SEMA3A

The SEMA3A gene is a member of the semaphorin family and encodes a protein with an Ig-like C2-type (immunoglobulin-like) domain, a PSI domain and a Sema domain. This secreted Sema3A protein can function as either a chemorepulsive agent, inhibiting axonal outgrowth, or as a chemoattractive agent, stimulating the growth of apical dendrites. In both cases, the protein is vital for normal neuronal pattern development.

Molofsky et al. showed that postnatal spinal cord astrocytes express several region-specific genes, and that ventral astrocyte-encoded semaphorin 3a (Sema3a) is required for proper motor neuron and sensory neuron circuit organization. Loss of astrocyte-encoded Sema3a leads to dysregulated α-motor neuron axon initial segment orientation, markedly abnormal synaptic inputs, and selective death of α- but not of adjacent γ-motor neurons. In addition, a subset of TrkA(+) sensory afferents projects to ectopic ventral positions. These findings demonstrate that stable maintenance of a positional cue by developing astrocytes influences multiple aspects of sensorimotor circuit formation. More generally, they suggest that regional astrocyte heterogeneity may help to coordinate postnatal neural circuit refinement [1)].

Neuropilin-1 is an agonist of angiogenesis through complex-binding of VEGF-A, but it can also work as an inhibitor through competitive binding of semaphorin-3A. The complex binding of semaphorin-3A to neuropilin-1 can also induce endothelial cell apoptosis, thus working as an antagonist of angiogenesis [2)].

Lee et al. have generated anti-SEMA3A monoclonal antibody as a potential therapeutic antibody against GBM progression.

Lee et al. employed public glioma datasets, Repository of Molecular Brain Neoplasia Data and The Cancer Genome Atlas, to analyze SEMA3A mRNA expression in human GBM specimens. We also evaluated for protein expression level of SEMA3A via tissue microarray (TMA) analysis. Cell migration and proliferation kinetics were assessed in various GBM patient-derived cells (PDCs) and U87-MG cell-line for SEMA3A antibody efficacy. GBM patient-derived xenograft (PDX) models were generated to evaluate tumor inhibitory effect of anti-SEMA3A antibody in vivo. RESULTS: By combining bioinformatics and TMA analysis, we discovered that SEMA3A is highly expressed in human GBM specimens compared to non-neoplastic tissues. We developed three different anti-SEMA3A antibodies, in fully human IgG form, through screening phage-displayed synthetic antibody library using a classical panning method. Neutralization of SEMA3A significantly reduced migration and proliferation capabilities of PDCs and U87-MG cell-line in vitro. In PDX models, treatment with anti-SEMA3A antibody exhibited notable tumor inhibitory effect through down-regulation of cellular proliferative kinetics and tumor-associated macrophages recruitment. CONCLUSION: In present study, we demonstrated tumor inhibitory effect of SEMA3A antibody in GBM progression and present its potential relevance as a therapeutic agent in a clinical framework [3)].

1)
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2)

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3)

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