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Title: TLR7 and TLR9-activated inflammation is differentially regulated in asthma

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Body: Background: Innate immunity is the first line of our defence in response to pathogens. Pattern recognition receptors, including the toll-like receptors (TLRs), recognise several pathogen-associated microbial patterns (PAMPs) and trigger immune and inflammatory responses to destroy invaders. RNA viruses such as rhinovirus, are a common cause of exacerbations of asthma. Severe asthma patients have an increased incidence of asthma exacerbations and are usually treated with high doses of corticosteroids. Aims & Objectives: Determine the effect of TLR7 and TLR9 activation on inflammatory cytokine release and the modulation of these responses by corticosteroids in blood monocytes from severe asthmatic patients. Methods: Human blood monocytes were obtained from whole blood from healthy volunteers and asthmatic subjects. Cells were treated with increasing concentrations of dexamethasone (10^{-9} – 10^{-6} M) for 1 hr or left untreated, prior to overnight stimulation with either 5 µg/ml imiquimod (TLR7 agonist) or 5 µg/ml CpG DNA (TLR9 agonist). Supernatants were collected for CXCL8 cytokine release by ELISA. Results: TLR7 and TLR9 agonists induced CXCL8 release in blood monocytes. Dexamethasone inhibited this response in a concentration-dependent manner in all subject groups. However, the induction of CXCL8 release was significantly higher in blood monocytes from healthy volunteers and non-severe asthmatics compared to severe asthmatics. Conclusion: Both TLR agonists show a differential inflammatory response in severe asthma. We are currently investigating whether this effect is mirrored at the transcriptional level. The pathway(s) leading to these differential responses in human blood monocytes will be investigated.