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Title: Monocyte inflammatory responsiveness and potential therapeutic target for pigeon fancier's hypersensitivity pneumonitis (HP)

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Body: Objective: HP is an interstitial lung disease caused by an immune-hypersensitivity to inhaled antigens. Lung 'foamy' macrophages are characteristic of HP, and monocytes may already be primed towards this phenotype, therefore we studied the phenotype and function of blood monocytes in HP among pigeon fanciers. Method: Pigeon fanciers: 22 with and 23 without HP symptoms. Measures: spirometry, serum IgG to pigeon antigens, and cytokines (ELISA). Monocyte function assessed by in vitro cytokine response to relevant doses of LPS or antigen. Results: LPS stimulation produced high (pg/ml, median [IQR]) IL-1b (976 [39, 140]), IL-6 (5161 [2000-20000]) and TNFa (521 [200, 1833]) compared with low concentrations in antigen cultures. LPS or antigen induced equal concentrations of IL-4, IL-8, IL-12 and CCL5. In contrast to LPS, antigen stimulated high concentrations (ng/ml) of CCL2 (12.5 [7.7, 16.3]) and IL-1RA (4.4 [1.3, 5.4]). The IL-1Ra concentration correlated with the serum IgG antibody titer ($r=0.716$, $p<0.001$) and with lung function (FEV1 %predicted; $r= -0.408$, $p=0.01$). The in vitro production of most cytokines by either stimulus was dose-dependently inhibited by dexamethasone (10e-8 and 10e-6M) except for CCL3 and CCL4, and there was a trend for monocytes from subjects with HP to be less steroid responsive. Conclusion: Development of HP was not limited by the potential of subjects' monocytes to produce pro-inflammatory cytokines. There appeared to be different LPS and antigen-driven cytokine endotypes. The relative steroid-insensitivity of some cytokines suggests that additional anti-inflammatory strategies might be useful in treating HP.