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Title: IL33 and TNFα synergistically enhance store operated Ca^{2+} entry in cultured human airway smooth muscle cells

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Body: Asthma is an inflammatory disease, characterised by a TH2-mediated immune response resulting in over-production of cytokines such as Interleukins and Tumour Necrosis Factor (TNF). Both TNFα and IL33 are expressed in human airway smooth muscle (HASM) cells and are implicated in severe asthma. TNFα was shown to up-regulate the expression of IL33 in a dose-dependent manner in HASM cells (1). We have previously recorded store-operated Ca^{2+} entry (SOCE) in response to Ca^{2+} store depletion in HASM cells (2), a process which may be involved in airway smooth muscle contraction. In the present study we tested the hypothesis that IL33 and TNFα may potentiate SOCE in cultured HASM cells. Methods: Dynamic changes in intracellular Ca^{2+} were recorded in HASM cells pre-treated with IL33 or TNFα for 24 or 48 hours using the FLIPR Calcium-5 kit and a Flexstation 3. Area under the curve (AUC) was used to compare different groups using one-way ANOVA. Results: 24-hour treatment of cells with IL33 or TNFα produced a small increase in SOCE, while they had no effect on Ca^{2+} release induced by either cyclopiazonic acid (CPA) or bradykinin (BK). 48-hour treatment of cells with TNFα (10 ng/ml) produced a marked increase of SOCE activated by CPA (by 39.5%; n=7, p=0.012) or BK (by 32.1%; n=7, p=0.027). In the presence of TNFα (1 ng/ml), IL33 (100 ng/ml) produced a marked increase in SOCE activated by CPA (by 19.7%; n=7, p=0.003) or BK (by 27.1%; n=7, p= 0.001) compared with TNFα only. Conclusion: IL33 and TNFα synergistically potentiated SOCE in a concentration dependent manner in cultured HASM cells. 1. Préfontaine, D, et al. J Immunol 2009; 183:5094-5103 2. Peel S, et al. Respir Res 2006; 7(1): 119.