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Basic Science

Abstract Title
Oxidized Phosphatidylcholines Induce MAP Kinase-Dependent Production of Asthma Mediators in Human Airway Fibroblasts

Background
Asthma is a primary reason for ER visits by children. Oxidized phosphatidylcholines (OxPAPC) accumulate in the asthmatic lung and activate intracellular kinases, TRPA1-mediated Ca2+ influx, and inflammatory mediator biosynthesis by airway smooth muscle.

Objective
We investigated whether OxPAPC “activate” nearby airway fibroblasts that regulate inflammation and tissue remodeling.

Methods
With cultured human airway fibroblasts (HAF) we used qRT-PCR to measure IL-6, IL-8, GM-CSF, COX2 (24-hr OxPAPC, 80μg/mL) with and without TRPA1 antagonist A967079 (1μM) or MAPK inhibitors (U0126, SB202190 (10μM). Luminex assay measured GM-CSF, IL-8, and IL-6 release, and we monitored p42/p44 and p38 MAPK phosphorylation by immunoblotting. OxPAPC-induced Ca2+ influx was measured in Fluo4-loaded HAF. Analysis was with one-way ANOVA and Tukey’s post hoc (N ≥ 5).

Results
OxPAPC increased IL-6 (3-fold), GM-CSF (3-fold), IL-8 (9-fold) and COX2 (8-fold) mRNA, and IL-6 and IL-8 release by 3-fold and 6-fold. TRPA1 inhibition decreased induction of GM-CSF, IL-8 and COX2 mRNA by 70-85%, and significantly decreased IL-6 release. OxPAPC rapidly induced a 6-fold increase in phospho-p42/p44 and p38 MAPK, and was maintained ~50% of peak for up to 4 hours. TRPA1 inhibition did not affect MAPK phosphorylation, but p42/p44 and p38 MAPK inhibition abrogated OxPAPC induced GM-CSF and IL-8 mRNA, and inhibited OxPAPC-induced Ca2+ flux by 28-32%.

Conclusion
OxPAPC induce biosynthesis of inflammatory genes in HAF by triggering signaling pathways involving TRPA1 and MAPKs. These data further support a role for OxPAPC as a mediator of asthma pathobiology by activating airway structural cells such as HAF.

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