Prostaglandin E_2 promotes EGFR nuclear translocation in human non-small cell lung cancer cells.

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Epidermal growth factor receptor (EGFR) plays a critical role in tumor development and progression and it is one of the main oncogenic drivers in lung cancer (1). In addition to the classical signaling pathways initiated at the cell surface, EGFR nuclear localization has been reported to be involved in the development of an aggressive phenotype and resistance to therapies (2). Within the nucleus, EGFR serves as a: transcriptional co-activator for a series of genes involved in multiple biological functions, including cell proliferation, tumor progression, DNA repair and replication, chemo and radioresistance; protein kinase and protein-protein interactor (3).
Chronic inflammation is a critical component of 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 E_2 (PGE_2), a well-known inflammatory mediator, contributes to EGFR nuclear translocation. Lung cancer cell lines (A549, GLC82) representative of tumor with high dependency on EGFR axis were chosen as a model. Here we reported the mechanism of PGE_2-induced EGFR nuclear translocation in which Prostaglandin EP3 receptor promotes shedding of membrane-bound EGF-like ligands via Src family kinases/ADAM proteases leading to EGFR activation and consequent internalization. Furthermore, we also demonstrated that following PGE_2 treatment, EGFR undergoes endocytosis and the association with Importin β1 promotes its nuclear import. Interestingly, we found that PGE_2 drives EGFR interaction with STAT3 inside the nucleus leading to transcription of genes such as *COX-2, iNOS*, *c-Myc and cyclin D1*, which can fuel a pro-inflammatory microenvironment and tumor progression.
In conclusion our findings indicate that PGE_2 promotes EGFR nuclear translocation contributing to sustain its oncogenic drive, and suggest the pharmacological targeting of PGE_2 as a strategy in combination with chemo and targeted therapy.

References:

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