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EDITORIAL

Activated CYPD in COPD: Filling in the Puzzle of how Perturbed Epithelial Respiration Leads to Disturbed Respiratory Function

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As COPD remains a disease of tremendous public health importance worldwide [1], there is urgent need for ongoing research into its pathogenesis that may help engineer new preventative and therapeutic measures. Recently, the power engines of the cell, mitochondria, were found to play a central role in COPD development. In diseased lungs, mitochondrial dysfunction in mesenchymal and epithelial cells leads to increased reactive oxygen species (ROS) generation, mitophagy, senescence or autophagy; the resulting cellular dysfunction is thought to be a central contributor to the development of inflammation, emphysema and inflammation [2]. However, much of the pathophysiology of mitochondria-mediated cell injury in COPD remains elusive. The research by Zhang et al. published in this issue of Lung [3], fills in important information in this area.

In their work, Zhang et al. demonstrate that Cyclophilin D (CypD), an important mitochondrial permeability pore component, is induced in vivo in human COPD lung epithelia, and in vitro in a dose—and time-dependent manner after cigarette smoke extract (CSE) exposure. CypD is a highly conserved mitochondrial protein whose induction leads to the activation of the mitochondrial permeability transition pore, with subsequent loss of inner mitochondrial membrane potential and ATP production, ultimately resulting in cell death. Indeed, Zhang et al. demonstrate ultrastructural mitochondrial changes in human COPD lungs, confirming prior reports [4], and go on to show that CSE-induced CypD is associated with an increase in cellular levels of ROS, activation of the mitochondrial death-inducing protein Bax and inhibition of anti-apoptotic Bcl-2, and cellular apoptosis. Thus, the work by Zhang et al. [3] identifies CypD as an important putative treatment target in COPD.

Although a strength of this work by Zhang et al. [3] is their examination of human COPD tissue, some weaknesses should be noted: the mechanistic experiments were performed in vitro using human epithelial cell lines, and there was no firm proof in this work that CypD inhibition can be used as a treatment for cigarette smoke-induced lung inflammation at the organismal level. Furthermore, despite the novel findings in this research, important knowledge gaps remain. For example, the pathway by which cigarette smoke exposure activates CypD is unknown. Transcriptional regulation of CypD expression is very poorly understood; however, recently bone morphogenetic protein (BMP) and Small-mother-against-decapentaplegic (SMAD) protein were found to suppress CypD expression [5]. Both of these proteins are involved in COPD pathogenesis [6, 7]; thus, they may also play a role in CypD regulation in the context of COPD. In addition, the mitochondrial protein Parkin (PARK2) plays an important role in COPD [2] and was shown to regulate CypD [8]. Furthermore, CypD can undergo many post-translational modifications including oxidation, S-nitrosylation, S-palmitoylation, S-glutathionylation, phosphorylation, and acetylation [9]; these modifications may happen after cigarette smoke exposure, but this has not been studied in the context of CypD and mitochondrial injury. Thus, crucial connections in the mitochondrial injury pathway can be hypothesized and experimentally addressed in future research.

Mechanistically, the molecular mechanism by which CypD regulates mitochondrial pore formation and mitochondrial function remains to be elucidated. Finally, therapeutic implications are still unexplored. CypD takes its name from its strong affinity to cyclosporin A. Very low dose cyclosporin A was found to be anti-inflammatory in COPD-derived cells [10] and ameliorated lung inflammation in a rat model [11]. The use of these, or other cyclosporin-derived and CypD-inhibitory therapeutics is inspired by studies such

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as the one by Zhang et al. [3], and has the potential to significantly impact treatment approaches to chronic lung diseases such as COPD. Improving mitochondrial function could help lung cells "breathe better" and may indeed be a novel way to help COPD patients breathe better too.

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