ROLE OF PKA IN EGFR TRANSACTIVATION INDUCED BY PGE2 IN A431 CELLS

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In epithelial tumors upregulation of EGF receptor (EGFR) is responsible for tumor growth, metastasis and angiogenesis. Several line of evidence indicate that inflammatory mediators such as PGE2, significantly contribute to tumor progression by activating the EGFR signalling. The present study examined the molecular mechanisms leading to EGFR trans-activation promoted by PGE2 in a model of squamous cell carcinoma, A431. Exposure of the cells to increasing concentration of PGE2 or its stable derivative misoprostol, resulted in a dose dependent increase of cell invasion and proliferation. PGE_2 effects were confined to the selective stimulation of the EP2 receptor subtype, which lead to epidermal growth factor receptor (EGFR) transactivation and ERK1/2 phosphorylation. EP2-mediated ERK1/2 activation and cell functions were abolished by inhibitors of PKA, c-Src, and EGFR, as well as by inhibiting iNOS pathway. Silencing of PKA or iNOS also impaired the EGFR-induced ERK1/2 phosphorylation. These results indicate that PKA is up-stream to EGFR transactivation promoted by the PGE2/EP2 system and that the iNOS/GC signalling is a downstream player in the control of PGE2 induced tumor cell proliferation and invasion.

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