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Title: TLR7 gene deficiency and early-life pneumovirus infection interact to predispose toward the development of asthma-like pathology in mice

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Body: Respiratory viruses are a major risk factor for both asthma inception and exacerbations, an association that may be related to a genetic defect in toll-like receptor (TLR)7-mediated signalling and impaired type I IFN responses, both reported in asthmatics. Wildtype (WT) and TLR7 gene-deleted mice were inoculated with rodent-specific pathogen pneumonia virus of mice (PVM) at 1 (primary), 7 (secondary) and 13 (tertiary) weeks of age and pathological features of bronchiolitis or asthma assessed. In some experiments, low dose cockraoch antigen was administered intransally at 3, 10, 17, and 31 days post primary infection. Here, we demonstrate that in absence of TLR7, PVM infection increased inflammasome activation, sloughing and viral load in the mucosal epithelium. This damage was associated with greater T helper 2 (Th2) immunity as evidenced by elevated nuocyte recruitment, and IL-33 and Th2 type cytokine expression. A secondary or tertairy infection of TLR7-deficient but not WT mice induced all of the cardinal pathophysiologic features of asthma, including Th2 cytokine and IgE production, eosinophilia, mast cell hyperplasia, increased airway smooth muscle and airways hyper-reactivity in a memory CD4+ T cell-dependent manner. PVM infection potentiated allergic sensitisation to cockroach antigen and exacerbated cockroach-induced allergic asthma. Moreover, this phenotype was significantly greater in TLR7-deficient mice. Our findings highlight how a clinically relevant gene-environment interaction may be causal in the development of asthma, and predispose toward an aberrant adaptive response that underlies virus-induced exacerbations in later life.