Gab1

Grb2-associated binding 1 (Gab1) expression and microRNA-29a-3p ("miR-29a-3p") expression in human glioma cells and tissues were tested by Western blotting assay and qRT-PCR assay. shRNA/siRNA strategy was applied to silence Gab1 in human glioma cells. miR-29a or anti-sense miR-29a construct was transfected to human glioma cells. Cell proliferation was tested by BrdU ELISA assay and cell counting assay.

Shao et al., from the Department of Neurosurgery, the Third Affiliated Hospital of Soochow University, Changzhou, China show that expression of Gab1 was significantly elevated in human glioma tissues and cells, which correlated with downregulation of its putative microRNA: miR-29a-3p. In A172 glioma cells and primary human glioma cells, Gab1 shRNA/siRNA inhibited Akt-Erk activation and cell proliferation. Forced-expression of miR-29a-3p downregulated Gab1, inhibiting glioma cell proliferation, whereas miR-29a-3p was in-effective on cell proliferation in Gab1-silenced A172 cells. Furthermore, introduction of a 3'-untranslated region (3'-UTR) mutant Gab1 (UTR-G160A) blocked miR-29a-3p-induced inhibition on Akt signaling and A172 cell proliferation.

miR-29a-3p downregulation leads to Gab1 upregulation to promote glioma cell proliferation [1)].

Pediatric meningiomas share certain phenotypic and cytogenetic characteristics with adult counterparts, but GAB and stathmin co-expression in the majority of cases and non-significant difference in frequency of 1p/14q co-deletion between low- and high-grade meningiomas indicate an inherently aggressive nature. Characteristic AKT/SMO, KLF4/TRAF7 and pTERT genetic alterations seen in adults are distinctly absent in pediatric meningiomas [2)].

Immunoprecipitation analyses with ErbB-modulated cells indicate that association between SHP-2 and Grb2-associated binder 1 (Gab1) is the critical step in the formation of the signalosome linking EGFR to NF-kappaB activation. We also show that EGFR-induced NF-kappaB activation is mediated by the PI3-kinase/Akt activation loop. Overexpression of SHP-2, Gab1, and myristoylated Akt significantly upregulated NF-kappaB transcriptional activity and DNA binding activity in glioblastoma cells. Interestingly, overexpression of either one of the two SH2 domain mutants of SHP-2, R32E or R138E, slightly reduced NF-kappaB activity relative to that of wild-type SHP-2, indicating that the SH2 domains of SHP-2 are required for EGFR-induced NF-kappaB activation. On the other hand, ectopic overexpression of either a Gab1 mutant incapable of binding to SHP-2 (Y627F) or a phosphatase-inactive SHP-2 mutant (C459S) caused a significant increase in NF-kappaB activity. Moreover, SHP-2 C459S-expressing cells displayed higher Gab1 phosphotyrosine content, suggesting that SHP-2 regulates Gab1 phosphorylation through its phosphatase domain, which confers a negative regulatory effect on NF-kappaB activity. These results indicate that SHP-2/Gab1 association is critical for linking EGFR to NF-kappaB transcriptional activity via the PI3-kinase/Akt signaling axis in glioblastoma cells and that SHP-2 acts as a dual regulator of NF-kappaB activation [3)].

1)
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2)

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