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Roles of beta-arrestin1/2 in prostaglandin-mediated signaling and tumor development

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Prostaglandin (PG) E_2 manifest its biological activity by signalling via four G protein coupled receptors (GPCRs) identified as EP1, EP2, EP3 and EP4. GPCRs represent the most numerous class of receptors in the mammalian genome. Ligand binding to the GPCR results in the activation of the Gαs subunit and disassociation of the Gαs and Gβγsubunits. Early on the binding of β-arrestin1 or 2 to the GPCR was thought to terminate GPCR signalling by preventing further G protein interaction and to cause receptor internalization/desensitization. However, recent studies have indicated that the GPCR/β-arrestin1 or 2 interactions can actually provide a mechanism for GPCR-mediated signalling.

In the research to be presented, the signalling pathways activated by butaprost, an EP2 agonist, and EP2's contributions to keratinocyte replication and skin tumor development are described. Butaprost stimulation of EP2 led to the activation of PKA and down stream effectors. In addition, butaprost stimulation of EP2 led to EP2-β-arrestin1 complex formation with subsequent Src activation and transactivation of EGFR and down stream effectors. The necessity for β-arrestin1 in the activation of Src/EGFR was indicated by the significantly decreased activation of Src/EGFR and down stream effectors in β-arrestin1-/- mouse skin. In addition, selective inhibition of PKA, EGFR or the use of β-arrestin1-/- mice significantly reduced mouse skin tumor formation. Thus, the data indicate that the PGE_2 receptor, EP2, plays an important role in skin tumor formation; and that both G protein dependent and β-arrestin1 dependent signalling pathways are involved.

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