

## IL-33 Production in Murine Macrophages via PGE2-E Prostanoid Receptor 2/4 Signaling

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**Abstract :** IL-33, a recently discovered member of the IL-1 cytokine family, binds to the TLR/IL1R super family receptor ST2 and induces type 2 immune responses. IL-33 is constitutively expressed in structural cells at barrier sites such as skin, lung, and intestine, and also inducibly expressed by hematopoietic cells including macrophages. Stimulation of macrophages by Lipopolysaccharide (LPS) can induce de novo IL-33 expression, and also causes the production of prostaglandin-E2 (PGE2) via cyclooxygenase (COX)-2 and microsomal PGE2 synthase-1 (mPGES-1). Because PGE2 can regulate macrophage functions through both autocrine and paracrine mechanisms, the potential interplay of endogenous PGE2 on IL-33 production was explored. Bone-marrow derived murine macrophages (bmMF) that lack either mPGES-1 or EP2 receptor expression were stimulated with LPS in the absence or presence of exogenous PGE2 along with pharmacological agonists and antagonists. The study results demonstrate that endogenous PGE2 markedly enhances LPS-induced IL-33 production by bmMFs via EP2 receptors. Moreover, exogenous PGE2 can amplify LPS-induced IL-33 expression dominantly by EP2 and partly by EP4 receptors by a pathway involving cAMP and exchange protein activated by cAMP (EPAC), but not protein kinase A (PKA). Though both IL-33 production and PGE2 generation in response to LPS require activation of both p38 MAPK and NF- $\kappa$ B, PGE2 did not influence this activation. In conclusion, it is demonstrated that endogenous PGE2 signaling through EP2 and EP4 receptors is a prerequisite for LPS-induced IL-33 production in bmMFs and the underlying cAMP mediated pathway involves EPAC. Since IL-33 is a critical pro-inflammatory cytokine in various pathological disorders, this PGE2-EP2/EP4-cAMP mediated pathway can be exploited to intervene in IL-33 driven pathologies.

**Keywords :** bone marrow macrophages, EPAC, IL-33, PGE2

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