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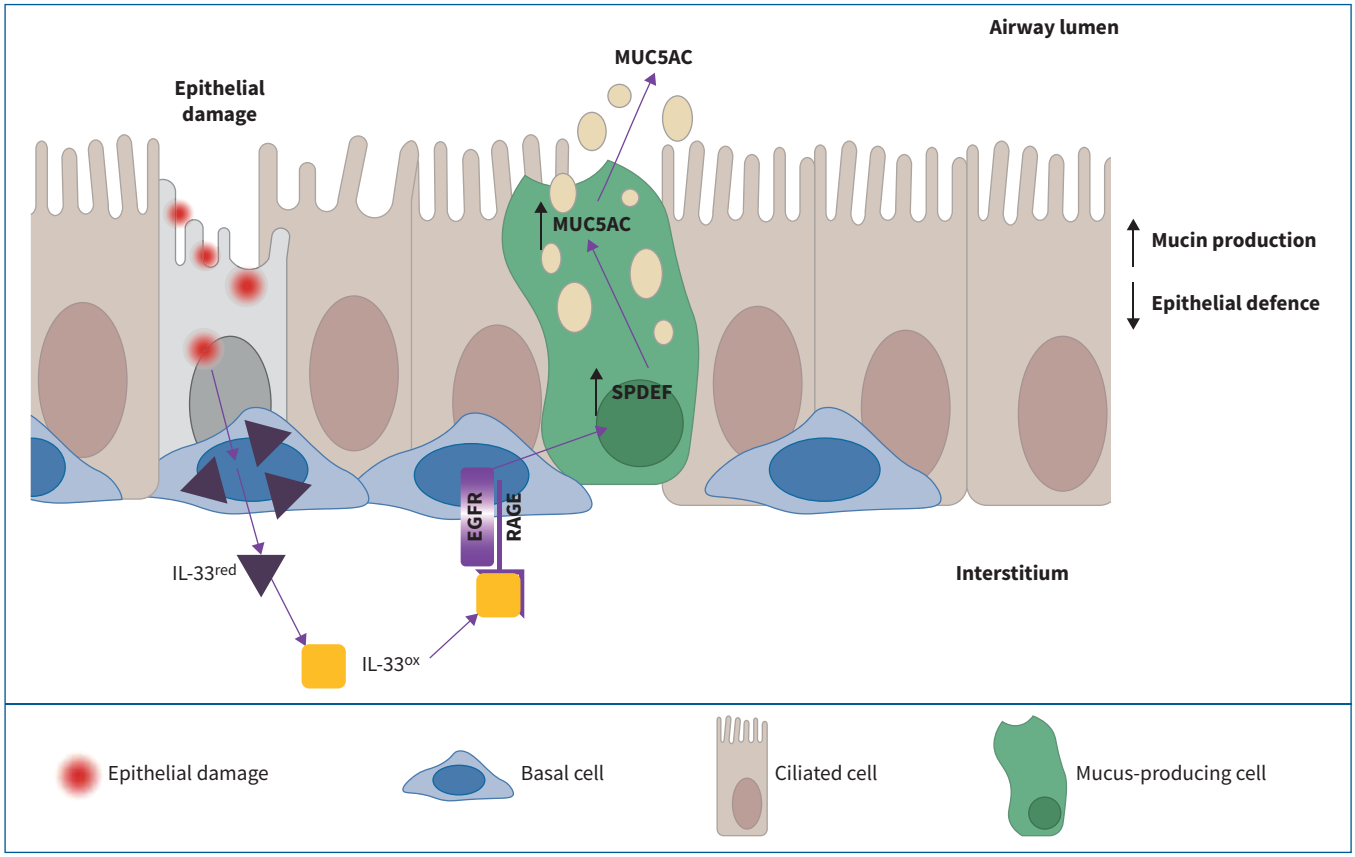

GRAPHICAL ABSTRACT IL-33^{ox} binds to receptor for advanced glycation end products (RAGE) to signal via epidermal growth factor receptor (EGFR). Activation of the IL-33^{ox}–RAGE/EGFR pathway redirects epithelial cell fate, promoting a mucin hypersecretion phenotype at the expense of epithelial defence functions.

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An ST2-independent signalling complex of oxidised IL-33, receptor for advanced glycation end products (RAGE) and epidermal growth factor receptor (EGFR) governs epithelial remodelling and mucin hypersecretion in COPD https://bit.ly/3pxgaqx

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Abstract

Background Epithelial damage, repair and remodelling are critical features of chronic airway diseases including chronic obstructive pulmonary disease (COPD). Interleukin (IL)-33 released from damaged airway epithelia causes inflammation *via* its receptor, serum stimulation-2 (ST2). Oxidation of IL-33 to a non-ST2-binding form (IL-33^{ox}) is thought to limit its activity. We investigated whether IL-33^{ox} has functional activities that are independent of ST2 in the airway epithelium.

Methods *In vitro* epithelial damage assays and three-dimensional, air–liquid interface (ALI) cell culture models of healthy and COPD epithelia were used to elucidate the functional role of IL-33^{ox}. Transcriptomic changes occurring in healthy ALI cultures treated with IL-33^{ox} and COPD ALI cultures treated with an IL-33-neutralising antibody were assessed with bulk and single-cell RNA sequencing analysis.

Results We demonstrate that IL-33^{ox} forms a complex with receptor for advanced glycation end products (RAGE) and epidermal growth factor receptor (EGFR) expressed on airway epithelium. Activation of this alternative, ST2-independent pathway impaired epithelial wound closure and induced airway epithelial remodelling *in vitro*. IL-33^{ox} increased the proportion of mucus-producing cells and reduced epithelial defence functions, mimicking pathogenic traits of COPD. Neutralisation of the IL-33^{ox} pathway reversed these deleterious traits in COPD epithelia. Gene signatures defining the pathogenic effects of IL-33^{ox} were enriched in airway epithelia from patients with severe COPD.

Conclusions Our study reveals for the first time that IL-33, RAGE and EGFR act together in an ST2-independent pathway in the airway epithelium and govern abnormal epithelial remodelling and muco-obstructive features in COPD.