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Title: LSC 2013 abstract - Abnormal neutrophil migration is a feature of early COPD, present across disease phenotypes and causally related to increased phosphoinositide-3-kinase signalling

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Body: All COPD clinical phenotypes have airway neutrophilia & neutrophil(PMN)-related damage. COPD PMNs are less accurate when migrating, however it is unclear if this is specific to COPD or a general feature of inflammation. Phosphoinositide-3-kinase (PI3K) has been shown to be important in migration, the mechanism involved is unclear. We aim to assess the role of PI3K in migration of PMNs from COPD patients. Method: PMNs from 60 patients with COPD (GOLD stages I-IV, emphysema, frequent exacerbators), chronic severe asthma, Bronchiectasis, A1ATD & Healthy Smokers(HS) migrated towards CXCL8, CXCL1, LTB4 & fMLP after incubation with Class 1 isoform selective PI3K inhibitors($\alpha,\beta,\delta,\gamma$), SHIP inhibitors or carrier control. PI3K, AKT & phosphatase activity was assessed. Results: COPD PMNs initiated migration faster(COPD 48s ± 13, HS 68s±19, p=0.001) with increased random movement but reduced accuracy towards stimuli($p \leq 0.01$ for all) in all COPD stages & phenotypes, but not in other inflammatory conditions. COPD PMNs had constitutive PI3K & AKT activity compared with HS. PI3K blocking strategies(specifically PI3K γ & δ) restored accuracy. SHIP inhibition worsened chemotaxis in COPD & HS PMNs. There was no difference in phosphatase activity(COPD 150MFI(51-203), HS122(43-192)). Conclusion: COPD PMNs show increased random migration, but are less accurate. This is an early disease phenomenon & may contribute to increased damage. Inaccurate migration is causally related to PI3K activity, a potential target for disease modification.