C1GALT1 in health and disease (Review)

XIAOJIE SUN1, MENGRU ZHAN2, XUN SUN3, WANQI LIU1 and XIANGWEI MENG1

Departments of 1Gastroenterology, 2Hepatobiliary and Pancreatic Medicine, and 3Pathology, The First Hospital of Jilin University, Changchun, Jilin 130021, P.R. China

Received March 18, 2021; Accepted May 18, 2021

DOI: 10.3892/ol.2021.12850

Abstract. O-linked glycosylation (O-glycosylation) and N-linked glycosylation (N-glycosylation) are the two most important forms of protein glycosylation, which is an important post-translational modification. The regulation of protein function involves numerous mechanisms, among which protein glycosylation is one of the most important. Core 1 synthase glycoprotein-N-acetylgalactosamine 3-β-galactosyltransferase 1 (C1GALT1) serves an important role in the regulation of O-glycosylation and is an essential enzyme for synthesizing the core 1 structure of mucin-type O-glycans. Furthermore, C1GALT1 serves a vital role in a number of biological functions, such as angiogenesis, platelet production and kidney development. Impaired C1GALT1 expression activity has been associated with different types of human diseases, including inflammatory or immune-mediated diseases, and cancer. O-glycosylation exists in normal tissues, as well as in tumor tissues. Previous studies have revealed that changes in the level of glycosyltransferase in different types of cancer may be used as potential therapeutic targets. Currently, numerous studies have reported the dual role of C1GALT1 in tumors (carcinogenesis and cancer suppression). The present review reports the role of C1GALT1 in normal development and human diseases. Since the mechanism and regulation of C1GALT1 and O-glycosylation remain elusive, further studies are required to elucidate their effects on development and disease.

Contents
1. Introduction
2. C1GALT1 in normal development and non-neoplastic diseases
3. C1GALT1 as an oncogene
4. C1GALT1 as a tumor suppressor
5. Cosmc and integrin β1
6. Itraconazole, an inhibitor of C1GALT1
7. Conclusion

1. Introduction

Dynamic regulatory mechanisms under a variety of physiological conditions affect the processing and maturation of proteins in mammalian cells. Glycosylation is an important type of post-translational modification. More than half of the proteins in human cells and 50-70% of serum proteins are glycosylated proteins (1). Mucin-type O-linked glycosylation (O-glycosylation) and N-linked glycosylation (N-glycosylation) are the two most important forms of glycosylation, and changes in either can lead to clinically significant pathogenesis (2-4). O-glycosylation is considered a protein modification occurring on proteins that are secreted and membrane-bound; it serves a key role in protein processing, secretion, stability, and ligand binding (5). O-glycosylation is associated with different types of biological processes, such as metabolism, translation, transcription, cytoskeletal formation, cell cycle progression and cell signal transduction (6,7). Abnormal O-glycosylation is associated with a number of human diseases, including the development of tumors (8). Tumor cells often contain numerous altered O-glycosylated proteins, which qualitatively and/or quantitatively change sugar molecule expression (9). Some O-glycosylated proteins are usually adopted as tumor biomarkers in the circulation, such as cancer antigen (CA) 19-9 and CA-125 (9).

O-glycosylation of proteins most commonly occurs in the serine and threonine residues, but it can also occur in the tyrosine, hydroxylysine and hydroxyproline residues. Glycosylation is initiated in the endoplasmic reticulum (ER) (10). However,
O-Xyl (proteoglycan) and N-acetylgalactosamine (GalNAc) type O-glycosylation (O-GalNAc) are initiated in the Golgi apparatus (10). More than 80% of cell membrane proteins and extracellular secreted proteins are O-GalNAc glycosylated proteins (11). This type of glycosylation is mediated through transferring GalNAc from UDPGalNAc to threonine or serine residues. The GalNAc aminotransferase peptide, which contains up to 20 isoenzymes, catalyzes this reaction (10,12). The protein encoded by core 1 synthase glycoprotein-GalNAc 3-β-galactosyltransferase 1 (CIGALTI) generates the common core 1 O-glycan structure, Gal-β-1-3GalNAc-R (T antigen), by the transfer of galactose (Gal) from UDP-Gal to GalNAc-α-1-R (Tn antigen) (13). The formation of complex O-glycan structures requires further modification of the T antigen (14). To date, at least eight different O-glycan core structures have been described. The core 1 type O-glycan forms the basis of O-glycosylation modification and its synthesis is mainly regulated by CIGALTI (15). The Tn antigen can form core 3 structure under the catalysis of β1,3-N-acetylglucosaminyltransferase 6. Core 1 and 3 structures are catalyzed by β1,6-N-acetylglucosaminyltransferase to form core 2 and 4, respectively (16).

There are three species of β1,6-N-acetylglucosaminyltransferases in mammals: Two of them catalyze the core 2 structure constitution, and one catalyzes the constitution of core 2 or 4 structures (17) (Fig. 1). In addition, there are several other core structures that are less common than the aforementioned ones (17).

The CIGALTI gene is located on chromosome 7p22.1-p21.3, and the protein T-synthase, encoded by the gene, has been considered to be a core mucin-type O-glycosyltransferase that resides in the Golgi apparatus (17), and is synthesized due to its particular chaperone, Cosmc, in the ER (18). Aryal et al. (18) reported that T-synthase could co-immunoprecipitate with Cosmc. Cosmc can interact with the deactivated T-synthase, partially restoring the enzyme activity in vitro, and is a specific partner of T-synthase folding and maturation (18). This enzyme adds β1,3-bonded galactose to the existing GalNAc to produce a common core O-glycan structure. Core 1 is the precursor of many cell surface mucin O-glycans and secreted glycoproteins, and is the basis for the formation of complex O-glycans, such as core 2 structure and sialylated T antigens (19). Furthermore, CIGALTI serves a vital role in numerous biological functions, including angiogenesis, platelet production and kidney development (20,21).

The expression of normal O-glycans is associated with health and homeostasis, whereas abnormal glycosylation is associated with cancer and other pathologies. Abnormal glycosylation is involved in cancer cell invasion, migration, angiogenesis, intercellular contact and epithelial-mesenchymal transition (EMT) (1,22-24). Previous studies have revealed that changes in the level of glycosyltransferase are associated with cancer (25,26). In addition, CIGALTI has been associated with the metastasis and progression of various types of cancer, such as liver and gastric cancer (27,28).

CIGALTI can act as an oncogene or a tumor suppressor gene in various types of conditions. CIGALTI high expression in liver cancer tissues is associated with advanced tumors, poor prognosis and metastasis (29). On the contrary, another study has presented CIGALTI as a tumor suppressor gene in various types of tumors (30).

Chugh et al. (30) discovered that CIGALTI expression is higher in well-differentiated pancreatic cancer tissues compared with in poorly differentiated pancreatic cancer tissues. Moreover, in cancer tissues, T antigen expression is lower compared with that of the Tn antigen (30). CIGALTI has been shown to be a tumor suppressor gene in pancreatic cancer since the absence of CIGALTI expression promotes the development and metastasis of pancreatic cancer (30). However, in another study, CIGALTI served a different role (31). Liu et al. (31) found that in CIGALTI-knockout mice, spontaneous gastroenteritis and consequently gastric antral adenocarcinoma were improved in the gastric mucosal epithelial cells, which indicates that CIGALTI-mediated O-glycosylation is very important for gastric mucosal and gastric homeostasis protection (31). However, the use of samples from different sources or at different tumor stages may have contributed to the observed dual function of CIGALTI; hence, the true role of the gene remains elusive. The present review focuses on the role of CIGALTI in health and disease.

2. CIGALTI in normal development and non-neoplastic diseases

CIGALTI in normal development. CIGALTI and glycosylation are essential for normal development, especially during angiogenesis, platelet production and kidney development (32). Impaired T-synthase activity has been associated with different types of human diseases, including inflammatory or immune-mediated diseases, and cancer (33).

Xia et al. (20) targeted deletion of the CIGALTI gene, resulting in normal development of heterozygous mice and the mating of 364 viable offspring. A total of 228 (63%) T-syn+/- progenies and 136 (37%) T-syn+/- progenies were identified by genotyping, but no T-syn/- progenies were identified (20). Whether deletion of two alleles of CIGALTI led to fetal death of 293 (E9-16) embryos was analyzed (20). Genotyping revealed the offspring of 142 (48%) T-syn+/-, 78 (27%) T-syn+/- and 73 (25%) T-syn-/- (20). T-synthase activity was decreased in T-syn+/- embryos at E12, and there was no activity in T-syn-/- embryos (20). These results confirm that all active T-synthase are encoded by CIGALTI at this stage of development. T-synthase was found to be different from the typical glycosyltransferase (34). T-syn-/- embryos in E9 developed normally, but then they gradually developed significant bleeding in the spinal cord and brain. The T-syn-/- embryos all died at E13 or E14 (20). In the T-syn-/- embryos, the only exception detected was poor angiogenesis (19,20). This phenomenon may be explained by isolation of endothelial cells from extracellular matrix and supporting pericytes (20). If mice lack growth factor B, they cannot recruit peripheral cells to the developing cerebral vessels, and bleeding will occur in late embryo or perinatal period (35). By contrast, the T-syn-/- embryo always died at E14; this means that in the process of angiogenesis, one or more endothelial proteins are inseparable from core-1-derived O-glycans (20). This possibility may be further explored by constructing an endothelial cell model of CIGALTI-targeted deletion (21).

Although O-glycans are considered to be ubiquitous in various tissues and types of cells, the expression of hematopoietic and endothelial cells is high throughout postpartum and
embryonic development (15,36,37). Fu et al (21) generated mice lacking T-synthase specifically in endothelial and hematopoietic cells (named EHC-T-syn-/- mice model). The Tn antigen can be expressed in hematopoietic, lymphatic and endothelial cells and arteries, but not in other types of cells (21). The mice developed lymphatic vessel defects and abnormal lymphatic function. Unlike mice with complete C1GALT1-knockout, EHC-T-syn-/- mice have no 'cerebral hemorrhage' and 'partial onset' embryonic lethality (21). The phenotypic difference may be due to O-glycans of other types of cells, such as nerve cells and parietal cells, which contribute to blood vessel development in nerve tissues (21). However, EHC-T-syn-/- mice exhibited high neonatal mortality, vascular system disorder and impaired lymphatic function (21). At the time of autopsy, ~75% of EHC-T-syn-/- mice exhibited extensive small intestinal bleeding, which may be one of the reasons for the lethality of EHC-T-syn-/- after birth (21). Abnormal blood vessels in the blind end of EHC-T-syn-/- mice exhibited abnormal function/development of lymphatic vessels, constituting abnormal links between lymphatic vessels and blood (21). These hyperemic lymphatic vessels are found in mice that lack fasting-induced adipokines and have defects in the signaling proteins SLP-76 and SYK (38). These observations suggest that constant O-glycoprotein expression is required for the maintenance of lymphatic vessels, angiogenesis and the separation of blood and lymphatic vessels during development.

In addition, C1GALT1 is very important in the formation of the follicular basal layer (FBL) and the follicular environment. The basement membrane provides structural and selective filters for molecules. The environment is regulated by the FBL in the follicle at the time of development (39). It has been demonstrated that the oocyte is important in producing FBL (40). Mice with C1GALT1 oocyte-specific deletion do not synthesize main 1β1,3-galactosyltransferase 1 (named T-synthase as well), and thus are not able to constitute main 1 derived O-glycan (41). Therefore, the FBL changes the distribution of laminin and collagen (39) and causes the follicles to combine to form multiple follicles, with two or more oocytes in a follicle. Therefore, C1GALT1 expression serves a part in keeping the normal structure of FBL and the follicular environment.

Additionally, a series of experiments have revealed that C1GALT1 is very important for platelet production and renal homeostasis. Kudo et al (42) conditionally knocked out
CIGALT1 and constructed ‘Mx1-C1’ mice, so that the deletion of the CIGALT1 gene was limited to bone marrow cells. Mx1-C1 mice exhibited severe thrombocytopenia. The hematological parameters indicated a marked decrease in platelet count. However, white and red blood cell counts, as well as the levels of hemoglobin, were normal. Notably, giant platelets were in the peripheral blood smear, while the morphology of other cells was normal. Compared with the platelets of wild-type (WT) mice, those of Mx1C1 mice were larger. Tail bleeding time measurement indicated that bleeding in WT mice was prevented 6 min after cutting the tail, while bleeding time in Mx1-C1 mice was markedly prolonged (>10 min), indicating that CIGALT1 expression is important for hemostasis and platelet production (42).

In plt1 mice constructed by Alexander et al (32), T-synthase showed residual enzyme activity, and through a series of experiments, it was revealed that CIGALT1 had a very important role in platelet production and renal homeostasis. Alexander et al (32) treated C57BL/6 mice with N-Ethyl-n nitrosourea (ENU) and produced generation III (G3). In lineage 76, multiple mice exhibited lower platelet counts, consistent with the isolation of ENU-induced mutations that cause thrombocytopenia. Lineage 76 with recessive mutation was called plt1 (32). plt1/plt1 mice had 40% of the platelet count of WT mice, and all major organs were histologically normal except the kidneys, which exhibited structural distortion of the glomerulus-renal tubules (32). The levels of creatinine, blood urea and urinary protein in plt1/plt1 mice were higher compared with those in WT mice. The kidneys exhibited inflammatory infiltration, ductal stenosis, glomerular loss and cortical atrophy. From the 10th week, plt1/plt1 mice began to get sick, and by day 200, 90% of the mice had died (32). It was demonstrated that the activity of T-synthase in plt1/plt1 mice was <5% of that in WT mice. Plt1 mutation could lead to severe but incomplete loss of T-synthase activity (32).

Decrease of T-synthase activity can lead to exposure to the Tn antigen. The Tn antigen could not be detected in WT mice, but could be detected in plt1 mice. plt1/plt1 mice died of a severe kidney disease accompanied by massive proteinuria and glomerulonephritis (32). Podocalyxin, which develops from podocytes of the kidney, has been discovered to be a core TN protein in the kidney (43). Mice with low levels of podocalyxin shortly died after birth from anuria and renal dysplasia, consistent with the anti-adhesion effects of podocalyxin on the podocyte surface for ensuring that the filtration gap is obstructed (44). Plt1/plt1 mice can produce urine, which proves that low glycosylated podocalyxin can maintain part of renal function. However, kidney disease in mice indicates that podocalyxin glycosylation mediated by T-synthase is crucial for the maintenance of normal renal function and structure (32). These results suggest that some pathological changes in the kidney may be associated with a decrease of T-synthase activity, which does not depend on the influence of intrinsic defects and immune factors. In addition to kidney diseases, further attention should be given to IgA nephropathy (IgAN).

IgAN. The decreased activity of T-synthase has a close association with human diseases, the most notable being IgAN (an ordinary important glomerulonephritis). IgAN has been considered to be the most common reason of renal failure and glomerulonephritis globally, and it is an immune-mediated disease characterized by abnormal glycosylation (45). IgAN accounts for 37-58% of biopsy-confirmed primary glomerulonephritis in China (46-48). Within 10 years after diagnosis, approximately one-third of patients with IgAN will progress to the final stage of kidney disease (49,50). Two case-control studies have discovered that Chinese population susceptibility and CIGALT1 gene polymorphism are associated with the IgAN variations of the CIGALT1 gene; in particular, the haplotypes YATIG, YAGDA and YATDG were associated with the susceptibility to IgAN (51,52). Abnormal O-glycosylation of IgA1 has been identified in IgAN, which was an important breakthrough in the study of its pathogenesis (53). IgA1 glycosylation defects result in elevated galactose-deficient IgA1 (Gd-IgA1) and immunocomplex, and are associated with IgAN development (53).

There is evidence that the Gd-IgA1 level is heritable (54,55). Using a genome-wide approach, Gale et al (56) identified common genetic factors that influence Gd-IgA1 levels in East Asian and Caucasian populations. Gale et al (56) studied hundreds of patients with IgAN from the UK and China, revealing that CIGALT1 is an important genetic determinant of Gd-IgA1 level, which is an independent risk factor for progressive IgAN. Compared with that in ethnicity-matched healthy subjects, the Gd-IgA1 level is increased in patients with IgAN and is associated with disease severity (56). Chinese patients with IgAN have lower levels of Gd-IgA1 than Caucasian patients (56). This suggests that there may be ethnic differences in the pathogenic importance of IgA1 O-glycosylation changes.

Kiryuk et al (57) used in vitro small interfering (si)RNA knockdown to demonstrate that CIGALT1 can determine the secretion rate of Gd-IgA1 in serum IgA1-producing cells. Xing et al (58) discovered that CIGALT1 expression in peripheral B lymphocytes of patients with IgAN has a negative correlation with increased Gd-IgA1 levels and is markedly downregulated compared with the increase of Gd-IgA1 level. The aforementioned study involved 30 patients with IgAN and 30 healthy volunteers in China (58). Gd-IgA1 level was measured by an enzyme-linked immunosorbent assay, and the results revealed that Gd-IgA1 levels ranged between 8.55 and 14.8 U/ml in patients with IgAN and between 3.97 and 12.15 U/ml in healthy controls (58). In comparison with those in healthy controls, Gd-IgA1 levels were determined to be significantly higher in patients with IgAN (P<0.001) (58). By reverse transcription-quantitative PCR, the expression levels of CIGALT1 were detected in peripheral B lymphocytes of both patients with IgAN and healthy controls, revealing that CIGALT1 expression was significantly downregulated in patients with IgAN compared with that in healthy controls (P=0.04) (58). It has been suggested that a decrease in CIGALT1 expression in B lymphocytes may contribute to the increased production of Gd-IgA1 and eventually lead to IgAN pathogenesis (59). One difficulty in exploring the role of CIGALT1 in IgAN is that only a small proportion of plasma cells secrete IgA1, which is associated with the disease. The identification and isolation of these plasma cells are difficult, but it is important for elucidating the role of CIGALT1 in IgAN. Studying the real cause of the lack of CIGALT1 expression may illustrate the pathogenesis of IgAN and contribute to finding new treatments for the disease.
**Tn syndrome.** In addition to IgAN, another disease that is closely associated with decreased T-synthase activity is Tn syndrome. Tn syndrome is an infrequent blood disorder characterized by exposure of the Tn antigen on the surface of human red blood cells, granulocytes, platelets and lymphocytes (60). Patients can present as asymptomatic, or can exhibit mild hemolysis, thrombocytopenia and/or leukopenia, which are usually considered to be caused by the reaction of Tn antigens with naturally occurring anti-Tn antibodies (61). These antibodies may be IgM condensation agglutinin-type and appear to be autoantibodies against carbohydrate I antigens on adult red blood cells (62). Another possible pathological mechanism is the abnormal function of glycoproteins on leukocytes or platelets. Since glycoproteins have an important role in the function of these cells, changes in glycosylation may impair the function of glycoproteins (62).

The expression of Tn antigen and T-synthase activity loss is the result of Cosmc mutation, which has been widely confirmed (36,63-66). A study by Vainchenker et al (60) has demonstrated the existence of the Tn antigen on stem cells of the Tn clone, and Tn syndrome is derived from acquired somatic changes in Cosmc in the early blood progenitor cells. Wang et al (67) constructed a mouse model with a targeted deletion of Cosmc in hematopoietic cells/endothelial cells (EHC Cosmc<sup>-/-</sup>), which caused fatal perinatal bleeding in ~90% of mice. The surviving mice developed macrothrombocytopenia and severely prolonged caudal bleeding time (67). Compared with those in wild-type (Cosmc<sup>+/+</sup>) mice, platelets in EHC Cosmc<sup>-/-</sup> mice were lacking T-synthase activity. The decrease in T-synthase activity was associated with the expression of the Tn antigens on the surfaces of most platelets from EHC Cosmc<sup>-/-</sup> mice (67). These experiments convincingly suggest that thrombocytopenia and hemorrhage in patients with Tn syndrome are primarily caused by the lack of functional Cosmc.

High expression of Tn antigen is associated with Tn syndrome, as well as with cancer (68). According to statistics, >70% of human cancers may express Tn antigen, including colon (69), breast, ovarian and uterine cervical epithelial cancer (70-72). The expression of Tn antigen is closely associated with a poor prognosis, and it is an attractive target for the development of new diagnostic and therapeutic methods (70).

**Inflammatory bowel disease.** Inflammatory bowel disease (IBD), consisting of ulcerative colitis (UC) and Crohn's disease (CD), is a chronic inflammatory disease. Although the exact cause of IBD remains unclear, it is generally believed to be jointly caused by environmental factors and genetic susceptibility. At the same time, intestinal microorganisms serve an important role in the occurrence and development of IBD (73).

The colonic mucus layer is divided into two layers. The inner layer adheres to epithelial cells, and in healthy conditions it is impermeable to bacteria. The primary mucin (MUC) secreted by colon cells is MUC2, which is generally O-glycosylated (74) (Fig. 2). Active human UC is associated with a mucus layer with structural and functional defects, such as a thinner mucus layer and increased permeability to bacteria (75,76). Studies have reported that patients with active UC have lower levels of carbohydrates in their mucus layer compared with those in healthy controls and patients with dormant disease (77-79). Defects in the inner mucus layer can result in increased bacterial association with epithelial cells, which may trigger inflammation (80). In serum, reduced galactosylation of IgG is considered a diagnostic marker for IBD disease (80). The function of suitable mucin glycosylation is also proven by the fact that mice defective in core Iergediv Glycans have poor glycosylated MUC2 and develop spontaneous colitis resembling UC (75).

Fu et al (75) established a mouse model of colitis evoked by intestinal epithelial cells lacking CIGALT1. The clinical manifestations and pathological features are very similar to those observed in humans (75). The mice developed transient colitis immediately at 3 weeks of age, which subsided at 6 weeks, but relapsed at 8 weeks; the severity of the disease could be reduced by broad-spectrum antibiotic treatment in mice with metronidazole and vancomycin (75). Additionally, the mice exhibited colon tumors when they were older. Immunohistochemistry and histology proved that these tumors were invasive adenocarcinoma, and the tumor tissue expressed abundant Tn antigen (75). The association between genetic variations in CIGALT1 and the microbiota in hundreds of patients with CD and healthy controls has also been studied (81). Polymorphisms around CIGALT1 (rs10486157) and COMSC (rs4825729) have been associated with changes in the composition of the microbiota of the colonic mucosa (81). These results support the association between CIGALT1 or O-glycosylation and host regulation of the microbiome and suggest a role for the intestinal microbiome in the pathogenesis of IBD. Improvements in understanding the molecular etiology of IBD, especially pathways involving glycans, may facilitate the development of therapeutic drugs.

The high embryonic lethality exhibited by CIGALT1-knockout mice prevents the development of an effective CIGALT1 deficiency animal model. Simultaneously, it also demonstrates that CIGALT1 and O-glycosylation are vital in normal development. One study has demonstrated that numerous membrane glycoproteins expressing Tn antigen and/or truncated O-glycans may be dysfunctional due to degradation and/or folding errors (82). Therefore, the expression of normal O-glycans is associated with health and homeostasis, while the truncation of O-glycans and Tn antigens is associated with pathologies. The association between the role of
CIGALT1 in angiogenesis, platelet production and kidneys, and the pathways it may regulate requires further research.

3. CIGALT1 as an oncogene

CIGALT1 functions as an oncogene in some cases. The role of the gene in tumor cells and its association with different types of related signaling pathways and molecules have been shown in previous research.

Liver cancer. It is known that O-glycosylation can regulate receptor tyrosine kinases (RTKs), such as fibroblast growth factor receptor 2, MET and epidermal growth factor receptor (EGFR) (27,83-86). Changes in RTK activities are associated with cancer progression and occurrence (27). The hepatocyte growth factor (HGF)/c-Met signaling pathway is important in tumor invasion and metastasis (87). The HGF/c-Met axis is involved in cell proliferation, movement, differentiation, invasion, angiogenesis and apoptosis via activation of multiple downstream signaling pathways (87-89). CIGALT1 can activate the HGF/c-Met signaling pathway and increase mucin O-glycan expression in liver cancer cells, which promotes the proliferation of cells (27). High protein and mRNA expression levels of CIGALT1 are usually associated with a poor prognosis and metastasis in hepatocellular carcinoma tumors (27). Overexpression of CIGALT1 in hepatocellular carcinoma activates the HGF signaling pathway through the regulation of dimerization and O-glycosylation level of the MET protein (27). Additionally, CIGALT1 expression can regulate the proliferation and viability of hepatoma cells both in vivo and in vitro (27).

Wu et al (27) reported that CIGALT1 enhanced cell proliferation triggered by HGF through MET. The aforementioned study revealed that CIGALT1 expression was upregulated in hepatocellular carcinoma. According to the immunohistochemical analysis of 32 non-tumor liver tissues and 72 primary hepatocellular carcinoma tissue specimens, CIGALT1 expression was upregulated in 54% of hepatocellular carcinoma tissues, but only in 19% of non-neoplastic liver tissues (Mann-Whitney U test, P=0.002) (27). Compared with non-tumor liver tissues, CIGALT1 expression was frequently upregulated in hepatocellular carcinoma tumors. High CIGALT1 expression was associated with poor prognosis and tumor metastasis (27). Moreover, the study revealed an important correlation between the expression levels of phospho-MET and CIGALT1 (R=0.73, P<0.0001) (27). Additionally, MET dimerization and phosphorylation were decreased by knocking out CIGALT1 in hepatocellular carcinoma cells, and MET HGF-induced activation was enhanced by CIGALT1 overexpression (27). The trypan blue rejection test revealed that CIGALT1-enhanced cell viability was significantly inhibited by blocked MET activity (27). The proliferation of the cells was decreased by knocking out CIGALT1 through HGF (27). On the contrary, the HGF-induced cell proliferation was enhanced by CIGALT1 overexpression (27). Therefore, the aforementioned study offers new insights into glycosylation in the regulation of RTK activities.

Gastric cancer. According to preclinical patterns of gastric cancer, activation of the HGF/c-Met signaling pathway is able to improve EMT (27,90); nevertheless, further studies are required to determine whether CIGALT1 can promote tumor malignancy or activate the HGF/c-Met signaling pathway in gastric cancer cells. One study has revealed that changes in RTK genome have been observed in ~37% of patients with gastric cancer (91). The occurrence and development of gastric cancer is promoted actively by RTK, which is considered as a target for cancer treatment (92,93).

The ephrin (EPH) receptor is the largest of the RTK family and is usually upregulating in tumors, which promotes tumor development (94-97). These receptors are popular drug targets (98,99). The human EPH receptor consists of a neighboring EPHA and five EPHB domains. Ephrin A1 is a ligand of the EPHA receptor and has been shown to be upregulated in gastric cancer, promoting EMT (100,101). Lee et al (28) observed that CIGALT1 expression increased in gastric adenocarcinoma and was associated with a poor prognosis. Soluble ephrin A1-mediated cell migration is promoted by CIGALT1 through the activation of EPHA2 in gastric cancer. Immunohistochemical staining of 25 cases of gastric adenocarcinoma revealed that CIGALT1 protein expression was higher in 80% of the gastric adenocarcinoma tissues than in matched non-tumor gastric tissues, and the low expression levels of CIGALT1 protein were observed in only 4% of the cases (28). In addition to lymph node metastasis and tumor invasion, high CIGALT1 expression is often associated with higher histological grade and advanced cancer stage (stage III and IV), and it is an independent prognostic factor of poor survival (28). CIGALT1 silencing inhibits gastric cancer cell invasion, migration and viability (MKN45 and AGS cells), as well as metastasis and tumor growth (28). CIGALT1-knockdown in AGS cells affects multiple functional pathways. Silencing CIGALT1 decreases phosphorylation and O-glycation levels of HER2 and EGFR, as well as inhibiting gastric cancer cell migration (28). Although other pathways are also involved, the viability of cells may be promoted by CIGALT1 at least in part through the activation of HER2 and EGFR.

Prostate cancer. There is increasing evidence that galectins may interact with abnormal glycosylation and may be associated with cancer progression. Galectin-4 expression is consistently lower in patients with primary prostate cancer compared with in patients with lethal metastatic prostate cancer (102). Galectin-4 activates HER2, EGFR, IGF1 and HER3 receptors in a carbohydrate-dependent manner (102). Tsai et al (102) discovered that CIGALT1 expression in primary tumors is lower than that in castration-resistant prostate cancer. In metastatic prostate cancer samples, it was demonstrated by immunohistochemical analysis that CIGALT1 was highly expressed in 70% of the samples, and this high expression was closely associated with advanced tumor stage (102). During prostate cancer progression, CIGALT1 expression is increased and castration resistance is promoted. Notably, metastatic prostate cancer cell lines exhibit high CIGALT1 gene and protein expression levels (102). The aforementioned findings indicate that there is a close association between tumor malignancy transformation and the change of protein O-glycosylation and castration resistance. Tumor metastasis may be promoted through interaction with lectin in prostate cancer. Therefore,
the significance of O-glycosylation in tumor diagnosis and treatment required to be further explored.

_Esophageal cancer._ MUC1 is a type 1 transmembrane mucin, consisting of two subunits, MUC1-N and MUC1-C. High MUC1 expression is associated with a poor prognosis and tumor progression in different types of cancer, making it an oncoprotein (103-106). MUC1 can regulate the WNT signaling pathway by forming intracellular complexes with β-catenin, which in turn can co-activate the expression of cyclin-D1 in the nucleus, ultimately promoting tumorigenesis by allowing cancer cells to avoid apoptotic pathways (107). MUC1 is greatly expressed in esophageal squamous cell carcinoma (ESCC) and ESCC cell migration and invasion can be inhibited by silencing MUC1.

Wang _et al_ (108) analyzed MUC1 expression through a large-scale database. MUC1 gene copy number in 102 ESCC tumor samples among 132 ESCC samples was greatly lower than that in 30 cases of adjacent esophageal squamous epithelium. Wang _et al_ (108) also analyzed _CIGALT1_ expression through the large-scale ONCOMINE database. The average gene copy number of _CIGALT1_ in 30 ESCC samples was higher than that in 102 normal esophageal epithelia (108). These data indicate that both MUC1 and _CIGALT1_ are abundantly expressed in ESCC. In addition, 7 of the 10 pairs of ESCC samples with high MUC1 O-glycosylation had significantly higher expression levels of _CIGALT1_ than normal tissues, indicating that _CIGALT1_ was positively associated with MUC1 O-glycosylation in ESCC (108). MUC1 O-glycosylation/CIGALT1 expression in ESCC without lymph node metastasis was greatly lower in ESCC with lymph node metastasis, and there was a negative association between survival and MUC1 O-glycosylation/CIGALT1 co-expression (108). The aforementioned results suggest that it is possible for MUC1 O-glycosylation/CIGALT1 to be prognostic elements and have diagnostic significance in ESCC, which proposes new insights for targeting MUC1 O-glycosylation and _CIGALT1_ for inhibiting ESCC metastasis.

Zhang _et al_ (51) demonstrated the role of _CIGALT1_ expression in the development of radioresistant esophageal cancer. _CIGALT1_ protein expression in esophageal cancer tissues was higher than that in adjacent normal tissues. Poor prognosis, lymph node metastasis and TNM staging were associated with upregulation of _CIGALT1_ expression. In addition, high levels of _CIGALT1_ increased the resistance of esophageal cancer cells to radiation therapy (51). Similarly, Dong _et al_ (109) demonstrated that _CIGALT1_ could enhance radiation resistance and malignant phenotype of laryngeal cancer cells. Thus, _CIGALT1_ is very important in carcinogenic resistance to radiotherapy.

_Chalangiocarcinoma._ _CIGALT1_ serves a role in the development of cholangiocarcinoma. Cholangiocarcinoma tissues have higher _CIGALT1_ expression than normal bile ducts (110). Additionally, elevated _CIGALT1_ expression in cancer tissues is associated with advanced cell grade, larger tumor size and tumor stage (110). The inhibition of _CIGALT1_ can significantly inhibit the viability, migration and invasion of cholangiocarcinoma cells, whereas overexpression of _CIGALT1_ can promote these abilities (111). This indicates that _CIGALT1_ is critical for cancer progression in cholangiocarcinoma.

_Head and neck cancer._ _CIGALT1_ expression is upregulated in head and neck squamous cell carcinoma (HNSCC), and high _CIGALT1_ expression is associated with poor clinicopathological characteristics. In addition, _CIGALT1_ can modify the O-glycans on the EGFR. Previous studies have revealed that O-glycan modification can influence the behavior of cancer cells and their signal transduction pathway (27,83,85,112). Phosphorylation RTK array assay in HNSCC indicated that the phosphorylation of MET and EGFR is mostly decreased by _CIGALT1_ knockout or knockdown (13). The EGFR signaling pathway is important in the invasion and survival of tumor cells in HNSCC (113). Lin _et al_ (13) provided evidence via mass spectrometry that EGFR has GalNAc type O-glycans, indicating that _CIGALT1_ can modify EGFR. Subsequently, SAS cells overexpressing _CIGALT1_ were constructed. The EGF-induced EGFR phosphorylation at Y1068 was improved by _CIGALT1_ overexpression, and HNSCC cell invasion, migration and activity was also improved (13). EGF-EGFR binding affinity was decreased by the knockout of _CIGALT1_ in SAS cells, and the EGFR signaling pathway was inhibited. Additionally, the invasion, migration and viability of SAS cells treated with erlotinib, an EGFR tyrosine kinase inhibitor, were reversed (13). The aforementioned results indicated that _CIGALT1_ may change the glycosylation of EGFR. In HNSCC cells, _CIGALT1_ enhances the binding affinity to the EGF ligand, as well as phosphorylation of EGFR, increasing the malignant phenotype.

_Ovarian cancer._ Immature truncated O-glycans have usually been detected in the ovarian cancer cells of human beings, and evidence indicates that these changes in glycosylation expression can contribute to various types of cancer, including colon and ovarian cancer, which usually express short O-glycans (114,115).

Chou _et al_ (116) evaluated the prognostic value of _CIGALT1_ expression through analysis of patients with ovarian cancer in a public database, generating survival curves of each patient. In all patients with ovarian cancer followed for 20 years, a low overall survival rate was associated with high _CIGALT1_ expression (hazard ratio, 1.19; 95% CI, 1.04-1.37; P=0.014) (116). These results indicate that targeting _CIGALT1_ may be a promising strategy for ovarian cancer (116). Further research on _CIGALT1_ is essential for an improved understanding of the occurrence of ovarian cancer.

Overall, the aforementioned findings indicate that _CIGALT1_ promotes tumor development. However, in other cases, _CIGALT1_ may also have a tumor-suppressing effect.

4. _CIGALT1_ as a tumor suppressor

In the aforementioned types of tumor, _CIGALT1_ expression is usually upregulated during tumorigenesis. However, the expression levels of _CIGALT1_ in colorectal and pancreatic cancer are different from the aforementioned types of tumor.

_Pancreatic cancer._ The loss of _CIGALT1_ in mice caused increased truncated O-glycan expression, which caused the
metastasis of pancreatic ductal adenocarcinoma (PDAC) (30). Genetically engineered KPC and KPCC mice models were created by breeding KrasG12D;Pdx1-Cre and LSLTrp53R172H/+ with C1galt1<ins>/Foxn<ins>P</ins> (30). The KPC pattern was adopted to create pancreas-specific CIGALTI deletion (KPC mice) and monitor pancreatic tumor progression and growth in these mice (30). The survival time of KPC mice (median, 102 days) was longer compared with that of KPC mice (median, 200 days), and KPC mice developed early pancreatic intraepithelial neoplasia at 3 weeks, PDAC at 5 weeks and metastases at 10 weeks compared with KPC mice (30). Moreover, metastases to distant organs in KPC mice were observed after 20 weeks (30). Compared with other PDAC animal patterns, KPCC is considered to be the predominant PDAC mouse pattern to present primary metastasis (117,118). Compared with KPC mice, pancreatic tumors in KPCC mice have been considered to be more metastatic and aggressive, and Tn production is increased, while the number of stromata is decreased (30). Pathological analysis of tumor tissues has shown that most KPCC tumors are poorly differentiated or undifferentiated, while most KPC animals have moderate to highly differentiated tumors (30). It is worth noting that when CIGALTI is conditionally inactivated without the background of carcinogenic mutations, the pancreas appears normal (30). This indicates that loss of CIGALTI alone does not lead to the formation of PDAC. Loss of CIGALTI is associated with p53 and KRAS mutations leading to faster progression of PDAC (30).

According to experiments performed in cell lines, human PDAC cells with CIGALTI gene knockout have greatly developed MUC16 abnormal glycosylation, tumorigenicity and invasion, proliferation and increased expression of Tn carbohydrate antigen compared with a control group (PDAC cells without CIGALTI-knockout) (30). Growth factor receptor activation, such as HER2 and EGFR, as well as activation of downstream effectors, such as Akt and focal adhesion kinase (FAK) proteins, is promoted, and MUC16 activates metastasis signals and interacts with FAK (119). PDAC cell migration is induced by the activated signals of Akt and FAK, which may possibly explain the increased migration of CIGALTI-knockout cells (30). It is necessary to conduct further research on this topic in the future.

Colorectal cancer (CRC). The expression of Tn antigen is associated with various types of cancer metastasis and progression (120). For example, immature truncated O-glycans (like the Tn antigen) can usually be detected in human CRC (121). Bergstrom et al (122) argued that there was no association between cancer progression and Tn antigen by adopting a CRC murine pattern. Instead, intestinal inflammation has been shown to lead to eventual tumorigenesis rather than abnormal O-glycosylation (122). Mice lacking core 1-derived O-glycans (IECC1ga1t1−/−) developed spontaneous colitis. Between 18 and 24 months, ~90% of mice developed colon tumors, with an average of 3 tumors, of various sizes (122). In vivo analysis revealed that Tn exposure itself did not significantly promote colon inflammation and tumorigenesis. Thus, the incidence of carcinogenesis in patients who have UC may be decreased by core inflammatory pathway inhibition. Nevertheless, Dong et al (123) indicated that forced knockout of CIGALTI in HCT116 cells significantly induced Tn antigen expression and contributed to metastasis and progression of CRC. It seems that Tn antigen can be adopted as an underlying target of therapeutic intervention (124,125). T-synthase deficiency in CRC cells may lead to the activation of the EMT signaling pathway. EMT is important in cancer progression (126,127). Knockout of CIGALTI in HCT116 cells can greatly enhance the adhesion and proliferation of cells and induce Tn antigen expression (123). Moreover, E-cadherin (a typical epithelial marker) was markedly decreased in CIGALTI-knockout HCT 116 cells, accompanied by an enhanced expression of mesenchymal markers including snail and fibronectin (123). These observations indicate that T-synthase deficiency can induce abnormal O-glycosylation in cells, subsequently promoting carcinogenesis by activating the EMT process (123).

The aforementioned studies reported the dual role of CIGALTI in cancer (carcinogenesis and cancer suppression), and the association between this gene and several molecules and signaling pathways has been explored. This may provide new therapeutic strategies for cancer treatment. Table I shows the role of CIGALTI in different types of cancer.

5. Cosmc and integrin β1

Cosmc is the molecular partner of T-synthase, helping T-synthetase to fold correctly in the ER (128). This chaperone is encoded by Cosmc in the X chromosome (human Xq24, mouse Xc3). Cosmc is located in the ER. The newly synthesized T-synthase needs Cosmc to avoid incorrect folding, aggregation and degradation. Human Cosmc is a type II transmembrane protein with 318 amino acids (36). It has a short N-terminal domain, a transmembrane domain and a large C-terminal domain in the cytoplasm, which can independently act as a molecular chaperone for T-synthase (36). Cosmc protein itself does not possess galactosyltransferase activity. However, the expression of functional T-synthase must be accompanied by the presence of Cosmc (129). There is 26% homology in amino acid sequence between human T-synthase and human Cosmc, indicating that they are from the same ancestor (36,129). In humans, Cosmc and T-synthase are universally expressed and work cooperatively, but their expression levels vary by tissue or cell type (15,130). Zeng et al (131) reported that the promoter structures of Cosmc and T-synthase are similar. The CPG islands in the 5′ flanking regions of human Cosmc and T-synthase are gene promoters, and they each contain two SP1/3 binding sites (131). Chromatin immunoprecipitation analysis and site-directed mutagenesis analysis of any SP1/3 site confirmed the important role of the SP1/3 sequence in regulating these two genes (131). In patients with Tn syndrome lacking functional Cosmc, T-synthase activity is completely absent, indicating that Cosmc is an important partner in the formation of active T-synthase (131). Upon lack of functional Cosmc, T-synthase will be reversely transported from the ER back to the cytoplasm, ubiquitinated and degraded in a 26S proteasome-dependent manner (131).

Lack of Cosmc is fatal to mice embryos (37,132). Knockout of Cosmc or T-synthase in mice causes the expression of Tn antigen and embryonic lethality (20,132). Wang et al (132) found that mice with obvious absence of Cosmc have lung and gastrointestinal bleeding, chylous ascites and growth retardation, and this state is similar to the conditional T-synthase
deletion in hematopoietic cells and endothelial cells observed in mice. These findings indicate that the lack of O-glycans in endothelial cells can lead to misconnection of blood/lymphatic vessels, and that T-synthase and its molecular chaperone Cosmc are both necessary for the proper development of blood vessels (21).

Table I. Role of C1GALT1 in different types of cancer.

| First author, year | Cell lines | Model | Effects | Expression in cancer | Type of cancer | (Refs.) |
|--------------------|------------|-------|---------|----------------------|----------------|--------|
| Wang et al, 2020   | HA22T, PLC5| In vitro, in vivo, human tissue | Regulation of the O-glycosylation level of the MET protein activates the HGF signaling pathway | Upregulation | Hepatocellular carcinoma | (87) |
| Zhang et al, 2018  | ECa109     | In vitro, in vivo, human tissue | Radiation resistance is inhibited by glycosylation of the modifier β1 integrin | Upregulation | Esophageal cancer | (51) |
| Lee et al, 2020    | AGS        | In vitro, in vivo, human tissue | Activation of EPHA2-promoted cell migration mediated by soluble Ephrin A1 | Upregulation | Gastric cancer | (28) |
| Huang et al, 2015  | HUCCT1     | In vitro, human tissue | C1GALT1-knockout inhibits the malignant behavior of bile duct cancer cells | Upregulation | Cholangiocarcinoma | (111) |
| Lin et al, 2018    | OEC-M1, FaDu| In vitro, in vivo, human tissue | C1GALT1-knockdown blocks O-glycan extension on EGFR and inhibits EGFR signal transduction | Upregulation | Head and neck squamous cell carcinoma | (13) |
| Chou et al, 2017   | ES-2       | In vitro, human tissue | Regulates the expression of multiple genes associated with tumor stem cells in ovarian cancer cells | Upregulation | Ovarian cancer | (116) |
| Chugh et al, 2018  | T3M4       | In vitro, in vivo, human tissue | C1GALT1-knockdown promotes the occurrence and metastasis of pancreatic adenocarcinoma | Downregulation | Pancreatic ductal adenocarcinoma | (30) |

C1GALT1, core 1 synthase glycoprotein-N-acetylgalactosamine 3-β-galactosyltransferase 1; EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; EPH, ephrin.
Acquired mutations in Cosmc are associated with a number of diseases, such as IgA nephropathy and Tn syndrome. Some of the Cosmc gene has genetic deletion in invasive human melanoma LOX cells, while point mutations exist in other cell lines, causing Cosmc inactivation and elevating Tn antigen expression (64). For example, human cervical cancer cells exhibit Cosmc deletion (65). In pancreatic cancer, epigenetic silencing by Cosmc promoter methylation leads to inactivation of T-synthase, accompanied by abnormal O-glycosylation (133). Additionally, Cosmc point mutations are found in several epithelial samples of patients with UC (75), but it is unclear if this is associated with an increased risk of colon cancer.

Cosmc is required for the functional expression of T-synthase. The expression of Tn antigen and T-synthase activity loss is a result of human Cosmc loss, which is associated with several diseases (60,61,63,66,134-136), such as Tn syndrome (61), IgAN (137) and human tumor (68). Thus, although these outcomes do not elucidate the Cosmc chaperone impact, the role of Cosmc in O-glycosylation seems to specifically rely on T-synthase. The proper function of T-synthase requires the molecular chaperone Cosmc, and the integrin β1 subunit may be involved in mediating these functions.

CIGALTI can regulate the activity and glycosylation of integrin β1 (29). Integrin β1 belongs to the integrin family, which consists of transmembrane proteins. It can transduce changes in the extracellular mechanical state and chemical environment of the cell, which can lead to cytoskeletal changes. It participates in a wide range of functional activities, such as cell proliferation, invasion, adhesion and inflammation (138). According to previous studies, there is a close association between integrin β1 and improvement in therapeutic drug resistance in different hematopoietic malignancies and solid tumors, and drug resistance of tumors is mediated by integrin β1 at the cellular level (139,140). A study has indicated that blocking integrin β1 inhibits breast cancer cell proliferation and induces apoptosis (141). Integrin β1 has a close association with TNM grade and tumor size in liver cancer (142). High expression levels of integrin β1 are associated with worse survival in patients with liver cancer (143). Moreover, a previous study has indicated that CIGALTI induces hepatocellular carcinoma cell adhesion to extracellular stroma proteins via integrin β1, as well as inducing cancer cell migration and invasion (29). CIGALTI regulates integrin β1 activity as well as its downstream signaling through the modification of the O-glycan on integrin β1 (29,144). The interaction between MET and integrin in the regulation of development, immunity and invasion of cancer cells has been previously reported (145-147). Since HGF-triggered cell proliferation is enhanced by CIGALTI via MET, it is a reasonable assumption that the signaling pathways of MET and integrin β1 promote CIGALTI-mediated HCC malignancies synergistically. These findings further prove that mucin-type O-glycosylation is important in regulating cancer malignancies, indicating that CIGALTI may be a promising therapeutic candidate.

Targeting integrin β1 with inhibitory antibodies can increase the sensitivity of hepatocellular carcinoma cells to radiation (148). Moreover, the inhibition of integrin β1 using antibodies or siRNAs causes dose-dependent radiation sensitization of head and neck cancer cells (149). The down-regulation of integrin β1 in laryngeal carcinoma can inhibit glycosylation-mediated radiation resistance (123). In esophageal cancer, CIGALTI can regulate the signaling pathway of the downstream FAK and modify the O-glycan structure on integrin β1 (51). Moreover, in esophageal cancer cells, integrin β1 blocking antibodies and FAK inhibitors can enhance radiation-induced apoptosis (51).

In conclusion, the aforementioned results indicate that CIGALTI and integrin β1 signaling pathways can synergistically promote intrinsic radiation resistance mediated by glycosylation, although the detailed mechanism of this phenomenon remains elusive.

6. Itraconazole, an inhibitor of CIGALTI

Itraconazole is a common antifungal drug with anticancer effects. Itraconazole has been beneficial in patients with ovarian cancer, recurrent non-small cell lung cancer, prostate cancer and other types of cancer, either as a single drug or in combination therapy in clinical trials (150-153). Lin et al (13) proposed itraconazole as a new important CIGALTI inhibitor in head and neck cancer. Lin et al (13) screened the ZINC database for compounds that could bind to the CIGALTI protein. A total of seven drugs were found not to be standard anticancer treatments and had fewer side effects. Only itraconazole significantly increased the expression of Tn antigens on several cell surfaces (13). At the same time, itraconazole significantly decreased the protein expression levels of CIGALTI, while mRNA expression was not significantly affected, suggesting that itraconazole may affect the protein level of CIGALTI through post-translational modification (13). In general, CIGALTI protein folding errors are transported to the proteasome and then degraded (154). The proteasome degradation pathway involves ubiquitination, and itraconazole increases ubiquitinated CIGALTI. The results of the cell thermal displacement analysis revealed that when using itraconazole to treat SAS and OEC-M1 cells, the melting temperature of CIGALTI decreased, and itraconazole decreased the protein expression levels of CIGALTI in a dose-dependent manner at a constant melting temperature (13). Vicia villosa agglutinin pull-down tests indicated that itraconazole increased the Tn antigen on EGFR (13). SAS cells that overexpressed CIGALTI and OEC-M1 cells with inhibited CIGALTI were injected in a mouse xenotransplantation model (13). The tumor growth rate and volume of SAS cells increased significantly, while the tumor growth of OEC-M1 cells decreased significantly (13). CIGALTI-mediated tumor growth was partially reversed by itraconazole in SAS cells (13). The aforementioned results indicate that CIGALTI greatly influences HNSCC, and silencing CIGALTI may potentially be an underlying treatment for tumors (13). Although CIGALTI expression in mice is partially inhibited by itraconazole, targeting CIGALTI via genetic molecular pathways can have great therapeutic potential for cancer treatment.

7. Conclusion

Glycosylation is a common, complex and diverse post-translational modification. This diverse polysaccharide has a wide scope of biological functions. Mammalian angiogenesis, platelet production and kidney development are inseparable from
O-glycosylation. The orderly construction of sugar molecules in normal cells involves substrate-specific glycosyltransferases (51,155). CIGALT1 and glycosylation are essential for normal development. Impaired T-synthase activity has been associated with different types of human diseases, including inflammatory or immune-mediated diseases, and cancer. The present review highlighted the relevance of CIGALT1 in the pathogenesis of IgAN, Tn syndrome, IBD and various types of cancer.

The change in glycosylation was discovered in a malignant transformation 60 years ago, and this change is considered to be one of the hallmarks of human cancer pathogenesis (156). Abnormal O-glycosylation, which found in various types of tumor, is very important in metastasis progression (83,157-159). The abnormal O-glycosylation of proteins on malignant tumor cell surface participates in different steps of tumor progression and regulates intercellular and intracellular signal transduction, thus inducing angiogenesis, EMT, metastasis and cell proliferation (157,160). The protein encoded by the CIGALT1 gene is a key mucin-type O-glycosyltransferase located in the Golgi apparatus (17). Galactose transfers to Tn antigen with its molecular chaperone Cosmc, forming Galβ1-3GalNACαSer/Thr structure (T antigen, core 1 structure) (83). In cases of hepatocellular carcinoma and cholangiocarcinoma, CIGALT1 expression is usually upregulated during tumorigenesis (27,109). Additionally, CIGALT1 silencing can inhibit cancer cell migration, invasion and proliferation, which inhibits metastasis and tumor growth (27,28). The CIGALT1 and integrin β1 signaling pathways can synergistically promote glycosylation-mediated intrinsic radiation resistance (149). Abnormal O-glycosylation is involved in the process of EMT (123). In addition, changes in CIGALT1 expression can cause short O-glycan expression in different types of cancer, which leads to cancer progression (120). CIGALT1 expression in mice is inhibited partially by itraconazole (13). Targeting CIGALT1 via genetic molecular pathways can have great therapeutic potential for cancer treatment. On the contrary, CIGALT1 acts as a tumor suppressor gene in colon and pancreatic cancer (30,123). Using samples from different sources or at different tumor stages may contribute to the observed duality in the CIGALT1 function, rendering the true role of this gene still elusive.

In conclusion, it is of great necessity to implement further studies for exploring the role of CIGALT1 and O-glycosylation, as well as its molecular chaperone Cosmc, and their interaction with different CIGALT1 targets, such as integrin β1, in the clinical setting. Future studies will help improve the understanding of certain pathologies and find new ways to treat and prevent disease in the future.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

XJS was in charge of the writing and revision of the manuscript. MZ and XS were involved in articles and data collection. WL was involved in the making of the table. XM was involved in figure preparation and supervision. Data authentication is not applicable. All authors read and approved the final manuscript.

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.

References

1. Apweiler R, Hermjakob H and Sharon N: On the frequency of protein glycosylation, as deduced from analysis of the SWISS-PROT database. Biochim Biophys Acta 1473: 4-8, 1999.
2. Theodoratou E, Thaçi K, Agakó F, Timofeeva MN, Stambuk J, Pučić-Baković M, Vučković F, Orchard P, Agakó A, Din FV, et al: Glycosylation of plasma IgG in colorectal cancer prognosis. Sci Rep 6: 28098, 2016.
3. Vajaria BN and Patel PS: Glycosylation: A hallmark of cancer. Glycocom 34: 147-156, 2017.
4. Munkley J and Elliott DF: Hallmarks of glycosylation in cancer. Onctarget 7: 35478-3589, 2016.
5. Shank A, Lu J, Xu Z, Li X, Xu Y, Li W, Liu F, Yang F, Sato T, Narimatsu H and Zhang Y: Polypeptide N-acetylgalactosaminyltransferase 18 non-catalytically regulates the ER homeostasis and O-glycosylation. Biochim Biophys Acta Gen Subj 1863: 870-882, 2019.
6. Tian E and Ten Hagen KG: Recent insights into the biological roles of mucin-type O-glycosylation. Glycocom 36: 325-334, 2019.
7. Kudelka MR, Antonopoulos A, Wang Y, Duong DM, Song X, Seyfried NT, Dell A, Haslam SM, Cummings RD and Ju T: Cellular O-Glycome Reporter/Amplifier to explore O-glycans of living cells. Nat Methods 13: 81-16, 2016.
8. Gupta R, Leon F, Rauth S, Batra SK and Ponussamy MP: A Systematic review on the implications of O-linked glycan branching and truncating enzymes on cancer progression and metastasis. Cells 9: 446, 2020.
9. Cervoni GE, Cheng JJ, Stackhouse KA, Heimbung-Molinaro J and Cummings RD: O-glycan recognition and function in mice and human cancers. Biochem J 477: 1541-1564, 2020.
10. Joshi HJ, Narimatsu Y, Schijfdager KT, Tytgat H, Abi M, Clausen H and Halim A: SnapShot: O-Glycosylation pathways across kingdoms. Cell 172: 632.e2, 2018.
11. Li LX, Ashikov A, Liu H, Griffith CL, Bakker H and Doerring TL: Cryptococcus neoformans UGT1 encodes a UDP-Galactose/UDP-GalNac transporter. Glycobiology 27: 87-98, 2017.
12. Bennett EP, Mandel U, Clausen H, Gerken TA, Fritz TA and Tabak LA: Control of mucin-type O-glycosylation: A classification of the polypeptide GalNAc-transferase gene family. Glycobiology 22: 736-56, 2012.
13. Lin MC, Chien PH, Wu HY, Chen ST, Juan HF, Lou PJ and Huang MC: CIGALT1 predicts poor prognosis and is a potential therapeutic target in head and neck cancer. Oncogene 37: 5780-5793, 2018.
14. Saeland E, Belo AI, Mongera S, van Die I, Meijer GA and van Kooyk Y: Differential glycosylation of MUC1 and CEACAM5 between normal mucosa and tumour tissue of colon cancer patients. Int J Cancer 131: 117-128, 2012.
Ju T, Breuer K, D’Souza A, Cummings RD and Canfield WM: Cloning and expression of human core 1 beta,3-galactosyltransferase. J Biol Chem 277: 178-186, 2002.

Pothuraju R, Atri P, Mahapatra S, Thapa I, Talmon GA et al: Genetic susceptibility to Mammalian pancreatic adenocarcinomas in Mice. Gastroenterology 155: 1608-1624, 2018.

Lin HH, Chen RJ, Shyu MK and Huang MC: C1GALT1 enhances proliferation of hepatocellular carcinoma cells. IUBMB Life 65: 409-422, 2013.

Wu YM, Liu CH, Hu RH, Huang MJ, Lai HS, Lee PH, Hu RH and Huang MC: C1GALT1 enhances proliferation of hepatocellular carcinoma cells via modulation of MET glycosylation and dimerization. Cancer Res 72: 5580-5590, 2013.

Ju T, Chen ST, Kuo TC, Lin TC, Lin MC, Huang J, Hung JS, Hsu CL, Juang SF and Lee PH and Huang MC: C1GALT1 is associated with poor survival and promotes soluble Ephrin A1-mediated cell migration through activation of EPHA2 in gastric cancer. Oncogene 39: 2724-2740, 2020.

Liu CH, Hu RH, Huang MJ, Lai IR, Chen CH, Liu HS, Wu YM and Huang MC: C1GALT1 promotes invasive phenotypes of hepatocellular carcinoma cells by modulating integrin β1 glycosylation and activity. PLoS One 9: e94995, 2014.

Chugh S, Barkeer S, Rachagani S, Nimmakayalu RK, Perumal N, Pothuraju R, Athi A, Mahapatra S, Thapa I, Talamon GA, et al: Disruption of C1GalT1 gene promotes development and metastasis of pancreatic adenocarcinomas in Mice. Gastroenterology 155: 1608-1624, 2018.

Liu F, Fu J, Bergstrom K, Shan X, D’Amico  G: Natural history of idiopathic IgA nephropathy and factors predictive of disease outcome. Semin Nephrol 24: 137-146, 2004.

Lin HH, Chen RJ, Shyu MK and Huang MC: C1GALT1 enhances proliferation of hepatocellular carcinoma cells. IUBMB Life 65: 409-422, 2013.

Jiang Z, Xie J, Mladkova N, Prakash S, Fischman C et al: Galactosylation of IgA1 is associated with common variation in serum galactose-deficient IgA1 implicates critical genes of the IgA1 pathway in endometrial cancer. Gynecol Oncol 128: 560-567, 2013.

Ju T, Xia B, Aryal RP, Wang W, Wang Y, Ding X, Mi R, He M, Zhang JG, Metcalf D, Kauppi M, Alexander WS, Viney EM, Tu L and Banfield DK: Localization of Golgi-resident glycosyltransferases. Cell Mol Life Sci 67: 29-41, 2010.

Aryal RP, Tu J and Cummings RD: The endoplasmic reticulum transferases. Cell Mol Life Sci 67: 29-41, 2010.

Tu L and Banfield DK: Localization of Golgi-resident glycosyltransferases. Cell Mol Life Sci 67: 29-41, 2010.

Xia L and McEver RP: Targeted disruption of the gene encoding core 1 beta1-3-galactosyltransferase (T-synthase) causes embryonic lethality and defective angiogenesis in mice. Methods Mol Biol 416: 313-325, 2007.

Abatihan F, Guerriero A, Sebza E, Lu MM, Zhou R, Mocsai A, Myers EE, Huang B, Jackson DG, Ferrari VA, et al: Regulation of blood and lymphatic vascular separation by signaling proteins SLP-76 and Syk. Science 299: 247-251, 2003.

Anderson WA and Spielman A: Permeability of the ovarian follicle: A mechanism of Aedes aegypti mosquitoes. J Cell Biol 50: 201-221, 1971.

Batista F, Lu L, Williams SA and Stanford P: Complex N-glycans are essential, but core 1 and 2 mucin O-glycans, O-fucos glycosyl, and NOTCH1 are dispensable, for mammalian spermatogenesis. Biol Reprod 86: 179, 2007.

Berkhof LB, Ynduraín TK and Shea LD: Distribution of extracellular matrix proteins type I collagen, type IV collagen, fibronectin, and laminin in mouse folliculogenesis. Histochem Cell Biol 126: 583-592, 2006.

Kudo T, Sato T, Hagiwara K, Kozuma Y, Yamaguchi T, Ikehara Y, Iramada M, Matsumoto K, Ema M, Murata S, Ohkohchi N, et al: C1galt1−/− deficient mice exhibit thrombocytopenia due to abnormal terminal differentiation of megakaryocytes. Blood 122: 1649-1657, 2013.

Ju T, Brewer K, D’Souza A, Cummings RD and Canfield WM: Cloning and expression of human core 1 beta,3-galactosyltransferase. J Biol Chem 277: 178-186, 2002.

Tu L and Banfield DK: Localization of Golgi-resident glycosyltransferases. Cell Mol Life Sci 67: 29-41, 2010.

Xia L and McEver RP: Targeted disruption of the gene encoding core 1 beta1-3-galactosyltransferase (T-synthase) causes embryonic lethality and defective angiogenesis in mice. Methods Mol Biol 416: 313-325, 2007.

Abatihan F, Guerriero A, Sebza E, Lu MM, Zhou R, Mocsai A, Myers EE, Huang B, Jackson DG, Ferrari VA, et al: Regulation of blood and lymphatic vascular separation by signaling proteins SLP-76 and Syk. Science 299: 247-251, 2003.

Anderson WA and Spielman A: Permeability of the ovarian follicle: A mechanism of Aedes aegypti mosquitoes. J Cell Biol 50: 201-221, 1971.

Batista F, Lu L, Williams SA and Stanford P: Complex N-glycans are essential, but core 1 and 2 mucin O-glycans, O-fucos glycosyl, and NOTCH1 are dispensable, for mammalian spermatogenesis. Biol Reprod 86: 179, 2007.

Berkhof LB, Ynduraín TK and Shea LD: Distribution of extracellular matrix proteins type I collagen, type IV collagen, fibronectin, and laminin in mouse folliculogenesis. Histochem Cell Biol 126: 583-592, 2006.

Kudo T, Sato T, Hagiwara K, Kozuma Y, Yamaguchi T, Ikehara Y, Iramada M, Matsumoto K, Ema M, Murata S, Ohkohchi N, et al: C1galt1−/− deficient mice exhibit thrombocytopenia due to abnormal terminal differentiation of megakaryocytes. Blood 122: 1649-1657, 2013.
The mucin glycosylating enzyme GALNT2 suppresses the malignant phenotype of hepatocellular carcinoma by modifying the EGF receptor. Cancer Res 71: 7270-7279, 2011.

86. Huang MJ, Hu RH, Chou CH, Hsu CL, Liu YW, Huang J, Huang JS, Lai IR, Juan HF, Yu SL, et al: Knockdown of GALNT1 suppresses malignant phenotype of hepatocellular carcinoma by suppressing EGFR signaling. Oncotarget 6: 50664-50665, 2015.

87. Wang H, Rao B, Lou J, Li J, Liu Z, Li A, Cui G, Ren Z and Yu Z: The Function of the HGFlc-Met Axis in Hepatocellular Carcinoma. Front Cell Dev Biol 8: 55, 2020.

88. Lee HE, Kim MA, Lee HS, Jung EJ, Yang HK, Lee BL, Bang YJ and Kim WE: MET in gastric carcinomas: Comparison between protein expression and gene copy number and impact on clinical outcome. Br J Cancer 107: 325-333, 2012.

89. Inokuchi M, Otsuki S, Fujimori Y, Sato Y, Nakagawa M and Kojima K: Clinical significance of MET in gastric cancer. World J Gastrointest Oncol 7: 317-327, 2015.

90. Toiyama Y, Yasuda H, Saigusa S, Matushita K, Fujikawa K, Tanaka K, Mohri Y, Inoue Y, Goel A and Kusunoki M: Co-expression of hepatocyte growth factor and c-Met predicts peritoneal dissemination established by autocrine hepatocyte growth factor-Met signaling in gastric cancer. Int J Cancer 130: 2912-2921, 2012.

91. Deng N, Goh LK, Wang H, Das K, Tao J, Tan IB, Zhang S, Lee M, Wu J, Lim KH, et al: A comprehensive survey of genomic alterations in gastric cancer establishes systems pattern of molecular exclusivity and co-occurrence among distinct therapeutic targets. Gut 61: 673-682, 2012.

92. Bradley CA, Salto-Tellez M, Laurent-Puig P, Bardelli A, Rolfo C, Tabernero J, Khawaja HA, Lawler M, Johnston PG and Van Schaeybroeck S: MerCurIC consortium: Targeting c-MET in gastrointestinal tumours: Rationale, opportunities and challenges. Nat Rev Clin Oncol 15: 150, 2018.

93. Sierra JC, Asim M, Verriere TG, Piazzuelo MB, Suarez G, Romero-Gallo J, Delgado AG, Wroblewski LE, Barry DP, Peek RM Jr, et al: Epidermal growth factor receptor inhibition downregulates Helicobacter pylori-induced epithelial inflammatory responses, DNA damage and gastric carcinogenesis. Gut 67: 1247-1268, 2018.

94. Xi HQ, Wu XS, Wei B and Chen L: Eph receptors and ephrins as targets for cancer therapy. J Cell Mol Med 16: 2894-2909, 2012.

95. Vaught D, Brantley-Sieders DM and Chen J: Eph receptors in breast cancer: Roles in tumor promotion and tumor suppression. Breast Cancer Res 10: 217, 2008.

96. Herath NI and Boyd AW: The role of Eph receptors and ephrin ligands in colorectal cancer. Int J Cancer 126: 2003-2011.

97. Lisle JE, Mertens-Walker I, Rutkowski R, Herkington AC and Van Schaeybroeck S: The role of Eph receptors and ephrin ligands in colorectal cancer. Cancer Biol Ther 14: 820-828, 2015.

98. Pasquale EB: Eph receptors and ephrins in cancer: Cytoskeletal remodelling and beyond. Nat Rev Cancer 10: 165-180, 2010.

99. Vaught D, Brantley-Sieders DM and Chen J: Eph receptors and ephrin ligands in colorectal cancer. Int J Cancer 126: 2003-2011.

100. Lisle JE, Mertens-Walker I, Rutkowski R, Herkington AC and Van Schaeybroeck S: The role of Eph receptors and ephrin ligands in colorectal cancer. Cancer Biol Ther 14: 820-828, 2015.
Sun X, Ju T and Cummings RD: Differential expression of C1Gal-T2, an enzyme synthesizing a core 1 structure of O-linked oligosaccharides, in Tn-polyagglutinable erythrocytes. Lancet 1: 1038-1039, 1978.

Song J, McDaniel JM, Ju T, Cummings RD: The molecular chaperone Cosmc in human leukocytes expressing Tn antigen. J Cell Biol 182: 531-542, 2018.

Shi M, Chen D, Yang D and Liu XY: CCL2-CCR7 promotes the lymph node metastasis of esophageal squamous cell carcinoma by up-regulating MUC1. J Exp Clin Cancer Res 34: 149, 2015.

Su H, Hu N, Yang HH, Wang C, Takikita M, Wang QH, Giffen C, Clifford R, Hewitt SM, Shou JZ, et al: Global gene expression profiling and validation in esophageal squamous cell carcinoma and its association with clinical phenotypes. Clin Cancer Res 17: 2955-2966, 2011.

Agata N, Ahmad R, Kawano T, Raina D, Kharrband S and Kufe D: MUC1 oncoprotein blocks death receptor-mediated apoptosis by inhibiting recruitment of caspase-8. Cancer Res 68: 6136-6144, 2008.

Kufe DW: MUC1-C oncoprotein as a target in breast cancer: Activation of signaling pathways and therapeutic approaches. Oncogene 32: 1073-1081, 2013.

Wang Y, Liu Y, Ye Q and Huang L: Clinical implication of MUC1 O-glycosylation and CIGALT1 in esophageus squamous cell carcinoma. Sci China Life Sci 61: 1389-1395, 2018.

Dong X, Luo Z, Wang Y, Meng L, Duan Q, Qiu L, Peng F and Shen L: Altered O-glycosylation is associated with inherent radiosensitivity and malignancy of human laryngeal carcinoma. Exp Cell Res 362: 302-310, 2018.

Chen P, Chang A, Huang M and Wu Y: Abstract 1400: CIGALT1 regulates malignant phenotypes of cholangiocarcinoma cells. Cancer Res 79, 2019 do: 10.1158/1538-7445. AM2019-1400.

Huang MC, Huang MJ and Wu YM: P0247: CIGALT1 is over-expressed in cholangiocarcinoma and CIGALT1 knockdown inhibits malignant behaviors of cholangiocarcinoma cells. J Hepatol 62 (Suppl): S399, 2015.

Chao CH, Huang MJ, Liu CH, Yang TL and Huang MC: GALNT2 enhances migration and invasion of oral squamous cell carcinoma by regulating EGFR glycosylation and activity. Oral Oncol 50: 478-484, 2014.

Leemans CR, Snijders P and Brakenhoff RH: The molecular landscape of head and neck cancer. Nat Rev Cancer 18: 269-282, 2018.

Ghazizadeh M, Ogawa H, Sasaki Y, Araki T and Aihara K: An expression of carbohydrate antigens (Tn, Tn and sialyl-Tn) in human ovarian carcinomas: Relationship with histopathology and prognosis. Hum Pathol 28: 960-966, 1997.

Davidson B, Gottlieb WH, Ben-Baruch G, Kopolovic J, Goldberg I, Nesland JM, Berner A, Bjämer A and Bryne M: Expression of carbohydrate antigens in advanced-stage ovarian carcinomas and their metastases-A clinicopathological study. Gynecol Oncol 77: 35-43, 2000.

Chao CH, Huang MJ, Liao YY, Chen CH and Huang MC: CIGALT1 promotes in vitro disease progression in ovarian cancer. Int J Gynecol Cancer 27: 863-871, 2017.

Leach SD: Mouse models of pancreatic cancer: The fur is finally flying. Cancer Cell 5: 7-11, 2004.

Mazur PK and Siveke JT: Genetically engineered mouse models of pancreatic cancer: Unravelling tumour biology and progressing translational oncology. Gut 61: 1488-1502, 2012.

Muniyani S, Haridas D, Chugh S, Rachagnani S, Lakshmanan G, Gupta S, Seshacharyula P, Smith LM, Ponnapasu MP and Batra SK: MUC16 contributes to the metastasis of pancreatic ductal adenocarcinoma through focal adhesion mediated signaling mechanism. Genes Cancer 7: 110-124, 2016.

Fujita-Yamaguchi Y: Renewed interest in basic and applied research involving monoclonal antibodies against an oncologic Tn-antigen. J Biochem 154: 103-105, 2013.

Sun X, Ju T and Cummings RD: Differential expression of C1Gal-T2 and mucins in Tn-positive colorectal cancers. BMC Cancer 18: 827, 2018.

Bergstrom K, Ju F, Johansson ME, Liu X, Gao N, Wu Q, Song J, McDaniel JM, McGee S, Chen W, et al: Core 1- and 3-derived O-glycans collectively maintain the colonic mucin barrier and protect against spontaneous colitis in mice. Mucosal Immunol 10: 91-103, 2017.

Dong X, Jiang Y, Liu J, Liu Z, Gao T and Wen T: T-synthese deficiency enhances oncogenic features in human colorectal cancer cells via activation of epithelial-mesenchymal transition. Biomed Res Int 2018: 9532389, 2018.

Schulz E, Major P, Berenger C1, Lin OM, Saltor RD, Eady R, Yassine-Diab B, Favre D, Perez Y, Landry C, et al: Tn-MUC1 DC vaccination of rhesus macaques and a phase I/II trial in patients with nonmetastatic castrate-resistant prostate cancer. Cancer Immunol Res 4: 881-892, 2016.

Sakata K, Yuasa N, Tsukamoto M, Yajima Y, Sato R, Kawakami H, Mizuno M, Takeyayangi A, Shimizu N, et al: Isolation and characterization of antibodies against three consecutive Tn-antigen clusters from a phage library displaying human single-chain variable fragments. J Biochem 147: 809-817, 2010.

Piyush T, Rhodes JM and Yu LG: MUC1 O-glycosylation contributes to anoikis resistance in epithelial cancer cells. Cell Death Discov 3: 17044, 2017.

Freire-de-Lima L, Gelfenbeyn K, Ding Y, Mandel U, Clausen H, Handa K and Hakomori SF: Involvement of O-glycosylation defining oncofetal fibronectin in epithelial-mesenchymal transition process. Proc Natl Acad Sci USA 108: 17690-17695, 2011.

An G, Wei B, Xia B, McDaniel JM, Ju T, Cummings RD, Braun J and Xia L: Increased susceptibility to colitis and colorectal tumors in C1Gal-T2-/- mice lacking core 3-derived O-glycans. J Exp Med 204: 1417-1429, 2007.

Kudo T, Iwai T, Kubota T, Iwasaki H, Takayama Y, Hiruma T, Inaba N, Zhang Y, Gotoh M, Togayachi A and Narimatsu H: Molecular cloning and characterization of a novel UDP-Gal:GalNAc(αlpha) peptide beta 1,3-galactosyltransferase (C1Gal-T2), an enzyme-synthesizing a core 1 structure of O-glycan. J Biol Chem 277: 47724-47731, 2002.

Ju T, Aryan RP, Stowell CJ and Cummings RD: Regulation of protein O-glycosylation by the endoplasmic reticulum-localized molecular chaperone Cosmc. J Cell Biol 182: 531-542, 2008.

Zeng J, Mi R, Wang Y, Li Y, Lin L, Yao B, Song L, van Die I, Chapman AB, Cummings RD, et al: Promoters of Human Cosmic And T-synthese genes are similar in structure, yet different in epigenetic regulation. J Biol Chem 290: 19018-19033, 2015.

Wang Y, Ju T, Ding X, Xia B, Wang W, Xia L, He M and Cummings RD: Cosmic is an essential chaperone for correct protein O-glycosylation. Proc Natl Acad Sci USA 107: 9228-9233, 2010.

Mi R, Song L, Wang Y, Ding X, Zeng J, Lehoux S, Aryan RP, Wang J, Crew VK, van Die I, et al: Epigenetic silencing of the chaperone Cosmic in human leukocytes expressing in antigen. J Biol Chem 287: 41523-41533, 2012.

Cartron JP and Norden AF: Galatosyltransferase and membrane glycoprotein abnormality in human platelets from Tn-syndrome donors. Nature 282: 621-623, 1979.

Cartron JP, Cartron J, Andreu G, Salmon C and Bird GW: Selective deficiency of 3-beta-d-galactosyltransferase (T-synthese) in Tn-polyagglutinable erythrocytes. Lancet 1: 856-857, 1978.

Ju T, Otto VI and Cummings RD: The Tn antigen-structural complexity and biological complexity. Angew Chem Int Ed Engl 50: 1770-1791, 2011.

Hiki Y: O-linked oligosaccharides of the IgA1 hinge region: Roles of its aberrant structure in the occurrence and/or progression of IgA nephropathy. Clin Exp Nephrol 13: 415-423, 2009.

Yang D, Tang Y, Fu H, Xu J, Hu Z, Zhang Y and Cai Q: Integrin β1 promotes gemcitabine resistance in pancreatic cancer through Cdc42 activation of PI3K p110β signaling. Biochem Biophys Res Comm 305: 212-218, 2002.

Desgrosellier JS and Cheresh DA: Integrins in cancer: Biological implications and therapeutic opportunities. Nat Rev Cancer 10: 1364-1376, 2010.

Matsunaga T, Fukai F, Miura S, Nakane Y, Owaki T, Kodama H, Tanaka M, Nagaya T, Takimoto R, Takayama T and Nitisu Y: Combination therapy of an anticancer drug with the FN1H14 peptide of fibronectin effectively overcomes cell adhesion-mediated drug resistance of acute myelogenous leukemia. Leukemia 22: 353-360, 2008.
141. Park CC, Zhang H, Pallavicini M, Gray JW, Baehner F, Park CJ and Bissell MJ: Beta1 integrin inhibitory antibody induces apoptosis of breast cancer cells, inhibits growth, and distinguishes malignant from normal phenotype in three dimensional cultures and in vivo. Cancer Res 66: 1526‑1535, 2006.

142. Li Y, Ren Z, Wang Y, Dang YZ, Meng BX, Wang GD, Zhang J, Wu J and Wen N: ADAM17 promotes cell migration and invasion through the integrin β1 pathway in hepatocellular carcinoma. Exp Cell Res 370: 373‑382, 2018.

143. Winkler J, Roessler S, Sticht C, DiGuilio AL, Drucker E, Holzer K, Eitemeuer E, Herpel E, Breuhahn K, Gretz N, et al: Cellular apoptosis susceptibility (CAS) is linked to integrin β1 and required for tumor cell migration and invasion in hepatocellular carcinoma (HCC). Oncotarget 7: 22883‑22892, 2016.

144. Fransvea E, Mazzocca A, Antonaci S and Giannelli G: Targeting transforming growth factor (TGF)-betaRI inhibits activation of beta1 integrin and blocks vascular invasion in hepatocellular carcinoma. Hepatology 49: 839‑850, 2009.

145. Trusolino L, Bertotti A and Comoglio PM: A signaling adapter function for alpha6beta4 integrin in the control of HGF‑dependent invasive growth. Cell 107: 643‑654, 2001.

146. Hakomori S: Glycosylation defining cancer malignancy: New wine in an old bottle. Proc Natl Acad Sci USA 99: 10231‑10233, 2002.

147. Wang ZQ, Bachvarova M, Morin C, Plante M, Greigier J, Renaud MC, Sebastianelli A and Bachvarov D: Role of the polypeptide N‑acetylgalactosaminyltransferase 3 in ovarian cancer progression: Possible implications in abnormal mucin O‑glycosylation. Oncotarget 5: 544‑560, 2014.

148. Rudin CM, Brahmer JR, Juergens RA, Hann CL, Ettenger DS, Sebree R, Smith R, Aftab BT, Huang P and Liu JO: Phase 2 study of pemetrexed and iraconazole as second-line therapy for metastatic nonsquamous non-small-cell lung cancer. J Thorac Oncol 8: 619‑623, 2013.