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Title: Plasminogen-stimulated inflammatory cytokine production by airway smooth muscle cells is regulated by annexin A2

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Body: Plasminogen has a potential role in airway inflammation and disease. Airway smooth muscle (ASM) cells cleave plasminogen into plasmin (Schuliga et al 2011, *Am J Respir Cell Mol Biol* 44), a protease with pro-inflammatory activity. In this study, the effect of plasminogen on cytokine production by human ASM cells was investigated in vitro. Levels of IL-6 and IL-8 in the medium of ASM cells were increased by incubation with plasminogen (5-50µg/mL) for 24h ($P < 0.05$, $n = 6-9$), as were the levels of cytokine mRNA at 4h. The effects of plasminogen were attenuated by $\alpha 2$ -antiplasmin (0.5µg/mL), a plasmin-inhibitor ($P < 0.001$, $n = 12$). Exogenous plasmin (5-15mU/mL) also stimulated cytokine production ($P < 0.05$, $n = 6-8$), in a manner sensitive to serine-protease inhibition by aprotinin (10 KIU/mL). Inhibition of plasmin-stimulated ERK1/2 and p38^{MAPK} or PI3K/Akt signalling by PD98059 (10µM), SB203580 (10µM) or LY294002 (10µM) respectively, modulated plasmin-stimulated cytokine production ($P < 0.05$, $n = 5$). The knock down of annexin A2, a component of the plasmin(ogen) receptor comprised of annexin A2 and S100A10 (p11), attenuated plasminogen conversion into plasmin and plasmin-stimulated cytokine production. In an acute experimental model of allergic airway inflammation, A2 knockout mice had lower levels of inflammatory cells and IL-6 in the BALF as compared to wild type mice following challenge with aerosolized ovalbumin ($P > 0.05$, $n = 5-14$). In conclusion, plasmin(ogen) stimulates ASM cytokine production in a manner regulated by annexin A2. Modulation of plasmin-evoked signalling could provide a novel therapeutic approach to the treatment of chronic airway inflammation in diseases such as asthma.