REVIEW
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Anti-alarmins in asthma: targeting the airway epithelium with next-generation biologics

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Blocking epithelial alarmins, upstream mediators triggered early in the asthma inflammatory response that orchestrate broad inflammatory effects, is a promising alternative approach to asthma treatment, which may be effective in a broad patient population https://bit.ly/2zqoXAw

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ABSTRACT Monoclonal antibody therapies have significantly improved treatment outcomes for patients with severe asthma; however, a significant disease burden remains. Available biologic treatments, including anti-immunoglobulin (Ig)E, anti-interleukin (IL)-5, anti-IL-5Rα and anti-IL-4Rα, reduce exacerbation rates in study populations by approximately 50% only. Furthermore, there are currently no effective treatments for patients with severe, type 2-low asthma. Existing biologics target immunological pathways that are downstream in the type 2 inflammatory cascade, which may explain why exacerbations are only partly abrogated. For example, type 2 airway inflammation results from several inflammatory signals in addition to IL-5. Clinically, this can be observed in how fractional exhaled nitric oxide (F_{eNO}), which is driven by IL-13, may remain unchanged during anti-IL-5 treatment despite reduction in eosinophils, and how eosinophils may remain unchanged during anti-IL-4Rα treatment despite reduction in F_{eNO}. The broad inflammatory response involving cytokines including IL-4, IL-5 and IL-13 that ultimately results in the classic features of exacerbations (eosinophilic inflammation, mucus production and bronchospasm) is initiated by release of "alarmins" thymic stromal lymphopoietin (TSLP), IL-33 and IL-25 from the airway epithelium in response to triggers. The central, upstream role of these epithelial cytokines has identified them as strong potential therapeutic targets to prevent exacerbations and improve lung function in patients with type 2-high and type 2-low asthma. This article describes the effects of alarmins and discusses the potential role of anti-alarmins in the context of existing biologics. Clinical phenotypes of patients who may benefit from these treatments are also discussed, including how biomarkers may help identify potential responders.