Update on the role of C1GALT1 in cancer (Review)

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Abstract. Cancer remains one of the most difficult diseases to treat. In the quest for early diagnoses to improve patient survival and prognosis, targeted therapies have become a hot research topic in recent years. Glycosylation is the most common posttranslational modification in mammalian cells. Core 1β1,3-galactosyltransferase (C1GALT1) is a key glycosyltransferase in the glycosylation process and is the key enzyme in the formation of the core 1 structure on which most complex and branched O-glycans are formed. A recent study reported that C1GALT1 was aberrantly expressed in tumors. In cancer cells, C1GALT1 is regulated by different factors. In the present review, the expression of C1GALT1 in different tumors and its possible molecular mechanisms of action are described and the role of C1GALT1 in cancer development is discussed.

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1. Introduction

The glycosylation of proteins is a sophisticated protein modification. Depending on the sugar-amino acid bond, glycosylation may be divided into two categories: N-glycosylation and O-glycosylation. Sugars are connected either to the amino group's lateral chain of asparagine residues (N-linked glycosylation) or, more commonly, to the hydroxyl group's lateral chains of serine (Ser) or threonine (Thr) residues (O-linked glycosylation) (1,2). N-glycosylation has been well studied, but less is known about O-glycosylation. O-glycosylation is also frequently referred to as mucin (MUC)-based glycosylation, as O-glycans make up >80% of the sugar chain (3).

O-glycosylation is initiated in the presence of polypeptide N-acetylgalactosamine-transferase-(GalNAc-T), which catalyzes the formation of the GalNAcα1-O-Ser/Thr linkage in O-glycoproteins. The synthesis process occurs in the Golgi apparatus (4). The addition of N-acetylgalactosamine (GalNAc) to Ser/Thr residues forms the GalNAc α1-Ser/Thr structure [also known as the Thomsen-nouvelle (Tn) antigen] (5-7). Subsequently, the Tn antigen further forms core I, II and III structures under the action of glycosyltransferases, such as core 1β1,3-galactosyltransferase (C1GALT1), core 2β-1,6-N-acetylglucosaminyltransferase and core 3β1,3 N-acetylglucosaminyltransferase (7,8). The formation of the core 1 structure is the most frequent modification of the Tn antigen (9,10).

Glycosylation is important for megakaryocyte development and platelet production *in vivo* (11). The pathogenesis of human tumors suggests that cells acquire a series of characteristic functions, such as maintenance of proliferation, evasion of growth inhibitors and perpetual replication, during the transition from the normal to the tumor state (12). Abnormal glycosylation affects cell adhesion, migration and proliferation (13). Glycosylation has recently been proposed to be associated with the acquisition of labeling capacity (14) and may be a biomarker of cancer (13). Based on the significance of glycosylation in the tumor pathway, the present review focuses on the key enzyme of glycosylation, C1GALT1, in tumorigenesis and therapy.

2. C1GALT1, a glycosyltransferase

C1GALT1 (also known as core 1 synthase or T-synthase), a glycosyltransferase with a molecular weight of 42-43 kDa, is encoded by chromosome 7p14-7p13. Analysis of the cDNA sequence of human C1GALT1 has revealed that it contains three exons (10). C1GALT1 is a mammalian cell-specific T-synthase that catalyzes the transfer of galactose (Gal) from UDP-Gal to the extant GalNAc (Galβ1, 3GalNAcα-O-Ser/Thr) that forms the core 1 O-glycan (15) (Fig. 1). ClGALT1 has an important

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role in numerous biological processes and alterations in its expression may cause developmental defects and affect the malignant behavior of a tumor (16). Numerous glycoproteins have regulatory roles in the development of the lymphatic system. Knockdown of the C1GALT1 gene in endothelial and hematopoietic cells in mice causes deletion of O-glycan chains in endothelial cells of blood vessels and lymphatic vessels, resulting in disruption of vascular-lymphatic connections and fatty liver (17). C1GALT1 is abnormally expressed in a variety of malignant tumor types, including pancreatic cancer (18), gastric cancer (19), head and neck squamous cancer (20), laryngeal cancer (21), ovarian cancer (22) and liver cancer (23). In summary, C1GALT1 has an important role in maintaining normal physiological functions and also participates in the development of tumors.

C1GALT1 and Tn antigen. Synthesis of the Tn antigen is the first step in the initiation of O-glycosylation; under normal conditions, GalNAc is first added to serine/threonine via an α-bond to form Tn antigen, and then galactose is transferred to Tn antigen via a β-glycosidic bond with the aid of C1GALT1 to form core 1-O glycans. However, in the absence of C1GALT1, Tn antigen is not properly converted to T antigen, resulting in overexpression of Tn antigen, followed by increased expression of sialyl-Tn antigen (sTn antigen) in the presence of increased Tn (24). Tn antigen and sTn antigen are expressed in numerous types of tumor, including colon, lung, cervical, ovarian, prostate and gastric cancers. The expression of Tn antigen and sTn antigen is positively associated with metastasis and poor prognosis of patients (25-27). In addition, Tn or sTn antigen expression is also present in the hinge region of IgA1 molecules in patients with IgA nephropathy as a result of abnormal O-glycosylation of IgA1 (28).

C1GALT1 and Cosmc. Cosmc (or C1GALT1C1) is a unique molecular chaperone essential for mammalian C1GALT1 (6,29). Similar to T-synthase, Cosmc was first purified from rat liver and its molecular weight is similar to that of T-synthase at 36-38 KDa according to SDS-PAGE analysis (7). Cosmc is located on chromosome Xq24 and includes one encoding exon of ~1 kb and it has 26 homologous sequences to C1GALT1 (30), which maintains the stability and folding of C1GALT1 in the endoplasmic reticulum (29).

Human T-leukemia Jurkat cells produce truncated O-glycan (Tn antigen) due to deficiency of T-synthase activity (31). The gene and transcript level of T-synthase are normal in Jurkat cells, but a T deletion is present at nucleotide position 478 in the Cosmc cDNA sequence, causing early appearance of the stop codon (6). However, the addition of wild-type Cosmc restores T-synthase activity and the normal extension of O-glycan (6,32). Cosmc is involved in the cotranslation of C1GALT1 and hinders the unfavorable clustering of C1GALT1 (29). In the absence of Cosmc, inactivated T-synthase accumulates and translocates from the endoplasmic reticulum back into the cytoplasm where it is degraded in a ubiquitin-/proteasome-dependent manner (33). However, Cosmc may reactivate the activity of denatured T-synthase (34). Molecular chaperones bind to non-natural proteins but not to natural proteins, forming stable complexes that result in efficient folding (35). Regarding the combination of Cosmc with unnatural C1GALT1, Ju *et al* (36) indicated that Cosmc does not affect natural T-synthase but forms stable complexes with unnatural T-synthase. Cosmc therefore provides a novel mechanism for regulating protein O-glycosylation. Several studies have indicated that Cosmc mutations cause C1GALT1 defects, resulting in Tn antigen exposure across multiple blood cell lineages to form Tn syndromes (37).

3. Molecular mechanisms of C1GALT1 in tumorigenesis

C1GALT1 expression is upregulated in most tumors. Numerous studies have indicated that C1GALT1 overexpression is closely associated with the malignant behavior of tumors, which involves multiple steps, including proliferation, invasion, tumor spread and immune evasion (38). In addition, C1GALT1 expression is associated with poor patient prognosis (39-41). To better analyze the role of C1GALT1 in tumors, the molecular mechanisms by which C1GALT1 exerts a regulatory role in cancer are discussed (Table I; Fig. 2).

Upstream regulators of C1GALT1

MicroRNA (miRNA/miR)-181d-5p. miRNAs are a class of small noncoding RNAs that regulate gene expression at the posttranscriptional level (42). miRNAs are involved in numerous cellular processes, including cell growth, development, differentiation and apoptosis (43,44). miR-181d-5p has been reported to affect tumorigenesis and malignant transformation in different signaling pathways (45,46). Of note, miR-181d-5p has been indicated to have an oncogenic role in non-small-cell lung cancer (47). Similarly, in lung adenocarcinoma (LUAD), the overall survival rate of patients with low miR-181d-5p expression was lower than that of patients with high miR-181d-5p expression. On this basis, Dong *et al* (48) indicated that miR-181d-5p was able to bind to the C1GALT1 3'UTR and act as an inhibitor of proliferation, migration and invasion of LUAD cells.

miR-152. miR-152 has also been reported to exhibit aberrant expression in a variety of malignancies (49-51). Dong *et al* (52) indicated that in gastric cancer, miR-152 is an upstream regulator of C1GALT1 and able to negatively regulate C1GALT1 expression by binding to the C1GALT1 3'-UTR. Overexpression of miR-152 decreased C1GALT1 expression, while downregulation of miR-152 increased C1GALT1 expression. They also demonstrated that the promoting effect of C1GALT1 on the growth and metastasis of gastric cancer was associated with miR-152.

Downstream regulators of C1GALT1

Rac family small GTPase 1 (RAC1). The Rho family of small GTPases has been identified as an important signaling effector in the regulation of cellular morphology and motility. RAC1 is a member of the Rho family of small GTPases (53) and is involved in cellular activities, such as phagocytosis, adhesion, migration, motility and proliferation (54). In recent years, RAC1 has been reported to be involved in numerous physiological and pathological processes, including cancer (55). Aberrant expression of RAC1 is considered a hallmark of cancer and increases the tumorigenic and metastatic properties of cancer cells (56). There is increasing evidence that

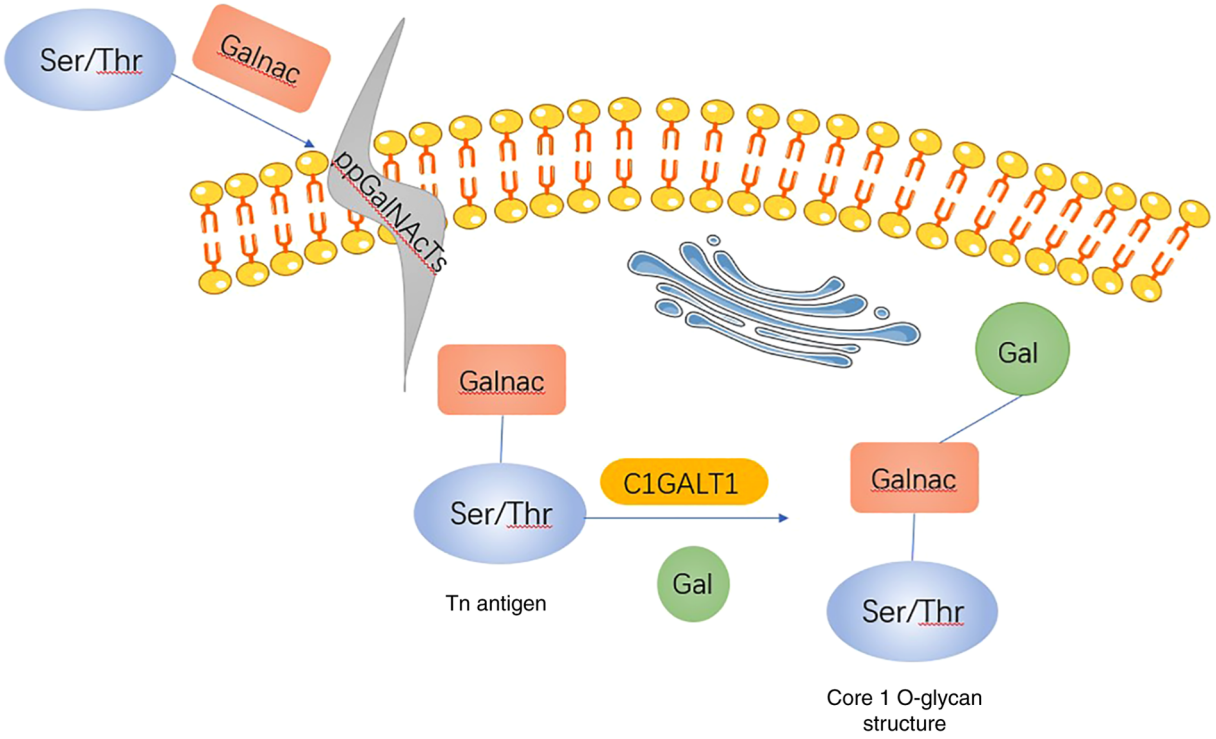

Figure 1. In the presence of GalNAc transferase, serine/threonine residues form a GalNAc α1-Ser/Thr structure (also known as Tn antigen) with GalNAc, followed by C1GALT1-catalyzed transfer of Gal from UDP-Gal to the existing Tn antigen to form a core 1 O-glycan structure. Gal, galactose; GalNAc, N-acetylgalactosamine; Tn, Thomsen-nouvelle; C1GALT1, core 1β1,3-galactosyltransferase.

different factors may affect RAC1 expression. For instance, lncRNA NR2F2AS1 overexpression promoted Rac1 expression in clear cell renal cell carcinoma (57), knockdown of RhoGDI2 decreased the mRNA expression of Rac1 in gastric cancer (58) and knockdown of DDX3 decreased the expression of RAC1 protein in medulloblastoma (59). De *et al* (55) indicated that the Rho GTPase signaling pathway is closely related to C1GALT1 expression, while RAC1 is a driver of tumor growth and metastasis. They further reported that RAC1 is positively regulated by C1GALT1 in LUAD, as high expression of C1GALT1 increased RAC1 expression, while low expression of C1GALT1 decreases RAC1 expression. Furthermore, knockdown of RAC1 reversed the oncogenic effect induced by C1GALT1 (48).

Receptor tyrosine kinase (RTK) signaling pathway

Ephrin receptor A2 (EPHA2). RTKs, such as epidermal growth factor receptors (EGFRs), fibroblast growth factor receptor 2 (FGFR2) and MET, have been reported to carry O-glycans (23,60-63). O-glycosylation is involved in the phosphorylation of various RTKs such as EGFR, FGFR2 and MET (20,23,60). Evidence suggests that RTKs actively contribute to gastric carcinogenesis and disease progression and are considered targets for cancer therapy (64,65). Ephrin receptors are the largest family of RTKs and affect a variety of developmental processes (66). The human ephrin receptor is composed of EPHAs and five EPHBs that preferentially bind their respective ephrin A and B ligands. Ephrin receptors are highly expressed in cancer and promote tumor development (67-70). Therefore, EPH receptors are considered to be attractive targets for tumor therapy (67,71,72). EPHA2 and its ligand ephrin A1 are highly expressed in gastric adenocarcinoma and overexpression of EPHA2 is associated with poor prognosis (73,74). Yuan *et al* (75) reported that C1GALT1 is highly expressed in gastric adenocarcinoma and that overexpression of C1GALT1 promotes malignant behavior in gastric cancer cells. C1GALT1 modifies the O-glycan on EPHA2 and regulates soluble ephrin A1-induced tyrosine phosphorylation of EPHA2, and silencing EPHA2 results in inhibition of gastric cancer cell growth and invasion. Knockdown of EPHA2 had no significant effect on cell viability but EPHA2 knockdown diminished cell migration and invasion. By contrast, high expression of C1GALT1 increased the tyrosine phosphorylation of EPHA2, promoted the binding of ephrin A1 to the cell surface and further enhanced soluble ephrin A1-induced migration of gastric cancer cells (19).

MET. RTKs are reported to have an important role in the proliferation of hepatocellular carcinoma (76,77). Previous studies focused on the effect of N-glycans on RTK, but in recent years, it has been indicated that O-glycosylation is also able to modulate their activity (62,78). In hepatocellular carcinoma, MET signaling is aberrantly activated when cell proliferation is abnormally enhanced (79-81). Hepatocyte growth factor (HGF)/MET signaling has been indicated to promote the invasion and metastasis of hepatocellular carcinoma cells (82,83). Wu *et al* (23) reported that C1GALT1 was highly expressed in hepatocellular carcinoma cells and that overexpression of C1GALT1 enhanced the proliferation of hepatocellular carcinoma cells, whereas knockdown of C1GALT1 resulted in inhibition of the proliferation of hepatocellular carcinoma cells *in vitro* and *in vivo*. In addition, C1GALT1 modified the

Table I. Regulatory factors that interact with C1GALT1 in different types of tumor.

Regulating factor	Tumor type	Upstream or downstream of C1GALT1	Regulation method	Biological function	(Refs.)
Integrin β1	Hepatocellular carcinoma	Downstream	(+)	Low expression inhibits cell adhesion, migration and invasion	(5)
EPHA2	Gastric cancer	Downstream	(+)	Low expression inhibits growth and invasion	(19)
EFGR	Head and neck squamous carcinoma	Downstream	(+)		(20)
miR-181d-5p	Lung adenocarcinoma	Upstream	(-)	Inhibition of proliferation, migration	(48)
RAC1	Lung adenocarcinoma	Downstream	(+)	Low expression inhibits tumor growth and metastasis	(48)
miR-152	Gastric cancer	Upstream	(-)		(52)
Integrin α5	Gastric cancer	Downstream	(+)	Low expression inhibits tumor cell adhesion and migration	(52)
FGFR2	Colon cancer	Downstream	(+)		(60)
MET	Hepatocellular carcinoma	Downstream	(+)		(82,83)
Integrin αv	Pancreatic ductal adenocarcinoma	Downstream	(+)	Low expression inhibits cell invasion	(112,113)
MUC1	Breast cancer, esophageal squamous carcinoma	Downstream	(+)		(116,126)

(-), negative regulation; (+), positive regulation; C1GALT1, core 1β1,3-galactosyltransferase; miR, microRNA; RAC1, Rac family small GTPase 1; EPHA2, ephrin receptor A2; FGFR2, fibroblast growth factor receptor 2; EGFR, epidermal growth factor receptor.

O-glycan chain of MET in RTK in hepatocellular carcinoma; low expression of C1GALT1 inhibited HGF-mediated phosphorylation of MET kinase, whereas overexpression of C1GALT1 enhanced the phosphorylation of MET (23). Receptor dimerization is a key regulatory step of RTK signaling and C1GALT1 is likely to regulate MET activity by enhancing its dimerization (84). The proliferative effect of C1GALT1 on hepatocellular carcinoma cells may be achieved by regulating MET glycosylation and dimerization (23).

FGFR2. FGFR2 and its isoforms are overexpressed in colorectal cancer and are involved in tumor growth, metastasis and angiogenesis (85). C1GALT1 is highly expressed in colorectal cancer; it enhances the proliferation, migration, invasion, sphere formation and tumor growth, as well as the metastatic potential of colorectal cancer cells, and affects patient prognosis. It has been reported that, when FGFR2 undergoes N-glycosylation, its N-glycan chain affects FGFR2 activation and intracellular transport (86). Hung *et al* (60) reported that C1GALT1 was able to regulate the O-glycan chain structure on FGFR2 in colon cancer cells, which suggests that FGFR2 carries short O-glycan chains, such as Tn and T antigen, in colon cancer cells. Furthermore, high expression of C1GALT1 promoted the phosphorylation of FGFR2 and the downstream signaling molecules ERK1/2. By contrast, low expression of C1GALT1 reduced the phosphorylation of FGFR2 and ERK1/2. Promotion of malignant behavior of colon cancer cells by high C1GALT1 expression may be achieved by altering the O-glycosylation and activity of FGFR2, while low C1GALT1 gene expression suppresses these malignant properties both *in vitro* and *in vivo* (60).

EFGR. The extracellular structural domain of EGFR is composed of four subregions, namely structural domains I, II, III and IV, where structural domains I and III are responsible for ligand binding (87). EGFR is overexpressed in head and neck squamous cell carcinoma (HNSCC) and its signaling pathway has an important role in cell proliferation and invasion (88). C1GALT is highly expressed in HNSCC and contributes to malignant behaviors such as increased cell proliferation, migration and invasion. Of note, Lin *et al* (20) reported that EGFR structural domain III carries an O-polysaccharide and that C1GALT1 regulates the O-glycan chain on EGFR. Low expression of the C1GALT1 gene blocks the extension of the O-glycan chain on EGFR, reduces the EGF-EGFR binding affinity, inhibits EGFR signaling and acts as a suppressor of malignant behavior (20). In prostate cancer cells, C1GALT1 regulates EGFR O-glycosylation to enhance galectin-4-mediated EGFR phosphorylation. When the C1GALT1 gene is lowly expressed, it decreases galectin-4-mediated EGFR phosphorylation but not ligand-mediated EGFR phosphorylation and downregulates EGFR protein levels (89). By contrast, in HNSCC cells, low expression of the C1GALT1 gene reduces EGF-mediated phosphorylation of EGFR without affecting EGFR protein levels. The differential effect of C1GALT1 on EGFR in prostate and

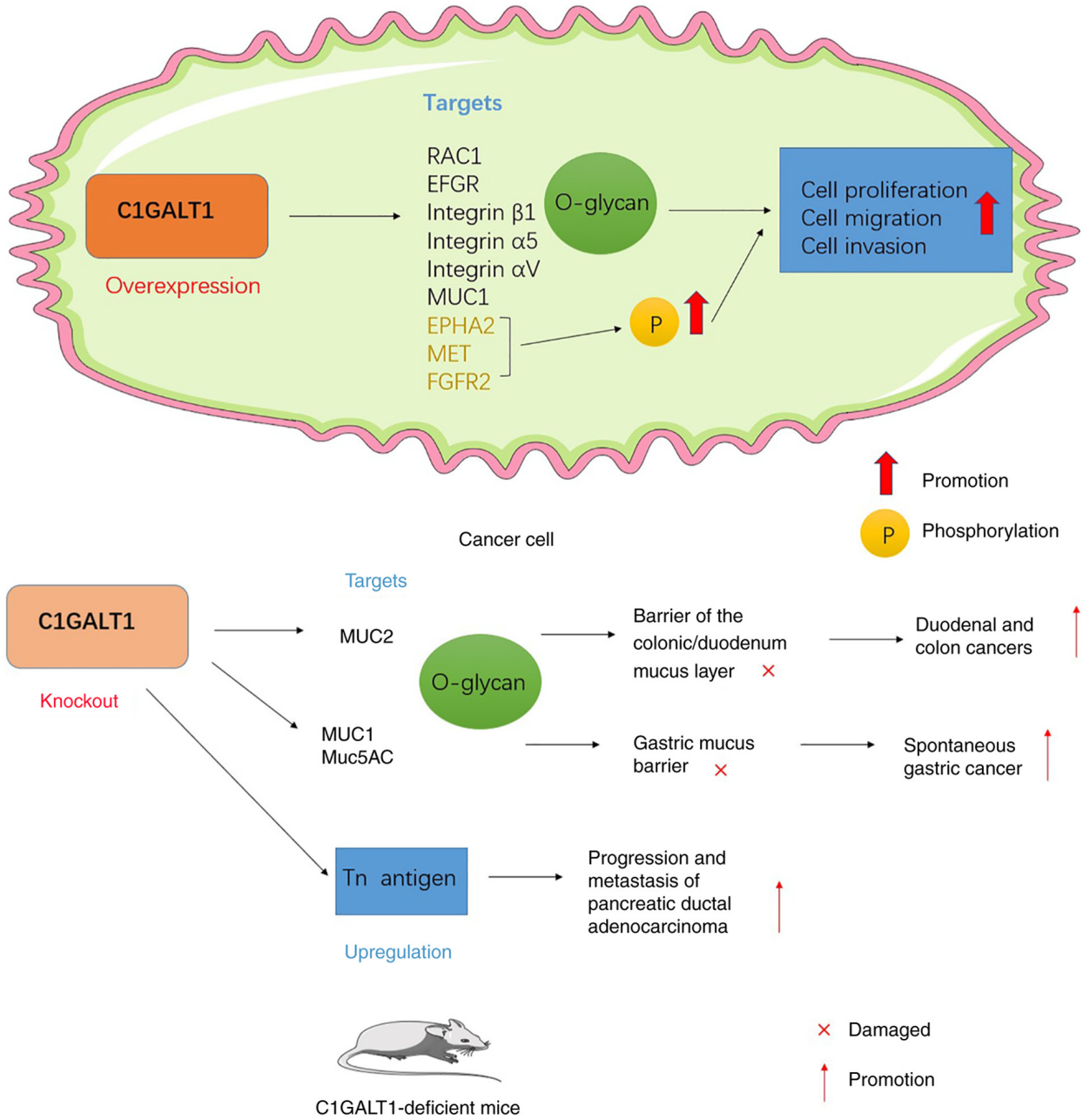

Figure 2 High expression of C1GALT1 in cancer cells promotes malignant tumor behavior; however, low expression of C1GALT1 in the constructed C1GALT1-knockout mice resulted in increased tumorigenicity in mice. MUC, mucin; Tn, Thomsen-nouvelle; C1GALT1, core 1β1,3-galactosyltransferase.

HNSCC cells may be due to cell-specific O-glycan groups on EGFR (20).

Integrin-focal adhesion kinase (FAK) signaling pathway

Integrin β1. Changes in the interaction between cancer cells and extracellular matrix (ECM) in the tumor microenvironment contribute to the metastasis of cancer cells (90-93). ECM receptors, such as integrins, are involved in cellular interactions with the ECM, are strongly associated with malignant tumorigenesis and have emerged as targets for cancer therapy (91,93). In addition, integrins have been suggested to be key factors in the invasion of hepatocellular carcinoma cells (94-96). It has been reported that integrin β1 is an O-glycosylated protein (97-99). Various studies have highlighted the critical nature of glycosyltransferases on ECM interactions through modification of integrins (100-103). Liu *et al* (5) indicated that C1GALT1 is overexpressed in hepatocellular carcinoma cells. C1GALT1 modifies the O-glycan on integrin β1, and the promotion of cell adhesion, migration and invasion by C1GALT1 was significantly attenuated by the use of integrin β1 blockers in high C1GALT1-expressing cells. By contrast, in cells with low C1GALT1 expression, these C1GALT1-induced malignant phenotypes were not further inhibited by integrin β1 blockers. In addition, C1GALT1 also affects FAK, a downstream signal of integrin β1. This indicates that C1GALT1 may regulate the malignant behavior of hepatocellular carcinoma cells by regulating the integrin β1 signaling pathway (5).

Integrin α5. Integrins consist of a large family of αβ heterodimeric transmembrane adhesion receptors that

regulate adhesion, survival and motility by activating multiple intracellular signaling molecules and reorganizing the actin cytoskeleton (104,105). It also has N- and O-linked glycosylation sites (106). Integrin α5 is involved in cancer development and progression by promoting tumor cell adhesion and migration through the activation of FAK (107-109). Integrin α5 is also an upstream regulator of the PI3K/AKT pathway and Wang *et al* (110) determined that integrin α5 is a downstream target of C1GALT1 in gastric cancer; low expression of C1GALT1 inhibited, while high expression of C1GALT1 promoted the activation of the PI3K/AKT pathway. Of note, the effects of high C1GALT1 expression on the malignant behavior of tumor cells in gastric cancer, such as proliferation, migration and invasion, were suppressed by low expression of integrin α5 (52).

Integrin αv. Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic cancer with abundant interstitial matrix, mainly ECM proteins, regulating tumor growth and metastasis (111). Kuo *et al* (18) indicated that C1GALT1 was overexpressed in PDAC and that overexpression of C1GALT1 promoted tumor migration and invasion. By contrast, low expression of the C1GALT1 gene diminished cell proliferation, migration and invasion and inhibited tumor growth and metastasis (18). In addition, low expression of the C1GALT1 gene resulted in upregulation of Tn antigen expression on integrins αv and α5 in PDAC cells, accompanied by reduced cell-ECM adhesion and phosphorylation of FAK, the most important downstream signaling molecule of integrins (112,113). FAK is a key downstream signaling molecule of integrins and is involved in the invasion of numerous cancer types (113-115). Of note, antibody-mediated knockdown of integrin αv significantly inhibited C1GALT1-mediated invasiveness of PDAC. This suggests that integrin αv carries O-glycan chains and that C1GALT1-mediated O-glycosylation regulates integrin αv function (18).

MUC1-β-catenin signaling pathway. MUC1 is a large transmembrane glycoprotein consisting of a highly glycosylated extracellular portion and a small cytoplasmic tail; it is a marker of poor prognosis and a potential therapeutic target (116-118). MUC1 is a type I transmembrane mucin that contains two subunits, MUC1-N and MUC1-C (119). MUC1 is expressed in almost all epithelial tissues of the respiratory, gastrointestinal, genitourinary and hepatobiliary tracts. High expression of MUC1 has been frequently associated with tumor progression and poor prognosis in colon, breast, ovarian, lung, prostate and pancreatic cancers, which has led to the emergence of MUC1 as a major direction for oncology treatment. Aberrant glycosylation of MUC1 is observed in cancer. This is due to the N-terminus of MUC1 containing a Variable Number Tandem Repeat segment, which contains Ser and Thr residues that may be involved in O-glycosylation binding (120-122). Core 1 glycans on MUC1 increase the degradation and accumulation of MUC1 (123). It has been reported that C1GALT1 is overexpressed in breast cancers and contributes to the enhanced invasive and migratory potential of tumors by modifying the O-glycan chain structure on MUC1, prompting increased detachment of the MUC1-N subunit from the membrane and activating the ERK phosphorylation level downstream of MUC1-C in breast cancer cells (16). MUC1 is able to regulate the Wnt signaling pathway by forming an intracellular complex with β-catenin, which in may turn synergistically activate cyclin D1 expression in the nucleus, ultimately promoting tumorigenesis by allowing cancer cells to avoid apoptosis (124). In addition, in pancreatic cancer, it has also been indicated that MUC1 glycosylation affects the invasiveness of pancreatic cancer cells (125). Wang *et al* (126) demonstrated that both MUC1 and C1GALT1 were highly expressed in esophageal squamous carcinoma and were positively correlated. Furthermore, C1GALT1 was determined to affect the survival and prognosis of patients with esophageal cancer by regulating the O-glycosylation of MUC1 (126). Abnormal MUC1 glycosylation may cause shortening of glycans such as the Tn antigen, leading to hidden antigen exposure; hidden antigens usually have peptide and carbohydrate properties that make MUC1 antigen epitopes tumor-specific (127). Transgenic T cells with the MUC1-Tn chimeric antigen receptor have been reported to be therapeutically effective in xenograft models of T-cell leukemia and pancreatic cancer (128). Based on this, Kato *et al* (129) screened an antibody specifically against the MUC1-Tn antigen epitope carrying the Tn antigen for study in LUAD; they indicated that the antibody identified by the MUC1-Tn epitope was highly specific for LUAD cells and that high expression of MUC1-Tn was present in LUAD, but not in normal lung tissue. Antibodies specific for MUC1-Tn epitopes are expected to be novel targets for LUAD therapy (129).

4. C1GALT1 has a tumor suppressor role in tumors

In the colorectum, C1GALT1 is essential for the formation of an important mucus barrier in the gastrointestinal tract. MUC2 is an important mucin involved in the formation of major gels of the intestine (130-132). MUC2 has a barrier-stabilizing role for the microbiota by forming an internal tissue adhesion layer with the assistance of O-glycans (133). In a mouse model of core 1- and core 3-derived O-glycan deficiency ($C1galt1^{-/-}$; $C3GnT^{-/-}$), Bergstrom *et al* (134,135) observed that core 1- and 3-derived O-glycan deletion causes microbial-dependent colitis as well as severe colitis-associated cancers by reducing their stability to bacterial-derived proteases, disrupting the barrier capacity of the colonic mucus layer and activating epithelial-mesenchymal transition. It is also accompanied by rapid degradation of MUC2 and loss in the lumen, loss of mucus in the duodenal lumen and disruption of homeostasis within the duodenal mucosa, which triggers duodenal cancer (136).

In addition, O-glycans are also major components of gastric mucins, including the membrane-bound MUC1 and the mucin Muc5AC, which is involved in gastric gel formation (137). In mice with deletion of gastric epithelial O-glycan (GEC $C1galt1^{-/-}$), Liu *et al* (15) determined that those GEC $C1galt1^{-/-}$ mice develop severe spontaneous chronic gastritis in the gastric sinus first and then progress to spontaneous gastric cancer with abnormal expression of Muc5AC and Muc1. They suggest that this is caused by casp1/11, a mucosal inflammatory vesicle similar to that of the colon (15).

Dysregulation of C1GALT1 activity causes increased expression of truncated O-glycans, and such high expression of truncated O-glycan structures (e.g., Tn and sTn) are observed

in PDACs. To investigate the effect of truncated O-glycans on PDACs, Chugh *et al* (138) further established a C1GALT1 knockout mouse model based on the constructed pancreatic tumor microenvironment (Kras and p53 mutations) and observed that C1GALT1 knockout together with Kras and p53 mutations accelerated the progression of pancreatic cancer and shortened overall survival. In addition, glycosylation affects the molecular weight of the protein and the molecular weight of the highly glycosylated mucin MUC16, which is bound to the membrane in PDAC, was indicated to decrease with the loss of C1GALT1. This was accompanied by activation of the MUC16/EFGR//FAK signaling pathway, which led to increased expression of the mesenchymal markers Slug, Snail and Vimentin and decreased expression of epithelial markers such as E-cadherin and Claudin-1, increasing the metastasis of PDAC (Fig. 2) (138).

5. Clinical applications of C1GALT1

Radiotherapy is an effective route for tumor treatment but radioresistance remains a major obstacle to tumor outcomes. Several studies have indicated that altered glycosylation is associated with the acquisition of a multidrug-resistant phenotype (139-141). Of note, reports suggested that numerous patients present with abnormal glycosylation when they are resistant to radiotherapy (21,142-145). Therefore, discovering the cause of the abnormalities that cause glycosylation is essential to increase radiosensitivity. After constructing intrinsically radiation-resistant (Hep-2max) and radiation-sensitive (Hep-2min) cell lines of the parental laryngeal carcinoma Hep-2 cell line, Dong *et al* (21) determined that the intrinsically radiation-resistant cell line Hep-2max had a higher content of core-type O-glycan chains than the radiation-sensitive cell line Hep-2max. By contrast, C1GALT1 modified O-glycan chains on Hep-2max and Hep-2min cells and high expression of C1GALT1 promoted the malignant behavior of laryngeal cancer cells. Furthermore, high expression of C1GALT1 was associated with increased tumor radioresistance, while knockdown of C1GALT1 increased tumor radiosensitivity. In addition, blocking integrin β1 attenuated the radioresistance induced by high C1GALT1 expression, suggesting that C1GALT1 radioresistance to laryngeal cancer cells may be associated with integrin β1 (21). Zhang *et al* (146) indicated that C1GALT1, a key enzyme in the glycosylation process, has an important role in the radioresistance of esophageal cancer. Esophageal cancer cells exhibiting high expression of C1GALT1 evaded cell death and had increased resistance to radiotherapy. Low expression of C1GALT1 resulted in reduced resistance to radiotherapy of esophageal cancer cells (146). Radiation promotes the invasive potential of certain cancer cells (147). For instance, an increase in radiation-induced invasiveness has been observed in breast cancer (148), as well as increased invasiveness of cancer cells after radiotherapy in pancreatic cancer (149). In esophageal cancer, irradiation by X-rays elevated C1GALT1 and core O-glycan expression in esophageal cancer cells and enhanced invasion, while knockdown of C1GALT1 diminished the invasive effect of irradiation on esophageal cancer cells. Normal transduction of FAK signaling downstream of β1-integrin facilitated cell proliferation and survival and correlated with the radioresistance of cancer cells (150). In esophageal squamous carcinoma cells with C1GALT1 knockdown, the phosphorylation level of FAK was reduced. Pretreatment with a FAK inhibitor promoted radiation-induced apoptosis in esophageal squamous carcinoma cells. It was demonstrated that the anti-radiation regulation of C1GALT1 in esophageal cancer cells was achieved by affecting O-glycosylated C1GALT1 in β1-integrin, which in turn affected the β1-integrin/FAK signaling pathway (146). Itraconazole is a common antifungal drug with anticancer and antiangiogenic effects (151,152). In HNSCC, Lin *et al* (20) indicated that itraconazole was able to directly interact with C1GALT1 and promote its proteasomal degradation, resulting in reduced C1GALT1 expression in HNSCC cells but not C1GALT1 mRNA expression, suggesting that the effect of itraconazole on C1GALT1 protein levels may be achieved through posttranslational modifications. In SAS cells, itraconazole acted as a C1GALT1 inhibitor and partially reversed C1GALT1-mediated effects on malignant behavior and EFGR activity in HNSCC cells. In addition, erlotinib and lapatinib also inhibited C1GALT1-mediated tumor cell viability and malignant behavior (19,20).

6. Conclusions

C1GALT1, a key enzyme for O-glycosylation, is receiving much attention. Recent oncological research has focused on the role of C1GALT1 in tumor development. C1GALT1 is considered a biomarker and potential therapeutic target for cancer diagnosis and prediction of prognosis. The present article reviewed the currently known mechanisms of action of C1GALT1 on the malignant behavior of cancer cells and provided a theoretical basis for its potential clinical role in cancer diagnosis and prognosis determination. The dual regulatory roles of C1GALT1 in tumors may be divided into roles of oncogenesis and tumor suppression. Its role in oncogenic effects is mainly reflected in three pathways. First, miR-181d-5p and miR-152 negatively regulate C1GALT1 to exert oncogenic effects. Furthermore, deletion of C1GALT1 triggers spontaneous gastric and duodenal cancers by disrupting the major mucus barrier of the gastrointestinal tract. In addition, loss of C1GALT1 elevates truncated Tn antigen expression, contributing to higher tumorigenic and metastatic potential. By contrast, C1GALT1 achieves procancer effects by modifying the O-glycans of downstream targets. Lapatinib, erlotinib and itraconazole, as C1GALT1 inhibitors, are able to exert anticancer effects by blocking the malignant effects of C1GALT1 in cancer cells.

However, most studies currently focus only on the predictive and poor prognostic value of high C1GALT1 expression with cancer, but continued research is required to determine whether there is consistency in its mechanism of action in different tumor types. Furthermore, based on the cancer-promoting effect of low C1GALT1 expression in the constructed mouse model, is it tempting to speculate that complete deletion of the C1GALT1 gene may be harmful to tumor patients. More in-depth studies are required on the clinical significance of low C1GALT1 expression in cancer patients. With novel methods and the efforts of research scientists, the understanding of the impact of C1GALT1 expression on tumor patients will be enhanced.

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Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Authors' contributions

TXia developed the concept for the study and drafted the manuscript. HX and TXiang reviewed and edited the manuscript. TXiang performed a literature search and selection. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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