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Title: LSC 2013 abstract - The role of damage associated molecular patterns in the genetic susceptibility towards cigarette smoke induced neutrophilic airway inflammation

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Body: Damage Associated Molecular Patterns (DAMPs) that are released from necrotic epithelial cells upon exposure to cigarette smoke (CS) have been proposed to contribute to neutrophilic lung inflammation in COPD. DAMPs can activate immune cells upon ligation of pattern recognition receptors. Only 20% of smoking individuals develop COPD, indicating a role for genetic susceptibility. We hypothesize that the profile of DAMPs released upon CS exposure contributes to the susceptibility to develop neutrophilic airway inflammation. 30 Inbred mouse strains were exposed to CS or air (control) in a 5-day exposure model. Subsequently, neutrophilic airway inflammation and the DAMP profile (e.g. HMGB1, HSP70, dsDNA, mtDNA) in the BAL fluid were determined in all mice by standard morphology, ELISA and qPCR. Haplotype Association Mapping (HAM), using 4 million SNPs, was performed to identify susceptibility genes for DAMP (dsDNA) release after CS exposure. Linear regression analysis showed a positive relation between neutrophilia and most, but not all, DAMPs. In a forward stepwise linear regression analysis dsDNA appeared to be the best predictor for neutrophilic airway inflammation. HAM analysis of dsDNA revealed several susceptibility genes contributing to DAMP release after CS exposure including genes that are functionally mapped to cell-death pathways. In conclusion, mice susceptible for neutrophilic airway inflammation after CS exposure also show increased DAMP release which is associated with genes involved in the regulation of cell-death pathways.