PGE2 PROMOTES EGFR TRANSACTIVATION AND SQUAMOUS CELL CARCINOMA GROWTH BY THE NOS AND ERK1/2 PATHWAYS

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In squamous cell carcinoma the levels of nitric oxide (NO) and prostaglandin E2 (PGE2), have been reported to correlate with tumor growth, metastasis and angiogenesis. The present study examined the role of iNOS signalling pathway in PGE_2-mediated tumor invasiveness and proliferation in squamous cell carcinoma, A431. Cell invasion and proliferation promoted by PGE_2 were blocked by iNOS/guanylate cyclase (GC) pharmacological inhibition. Consistently, iNOS-GC pathway inhibitors blocked mitogen activated protein kinase-ERK1/2 phosphorylation, which was required to mediate PGE_2 functions. In vivo, in A431 cells implanted in nude mice, GC inhibition also decreased tumor proliferation index and ERK1/2 activation. PGE_2 effects were confined to the selective stimulation of the EP2 receptor subtype, leading to epidermal growth factor receptor (EGFR) transactivation. These results indicate that iNOS/GC signalling is a downstream player in the control of EP2/EGFR-mediated tumor cell proliferation and invasion.