PGE2 SIGNALING INDUCES EGFR NUCLEAR TRANSLOCATION AND TUMOR GROWTH IN LUNG ADENOCARCINOMA CELLS

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Epidermal growth factor receptor (EGFR) is a critical component of tumor progression and it is one of the main oncogenic drivers in lung cancer (1). In addition to the canonical signaling pathways initiated at the cell membrane, EGFR can be translocated inside the nucleus, an event that has been associated with the development of an aggressive phenotype and resistance to therapies (2). Within the nucleus, EGFR acts as a: transcriptional co-activator for a series of genes involved in multiple biological functions, including cell proliferation, DNA repair, chemo and radioresistance; protein kinase and protein-protein interactor (3). Chronic inflammation plays a critical role in cancer progression and a cross-talk between inflammatory mediators and EGFR has been reported (4).

The aim of this study was to assess whether Prostaglandin E2 (PGE2), a well-known inflammatory mediator contributes to EGFR nuclear translocation. Lung cancer cell lines representative of tumor with high dependency on EGFR axis were chosen as a model. EGFR internalization was assessed by cell fractionation followed by western blot or by confocal analysis (5).

Here we demonstrate that in non-small cell lung carcinoma (NSCLC) cells, PGE2 promotes EGFR nuclear translocation, affects gene expression and induces cell growth. Indeed, cyclin D1, COX-2, iNOS and c-Myc mRNA levels are upregulated and cell proliferation is increased following PGE2 treatment. The nuclear localization sequence (NLS) of EGFR as well as its tyrosine kinase activity are required for the effect of PGE2 on nuclear EGFR and its downstream signaling activities. PGE2 binds EP3 receptor, which by activating SRC family kinase signaling, induces ADAM-MMP activation, which, in turn, releases EGFR-ligands from the cell membrane and promotes EGFR nuclear translocation. Amphiregulin (AREG) and Epiregulin (EREG) appear to be the major EGFR ligands released in the supernatant by activation of the PGE2/EP3-SRC axis. Pharmacological inhibition or silencing of the PGE2/EP3/SRC-ADAMs-MMPs signaling axis or AREG-EREG expression abolishes nuclear EGFR induced by PGE2.

In conclusion, PGE2 induces NSCLC cell proliferation by EP3 receptor, SRC-ADAMs-MMP activation, AREG-EREG shedding and finally, phosphorylation and nuclear translocation of EGFR. Since nuclear EGFR is a hallmark of cancer aggressiveness, our findings reveal a novel mechanism for the contribution of PGE2 to tumor progression.

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