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Receptors, Signal Transduction, & Genes

Up - regulation of EP_2 and EP_3 receptors in human tolerogenic dendritic cells boosts the immunosuppressive activity of PGE_2

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Abstract

Dendritic cells (DCs) are APCs essential in regulating the immune response. PGE_2, produced during inflammation, has a pivotal role in the maturation of DCs and, therefore, is vital for the immune response. The large variety of biologic functions governed by PGE_2 is mediated by its signaling through 4 distinct E - type prostanoid (EP) receptors. Immunogenic DCs express EP_2 and EP_4, which mediate the PGE_2 signaling. However, the expression and function of EP receptors in human tolerogenic DCs (tol - DCs), which present an inhibitory phenotype, have not yet, to our knowledge, been assessed. To clarify the role of EP receptors in tol - DCs, we examined the expression of different EP receptors and their effect using selective agonists in human cells. We find that EP_2 and EP_3 expression are up - regulated in in vitro–generated tol - DCs compared with mature DCs (mDCs). Activation of EP_2–EP_4 has a direct effect on the surface expression of costimulatory molecules and maturation receptors, such as CD80, CD83, and CD86 or MHCII and CCR7 in tol - DCs, the latter being exclusively modulated by PGE_2–EP_4 signaling. Importantly, we find that EP_2 and EP_3 receptors are involved in tolerance induction through IL - 10 production by tol - DCs. These results are in sharp contrast with the inflammatory role of EP_4. Moreover, we show that DCs generated in the presence of agonists for EP receptors, induce naive T cell differentiation toward polarized Th1/Th17 cells. Given the differential effects of EP receptors, our results suggest that EP receptor agonist/antagonists might become relevant novel drug templates to modulate immune response.

Citing Literature

Supporting Information