ABSTRACT SUBMISSION FORM

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CHRD
CHILD HEALTH RESEARCH DAYS

CHRD 2020: Abstract Submission Form

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Title
Prenyltransferases Regulate Inflammatory Mediator Release by Human Pulmonary Fibroblasts

Background
Prenyltransferases (PTs) catalyze conjugation of isoprenoid chains to signalling proteins, such as Ras superfamily members, to facilitate their membrane anchoring and activation. We previously reported expression of all three PTs, farnesyltransferase (FT), geranylgeranyltransferase 1 (GGT1) and Rab geranylgeranyltransferase (GGT2) is increased in the lungs of COPD patients. PT expression, abundance and activity also increases in human lung fibroblasts in response to cigarette smoke extract (CSE).

Objective
PT inhibition alters the release of cytokines and chemokines by human lung fibroblasts stimulated with cigarette smoke and pro-inflammatory signals.

Methods
We profiled lung cell-specific PT abundance in cryosectioned peripheral lung cores (n=6) obtained from current smoker adult organ donors. Cryosectioned lungs from adult donors (n=6) were co-labelled with antibodies for cell-specific markers for endothelial (PECAM-1), mesenchymal (Vimentin) or epithelial cells (EPCAM) and antibodies for individual PTs and imaged using confocal microscopy. Separate experiments measured the response to pro-inflammatory stimuli (CSE 10%, TNF 10ng/mL, IL-1b 10ng/mL, or Combo (TNF & IL-1b 10ng/mL each)) or selective PT inhibitors (Table 1) in lung fibroblasts (COPD, n=6) by assaying IL-8 or GM-CSF secretion (24 and 48h) using multiplex ELISA.

Results
PT localization was confirmed in endothelial, mesenchymal and epithelial cells. Proinflammatory exposure to CSE and Combo increased baseline secretion of IL-8 and GM-CSF by 6.48-fold and 6.79-fold, respectively ($p \leq 0.001$, n=6). CSE induced IL-8 secretion was blunted by up to 68% (48h,$p \leq 0.001$,n=6) using FTi-277. Using KB-DK-V-33-1, Combo-induced GM-CSF secretion was blunted by 31%

(48h,p≤0.001,n=6).

Conclusion
Fibroblast response to pro-inflammatory stimuli is partially mediated by PTs found throughout the lung suggesting an important role in orchestrating lung inflammation that should be explored in animal models.

Theme:
Basic Science

Do you have a table/figure to upload?
Yes

Untitled
Mahood_Table1.pdf

Are you willing to participate in Goodbear's Den?
Yes

Presenter Status:
PhD Student

What was your role in the project?
Designed, Performed Experiments, Analyzed Data and Wrote the Abstract

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Table 1: Prenyltransferase inhibitors used in this study

Inhibitor	Target	Working Concentration
FTi-277	FT	10μM
F-Zol-PC	GGT-2	10μM
KB-DK-V-149-1	GGT-2	10μM
Simvastatin	HMG-CoA Reductase	1μM
GGTi-2133	GGT-1	10μM
JL-VI-139_1	GGT-2	10μM
Psoromic Acid	GGT-2	10μM
KB-DK-V-33-1	GGT-2	10μM