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Controversial Sialoglycosphingolipids Functions in Tumor Biology

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Glycosphingolipid is a series of glycolipids and a representative ganglioside is biologically active and ubiquitous in mammalian cells, consisting of an anionic neuraminic acid or sialic acid. The hydrophilic glycan head group is linked to a hydrophobic ceramide tail group on the outer leaflet of the cell membrane (Figure 1). The gangliosides are used as cellular receptors, ligands and markers in specific cell-cell communication, signaling, infection, immune relertories response, cell cycle regulation cell movement control and cellular transformation [1-3]. Gangliosides are involved in regulation of a variety of cellular pathways including migration, adhesion, proliferation, senescence and apoptosis [3,4]. Since ganglioside levels change over time in tissues cells, particularly during differentiation, development, transformation, invasion, and progression, an alteration of the capacity of synthetic enzymes to regulate specific gangliosides synthesis could alter progressively the ability of cells to adapt to their microenvironment in tissues and organs.

It was reported that gangliosides of tumors play pivotal roles in specific and particularly microenvironmental vessel system. They are tightly expressed [5] and actively shed from the tumor cell surface, specifically *in vivo* system [6]. The shed forms of gangliosides may affect to the behavioral properties and extracellularly conveyed communicable capacity of normal cells co-located in the tumor microenvironments of cancer tissues. Then, what is the mission of those microenvironmentally expressed gangliosides? For the simplest answer is considered to be: (1) the potent immunosuppressive and immunoescape capacity of the shed gangliosides, (2) as antiangiogenesis-regulating capacity, the enhancing capacity of the shed gangliosides in growth hormone (GF)-growth hormone receptor (GFR)-mediated vascular endothelial cells's angiogenesis, (3) as anti-cell cycle and signaling regulators in the intracellular sites, and (4) direct communication for the tumor formation, invasion, progression and metastatic potentials.

The Immunosuppressive and Immune-escape Capacity by the Shed Tumor Gangliosides.

The immunological protection of tumor cells was evidenced with the accumulated reports from various tumor cells. The ability of tumor cells to evade and suppress the host immune system is decided by the differential levels of antigen recognition and immune activation between tumor cells and host immune cells. Tumors often display multiple mechanisms to avoid or suppress immune recognition from the host defense system. One such mechanism is the shedding of gangliosides into the local tumor microenvironment, and a high concentration of circulating and surrounding gangliosides in malignant tumor-invaded tissues is associated with poor prognosis. Gangliosides have long been known to suppress T-cell immunity, as reported on human tumor-derived gangliosides on immune responses. Aberrant expression of tumor cells-specific gangliosides has been demonstrated on malignant cells. Besides expression on tumor cell membranes, gangliosides are also shed in the tumor microenvironment and eventually circulate in patients blood to form tumor-protective region. Gangliosides derived from tumors posses the immune system's responses by altering the function of lymphocytes and antigen-presenting cells and promoting tumor growth. These molecules can be considered as tumor weapons directed to attack and destroy immune surveillance mechanisms to maintain and persist on cancer progression status [7]. For example for T cells dysfunction, gangliosides from neuroblastoma is known to arrest T and natural killer T (NKT) cells to block the cytokine secretion, eventually to suppressing the host bone marrow differentiation potentials. For dendritic cells (DC) dysfunction, the DC treatment with the gangliosides blocks DC generation and differentiation in host. Therefore, the tumor-produced specific gangliosides negatively regulate the differentiated DC, inducing the tumor-mediated immunosuppression and subsequent tumor escape from immune recognition and elimination of the host system [8]. Similarly, the tumor derived ganglioside induced MHC class I down-regulation was also reported in DC. In this case, the tumor cells upregulate the multiple glycosyltransferases responsible for the endogeneous ganglioside glycan synthesizing enzymes to inhibit the MHC class I expression in the host DC [9]. In occasion, tumor gangliosides induce the apoptosis of T cells. Ganglioside GM2 is reported to cause apoptosis of the host T cells and suppress IFN-gamma and interleukin-4 production in CD4+ T cells in renal carcinoma cells [10].

On the other hand, disialyl GD3 is highly expressed in human melanoma cells. Although GD3 is a relatively minor species among gangliosides present in the adult brain, it is considered to be not only for the tumor markers but also as targets of antibody therapy. In melanoma-specific expression of human melanoma SK-MEL-2 cells, the proliferating NF-κB plays a critical role in human GD3 synthase expression necessary for GD3 synthesis highly expressed in melanoma [11]. In arteriosclerosis, GD3 abolishes the vascular vessel thickness mediated by vascular smooth muscle cells through ERK1/2 and matrix metalloproteinase-9 regulation and apoptosis induction of the abnormal proliferation of inflamed smooth muscle cells [12]. The fashion of the GD3-mediated apoptosis of smooth muscle cell is somewhat similar to the melanoma cells. In GD3-expressing tumor cells like melanoma, GD3 interacts with its receptor siglec-7 on human NKT cells and monocytes, since siglec-7 recognizes the α2,8-disialic acids in GD3 [13]. It is then suggested that the NK cell cytotoxicity is raised from the communication between the α2,8-sialic acids in GD3 and siglec-7, inducing the downstream apoptotic signaling of the GD3-expressing melanoma cells. In the case of ovarial cancer cells, GD3 prevents the innate NKT cells by interaction of GD3 with lipid antigen presenting CD1d to T cells, The GD3 bound CD1d antigenic-binding site abolished the NKT cells function in a similar fashion of α-galactosylceramide-induced NKT cell activation, inhibiting the antitumor NKT cell function in ovarian cancer tumors [14]. Additionally, the O-acetylated forms of GD1b and GT1b are cytotoxic for rat glioma and human astrocytoma cells without any cytotoxicity of neurons or fibroblasts [15]. How does the enhanced antigenicity of

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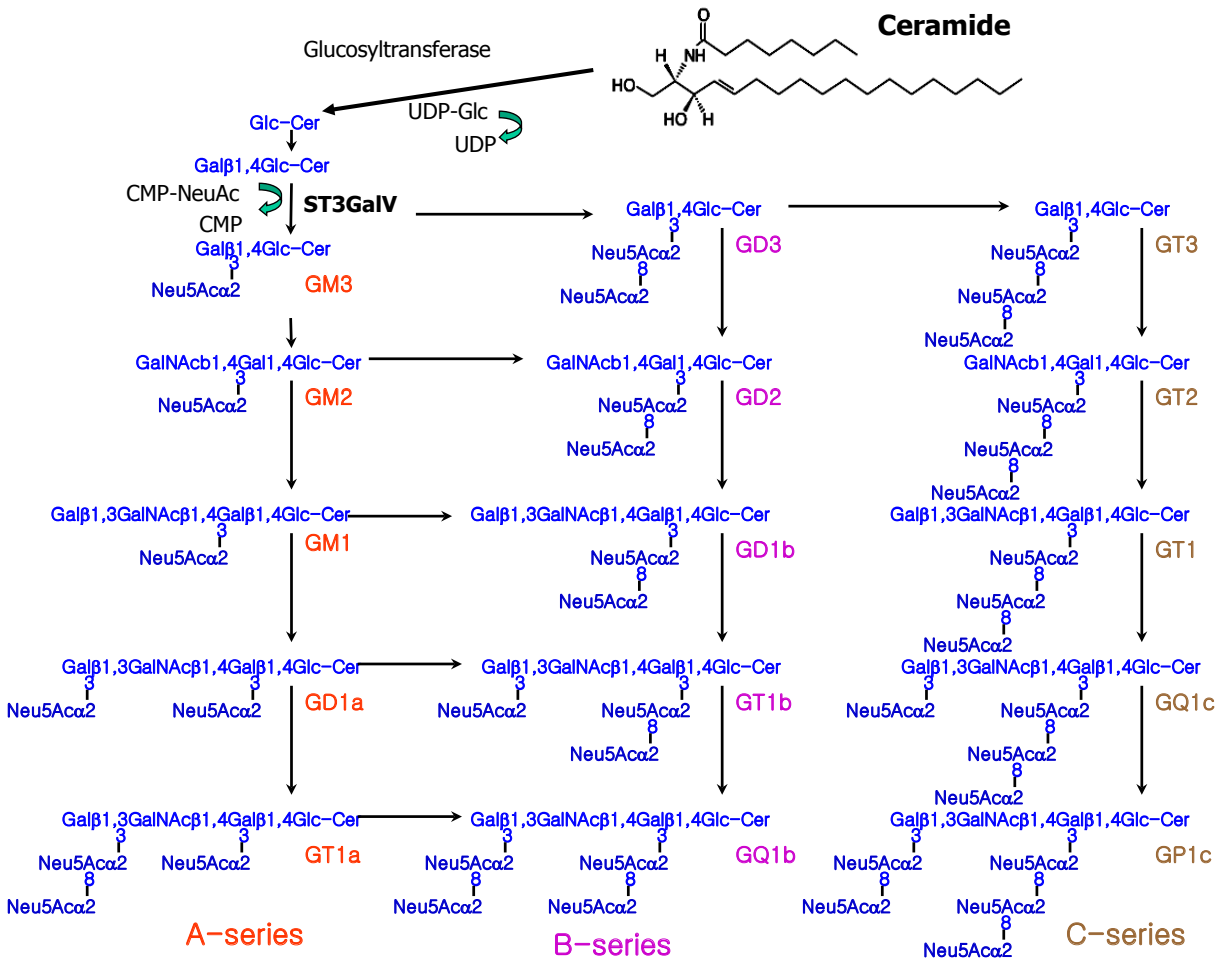

Figure 1: Structure of gangliosides. The starting precursor of ganglioside synthesis is a ceramide consisting of sphingosine and fatty acid with amide bond. The most simple ganglioside is the GM3 with a monosialic acid (NeuAc-alpha 2 → 3Gal-beta1 → 4Glc-beta1 → 1′ Ceramide).

O-acetylated GD1b and GT1b-treated glioma cells is made? Is it related to the increased expression of any targeted cell surfaced molecule? These O-acetylated GD1b and GT1b are interested in the correlation between diversity of gangliosides and antigenicity. Therefore, the immunological antitumor concept of each tumor specific ganglioside is accepted from the current cancer immunoglycobiology, as the shed gangliosides can disturb cellular immune repertories, responding to allow tumor immunity.

GF-GFR Mediated Angiogenic Capacity is Controlled by Gangliosides in the Tumor Microenvironment

This effect is in contrast with the above immune suppressive or immunoescape activities of gangliosides, but the 2 distinct mechanism(s) allow eventually the tumor cell proliferating activity in the limited animal tissues. Originally, gangliosides produced by the normal fibroblast cells activate GF-induced cellular receptor activation and cell proliferation of the vascular endothelial cells, resulting in the enhanced new tube formation with many different downstream signal pathways for angiogenesis [16,17]. Mechanistically, the cell surfaced gangliosides produced by vascular endothelial cells stimulate GF-induced cell growth and migration [18]. Among gangliosides, GM3 is well studied for the epidermic growth factor (EGF)-EGF receptor (EGFR) signaling. GM3 modulates several receptors function and controls cell proliferation and receptor mediated angiogenesis. The GFs known to date are the insulin-like growth factor-1, basic fibroblast growth factor, EGF, platelet-derived growth factor, vascular endothelial growth factor (VEGF), and cell adhesion molecules including the integrins [19-27].

Tumor progression requires normal endothelial cells to form new vascular networks, to call as angiogenesis. This fundamental process is dependent on vascular endothelial growth factor. To modulate angiogenesis by gangliosides expressed by tumor cells and shed into the tumor microenvironment, they are secreted in the surrounding microenvironment. Shedding of gangliosides protects tumor cells from host immune destruction and enhances tumor progression [6,18]. However, precise molecular mechanism for ganglioside-mediated tumor angiogenesis is still remained unknown and untroversial. For angiogenesis of tumors, aberrant activation of endothelial cells and induction of microvascular permeability by a VEGF receptor signaling pathway are required. In negative regulation, GM3 inhibited the downstream signaling pathways and biological events through the inhibition of VEGF-stimulated VEGFR-2 activation in vascular endothelial cells *in vitro* [3]. GM3 blocked VEGF-induced neovascularization *in vivo*, suppressing binding of VEGF to VEGFR-2 through a GM3-specific interaction with the extracellular domain of VEGFR-2. Primary tumor growth in mice was inhibited by

subcutaneous injection of GM3 with inhibition of angiogenesis and tumor cell proliferation with the suppression of VEGF-stimulated microvessel permeability in mouse skin capillaries. GM3 inhibits VEGFR-2-mediated changes in vascular endothelial cell function and angiogenesis, and might be of value in anti-angiogenic therapy. GM3 is angiogenic inhibitor and might be a therapeutic avenue for antiangiogenesis.

The Gangliosides Functions as the Anti-cell Cycle and Signaling Regulators in the Intracellular Sites

Gangliosides also reduce proliferation and enhances apoptosis of rapidly proliferating neural stem cells [2,28]. GM3 has anti-proliferative effects in several *in vitro* and *in vivo* cancer models, although the exact mechanism by which it prevents cell proliferation remains unclear. GM3 increases cyclin-dependent kinase (CDK) inhibitor p21 expression through the accumulation of p53 by the PTEN-mediated inhibition of the PI-3K/AKT/MDM2 survival signaling in cancer cells. The ganglioside induces p53-dependent transcriptional activity of p21 and enhances expression of CKI p27 through the PTEN-mediated inhibition of the PI-3K/AKT signaling. The down-regulation of the cyclin E and CDK2 was a point in GM3-treated colon cancer cells without the down-regulation of cyclin D1 and CDK4. Suppression of PTEN levels restores the expression of p53-dependent p21and p53-independent p27 through inactivating GM3-induced PTEN-mediated PI-3K/AKT signaling [28]. GM3-stimulated PTEN expression modulates cell cycle regulatory proteins, thus inhibiting cell growth. GM3 represents a modulator of cancer cell proliferation.

Other gangliosides including GM2, GM1, GD3, GD1a, GD1b, and GT1b are also known to induce the angiogenesis [29], raising the fundamental question of How do they specifically downregulate the angiogenic cellular and tissue events? One hypothesis has been raised, giving the rationale of conformational and stereo-selectivity of the GM3 structure with α2,3-sia-lactosylceramide during interaction with its cell membrane receptors. The resulting findings make several technologies that GM3 has a therapeutic potential against tumor growth and angiogenesis-mediated human diseases. Another GD1a enhanced VEGF-induced endothelial cells upon VEGF-signaling [30]. GD1a increase in DNA synthesis and migration of endothelial cells, indicating that gangliosides shed by tumor cells can promote tumor angiogenesis by enhancing the VEGF response of endothelial cells in the tumor microenvironment. In contrast to GM3 function in anti-tumor activity, GD3 showed the pro-angiogenic capacity. Although GM3 is also expressed in malignant tumors, GM3 in these tumors might serve to regulate or to counteract the pro-angiogenic action of GD3 and other gangliosides.

The Gangliosides can Directly Upregulate the Communication for the Tumor Formation, Invasion, Progression and Metastatic Potentials

The enforced overexpression of the cell surfaced gangliosides in nonmalignant tumor cells induces much higher tumorigenicity in the parent tumor cells [31], indicating the direct effect on malignant tumor cell formation by the artificial gangliosides enrichment. In clinical aspect with diagnosis, the gangliosides expression levels of the circulating tumors were directly related with tumor progression [32]. The above 4 specific points on the cell surfaced gangliosides suggest that they are linked to tumor formation and progression. For fundamental role of the gangliosides in animal models, knockout (KO) animals lacking ganglioside expression or transgenic animals overexpressing gangliosides are important to biologically functionalize. Previously, double KO fibroblast cells, lacking the GM3 synthase and GM2 synthase as the key ganglioside synthesis enzymes were established [33]. Oncogene-transformed double KO cells showed impaired cell growth and migration [34], indicating that the gangliosides function as a tumor initiating and progressive factor. Thus, it is concluded that tumor cells surfaced specific gangliosides are closely linked to specific tumor progression.

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