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Student: PHAN THI THANH HUYEN

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PPAR-? SIGNALING TRIGGERS A METABOLIC SWITCH ESSENTIAL FOR BRONCHIOLAR REGENERATION

Phan Thi-Thanh-Huyen; Manu M. Kanti; Silvia Schauer; Leigh M. Marsh; Grazyna Kwapiszewska; Paul W. Vesely; and Gerald Höfler

Dysregulation of energy homeostasis often leads to development of metabolic syndrome, associated with cardiovascular disease, diabetes, liver steatosis, and cancer. The influence on the lung, however, is poorly characterized. Nevertheless, central obesity, type-2 diabetes, hypertension, and enhanced blood triglyceride levels are linked to reduced lung function in several epidemiological studies. Our data show that Peroxisomal Proliferator Activated Receptor-? (PPAR-?) signaling is essential for lung regeneration (Kanti et al., 2022). Upon binding of fatty acids the nuclear receptor PPAR-? drives the transcriptional program for fatty acid ?-oxidation and mitochondrial biosynthesis. To induce airway epithelial injury we challenged mice with naphthalene (NA). This led to bronchiolar epithelial denudation after few days. In the following week, the bronchiolar epithelium fully recovered. Using RNA in situ hybridization we found that PPAR-? target genes were selectively upregulated in the bronchiolar epithelium during repair. Pyruvate Dehydrogenase Kinase 4 (Pdk4) mRNA showed the strongest induction post NA exposure. Intriguingly, PDK-4 inhibits Pyruvate Dehydrogenase activity, and thereby, induces a metabolic shift from sugar to fatty acid catabolism. Pharmacological activation of PPAR-? signaling enhanced the bronchiolar regeneration potential in mice (Kanti et al., 2022). Therefore, we hypothesize that PPAR-? signaling triggers a metabolic switch, essential for bronchiolar regeneration. Adopting a powerful and novel combination of RNAscope in situ hybridization and immunofluorescence, we aim to understand which cell type(s) of the airway epithelium undergo metabolic shift for injury-repair. Our ongoing mechanistical analyses in vivo and in bronchiolar organoids should clarify the metabolic requirements for bronchiolar regeneration. In future this may allow us to develop targeted treatment strategies for diseases linked to failure of lung epithelial regeneration.