



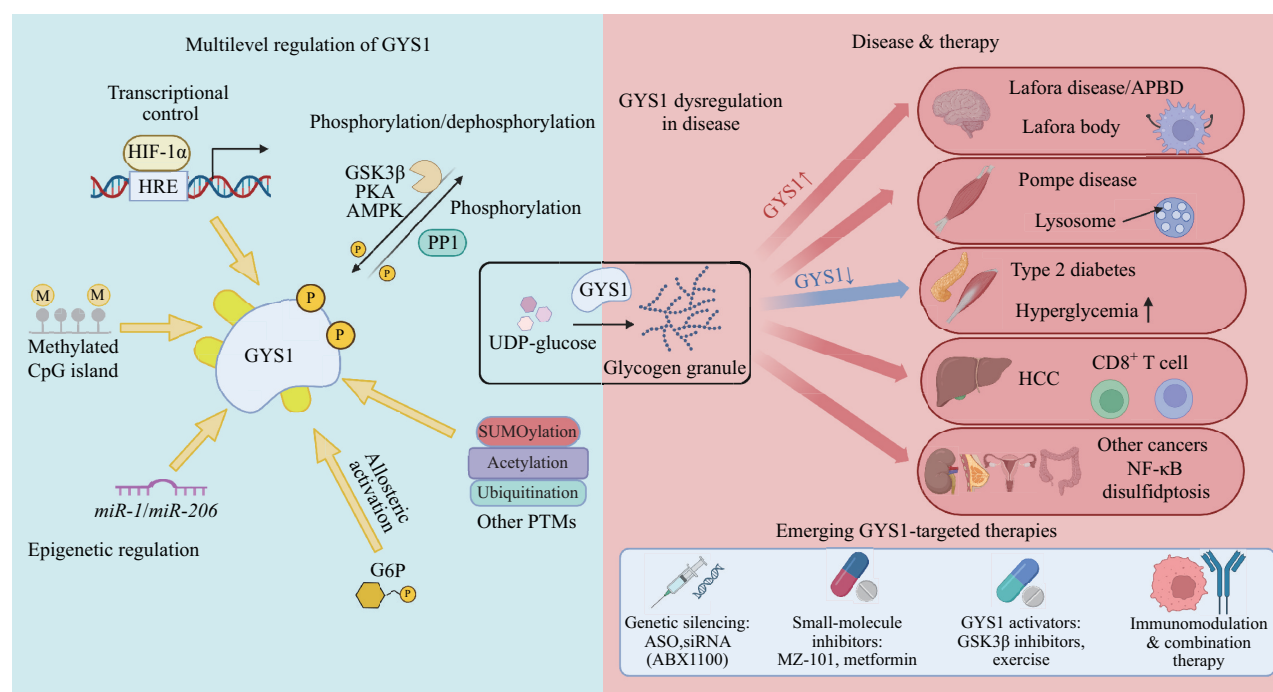
Targeting GYS1: From Metabolic Regulatory Mechanisms to Precision Therapeutic Strategies*

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Graphical abstract



Abstract Glycogen synthase 1 (GYS1) is the rate-limiting enzyme responsible for glycogen synthesis in skeletal muscle, heart, brain, and other extrahepatic tissues, playing a central role in systemic energy homeostasis. The human *GYS1* gene maps to chromosome 19q13.33, comprises 16 exons, and encodes a 737-amino-acid polypeptide that is highly conserved across mammals. GYS1 activity is subject to multilayered and precisely coordinated regulation. At the transcriptional level, the *GYS1* promoter contains a hypoxia response element (HRE) that mediates HIF-1α-dependent induction under low-oxygen conditions, as well as a muscle-specific enhancer harboring MEF2 and MyoD binding sites that confers tissue-restricted expression. At the post-translational

* This work was supported by grants from Zhejiang Provincial Natural Science Foundation of China (LMS25H030005), Ningbo Major Research and Development Plan Project (2024Z215), General Surgery Clinical Key Specialty Construction Project of Zhejiang Province (2023-SZZ), Zhejiang Provincial Natural Science Foundation (LY24C050001), Natural Science Foundation of Ningbo (2024J037), and The National Natural Science Foundation of China (32570835, 32270821, 62427812).

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Received: April 10, 2026 Accepted: May 28, 2026

level, a hierarchical phosphorylation cascade serves as the primary activity switch: glycogen synthase kinase 3 β (GSK3 β) sequentially phosphorylates four C-terminal serine residues following casein kinase II priming, while protein kinase A (PKA) and AMP-activated protein kinase (AMPK) provide parallel inhibitory inputs at both N- and C-terminal sites. Dephosphorylation and reactivation are mediated by protein phosphatase 1 (PP1) through tissue-specific glycogen-targeting regulatory subunits such as PPP1R3A and PPP1R3B, which anchor PP1 to glycogen particles and direct its activity toward GYS1. The allosteric activator glucose-6-phosphate (G6P) binds at the dimer interface, simultaneously enhancing catalytic efficiency and promoting dephosphorylation susceptibility, thereby establishing a feed-forward activation loop that couples substrate availability to glycogen synthesis. Beyond phosphorylation, GYS1 is regulated by ubiquitination (mediated by the E3 ligase PJA1), acetylation, O-linked β -N-acetylglucosamine (O-GlcNAc) modification, and SUMOylation, which collectively modulate protein stability, subcellular localization, and protein-protein interactions. Epigenetic mechanisms, including CpG island methylation and histone acetylation dynamics, govern chromatin accessibility at the GYS1 locus, while muscle-specific microRNAs such as *miR-1* and *miR-206* fine-tune GYS1 expression at the post-transcriptional level. Dysregulation of GYS1 has been identified as a central pathogenic driver in a spectrum of human diseases. In inherited glycogen storage disorders—including Lafora disease, adult polyglucosan body disease (APBD), and Pompe disease—loss of upstream regulatory control leads to GYS1 hyperactivation and the accumulation of structurally abnormal or excessive glycogen, resulting in progressive neurodegeneration, myopathy, and multiorgan dysfunction. In type 2 diabetes mellitus (T2DM), impaired insulin signaling through the PI3K-AKT-GSK3 β axis maintains GYS1 in a hyperphosphorylated inactive state in skeletal muscle, compromising postprandial glucose disposal and exacerbating hyperglycemia. In oncology, GYS1 exhibits context-dependent roles across multiple cancer types. In hepatocellular carcinoma, FMO2⁺ cancer-associated fibroblasts stabilize GYS1 by competitively inhibiting PJA1-mediated ubiquitination, and stabilized GYS1 subsequently activates NF- κ B/CCL19 signaling to promote tertiary lymphoid structure formation and enhance anti-PD-1 immunotherapy responsiveness. In clear cell renal cell carcinoma, GYS1 promotes tumor progression through non-canonical NF- κ B pathway activation *via* the scaffold protein RPS27A. In triple-negative breast cancer, GYS1 has been identified as a trigger of disulfidptosis and an activator of NF- κ B signaling through non-enzymatic facilitation of I κ B α degradation. In colorectal cancer, mitochondrial fission deficiency drives AMPK-dependent GYS1 upregulation and glycogen accumulation as a compensatory survival mechanism, while in cervical cancer, GYS1-maintained glycogen reserves fuel the pentose phosphate pathway to generate NADPH for ROS clearance, thereby conferring cisplatin resistance in cancer stem cells. Therapeutic strategies targeting GYS1 have gained substantial momentum across these disease contexts. For glycogen storage disorders, antisense oligonucleotides, small interfering RNAs (*e.g.*, ABX1100), and small-molecule inhibitors (*e.g.*, MZ-101) have demonstrated preclinical and early clinical efficacy in reducing pathological glycogen accumulation. For T2DM, pharmacological activation of GYS1 through GSK3 β inhibition or enhancement of PP1-mediated dephosphorylation is being explored to restore insulin-stimulated glycogen synthesis. In cancer, GYS1-directed interventions—including targeted silencing to sensitize tumors to chemotherapy and immune microenvironment modulation to enhance immunotherapy—represent emerging precision oncology approaches. This review provides a comprehensive and integrated account of *GYS1* gene structure, tissue-specific distribution, regulatory networks, and pathogenic roles in metabolic disorders and malignancies, with the aim of establishing a theoretical framework for the development of GYS1-targeted precision therapies.

Key words GYS1, glycogen metabolism, glycogen storage diseases, type 2 diabetes mellitus, cancer, post-translational regulation, therapeutic target, signaling pathways

DOI: 10.3724/j.pibb.2026.0183

CSTR: 32369.14.pibb.20260183

Glycogen synthesis in eukaryotes proceeds through three sequential stages. Initially, glucose is converted to glucose-1-phosphate (G1P) *via* phosphorylation catalyzed by hexokinase/glucokinase, followed by isomerization mediated by phosphoglucomutase. Subsequently, G1P is transformed into its activated form, uridine diphosphate glucose (UDP-glucose, UDP-Glc), under the catalytic action of UDP-glucose pyrophosphorylase. As the sole sugar donor for glycogen biosynthesis, glucose residues are appended to a glycogen primer by glycogen synthase (GYS), leading to the progressive elongation of linear glycogen chains linked *via* α -1,4-glycosidic bonds. Given the low storage efficiency of linear glycogen, glycogen branching enzyme (GBE) subsequently mediates branch formation, converting glycogen into

a dense spherical structure—each gram of glycogen can bind 3–4 g of water, endowing it with high energy storage density. Concomitantly, this branching process increases the number of non-reducing ends in glycogen, providing additional initiation sites for subsequent glycogenolysis to fulfill the demand for rapid energy supply. Throughout glycogen synthesis, GYS serves as the rate-limiting enzyme, functioning as a molecular switch regulated synergistically by hormonal signals and phosphorylation events^[1]. In humans, GYS exists in two distinct isoforms: muscle-type glycogen synthase (GYS1) and liver-type glycogen synthase (GYS2). These isoforms exhibit unique structural features within their N-terminal regulatory domains: GYS1 possesses a relatively longer N-terminal fragment, and the topological arrangement of its phosphorylation sites differs from

that of GYS2. These structural disparities underpin subtle yet functionally relevant differences in their sensitivity to kinase-mediated regulation, laying the molecular foundation for their tissue-specific expression patterns and functional specialization. This review focuses on GYS1, discussing its gene structure, regulatory mechanisms, physiological functions, and critical roles in human diseases.

1 *GYS1* gene structure and expression regulation

GYS1 gene, a pivotal determinant encoding muscle-type glycogen synthase, serves as the rate-limiting enzyme-encoding gene in the glycogen biosynthetic pathway. Dysregulation of its function is intimately linked to glycogen storage diseases, type 2 diabetes mellitus (T2DM), cardiovascular disorders, and other pathological conditions, with predominant expression restricted to tissues including skeletal muscle and myocardium. In the human genome, this gene maps to chromosome 19q13.33 (long arm of chromosome 19, region 1, band 3, sub-band 3), encompassing a total length of approximately 30 kb. It comprises 16 exons and 15 introns, and its transcribed complementary DNA (cDNA) spans ~2.9 kb, encoding a functional polypeptide consisting of 737 amino acid residues. Across mammals, the *GYS1* gene exhibits high evolutionary conservation: orthologous genes in *Mus musculus* (mouse) and *Rattus norvegicus* (rat) localize to chromosomes 7 and 10, respectively, with the encoded proteins sharing over 90% sequence homology with the human ortholog—underscoring its indispensable biological function.

The precise regulation of the *GYS1* transcriptional regulatory network is crucial for maintaining tissue-specific metabolic homeostasis and systemic energy balance. In recent years, mechanistic studies have gradually unraveled its multidimensional and hierarchical regulatory characteristics, providing a solid theoretical foundation for understanding the physiological and pathological processes associated with glycogen metabolism^[2]. Accumulating evidence has clearly established that the structural elements within the promoter region of the human *GYS1* gene serve as the core molecular basis for its transcriptional regulation: the core transcription region (–250–+59 bp) contains basal transcriptional elements such as the TATA box and GC box, which are essential for sustaining the basal expression of the gene. Meanwhile, the muscle-specific enhancer (–692––544 bp) harbors binding sites for myocyte-specific

transcription factors (*e. g.*, *MEF2*, *MyoD*). This structural feature constitutes a key mechanism driving the highly specific expression of GYS1 in skeletal muscle, and the enhancer-mediated regulatory mode is also widely recognized as one of the core mechanisms underlying the specialization of glycogen synthesis function during myocyte differentiation.

Furthermore, the hypoxia response element (HRE) within the *GYS1* promoter can be specifically recognized and bound by hypoxia-inducible factor HIF-1 α , which significantly activates *GYS1* transcription by recruiting co-activators such as p300/CBP^[3]. This regulatory pathway plays a pivotal role in glycogen accumulation and energy adaptation under hypoxic microenvironments (*e. g.*, strenuous exercise, tumor microenvironment) and has emerged as a research hotspot in the field of metabolic reprogramming.

At the level of signaling pathway regulation, the energy stress-related AMP-activated protein kinase (AMPK) pathway and the hormone stress-related PKA pathway inhibit *GYS1* promoter activity through the phosphorylation of downstream transcription factors. In contrast, GSK3 β indirectly suppresses *GYS1* transcription by regulating the DNA-binding capacity of the p65 subunit in the NF- κ B pathway^[4], collectively forming a multi-layered negative regulatory network for *GYS1* transcription. In contrast to its strong post-translational activation of *GYS1*, insulin only weakly regulates *GYS1* transcription directly. The promoting effect of insulin on glycogen synthesis primarily relies on protein phosphatase 1 (PP1)-mediated dephosphorylation modification—a functional division of labor between transcriptional and post-translational regulation that has been widely acknowledged in the academic community.

As an important complement to transcriptional regulation, epigenetic modifications participate in the regulation of *GYS1* tissue-specific expression by modulating chromatin status: the hypomethylated state of the CpG island in the *GYS1* promoter region of muscle tissue is a prerequisite for maintaining its high expression. The dynamic balance between histone acetyltransferases (HATs) and histone deacetylases (HDACs) affects the binding efficiency of transcription factors by regulating chromatin accessibility, thereby modulating *GYS1* transcription. Meanwhile, the 3' untranslated region (3'UTR) of *GYS1* mRNA is enriched in AU-rich elements (AREs), and RNA-binding proteins such as HuR can regulate mRNA stability by recognizing these elements, constituting a key link in the post-transcriptional regulation of *GYS1* and further

enriching the complexity of its regulatory network.

Post-transcriptional regulation of *GYS1* expression is characterized by exquisite precision. The primary transcript (precursor mRNA) undergoes sequential processing events, including splicing, 5' capping, and 3' polyadenylation, to generate mature mRNA. Alternative splicing of exon 15 yields two distinct isoforms, GYS1a and GYS1b, wherein GYS1a constitutes the predominant functionally active isoform. The 3'UTR of the mature mRNA harbors binding motifs for muscle-specific microRNAs (miRNAs), such as *miR-1* and *miR-206*. These miRNAs modulate *GYS1* expression *via* translational repression or mRNA degradation; for instance, exercise-induced downregulation of *miR-1* alleviates its inhibitory effect on *GYS1*^[5]. Collectively, *GYS1* expression is precisely tuned at the transcriptional and post-transcriptional levels through promoter architecture, transcription factors, epigenetic modifications, and miRNAs. Having established these regulatory layers, the following sections will first describe the tissue-specific distribution and physiological functions of GYS1 (Section 2), followed by a detailed discussion of its post-translational regulation *via* phosphorylation and upstream signaling pathways (Section 3).

2 Physiological functions and tissue-specific distribution

GYS1, encoded by the *GYS1* gene, displays a pronounced tissue-specific distribution that is tightly coupled to the glycogen metabolic requirements of individual tissues. Its expression profile is characterized by high enrichment in muscle tissues, low expression across multiple organs, and weak expression in the liver (with exceptions under specialized physiological contexts)^[6]. Within the muscular system, skeletal muscle exhibits the highest GYS1 expression, accounting for over 90% of total glycogen synthase activity. GYS1 is predominantly localized near the sarcoplasmic reticulum, with marginally higher expression in fast-twitch fibers compared to slow-twitch fibers. Cardiac muscle also shows moderately high GYS1 expression (contributing 60%–70% of total activity), concentrated around mitochondria and within intermyofibrillar spaces. In the brain and neural tissues, GYS1 is primarily expressed at moderate-to-low levels in glial cells, particularly astrocytes, where it accumulates in cell processes and perisynaptic regions; neuronal expression of GYS1 is less than 10% of that in glial cells, with only minimal

expression detected in microglia and oligodendrocytes. Adipose tissue and kidney exhibit low GYS1 expression: GYS1 is detectable in the cytoplasmic periphery of white adipocytes and in epithelial cells of the renal proximal convoluted tubule, with slightly higher expression in brown adipose tissue relative to white adipose tissue. In the normal adult liver, GYS1 expression is extremely low (representing less than 5% of total glycogen synthase activity), but it is transiently upregulated during embryonic development (from mid-gestation to pre-birth) and liver injury repair. This tissue-specific distribution is highly congruent with the functional roles of GYS1: in skeletal muscle, GYS1 acts as the predominant glycogen synthase, mediating glycogen storage under insulin stimulation at rest and energy provision during exercise to support endurance performance; long-term training can upregulate GYS1 expression, thereby enhancing athletic capacity. In cardiac muscle, GYS1-synthesized glycogen serves as an emergency energy reserve, supplying ATP during ischemia to prevent cardiomyocyte necrosis and augmenting energy stores to maintain cardiac function under high workloads. In brain glia, GYS1-derived glycogen supports neuronal energy metabolism *via* the lactate shuttle mechanism during blood glucose fluctuations or cerebral hypoperfusion, while also sustaining glial cell function to facilitate neural signal transmission. Low-level GYS1 expression in adipose tissue modulates glycogen turnover to bidirectionally regulate lipid metabolism and maintain metabolic homeostasis. In the kidney, minimal GYS1 stores glycogen during euglycemia and releases glucose during hypoglycemia, ensuring renal tubular function. Transient GYS1 upregulation in the liver supports neonatal energy reserves during embryonic development and promotes hepatocyte repair during liver injury, facilitating the restoration of liver function. The tissue-specific segregation of GYS isoforms enables organisms to independently regulate glycogen metabolism in muscle and liver in response to distinct physiological cues, thereby precisely coordinating energy storage and systemic glucose homeostasis.

Glycogen metabolism, as the core regulatory pathway for systemic energy homeostasis, achieves the storage and efficient utilization of glucose under different physiological states through the dynamic balance between glycogen synthesis (with the GYS family as core catalytic enzymes) and glycogen breakdown (relying on key molecules such as glycogen phosphorylase). Once this balance is disrupted—whether due to mutations in key enzyme

genes, abnormalities in signal regulatory pathways, or failure to meet tissue-specific metabolic demands—it may lead to glycogen synthesis disorders, uncontrolled breakdown, or abnormal deposition, thereby triggering multisystem diseases. Examples include glycogen storage diseases (GSDs) caused by hereditary glycogen metabolism abnormalities^[6-7], T2DM induced by metabolic disorders^[8], cardiovascular diseases associated with myocardial glycogen deposition^[9] and vascular metabolic abnormalities^[10], neurodegenerative diseases resulting from cerebral glycogen metabolism dysfunction and neuronal damage, as well as cancers related to abnormal glycogen metabolism^[11-12].

The tissue-specific expression pattern of GYS1 also has important implications for therapeutic targeting. For instance, high GYS1 expression in skeletal muscle makes it a key node for treating insulin resistance, whereas its low baseline expression in the liver minimizes the risk of off-target hypoglycemia when systemically administering GYS1 inhibitors. In the brain, moderate GYS1 expression in astrocytes provides a therapeutic window for antisense oligonucleotide-mediated knockdown in Lafora disease. Understanding these distribution nuances is essential for developing safe and effective GYS1-targeted therapies.

In summary, GYS1 is a core regulator of muscle glycogen synthesis, with its structural features and tissue-specific distribution underscoring its pivotal role in energy metabolism. GYS1 dysregulation—encompassing abnormal expression, genetic mutations, or perturbed regulatory pathways—directly impairs glycogen storage and energy supply in skeletal and cardiac muscles, and is closely linked to the pathogenesis of myopathies, metabolic syndrome, and cardiovascular disorders. In-depth exploration of GYS1's functional mechanisms, regulatory networks, and pathological relevance in diseases not only yields novel insights into disease etiology but also holds substantial promise for identifying diagnostic biomarkers and developing targeted therapeutic strategies. Collectively, GYS1 exhibits considerable value in basic research and notable potential for clinical translation, highlighting its significance as a key focus in disease-related investigations.

3 Regulatory mechanisms of GYS1

3.1 Phosphorylation and dephosphorylation: the core regulatory switch

The enzymatic activity of GYS1 is predominantly governed by its phosphorylation status,

which functions as a binary molecular switch between the inactive phosphorylated (D-form, glucose-dependent) and active dephosphorylated (I-form, glucose-independent) states. This switch is orchestrated by a network of kinases and phosphatases that converge on at least nine conserved phosphorylation sites clustered within the N- and C-terminal regulatory domains.

(1) Hierarchical multi-site phosphorylation. GSK3 β serves as the predominant inhibitory kinase^[13], catalyzing the sequential phosphorylation of four C-terminal serine residues (Ser641, Ser645, Ser649, and Ser653)^[12]. This process follows a strict hierarchical mechanism: prior phosphorylation of Ser657 by casein kinase II (CK2) creates a priming phosphate recognized by GSK3 β , which then processively phosphorylates the remaining sites in a C-to-N direction. Each successive phosphorylation incrementally reduces GYS1 activity, with full inhibition requiring phosphorylation of all four sites. PKA provides parallel inhibitory input by directly phosphorylating both N-terminal (Ser8) and C-terminal (Ser641/Ser645) residues in response to glucagon and epinephrine signaling. AMPK, activated by energy stress (elevated AMP/ATP ratio), phosphorylates Ser7 at the N-terminus, which alters the enzyme's affinity for its allosteric activator glucose-6-phosphate (G6P) and provides a mechanism for energy status to directly tune glycogen synthesis^[14].

(2) Substrate-specific phosphatase targeting. Dephosphorylation and reactivation of GYS1 is catalyzed primarily by PP1, but PP1 itself is a promiscuous enzyme whose specificity *in vivo* is conferred by glycogen-targeting regulatory subunits. These subunits—including PPP1R3A (G_M), PPP1R3B (G_L), PPP1R3C (PPP1R5), and PPP1R3D (PPP1R6) — anchor PP1 to the glycogen particle and simultaneously bind GYS1, thereby directing phosphatase activity specifically toward its physiological substrate^[15]. The tissue-specific expression of these regulatory subunits (*e. g.*, PPP1R3A in skeletal muscle, PPP1R3B in the liver) provides an additional layer of metabolic control, enabling insulin and other signals to activate glycogen synthesis in a cell-type-appropriate manner^[16] (Figure 1).

3.2 Allosteric regulation by glucose-6-phosphate (G6P)

Beyond covalent modification, GYS1 is potently regulated by the allosteric activator G6P. G6P binds to a conserved pocket at the dimer interface of GYS1,

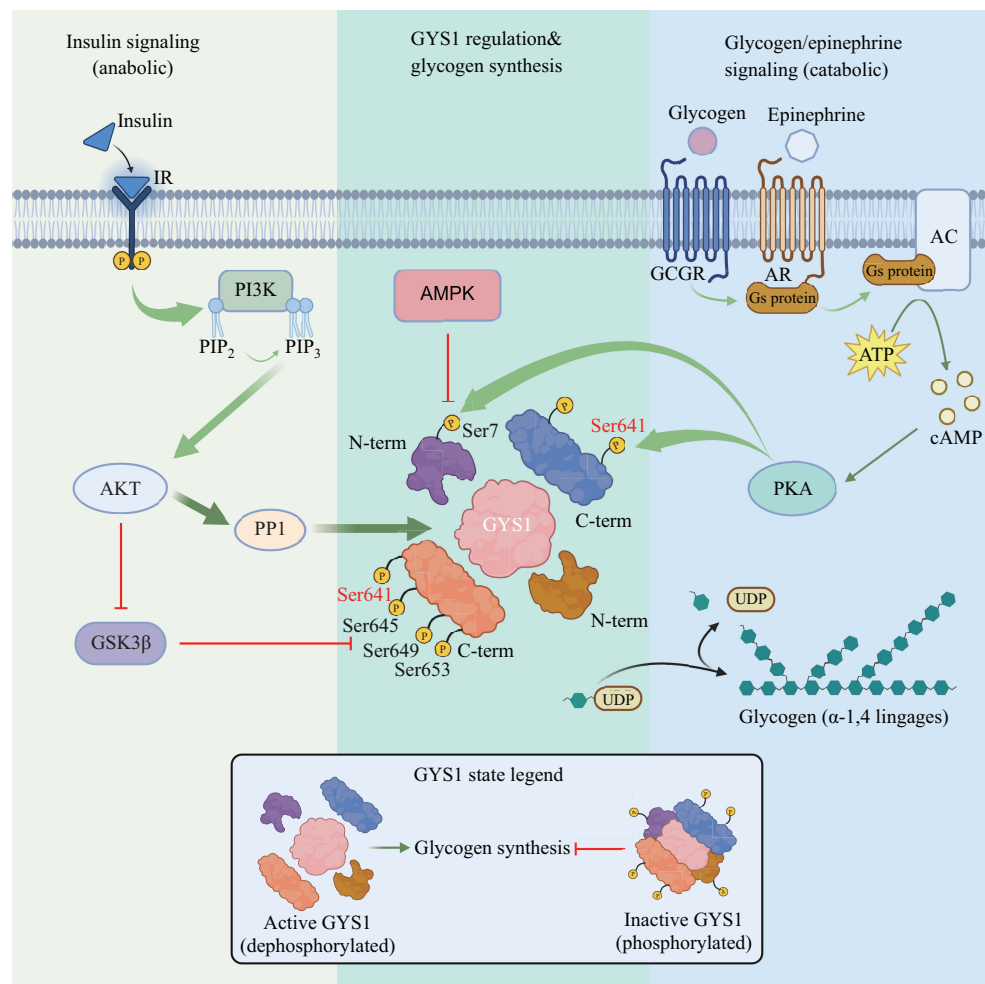


Fig. 1 Regulation of GYS1 activity by insulin and epinephrine signaling in glycogen metabolism

Insulin promotes glycogen synthesis (anabolic) upon binding to its receptor (IR), activating the PI3K-PIP3-AKT signaling axis. AKT phosphorylates and inhibits GSK3 β , thereby reducing C-terminal inhibitory phosphorylation of GYS1 at Ser641, Ser645, Ser649, and Ser653. In parallel, AKT activates PP1, which dephosphorylates these sites, maintaining GYS1 in its active (dephosphorylated) state to facilitate UDP-glucose incorporation into α -1,4-linked glycogen chains. Conversely, epinephrine drives catabolic glycogen breakdown via the glucagon receptor (GCGR) and adrenergic receptors (AR), which couple to the stimulatory G protein (Gs) protein and adenylate cyclase (AC). The resulting increase in cAMP activates PKA, which directly phosphorylates the same C-terminal serine residues of GYS1, rendering it inactive (phosphorylated state). Under energy stress, AMPK can also phosphorylate GYS1. Thus, the opposing actions of insulin and epinephrine, along with energy status, determine GYS1 activity and glycogen homeostasis.

inducing a conformational change that simultaneously increases the enzyme's catalytic efficiency and, critically, enhances its susceptibility to dephosphorylation by PP1. This dual effect creates a feed-forward activation loop: elevated intracellular glucose (reflected by increased G6P levels) promotes GYS1 dephosphorylation and activation, thereby accelerating glycogen synthesis precisely when substrate is abundant^[17].

The allosteric mechanism is of particular pathophysiological relevance. In insulin-resistant states, impaired glucose uptake reduces intracellular G6P concentrations, diminishing this feed-forward activation and further attenuating glycogen synthesis

despite the presence of hyperglycemia. Conversely, in certain glycogen storage diseases, supraphysiological G6P levels may inappropriately drive GYS1 activation even under conditions of limited downstream glycogen branching, thereby exacerbating the accumulation of aberrant glycogen. Pharmacological targeting of the G6P-binding site—either to enhance or to disrupt allosteric activation—represents a strategy to modulate GYS1 activity independent of its phosphorylation status^[18].

3.3 Ubiquitination, acetylation, and additional post-translational modifications

In addition to phosphorylation, GYS1 is subject to ubiquitination, acetylation, and other modifications

that regulate its protein stability, subcellular localization, and protein-protein interactions (Figure 2).

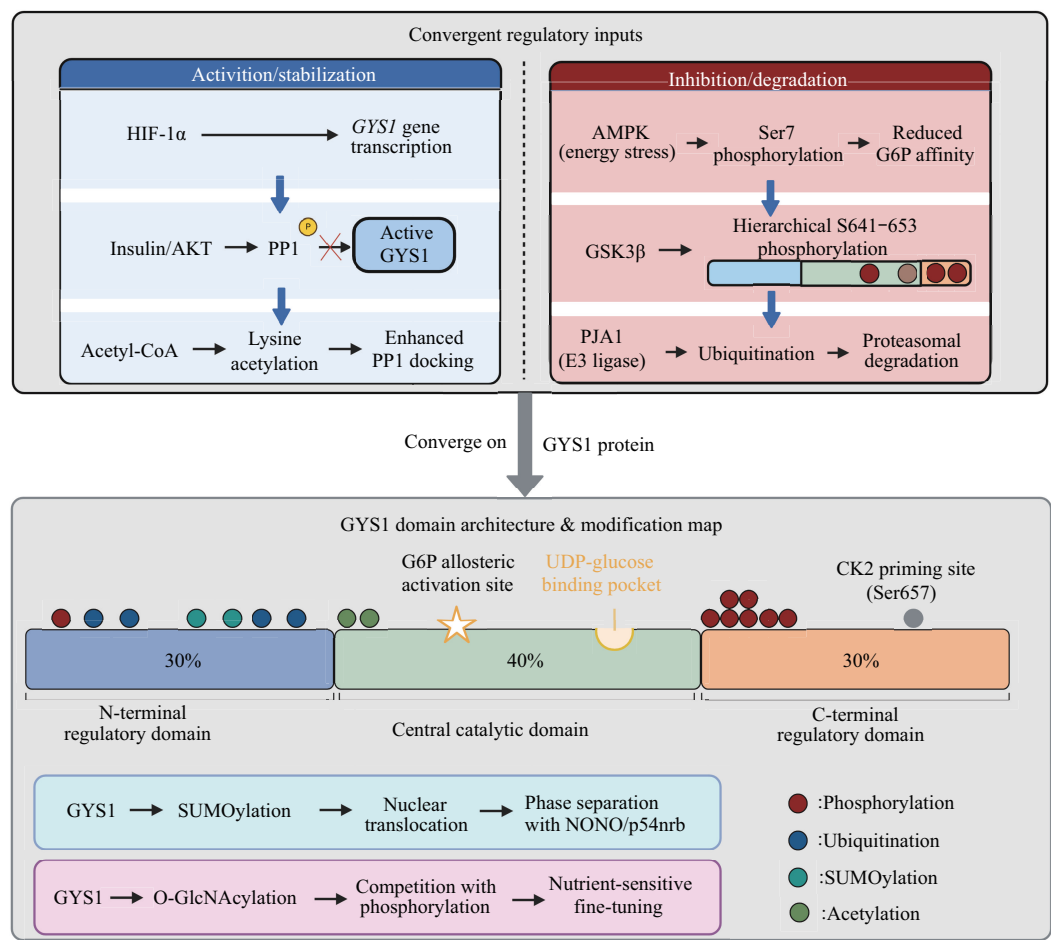


Fig. 2 Convergent regulatory networks and post-translational modification landscape of GYS1
GYS1 activity is tightly controlled by multiple signaling inputs (insulin, AMPK, GSK3β, PKA, etc.), allosteric regulation by G6P, and diverse post-translational modifications including phosphorylation, ubiquitination, acetylation, O-GlcNAcylation, and SUMOylation. The domain architecture and key modification sites are mapped to illustrate the structural basis of GYS1 regulation.

3.3.1 Ubiquitination

GYS1 undergoes ubiquitin-proteasome-mediated degradation under conditions of sufficient glycogen storage, serving as a negative feedback mechanism to prevent excessive glycogen accumulation. The E3 ubiquitin ligase PJA1 has recently been identified as a key mediator of GYS1 ubiquitination in the context of hepatocellular carcinoma, where its activity is counteracted by competitive binding with FMO2. This ubiquitination-dependent regulation represents a post-translational layer distinct from acute activity modulation by phosphorylation, operating instead on longer timescales to adjust total GYS1 protein abundance^[11].

3.3.2 Acetylation

Acetylation at specific lysine residues within the

GYS1 regulatory domain potentiates its interaction with PP1, thereby facilitating dephosphorylation and activation. This modification provides an additional input point through which cellular metabolic status (reflected by acetyl-CoA levels and acetyltransferase/deacetylase activities) can fine-tune GYS1 activity^[19].

3.3.3 O-GlcNAcylation

A growing body of evidence indicates that GYS1 is modified by O-linked β-N-acetylglucosamine (O-GlcNAc), a nutrient-sensitive post-translational modification that utilizes UDP-GlcNAc as the donor substrate. O-GlcNAcylation and phosphorylation can compete for the same or adjacent serine/threonine residues, establishing a direct molecular crosstalk between the hexosamine biosynthetic pathway and glycogen synthesis. Under hyperglycemic conditions,

elevated O-GlcNAcylation of GYS1 may antagonize inhibitory phosphorylation at key residues, providing an additional mechanism by which glucose flux can modulate GYS1 activity^[20].

3.3.4 SUMOylation and phase separation

Recent work has identified that GYS1 undergoes SUMOylation, which promotes its nuclear translocation and condensation with the RNA-binding protein NONO/p54nrb. This spatiotemporally regulated nuclear localization is implicated in coordinating glycogen synthesis with myogenic differentiation, highlighting a non-canonical function of GYS1 that extends beyond cytoplasmic glycogen metabolism^[21].

3.4 Transcriptional and post-transcriptional control

Post-translational regulation of GYS1 is complemented by transcriptional and post-transcriptional mechanisms that determine its basal expression levels and tissue specificity. As discussed in detail in Section 1, the human *GYS1* promoter contains a core transcription region (−250 to +59 bp) harboring basal elements such as the TATA box and GC box, while a muscle-specific enhancer region (−692 to −544 bp) mediates highly specific expression in skeletal muscle^[22]. The promoter also contains a hypoxia response element (HRE) that is specifically recognized and bound by HIF-1 α ^[3], which significantly activates *GYS1* transcription by recruiting co-activators such as p300/CBP. This regulatory pathway plays a pivotal role in glycogen accumulation under hypoxic microenvironments, including the tumor microenvironment and strenuous exercise.

3.5 Integration and crosstalk among regulatory layers

The regulatory mechanisms described above do not operate in isolation but are extensively interconnected, forming a signaling network of considerable complexity. The insulin and epinephrine/glucagon axes serve as master regulators that integrate multiple layers of GYS1 control.

In the postprandial state, insulin binding to its receptor activates the PI3K-AKT signaling cascade. AKT directly phosphorylates and inhibits GSK3 β , relieving inhibitory phosphorylation of GYS1 at the C-terminal serine cluster. Concurrently, AKT-mediated activation of PP1 glycogen-targeting subunits promotes GYS1 dephosphorylation, converting the enzyme to its active I-form. Increased glucose influx elevates intracellular G6P, which allosterically activates GYS1 and enhances its susceptibility to dephosphorylation, reinforcing the

insulin-driven activation signal.

In the fasting state and during exercise, glucagon and epinephrine activate the cAMP-PKA axis, which directly phosphorylates GYS1 at multiple residues to maintain it in the inactive D-form while simultaneously activating glycogen phosphorylase. AMPK contributes an additional energy-sensing input: under conditions of energetic stress (exercise, hypoxia), AMPK phosphorylates GYS1 at Ser7, reducing its affinity for G6P and providing a rapid, insulin-independent mechanism to curtail glycogen synthesis and redirect glucose toward glycolysis^[23].

This multi-layered regulatory architecture enables GYS1 to integrate signals from systemic hormones (insulin, glucagon, epinephrine), local energy status (AMP/ATP ratio), and substrate availability (glucose/G6P), thereby ensuring that glycogen synthesis is precisely matched to the metabolic demands of the organism. Dysregulation at any node in this network—whether through impaired insulin signaling, constitutive kinase activation, or altered phosphatase targeting—can lead to the pathological glycogen accumulation or depletion observed in the diseases discussed in subsequent sections.

4 GYS1 dysregulation and inherited metabolic disorders

4.1 Lafora disease: a dual-faceted disorder of glycogen metabolism and therapeutic targeting

Lafora disease is a rare autosomal recessive disorder belonging to the spectrum of progressive myoclonus epilepsies, with adolescent onset as a typical clinical feature. It is caused by loss-of-function mutations in the *EPM2A* gene, which encodes laforin, and the *EPM2B* (also known as *NHLRC1*) gene, which encodes malin. These pathogenic mutations disrupt normal glycogen metabolism, leading to aberrant elongation and aggregation of glycogen chains, followed by the formation of pathognomonic Lafora bodies that accumulate in neurons and other tissues, ultimately triggering progressive neuronal dysfunction and degeneration. Clinically, patients present with escalating myoclonus, generalized seizures, rapid cognitive deterioration, ataxia, and a spectrum of neuropsychiatric disturbances^[24-25]. The disease follows an aggressive clinical course and confers a poor prognosis. To date, curative interventions remain unavailable, and clinical management is restricted to antiepileptic symptomatic treatment and supportive care.

Despite being caused by mutations in *EPM2A*

and EPM2B, Lafora disease is mechanistically tightly linked to GYS1, which serves as a central executor in the pathological cascade. Under physiological conditions, laforin and malin cooperatively negatively regulate GYS1 activity to suppress aberrant glycogen synthesis. Loss-of-function mutations in either gene abolish this inhibitory control, resulting in unrestrained hyperactivation of GYS1. This dysregulation drives the production of structurally abnormal glycogen, which precipitates into insoluble Lafora bodies and mediates progressive neurotoxicity. Therapeutic strategies targeting GYS1 in Lafora disease, including antisense oligonucleotides and small-molecule AMPK activators, are discussed in detail in Section 6.

4.2 Adult polyglucosan body disease: a fatal convergence of polyglucosan accumulation and progressive neurological decline

Adult polyglucosan body disease (APBD) is an ultrarare autosomal recessive disorder resulting from mutations in the *GBE1* gene, classified as the adult-onset form of glycogen storage disease type IV. The disease is pathologically characterized by a deficiency in glycogen branching enzyme activity, which disrupts normal glycogen synthesis and leads to the accumulation of structurally aberrant, poorly branched, and insoluble glycogen molecules. These aggregates progressively form characteristic polyglucosan bodies within neuronal axons in both the central and peripheral nervous systems, clinically manifesting as a classic triad of progressive spastic paraparesis, neurogenic bladder, and distal sensory impairment, typically emerging after the fourth decade of life.

At the molecular level, the glycogen synthase encoded by the *GYS1* gene plays a pivotal role as a downstream effector in disease pathogenesis: the loss of functional *GBE1* impairs glycogen branching, while GYS1-mediated chain elongation proceeds unopposed, driving the synthesis and deposition of pathogenic glycogen. This central role of GYS1 as the unopposed driver of pathogenic glycogen synthesis has motivated the development of therapeutic strategies aimed at its pharmacological or genetic inhibition. These approaches are discussed in Section 6.

4.3 Pompe disease: a metabolic storm in the lysosome and beyond

Pompe disease (glycogen storage disease type II, GSD II) is an autosomal recessive lysosomal storage disorder resulting from pathogenic mutations in the acid alpha-glucosidase (*GAA*) gene, which encodes the enzyme GAA. The consequent deficiency or

complete loss of GAA activity disrupts the hydrolytic breakdown of glycogen to glucose within the lysosome, leading to progressive accumulation of structurally normal glycogen primarily in cardiac, skeletal, and smooth muscles. This pathological glycogen storage drives a spectrum of clinical manifestations, ranging from the severe, rapidly progressive infantile form—characterized by profound hypotonia, hypertrophic cardiomyopathy, and respiratory failure—to the more heterogeneous late-onset phenotype, which typically presents with slowly progressive proximal muscle weakness and diaphragmatic dysfunction.

At the molecular level, the glycogen synthase isoform encoded by the *GYS1* gene has emerged as a critical downstream effector and a key pathophysiological node in Pompe disease. Recent evidence indicates that lysosomal glycogen accumulation initiates a detrimental feed-forward loop: it enhances cellular glucose uptake and activates G6P-mediated allosteric regulation, which paradoxically upregulates GYS1 activity in the cytoplasm, thereby exacerbating *de novo* glycogen synthesis and further amplifying pathological storage. In this context, GAA deficiency functions as the primary upstream trigger, while GYS1-driven glycogen synthesis serves as a secondary amplifier of disease progression. This mechanistic framework suggests that therapeutic strategies solely aimed at clearing pre-existing glycogen (*e. g.*, ERT) may be insufficient to fully arrest disease progression, and that upstream inhibition of GYS1 represents a rational approach to curtailing ongoing glycogen synthesis at its source^[26].

Common mechanistic theme across glycogen storage disorders. The three diseases discussed above—Lafora disease, APBD, and Pompe disease—share a unifying pathogenic cascade despite their distinct genetic etiologies. This sequential cascade—starting from an upstream enzyme deficiency, proceeding to GYS1 overactivation, and culminating in pathological glycogen accumulation—positions GYS1 as a common final executor and a promising therapeutic node. Consequently, pharmacological or genetic inhibition of GYS1 has demonstrated efficacy across all three disorders in preclinical or early clinical studies, underscoring the value of targeting this rate-limiting enzyme as a unified strategy for treating glycogen storage diseases.

4.4 Type 2 diabetes, insulin resistance, and exercise

Skeletal muscle serves as the principal site of postprandial glucose disposal, accounting for

approximately 70%–80% of insulin-stimulated glucose uptake. In this tissue, glycogen synthesis, catalyzed by the rate-limiting enzyme GYS1, represents a critical pathway for glucose storage. A well-documented defect in individuals with insulin resistance and T2DM is reduced GYS1 activity in skeletal muscle, which impairs the conversion of G6P to glycogen and contributes to postprandial hyperglycemia^[27-28].

At the molecular level, insulin resistance disrupts the canonical PI3K-AKT signaling cascade. Under physiological conditions, insulin binding to its receptor activates AKT, which in turn phosphorylates and inactivates glycogen synthase kinase 3 β (GSK3 β). This relieves the inhibitory phosphorylation of GYS1 imposed by GSK3 β , enabling PP1 to dephosphorylate and activate GYS1. In the insulin-resistant state, this signaling axis is compromised: AKT activation is impaired, GSK3 β remains active, and GYS1 is maintained in a hyperphosphorylated, inactive state^[13, 29]. The resultant reduction in glycogen synthesis not only exacerbates glucose intolerance but also promotes the accumulation of intracellular glucose intermediates, which have been implicated in oxidative stress and further impairment of insulin signaling.

Genetic evidence supports the pathophysiological relevance of GYS1 in T2DM^[30]. Polymorphisms in the *GYS1* gene, particularly within the promoter and 3' untranslated regions, have been associated with reduced GYS1 expression and activity

across multiple populations, including Pima Indians and Danish twins, underscoring its potential role as a genetic susceptibility factor for T2DM^[27]. Moreover, studies in adipose tissue have revealed a tissue-specific role for GYS1 in glucose homeostasis: adipose-specific ablation of *Gys1* in mice exacerbates high-fat diet-induced insulin resistance, suggesting that peripheral glycogen synthesis may exert a protective effect on systemic metabolic homeostasis^[28]. Pharmacological strategies to restore GYS1 activity in insulin-resistant states are discussed in Section 6.

5 GYS1 in cancer

Glycogen metabolism disorder represents a critical aspect of metabolic reprogramming in tumors. As a key molecule in this pathway, GYS1 exerts functions in cancer that extend beyond mere metabolic regulation, encompassing complex pro-tumorigenic or tumor-suppressive effects^[31-32]. Current studies have revealed that the expression and activity of GYS1 exhibit substantial heterogeneity across different tumor types and within the tumor microenvironment. GYS1 modulates malignant phenotypes by regulating key signaling pathways, including the Wnt/ β -catenin and PI3K/AKT cascades. On this basis, we focus on the specific roles and underlying mechanisms of GYS1 in hepatocellular carcinoma, renal cell carcinoma, and breast cancer, with a detailed discussion provided for each (Table 1).

Table 1 Comparison of GYS1 features across five cancer types

Cancer type	Expression status	Key mechanisms & signaling pathways	Functional impact	Clinical significance	Reference
HCC	Upregulated	NF- κ B/CCL19, immune modulation	Pro-tumorigenic, immune microenvironment shaping	Anti-PD-1 response biomarker	[11]
ccRCC	Upregulated	NF- κ B pathway, PI3K/AKT	Promotes proliferation	Poor prognosis, sunitinib sensitizer	[33]
Breast cancer (TNBC)	Upregulated	NF- κ B, disulfidptosis, Wnt/ β -catenin	Promotes invasion, metabolic adaptation	Therapeutic target	[34-36]
Colorectal cancer	Upregulated	AMPK/GYS1 axis	Glycogen as survival reserve under glucose starvation	Glycogenolysis inhibition sensitizes to chemotherapy	[31]
Cervical cancer	Upregulated	PCK1/PYGL/PPP/NADPH axis	Fuels ROS clearance, supports chemoresistance	GYS1 or PYGL silencing restores cisplatin sensitivity	[37]

5.1 GYS1 in hepatocellular carcinoma

Hepatocellular carcinoma (HCC) remains one of the most prevalent malignancies worldwide, with persistently high incidence and mortality rates. According to the latest statistics, approximately

900 000 new cases and 830 000 deaths are reported annually, representing a substantial global disease burden. In China, due in part to the high prevalence of hepatitis B virus infection^[38], the five-year survival rate for HCC remains suboptimal. Consequently, a

deeper understanding of the molecular mechanisms underlying HCC pathogenesis is of great significance for advancing diagnostic and therapeutic strategies^[39].

Aberrant glycogen metabolism represents a hallmark of metabolic reprogramming in tumors^[40]. GYS1, the rate-limiting enzyme in glycogen synthesis, has recently garnered increasing attention for its functional and regulatory roles in HCC. Emerging evidence has begun to elucidate its multifaceted involvement in HCC cell proliferation, metabolic adaptation, and drug resistance. we systematically summarize the expression patterns, biological functions, molecular regulatory networks, and clinical implications of GYS1 in HCC, aiming to provide a reference for future investigations.

5.1.1 Prognostic value of GYS1 as a disulfidptosis-associated gene

Current research on GYS1 in HCC has primarily focused on its prognostic relevance and functional role as a disulfidptosis-associated gene. Two recent studies have employed public databases and bioinformatics approaches to incorporate GYS1 into disulfidptosis-related prognostic models for HCC. One study developed a risk model comprising RPN1, SLC7A11, and GYS1, demonstrating its effectiveness in predicting patient survival^[41]. The other study, focusing on hepatitis B virus-related HCC (HBV-HCC), integrated transcriptomic analysis with Mendelian randomization and further confirmed that GYS1 plays a pivotal role in the pathogenesis of this HCC subtype^[42]. Collectively, these findings suggest that GYS1 may serve as a potential biomarker or therapeutic target in HCC.

5.1.2 Functional validation of GYS1 in the regulation of glucose metabolism in HCC

From a metabolic perspective, one study has explored the functional role of GYS1 in HCC cells. The natural compound corosolic acid was shown to modulate several key glucose metabolism enzymes, including GYS1, thereby increasing glucose consumption and altering the glucose metabolic profile of HCC cells. This study provides functional evidence supporting the involvement of GYS1 in the metabolic regulation of HCC^[30].

5.1.3 Emerging mechanisms of GYS1 in the immune microenvironment of HCC

In the context of elucidating the heterogeneity of responses to immunotherapy in HCC, functional subsets of cancer-associated fibroblasts (CAFs) have emerged as critical determinants of therapeutic resistance. A recent study integrating single-cell transcriptomics, spatial transcriptomics, and bulk RNA sequencing identified, for the first time, an

FMO2⁺ CAF subset that is strongly associated with favorable responses to anti-PD-1 therapy and improved clinical outcomes. Mechanistically, FMO2⁺ was found to competitively bind to GYS1, thereby inhibiting the E3 ligase PJA1-mediated ubiquitination and degradation of GYS1, leading to its protein stabilization. Stabilized GYS1 subsequently enhances NF-κB/p65-driven C-C motif chemokine ligand 19 (CCL19) expression. Secreted CCL19, acting through its receptor C-C motif chemokine receptor 7 (CCR7), promotes the formation of intratumoral tertiary lymphoid structures and increases the infiltration of CD8⁺ T cells and M1-like macrophages, thereby reshaping the tumor immune microenvironment^[11]. This study significantly expands the functional scope of GYS1 beyond conventional glucose metabolism to include the regulation of anti-tumor immunity. The translational implications of these findings are discussed in Section 6.

In summary, current evidence links GYS1 to disulfidptosis, a novel form of regulated cell death, highlighting its importance in HCC prognosis and tumor progression. In parallel, GYS1 has been implicated in the regulation of glucose metabolism in HCC cells, and more recent findings have uncovered its previously unrecognized role in modulating the immune microenvironment. These advances lay a foundation for further exploration of GYS1 as a diagnostic biomarker or therapeutic target in HCC.

5.2 GYS1 and renal cell carcinoma

Clear cell renal cell carcinoma (ccRCC) is a prototypical metabolic reprogramming-associated malignancy, characterized by substantial intracellular glycogen accumulation—a pathological hallmark whose underlying molecular drivers have remained elusive^[43]. GYS1, the rate-limiting enzyme in glycogenesis, is tightly regulated in normal tissues but exhibits aberrant upregulation in ccRCC. Clinical sample analyses reveal a positive correlation between GYS1 expression and tumor glycogen content, with high GYS1 levels significantly correlating with reduced overall survival^[44]. These findings establish a direct link between the glycogen-rich phenotype of ccRCC and dysregulation of GYS1, implicating GYS1 not merely as a mediator of metabolic perturbation but also as a critical node driving tumor malignancy.

Mechanistically, the oncogenic function of GYS1 extends beyond its canonical metabolic activity to encompass non-canonical signaling roles. Specifically, GYS1 interacts indirectly with the NF-κB pathway *via* the scaffold protein RPS27A, facilitating phosphorylation and nuclear translocation

of the p65 subunit, which in turn activates downstream proliferative gene expression and promotes tumor cell proliferation and *in vivo* tumorigenicity. This mechanism exemplifies an integrated “metabolic-signaling” dual functionality of a metabolic enzyme in ccRCC^[33].

Nonetheless, the role of GYS1 in renal cancer remains contentious. While the above findings support a pro-tumorigenic role, a recent study reported that glycogen metabolism is dispensable for renal cancer cell proliferation^[45]. This discrepancy likely stems from differences in experimental models: Chen *et al.*^[32] observed GYS1-dependent tumor growth in xenograft models, whereas Xie *et al.*^[45] concluded that GYS1 is non-essential based primarily on *in vitro* proliferation assays. These divergent observations raise the possibility that GYS1 may contribute to tumor progression primarily through modulation of the tumor microenvironment rather than *via* cell-autonomous mechanisms—a notion consistent with its non-enzymatic, signaling-related functions. Additionally, variations in gene-editing strategies and cell line backgrounds may contribute to phenotypic heterogeneity. Future studies employing physiologically relevant *in vivo* models that preserve the native tumor microenvironment, complemented by multi-omic analyses of clinical specimens, are warranted to precisely define the functional role of GYS1 in ccRCC and to evaluate its viability as a therapeutic target.

5.3 GYS1 in breast cancer

In recent years, accumulating evidence has revealed that GYS1 is aberrantly expressed in breast cancer, particularly in triple-negative breast cancer (TNBC), a subtype characterized by high malignancy and limited treatment options, and is closely associated with tumor initiation and progression. GYS1 not only supports tumor cell survival and proliferation under stress conditions such as hypoxia through classical metabolic pathways (*e.g.*, glycogen metabolism), but also regulates key signaling cascades *via* non-enzymatic functions and participates in disulfidptosis, a novel form of cell death, thereby promoting tumor progression through multiple mechanisms. Moreover, GYS1 itself is subject to upstream regulation by molecules such as microRNAs, forming a complex regulatory network. These findings suggest that GYS1 may represent a highly promising therapeutic target in breast cancer, particularly in TNBC. We systematically summarize recent advances in understanding the role of GYS1 in breast cancer and provide perspectives on future directions.

With respect to metabolic adaptation, Favaro *et al.*^[46] first demonstrated that under hypoxic conditions, breast cancer cells upregulate GYS1 to synthesize glycogen, and that glycogen breakdown supports cell proliferation and prevents senescence, revealing a critical metabolic survival pathway. In terms of upstream regulation, Mutlu *et al.*^[47] identified *miR-564* as a suppressor of breast cancer cell proliferation and invasion by targeting GYS1 alongside other genes, concomitantly inhibiting the PI3K and MAPK pathways, thereby establishing a mechanistic foundation for subsequent studies. Subsequent investigations have increasingly focused on TNBC as a challenging subtype. Additionally, although focused on neutrophils, the study by Sadiku *et al.*^[48] on the role of glycogen metabolism in immune cells provides important context for understanding GYS1-mediated tumor-immune interactions in breast cancer.

Collectively, research on GYS1 in breast cancer has become increasingly systematic and in-depth: its role has expanded from a classical metabolic enzyme to encompass non-enzymatic signaling functions; the focus has shifted from breast cancer in general to the clinically challenging TNBC subtype; and the perspective has extended from tumor cell-intrinsic mechanisms to the tumor-immune interaction within the microenvironment. While the research landscape continues to broaden and the underlying mechanistic network is becoming clearer, several critical questions remain to be addressed. The clinical relevance of GYS1 in breast cancer patients, including its expression levels and association with prognosis, requires validation through large-scale clinical cohorts. The therapeutic potential of targeting GYS1 in TNBC, including its roles in inducing disulfidptosis and inhibiting NF- κ B-driven tumor progression, is discussed in Section 6.

5.4 GYS1 in colorectal cancer

In colorectal cancer, a novel link between mitochondrial dynamics and glycogen metabolism has recently been uncovered. Hasani *et al.*^[31] demonstrated that knockdown of Drp1, a key mitochondrial fission regulator, paradoxically decreases both mitochondrial respiration and glycolytic activity, yet increases glucose uptake in colon cancer cells. This metabolic shift results in the accumulation of G6P and subsequent upregulation of GYS1 expression through an AMPK-dependent transcriptional mechanism. The consequent glycogen accumulation serves as a compensatory survival mechanism: under glucose starvation, Drp1-deficient cells mobilize glycogen stores to sustain viability.

In vivo, genetic deletion of Drp1 in Apc-driven tumor organoids and xenograft tumors recapitulated the elevation in GYS1 expression and glycogen storage. These findings reveal a previously unrecognized metabolic adaptation in which mitochondrial dysfunction triggers AMPK-mediated GYS1 upregulation and glycogen accumulation to support cancer cell survival under metabolic stress.

5.5 GYS1 in cervical cancer

Emerging evidence has also implicated GYS1-mediated glycogen synthesis in the chemoresistance of cervical cancer. Chen *et al.*^[37, 49] recently reported that CD133⁺ cervical cancer stem cells (CSCs) harbor elevated glycogen levels, and that GYS1 is essential for maintaining this glycogen pool. Silencing GYS1 disrupts the glycogen reservoir and, upon cisplatin treatment, results in decreased nicotinamide adenine dinucleotide phosphate (NADPH) production, impaired reactive oxygen species (ROS) clearance, and loss of the drug-resistant phenotype. Mechanistically, the gluconeogenic enzyme phosphoenolpyruvate carboxykinase 1 (PCK1) competes with the phosphatase PP1c for binding to glycogen phosphorylase glycogen phosphorylase L (PYGL), thereby enhancing PYGL phosphorylation and glycogenolysis. The G6P released from glycogen is funneled into the pentose phosphate pathway (PPP) to generate NADPH, which scavenges chemotherapy-induced ROS and promotes CSC survival. These findings position GYS1 as a critical upstream facilitator of the PCK1-PYGL-PPP-NADPH axis that underlies chemoresistance in cervical cancer.

6 Therapeutic strategies targeting GYS1

The centrality of GYS1 in glycogen metabolism and its mechanistic involvement in diverse diseases have established this enzyme as an attractive therapeutic target. Notably, the direction of therapeutic intervention is highly context-dependent: in glycogen storage diseases and certain cancers, GYS1 hyperactivation drives pathological glycogen accumulation or tumor progression, necessitating inhibition of GYS1; in T2DM, impaired GYS1 activity in skeletal muscle compromises insulin-stimulated glucose disposal, calling for activation of GYS1. This section reviews current therapeutic strategies according to their mechanistic approach, spanning genetic silencing, small-molecule inhibition, pharmacological activation, and emerging cancer-specific applications.

6.1 Genetic silencing strategies

Genetic approaches to reduce GYS1 expression

offer the advantage of sustained target suppression and, in some cases, tissue-specific delivery. Three major platforms have been explored across glycogen storage disorders.

In Lafora disease, GYS1-targeted antisense oligonucleotides (ASOs) are designed to specifically bind *GYS1* mRNA expressed in the central nervous system. Following intrathecal administration *via* lumbar puncture, these ASOs distribute broadly to cells across nearly all brain regions, exhibit stable pharmacodynamic profiles across dose ranges, and maintain sustained activity for several months. Importantly, owing to their inability to penetrate the blood-brain barrier or arachnoid barrier, such ASOs spare GYS1 function in peripheral organs, including the heart. Preclinical and emerging clinical evidence supports the efficacy of GYS1 ASOs at any disease stage, with superior therapeutic outcomes achieved through early initiation and sustained treatment^[50].

In APBD, genetic inhibition of GYS1—including gene knockout and RNA interference—has been explored as a strategy to target the upstream node of pathological glycogen synthesis^[51-52]. Preclinical studies have demonstrated that GYS1 deficiency significantly reduces polyglucosan accumulation and mitigates neurological decline, establishing GYS1 inhibition as one of the most promising disease-modifying strategies currently under investigation for APBD^[10, 53].

In Pompe disease, small interfering RNA (siRNA)-based GYS1 suppression has been pursued as a substrate reduction therapy. ABX1100, an siRNA therapeutic targeting *GYS1* mRNA, is conjugated to a CD71-targeting Centyrin to facilitate muscle-specific delivery. Preclinical studies in a mouse model of Pompe disease demonstrated that ABX1100 significantly reduces glycogen synthesis and glycogen levels in muscle tissue. ABX1100 has recently entered clinical trials, representing the first GYS1-directed therapy to advance into human studies and holding promise as a disease-modifying adjunct to enzyme replacement therapy^[6, 54].

6.2 Small-molecule inhibitors

Small-molecule inhibitors provide a pharmacologically accessible alternative to genetic silencing, with the advantages of oral bioavailability and dose flexibility.

MZ-101 is a small-molecule inhibitor of GYS1 enzymatic activity developed for Pompe disease and other glycogen storage disorders. By reducing *de novo* glycogen production at the level of the rate-limiting enzyme, MZ-101 functions as a substrate reduction therapy that complements the glycogen clearance

achieved by enzyme replacement therapy with recombinant human GAA. Preclinical studies have demonstrated that pharmacological inhibition of GYS1 with MZ-101 significantly attenuates glycogen accumulation in muscle tissue and improves motor function^[55].

In APBD, guaiacol has been identified as a drug candidate with potential disease-modifying effects. Although its precise mechanism of action requires further elucidation, guaiacol treatment has been shown to alleviate aspects of the polyglucosan storage disorder, possibly through the enhancement of autophagic glycogen catabolism^[52].

In Lafora disease, metformin exerts its therapeutic potential by activating the AMPK signaling pathway, which in turn suppresses GYS1 activity in the brain. This inhibition attenuates excessive synthesis and deposition of pathological glycogen, thereby preventing the formation and accumulation of Lafora bodies. Beyond modulating glycogen metabolism, metformin improves mitochondrial function, mitigates oxidative stress and neuroinflammation, and enhances cellular autophagy, collectively conferring additional neuroprotective effects and slowing the progression of neuronal damage and disease^[56].

6.3 Small-molecule activators and insulin sensitizers

In contrast to the inhibitory strategies required for glycogen storage disorders, restoration of GYS1 activity in insulin-resistant skeletal muscle represents a therapeutic goal for T2DM. Given the central role of GYS1 in insulin-stimulated glucose disposal, pharmacological strategies aimed at restoring its activity in skeletal muscle represent a rational approach to improving glycemic control. Small-molecule GYS1 activators, GSK3 β inhibitors, and interventions that enhance PP1-mediated dephosphorylation are currently being explored as potential adjuncts to existing antidiabetic therapies^[29]. Importantly, the context-dependent nature of GYS1 modulation warrants careful consideration: while enhancing GYS1 activity in skeletal muscle and adipose tissue may improve insulin sensitivity, GYS1 inhibition has demonstrated therapeutic benefit in certain glycogen storage diseases, highlighting the importance of tissue-specific targeting in future drug development efforts.

Regular physical activity serves as a potent physiological modulator of GYS1 activity, exerting bidirectional and time-dependent effects. During acute exercise, an elevated AMP/ATP ratio activates AMPK, which directly phosphorylates GYS1 at Ser7,

leading to its rapid inactivation. This transient suppression of glycogen synthesis redirects metabolic flux toward glycogenolysis and glucose utilization, thereby ensuring adequate energy supply for contracting skeletal muscle. In contrast, sustained long-term exercise training promotes adaptive upregulation of GYS1 protein expression in skeletal muscle, as highlighted in the **Introduction**. This chronic adaptation enhances glycogen storage capacity and improves insulin sensitivity, partially through increased GYS1 expression and enhanced PP1-mediated dephosphorylation. Moreover, exercise training attenuates the inhibitory phosphorylation of GYS1 by GSK3 β , restores insulin-stimulated AKT activation, and facilitates GLUT4 translocation to the sarcolemma. These exercise-induced adaptations directly counteract the molecular abnormalities characteristic of insulin-resistant and T2DM muscles. Consequently, incorporating regular physical activity not only constitutes a first-line lifestyle intervention for T2DM but also provides a mechanistic foundation for developing exercise-mimetic therapeutics targeting the AMPK-GYS1 axis.

6.4 GYS1 modulation in cancer therapy

The role of GYS1 in cancer is highly context-dependent, and therapeutic strategies must be tailored to the specific tumor type and molecular setting. In certain cancers, GYS1 inhibition has shown promise; in others, the GYS1-mediated immune microenvironment modulation offers a distinct angle that may be exploited for immunotherapy sensitization.

In HCC, a distinct therapeutic angle has emerged from the discovery that FMO2⁺ cancer-associated fibroblasts (CAFs) stabilize GYS1 through competitive inhibition of the E3 ligase PJA1, thereby enhancing NF- κ B/p65-driven CCL19 expression and promoting intratumoral tertiary lymphoid structure formation (see Section 5.1.3 for mechanistic details). This discovery carries two translational implications. First, it provides a rationale for patient stratification: the abundance of FMO2⁺ CAFs or the serum level of CCL19 could serve as predictive biomarkers to identify HCC patients most likely to benefit from anti-PD-1 immunotherapy. Second, it suggests a potential combination therapeutic strategy in which CCL19, either as a recombinant protein or through pharmacological induction, is administered alongside immune checkpoint blockade to convert immunologically “cold” tumors into “hot” ones, thereby improving response rates. These findings significantly broaden the therapeutic scope of GYS1 beyond its canonical enzymatic activity, positioning it

as a node for immunomodulatory intervention in HCC^[11].

In ccRCC, targeted silencing of GYS1 potentiates the cytotoxicity of sunitinib, a first-line targeted therapy, suggesting that concurrent targeting of GYS1 and sunitinib may represent a synthetic lethal strategy to overcome drug resistance^[40]. This finding positions GYS1 as a promising metabolic target for precision therapy in ccRCC^[33].

In TNBC, GYS1 targeting has been shown to effectively suppress tumor growth^[34]. Mechanistically, GYS1 has been identified as a key trigger of disulfidptosis, a novel form of regulated cell death, providing a potential therapeutic strategy for TNBC^[35]. Moreover, GYS1 promotes breast cancer progression by facilitating I κ B α ubiquitination and degradation in a non-enzymatic manner, thereby activating the NF- κ B signaling pathway^[36]. This non-canonical function of GYS1 expands the therapeutic rationale beyond its enzymatic activity.

In colorectal cancer, inhibition of glycogenolysis has emerged as a potential strategy to overcome the survival advantage conferred by glycogen accumulation. Treatment with the glycogen phosphorylase inhibitor DAB selectively reduced the viability of Drp1-deficient colon cancer cells, and combination of DAB with the chemotherapeutic agent irinotecan produced synergistic cytotoxicity^[31]. These findings suggest that targeting glycogen metabolism, particularly when mitochondrial function is compromised, may enhance chemosensitivity in colorectal cancer.

In cervical cancer, the PCK1-PYGL-glycogenolysis-PPP-NADPH signaling axis has been identified as a key mediator of chemoresistance in CSCs. Silencing either GYS1 or PYGL disrupts this cascade, reduces NADPH production, elevates ROS levels, and restores sensitivity to cisplatin. Notably, *in vivo* delivery of PCK1 or PYGL siRNA *via* lipid nanoparticles significantly enhanced the antitumor efficacy of cisplatin in xenograft models^[37]. These results identify the glycogen metabolic pathway as a targetable vulnerability in cervical cancer and provide a rationale for combining glycogen-metabolism-targeted agents with conventional chemotherapy.

The development of GYS1-targeted therapeutics for cancer is still at an early stage, and achieving specific targeting of GYS1 in tumor cells without disrupting normal glycogen metabolism in healthy tissues represents a central challenge for translational research (Figure 3).

6.5 Challenges and future directions

Despite the therapeutic promise of GYS1-targeted strategies, several challenges remain. First, achieving isoform selectivity is essential to avoid off-target effects on hepatic GYS2, particularly when systemic administration is employed. Second, tissue-specific delivery—whether through CNS-targeted ASOs, muscle-directed siRNA conjugates, or tumor-selective carriers—remains a key technical hurdle. Third, the context-dependent nature of GYS1 in cancer necessitates the development of robust predictive biomarkers to identify patients who are most likely to benefit from GYS1 inhibition or modulation. Advances in drug delivery, chemical biology, and precision medicine will be instrumental in translating GYS1-targeted therapies from the laboratory to clinical practice.

7 Discussion and perspective

GYS1 functions as the rate-limiting enzyme in glycogen synthesis in muscle and other extrahepatic tissues, and accumulating evidence positions its dysregulation as a central hub in the pathogenesis of multiple human diseases. As detailed in this review, GYS1 operates at the interface of metabolic control, signal transduction and disease progression, with functions that extend far beyond conventional energy homeostasis. Its involvement spans rare inherited metabolic disorders (Lafora disease, APBD, Pompe disease) as well as common complex conditions such as T2DM and several cancer types. In each setting, GYS1 emerges both as a critical effector of pathophysiology and as a promising therapeutic target.

A striking insight from recent studies is the context-dependent duality of GYS1 function. In neurological glycogen storage disorders, GYS1 overactivity drives the accumulation of insoluble pathogenic glycogen aggregates. In T2DM, by contrast, reduced GYS1 activity in skeletal muscle impairs insulin-stimulated glucose disposal. In oncology, GYS1 exhibits either pro-tumorigenic or, in certain contexts, tumor-suppressive effects, and its recently identified non-enzymatic roles in immune modulation and cell signaling add further complexity. This functional plasticity underscores that GYS1 must be approached in a tissue-specific and disease-contextualized manner when considering it as a therapeutic target.

From a translational perspective, GYS1-directed interventions have gained significant momentum. ASOs, siRNAs and small-molecule inhibitors (*e.g.*, MZ-101) have shown preclinical and early clinical

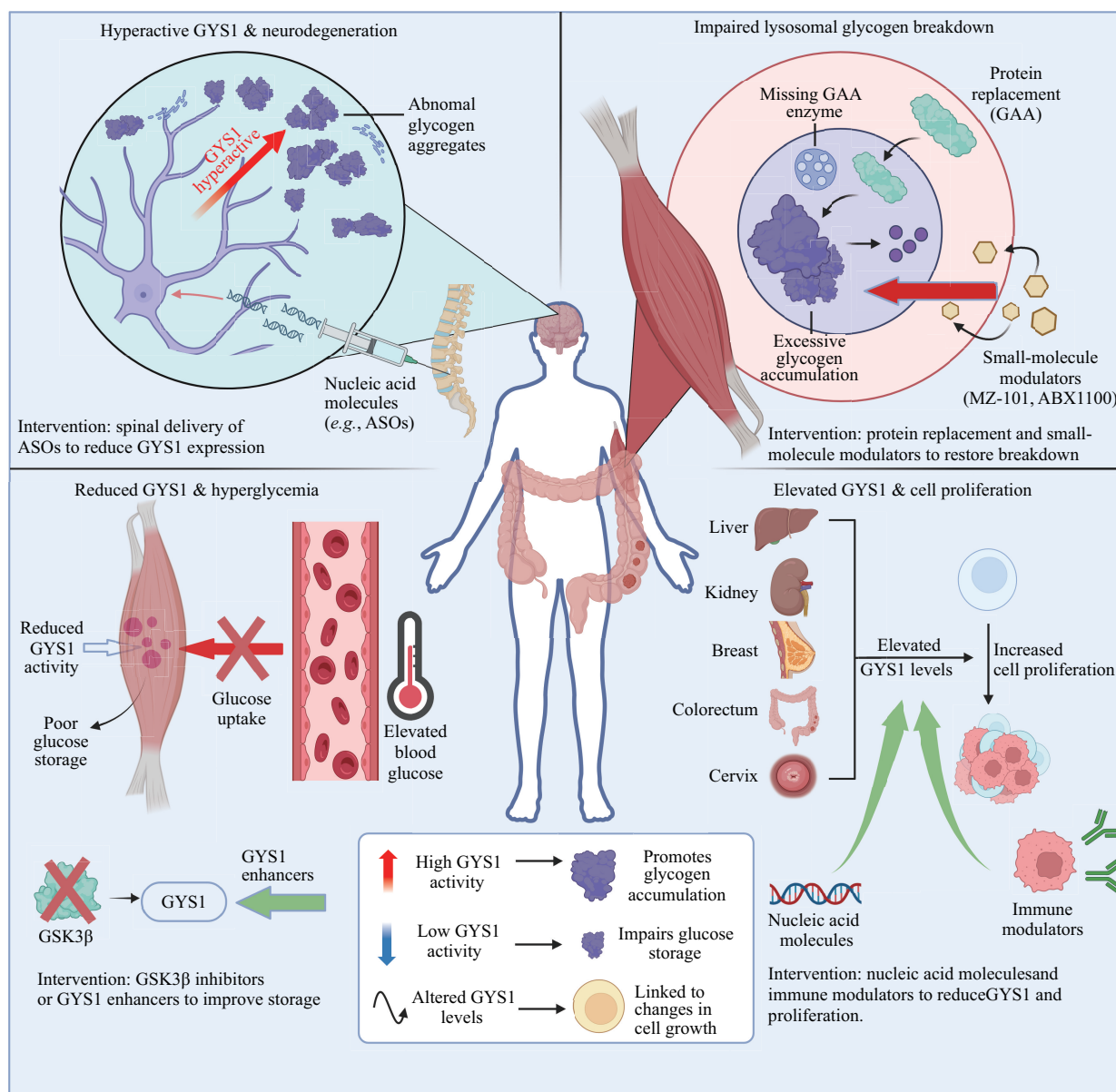


Fig. 3 Effects of dysregulated GYS1 activity on glycogen metabolism, cell proliferation, and neurodegeneration: therapeutic intervention strategies

This figure illustrates the pathological consequences of aberrant GYS1 activity and its associations with neurodegeneration, systemic metabolism, and cell growth, while also highlighting potential therapeutic interventions. In the core pathway, hyperactivated GYS1 impairs lysosomal glycogen breakdown, leading to excessive glycogen accumulation and ultimately neurodegeneration; interventions targeting this pathway include intrathecal ASO delivery to reduce GYS1 expression, protein replacement therapy (e.g., GAA), and small molecule modulators (MZ-101, ABX1100) to restore glycogenolytic function. Conversely, reduced or absent GYS1 activity compromises muscle glycogen synthesis and storage, resulting in hyperglycemia and impaired glucose uptake, with proposed strategies including GSK3 β inhibitors or GYS1 agonists to improve muscle glycogen storage and blood glucose levels. Furthermore, aberrant GYS1 expression is also linked to changes in cell proliferation: elevated GYS1 promotes cell growth (e.g., in liver, kidney, breast tissues, colorectum and cervix), thereby contributing to cancer development and progression, and current therapeutic approaches for these cancers primarily involve targeted GYS1 silencing to enhance antitumor drug efficacy, as well as immune microenvironment modulation to boost immune responses and improve treatment outcomes.

promise in reducing pathological glycogen accumulation in Lafora disease, APBD and Pompe disease. Conversely, GYS1 activation strategies—including GSK3 β inhibition or enhancement of PP1-mediated dephosphorylation—are being explored

for T2DM. This therapeutic divergence highlights the need for precision targeting: systemic modulation of GYS1 could lead to unintended metabolic consequences such as hypoglycemia or cardiac glycogen depletion. A key technical hurdle remains

the development of isoform-selective or tissue-restricted GYS1 modulators, as current strategies often lack the ability to distinguish between GYS1 and its liver counterpart GYS2, or between muscle and immune cell compartments.

Several critical gaps warrant future investigation. First, the molecular mechanisms governing tissue-specific expression and post-translational regulation of GYS1—particularly its crosstalk with hypoxia, nutrient sensing and inflammatory signaling—remain incompletely understood. Second, the non-canonical, non-enzymatic roles of GYS1, such as its interactions with NF- κ B, RPS27A and FMO2⁺ in cancer^[11, 33], are underexplored and may hold the key to its context-dependent functions. Third, the development of isoform-selective or tissue-restricted GYS1 modulators is a major unmet technical challenge, as current strategies often lack the ability to discriminate between GYS1 and its liver-specific isoform GYS2, or between muscle and immune cell compartments.

Looking forward, several priorities emerge for translational research on GYS1. Elucidating the structural dynamics and interactome of GYS1 under different physiological and pathological conditions—using cryo-electron microscopy, single-cell transcriptomics and spatial metabolomics—may reveal previously unrecognized regulatory layers. Integrating GYS1-targeted therapies with existing treatments, such as enzyme replacement therapy in Pompe disease or immune checkpoint blockade in hepatocellular carcinoma, represents a promising avenue for synergistic efficacy. Longitudinal studies in large patient cohorts will be essential to validate GYS1 as a prognostic biomarker and to guide patient stratification for emerging GYS1-based therapies.

8 Conclusion

GYS1 stands at the intersection of metabolism and disease, offering a rich landscape for both mechanistic discovery and therapeutic innovation. A deeper understanding of its regulatory networks, coupled with advances in targeted drug delivery and genetic medicine, is likely to position GYS1 as a cornerstone in the next generation of precision therapies for metabolic, neuromuscular and neoplastic diseases.

References

- [1] Marr L, Biswas D, Daly L A, *et al.* Mechanism of glycogen synthase inactivation and interaction with glycogenin. *Nat Commun*, 2022, **13**: 3372
- [2] Fredriksson J, Ridderstråle M, Groop L, *et al.* Characterization of the human skeletal muscle glycogen synthase gene (*GYS1*) promoter. *Eur J Clin Invest*, 2004, **34**(2): 113-121
- [3] Qian L, Chen X Q, Kong D, *et al.* MK8617 inhibits M1 macrophage polarization and inflammation *via* the HIF-1 α /GYS1/UDPG/P2Y₁₄ pathway. *PeerJ*, 2023, **11**: e15591
- [4] Wang Y, Wang Y, Zhong T, *et al.* Transcriptional regulation of pig GYS1 gene by glycogen synthase kinase 3 β (GSK3 β). *Mol Cell Biochem*, 2017, **424**(1): 203-208
- [5] Pescador N, Villar D, Cifuentes D, *et al.* Hypoxia promotes glycogen accumulation through hypoxia inducible factor (HIF)-mediated induction of glycogen synthase 1. *PLoS One*, 2010, **5**(3): e9644
- [6] Ullman J C, Mellem K T, Xi Y, *et al.* Small-molecule inhibition of glycogen synthase 1 for the treatment of Pompe disease and other glycogen storage disorders. *Sci Transl Med*, 2024, **16**(730): eadf1691
- [7] Hedberg-Oldfors C, Oldfors A. Polyglucosan storage myopathies. *Mol Aspects Med*, 2015, **46**: 85-100
- [8] Wang G, Li Q, Niu T, *et al.* Association of *GYS1* and beta(3)-AR gene with postprandial hyperglycemia and serum uric acid in type 2 diabetes mellitus. *Chin Med J*, 2002, **115**(9): 1308-1311
- [9] Conte F, Sam J E, Lefeber D J, *et al.* Metabolic cardiomyopathies and cardiac defects in inherited disorders of carbohydrate metabolism: a systematic review. *Int J Mol Sci*, 2023, **24**(10): 8632
- [10] Nitschke S, Montalbano A P, Whiting M E, *et al.* Glycogen synthase GYS1 overactivation contributes to glycogen insolubility and malto-oligoglucan-associated neurodegenerative disease. *EMBO J*, 2025, **44**(5): 1379-1413
- [11] Xu W, Weng J, Zhao Y, *et al.* FMO2⁺ cancer-associated fibroblasts sensitize anti-PD-1 therapy in patients with hepatocellular carcinoma. *J Immunother Cancer*, 2025, **13**(5): e011648
- [12] Liang H Y, Luo R Z, Deng R, *et al.* Glycogen stores mediated by the p53-GYS1 feedback circuit engenders platinum resistance in ovarian clear cell carcinoma. *Cell Death Differ*, 2025, **32**(9): 1707-1721
- [13] Röder P V, Wong X, Hong W, *et al.* Molecular regulation of insulin granule biogenesis and exocytosis. *Biochem J*, 2016, **473**(18): 2737-2756
- [14] Wang F, Li Y, Bai L, *et al.* Advances in targeting glycogen synthase kinase 3 β for diabetes therapy. *Bioorg Chem*, 2025, **166**: 109051
- [15] Semrau M S, Giachin G, Covaceuszach S, *et al.* Molecular architecture of the glycogen-committed PPI/PTG holoenzyme. *Nat Commun*, 2022, **13**(1): 6199
- [16] McCorvie T J, Loria P M, Tu M, *et al.* Molecular basis for the regulation of human glycogen synthase by phosphorylation and glucose-6-phosphate. *Nat Struct Mol Biol*, 2022, **29**(7): 628-638
- [17] Bouskila M, Hunter R W, Ibrahim A F M, *et al.* Allosteric regulation of glycogen synthase controls glycogen synthesis in muscle. *Cell Metab*, 2010, **12**(5): 456-466
- [18] Schwartz A L, Rall T W. Hormonal regulation of glycogen metabolism in human fetal liver. II. Regulation of glycogen synthase activity. *Diabetes*, 1975, **24**(12): 1113-1122
- [19] Zhang T, Wang S, Lin Y, *et al.* Acetylation negatively regulates glycogen phosphorylase by recruiting protein phosphatase 1. *Cell Metab*, 2012, **15**(1): 75-87
- [20] Parker G, Taylor R, Jones D, *et al.* Hyperglycemia and inhibition of glycogen synthase in streptozotocin-treated mice: role of O-linked N-acetylglucosamine. *J Biol Chem*, 2004, **279**(20): 20636-20642
- [21] Peng S, Li C, Wang Y, *et al.* The metabolic enzyme GYS1

- condenses with NONO/p54nrb in the nucleus and spatiotemporally regulates glycogenesis and myogenic differentiation. *Cell Death Differ*, 2025, **32**(11): 2111-2125
- [22] Advani A, Marshall S M, Thomas T H. Impaired neutrophil store-mediated calcium entry in type 2 diabetes. *Eur J Clin Invest*, 2004, **34**(1): 43-49
- [23] Zhou Y, Wang L, Cheng K, *et al.* Quercetin inhibits glycolysis and tumor progression in a cell line-dependent manner, involving PI3K/AKT signaling predominantly in HOS cells. *Naunyn Schmiedebergs Arch Pharmacol*, 2026, **399**(7): 9997-10015
- [24] Turnbull J, Tiberia E, Striano P, *et al.* Lafora disease. *Epileptic Disord*, 2016, **18**(s2): S38-S62
- [25] Mitra S, Gumusgoz E, Minassian B A. Lafora disease: current biology and therapeutic approaches. *Rev Neurol*, 2022, **178**(4): 315-325
- [26] Canibano-Fraile R, Harlaar L, dos Santos C A, *et al.* Lysosomal glycogen accumulation in Pompe disease results in disturbed cytoplasmic glycogen metabolism. *J Inherit Metab Dis*, 2023, **46**(1): 101-115
- [27] Majer M, Mott D M, Mochizuki H, *et al.* Association of the glycogen synthase locus on 19q13 with NIDDM in Pima Indians. *Diabetologia*, 1996, **39**(3): 314-321
- [28] miR-Coll J, Duran J, Slebe F, *et al.* Genetic models rule out a major role of beta cell glycogen in the control of glucose homeostasis. *Diabetologia*, 2016, **59**(5): 1012-1020
- [29] Zhuo S, Bai M, Wang Z, *et al.* Glycogen synthesis is required for adaptive thermogenesis in beige adipose tissue and affects diet-induced obesity. *Am J Physiol Endocrinol Metab*, 2024, **326**(5): E696-E708
- [30] Xu S, Wang G, Peng W, *et al.* Corosolic acid isolated from *Eriobotrya Japonica* leaves reduces glucose level in human hepatocellular carcinoma cells, zebrafish and rats. *Sci Rep*, 2019, **9**(1): 4388
- [31] Hasani S, Young L E A, van Nort W, *et al.* Inhibition of mitochondrial fission activates glycogen synthesis to support cell survival in colon cancer. *Cell Death Dis*, 2023, **14**(10): 664
- [32] Fang K, Jiang S, Xu Z, *et al.* Pan-cancer landscape of disulfidptosis across human tumors. *Heliyon*, 2024, **10**(22): e40122
- [33] Chen S L, Huang Q S, Huang Y H, *et al.* GYS1 induces glycogen accumulation and promotes tumor progression *via* the NF- κ B pathway in Clear Cell Renal Carcinoma. *Theranostics*, 2020, **10**(20): 9186-9199
- [34] de Heer E C, Zois C E, Bridges E, *et al.* Glycogen synthase 1 targeting reveals a metabolic vulnerability in triple-negative breast cancer. *J Exp Clin Cancer Res*, 2023, **42**(1): 143
- [35] Xie J, Deng X, Xie Y, *et al.* Multi-omics analysis of disulfidptosis regulators and therapeutic potential reveals glycogen synthase 1 as a disulfidptosis triggering target for triple-negative breast cancer. *MedComm*, 2024, **5**(3): e502
- [36] Zhuo S, Wang Z, Zhang Y, *et al.* Glycogen synthase 1 promotes breast cancer progression by promoting I κ B α ubiquitination and degradation independent of its canonical enzyme function. *Cell Commun Signal*, 2026, **24**(1): 197
- [37] Chen X, Yang N, Wang Y, *et al.* PCK1-mediated glycogenolysis facilitates ROS clearance and chemotherapy resistance in cervical cancer stem cells. *Sci Rep*, 2024, **14**(1): 13670
- [38] Jiang Y, Han Q, Zhao H, *et al.* The mechanisms of HBV-induced hepatocellular carcinoma. *J Hepatocell Carcinoma*, 2021, **8**: 435-450
- [39] Koshy A. Evolving global etiology of hepatocellular carcinoma (HCC): insights and trends for 2024. *J Clin Exp Hepatol*, 2025, **15**(1): 102406
- [40] Zois C E, Favaro E, Harris A L. Glycogen metabolism in cancer. *Biochem Pharmacol*, 2014, **92**(1): 3-11
- [41] Zhang R, Zhou K, Wu M, *et al.* Disulfidptosis-related genes *RPNI* inhibits the progression of hepatocellular carcinoma by regulating cell cycle, may be a new therapeutic targets. *Inflamm Res*, 2025, **74**(1): 105
- [42] Wang X, Xiao K, Liu Z, *et al.* Unveiling disulfidptosis-related genes in HBV-associated hepatocellular carcinoma: an integrated study incorporating transcriptome and Mendelian randomization analyses. *J Cancer*, 2024, **15**(17): 5540-5556
- [43] Wang H, Xiao T, Zhuang H, *et al.* STBD1 mediates the crosstalk between glycogen and lipid droplets in clear cell renal cell carcinoma. *Cell Rep*, 2025, **44**(10): 116429
- [44] Zhang D, Zhang X, Liu Z, *et al.* An integrative multi-omics analysis based on disulfidptosis-related prognostic signature and distinct subtypes of clear cell renal cell carcinoma. *Front Oncol*, 2023, **13**: 1207068
- [45] Xie H, Song J, Godfrey J, *et al.* Glycogen metabolism is dispensable for tumour progression in clear cell renal cell carcinoma. *Nat Metab*, 2021, **3**(3): 327-336
- [46] Favaro E, Bensaad K, Chong M G, *et al.* Glucose utilization *via* glycogen phosphorylase sustains proliferation and prevents premature senescence in cancer cells. *Cell Metab*, 2012, **16**(6): 751-764
- [47] Mutlu M, Saatci Ö, Ansari S A, *et al.* miR-564 acts as a dual inhibitor of PI3K and MAPK signaling networks and inhibits proliferation and invasion in breast cancer. *Sci Rep*, 2016, **6**: 32541
- [48] Sadiku P, Willson J A, Ryan E M, *et al.* Neutrophils fuel effective immune responses through gluconeogenesis and glycogenesis. *Cell Metab*, 2021, **33**(5): 1062-1064
- [49] Ailun, Dalai, Daite R, *et al.* Research progress and potential therapeutic targets of a novel disulfide stress-driven cell death-disulfidptosis in gynecological tumors and other gynecological disorders. *Am J Cancer Res*, 2025, **15**(10): 4394-4414
- [50] Ahonen S, Nitschke S, Grossman T R, *et al.* Gys1 antisense therapy rescues neuropathological bases of murine Lafora disease. *Brain*, 2021, **144**(10): 2985-2993
- [51] Kakhlon O, Vaknin H, Mishra K, *et al.* Alleviation of a polyglucosan storage disorder by enhancement of autophagic glycogen catabolism. *EMBO Mol Med*, 2021, **13**(10): e14554
- [52] Kakhlon O, Ferreira I, Solmesky L J, *et al.* Guaiacol as a drug candidate for treating adult polyglucosan body disease. *JCI Insight*, 2018, **3**(17): e99694
- [53] Chown E E, Wang P, Zhao X, *et al.* GYS1 or PPP1R3C deficiency rescues murine adult polyglucosan body disease. *Ann Clin Transl Neurol*, 2020, **7**(11): 2186-2198
- [54] Koch R L, Cocanougher B T, Lim J A, *et al.* Expanding therapeutic options for Pompe disease: a new small molecule inhibitor of glycogen synthase 1 (GYS1) shows preclinical promise in Pompe disease. *Ann Transl Med*, 2024, **12**(6): 123
- [55] Holt B D, Elliott S J, Meyer R, *et al.* A novel CD71 Centyrin: Gys1 siRNA conjugate reduces glycogen synthesis and glycogen levels in a mouse model of Pompe disease. *Mol Ther*, 2025, **33**(1): 235-248
- [56] Burgos D F, Machío-Castello M, Iglesias-Cabeza N, *et al.* Early treatment with metformin improves neurological outcomes in lafora disease. *Neurotherapeutics*, 2023, **20**(1): 230-244

靶向GYS1: 从代谢调控机制到精准治疗策略*

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摘要 糖原合成酶1 (GYS1) 是肌肉、心脏、大脑及其他肝外组织中糖原合成的限速酶, 在维持机体能量稳态中发挥核心作用。人GYS1基因定位于19q13.33, 包含16个外显子, 编码737个氨基酸的功能多肽, 其蛋白质序列在哺乳动物中高度保守。GYS1的活性受到多层次、多维度的精密调控: 在转录水平, 启动子区的缺氧应答元件 (HRE) 和肌肉特异性增强子分别介导缺氧诱导和组织特异性表达; 在翻译后水平, 糖原合成酶激酶3 β (GSK3 β)、蛋白激酶A (PKA) 和腺苷酸活化蛋白激酶 (AMPK) 通过层级磷酸化抑制其活性, 而蛋白磷酸酶1 (PP1) 经糖原靶向亚基介导去磷酸化激活, 葡萄糖-6-磷酸 (G6P) 则作为变构激活剂形成前馈激活环路; 此外, 泛素化、乙酰化、O-GlcNAc修饰和SUMO化等多种翻译后修饰进一步调节GYS1的蛋白质稳定性、亚细胞定位及蛋白质相互作用。在表观遗传层面, CpG岛甲基化状态和组蛋白乙酰化影响染色质可及性, 而miR-1、miR-206等微RNA则在转录后水平精细调控GYS1表达。GYS1的调控失常是多种人类疾病的核心驱动因素: 在Lafora病、成人多聚葡聚糖体病 (APBD) 和Pompe病中, GYS1过度激活导致病理性糖原沉积和进行性神经肌肉损伤; 在2型糖尿病中, 骨骼肌GYS1活性降低损害胰岛素刺激的葡萄糖储存, 加剧餐后高血糖; 在肝细胞癌、透明细胞肾细胞癌、三阴性乳腺癌、结直肠癌和宫颈癌中, GYS1通过NF- κ B信号激活、二硫化物死亡调控、免疫微环境重塑及化疗耐药等多种机制发挥促癌或代谢适应作用。针对GYS1的治疗策略已取得显著进展, 包括反义寡核苷酸 (ASO)、小干扰RNA (如ABX1100) 和小分子抑制剂 (如MZ-101) 用于糖原贮积症的底物减少治疗, 以及GSK3 β 抑制剂和PP1激活策略用于恢复2型糖尿病中的GYS1功能。本文系统综述了GYS1的基因结构、组织分布、调控网络及其在代谢性疾病与恶性肿瘤中的致病机制和治疗靶向价值, 旨在为糖原代谢相关疾病的精准治疗提供理论依据。

关键词 GYS1, 糖原代谢, 糖原贮积症, 2型糖尿病, 癌症, 翻译后调控, 治疗靶点, 信号通路

中图分类号 Q5;R73

DOI: 10.3724/j.pibb.2026.0183

CSTR: 32369.14.pibb.20260183

* 浙江省自然科学基金 (LMS25H030005), 宁波市“科创甬江2035”关键技术突破计划项目 (2024Z215), 浙江省普外科临床重点专科建设项目 (2023-SZZ), 浙江省自然科学基金 (LY24C050001), 宁波市自然科学基金 (2024J037) 和国家自然科学基金 (32570835, 32270821, 62427812) 资助。

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收稿日期: 2026-04-10, 接受日期: 2026-05-28