SPRY2

This gene encodes a protein belonging to the sprouty family. The encoded protein contains a carboxyl-terminal cysteine-rich domain essential for the inhibitory activity on receptor tyrosine kinase signaling proteins and is required for growth factor stimulated translocation of the protein to membrane ruffles. In primary dermal endothelial cells this gene is transiently upregulated in response to fibroblast growth factor two. This protein is indirectly involved in the non-cell autonomous inhibitory effect on fibroblast growth factor two signaling. The protein interacts with Cas-Br-M (murine) ectropic retroviral transforming sequence, and can function as a bimodal regulator of epidermal growth factor receptor/mitogen-activated protein kinase signaling. This protein may play a role in alveoli branching during lung development as shown by a similar mouse protein.

SPRY2 is a negative feedback regulator of multiple receptor tyrosine kinases (RTK's) including receptors for fibroblast growth factor (FGF), epidermal growth factor (EGF), and hepatocyte growth factor (HGF). Antagonization of growth factor mediated pathways, cell migration, and cellular differentiation occurs through the ERK pathway.

Spry2 can also enhance EGFR signaling by sequestering CBL. Spry gene expression has been reported silenced or repressed in cancer of the breast, liver, lung, prostate, and in lymphoma.

Human spry2 expression is localized to the microtubules in unstimulated cells. All sprouty isoforms inhibit the ERK pathway by themselves, but can also form heterodimers and homodimers which have enhanced inhibition.

SPRY2 can antagonize FGFR2-induced proliferation and invasion via suppressing ERK phosphorylation in gastric cancer cells, indicating SPRY2 as a potential therapeutic target for gastric adenocarcinoma treatment [1)].

Sprouty homolog 2 (Spry2), which has been reported to be associated with invasive glioma, was identified as a novel target of miR-27b in U251 glioma cells, and the protein expression of Spry2 was negatively regulated by miR-27b in U251 cells. Additionally, inhibition of miR-27b and upregulation of Spry2 suppressed glioma cell invasion, while downregulation of Spry2 reversed the suppressive effect of miR-27b inhibition on glioma cell invasion. These data suggest that miR-27b may promote glioma cell invasion through direct inhibition of Spry2 expression. The data also suggest that miR-27b may become a promising molecular target for inhibiting the invasion and metastasis of glioma [2)].

Sprouty2 (SPRY2), a known regulator of receptor tyrosine kinases (RTK), as one such regulator. SPRY2 knockdown reduced proliferation and anchorage-independent growth in GBM cells and slowed xenograft tumor growth in mice. SPRY2 knockdown also promoted cell death in response to coinhibition of the epidermal growth factor receptor (EGFR) and the c-MET receptor in GBM cells, an effect that involved regulation of the ability of the p38 mitogen-activated protein kinase (MAPK) to drive cell death in response to inhibitors. Analysis of data from clinical tumor specimens further demonstrated that SPRY2 protein is definitively expressed in GBM tissue, that SPRY2 expression is elevated in GBM tumors expressing EGFR variant III (EGFRvIII), and that elevated SPRY2 mRNA expression portends reduced GBM patient survival. Overall, these results identify SPRY2 and the pathways it regulates as novel candidate biomarkers and therapeutic targets in GBM.

IMPLICATIONS: SPRY2, counter to its roles in other cancer settings, promotes glioma cell and tumor growth and cellular resistance to targeted inhibitors of oncogenic RTKs, thus making SPRY2 and the

cell signaling processes it regulates potential novel therapeutic targets in glioma [3].

miR 21 enhances the resistance of human glioma cells to BCNU by decreasing the expression of Spry2 protein. Thus, Spry2 may be a novel therapeutic target for treating glioma BCNU-resistance [4] [5].

1)
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