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Title: Cigarette smoke suppresses mast cell maturation and cytokine release independent of TLR4 signaling

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Body: Chronic obstructive pulmonary disease (COPD) is a multicomponent disease characterized by emphysema and/or chronic bronchitis. COPD is mostly associated with cigarette smoking. Many inflammatory cells are present in the airways of patients with COPD. Cigarette smoke contains over 4,700 chemical compounds, including free radicals and LPS (a Toll Like Receptor 4 agonist) at concentrations which may contribute to the pathogenesis of diseases like COPD. Toll-like receptors (TLRs) are an integral part of the innate immune system and these receptors recognize conserved pathogen-associated molecular patterns. We have previously shown that cigarette smoke medium (CSM) can stimulate several inflammatory cells via TLR4 and that CSM reduces the degranulation of bone marrow-derived mast cells (BMMCs). Moreover, CSM causes the release of chemokines but reduces IgE/antigen-induced degranulation and cytokine release. Interestingly, CSM had no effect on the surface expression of the IgE receptor (FcRI), but did reduce Syk kinase signaling. In the current study, the effect of CSM on mast cells maturation and function was investigated during a prolonged time period of 3 weeks. Co-culturing of BMMC with CSM during the last week suppressed the number of granules, degranulation and the release of Th2 and Th1 cytokines. Moreover, the surface expression of c-Kit and FcRI receptors were decreased. Interestingly, these effects were not observed with LPS. Thus, we conclude that CSM differentially affects mast cells dependent upon the duration of exposure and that these effects are TLR4-independent.