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Press release
For immediate publication

Pulmonary fibrosis: Research to counter pathological connective tissue proliferation in the lung

Limits to therapy: Pirfenidone not suitable for every type of pulmonary fibrosis

Graz, 14/06/2022: Pulmonary fibrosis is a serious disease that causes dramatic changes in lung tissue including hardening and scarring. Individuals who have it suffer from severe breathing difficulties and oxygen deficiency, which significantly diminishes their quality of life. To obtain a better understanding of the underlying disease mechanisms and develop optimal treatment strategies for patients with pulmonary fibrosis, researchers at the Medical University of Graz and the Ludwig Boltzmann Institute for Lung Vascular Research have investigated a new approach that employs a known drug. The research project focused on *pirfenidone*, which was analyzed for its benefits and risks.

When the lungs stiffen and breathing is difficult

In pulmonary fibrosis, connective tissue in the lung is chronically inflamed, causing not only its pathological proliferation but also hardening and scarring. The walls of the alveoli become thicker, the distance between the air that is inhaled and the blood vessels becomes greater and gas exchange is impaired. Ultimately the blood oxygen level is affected, and individuals may experience shortness of breath as well as a bluish color to the skin. The causes of disease and risk factors for pulmonary fibrosis have still not been fully explained, yet several triggers are known that encourage inflammation of the alveoli. The disease may be triggered by infections, harmful substances, allergens and drugs as well as by autoimmune diseases, for example the connective tissue disease scleroderma. The idiopathic form of pulmonary fibrosis appears spontaneously; its causes remain largely unknown. It usually progresses rapidly and is accompanied by a shorter life expectancy.

The antifibrotic effect of the drug pirfenidone

Scleroderma (also known as systemic sclerosis) may affect not only connective tissue and skin but also muscles, joints and internal organs. "If the lung is also affected, pulmonary hypertension and pulmonary fibrosis are often the result. Our current research focuses on scleroderma-induced pulmonary fibrosis," explains Anna Birnhuber from the Division of Physiology of the Otto Loewi Research Center at Med Uni Graz and the LBI for Lung Vascular Research. Although current treatments can slow down the progression of pulmonary fibrosis, they do not offer any possibility of a cure. This is reason enough for Anna Birnhuber and her colleagues to look into disease mechanisms in order to find new therapeutic approaches. Scientists used a mouse model to test whether the drug *pirfenidone*, which has been applied to treat idiopathic pulmonary fibrosis, was able to

produce similarly promising results in the treatment of scleroderma-induced disease. This drug is known to slow down scarring to the lungs in idiopathic pulmonary fibrosis.

Severe side effects in scleroderma-induced pulmonary fibrosis

In the model of idiopathic pulmonary fibrosis, the drug exhibited the known antifibrotic effect and reduced scarring in the lungs. "Yet when *pirfenidone* was applied to the model of scleroderma-induced pulmonary fibrosis, it led to severe side effects with more foci of inflammation and even more scarring in the lungs," said Anna Birnhuber, describing her observations. More detailed investigations indicated what triggered these side effects: In the scleroderma model, the drug results in additional injury to the endothelial cells, the cells that line our blood vessels. The research group claims that in scleroderma, endothelial cells have already been damaged by specific inflammatory processes and mediators and thus react more sensitively to treatment with *pirfenidone*. "Thus the drug leads to increased permeability of the blood vessels in predamaged endothelial cells, which allows more inflammatory cells to migrate into the lung tissue and pulmonary fibrosis to worsen," concludes the scientist.
The study was published in the acclaimed European Respiratory Journal and underlines again how important it is to have an exact understanding of underlying disease mechanisms in order to identify the optimal treatment strategy for patients with pulmonary fibrosis.

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Profile

Anna Birnhuber researches pathomechanisms of pulmonary vascular remodeling at the Division of Physiology of the Otto Loewi Research Center at Med Uni Graz and the LBI for Lung Vascular Research. Pathological changes due to pulmonary disease induce remodeling of pulmonary circulation and a massive change in the lumen of medium and small pulmonary arteries. With her research, Anna Birnhuber hopes to contribute to the decoding of molecular and cellular mechanisms that underlie the pathobiology of pulmonary vascular remodeling.

Publication

Pirfenidone exacerbates Th2-driven vasculopathy in a mouse model of SSc-ILD
https://erj.ersjournals.com/content/early/2022/03/17/13993003.02347-2021.long