CHRD 2024: Abstract Submission Form

Presenter Name
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Presenter Status
Non-Trainee

Role in the project
Perform Experiments
Analyze Data
Write Abstract

Research Category
Basic Science

Title
Oxidized Phospholipids Promote Inflammation and Disrupt Anti-Inflammation Gene Regulation by Corticosteroids in Airway Epithelial Cells

Background
In asthmatic airways we identified an increase in oxidized phosphatidylcholine (OxPAPC) and show that they promote cytokine release, and airway narrowing and hyperresponsiveness (AHR). Inhaled corticosteroids (ICS) are essential for asthma management. ICS inhibit lung inflammation both by stimulating glucocorticoid receptor (GR)-mediated transcriptional activation of anti-inflammatory genes, and via the repression of pro-inflammatory NF-κB-induced gene transcription.

Objective
We tested the hypothesis that OxPAPC promotes inflammatory gene expression and disrupts corticosteroid gene regulation in lung cells.

Methods
Transcriptional activation by fluticasone propionate (FP; 1μM, 5 hrs) was measured in human bronchial epithelial 2XGRE-BEAS 2B cells. FP repression effects were measured in 3kBU NF-κB-BEAS 2B luciferase reporter cells after exposure to tumor necrosis factor (TNF; 10ng/mL, 5 hrs). Some cells were pre-exposed to OxPAPC (80μg/mL) for up to 18 hours. Expression data for GR-sensitive genes was measured using luciferase assays and qRT-PCR, and analyzed using one-way ANOVA and Dunnett's post hoc testing.

Results
In 2xGRE BEAS-2B cells, OxPAPC exhibited a time-dependent (up to 18 hrs), 62% maximum reduction of FP-induced, GR-dependent luciferase activity (eg. 3,641±29.7 vs 9,622±705.7 units). OxPAPC also attenuated FP-induced expression of anti-inflammatory genes: KLF9 (-93.7%, $p<0.01$), FKBP5 (-94.8%, $p<0.001$) and GILZ (-79.8%, $P<0.058$). In 3kBU NF-κB-BEAS 2B luciferase reporter cells, FP significantly repressed TNF-induced luciferase activity by -46.8% ($p<0.001$). Although OxPAPC alone did not increase NF-κB-dependent gene activation, it did significantly reduce FP repression of TNF-induced NF-κB dependent luciferase activity by 63.3% ($p<0.001$).

Conclusion
Though OxPAPC does not appear to directly induce NF-κB dependent gene transcription, it is sufficient to impair GC-mediated transcriptional activation and repression in airway epithelial cells. This suggests that OxPAPC may contribute to steroid insensitivity in promoting persistent inflammation in asthma.

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No

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