Gene therapy may be effective in treating PAH

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Gene therapy has been shown to have positive effects in rat models of pulmonary arterial hypertension (PAH), according to researchers at the University of Adelaide in Australia.

PAH is a life-threatening disease in which pressure in the blood vessels of the lungs increases, causing a back-pressure strain on the heart. In inherited forms of the disease, PAH is caused by a mutation in a receptor called bone morphogenetic protein receptor, type II (BMPR2). Even in some non-inherited forms of the disease, BMPR2 levels are low.

There have been many improvements to outcomes in PAH in recent years with new drug therapies, but many patients still ultimately die of the disease and thus new treatments are still needed.

"We investigated whether increasing BMPR2 levels might improve pulmonary hypertension. We used two rat models of pulmonary hypertension, and increased BMPR2 levels in the lungs using a gene therapy approach," said Paul Reynolds, M.D., Ph.D, FRACP, principal investigator. "We found in both models that BMPR2 gene delivery significantly reduced pulmonary hypertension and the strain it causes on the heart."

The results will be reported at the ATS 2010 International Conference in New Orleans.

Dr. Reynolds and colleagues induced PAH in Sprague-Dawley rats by keeping them in a hypoxic (10 percent oxygen) chamber for three weeks. Half of the rats were then treated with a viral vector bearing a pulmonary endothelial targeting conjugate designed to boost BMPR2; half were treated with a placebo vector. Then all rats were subjected to a further three weeks of hypoxia at which time PAH was assessed. In a separate model, the researchers induced PAH by injecting the chemical monocrotaline (MCT), which causes inflammation in the pulmonary blood vessels. Rats were first injected with MCT to induce PAH, then half were given the BMPR2 vector or a placebo vector and PAH was assessed 10 days later.

The researchers found in both models that the rats that were treated with the BMPR2 vector compared to placebo had significantly reduced right ventricular hypertrophy, reduced pulmonary vascular resistance, and improved cardiac output.

"These findings were based on the knowledge that low BMPR2 levels are associated with pulmonary hypertension, but it has not previously been shown that increasing BMPR2 levels might be used as a therapy," said Dr. Reynolds. "This research strongly suggests that increasing BMPR2 levels might offer a new therapeutic target in pulmonary hypertension."

Further research is need to better understand how and why increasing BMPR2 signalling in the lungs leads to improvements in PAH, and improvements to the gene delivery vectors would be needed for application to human patients.

"We feel encouraged to see such strong therapeutic results from increasing BMPR2 in the rat model," said Dr. Reynolds. "To apply the gene therapy approach to human patients will require more refinement of the gene therapy vector system, which is something we are working

on. However, the principal established here also identifies BMPR2 upregulation as a target for the development of more conventional pharmaceuticals. Either way, there is hope that this approach will ultimately lead to more effective therapies for this potentially deadly condition."

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