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EP4-mediated prostanoid signalling promotes oral cancer progression

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Cyclooxygenase-2 (COX-2) enzyme is upregulated in oral cancer (OSCC), where it catalyses PGE_2 synthesis. We have shown previously that PGE_2 promotes integrin-dependent OSCC invasion (1). PGE_2 has four receptors (EP1-4), each coupled to different intracellular signaling pathways. We therefore investigated the role of EP receptor signaling in the invasive process.

We used immunochemistry and RT-PCR to examine EP receptor expression in OSCC cell lines and OSCC *in vivo*, and found marked upregulation of EP4. Chemical inhibition or transient knockdown of EP4 in OSCC lines significantly reduced levels of intracellular cyclic AMP ($cAMP_i$), whereas EP4 overexpression increased $cAMP_i$. Using Transwell and organotypic invasion assays, we studied the functional role of EP4. Overexpression of EP4 promoted OSCC invasion, with confocal microscopy revealing that EP4 localized to filopodia, processes associated with cell motility. Conversely, inhibition of either EP4 or $cAMP_i$ suppressed invasion. Treatment of cells with the cAMP agonist, forskolin, restored invasion following PGE_2 suppression. We identified the GTP-ase, Rac1, as a downstream target of $cAMP_i$, where inhibition of EP4 or $cAMP_i$ suppressed Rac1 activation, and RNA_i abrogation of Rac1 inhibited invasion.

Our data describe a novel signaling pathway in cancer invasion, and suggest that COX-2/PGE_2-dependent OSCC signaling is primarily modulated through the EP4 receptor, leading to increased $cAMP_i$ and Rac1 activation. Targeting EP4 may be an important strategy to suppress tumor progression, and may avoid the side-effects associated with systemic administration of COX-2 inhibitors.

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