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Title: Activation of both transcription factors STAT5 and IRF-1 is insensitive to corticosteroids in asthmatic bronchial smooth muscle cells exposed to TNFα/IFNγ

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Body: We have previously developed a cellular model in healthy airway smooth muscle (ASM) cells where corticosteroids (CS) lose their anti-inflammatory action when cells are exposed to TNFα in combination with IFNγ. The molecular mechanisms by which TNFα/IFNγ promote CS insensitivity has not been completely investigated although an increased activation of transcription factors such as STAT5 has been implicated in other cell types. It is also not known whether TNFα/IFNγ also interfere with CS in ASM cells derived from asthmatic patients. In the present study, we found that TNFα/IFNγ-induced the expression of different steroid-resistant chemokines CX3Cl1, CCl5 and CCl11 in asthmatic ASM cells (n=3). We also found that TNFα/IFNγ (0-6hr)-increased phosphorylation of STAT5 in a time-dependent fashion reaching a maximum at 30 min followed by a lower activated state that was sustained up to 6 hr. Prior treatment with fluticasone (0.1-100 nM) did not affect cytokine-induced STAT5 activation but dose-dependently increased STAT5 phsophorylation. Similarly, the sustained activation of the transcription factor IRF-1 by TNFα/IFNγ (up to 6 hr) was also unaffected by fluticasone (01-100 nM). Together, these data show for the first time that TNFα/IFNγ induced a sustained activation of corticosteroid-resistant STAT5 and IRF-1 in asthmatic ASM cells (n=3). Because STAT5 and IRF-1 have been associated with reduced CS action in other cell types, our findings suggest the possible of involvement of these transcription factors in driving CS insensitivity in asthmatic airway smooth muscle cells.