INFLAMMATORY DISEASES

Targeting prostanoid receptors

A paper published in *Nature Medicine* has shown that the G protein-coupled prostanoid EP4 receptor might be a new target for immuno-inflammatory disorders.

T_H1 and T_H17 T helper cells mediate tissue damage and inflammation and are crucial to the pathogenesis of various immune disorders. Therefore, one therapeutic strategy is to modulate the cytokines that control the differentiation of T_H1 and T_H17 cells. Indeed, inhibiting interleukin 12 (IL-12) and IL-23 in Crohn's disease and psoriasis has beneficial effects. However, T helper cells are also modulated by non-cytokines, such as prostaglandin E2 (PGE2). A recent improvement in our understanding of T cell biology and a lack of *in vivo* studies on the effect of PGE2 on T helper cells prompted Yao and colleagues to re-examine the effects of PGE2 on T_H1 and T_H17 cells.

The authors first conducted *in vitro* studies using isolated T cells. In contrast to previous studies, PGE2 (at low concentrations) promoted T_H1 cell differentiation. Using subtype-selective prostanoid receptor agonists, the authors showed that PGE2 mediated its effects through EP2 and EP4 receptors, and these receptors activated phosphoinositide 3-kinase signalling. Moreover, facilitation of T cell differentiation by PGE2 was specific to the T_H1 subset, as PGE2 had no effect on T_H17, T_H2 or regulatory T cell differentiation.

Next, the effects of PGE2 on T_H17 expansion were studied. T_H17 expansion is stimulated by IL-23 that is produced by activated dendritic cells (DCs); IL-23 production from DCs required PGE2–EP4 signalling. Although IL-23 alone induced a limited expansion of T_H17 cells, the addition of PGE2 markedly expanded the number of IL-17-producing cells, showing that PGE2 potently stimulates IL-23 action on T_H17 expansion. In addition, EP2 and EP4 agonists mimicked the effect of PGE2 on T_H17 expansion, in this case by signalling through the cyclic AMP pathway.

Finally, the authors used two animal models — contact hypersensitivity and experimental autoimmune encephalomyelitis (EAE; a model of multiple sclerosis) — in which T_H1 and T_H17 cells are involved in pathogenesis. In the contact hypersensitivity model, oral administration of the EP4 antagonist ONO-AE3-208 inhibited inflammation; and in EAE, the antagonist (administered orally once per day for 10 days) almost completely suppressed disease development. In both disease models, ONO-AE3-208 suppressed T cell activation and decreased production of interferon-γ and IL-17 in lymph node cells, suggesting that EP4 receptor signalling regulates T_H1 differentiation and T_H17 cell expansion *in vivo*.

In summary, this paper revealed that EP2 and EP4 receptors can regulate immune responses. Given that G protein-coupled receptor antagonists will be easier to manufacture and administer than cytokine-targeting biologics, such receptors might be an attractive target for treating immuno-inflammatory disorders.

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ORIGINAL RESEARCH PAPER Yao, C. *et al.* Prostaglandin E2–EP4 signaling promotes immune inflammation through T_H1 cell differentiation and T_H17 cell expansion. *Nature Med.* **15**, 633–640 (2009)