH, the rats developed plexiform and other complex lesions indistinguishable from those observed in human patients," said Dr. Abe. "In addition to the plexiform lesion, this model also closely mimics the high pulmonary blood pressure and decreased heart function of human PAH."

Dr. Abe and colleagues believe this model will reveal more detailed cellular and molecular mechanisms of severe PAH.

"Next, we will investigate how the plexiform lesion forms and determine whether it is the cause or the effect of the PAH in this model," concluded Dr. Abe. "This model allows rigorous preclinical drug testing to discover more effective treatments for severe PAH."

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