Research progress in the role and mechanism of GALNT3 in human diseases (Review)

LINHONG SU[1*], YONGXIU LIN[2*], XIAOXIA HU[2] and ZHEN LIU[2]

[1]Medical Genetics and Prenatal Diagnosis Center, The People's Hospital of Guangxi Zhuang Autonomous Region, Guangxi Academy of Medical Sciences, Nanning, Guangxi 530021, P.R. China; [2]Department of Gynecology, The People's Hospital of Guangxi Zhuang Autonomous Region, Guangxi Academy of Medical Sciences, Nanning, Guangxi 530021, P.R. China

Received September 2, 2025; Accepted January 29, 2026

DOI: 10.3892/br.2026.2137

Abstract. Protein glycosylation is a crucial post-translational modification. Polypeptide N-acetylgalactosaminyltransferase 3 (GALNT3) is a glycosyltransferase that plays an essential role in various human diseases by modifying proteins, including fibroblast growth factor 23 and mucins. In non-tumor conditions, mutations in GALNT3 result in hyperphosphatemia in familial tumoral calcinosis, and its dysregulation has been linked to coronary artery disease. Notably, GALNT3 plays a seemingly opposing role in influenza A virus infection by potentially aiding early viral replication, and later exerting antiviral effects. In cancer, the functions of GALNT3 vary by context: it acts as a tumor suppressor in lung cancer but promotes tumor progression in colorectal and ovarian cancer. GALNT3 plays a context-dependent, dual role by exerting both tumor-suppressive and tumor-promoting functions in specific subtypes of pancreatic and breast cancers. This duality is influenced by the tissue environment, substrate specificity, and regulatory networks. Therefore, GALNT3 is emerging as a promising biomarker and therapeutic target across different pathological conditions owing to its pivotal role in disease processes.

Contents

Correspondence to: Mr. Zhen Liu, Department of Gynecology, The People's Hospital of Guangxi Zhuang Autonomous Region, Guangxi Academy of Medical Sciences, 6 Taoyuan Road, Nanning, Guangxi 530021, P.R. China
E-mail: lz791375@163.com

*Contibuted equally

Key words: polypeptide N-acetylgalactosaminyltransferase 3, biomarker, therapeutic target

1. Introduction

Protein glycosylation is a crucial post-translational modification that regulates numerous physiological and pathological processes. Of the various types, O-glycosylation, which is initiated by a family of polypeptide N-acetylgalactosaminyltransferases (GALNTs), plays an essential role in maintaining protein stability, facilitating cell communication, and supporting immune responses (1-3). GALNT3, a key member of this enzyme family, has become a crucial regulator in various human diseases owing to its specific substrate preferences and intricate expression control.

The role of GALNT3 in phosphate metabolism via fibroblast growth factor 23 (FGF23) glycosylation has been increasingly characterized (4), however, only limited information is available on its broader and often context-dependent functions across various disease settings. Earlier reviews have typically examined the GALNT family as a whole or focused on specific diseases (5,6). Therefore, there is scope for a more integrated examination of the tissue-specific mechanisms of GALNT3, particularly its dual role as an oncogene and a tumor suppressor. Furthermore, the translational potential of the regulatory networks of GALNT3, including those involving noncoding RNAs (ncRNAs) and signaling pathways, warrants further exploration for potential diagnostic and therapeutic applications.

This review attempts to address these issues by synthesizing recent findings on GALNT3 across rare genetic disorders, metabolic conditions, and cancer types. The present review focuses on the context-specific behavior of GALNT3 and the related therapeutic challenges, such as its functional redundancy with GALNT6 in ovarian cancer. By combining mechanistic and clinical data, the present review aims to provide a comprehensive overview of GALNT3 as a versatile regulator with potential as a target for precision medicine.

2. Structural features of GALNT3

GALNT3 is a prototypical type II transmembrane protein located on chromosome 2q24.3 (7). Its structure comprises an N-terminal cytoplasmic tail, a transmembrane domain, a stem region, and C-terminal catalytic and lectin domains (Fig. 1). An N-terminal GT1 motif and a C-terminal galactose (Gal)/N-acetylgalactosamine (GalNAc)-T motif, which bind the Mn^{2+} cofactor and the uridine diphosphate (UDP)-GalNAc donor substrate, respectively, are present in the catalytic domain. Processive glycosylation of adjacent acceptor sites is facilitated by the lectin domain, which recognizes the newly incorporated GalNAc moieties.

3. Transcriptional regulation of GALNT3 expression

The regulation of *GALNT3* expression at the transcriptional level is intricate, affected by numerous factors and signaling pathways. Notably, the osteogenic transcription factor runt-related transcription factor 2 (Runx2), which plays vital roles in pulmonary fibrosis, cancer development, and metastasis (8-10), directly regulates GALNT3 transcription by binding to specific sites within its promoter region (11). This regulation is essential for maintaining the optimal levels of FGF23, which is a vital hormone in phosphorus metabolism. GALNT3 inhibits the proteolytic processing of FGF23, which helps stabilize its levels (11).

In addition to transcription factors, extracellular phosphate (Pi) influences the GALNT3 expression via the Pi/MEK/ERK-signaling pathway. Increased Pi causes phosphorylation of fibroblast growth factor receptor 1c (FGFR1c) in osteoblasts, causing a temporary activation of the MEK/ERK cascade (12). This cascade promotes the expression of transcription factors, including early growth response 1 (Egr1) and ETS variant transcription factor 5 (Etv5), which are involved in the transcriptional upregulation of GALNT3. Supporting this notion, small-interfering RNA (siRNA)-mediated knockdown of Egr1 or Etv5 attenuates GALNT3 induction by high Pi, indicating their functional role in this regulatory pathway (13). However, direct binding of these transcription factors to the GALNT3 promoter, such as via promoter-luciferase assays or chromatin accessibility studies, has not yet been experimentally demonstrated.

Epigenetic mechanisms further refine GALNT3 transcription. In mouse trophoblast stem cells, mitogen-activated protein kinase kinase kinase 4 (MAP3K4) kinase promotes an epithelial phenotype by inhibiting the histone deacetylase histone deacetylase 6 (HDAC6). When MAP3K4 is lost, the HDAC6 levels rise and are recruited to the *Galnt3* promoter, where they deacetylate histone H2B at lysine 5 acetylation (H2BK5ac), a mark that represses *Galnt3* transcription. Knocking down HDAC6 restores H2BK5 acetylation and reactivates the *Galnt3* expression. This MAP3K4-HDAC6-H2BK5ac-regulatory pathway is also present in human mammary epithelial and claudin-low breast cancer cells, highlighting HDAC6 as a direct transcriptional repressor of GALNT3 during the epithelial-mesenchymal transition (EMT) (14).

ncRNAs, which include microRNAs (miRNAs or miRs), circular RNAs (circRNAs), and long ncRNAs (lncRNAs), are crucial in regulating gene expression at both the transcriptional and post-transcriptional levels, including GALNT3. Certain miRNAs, such as miR-885-5p, miR-30e-5p, miR-378a-3p, miR-26a, miR-545-5p, miR-17-3p, and miR-221, act as negative regulators of GALNT3 by binding to its 3'-untranslated region (UTR) in various disease contexts (15-20). Conversely, circSPIRE1 was shown to increase the GALNT3 levels by influencing interactions with RNA-binding proteins. It was demonstrated to specifically associate with ELAV-like RNA-binding protein 1, which, in turn, stabilized GALNT3 mRNA and enhanced its translation (21). circ-RAPGEF5 was revealed to upregulate GALNT3 expression by sponging miR-545-5p in colorectal cancer (CRC). LncRNAs, which frequently function as competing endogenous RNAs, play a vital role in regulating gene expression across various biological processes and diseases. Specifically, lncRNA PSMA3-AS1 and LINC01296 have been recognized as the key regulators of GALNT3 across different cancer types (17,19). Together, these findings highlight the intricate relationships among lncRNAs, miRNAs, and protein-coding genes that regulate the GALNT3 expression and its downstream effects. The key factors and their integrated mechanisms are presented in Table I, and the overarching model is depicted in Fig. 2.

4. Molecular functions of GALNT3

As a key enzyme in mucin-type O-glycosylation, GALNT3 initiates this post-translational modification by transferring GalNAc to serine or threonine residues on the target proteins. This enzymatic function enables GALNT3 to play a pertinent role in regulating protein stability, subcellular localization, and molecular interactions, with its effects largely determined by its strict substrate specificity. One of its well-known substrates is FGF23 (22,23), whose glycosylation by GALNT3 is essential for its secretion and bioactivity in maintaining phosphate homeostasis, and mucins (24,25), whose structural integrity and mucosal barrier functions rely on GALNT3-mediated glycosylation.

In vivo studies using genetic mouse models have confirmed the indispensable role of GALNT3 in processing FGF23 and regulating the systemic phosphate levels. For example, Ichikawa *et al* (23) demonstrated that genetic ablation of *Galnt3* in mice caused hyperphosphatemia, although the FGF23 mRNA levels increased in the bone tissue. The circulating levels of intact FGF23 decreased by ~50% in Galnt3-deficient mice, along with an accumulation of C-terminal FGF23 fragments in the bone. This finding underscores the importance of GALNT3-driven O-glycosylation in protecting FGF23 from proteolytic cleavage. Additionally, these knockout mice displayed inappropriate normalization of serum 1,25-dihydroxyvitamin D, reduced alkaline phosphatase activity, and an increased expression of renal sodium-phosphate cotransporters and Klotho. Sexual dimorphism was also observed, with the male knockout mice experiencing growth retardation, infertility, and significantly higher bone mineral density compared to their female counterparts (23). Overall, these results confirm that GALNT3 is essential for secreting biologically active FGF23 and for maintaining systemic phosphate balance.

GALNT3 also plays a vital role in maintaining epithelial integrity by regulating cell adhesion molecules, especially E-cadherin (14). GALNT3-mediated O-GalNAc

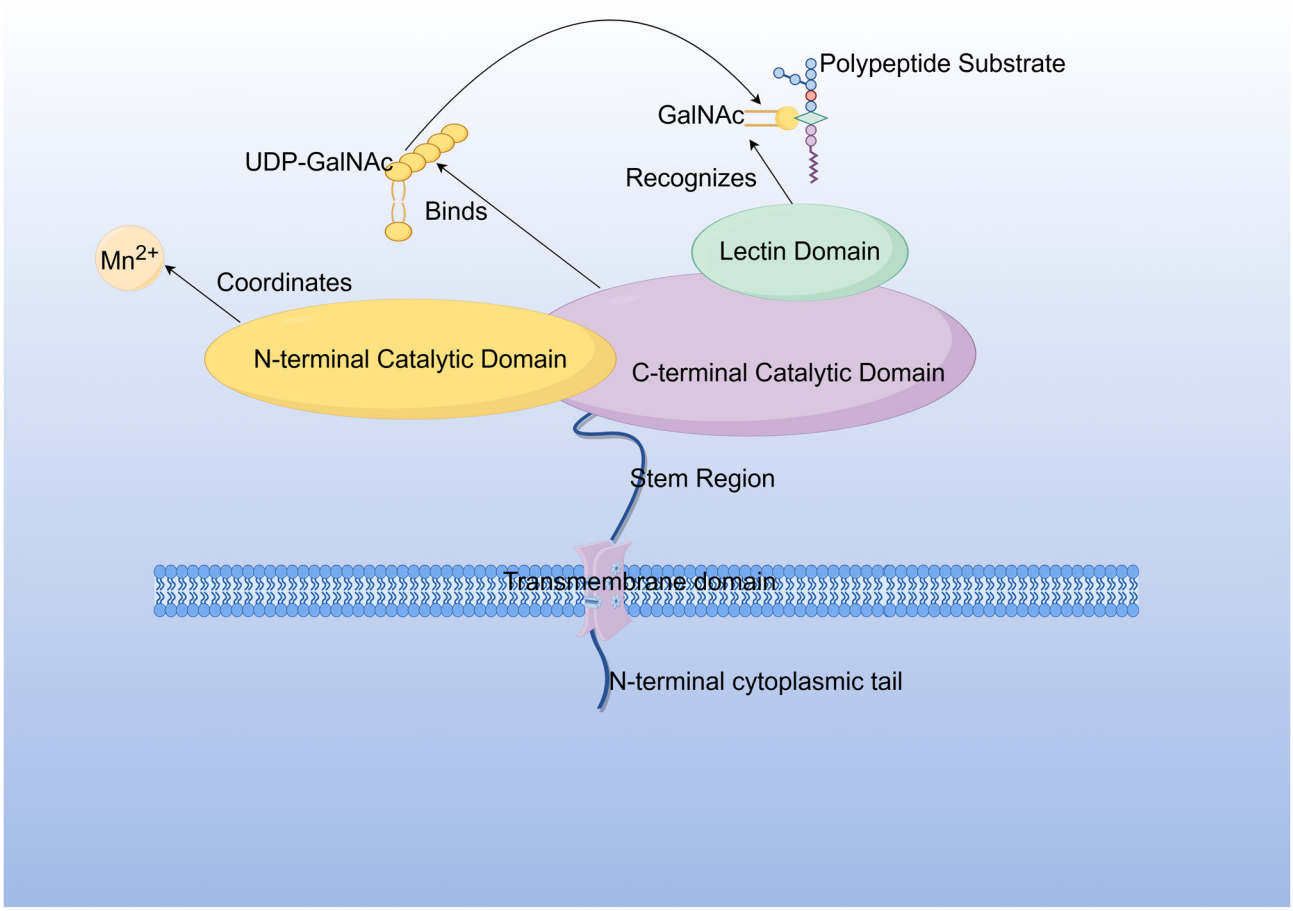

Figure 1. Schematic depiction of GALNT3 protein structure and functional domains. The structure, based on the AlphaFold-predicted model (AF-Q14435-F1), displays the spatial arrangement of the main domains of GALNT3. The catalytic domain includes an N-terminal region (GT1 motif, which binds Mn^{2+}) and a C-terminal region (Gal/GalNAc-T motif, which binds UDP-GalNAc and performs the catalytic transfer). The lectin domain guides a 'stepping' mechanism by recognizing the newly added GalNAc sugar, allowing the enzyme to achieve processive glycosylation on the same substrate. GALNT3, polypeptide N-acetylgalactosaminyltransferase 3; UDP-GalNAc, uridine diphosphate N-acetylgalactosamine. The figure was generated using FigDraw (https://www.figdraw.com).

glycosylation of E-cadherin is necessary for its correct trafficking from the Golgi apparatus to the plasma membrane. The loss of GALNT3 causes E-cadherin to be retained inside the cell, disrupts adherens junction formation, and triggers EMT, a process linked to increased cell motility and invasiveness. This regulatory process is maintained across different epithelial systems, including trophoblast stem cells, blastocyst trophectoderm, and human mammary epithelial cells, highlighting the crucial role of GALNT3 in maintaining epithelial structure.

In addition to these roles, GALNT3 functionally redundant with GALNT6, participates in modulating the glycosylation of ECM proteins such as fibronectin 1 (FN1), which impacts cancer cell adhesion and metastasis (26). Moreover, it influences inflammatory responses by glycosylating tumor necrosis factor receptor 1 (TNFR1), which suppresses NF-κB signaling (27). The dysregulation of these substrate-specific glycosylation processes plays a role in several diseases, such as hyperphosphatemia, tumor growth, and chronic inflammation (23,26,27). The subsequent sections thoroughly explore the functions of these glycosylated targets in biological activities, their mechanistic roles in disease development, and their potential for therapy.

Although O-glycosylation is recognized as a crucial factor in neuronal development and synaptic connectivity (28), the specific roles of GALNT3 in these processes remain largely unknown. Since it is well established that GALNT3 glycosylates adhesion molecules such as E-cadherin in epithelial systems (14), it is reasonable to suggest that GALNT3 may also modify neuronal adhesion proteins, such as cadherins or integrins, to affect synapse formation, stability, or function. This gap in the current knowledge offers an opportunity for future research to uncover the potential roles of GALNT3 in neural development and function. These diverse molecular functions collectively represent a unifying framework, as summarized in Fig. 3.

5. Role of GALNT3 in non-tumor diseases

Familial tumoral calcinosis/hyperostosis-hyperphosphatemia syndrome (FTC/HHS) and GALNT3. FTC/HHS is a rare autosomal recessive disorder marked by ectopic soft tissue calcifications, especially around large joints, along with bone hyperostosis and ongoing hyperphosphatemia. The condition is closely linked to mutations in *GALNT3*, which is vital for the glycosylation pathway that regulates the phosphaturic

Table I. Key regulatory factors and mechanisms regulating GALNT3 expression.

Category	Regulator/Pathway	Type of regulation	Effect on GALNT3	Key notes/evidence	(Refs.)
Transcription Factors	Runx2	Direct	Positive	Binds GALNT3 promoter; crucial for FGF23 stability	(11)
Signaling Pathways	Pi/MEK/ERK/Egr1 Etv5	Indirect	Positive	High Pi → FGFR1c → MEK/ERK → Egr1/Etv5 → GALNT3 upregulation; no direct promoter binding shown.	(12,13)
Epigenetic Mechanisms	MAP3K4-HDAC6-H2BK5ac axis	Indirect	Negative (HDAC6)	HDAC6 deacetylates H2BK5; represses GALNT3 in EMT contexts	(14)
Non-coding RNAs	miR-885-5p, miR-30e-5p, miR-378a-3p, miR-26a, miR-17-3p, miR-221, miR-545-5p	Post-transcriptional	Negative	Bind 3' UTR of GALNT3 mRNA	(15-20)
	circSPIRE1	Post-transcriptional	Positive	Binds ELAVL1; stabilizes GALNT3 mRNA	(21)
	circ-RAPGEF5	Competing endogenous RNA	Positive	Sequesters miR-545-5p to upregulate GALNT3	(15)
	PSMA3-AS1, LINC01296	Competing endogenous RNA	Positive	Sequester miRNAs to upregulate GALNT3	(17,19)

GALNT3, polypeptide N-acetylgalactosaminyltransferase 3; FGF23, fibroblast growth factor 23; Pi, extracellular posphate; Egr1, early growth response 1; Etv5, ETS variant transcription factor 5; FGFR1c, fibroblast growth factor receptor 1c; MAP3K4, mitogen-activated protein kinase kinase kinase 4; HDAC6, histone deacetylase histone deacetylase 6; H2BK5ac, histone H2B at lysine 5 acetylation; EMT, epithelial-mesechymal transition; miR-, microRNA; ELAVL1, embryonic lethal abnormal vision-like 1.

hormone FGF23 (29,30). FGF23 was shown to inhibit renal phosphate reabsorption and modulate vitamin D metabolism, thereby regulating the serum phosphate levels (31). Improper processing of FGF23 can result from mutations in *GALNT3*, leading to defective secretion and function, which ultimately causes hyperphosphatemia (22,23,32). When the levels are elevated, serum phosphate reacts with calcium to form hydroxyapatite crystals, which deposit in the soft tissues such as those of the shoulders and hips, leading to the development of painful calcified masses and abnormal bone growth. In addition, the phenotypic expression of FTC and HHS differs greatly among individuals with *GALNT3* mutations. Some may exhibit extensive calcifications and cortical hyperostosis, while others may show dental anomalies or other clinical features (33). Despite this variability, persistent hyperphosphatemia frequently occurs in the affected individuals. This phenotypic heterogeneity highlights the importance of genetic analysis in diagnosing and comprehending the full spectrum of these disorders.

Diagnosing FTC/HHS involves genetic testing for *GALNT3* mutations, as well as imaging techniques such as X-rays or computed tomography (CT) scans that show lobulated calcified masses, and biochemical markers, including hyperphosphatemia with low intact FGF23 levels. The current treatment primarily involves surgical removal of calcified lesions and management of the phosphate levels via dietary adjustments and the use of binders (34). Targeted therapies modulating the GALNT3-FGF23 pathway are still under development.

Coronary artery disease (CAD) and GALNT3. CAD is a complex condition affected by various genetic and molecular factors. One of the factors is the dysregulation of *GALNT3*, which has been linked to the development of CAD. Research has identified specific *GALNT3* genetic variants that increase susceptibility to diseases. For instance, a study involving a Chinese cohort identified two single-nucleotide polymorphisms, rs13427924 and rs4621175, which were significantly associated with CAD. The risk A allele of rs4621175 was correlated with reduced GALNT3 expression at both the mRNA and protein levels, indicating a genetic predisposition to CAD owing to reduced GALNT3 expression (35). Another study found that low GALNT3 levels in patients with CAD were linked to vascular endothelial damage. This damage occurs by inducing apoptosis and increasing matrix metalloproteinase (MMP) expression via the activation of the p38 mitogen-activated protein kinase (MAPK) signaling pathway (36). This finding underscores the role of genetic

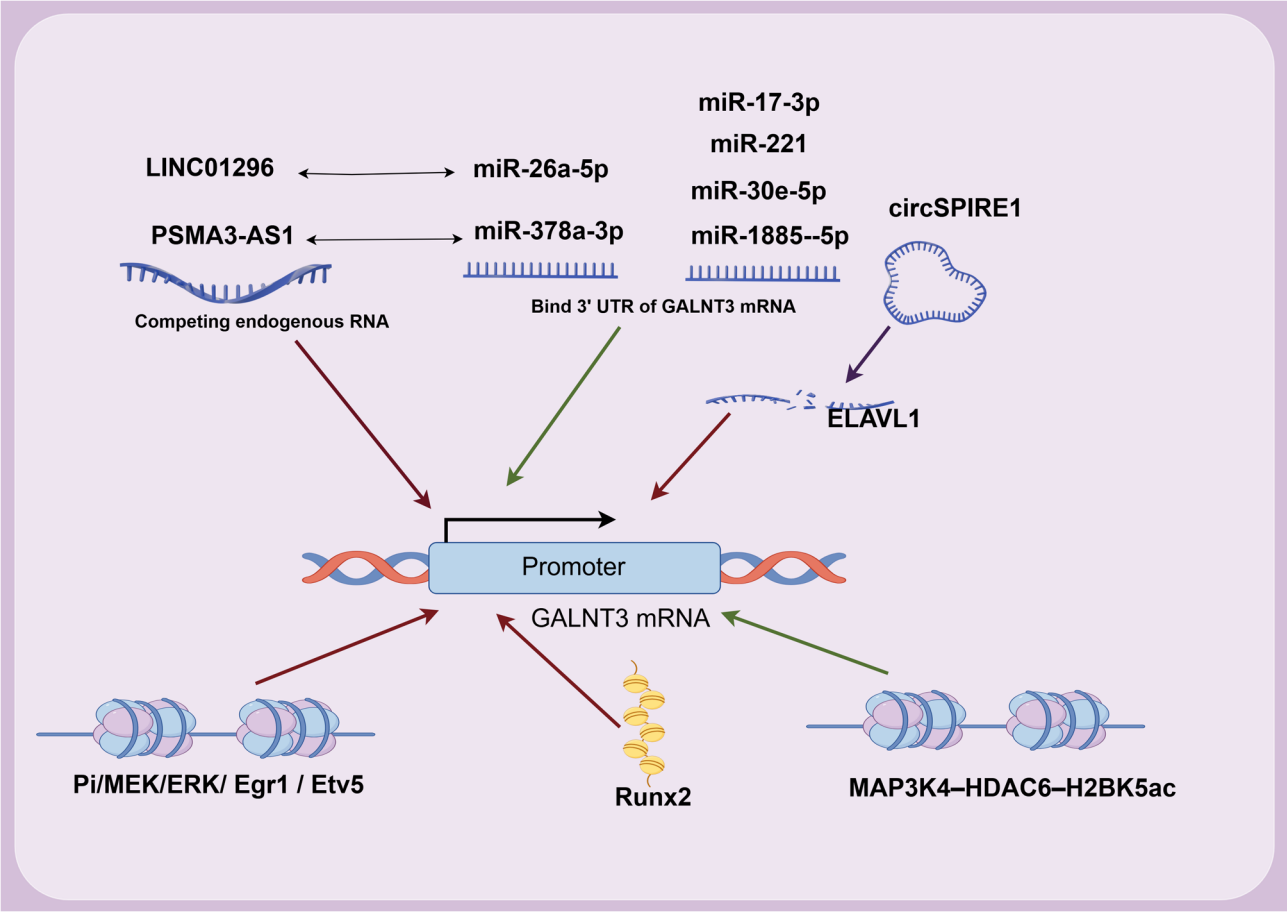

Figure 2. Schematic overview of the transcriptional and epigenetic regulation of GALNT3. [Arrows denote regulatory effects: Red for positive (activation) and green for negative (inhibition)]. GALNT3, polypeptide N-acetylgalactosaminyltransferase 3; miR-, microRNA; ELAVL1, embryonic lethal abnormal vision-like 1; Runx2, runt-related transcription factor 2; Pi, extracellular posphate; Egr1, early growth response 1; Etv5, ETS variant transcription factor 5; MAP3K4, mitogen-activated protein kinase kinase kinase 4; HDAC6, histone deacetylase histone deacetylase 6; H2BK5ac, histone H2B at lysine 5 acetylation. The figure was generated using FigDraw (https://www.figdraw.com).

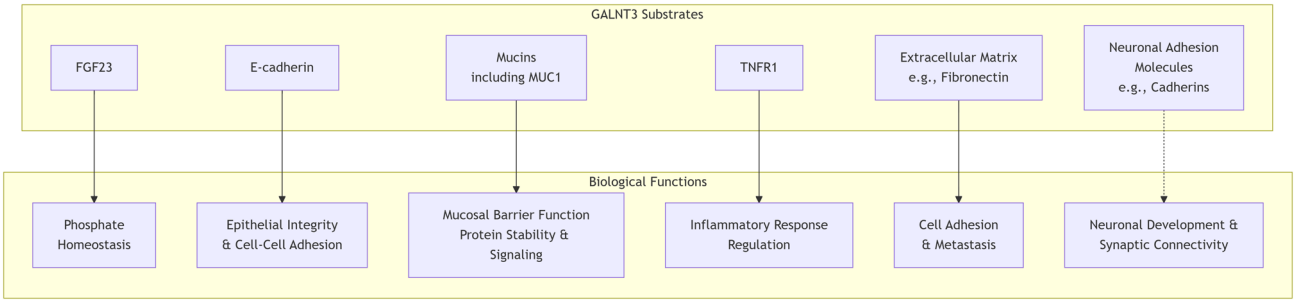

Figure 3. Depiction of a unifying framework of GALNT3 molecular functions (dashed line proposes a potential link between GALNT3 and neural development/function). GALNT3, polypeptide N-acetylgalactosaminyltransferase 3; FGF23, fibroblast growth factor 23; MUC1, mucin 1; TNFR1, tumor necrosis factor receptor 1. The figure was generated using FigDraw (https://www.figdraw.com).

regulation in CAD development and highlights the potential of GALNT3 as a novel gene influencing CAD risk.

Furthermore, GALNT3 dysregulation is a part of a complex network of molecular interactions that contribute to CAD. For example, reduced GALNT3 downregulation has been linked to increased expression of MMP-2 and MMP-14, enzymes that degrade ECM components and promote vascular remodeling and plaque instability. This molecular pathway emphasizes the importance of GALNT3 in maintaining vascular health and its possible role in the progression of CAD (35,36).

In summary, the dysregulation of GALNT3 plays a crucial role in the development of CAD by affecting endothelial cell function and influencing its molecular pathogenesis. The genetic variants of GALNT3 further modulate CAD risk, offering valuable insights into potential treatments and genetic markers for early diagnosis and intervention.

Table II. Comparative summary of the roles of GALNT3 in non-tumor diseases.

Disease	Genetic/regulatory context	Core mechanism involving GALNT3
FTC/HHS	Loss-of-function mutations in *GALNT3*.	Deficient O-glycosylation of FGF23 → impaired secretion and proteolytic processing of active FGF23 → reduced renal phosphate excretion.
CAD	Risk-associated SNPs (such as rs4621175) linked to reduced GALNT3 expression.	Downregulation of GALNT3 → endothelial cell apoptosis and increased MMP expression via p38 MAPK activation → vascular endothelial damage and plaque instability.
IAV infection	Virus-induced alteration of GALNT3 expression (for example via host miRNAs).	Early Stage (Proviral): GALNT3-mediated O-glycosylation supports efficient viral replication. Late Stage (Antiviral): GALNT3 suppresses NF-κB signaling, dampening pro-inflammatory response and potentially limiting overall damage.

GALNT3, polypeptide N-acetylgalactosaminyltransferase 3; FTC/HSS, familial tumoral calcinosis/hyperostosis-hyperphosphatemia syndrome; FGF23, fibroblast growth factor 23; CAD, coronary artery disease; SNPs, single nucleotide polymorphisms; MMP, matrix metalloproteinase; MAPK, mitogen-activated protein kinase; IAV, influenza A virus; miRNAs, microRNAs.

Influenza A virus (IAV) and GALNT3. During IAV infection, the GALNT3 expression is markedly altered, which can significantly influence viral replication and the host immune response. However, the role of GALNT3 in IAV infection is complex and appears paradoxical, with studies displaying both proviral and antiviral effects.

One study suggested that the induced GALNT3 enhances mucin-type O-glycosylation in infected respiratory epithelial cells. This modification appears to be vital for effective viral replication, as knockdown of GALNT3 or its upstream miRNAs significantly decreases viral titers and genomic RNA levels during the early stages of infection (20). A minireplicon assay revealed that GALNT3 enhances the activity of the viral polymerase complex. *In vivo*, *Galnt3*-knockout mice exhibited lower initial viral loads in the lungs, but ultimately developed significantly higher viral titers, more severe lung damage, and increased mortality when compared with the wild-type mice (20). This observation suggested a dual role: GALNT3 promotes intracellular viral replication while also potentially regulating the overall viral spread and lung damage, possibly through its involvement in mucin production and airway defense.

By contrast, Wang *et al* (37) conducted a study that identified an antiviral role for GALNT3. They found that, following an infection, the levels of GALNT3 protein were notably reduced in the lungs of mice susceptible to IAV (37). Unlike the findings of Nakamura *et al* (20), their experiments revealed that overexpressing GALNT3 in cell lines significantly reduced IAV replication. Wang *et al* (37) associated this antiviral effect with the inhibition of the NF-κB-signaling pathway, which plays a central role in inflammation and viral replication. They found that GALNT3 overexpression suppressed the NF-κB-promoter activity and, importantly, prevented the nuclear translocation of phosphorylated p65 (RelA) after IAV infection. By preventing the translocation of this critical transcription factor, GALNT3 dampens the expression of proinflammatory genes and other host factors that the virus may utilize to promote its own replication (37).

The seemingly contradictory roles of GALNT3 in IAV infection, that is, enhancing viral replication according to Nakamura *et al* (20) but inhibiting it as per Wang *et al* (37) likely results from different biological contexts and time points studied. Its proviral activity can mainly be observed during the initial infection phases, where GALNT3-driven O-glycosylation may support early viral replication. Conversely, its antiviral effect appears later, via the suppression of the NF-κB-signaling pathway, which reduces inflammation. This dual function suggests that GALNT3 operates at the intersection of viral replication processes and host immune responses, and its overall impact depends on the specific cellular environment and the stage of infection.

The distinct and common roles of GALNT3 in FTC/HHS, CAD, and IAV have been systematically summarized in Table II, whereas Fig. 4 provides a unified schematic of the underlying pathophysiological mechanisms.

6. Tumors and GALNT3

Lung cancer and GALNT3. In lung cancer, GALNT3 functions as a powerful tumor suppressor via two main mechanisms: Influencing the intrinsic characteristics of tumor cells and the tumor microenvironment (TME) (38). Clinically, reduced GALNT3 expression has been shown to be correlated with advanced tumor stage, poor differentiation, and decreased patient survival (39-41). *In vivo* experiments demonstrated that overexpressing GALNT3 inhibits tumor growth in xenograft (H2030 and PC9) and syngeneic (LLC) models, whereas its knockdown accelerates tumor development (38). Mechanistically, GALNT3 combats lung cancer via the following two connected pathways: i) Inhibiting cancer stemness by decreasing the catenin mRNA/protein levels, limiting its nuclear translocation, and downregulating Wnt target genes such as homeobox B9 (*HOXB9*) and jagged canonical notch ligand 2 (*JAG2*), which reduces tumor-initiating ability; ii) altering the immunosuppressive TME via O-GalNAcylation-mediated suppression of

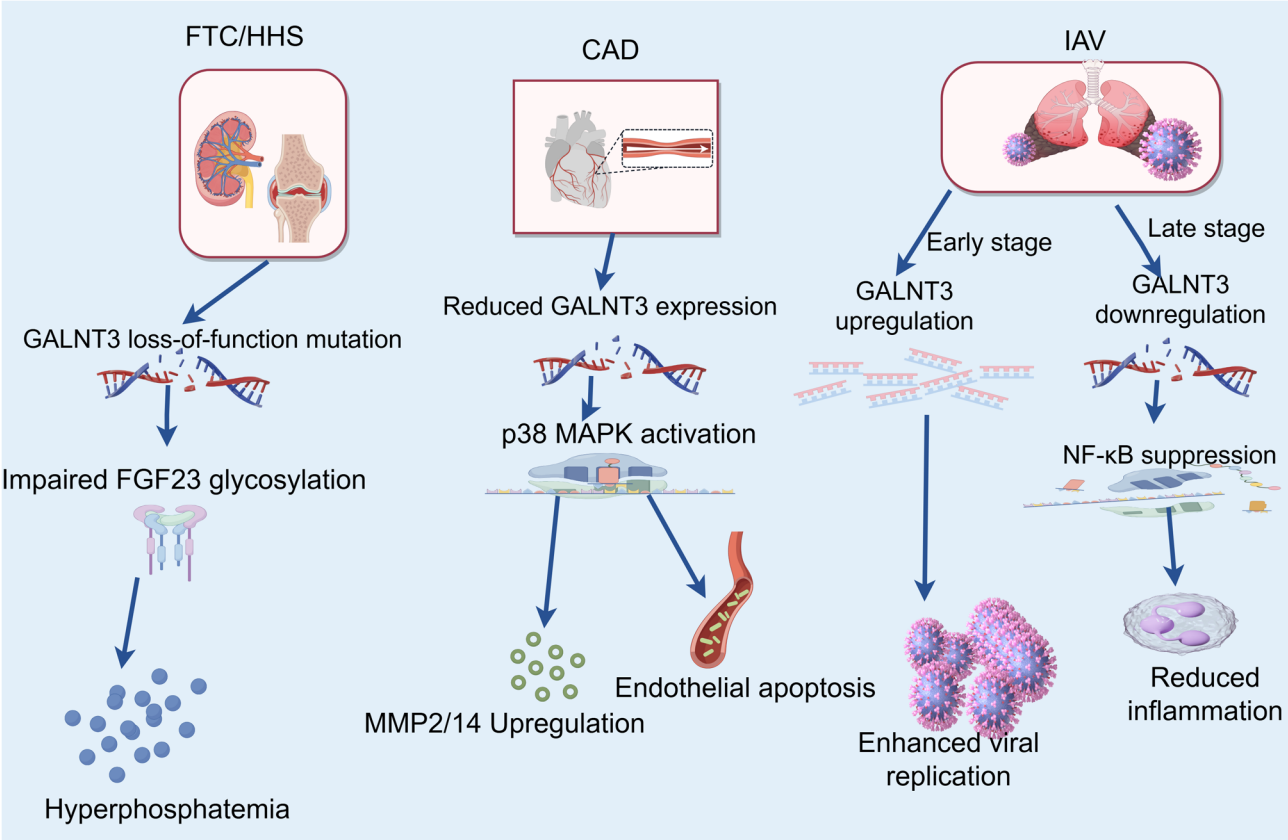

Figure 4. Pathophysiological roles of GALNT3 in non-tumor diseases. GALNT3, polypeptide N-acetylgalactosaminyltransferase 3; FTC/HSS, familial tumoral calcinosis/hyperostosis-hyperphosphatemia syndrome; CAD, coronary artery disease; IAV, influenza A virus; FGF23, fibroblast growth factor 23; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase. The figure was generated using FigDraw (https://www.figdraw.com).

TNFR1-NF-κB- and c-MET-PI3K-AKT-signaling pathways, which lead to decreased C-X-C motif chemokine ligand 1 (CXCL1) secretion. This decrease suppresses the recruitment of proangiogenic polymorphonuclear-myeloid-derived suppressor cells (PMN-MDSCs) ($CD11b^+Gr1^+Ly6G^+$), ultimately disrupting tumor vascularization, as evidenced by diminished $CD31^+$ vasculature. Therapeutically, the GALNT3-regulated gene signature serves as a prognostic biomarker for favorable survival outcomes, while GALNT3 itself appears to be a promising therapeutic target. Restoring GALNT3 offers a multifaceted approach to combating lung cancer by simultaneously reducing cancer stemness and disrupting MDSC-driven immunosuppression and angiogenesis (38). Considering the complexity of these interacting pathways, the multifaceted tumor-suppressive mechanism of GALNT3 is schematically summarized in Fig. 5 to provide a clearer overview.

CRC and GALNT3. GALNT3 plays an essential oncogenic role in CRC progression. Evidence from clinical studies indicates that GALNT3 is considerably upregulated in CRC tissues compared with that in the adjacent normal tissues, with higher expression linked to advanced tumor stages, metastasis, and poorer prognosis (15,19). Mechanistically, its dysregulation is regulated by ncRNA networks. For example, circ-RAPGEF5 was shown to act as a sponge for miR-545-5p, reducing its suppression of GALNT3. The circ-RAPGEF5/miR-545-5p/GALNT3 axis was demonstrated to enhance CRC cell proliferation, migration, and invasion, while decreasing apoptosis and promoting tumor growth *in vivo*. The knockdown of GALNT3 reversed these malignant characteristics, highlighting its critical role in CRC development (15).

GALNT3-mediated O-glycosylation has a direct influence on oncogenic signaling pathways in CRC. A key regulatory axis involves the lncRNA linc01296, which binds miR-26a to suppress the GALNT3 expression. GALNT3 catalyzes aberrant O-glycosylation of mucin 1 (MUC1), stabilizing its active form and activating the PI3K/AKT pathway (19). This sequence of events fosters increased cell survival, metastasis, and resistance to chemotherapy (such as 5-fluorouracil). Animal studies have demonstrated that targeting the linc01296/miR-26a/GALNT3 axis can reduce CRC liver metastasis and tumor growth in xenograft models, positioning GALNT3 as a key link between glycosylation and oncogenic signaling in CRC (19). As detailed above, GALNT3 sits at the center of a complex ceRNA network in CRC. A consolidated overview of these regulatory axes is shown in Table III. The critical downstream mechanism, whereby GALNT3-mediated MUC1 glycosylation drives oncogenic signaling and chemoresistance, can be observed in Fig. 6.

Ovarian cancer and GALNT3. In epithelial ovarian cancer (EOC), GALNT3 is frequently overexpressed in advanced tumors and linked to poor outcomes. Its oncogenic function involves complex regulatory networks, particularly involving

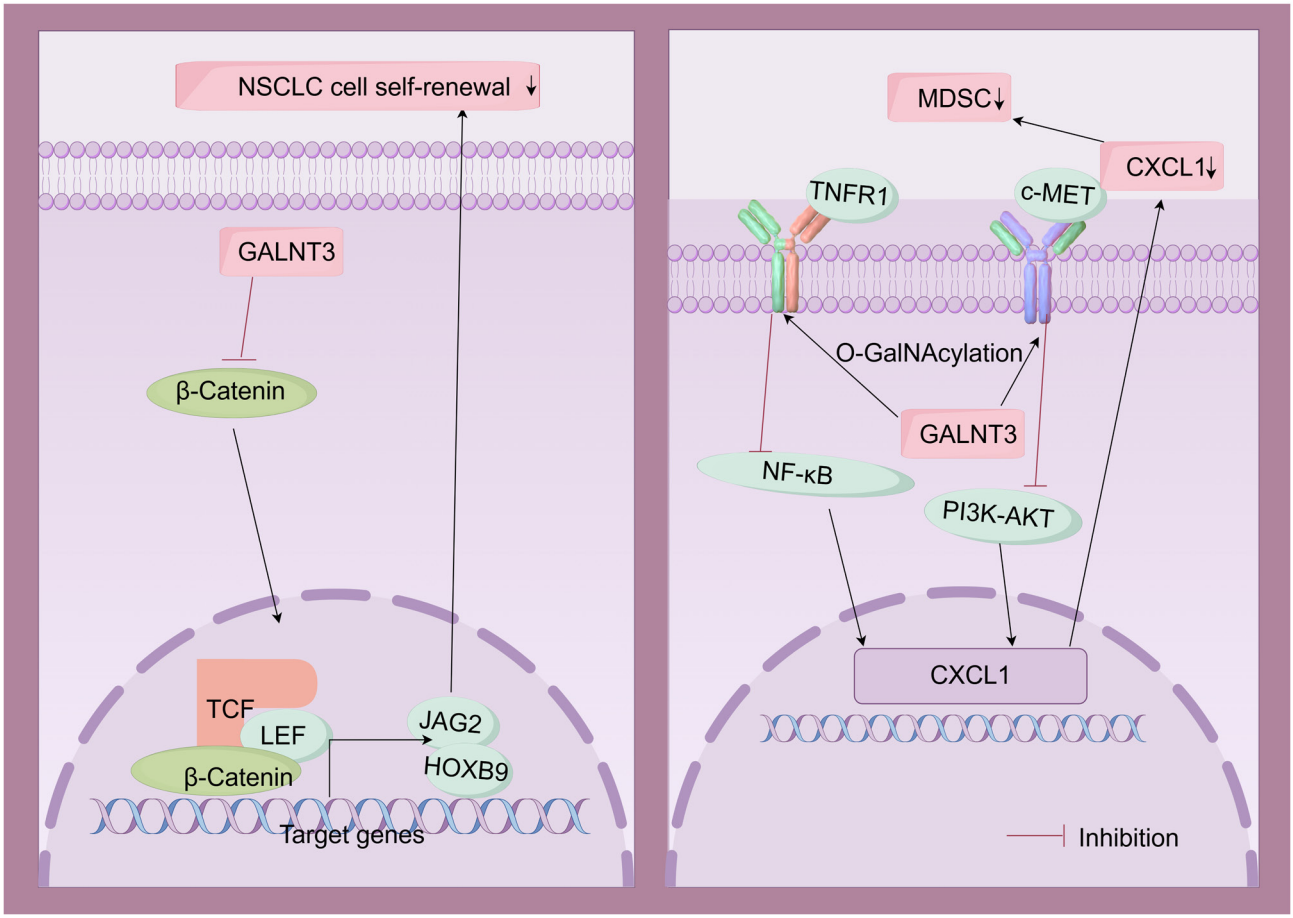

Figure 5. Mechanism supporting the tumor-suppressive role of GALNT3 in lung cancer. GALNT3, polypeptide N-acetylgalactosaminyltransferase 3; NSCLC, non-small cell lung cancer; TCF, T-cell factor; LEF, lymphoid enhancer-binding factor; HOXB9, homeobox B9; JAG2, jagged canonical notch ligand 2; MDSC, myeloid-derived suppressor cell; TNFR1, tumor necrosis factor receptor 1; CXCL1, C-X-C motif chemokine ligand 1. The figure was generated using FigDraw (https://www.figdraw.com).

the lncRNA PSMA3-AS1, which binds to miR-378a-3p to increase the GALNT3 levels (17). GALNT3 promotes O-glycosylation, which stabilizes oncoproteins such as MUC1 (26), leading to the activation of the prosurvival PI3K/Akt pathway and driving tumor growth, invasion, and metabolic changes.

A key feature of GALNT3 in ovarian cancer is its functional redundancy with GALNT6 (26). Suppressing GALNT3 alone causes a compensatory upregulation of GALNT6, which maintains the O-glycosylation of shared substrates and partially restores the oncogenic phenotypes. Therefore, the dual suppression of GALNT3 and GALNT6 is necessary to maximize therapeutic effects, resulting in a greater reduction in proliferation, migration, invasion, and intraperitoneal tumor formation when compared to targeting either enzyme alone (26). This redundancy highlights the importance of combination strategies in overcoming adaptive resistance and identifies GALNT3 and GALNT6 as synergistic biomarkers and therapeutic targets in EOC. The therapeutic challenge posed by the functional redundancy between GALNT3 and GALNT6 and the superior efficacy of their co-suppression is illustrated in Fig. 7.

Breast cancer and GALNT3. Research on the expression and role of GALNT3 in breast cancer suggests that it influences tumor development. A 2005 immunogenomics study identified GALNT3 as one of five tumor-associated antigens whose expression increased in proportion to the tumor size in a HER2-driven murine mammary carcinoma model (BALB-neuT) (42). Although the GALNT3 levels were lower than those of HER2, it was consistently present in human breast tumors, indicating its potential as a target for immunopreventive therapies (42).

Conversely, a study by Raghu *et al* (14) showed that GALNT3 is a key suppressor of EMT in breast cancer. According to their results, GALNT3 expression is significantly decreased in aggressive, mesenchymal-like claudin-low breast cancer cells, such as SUM159, when compared with normal human mammary epithelial cells. This reduction in GALNT3 has significant functional consequences, resulting in a widespread decrease in O-GalNAc glycosylation. Notably, GALNT3 directly facilitates the O-GalNAc glycosylation of E-cadherin. Without GALNT3, E-cadherin cannot reach the plasma membrane and instead remains inside the cell within the Golgi apparatus. This mislocalization hinders the formation of adherens junctions, weakens cell-cell adhesion, and promotes the development of mesenchymal features, such as increased motility and invasiveness. While restoring GALNT3 can reverse EMT in some cell models, doing so in established claudin-low breast cancer cells does not restore epithelial traits,

Table III. Summary of ncRNA-GALNT3-regulatory axes in colorectal cancer.

ncRNA axis	Regulatory mechanism	Effect on GALNT3	Downstream consequences	Clinical relevance
circ-RAPGEF5/ miR-545-5p	circ-RAPGEF5 sponges miR-545-5p, relieving its suppression of GALNT3	Upregulation	Promotes proliferation, migration, invasion; inhibits apoptosis; accelerates tumor growth *in vivo*	Associated with advanced stage and poor prognosis
linc01296/ miR-26a	linc01296 sequesters miR-26a, derepressing GALNT3 expression	Upregulation	GALNT3 glycosylates MUC1 → activates PI3K/ AKT → enhances cell survival, metastasis, and 5-FU resistance	Promotes liver metastasis; potential target for combination therapy

ncRNA, noncoding RNA; GALNT3, polypeptide N-acetylgalactosaminyltransferase 3; circ-, circular RNA; miR-, microRNA; long ncRNAsMUC1, mucin 1; 5-FU, 5-fluorouracil.

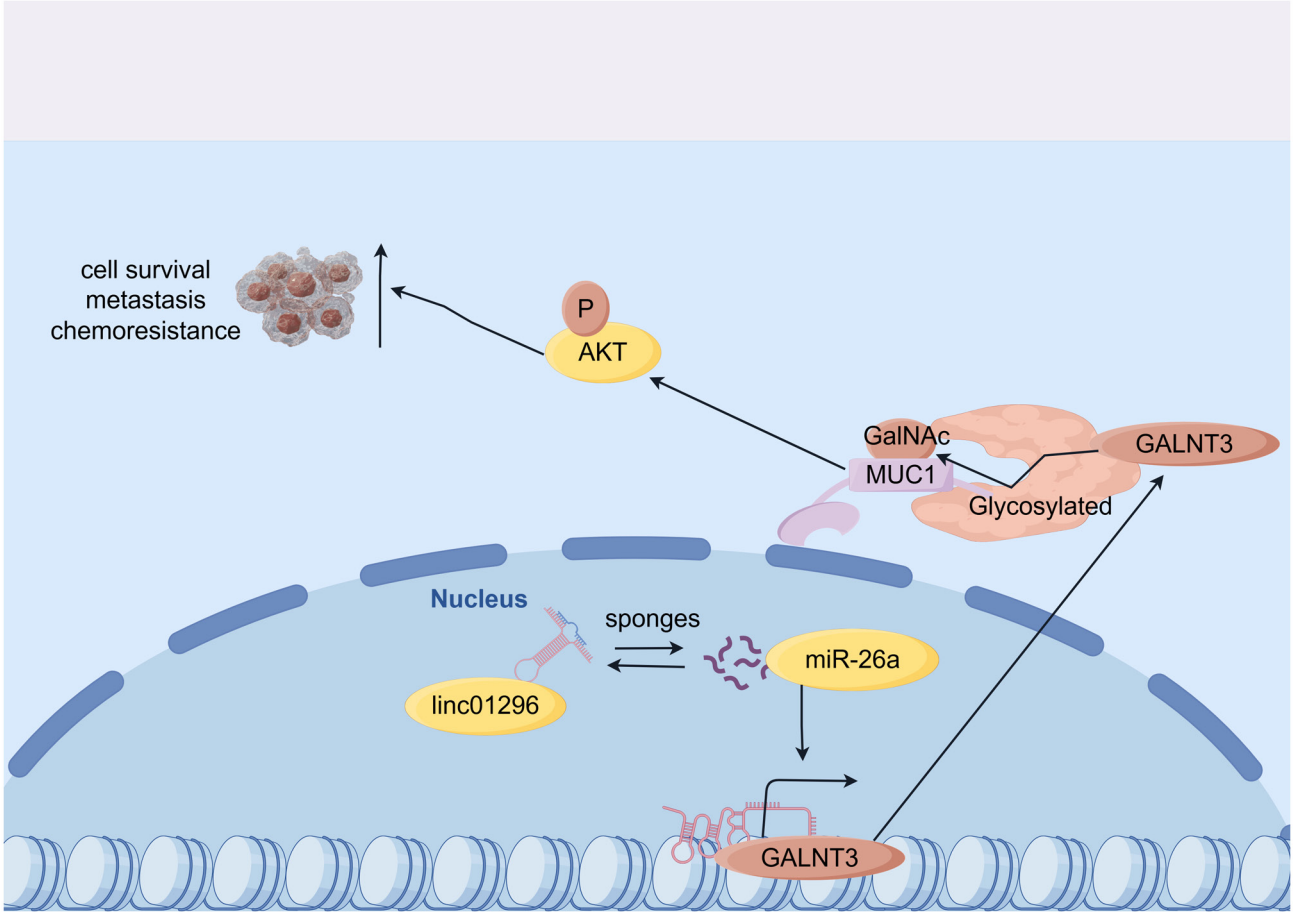

Figure 6. GALNT3 promotes colorectal cancer progression and chemoresistance via MUC1 glycosylation and PI3K/AKT activation. GALNT3, polypeptide N-acetylgalactosaminyltransferase 3; MUC1, mucin 1; GalNAc, N-acetylgalactosamine; miR-, microRNA. The figure was generated using FigDraw (https://www.figdraw.com).

hinting that GALNT3 loss may be an early, pivotal event in a wider, possibly irreversible EMT process during breast cancer development (14). Overall, GALNT3 is a crucial post-translational regulator of epithelial integrity, and its decreased expression is a characteristic of the aggressive, mesenchymal breast cancer subtype.

These apparently contradictory findings can be explained by the heterogeneity of breast cancer. Although GALNT3 might be upregulated in certain subtypes as a part of a tumor-associated antigen profile, its loss in aggressive claudin-low cancers could promote mesenchymal transition and invasion. Therefore, GALNT3 may serve as a double-edged sword in breast

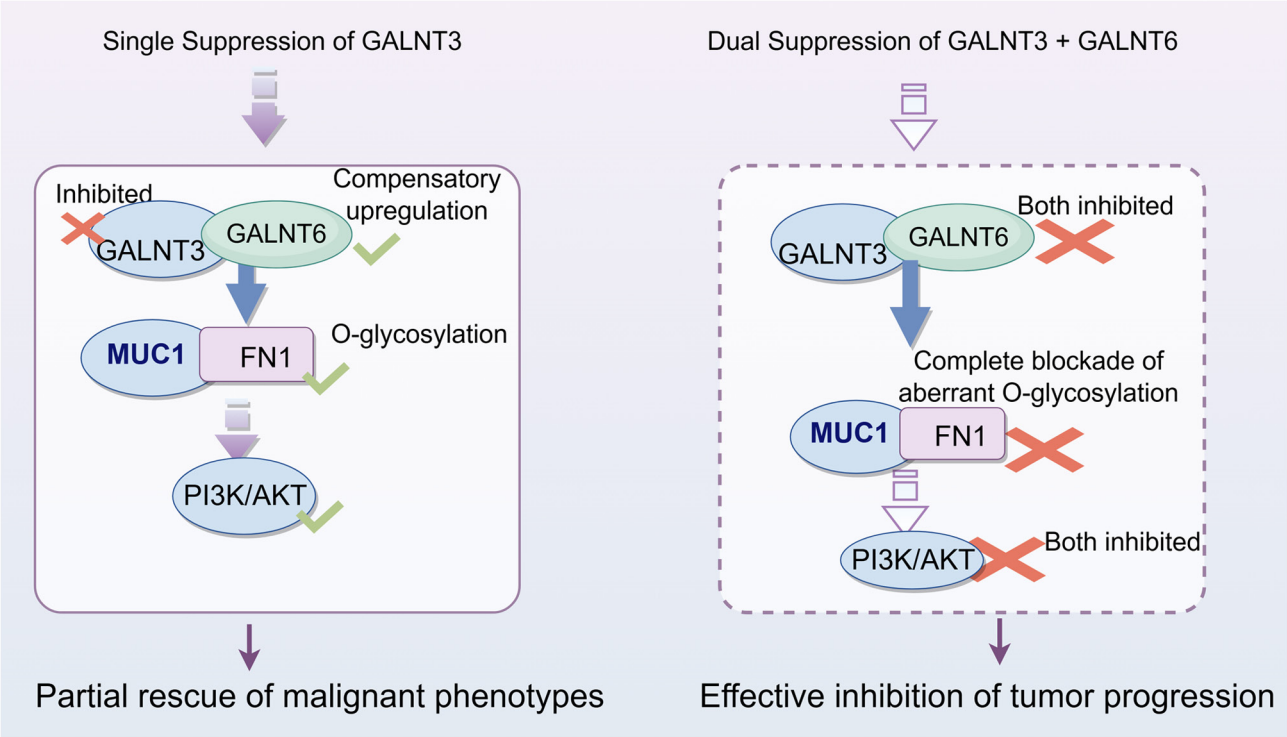

Figure 7. Functional redundancy between GALNT3 and GALNT6 in ovarian cancer and the rationale for combinatorial targeting. GALNT3, polypeptide N-acetylgalactosaminyltransferase 3; GALNT6, polypeptide N-acetylgalactosaminyltransferase 6; MUC1, mucin 1; FN1, fibronectin. The figure was generated using FigDraw (https://www.figdraw.com).

cancer: Enhancing tumor antigenicity in some situations while maintaining epithelial integrity in others. Additional research is thus necessary to comprehend the regulatory mechanisms and context-specific roles of GALNT3 across various breast cancer subtypes. The context-dependent dual role of GALNT3 in different breast cancer subtypes is summarized in Fig. 8, aiding to understand its seemingly contradictory functions.

Pancreatic cancer and GALNT3. The role of GALNT3 in pancreatic ductal adenocarcinoma (PDAC) is complex and context-dependent. Foundational work has established its tumor-promoting function, suggesting that GALNT3 is overexpressed in the majority of PDAC cell lines (6 of 8) while being undetectable in poorly differentiated lines such as PANC-1 and MIA PaCa-2 (43). Functionally, GALNT3 suppression attenuated cancer cell growth both *in vitro* and *in vivo* by inducing apoptosis, partly through O-glycosylation of its substrate guanine nucleotide-binding protein G(t) subunit α1 (GNAT1), which regulates GNAT1 stability and subcellular distribution (43).

Subsequently, Chugh *et al* (44) systematically elucidated the context-dependent duality of GALNT3. Their study first revealed that, in poorly differentiated PDAC, GALNT3 expression is significantly lost and that its knockdown enhances proliferation, motility, and tumor-endothelium adhesion. This phenotype was mechanistically linked to aberrant O-glycosylation and hyperactivation of ErbB receptors (namely EGFR and Her2) (44).

Subsequently, the same team identified a contrasting role for GALNT3 in pancreatic cancer stem cells (PCSCs), where it is highly expressed and essential for maintaining stemness. GALNT3 knockdown in PCSCs reduced the core stemness markers (SOX2, OCT3/4) and surface marker epithelial-specific antigen, which led to the impairment of the self-renewal capacity and tumorigenicity (45).

The role of GALNT3 in PDAC is complex and exhibits striking context-dependent duality, functioning as both a tumor promoter and a tumor suppressor. This paradox is resolved when considering the cellular differentiation state, that is, while GALNT3 promotes tumor growth in well-differentiated contexts and is essential for maintaining stemness in PCSCs, its loss in poorly differentiated carcinomas is associated with enhanced aggressiveness. To integrate these seemingly contradictory findings and provide a unified visual model, this context-dependent duality is summarized in Fig. 9. Collectively, these studies illustrate the context-dependent duality of GALNT3 in PDAC. However, it must be acknowledged that the overall research specifically focusing on GALNT3 in this malignancy remains limited. The scarcity of data, particularly concerning its direct mechanistic link to survival pathways such as PI3K/AKT/MAPK in PCSCs, represents a significant knowledge gap that future work must address to fully elucidate its roles.

7. Dual role of GALNT3 in cancer: Mechanisms underlying context-dependent functions

As detailed throughout this review, GALNT3 exhibits a notable duality in cancer, functioning as a tumor suppressor in malignancies such as lung cancer, while promoting tumor aggressiveness in colorectal and ovarian cancer. The most striking examples of this context-dependent role are found

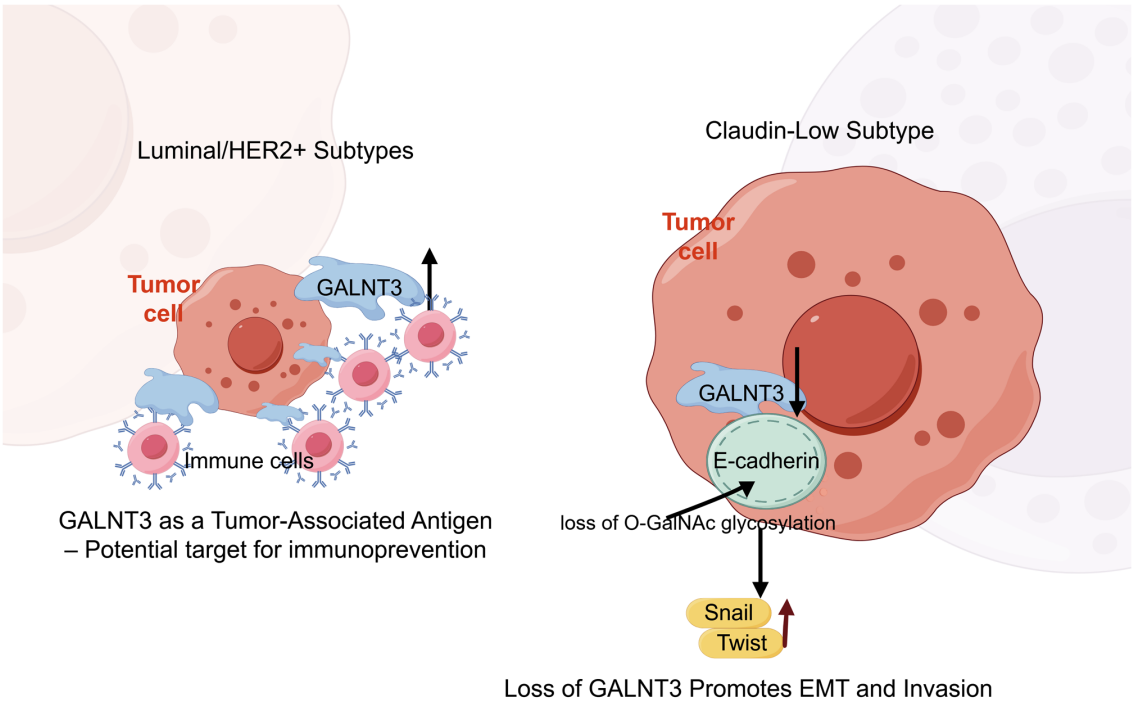

Figure 8. Context-dependent dual roles of GALNT3 in breast cancer subtypes. GALNT3, polypeptide N-acetylgalactosaminyltransferase 3; O-GalNAc, O-linked N-acetylgalactosamine; EMT, epithelial-mesenchymal transition. The figure was generated using FigDraw (https://www.figdraw.com).

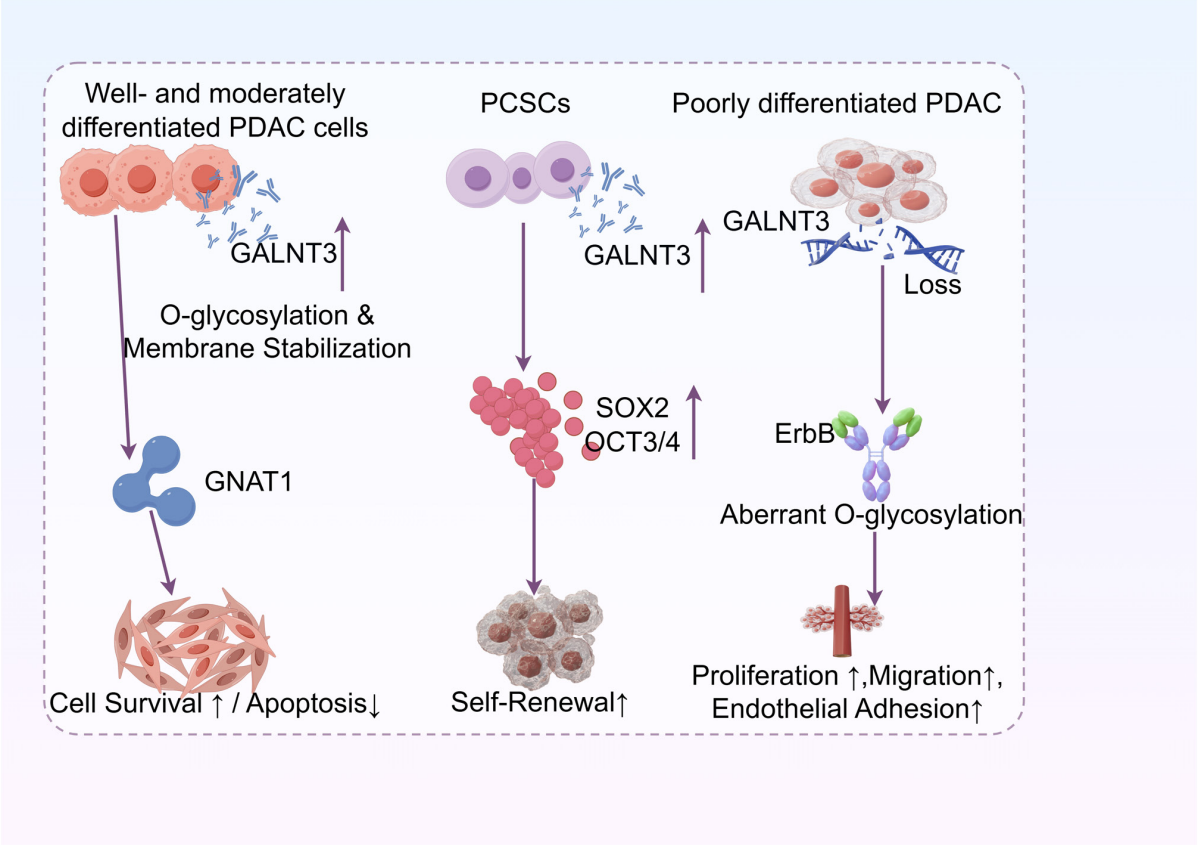

Figure 9. Context-dependent dual roles of GALNT3 in PDAC. GALNT3, polypeptide N-acetylgalactosaminyltransferase 3; PDAC, pancreatic ductal adenocarcinoma; PCSCs, pancreatic cancer stem cells; GNAT1, guanine nucleotide-binding protein G(t) subunit α1. The figure was generated using FigDraw (https://www.figdraw.com).

Table IV. Summary of the roles of GALNT3 in human cancers.

Cancer type	Expression pattern	Role	Key mechanisms	Prognostic association
Lung cancer	Downregulated	Tumor suppressor	Inhibits Wnt/β-catenin signaling to reduce stemness; suppresses TNFR1/NF-κB and c-MET/PI3K/AKT pathways to alter the immune microenvironment and angiogenesis.	Low expression is correlated with advanced stage and poor survival.
Colorectal cancer	Upregulated	Oncogene	Core of ceRNA networks (such as circ-RAPGEF5/miR-545-5p, linc01296/miR-26a); stabilizes MUC1 via O-glycosylation to activate the PI3K/AKT pathway.	High expression is correlated with advanced stage, metastasis, and poor prognosis.
Ovarian cancer	Upregulated	Oncogene	Regulated by the lncRNA PSMA3-AS1/miR-378a-3p axis; glycosylates MUC1 and FN1; exhibits functional redundancy with GALNT6.	High expression is correlated with poor outcomes.
Breast cancer	Context-dependent	Dual role	Claudin-low subtype: Loss of GALNT3 disrupts E-cadherin trafficking, promoting EMT. Other subtypes: Upregulated as a tumor-associated antigen.	Context-dependent; loss in aggressive subtypes is associated with poor differentiation.
Pancreatic cancer	Context-dependent	Dual role	Well-differentiated/CSCs: Promotes growth and stemness. Poorly differentiated: Loss enhances aggressiveness and ErbB signaling.	Complex; associated with differentiation state and stemness.

GALNT3, polypeptide N-acetylgalactosaminyltransferase 3; TNFR1, tumor necrosis factor receptor 1; ceRNA, competing endogenous RNA; circ-, circular RNA; miR, microRNA; lncRNA, long noncoding RNA MUC1, mucin 1; FN1, fibronectin; GALNT6, polypeptide N-acetylgalactosaminyltransferase 6; EMT, epithelial-mesenchymal transition; CSCs, cancer stem cells.

in breast and pancreatic cancers; both exhibit paradoxical functions for GALNT3. The context-dependent expression patterns, roles, molecular mechanisms, and clinical associations of GALNT3 across major cancer types have been systematically summarized in Table IV. In breast cancer, it is associated with increased tumor antigenicity, yet it also suppresses the EMT. Similarly, in PDAC, GALNT3 can either promote tumor growth and stemness or suppress aggressiveness, depending on the cellular context. Such context-dependent duality is not unique to GALNT3; rather, it represents a broader biological phenomenon, wherein the functional output of a gene is governed by a complex interplay of tissue-specific and subtype-specific factors (46,47).

Tissue- and subtype-specific microenvironment. The composition of the TME, encompassing the ECM, immune cell infiltration, and stromal interactions, varies between tissues and cancer subtypes (48). For example, in breast cancer, the claudin-low subtype has a microenvironment that is different from that of HER2-driven tumors (14,42,49). These variations probably affect the substrates accessible to GALNT3 and influence the downstream effects of its glycosylation, thereby impacting tumor development.

Substrate specificity and signaling pathway crosstalk. The function of a gene is not executed in isolation, but is critically determined by its specific molecular partners and the broader signaling network in which it operates, a phenomenon aptly described as 'substrate specificity and signaling pathway crosstalk' (50-52). The functional role of GALNT3 depends on its key protein substrates within a specific cellular environment. In lung cancer (38), GALNT3-driven O-GalNAcylation was shown to suppress oncogenic signaling by modifying receptors such as TNFR1 and c-MET, leading to decreased activity of the NF-κB and PI3K/AKT pathways. By contrast, in CRC (19), GALNT3 was demonstrated to glycosylate and stabilize oncoproteins such as MUC1, resulting in the activation of the prosurvival PI3K/AKT pathway. The contradictory effects observed in breast cancer can be explained by different substrate choices: In aggressive claudin-low subtypes, GALNT3 has been shown to glycosylate E-cadherin to maintain epithelial integrity and prevent EMT, whereas, in other contexts, it may target different substrates that promote tumorigenicity.

Regulatory networks. The expression and function of a gene are profoundly influenced by its position within tissue-specific and subtype-specific regulatory networks (53). For instance,

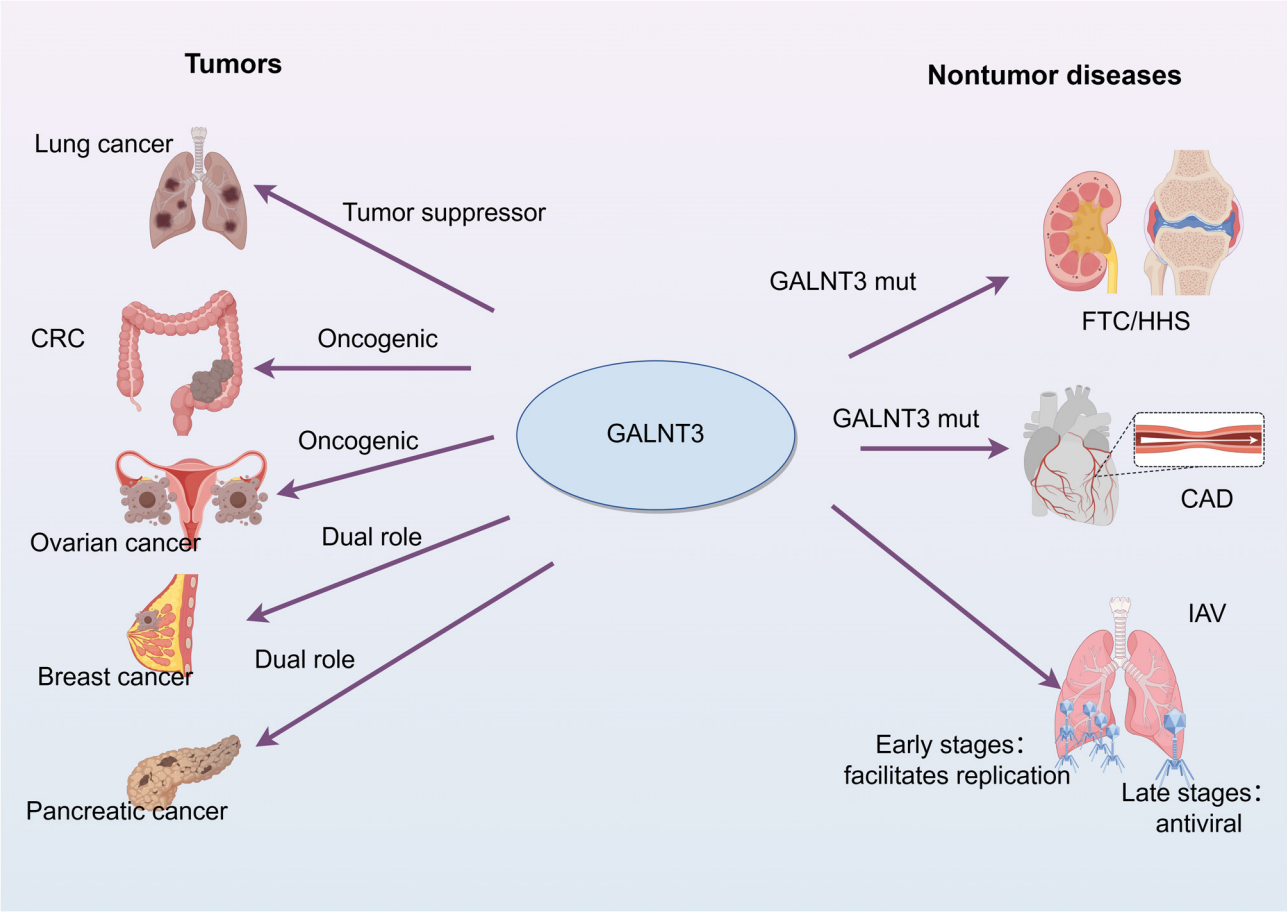

Figure 10. Summary of the roles of GALNT3 across human diseases. GALNT3, polypeptide N-acetylgalactosaminyltransferase 3; CRC, colorectal cancer; FTC/HSS, familial tumoral calcinosis/hyperostosis-hyperphosphatemia syndrome; CAD, coronary artery disease; IAV, influenza A virus. The figure was generated using FigDraw (https://www.figdraw.com).

specific ceRNA networks involving lncRNAs, miRNAs, and mRNAs have been identified in various cancers, which post-transcriptionally regulate oncogenes or tumor suppressors in a manner that is often dependent on clinical features such as tumor stage, subtype classification, or patient survival (54-56). The expression of GALNT3 is governed by distinct, tissue-specific, and subtype-specific regulatory networks involving ncRNAs (15-19,21). These networks determine GALNT3 expression, effectively positioning it either as a protector against tumor development or as a promoter of malignant progression.

In summary, the dual role of GALNT3 in cancer exemplifies context-dependent biology, influenced by the tissue type, molecular subtype, TME, substrate choice, and signaling crosstalk within the GALNT enzyme family.

8. Clinical translation and therapeutic targeting of GALNT3

The strong evidence linking GALNT3 to various human diseases highlights its promise as a biomarker and therapeutic target. However, turning this promise into clinical use is challenging mainly because its functions depend on specific contexts. Several promising therapeutic approaches are emerging to target GALNT3. These include developing small-molecule modulators to directly inhibit or activate its enzymatic function (57), though achieving isoform specificity remains challenging. RNA-based therapies (58,59), such as siRNA or antisense oligonucleotides, offer a viable alternative by silencing GALNT3 or its positive ncRNA regulators. In addition, immunotherapy aims to exploit GALNT3-mediated glycosylation by targeting tumor-specific glycopeptides with monoclonal antibodies or CAR-T cells (60,61). Finally, for loss-of-function conditions such as FTC/HHS, gene therapy offers a logical strategy to restore GALNT3 activity, with initial proof-of-concept demonstrated in animal models (32). To date, all therapeutic approaches aimed at directly modulating GALNT3, including small-molecule modulators, RNA-based therapies, and immunotherapeutic strategies targeting its glycopeptide products, remain in the preclinical research phase. No clinical trials specifically targeting GALNT3 have been initiated or reported, underscoring a significant translational gap that must be addressed in future studies.

Notably, fully understanding the biology of GALNT3 and realizing its therapeutic potential is quite challenging owing to the widespread phenomenon of functional redundancy among GALNT family members (26). This phenomenon of functional redundancy presents a distinct layer of complexity in understanding the biology of GALNT3 and, more importantly, in developing an effective

therapeutic strategy. This compensatory mechanism has profound therapeutic implications. It suggests that targeting GALNT3 alone is likely to be insufficient, as the system can bypass its inhibition through the action of GALNT6. Consequently, a combinatorial targeting strategy that simultaneously inhibits both GALNT3 and GALNT6 has been proposed to achieve a more robust and durable antitumor effect in ovarian cancer models. Beyond ovarian cancer, this paradigm of redundancy may extend to other contexts. For instance, in pancreatic cancer, the loss of one GALNT member might be compensated for by another, which adds another dimension to the context-dependent functions of these enzymes. Therefore, appreciating the interconnectedness and compensatory potential within the GALNT family is crucial for overcoming adaptive resistance and designing successful glycosylation-targeted therapies.

To address these challenges and unlock the therapeutic potential of GALNT3, future research should focus on several key areas. Developing isoform-specific pharmacological agents, guided by advanced structural biology, is crucial. Meanwhile, large-scale clinical trials are needed to confirm GALNT3-related biomarkers for improved patient stratification. In addition, investigating rational combination therapies, such as co-targeting GALNT3 and related pathways, such as GALNT6, or combining its modulators with existing treatments, using physiologically relevant preclinical models, will be vital for creating effective, targeted therapies.

9. Conclusion

As summarized in the accompanying Fig. 10, GALNT3 is an attractive and versatile target in oncologic, metabolic, and genetic diseases. However, its clinical application requires addressing complex biological and pharmacological challenges. Gaining a thorough understanding of its context-dependent mechanisms and creating advanced, targeted therapies are thus crucial for unlocking its full therapeutic potential as a key glycosyltransferase.

Acknowledgements

Not applicable.

Funding

The present review was supported in part by a grant from the Guangxi Youth Science Foundation-Collaborative Program on Proactive Health and Common & Frequently Occurring Diseases (grant no. 2024GXNSFBA010042).

Availability of data and materials

Not applicable.

Authors' contributions

All authors made substantial contributions to this review article. LS and YL contributed equally to this work. XH and ZL conceived the review and designed the review framework. LS and YL performed the primary literature search and drafted the initial manuscript. ZL contributed significantly to the critical analysis, interpretation of findings, and revision of the manuscript for intellectual content. XH provided expert guidance and supervision throughout the project. Data authentication is not applicable. All authors critically reviewed, edited, and approved the final manuscript for submission and publication.

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. Tran LS, Chia J, Le Guezennec X, Tham KM, Nguyen AT, Sandrin V, Chen WC, Leng TT, Sechachalam S, Leong KP and Bard FA: ER O-glycosylation in synovial fibroblasts drives cartilage degradation. Nat Commun 16: 2535, 2025.
2. Mereiter S, Balmaña M, Campos D, Gomes J and Reis CA: Glycosylation in the era of cancer-targeted therapy: Where are we heading? Cancer Cell 36: 6-16, 2019.
3. RodrÍguez E, Schetters STT and van Kooyk Y: The tumour glyco-code as a novel immune checkpoint for immunotherapy. Nat Rev Immunol 18: 204-211, 2018.
4. Kato K, Jeanneau C, Tarp MA, Benet-Pagès A, Lorenz-Depiereux B, Bennett EP, Mandel U, Strom TM and Clausen H: Polypeptide GalNAc-transferase T3 and familial tumoral calcinosis. Secretion of fibroblast growth factor 23 requires O-glycosylation. J Biol Chem 281: 18370-18377, 2006.
5. Miao C, Sun R, Ji D, Wu M, Fu Q, Mei L and Wu Z: Mechanism of the GALNT family proteins in regulating tumorigenesis and development of lung cancer (Review). Mol Clin Oncol 22: 37, 2025.
6. Kato K, Hansen L and Clausen H: Polypeptide N-acetylgalactosaminyltransferase-associated phenotypes in mammals. Molecules 26: 2204, 2021.
7. Bennett EP, Weghuis DO, Merkx G, van Kessel AG, Eiberg H and Clausen H: Genomic organization and chromosomal localization of three members of the UDP-N-acetylgalactosamine: Polypeptide N-acetylgalactosaminyltransferase family. Glycobiology 8: 547-555, 1998.
8. Fang Y, Chung SSW, Xu L, Xue C, Liu X, Jiang D, Li R, Korogi Y, Yuan K, Saqi A, *et al*: RUNX2 promotes fibrosis via an alveolar-to-pathological fibroblast transition. Nature 640: 221-230, 2025.
9. Huang Z, Liu B, Li X, Jin C, Hu Q, Zhao Z, Sun Y and Wang Q: RUNX2 enhances bladder cancer progression by promoting glutamine metabolism. Neoplasia 60: 101120, 2025.
10. Huang J, Jia R and Guo J: RUNX2 isoform II protects cancer cells from ferroptosis and apoptosis by promoting PRDX2 expression in oral squamous cell carcinoma. Elife 13: RP99122, 2025.
11. Jiang Q, Qin X, Moriishi T, Fukuyama R, Katsumata S, Matsuzaki H, Komori H, Matsuo Y, Sakane C, Ito K, *et al*: Runx2 regulates Galnt3 and Fgf23 expressions and Galnt3 decelerates osteoid mineralization by stabilizing Fgf23. Int J Mol Sci 25: 2275, 2024.
12. Takashi Y and Fukumoto S: Phosphate-sensing. Adv Exp Med Biol 1362: 27-35, 2022.
13. Takashi Y, Kosako H, Sawatsubashi S, Kinoshita Y, Ito N, Tsoumpra MK, Nangaku M, Abe M, Matsuhisa M, Kato S, *et al*: Activation of unliganded FGF receptor by extracellular phosphate potentiates proteolytic protection of FGF23 by its O-glycosylation. Proc Natl Acad Sci USA 116: 11418-11427, 2019.
14. Raghu D, Mobley RJ, Shendy NAM, Perry CH and Abell AN: GALNT3 maintains the epithelial state in trophoblast stem cells. Cell Rep 26: 3684-3697.e7, 2019.

15. Cheng D, Chu F, Liang F, Zhang N, Wang J and Yue W: Downregulation of circ-RAPGEF5 inhibits colorectal cancer progression by reducing the expression of polypeptide N-acetylgalactosaminyltransferase 3 GALNT3). Environ Toxicol 39: 4249-4260, 2024.
16. Mao W, Zhang L, Wang Y, Sun S, Wu J, Sun J, Zou X, Chen M and Zhang G: Cisplatin induces acute kidney injury by down-regulating miR-30e-5p that targets Galnt3 to activate the AMPK signaling pathway. Environ Toxicol 39: 1567-1580, 2024.
17. Xu Z, Jin H, Duan X, Liu H, Zhao X, Fan S, Wang Y and Yao T: LncRNA PSMA3-AS1 promotes cell proliferation, migration, and invasion in ovarian cancer by activating the PI3K/Akt pathway via the miR-378a-3p/GALNT3 axis. Environ Toxicol 36: 2562-2577, 2021.
18. Lixin S, Wei S, Haibin S, Qingfu L and Tiemin P: miR-885-5p inhibits proliferation and metastasis by targeting IGF2BP1 and GALNT3 in human intrahepatic cholangiocarcinoma. Mol Carcinog 59: 1371-1381, 2020.
19. Liu B, Pan S, Xiao Y, Liu Q, Xu J and Jia L: LINC01296/miR-26a/GALNT3 axis contributes to colorectal cancer progression by regulating O-glycosylated MUC1 via PI3K/AKT pathway. J Exp Clin Cancer Res 37: 316, 2018.
20. Nakamura S, Horie M, Daidoji T, Honda T, Yasugi M, Kuno A, Komori T, Okuzaki D, Narimatsu H, Nakaya T and Tomonaga K: Influenza A virus-induced expression of a GalNAc transferase, GALNT3, via micrornas is required for enhanced viral replication. J Virol 90: 1788-1801, 2015.
21. Shu G, Lu X, Pan Y, Cen J, Huang K, Zhou M, Lu J, Dong J, Han H, Chen W, *et al*: Exosomal circSPIRE1 mediates glycosylation of E-cadherin to suppress metastasis of renal cell carcinoma. Oncogene 42: 1802-1820, 2023.
22. de Las Rivas M, Paul Daniel EJ, Narimatsu Y, Compañón I, Kato K, Hermosilla P, Thureau A, Ceballos-Laita L, Coelho H, Bernadó P, *et al*: Molecular basis for fibroblast growth factor 23 O-glycosylation by GalNAc-T3. Nat Chem Biol 16: 351-360, 2020.
23. Ichikawa S, Sorenson AH, Austin AM, Mackenzie DS, Fritz TA, Moh A, Hui SL and Econs MJ: Ablation of the Galnt3 gene leads to low-circulating intact fibroblast growth factor 23 (Fgf23) concentrations and hyperphosphatemia despite increased Fgf23 expression. Endocrinology 150: 2543-2550, 2009.
24. Peluso G, Tian E, Abusleme L, Munemasa T, Mukaibo T and Ten Hagen KG: Loss of the disease-associated glycosyltransferase Galnt3 alters Muc10 glycosylation and the composition of the oral microbiome. J Biol Chem 295: 1411-1425, 2020.
25. Yoshida CA, Kawane T, Moriishi T, Purushothaman A, Miyazaki T, Komori H, Mori M, Qin X, Hashimoto A, Sugahara K, *et al*: Overexpression of Galnt3 in chondrocytes resulted in dwarfism due to the increase of mucin-type O-glycans and reduction of glycosaminoglycans. J Biol Chem 289: 26584-26596, 2014.
26. Sheta R, Bachvarova M, Macdonald E, Gobeil S, Vanderhyden B and Bachvarov D: The polypeptide GALNT6 displays redundant functions upon suppression of its closest homolog GALNT3 in mediating aberrant O-glycosylation, associated with ovarian cancer progression. Int J Mol Sci 20: 2264, 2019.
27. Wang YK, Li SJ, Zhou LL, Li D and Guo LW: GALNT3 protects against vascular calcification by reducing oxidative stress and apoptosis of smooth muscle cells. Eur J Pharmacol 939: 175447, 2023.
28. Noel M, Zürcher YM, Tulin EKC and Cummings RD: The importance of N- and O-glycosylation of brain cell surface glycoproteins. Glycobiology 35: cwaf054, 2025.
29. Gok F, Chefetz I, Indelman M, Kocaoglu M and Sprecher E: Newly discovered mutations in the GALNT3 gene causing autosomal recessive hyperostosis-hyperphosphatemia syndrome. Acta Orthop 80: 131-134, 2009.
30. Yancovitch A, Hershkovitz D, Indelman M, Galloway P, Whiteford M, Sprecher E and Kılıç E: Novel mutations in GALNT3 causing hyperphosphatemic familial tumoral calcinosis. J Bone Miner Metab 29: 621-625, 2011.
31. Navarro-González JF, Mora-Fernández C, Diaz-Tocados JM, Bozic M, Bermúdez-López M, Martín M and Valdivielso JM: Serum phosphate levels modify the impact of FGF23 levels on hemoglobin in chronic kidney disease. Nutrients 14: 4842, 2022.
32. Ichikawa S, Gray AK, Padgett LR, Allen MR, Clinkenbeard EL, Sarpa NM, White KE and Econs MJ: Genetic rescue of glycosylation-deficient Fgf23 in the Galnt3 knockout mouse. Endocrinology 155: 3891-3898, 2014.
33. Ichikawa S, Baujat G, Seyahi A, Garoufali AG, Imel EA, Padgett LR, Austin AM, Sorenson AH, Pejin Z, Topouchian V, *et al*: Clinical variability of familial tumoral calcinosis caused by novel GALNT3 mutations. Am J Med Genet A 152A: 896-903, 2010.
34. Ramnitz MS, Gafni RI and Collins MT: Hyperphosphatemic familial tumoral calcinosis. In: GeneReviews®. Adam MP, Bick S, Mirzaa GM, Pagon RA, Wallace SE and Amemiya A (eds). University of Washington, Seattle, WA, 1993.
35. Guo L, Li D, Li M, Li L and Huang Y: Variant in GALNT3 gene linked with reduced coronary artery disease risk in Chinese population. DNA Cell Biol 36: 529-534, 2017.
36. Guo L, Wang L, Li H, Yang X, Yang B, Li M, Huang J and Gu D: Down regulation of GALNT3 contributes to endothelial cell injury via activation of p38 MAPK signaling pathway. Atherosclerosis 245: 94-100, 2016.
37. Wang B, Zhang Y, Jiang W, Zhu L, Li K, Zhou K, Dai D, Chang S and Fang M: GALNT3 inhibits NF-κB signaling during influenza A virus infection. Biochem Biophys Res Commun 503: 2872-2877, 2018.
38. Park MS, Yang AY, Lee JE, Kim SK, Roe JS, Park MS, Oh MJ, An HJ and Kim MY: GALNT3 suppresses lung cancer by inhibiting myeloid-derived suppressor cell infiltration and angiogenesis in a TNFR and c-MET pathway-dependent manner. Cancer Lett 521: 294-307, 2021.
39. Dosaka-Akita H, Kinoshita I, Yamazaki K, Izumi H, Itoh T, Katoh H, Nishimura M, Matsuo K, Yamada Y and Kohno K: N-acetylgalactosaminyl transferase-3 is a potential new marker for non-small cell lung cancers. Br J Cancer 87: 751-755, 2002.
40. Gu C, Oyama T, Osaki T, Li J, Takenoyama M, Izumi H, Sugio K, Kohno K and Yasumoto K: Low expression of polypeptide GalNAc N-acetylgalactosaminyl transferase-3 in lung adenocarcinoma: Impact on poor prognosis and early recurrence. Br J Cancer 90: 436-442, 2004.
41. Zhao S, Guo T, Li J, Uramoto H, Guan H, Deng W and Gu C: Expression and prognostic value of GalNAc-T3 in patients with completely resected small (≤2 cm) peripheral lung adenocarcinoma after IASLC/ATS/ERS classification. Onco Targets Ther 8: 3143-3152, 2015.
42. Cavallo F, Astolfi A, Iezzi M, Cordero F, Lollini PL, Forni G and Calogero R: An integrated approach of immunogenomics and bioinformatics to identify new tumor associated antigens (TAA) for mammary cancer immunological prevention. BMC Bioinformatics 6 (Suppl 4): S7, 2005.
43. Taniuchi K, Cerny RL, Tanouchi A, Kohno K, Kotani N, Honke K, Saibara T and Hollingsworth MA: Overexpression of GalNAc-transferase GalNAc-T3 promotes pancreatic cancer cell growth. Oncogene 30: 4843-4854, 2011.
44. Chugh S, Meza J, Sheinin YM, Ponnusamy MP and Batra SK: Loss of N-acetylgalactosaminyltransferase 3 in poorly differentiated pancreatic cancer: Augmented aggressiveness and aberrant ErbB family glycosylation. Br J Cancer 114: 1376-1386, 2016.
45. Barkeer S, Chugh S, Karmakar S, Kaushik G, Rauth S, Rachagani S, Batra SK and Ponnusamy MP: Novel role of O-glycosyltransferases GALNT3 and B3GNT3 in the self-renewal of pancreatic cancer stem cells. BMC Cancer 18: 1157, 2018.
46. Ungefroren H and Marquardt JU: Dynamic allostery: A novel mechanism regulating autocrine and paracrine TGF-β signalling. Signal Transduct Target Ther 10: 3, 2025.
47. Wang J, Zhang L, Li R, Yang R, Yang F, Yu F and Zhang J: Gambogic acid restores wild-type-like p53 functions to induce ferroptosis in mutant p53 cancer cells. Biochem Pharmacol 243: 117533, 2026.
48. David CJ and Massagué J: Contextual determinants of TGFβ action in development, immunity and cancer. Nat Rev Mol Cell Biol 19: 419-435, 2018.
49. Okano M, Oshi M, Mukhopadhyay S, Qi Q, Yan L, Endo I, Ohtake T and Takabe K: Octogenarians' breast cancer is associated with an unfavorable tumor immune microenvironment and worse disease-free survival. Cancers (Basel) 13: 2933, 2021.
50. Palmer MJ, Mahajan VS, Trajman LC, Irvine DJ, Lauffenburger DA and Chen J: Interleukin-7 receptor signaling network: An integrated systems perspective. Cell Mol Immunol 5: 79-89, 2008.
51. Mayer BJ, Blinov ML and Loew LM: Molecular machines or pleiomorphic ensembles: Signaling complexes revisited. J Biol 8: 81, 2009.
52. Sanz-Martinez I, Pereira S, Merino P, Corzana F and Hurtado-Guerrero R: Molecular recognition of GalNAc in mucin-type O-glycosylation. Acc Chem Res 56: 548-560, 2023.

53. Sonawane AR, Platig J, Fagny M, Chen CY, Paulson JN, Lopes-Ramos CM, DeMeo DL, Quackenbush J, Glass K and Kuijjer ML: Understanding tissue-specific gene regulation. Cell Rep 21: 1077-1088, 2017.
54. Verma D, Siddharth S, Yende AS, Wu Q and Sharma D: LUCAT1-mediated competing endogenous RNA (ceRNA) network in triple-negative breast cancer. Cells 13: 1918, 2024.
55. Qin L, Liu Y, Li M, Pu X and Guo Y: The landscape of miRNA-related ceRNA networks for marking different renal cell carcinoma subtypes. Brief Bioinform 21: 73-84, 2020.
56. Li X, Peng C, Liu H, Dong M, Li S, Liang W, Li X and Bai J: Constructing methylation-driven ceRNA networks unveil tumor heterogeneity and predict patient prognosis. Hum Mol Genet 34: 251-264, 2025.
57. Sørensen DM, Büll C, Madsen TD, Lira-Navarrete E, Clausen TM, Clark AE, Garretson AF, Karlsson R, Pijnenborg JFA, Yin X, *et al*: Identification of global inhibitors of cellular glycosylation. Nat Commun 14: 948, 2023.
58. Davis ME, Zuckerman JE, Choi CH, Seligson D, Tolcher A, Alabi CA, Yen Y, Heidel JD and Ribas A: Evidence of RNAi in humans from systemically administered siRNA via targeted nanoparticles. Nature 464: 1067-1070, 2010.
59. Dalpke A and Helm M: RNA mediated Toll-like receptor stimulation in health and disease. RNA Biol 9: 828-842, 2012.
60. Heard A, Landmann JH, Hansen AR, Papadopolou A, Hsu YS, Selli ME, Warrington JM, Lattin J, Chang J, Ha H, *et al*: Antigen glycosylation regulates efficacy of CAR T cells targeting CD19. Nat Commun 13: 3367, 2022.
61. Li J, Sun H, Li W, Zhao N, Guo Z, Chen J and Yu J: Protein post-translational modifications in CAR-T cells: Novel strategies to amplify antitumor efficacy via epigenetic and metabolic circuitry. Crit Rev Oncol Hematol 216: 104968, 2025.