S08-1 Cell growth and thromboxane A2 receptor

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Thromboxane A_2 (TXA_2), released from cancerous tissues, contributes to the growth of cancer cells. In the present study, we examined TXA_2 receptor (TP)-mediated transactivation of epidermal growth factor (EGF) receptor (EGFR) through the shedding of EGFR ligands. TP agonist U46619 caused the phosphorylation of EGFR and extracellular signal-regulated kinase 1/2 (ERK1/2) in 1321N1 human astrocytoma cells, both of which were inhibited by TAPI-2, a disintegrin and metalloprotease (ADAM) inhibitor, indicating the TP-mediated transactivation of EGFR through the EGFR ligand shedding. Since 1321N1 cells expressed heparin binding-EGF (HB-EGF) and transforiming growth factor-α (TGFα) at mRNA levels, the mechanism of TP-mediated EGFR transactivation was examined in HEK293 cells expressing TP and HB-EGF or TGFα. U46619 caused the shedding of HB-EGF and TGF-α in a time- and concentration-dependent manner. The TP-mediated shedding was inhibited by TAPI-2, dominant-negative $G\alpha_q$, and $G_{q/11}$ inhibitor YM254890. The shedding was reduced by a non-selective protein kinase C (PKC) inhibitor GF109203X and PKC down-regulation, but not by conventional PKC inhibitor Gö6976. U46619 caused translocation of PKCδ and PKCε into plasma membranes, and siRNAs of PKCδ and PKCε inhibited U46619-induced EGFR ligand shedding. These results suggest that TP-mediated phosphorylation of EGFR and ERK1/2 is partially caused by EGFR transactivation through EGFR ligand shedding, which involves ADAM via novel types of PKCs (PKCε and PKCδ) through $G_{q/11}$.