Ganglioside GD3

Gangliosides, the major sialic acid containing glycosphingolipids in the mammalian brain, play important roles in brain development and neural functions.

Wang et al. showed that the b-series ganglioside GD3 and its biosynthetic enzyme, GD3-synthase (GD3S), were up-regulated predominantly in the microglia of mouse hippocampus from 2 to 7 days following global cerebral ischemia (GCI). Interestingly, GD3S knockout (GD3S-KO) mice exhibited decreased hippocampal neuronal loss following GCI, as compared to wild-type (WT) mice. While comparable levels of astrogliosis and microglial proliferation were observed between WT and GD3S-KO mice, the phagocytic capacity of the GD3S-KO microglia was significantly compromised after GCI. At 2 and 4 days following GCI, the GD3S-KO microglia demonstrated decreased amoebic morphology, reduced neuronal material engulfment, and lower expression of the phagolysosome marker CD68, as compared to the WT microglia. Finally, by using a microglia-primary neuron co-culture model, we demonstrated that the GD3S-KO microglia isolated from mouse brains at 2 days after GCI are less neurotoxic to co-cultured hippocampal neurons than the WT-GCI microglia. Moreover, the percentage of microglia with engulfed neuronal elements in the co-cultured wells was also significantly decreased in the GD3S-KO mice after GCI. Interestingly, the impaired phagocytic capacity of GD3S-KO microglia could be partially restored by pre-treatment with exogenous ganglioside GD3. Altogether, this study provides functional evidence that ganglioside GD3 regulates phagocytosis by microglia in an ischemic stroke model. This data also suggest that the GD3-linked microglial phagocytosis may contribute to the mechanism of delayed neuronal death following ischemic brain injury [1)].

In particular, gangliosides GD3 and GD2 are expressed in human gliomas. It has been reported that their expression levels increase along with increased malignant properties. However, the implication of GD3/GD2 in human glioma cells has never been clarified, at least to the best of our knowledge. In this study, we introduced the cDNA of GD3 synthase (GD3S)(ST8SIA1) into a glioma cell line, U-251MG, that expresses neither GD3 nor GD2, thereby establishing transfectant cells U-251MG-GD3S(+) expressing high levels of GD3 and GD2 on the cell surface. In these U-251MG-GD3S(+) cell lines, signaling molecules such as Erk1/2, Akt, p130Cas, paxillin and focal adhesion kinase were activated, leading to the enhancement of invasion activity and motility. It was then demonstrated that the U-251MG-GD3S(+) cells could proliferate under culture conditions with low or no serum concentrations without undergoing cell cycle arrest by escaping the accumulation of p16 and p21. All these results suggested that GD3 and GD2 highly expressed in gliomas confer increased invasion and mobility, cell growth abilities under low serum conditions, and increased ratios of the S-G2/M phase in the cell cycle [2)]

Ohkawaet al. employed a genetically engineered mouse model of glioma to clarify the functions of GD3 in gliomas. Forced expression of platelet-derived growth factor B in cultured astrocytes derived from p53-deficient mice resulted in the expression of GD3 and GD2. GD3-positive astrocytes exhibited increased cell growth and invasion activities along with elevated phosphorylation of Akt and Yes kinase. By enzyme-mediated activation of radical sources reaction and mass spectrometry, we identified PDGF receptor α (PDGFRα) as a GD3-associated molecule. GD3-positive astrocytes showed a significant amount of PDGFRα in glycolipid-enriched microdomains/rafts compared with GD3-negative cells. Src kinase family Yes was co-precipitated with PDGFRα, and its pivotal role in the

increased cell invasion of GD3-positive astrocytes was demonstrated by silencing with anti-Yes siRNA. Direct association between PDGFRα and GD3 was also shown, suggesting that GD3 forms ternary complex with PDGFRα and Yes. The fact that GD3, PDGFRα, and activated Yes were colocalized in lamellipodia and the edge of tumors in cultured cells and glioma tissues, respectively, suggests that GD3 induced by platelet-derived growth factor B enhances PDGF signals in glycolipid-enriched microdomain/rafts, leading to the promotion of malignant phenotypes such as cell proliferation and invasion in gliomas [3)]

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