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| **IL-33 induced neutrophilic inflammation and NETosis underlie rhinovirus-triggered exacerbations of asthma.** |
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| **Introduction/Aim:**  Rhinovirus-induced neutrophil extracellular traps (NETs) contribute to acute asthma exacerbations, however the molecular factors that trigger NETosis in this context remain ill-defined. Therefore we sought to determine a role for IL-33, an epithelial cell-derived alarmin rapidly released in response to infection.  **Methods:**  Mice with chronic experimental asthma (CEA) were inoculated with rhinovirus or IL-33, and treated with HPARI (H. polygyrus Alarmin Release Inhibitor), which blocks IL-33 release and signalling, or Cl-Amidine, an inhibitor of PAD4-mediated NETosis. DsDNA, neutrophil elastase, and IL-33 were measured in nasal samples obtained from rhinovirus-infected asthmatics and healthy controls.  **Results:**  In mice with chronic experimental asthma (CEA), but not naïve controls, rhinovirus inoculation induced an early (1 day post infection; dpi) inflammatory response dominated by neutrophils, neutrophil-associated cytokines (IL-1α, IL-1β, CXCL1) and NETosis, followed by a later, type-2 inflammatory phase (3-7 dpi), characterized by eosinophils, elevated IL-4 levels, and goblet cell hyperplasia. Notably, both phases were ablated by HpARI (*Heligmosomoides* *polygyrus* Alarmin Release Inhibitor), which blocks IL-33 release and signalling. Instillation of exogenous IL-33 recapitulated the rhinovirus-induced early phase, including the increased presence of NETs in the airway mucosa, in a PAD4-dependent manner. *Ex vivo* IL-33-stimulated neutrophils from mice with CEA, but not naïve mice, underwent NETosis, and produced greater amounts of IL-1β, IL-4, and IL-5. In nasal samples from rhinovirus-infected people with asthma, but not healthy controls, IL-33 levels correlated with neutrophil elastase and dsDNA.  **Conclusion:**  IL-33 blockade ameliorates the severity of an asthma exacerbation by attenuating neutrophil recruitment and the downstream generation of NETs.  **Grant Support:**  This work was supported by an NHMRC grant awarded to S.P. (1141581), and grants to H.J.M from LONGFONDS Accelerate as part of the AWWA project, and the Medical Research Council (MR/S000593/1). |