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Mitophagy in macrophages is a key step toward pulmonary fibrosis

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Idiopathic pulmonary fibrosis is a devastating disease, and recently approved therapies have limited efficacy. Lungs become damaged with fibrotic scarring, and the median length of survival after diagnosis is three to five years.

The lung immune cells called alveolar macrophages are known to play a role in disease progression by starting an immune response and producing the reactive oxygen species that somehow lead to increased amounts of transforming growth factor beta, or TGF-β1. Macrophages are large white blood cells that are the initial defense-fighting cells in the lung.

In a paper published Feb. 23 in the journal *Immunity*, University of Alabama at Birmingham researchers show that the pathway leading to increased expression of TGF-β1—which provokes the destructive lung remodeling—involves Akt1 kinase-induction of reactive oxygen species and mitophagy. They also show that alveolar macrophages are the primary source of the damage-inducing TGF-β1 in the lung. Understanding such basic molecular mechanisms in the development and progression of pulmonary fibrosis may reveal ways to treat this disorder.

Mitophagy is a normal cell-protecting biological process in which mitochondria—the organelles that are the powerhouses of the cell —are selectively degraded if they are dysfunctional or damaged. Components from the degraded mitochondria are recycled to create new, functional mitochondria in the cell. Normally, mitophagy is a beneficial process.

But the evidence from A. Brent Carter, M.D., professor in the Division of Pulmonary, Allergy and Critical Care Medicine, UAB Department of Medicine, and his colleagues shows that mitophagy plays a pathological role in alveolar macrophages to produce pulmonary fibrosis in a mouse model of pulmonary fibrosis.

"The biggest surprise," Carter said, "was something that intuitively makes no sense: We show that mitophagy is required for TGF-β1 production."

The UAB researchers found several lines of evidence for their conclusions, using either alveolar macrophages from a mouse model with bleomycin-induced lung injury, or human alveolar macrophages from patients with idiopathic pulmonary fibrosis.

First, conditional deletion of the TGF-β1 gene in mouse alveolar macrophages showed that TGF-β1 produced by the macrophages was required for pulmonary fibrosis in the mouse model. Second, mice with a conditional deletion of Akt1 in alveolar macrophages had impaired mitophagy and reduced production of TGF-β1.

Third, while Akt1 expression increases TGF-β1 expression, if the researchers inhibited mitophagy in vitro—using a mitochondria-targeted antioxidant or mRNA silencing of Parkin2, one of the proteins necessary for mitophagy—this abrogated TGF-β1 expression and fibroblast differentiation, despite elevated Akt1 expression. In vivo, mouse alveolar macrophages that had a conditional Park2 mutation, the gene for Parkin2, had abrogated production of TGF-β1 in bronchoalveolar lavage fluid.

Importantly, when the alveolar macrophages had a conditional Akt1 gene mutation or a conditional Park2 gene mutation, the mice showed increased alveolar macrophage apoptosis (the programmed cell death of

old or damaged cells), and the mice were protected against pulmonary fibrosis.

Moreover, examination of human alveolar macrophages from idiopathic pulmonary fibrosis patients showed increased pro-fibrotic gene expression and TGF-β1 gene expression in macrophages, compared with normal controls. These alveolar macrophages also showed increased mitophagy and apoptosis resistance, as compared with normal controls.

Altogether, these data suggest that Akt1-mediated mitophagy contributes to alveolar macrophage apoptosis resistance and pro-fibrotic polarization, and that autophagy in alveolar macrophages is required for pulmonary fibrosis development.

Pulmonary fibrosis

- Means scarring in the lungs. Eventually, scar tissue makes it hard for oxygen to get into the blood.
- Is a family of more than 200 different diseases that look very much alike, some with known causes. When the cause is not identified, it is called idiopathic PF.
- The most common symptoms of PF are cough and shortness of breath.

More information: Macrophage Akt1 Kinase-Mediated Mitophagy Modulates Apoptosis Resistance and Pulmonary Fibrosis. DOI: dx.doi.org/10.1016/j.immuni.2016.01.001

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