Functional Role of Glycosphingolipids in Cancer

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Abstract: Glycosphingolipids (GSLs) are ubiquitous components on animal cell membranes, and exposed on the outer surface. Various studies have demonstrated that they play key roles in cells proliferation, adhesion, motility and differentiation. Usually, the specific types of GSLs are expressed more highly in tumors than in normal tissues, which are known as tumor-associated antigens. It has been revealed that most tumor cells show altered GSLs patterns on their surface, abnormal GSLs signaling and biosynthesis, which together play a major role in tumor development. Tumor-associated GSL antigens have been used in the development of antitumor vaccines. It is no doubt that GSLs play a crucial role in tumor progression and would be a promising target for cancer treatment.

Keywords: glycosphingolipids, tumor-associated antigens, GSL signaling, carbohydrates, medicinal chemistry, cancer.

1. Introduction

Glycosphinolipids (GSLs) consist of a hydrophobic ceramide (Cer) moiety and a glycosidically bound carbohydrate moiety [1]. In general, GSLs can be categorized into two groups: neutral and negatively charged (sialic acid or sulfate group) GSLs, and the four most common ones are globo-, lacto-, neolacto- and ganglio- series [2]. The typical examples of GSLs are listed in Figure 1.

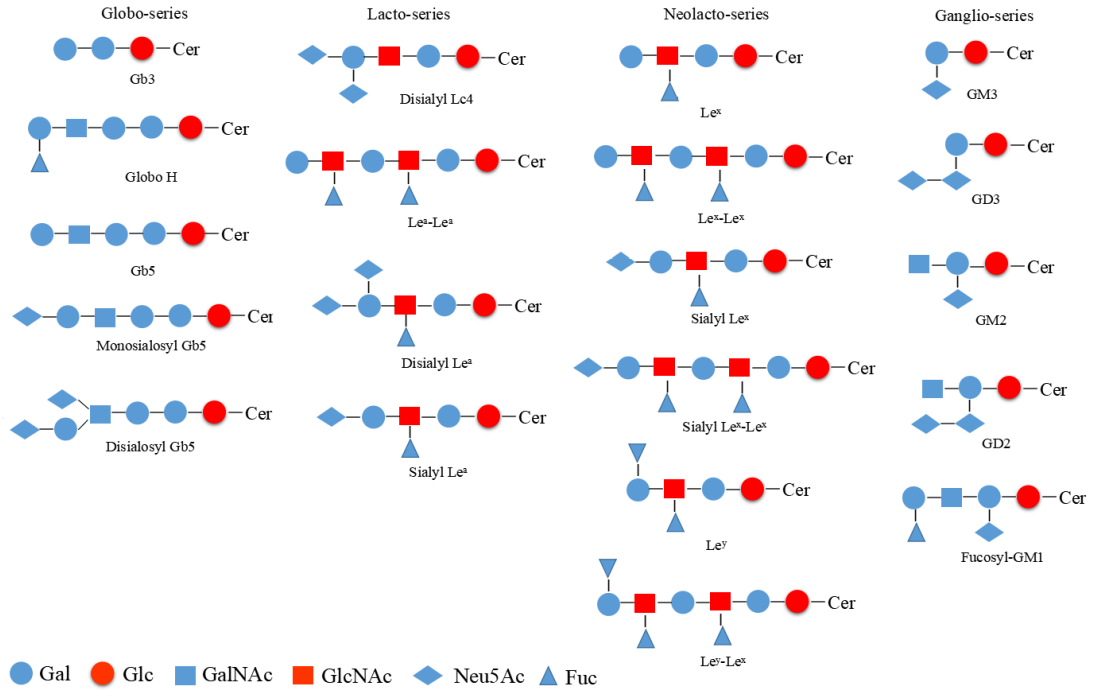

Figure 1. Structure of typical GSLs

More and more evidences showed that GSLs have significant effects on tumor development and progression, which can modulate the cancer cells proliferation, adhesion, invasion and apoptosis [3-5]. It is well known that GSLs are tumor-associated carbohydrate antigens (TACAs) on some types of cancers. They are present in both normal tissues and cancer cells, but highly expressed in tumor cells, and changes in GSLs synthesis occur frequently in cancers, especially the aberrant

sialylation of GSLs [6]. The expression of GSLs on some human cancers is shown in Table 1. The abnormal expression of GSLs on different cancers can provide the valuable sight to develop the new strategies for cancer treatment. This mini-review will present the role of GSLs in some common happened cancers.

Table 1. Expression of GSLs on some types of cancers

GSLs	Tumor types
GM3	melanoma, medulloblastoma, superficial bladder cancer
De-N-acetyl GM3	melanoma
Neu5Gc GM3	melanoma, colon and breast cancers, retinoblastoma
9-O-acetyl GM3	melanoma, glioblastoma
GM2	melanoma, neuroblastoma, medulloblastoma
GM1	small cell lung carcinoma, renal cell carcinoma
Fucosyl-GM1	small cell lung carcinoma
9-O-acetyl GD3	melanoma, neuroblastoma, breast cancer
GD2	melanoma, neuroblastoma, retinoblastoma
9-O-acetyl GD2	ovarian cancer, neuroblastoma, small cell lung cancer
Gb3	ovarian cancer, burkitt lymphoma
Globo H	ovarian and breast cancers, teratocarcinoma
Disialosyl galactosyl globoside	renal cell carcinoma
Gb5	teratocarcinoma
Monosialyl Gb5	renal cell carcinoma
Disialyl Gb5	renal cell carcinoma
Disialyl Lc4	colon cancer
Le^a-Le^a	gastric, colon, bladder and breast cancers, Hodgkin's lymphoma
Sialyl Le^a	colon, pancreatic and gastric cancers
Disialyl Le^a	colon cancer
Le^x	gastric, breast and colorectal cancers
Le^x-Le^x	colon, gastric, breast, lung and liver cancers

Sialyl Le^x	colon and bladder cancers, T cell leukemia
Sialyl Le^x-Le^x	colon, gastrointestinal, colorectal, lung and breast cancers
Le^y	colon, gastric and lung cancers
Le^y-Le^x	colon, liver, lung, colorectal and pancreatic cancers

2. Bladder cancer

Some studies reported that exogenous ganglioside GM3 has significant antitumor effects on bladder cancer cells. For example, in cell lines YTS-1, T24, T5637 and KK47, increasing GM3 can reduce cells proliferation, adhesion and epidermal growth factor receptor (EGFR) phosphorylation [7]. The antitumor effect of exogenous GM3 has also been revealed in the murine bladder cancer cell line MBT-2, and apoptosis was induced when cells were transfected with GM3 synthase cDNA [8]. Other studies showed that adding GM3 to the human bladder cancer cell lines KK47 and T24, the invasive property was decreased [9]. Exogenous GM3 can inhibit bladder tumor cells invasion which indicated that GM3 expression can reflect the invasion potential to some extent.

Moreover, some data demonstrated that a specific microdomain ("Glycosynapse 3") can control phenotypic conversion and reversion of bladder cancer cells through GM3-mediated interaction of α3β1 integrin with CD9 [10]. Through studying the functions of GM2 and GM3 in cell motility and growth in bladder cancer, it has been showed that GM2/GM3 complex affixed on silica nanospheres strongly inhibits cell motility through CD82/cMet-mediated pathway [11,12].

Now it is known that up to 90% of bladder tumors express Le^X antigen [13]. In particular, the sialyl Le^X antigen has closely associated with the invasive and metastatic potential of bladder cancer, and the importance of sialyl Le^X as a marker of invasive and metastatic potential was noted [14].

3. Renal cancer

It was reported that after implantation of renal tumor cells into BALB/c mice, tumor volume was increased when LacCer was upregulation. However, tumor volume was greatly reduced by treatment with D-PDMP, an inhibitor of GlcCer synthase (GCS) and LacCer synthase [15]. In addition, the expression of GM3 in renal cancer patients was higher than in healthy controls [16]. The high disialosyl globopentaosylceramide (DSGb5) expression levels exhibit stronger migration potential in renal cancer cells [17]. The results suggest that certain GSLs play a very complex role during the development and progression in renal tumor.

Next, the disialosyl-galactosylgloboside was also found to be highly expressed in human renal cancer [18], and the expression of disialosyl-galactosylgloboside is associated with the potential of renal tumor cells metastasizing to the lung. Further study showed that expressing high levels of disialosyl-galactosylgloboside adhere strongly to perialveolar lung tissue sections, and it can be inhibited by a mAb (RMZ), which specifically direct to disialosyt-galactosylgloboside. It is resumed that a specific receptor may be present in lung tissue, and specific interaction between receptor and disialosyl-galacrosytgloboside can mediate the metastasis of renal cancer to the lung [19,20].

4. Colon cancer

GSLs and related enzymes abnormally expressed in colon cancer have been studied. Studies on colon cancer patients showed that Gb3 expression is increased, which is the receptor of Shiga toxin and binds to the B-subunit or its derivatives [21,22]. The expression of Gb3 strongly correlates with the metastatic potential, and high levels of its expression and a migratory phenotype were found based on three colon cancer cell lines established from metastatic human colon cancers [23]. Furthermore, in human colon adenocarcinoma SW620 cells, the antitumor effect of anti-epithelial cell adhesion molecule (EpCAM) mAb can be enhanced strongly by

gangliosides GD1a and GM1 expression [24]. The tests also showed that α-GalCer has the therapeutic effect on colorectal cancer. In AOM/DSS mice, when treated with α-GalCer, the number of colorectal tumors was significantly reduced [25].

It has been reported that in human colorectal carcinoma HCT116 cells, Gb4 can enhance activation of EGFR induced MAPK/ERK signaling by direct interaction with EGFR [26]. Another study demonstrated a better cytotoxicity of GM3 analogues against colorectal carcinoma HCT116 cells than HaCaT normal cells, and the cytotoxicity of these derivatives was thought to be caused by their inhibition on activity of various growth factor receptor (GFR)-associated tyrosine kinases [27]. Besides, it is well known that cisplatin is used for colorectal cancer therapy, and in HCT116 cells, oxidative apoptosis mediated by GM3 was shown to be associated with cisplatin-induced apoptosis [28].

NEU3 that is a human plasma membrane-associated sialidase, is upregulated in colorectal tumor. NEU3 plays an important role in malignancy [29], and is also involved in inflammation-dependent cancer development [30]. The EGFR activation is enhanced by NEU3 through desialylation with no effects on EGFR mRNA or protein expression [31]. Furthermore, silencing NEU3 results in significant decrease in clonogenicity along with down-regulation of stemness and Wnt-related genes in HT-29 and HCT116 cell lines [32].

5. Melanoma

Ganglioside GM2 antibodies in melanoma patients associating with improved disease-free and overall survival were observed [33]. It has been confirmed that GM2 is the most immunogenic ganglioside in the melanoma [34]. Besides, ganglioside GD2 can block programmed death receptor 1 (PD-1), and PD-1 blockade enhanced both chimeric antigen receptor (CAR) T-cells survival and promoted killing of PD-L1(+) tumor cell line [35]. In HT-144 cell line, the ganglioside GM4, GM3 and GD3, purified from human melanomas, can inhibit the phenotypic and functional

differentiation of monocyte-derived dendritic cells induced by CD154. Furthermore, increasing GM3 and GD3 not only induce strong monocyte-derived dendritic cells apoptosis, but also decrease interleukin-2 (IL-2) and interleukin-10 (IL-10) concentration [36].

In human melanomas, GD3 is the predominant ganglioside component [37,38]. Activation of natural killer T (NKT) cells produces cytokines to influence immune responses against cancers, and GD3 can induce NKT cells response in melanoma. Moreover, it has been confirmed that GD3 can enhance malignant properties of melanomas, and the mechanism is shown in Figure 2. The molecules involved in GD3-mediated signaling pathways include focal adhesion kinase (FAK), p130Cas and paxillin. RNAi can block p130Cas and paxillin, which can obviously suppress melanoma growth [39]. In $GD3^{+}$, not $GD3^{-}$, human melanoma N1 cells, the proliferation and apoptosis resistance were enhanced through hepatocyte growth factor (HGF) or adhesion to collagen type I via MAPK and Akt signaling pathways. Increased GD3 expression can promote melanoma cells adhesion to surrounding tissues and susceptibility to HGF presenting in the tumor microenvironment [40,41]. Other results further showed that the melanoma malignancy is enhanced by GD3 through g-secretase recruiting to rafts and facilitating efficient cleavage of neogenin [42]. It has also been found that 9-O-acetylated GD3 presents in malignant melanomas [43].

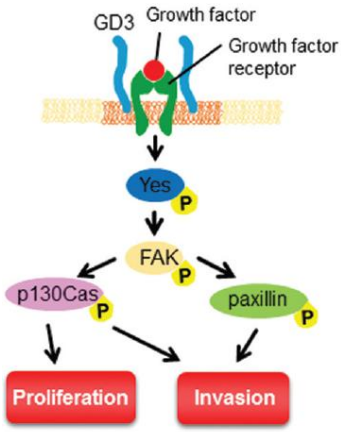

Figure 2. Mechanism for malignancy enhancement by GD3 in melanomas. GD3 can activate FAK, p130Cas and paxillin, thus promoting cells proliferation and invasion.

The expression of GM3 on the invasive and metastatic properties in four mouse melanoma Bl6 variants has been studied. In B16, the GM3 expression is the highest, and it is the most invasive and metastatic type, followed by F10, F1 and WA4. It has been reported that GM3 can be regarded as an adhesion molecule for another two GSLs, gangliotriaosylceramide (Gg3Cer) and LacCer. The metastasis of Bl6 is triggered through the recognition of GM3 by Gg3Cer or LacCer on endothelial cells, which is a type of GSL-GSL interaction, and the interaction results in signals conduction [44,45]. In addition, 5-N-deacetylation of GM3 has already been confirmed to specially express in metastatic melanomas, but not in normal tissues or in the most of primary melanomas or benign nevi [46]. Further results demonstrated that 5-N-deacetylation of GM3 can stimulate both cells migration and invasion through increasing the expression and activation of urokinase-like plasminogen activator (*u*PA) and matrixmetalloproteinase-2 [47]. Another study showed that in melanoma B16 cells "GSL signaling domains" are present [48], and the related results indicated that clustered GSLs associated with c-Src, Rho A and FAK are involved in GSL-dependent cells adhesion coupled with signal transducers activation [49,50]. For example, GM3 clustering forms a "glycosignaling domain" (GSD), and in this case, the antigenicity, adhesion, and signaling conduction associated GM3 are maintained by GSD [48,51].

6. Breast cancer

It has been found that GD3/GD2 synthase ST8SIA1 is over expressed in estrogen receptor (ER)-negative breast tumor, resulting in accumulation of GD2 [52]. Furthermore, accumulation of GD2 can enhance proliferation and tumorigenicity of MDA-MB-231 breast cancer cells by ganglioside-mediated activation of c-Met

receptor [53], and the detailed mechanism is shown in Figure 3. GD2 has been studied as a breast cancer marker that promotes tumorigenesis [54]. The expression of GSLs in $CD44^{hi}/CD24^{lo}$ breast cancer stem cells (CSCs) and non-CSCs was studied by flow cytometry, and up-regulation of GD2, GD3, GM2, and GD1a in CSCs were detected. Moreover, it was showed that the phenotype can be changed from CSCs to non-CSCs through knockdown ST8SIA1 synthase, and ST8SIA1 synthase can maintain stem cell phenotype in breast CSCs [55]. Interaction of GD3 and GD2 with growth factor receptors also plays a role in maintaining breast CSCs phenotype. In EGFR-positive breast cancer cells, GD3 synthases perhaps involved in gefitinib-resistance [56].

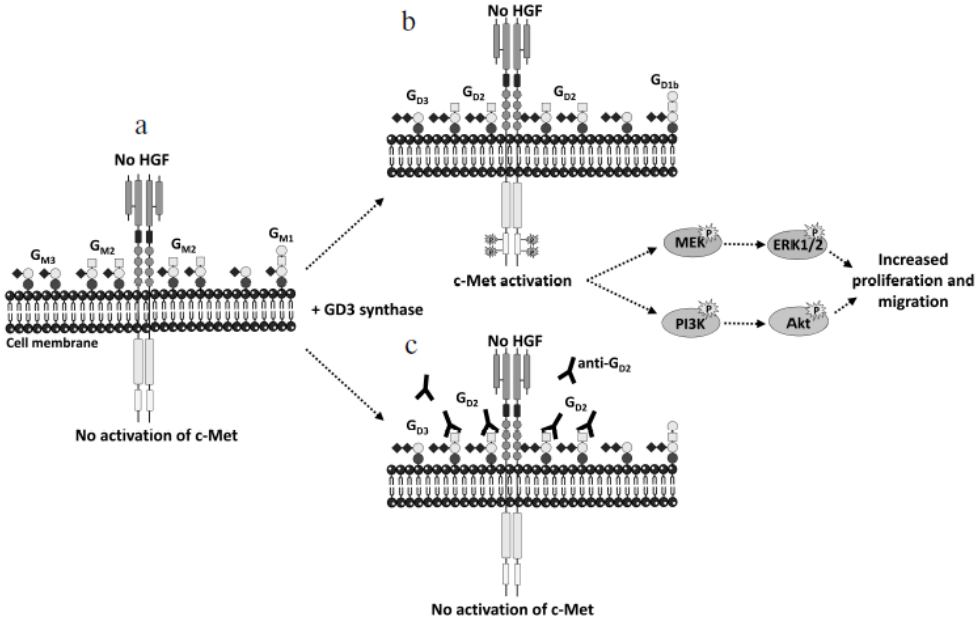

Figure 3. Activation of c-Met by GD2. a) MDA-MB-231 breast cancer cells express mainly GM3 and GM2. b) GD3 synthase expression induces the accumulation of b- and c-series gangliosides, mainly GD2, which can lead to activation of c-Met in the absence of HGF and increase proliferation and migration through the PI3K/Akt and MEK/Erk pathways. c) Anti-GD2 mAb used in competition assays can inhibit c-Met phosphorylation and cells proliferation.

In addition, Gb5 is another potential marker for breast CSCs [57]. Next, exogenous or endogenous expression of GD1b in MCF-7 cell line can result in apoptosis [58]. And over expression of GD1a or its synthase in breast cancer cells can enhance adhesion to brain endothelial cells and reduce interactions with the

blood-brain barrier, leading to promote metastasis to brain [5,59]. Furthermore, in MCF-7 breast cancer cells, the recognition, clustering and assembly of specific membrane proteins and signal transducers with GSLs in membrane microdomains result in loss of cell-cell adhesion, and subsequently, invasiveness was increased. The loss of cell-cell adhesion was due to sterical hindrance of E-cadherin both localized in and associated with clusters of the GSLs, monosialosyl globopentaosylceramide (MSGb5), and by activation of MSGb5-associated FAK/cSrc signaling complexes and downstream extracellular signal–regulated kinases (ERKs) leading to increased expression and activation of matrix metalloproteinases (MMPs) result in invasion [60,61].

N-glycolyl-GM3 (Neu5Gc GM3) containing N-glycolylneuraminic acid instead of N-acetylneuraminic acid has been detected in many human cancers, such as colon carcinomas and breast cancers, but not in normal human cells [62]. Recent evidences showed that in breast cancer, LacCer, Globo-H, and Fuc-LacCer are significantly increased, and GlcCer and Gb3 are greatly decreased. The cellular effects are mediated by an altered composition of GSLs-enriched microdomains. Importantly, the abnormal Fuc-LacCer is specific to breast cancer. Further studies indicated that fucosyltransferase 1 (FUT1) is as a central player in the biosynthesis of Globo-H and Fuc-LacCer in MDA-MB-453 and MCF-7 cells, and suppressing FUT1 reduces the expression of Globo-H and Fuc-LacCer [63]. The UDP-glucose ceramide glucosyltransferase (UGCG) is also a key enzyme in the synthesis of GSLs. The enhanced proliferation and multidrug resistance in UGCG over expressed breast cancer cells were observed [64].

7. **Lung cancer**

Many studies have demonstrated that GSLs play important roles in lung cancer transformation and progression. α-GalCer, which is a specific ligand of invariant natural killer T (iNKT) cells, shows an inhibitory effect on tumor growth by

increasing the tumor growth suppressor IFN-r [65]. Besides, it can inhibit inducible nitric oxide synthase (iNOS) expression in lung cancer [66]. In addition, the study showed that α-GalCer combined with lipopolysaccharide can obviously promote tumor antigen-specific immune responses and suppress tumor growth [67]. Furthermore, for lung metastasis, host CD40, which is a costimulatory protein, obviously plays an essential role in the effectiveness of α-GalCer treatment [68].

It has also been confirmed that increased Gb3 expression not only can result in acquisition of cisplatin resistance, but also reduce GCS-potentiated cisplatin cytotoxicity in non-small cell lung cancer (NSCLC) H1299 cells [69]. In addition, galactocerebrosidase expression that removes galactose from GSLs is reduced in lung cancer [70]. NeuGc-containing gangliosides such as Neu5Gc GM3, are widely expressed in NSCLC, and there are different effects between Neu5Gc GM3 and GM3 on the inhibition of EGFR tyrosine kinase. In addition, GM2 expressed small cell lung cancer (SCLC) shows multiple organ metastases in a severe combined immunodeficient mouse model. However, metastases can be inhibited by treatment with humanized anti-GM2 antibodies, including BIW-8962 and KM8927 [71].

8. **Neural tumor**

The GSLs composition in an F-11 neuroblastoma cell line has been studied, and the results showed that major neutral GSLs are Gb4, Gb3, LacCer, and GlcCer, and major gangliosides are GM3, GD3, O-acetylated GD3, and GD1a, with trace amounts of GD2. Further studies indicated that ganglioside composition alteration, especially GD3 and O-acetylated GD3, is associated with the morphological changes. Other studies have already described a link between certain ganglioside expression and neuroblastomas behavior, and specific gangliosides expression may be as a cancer marker [72,73].

It should be noted that some gliomas contain unusual gangliosides. It has been confirmed that a ratio between GD3 and 9-O-acetylated GD3 on glioblastoma

promotes tumor survival. Restoring GD3 through removing acetyl group can reduce cancer cells viability by inducing mitochondrial-mediated apoptosis [74,75]. Sulfated glucuronosyl glycosphingolipids (SGGLs) having the Human Natural Killer-1 (HNK-1) epitope are known to be present on a variety of cell adhesion molecules of cancers. Especially for these from neural origin, and regarded as an important biomarker for neural tumors [76]. Further, it has been recognized that there are basically three types of GSL component patterns for gliomas. From several human gliomas, it has been revealed GSL component may reflect subtle differences in cancer growth and state of cells differentiation [77].

Moreover, by adding l-phenyl-2-decanolyamlno-3-morpholino-l-propanol (PDMP), an effective inhibitor of ceramide glucosyltransferase, the inhibitory effects on GSLs biosynthesis and neurite outgrowth in murine neuroblastoma cell lines were observed [78]. Shedding of membrane gangliosides is characteristic for both human and experimental tumors, and significant ganglioside shedding could influence tumor progression. It has been concluded that shed neuroblastoma gangliosides play an important role in accelerating tumor progression [79].

9. Leukemia

In adult T-cell leukemia, glycosyltransferase FUT_7 transcription is constitutively activated by Tax protein, leading to sialyl Le^x synthesis significantly [80]. Caffeic acid phenethyl ester (CAPE) inducing human chronic myelogenous leukemia (CML) K562 cells differentiate to megakaryocytic lineage showed GM3 level was increased [81]. GM3 expression was also upregulated during differentiation of human acute monocytic leukemia THP-1 cells into macrophages [82]. Moreover, it was found that the levels of GM3, lactotriaosylceramide (Lc3) and neolactotetraosylceramide (nLc4) are higher in acute myeloid leukemia (AML) patients than healthy controls, especially the M1 subtype of AML. AML-associated GSLs GM3, Lc3 and nLc4 are possibly involved in initiation and differentiation of AML [83]. In Neu5Gc GM3 expressing

L1210 mouse lymphocytic leukemia B cells, after silencing of *cmah*, these cells displayed enhanced NeuAcGM3 expression and an inhibitory effect on anchorage-independent cell growth and tumor progression [84,85].

Three human myeloid leukemia cell lines, including K562, KG1, and HL-60, have been used to study changes in neutral GSLs synthesis with myeloid cell differentiation. The results showed that for K562 and KG1 cells are similar to cells from patients with acute leukemia in expressing two series (globo and neolacto), and for HL-60 cells are similar to mature human myeloid cells in expressing only one series (neolacto). Human myeloid leukemia cells blocked at different stages of differentiation vary in their ability to synthesize neutral GSLs [86]. Other result showed that in primary chronic lymphocytic leukemia (CLL) cells, anti-apoptotic effect from α-GlcCer was strongly enhanced by B-cell receptor stimulation [87]. Moreover, in K562 cells, which is a multidrug-resistant variant with GCS and B-cell lymphoma 2 (Bcl-2) co-overexpression, apoptosis was enhanced by adriamycin due to downregulation of Bcl-2 via the ERK pathway, and GCS inhibition also can suppress Bcl-2 [88].

10. Conclusions and Perspectives

GSLs are strongly related with tumors, and more and more evidences indicate that they have obvious effects on cancer development and progression. In many types of human cancers, aberrant expression of specific GSLs and related enzymes is associated with tumor progression. Differential expression profiles of GSLs are associated with oncogenic transformation. It is well known that certain GSLs are regarded as tumor-associated antigens. GSLs would become a promising target for cancer therapy.

The expression of GSLs in different cancers is altered, and they can be regarded as biomarkers for some types of cancers or other diseases. Furthermore, external factors can influence the processes that involve in GSLs alterations, such as dietary or

other lifestyles [89]. Study demonstrated that diets or foods can affect the metabolism-related gene expression of gangliosides resulting in altering ganglioside metabolism as well as ganglioside expression [90]. In addition, some reports also showed that life style-related diseases are strongly associated with aberrant expression of gangliosides [91]. Moreover, molecular pathological epidemiology (MPE) can investigate these external factors. GSL-related biomarkers can be used in MPE study, and GSLs-based MPE study will be a promising direction.

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