# Prostaglandin E2 directly inhibits the conversion of inducible regulatory T cells through EP2 and EP4 receptors via antagonizing TGF-β signalling.


## Abstract

Regulatory T (Treg) cells are essential for control of inflammatory processes by suppressing effector T-cell functions. The actions of PGE2 on the development and function of Treg cells, particularly under inflammatory conditions, are debated. In this study, we employed pharmacological and genetic approaches to examine whether PGE2 had a direct action on T cells to modulate de novo differentiation of Treg cells. We found that TGF-β-induced Foxp3 expression and iTreg cell differentiation in vitro is markedly inhibited by PGE2, which was mediated by the receptors EP2 and EP4. Mechanistically, PGE2-EP2/EP4 signalling interrupts TGF-β signalling during iTreg differentiation. Moreover, EP4 deficiency in T cells impaired iTreg cell differentiation in vivo. Thus, our results demonstrate that PGE2 negatively regulates iTreg cell differentiation through a direct action on T cells, highlighting the potential for selectively targeting the PGE2-EP2/EP4 pathway to control T cell-mediated inflammation.


16,16-dimethyl prostaglandin E2 (dm-PGE2) and PGE2 were purchased from Cayman Chemical. Highly selective agonists for EP1 (ONO-DI-004), EP2 (ONO-AE1-259–01), EP3 (ONO-AE-248) or EP4 (ONO-AE1-329) were gifts from Ono Pharmaceutical Co., Japan. Selective antagonists against EP2 (PF-04418948) and EP4 (L-161,982) were purchased from Cayman. Recombinant human TGF-β1 and mouse or human IL-2 were purchased from R&D system or Biolegend. Indomethacin, dibutyryl-cAMP (db-cAMP), 3-isobutyl-1-methylxanthine (IBMX), H-89, LY-294002, AS1842856 and STAT5 inhibitor were purchased from Sigma or Calbiochem. Treg cells actively suppress immune responses against autologous and foreign antigens in vitro and in vivo. Evidence from mouse models and human diseases indicates that eliminating Treg cell numbers or abrogation of their functions leads to a variety of immune-mediated pathologies, including autoimmunity (e.g., multiple sclerosis, active rheumatoid arthritis and type 1 diabetes), allergies and graft rejection [3-8]. Treg cells are characterized as expression of the surface marker CD25 (i.e., IL-2 receptor α chain, IL-2Rα) and the master transcription factor Forkhead box P3 (Foxp3) and produce the anti-inflammatory cytokine IL-10.

## BIOGRAPHY


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