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### **Glutamate Promotes Cell Growth by EGFR Signaling on U-87MG Human Glioblastoma Cell Line.**

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Accumulating evidences suggest that glutamate plays a key role in the proliferation and invasion of malignant glioblastoma (GBM) tumors. It has been shown that GBM cells release and exploit glutamate for proliferation and invasion through AMPA glutamate receptors. Additionally, amplification of the epidermal growth factor receptor (EGFR) gene occurs in 40-50% of GBM. Since, PI3K/Akt is considered one of the main intracellular pathways involved in EGFR activation, AKT functions could trigger EGFR signaling. Thus, we investigated whether EGFR-phospho-Akt pathway is involved on the glutamate inducing U-87MG human GBM cell line proliferation. For these purpose, we treated the U-87MG cell line with 5 to 200 mM of glutamate and assessed the number of viable cells by trypan blue dye exclusion test. An increase in cell number (50%) was found at 5 mM glutamate, while the addition of DNQX (500 microM), an antagonist of AMPA receptor, inhibited the effect of glutamate on the U87-MG cells proliferation. Also, at 5 mM glutamate we observed an increase on the EGFR and phospho-Akt contents evaluated by immunohistochemistry. Moreover, U-87MG cells treated with glutamate exhibited an increase about 2 times in the EGFR mRNA expression. While, in the presence of the anti-EGFR gefitinib (50 muM) or the PI3K inhibitor wortmannin (5 muM), the U-87MG proliferation was restored to control levels. Together, our data suggest that glutamate signaling mediated by AMPA receptor induces U-87MG human GBM cell line proliferation via EGFR-phospho-Akt pathway.

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