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Title: Inhibitors of apoptosis proteins in asthmatic airway inflammation

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Body: Background: In atopic asthma aero-allergens and infections cause chronic airway inflammation, even when ‘well’. Transcription factor NF-kB is central in the response, but its regulation is compromised in asthma leading to constitutive activation. Inhibitors of Apoptosis (IAPs) may regulate NF-kB inflammation via TRAF6 activation. Endogenous IAP antagonist (Smac) regulates IAPs and pharmacological depletion by Smac-mimetics inhibits NF-kB and inflammation. IAPs may significantly contribute to the innate immune response in asthma. Methods: Adult Primary Nasal Epithelial cells (PNECs, atopic asthma, non-asthmatic controls, n=3) were stimulated with LPS (P.aeruginosa, 100ng/ml) or PolyI:C (50µg/ml). Protein and mRNA expression of IAPs/Smac and NF-kB p65 mRNA were determined. Cells were pre-incubated with smac-mimetic SM164 and IL-8 analysed. Results: Basal IAP1/2 and p65 mRNA are increased in atopic-asthmatics (all $p<0.05$), Smac is significantly lower. LPS had little effect on IAPs/Smac, but PolyI:C caused a time-dependent increase in cIAP2 mRNA ($p<0.01$), which was higher in controls ($p<0.001$). p65 mRNA was significantly higher in atopic-asthmatics. IAP proteins were only detectable after immunoprecipitation: PolyI:C induced cIAP2 in controls and significantly less in atopic-asthmatics. IL-8 release after PolyI:C was higher in controls and was significantly reduced by SM164. Conclusion: Although atopic asthmatics have increased basal levels of IAPs, they show a blunted cIAP2 response to PolyI:C. Degradation of IAP1/2 only reduces the inflammatory response in controls, suggest a beneficial role for increased cIAP2 in airway epithelium. The role of the natural inhibitor Smac in atopic asthma needs further investigation.