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Review

# Advances in the relationship between glycosyltransferases and multidrug resistance in cancer

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ABSTRACT

Despite great progress in clinical treatment, cancer remains a serious health problem contributing to significant morbidity and mortality worldwide. Although chemotherapy is a common therapeutic measure, multidrug resistance (MDR) presents a major challenge that often leads to poor prognosis. The abnormal expression of glycosyltransferases (GTs) leading to aberrant glycosylation patterns are considered a marker of cancer. Furthermore, the biosynthesis of these glycoconjugates has been associated with tumor proliferation, invasion and metastasis. Recently, studies have found that GTs are involved in mediating MDR in cancer cells through complex mechanisms and can influence therapeutic effect. In this review, we focus on several types of cancers and summarize previous studies on the correlation between GTs and MDR.

## 1. Introduction

Cancer is a serious health concern worldwide, and it is the second leading cause of death in the United States [1]. There have been significant advances in clinical cancer treatments, including chemotherapy, surgical treatment, radiation therapy, and other new treatment methods. Finding a cure for cancer still faces many challenges, including relapse, metastasis, and multidrug resistance (MDR). These challenges can result in a poor prognosis and high cancer mortality rates. MDR has become the significant cause of failure for chemotherapeutic treatments of cancer, and it leads to metastasis and reoccurrence.

MDR involves multiple physiological phenomena, including reduced drug intake, increased drug efflux, and resistance to apoptosis. The molecular mechanisms of MDR have been well studied but are not clearly understood yet. Currently, the underlying mechanisms that have been reported are the ATP-binding cassette (ABC) transporter family, anti-apoptosis, cancer stem cell regulation, microRNA (miRNA) regulation, and epithelial-mesenchymal transition (EMT) (Table 1) [2–8].

Glycosylation is a common modification process of lipids and proteins that produces a wide variety of glycoconjugates, and it is associated with biological processes, including cell recognition and adhesion, signal transduction, and molecular transport. Glycosyltransferase (GT) is a large enzyme family that is responsible for the glycosylation progress. Increasing evidence has shown that the abnormal expression of GTs is associated with cancer occurrence, development, and chemotherapy resistance. The overexpression of UDP-glucose ceramide glycosyltransferase significantly activates the AKT and ERK1/2 signaling pathway. This leads to increased gene expression of multidrug resistance protein 1 (MDR1), which encodes the protein P-glycoprotein (P-gp) and results in MDR [9]. Here, we attempt to advance our current understanding of recent research developments on the correlation between several key GTs and MDR in cancer.

## 2. Glycosylation

Glycosylation as an important biological process that produces many substances that are essential for organisms at the molecular and

*Abbreviations:* Glycosyltransferase, GT; multidrug resistance, MDR; ATP-binding cassette, ABC; multidrug resistance protein 1, MDR1; P-glycoprotein, P-gp; endoplasmic reticulum, ER; topoisomerase II, TOP2; Forkhead box O3, FOXO3; epithelial-mesenchymal transition, EMT; glycophosphatidylinositol, GPI; N-Acetylglucosamine, GlcNAc; fucosyltransferase, Fut; sialyltransferase, ST; galactose, Gal; *N*-acetylgalactosamine, GalNAc; *N*-acetylglucosaminyltransferase, GnT; Hepatocellular carcinoma, HCC; human hepatocellular carcinoma cell lines, MHCC97-H, Huh7 and BEL7402; 5-fluorouracil, 5-FU; MDR-related protein 1, MRP1; human HCC adriamycin resistant cell line, SMMC7721/R; sialyl-glycolipid stage-specific embryonic antigen 4, SSEA4; human breast cancer cell line, T47D; epidermal growth factor receptor, EGFR; tyrosine kinase, TK; non-small cell lung cancer, NSCLC; chronic myeloid leukemia, CML; CML cell line with imatinib resistance, K562R; adriamycin-resistant human acute myeloid leukemia cell, HL60/ADR

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**Table 1**
Major mechanisms that are involved in multidrug resistance[a].

| Mechanism | Member or signaling pathway | Physiological phenomena | Ref |
|---|---|---|---|
| ABC-transporter | P-gp, MRP1 and BCRP | Increased drug efflux | [2] |
| Anti-apoptosis | p53, PI3K pathway and TOP2 | Reduced apoptosis or DNA repair | ([3]; [4]; [5]) |
| Cancer stem cells | CD133, Akt/PKB and Bcl-2 | Self-renewal and tumorigenicity | [6] |
| miRNAs | miR-153 and FOXO3 transcription factor | Reduced apoptosis | [7] |
| EMT | E-cadherin and Zeb-1 | Increased invasion and metastasis | [8] |

[a] Multidrug resistance is a complex process which involves a variety of molecular mechanisms, and we list several of them briefly.

cellular levels. Carbohydrates combine with other molecules through glycosidic linkages and thus form a wide variety of glycoconjugates. In organisms, saccharides are typically attached to lipids or proteins and produce a significant amount of glycolipids and glycoproteins [10]. Glycolipids encompass glycosphingolipids, glycerolipids, cholesterol-derived glycolipids, and glycophosphatidylinositol (GPI). Glycosphingolipid is a structural component of the cell membrane, and it takes part in the regulation of membrane protein function, cell-cell recognition, and signal transduction. However, glycerolipid is mainly found in plants and microorganisms. Cholesterol-derived glycolipids are a type of cardiac glycoside that can be used for the treatment of heart failure. GPI usually links with proteins known as GPI anchors. These GPI anchors are a common way to fix proteins on the cell membrane and present them to the external environment [11].

Glycosylation of protein is an important post-translational modification process that has a significant effect on the folding, structure, function, stability, and binding affinities of proteins [12]. Protein glycosylation is classified as N-glycosylation and O-glycosylation based on the type of linkages between the polypeptide and glycan [13]. N-glycosylation has been highly studied, and it has been estimated that most glycoproteins contain N-glycan structures [14]. In the membranes of the endoplasmic reticulum of eukaryotic organisms, glycans connect with acceptor peptides through amide linkages between N-Acetylglucosamine (GlcNAc) and Asn residues. However, only when Asn is at the Asn-X-Ser/Thr sequons (X denotes any amino acid except for Pro) will it have the ability to link with GlcNAc [15]. *N*-glycans share a common pentasaccharide core region, and they can be divided into the following three categories based on the lateral chain: high-mannose type, complex type, and hybrid type [16]. O-glycosylation is also referred as mucin-type O-glycosylation, and it is found in the mucus of the submandibular gland, the digestive tract, and the beginning of the respiratory tract. Typically, protein glycosylation is characterized by the initial addition of *N*-acetylgalactosamine (GalNAc) to the hydroxyl group of Ser or Thr residues [17]. Of course, there are other types of O-glycans, such as O-mannose (O-Man), O-fucose (O-Fuc), and O-galactose (O-Gal) [16]. Because of the complexity of glycosylation, glycoconjugates have countless functions in organisms.

## 3. Glycosyltransferases

Glycosyltransferase (GT) is a large enzyme family that exists in the endoplasmic reticulum (ER) and Golgi apparatus, and they are responsible for adding a single sugar residue to the oligosaccharide chain, protein, or lipid in the proper order [18–20]. Based on the type of substrate sugar donor and glycosidic bond formation, GTs can be divided into several families, including fucosyltransferase, sialyltransferase, and *N*-acetylglucosaminyltransferase. GTs contribute to the biological functions of proteins, lipids, or oligosaccharides, and they are involved in physiological activities, such as cell adhesion and signal transduction. Previous studies have suggested that the abnormal expression and activity of GT may be associated with various human diseases [10,12,16,21–23]. Here, we focus on the three main subfamilies of GTs: fucosyltransferase, sialyltransferase, and *N*-acetylglucosaminyltransferase.

### 3.1. Fucosyltransferase

Fucosyltransferase (Fut) is a member of GT superfamily, and it occurs widely in vertebrates, invertebrates, plants, and bacteria. Fut catalyzes the transfer of fucose from GPD-fucose to oligosaccharides, glycoproteins or glycolipids. Based on the type of glycosidic bond, Futs can be classified into Fut1, Fut2 (form α1,2 glycosidic bond), Fut3–7, Fut9 (form α1,3 or α1,4 glycosidic bond), Fut8 (form α1,6 glycosidic bond), and the unclear Fut10 and Fut11 [24,25]. Among them, Fut8 is well studied because it is the only enzyme that catalyzes the transfer of fucose to the innermost GlcNAc residue of N-glycan. This produces the "core fucose", which is associated with tumor metastasis, malignant transformation, and invasion [26–28].

### 3.2. Sialyltransferase

Sialylation is one of the most common glycosylation progresses. During this process, sialic acids are added to the terminal portions of glycans, glycolipids, or glycoproteins, and sialyltransferase (STs) are responsible for the transfer of sialic acid [29]. In mammals, the ST family includes 20 members, and each member is specific for a particular substrate. Based on the resulting glycosidic bonds in the products, STs can be classified into four families. The ST3Gal I-VI family has sialic acid that links with a galactose (Gal) residue in an α2,3 glycosidic bond. The ST6Gal I, II family has an α2,6 linkage between sialic acid and Gal. In the ST6GalNAc I-VI family, sialic acid links with a GalNAc (*N*-acetylgalactosamine) residue through an α2,6 linkage. In the ST8Sia I-VI family, sialic acid is added to another terminal sialic acid residue through an α2,8 glycosidic bond [23]. Previous studies have suggested that aberrant expression of STs is often associated with tumor occurrence, development, invasion, and metastasis in organisms [30,31].

### 3.3. N-acetylglucosaminyltransferase

Similar to the Futs and STs, *N*-acetylglucosaminyltransferase (GnT) is another typical N-glycan branching enzyme that catalyzes the transfer of *N*-acetylglucosamine (GlcNAc). The GnTs are responsible for the formation of N-glycan branches based on the common core pentasaccharide ($Man_3GlcNAc_2$-Asn) [32]. Based on the catalytic sites, GnTs can be divided into GnT-I through GnT-VI. GnT-III transfers the GlcNAc to the mannose residue at the core structure of N-linked glycans to produce a "bisecting GlcNAc". GnT-IV catalyzes the transfer of GlcNAc to the N-glycan core through a β1, 4 linkage, and GnT-V catalyzes the transfer of GlcNAc to the N-glycan core *via* a β1,6 linkage [22]. Among them, GnT-V is related to cancer metastasis, and GnT-III has been reported to be associated with cancer suppression [33].

## 4. Multidrug resistance

As mentioned above, GTs are involved in the glycosylation modification process, and their expression and regulation are closely related to various physiological and pathological processes. Thus, GTs are increasingly drawing the attention of researchers [34,35]. In the progression of cancerization, there is aberrant glycosylation in cancer, and it can be described as a specific tumor characteristic that is associated

with tumor proliferation, invasion, metastasis, and angiogenesis [16,36]. In the clinical treatment of cancer, chemotherapy is an important method of treatment. However, tumor cells can easily develop MDR and can lead to poor efficacy of chemotherapy [37]. Recently, studies have increased focus on the role of GTs in MDR, and they hope to provide a clear theoretical basis for clinical MDR reversal and new drug treatment strategies [38–40].

### 4.1. Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is a highly fatal cancer with a high malignant degree. Chemotherapy is one of main methods of treatment for liver cancer, and drug resistance frequently contributes to the poor therapeutic efficacy. For example, sorafenib is a multi-targeted kinase inhibitor, and it is a first-line treatment for HCC. However, patients often develop an acquired resistance within 6 months, and this reduces the efficacy of sorafenib [41,42]. Docetaxel is a common chemotherapeutic drug that participates in strengthening the tubulin polymerization and inhibits microtubule disassembly. Therefore, it hinders the mitosis of tumor cells [43]. In our previous study, we found that ST6Gal I can modulate the sensitivity of hepatocellular carcinoma to docetaxel *via* the p38 MAPK/caspase pathway [44]. This finding indicates that silencing ST6Gal I could increase MHCC97-H cell apoptosis following docetaxel treatment. Furthermore, hepatocarcinoma Huh7 cells that overexpress ST6Gal I had a lower sensitivity to docetaxel. In addition, 5-fluorouracil (5-FU) is also a common antitumor drug that functions by inhibiting DNA synthesis. However, resistance to 5-FU in hepatocellular carcinoma is a critical problem that needs to be solved. Cheng et al. reported that Fut4, Fut6, or Fut8 mediates chemoresistance in human hepatocellular carcinoma *via* the PI3K/Akt signaling pathway [45]. Overexpression of Fut4, Fut6, or Fut8 increases resistance to 5-FU in BEL7402 cells by modulating the PI3K/Akt signaling pathway and the expression of MDR-related protein 1(MRP1). In addition, the knockdown of GnT-V may improve chemotherapeutic sensitivity in the human HCC cell line that is adriamycin-resistant, SMMC7721/R, and it inhibited proliferation, migration, and invasion through the mitochondrial-mediated apoptosis pathway [46].

### 4.2. Breast cancer

Breast cancer is the most common cancer, and it is the leading cause of cancer deaths among females [1]. In breast cancer treatment, chemotherapy is a first-choice therapy, but drug resistance remains a challenge. Trastuzumab is used in the treatment of HER2-positive breast cancer, and it is associated with a 33% reduction in the risk of death among surgical patients [47]. However, clinical trials indicated that the majority of the patients (66%–88%) demonstrated drug resistance within 12 months, which results in decreased efficacy [48–50]. Aloia et al. reported that increased expression of sialyl-glycolipid stage-specific embryonic antigen 4 (SSEA4) and ST3Gal II (the rate-limiting enzyme of SSEA4 synthesis) in breast cancer could be predictive markers of poor prognosis. Thus, elevations in these markers are associated with resistance to multiple chemotherapeutic drugs, including doxorubicin and cyclophosphamide [51]. In addition, Feng et al. found that the Fut4 gene is targeted by miR-224-3p, and the expression of Fut4 was significantly higher in adriamycin-resistant breast cancer cells. Moreover, the overexpression of Fut4 dramatically enhanced the resistance of T47D cells (a human breast cancer cell line) to adriamycin, vincristine, and paclitaxel both *in vitro* and *in vivo* [52].

### 4.3. Ovarian cancer

The most lethal gynecological cancer in the United States is ovarian malignant tumors, and it is the fifth leading cause of cancer death among females [53]. A frontline therapy of ovarian cancer is cisplatin; it is a commonly used chemotherapy drug. Cisplatin can react with many cellular components, such as RNA, proteins, DNA, and microfilaments, causing DNA damage and changes to the cytoskeletal structure [54]. Platinum-based therapy has achieved great curative effects for a large majority of ovarian cancer patients, but up to 75% of patients will relapse and most will develop a drug-resistant disease [55]. Schultz et al. reported that ST6Gal I overexpression is a hallmark of ovarian cancer, and it is closely related to cisplatin-induced cell death [56]. The overexpression of ST6Gal I reduced the activation of caspase 3, and it protected against cell death after cisplatin treatment. This indicates that ST6Gal I may be a novel contributor to cisplatin resistance. In the frontline treatment of advanced epithelial ovarian carcinoma, Taxol (paclitaxel) combined with platinum chemotherapy has been the standard of care for the last decade [57]. Similar to cisplatin, the drug resistance of cancer cells to Taxol also attracts widespread attention. ST3Gal III is a member of the ST family, and it could decrease Taxol-induced apoptosis of ovarian cancer cells by inhibiting caspase 8 activation. Therefore, it could reduce the curative effects of Taxol [58]. Interestingly, ST3Gal V (GM3 synthase) plays a similar role in ovarian cancer cells treated with Taxol compared to ST3Gal III. However, ST3Gal V prevents Taxol-induced apoptosis in ovarian cancer cells by inhibiting caspase-3 activation [59].

### 4.4. Lung cancer

Lung cancer is the leading cause of cancer death among males, and it surpassed breast cancer among females in more developed countries in 2012 [1]. Gefitinib is an inhibitor of epidermal growth factor receptor (EGFR)-tyrosine kinase (TK), and it is used as a first-line treatment for non-small cell lung cancer (NSCLC) with EGFR mutations [60]. However, the majority of patients show resistance within 1 to 2 years after initiation of gefitinib treatment; thus, it cannot achieve satisfactory effects [61,62]. Previous studies have suggested that GM3 synthase (ST3Gal V) is associated with gefitinib sensitivity, and non-small cell lung cancer cells that have high levels of ST3Gal V mRNA tend to be sensitive to gefitinib and associated with *SAT-I* mRNA levels [63]. Interestingly, Yen et al. also reported that suppressing the sialylation of EGFR increases phosphorylation and resistance to gefitinib in TKI (Tyrosine kinase inhibitor)-resistant lung cancer cell lines. This may be because sialylation can attenuate the dimerization of the EGFR extracellular domain [64].

### 4.5. Leukemia

Leukemia is a clonal malignancy of the hematopoietic system, and it includes chronic myeloid leukemia, acute myeloid leukemia, and chronic lymphocytic leukemia [65]. Currently, clinical therapeutic strategies of leukemia include bone marrow transplantation, radiotherapy, chemotherapy, or a combination of these therapies [66,67]. However, drug resistance often causes the failure of chemotherapeutic treatments, and it leads to poor prognosis in patients with leukemia. For example, imatinib is the frontline drug in chronic myeloid leukemia (CML) therapy; however, about 15%–25% of patients with CML in the chronic phase demonstrated resistance or intolerance to imatinib [68,69]. Che et al. reported that Fut1 is upregulated in human CML multidrug-resistant cell lines. They also found that overexpression of Fut1 enhanced the chemoresistance of CML cells to adriamycin *in vitro and in vivo* by modulating the EGFR/MAPK signaling pathway and P-gp expression [70]. In addition, Zhou et al. demonstrated that miR-224 and let-7i directly regulate the expression of the ST3GAL IV gene. ST3Gal IV is highly expressed in K562R cells, which are CML cells with an imatinib-resistant phenotype, and it is highly expressed in CML patients with MDR. Moreover, elevated expression of ST3Gal IV promotes the survival of CML cells, and thus, it reduces the effectiveness of imatinib treatment [71]. Interestingly, Ma et al. reported that human acute myeloid leukemia MDR cells had higher levels of ST8Sia VI but drug-sensitive cells express more ST3Gal V. They also found that

**Table 2**
Multidrug resistance in cancers associated with glycosyltransferases.

| Cancer | Glycosyltransferase | Drug | Mechanism | Ref |
|---|---|---|---|---|
| Hepatocellular Carcinoma | ST6Gal I | Docetaxel | The p38 MAPK/caspase pathway | [30] |
| | Fut4, Fut6, Fut8 | 5-fluorouracil | The PI3K/Akt pathway | [31] |
| | GnT-V | Adriamycin | The caspase-3/Bcl-2/MMPs pathway | [32] |
| Breast cancer | ST3Gal II | Doxorubicin, cyclophosphamide | The EMT pathway and SSEA4 expression | [33] |
| | Fut4 | Adriamycin, vincristine, paclitaxel | Targeted by miR-224-3p | [34] |
| Ovarian cancer | ST6Gal I | Cisplatin | The caspase-3 pathway | [37] |
| | ST3Gal III | Paclitaxel | The caspase-8 pathway | [39] |
| Lung cancer | ST3Gal V | Gefitinib | The *SAT-I* expression | [42] |
| Leukemia | Fut1 | Adriamycin | The EGFR/MAPK signaling pathway and P-gp expression | [44] |
| | ST3Gal IV | Imatinib | Regulated by miR-224 and let-7i | [45] |
| | ST8Sia VI, ST3Gal V | Adriamycin | The PI3K/Akt pathway and P-gp, MRP1 expression | [46] |

silencing the ST8Sia VI gene or overexpressing the ST3Gal V gene facilitates the chemosensitivity of HL60/ADR cells (adriamycin-resistant cells) both *in vitro* and *in vivo* by regulating the PI3K/Akt signaling pathway and the expression of P-gp and MRP1 [72].

## 5. Conclusions

In the chemotherapeutic treatment of cancer, radiotherapy and surgery strategies have made significant progress in the past decades, but MDR is still a critical problem. The molecular mechanism of MDR is a point of common interest, and targeted drugs are a hopeful avenue to reverse drug resistance. The curative effects of drugs that target the classical markers are unsatisfactory. For example, Zosuquidar is a modulator of P-gp and may reverse P-gp–mediated resistance in acute myeloid leukemia. However, clinical trials have suggested that Zosuquidar cannot improve outcomes in advanced acute myeloid leukemia; the remission rate was 51.9% in the Zosuquidar group and 48.9% in the placebo group [73]. There is no doubt that GTs play an important role in chemoresistance. For example, abnormal expression of GTs mediates chemotherapy drugs that induce cell death by various mechanisms, including the p38 MAPK/caspase signaling pathway and the PI3K/Akt signaling pathway. Therefore, GTs are likely to reverse resistance by influencing one mechanism or by influencing various signaling pathways or markers. Here, we review and summarize the recent studies on the correlation between the three key GTs and MDR in cancer (Table 2). Despite the numerous studies on the correlation between GTs and MDR, the specific mechanism by which GTs mediate the sensitivity of cancer cells to chemotherapy drugs is not fully understood. In addition, the clinical application of GTs to reduce tumor drug resistance is still challenging. However, the correlation between GTs and MDR provides a theoretical basis for clinical MDR reversal and a new strategy for drug treatments.

## Conflicts of interest

The authors do not report any conflict of interest.

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