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Abstract Title

Oxidized Phosphatidylcholines Increase Extracellular Matrix-Associated Gene Transcripts in Human Airway Fibroblasts

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Background

Chronic airway inflammation in asthma leads to structural changes of the airway wall—including the accumulation of extracellular matrix (ECM) proteins (fibrosis)—that contribute to fixed airway obstruction. Oxidative stress is linked to persistent airway inflammation, and oxidized phosphatidylcholines (OxPCs; mediators of oxidative stress) accumulate in the lungs of asthmatics. OxPCs can trigger inflammatory and contractile responses in airway smooth muscle. Human airway fibroblasts (HAFs) contribute to the accumulation of ECM in the airway wall in asthma. Here, we investigated if OxPCs induce a fibrotic response in HAFs.

Objective

To determine if OxPCs increase abundance of mRNA for ECM genes in HAFs.

Methods

Primary HAFs were generated from 2nd-4th generation bronchi of surgically resected lung specimens from male and female ex-smoker, non-asthmatic human donors (N=5). Passage 3-6 cultures were serum-starved overnight and treated with OxPCs (80µg/mL) for 24h and 48h. We used qRT-PCR to determine ECM-associated gene abundance. Statistical analysis: one-way ANOVA followed by Tukey's post-hoc test,

with $p < 0.05$ considered a significant difference.

Results

OxPCs (48h) significantly induced abundance of mRNA for the ECM proteins, collagen 1A1 (+50%), collagen 3A1 (+85%), fibronectin (+85%), and laminin- α 2 (+60%), and doubled mRNA for the fibroblast activation marker, periostin. mRNA for plasminogen activator inhibitor-1 (PAI-1), an inhibitor of fibrinolysis and matrix metalloproteinases, peaked at 24h after OxPC exposure (~4-fold increase).

Conclusion

OxPCs increase the abundance of mRNA for ECM-associated genes in primary HAFs. This reveals that OxPCs elicit a fibrotic response in airway fibroblasts, adding to known effects of OxPCs to promote asthma pathobiology in airway epithelial and smooth cells. Collectively, these data support a role for OxPCs to promote airway inflammation and remodeling.