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Title: Impaired inhibitory action of corticosteroids on chemokine expression induced by TNFα in airway smooth muscle (ASM) cells from patients with severe asthma

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Body: Although the mechanisms mediating corticosteroid resistance in severe asthma are still unknown, evidence suggests the existence of corticosteroid insensitive pathways in ASM cells. Here we investigated the sensitivity of TNF-induced chemokine production by human ASM cells to corticosteroids in healthy controls and patients with mild and severe asthma. Cells pre-treated with fluticasone (FP) and dexamethasone (Dex) for 2 hours were exposed to TNF (10 ng/ml) for 24 hours. Chemokine levels were assessed in cell supernatants using ELISA. TNF induced CXCL10 and CLL5 production in all subjects irrespective of disease severity. Net increases in CCL5 levels were 3593 ± 395, 5019 ± 125 pg/ml and 5832 ± 1705 pg/ml in ASM cells from healthy controls (n=3), and patients with mild (n=4) and severe asthma (n=3). Net increases in CXCL10 levels were 12956 ± 1838, 14528 ± 2350 pg/ml and 25327 ± 6816 pg/ml in ASM cells from healthy controls (n=3), and patients with mild (n=4) and severe asthma (n=3). Both FP and Dex (0.1-1000 nM) dose-dependently inhibited TNF-induced production of CXCL10 and CCL5 in healthy subjects reaching a complete inhibition at 100 nM ($p<0.05$) with either corticosteroids while no inhibitory effect was seen on chemokine production by ASM cells from severe asthmatics (n=4). In ASM cells from mild asthmatics, the maximum inhibitory effect on CCL5 production seen at 100 nM steroid was 71% with FP and 32% with Dex while CXCL10 production was reduced by 70% and 80% and 32% with FP and Dex, respectively. This study further supports the existence of impaired corticosteroid sensitivity in ASM cells from patients with severe asthma.