Metabolic regulation by prostaglandin E 2 impairs lung group 2 innate lymphoid cell responses

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Abstract

Background: Group 2 innate lymphoid cells (ILC2s) play a critical role in asthma pathogenesis. Non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (NERD) is associated with reduced signaling via EP2, a receptor for prostaglandin E $_2$ (PGE $_2$). However, the respective roles for the PGE $_2$ receptors EP2 and EP4 (both share same downstream signaling) in the regulation of lung ILC2 responses has yet been deciphered. **Methods:** The roles of PGE $_2$ receptors EP2 and EP4 on ILC2-mediated lung inflammation were investigated using genetically modified mouse lines and pharmacological approaches in IL-33- and *Alternaria alternata* (A.A.)-induced lung allergy models. The effects of PGE $_2$ receptors and downstream signals on ILC2 metabolic activation and effector function were examined using *in vitro* cell cultures. **Results:** Deficiency of EP2 rather than EP4 augments IL-33-induced lung ILC2 responses and eosinophilic inflammation *in vivo*. In contrast, exogenous agonism of EP4 but not EP2 markedly restricts IL-33- and *Alternaria alternata*-induced lung ILC2 responses and eosinophilic inflammation. Mechanistically, PGE $_2$ directly suppresses IL-33-dependent ILC2 activation through the EP2/EP4-cAMP pathway, which downregulates STAT5 and MYC pathway gene expression and ILC2 energy metabolism. Blocking glycolysis diminishes IL-33-dependent ILC2 responses in mice lacking endogenous PG synthesis but not in PG-competent mice. **Conclusion:** We have defined a mechanism for optimal suppression of lung ILC2 responses by endogenous PGE $_2$-EP2 signaling which underpins the clinical findings of defective EP2 signaling in patients with NERD. Our findings also indicate that exogenously targeting the PGE $_2$-EP4-cAMP and energy metabolic pathways may provide novel opportunities for treating ILC2-initiated lung inflammation in asthma and NERD.

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