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Research Progress of Glucuronyl C5-Epimerase in Cancers: A Review

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Abstract: Glucuronyl C5-epimerase (GLCE) is a key enzyme in heparan sulfate biosynthesis. Mouse with a whole-genome knockout of *GLCE* exhibit embryonic lethality, highlighting its essential roles in growth and development and its involvement in processes such as obesity, neurogenesis, and immune regulation. Interestingly, GLCE exerts similar or even opposite effects in different cancers. The functional complexity of GLCE in cancers positions it as a promising biomarker and therapeutic target. However, current understanding of the roles and underlying mechanisms of GLCE in various cancers remains limited. This article reviews and discusses the functions and molecular mechanisms of GLCE in different cancers.

Keywords: Glucuronyl C5-epimerase; Biomarker; Tumor; Mechanism; Translation

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1. Introduction

Glucuronyl C5-epimerase (GLCE) is a key enzyme in the biosynthetic pathway of heparan sulfate (HS). It catalyzes the epimerization of D-glucuronic acid (GlcA) to L-iduronic acid (IdoA) [1], a critical step for HS function in ligand recognition and cell signaling [2]. *GLCE*-null mouse exhibit embryonic lethality with highly aberrant HS structure, accompanied by skeletal malformations, renal agenesis, and chondrodysplasia [3,4]. Caenorhabditis elegans with GLCE mutations display abnormal neuronal development characterized by specific axonal and cell guidance defects [5], indicating that GLCE plays a crucial role in organismal development. GLCE is highly conserved throughout evolution, and its crystal structure has been resolved. The overall structure of the dimer resembles an inverted W, with the full-length sequence containing a transmembrane α-helix at the N-terminus that likely anchors the GLCE dimer to the Golgi membrane for HS modification. The active site residues Tyr468, Tyr528, and Tyr546 have been identified as critical for the catalytic activity of glucuronyl C5-epimerase [6]. The elucidated structure of GLCE provides a foundation for future targeted drug development and modification.

Current research on the biological functions of GLCE is multifaceted, implicating its involvement in obesity [7], neurogenesis [8], immune regulation [9], and osteoarthritis [10]. Given its multifaceted biological interactions, the functional profile of GLCE is inherently complex. This complexity is particularly evident in tumor.

2. GLCE and reproductive system cancers

2.1. GLCE and breast cancer

Previous studies found that *GLCE* mRNA expression was downregulated or lost in 82-84% of human breast tumors, with a significant decrease in protein levels [11]. Prudnikova et al. further investigated its role in breast cancer [12] and found that GLCE inhibited the proliferation of MCF7 breast cancer cells by downregulating the expression of various key genes involved in cell cycle regulation, angiogenesis, and metastatic pathways, supporting the role of GLCE as a tumor suppressor in breast cancer. This broad-spectrum regulatory pattern suggests that GLCE may function as an upstream node in signaling networks rather than a downstream effector of a single pathway. The study primarily relied on the MCF7 cell line, which is representative of ER-positive, luminal-type breast cancer but does not fully capture subtypes such as triple-negative or HER2-positive breast cancer. GLCE rs3865014 is a common polymorphism in humans, showing negative correlations with hypertension, waist circumference, and BMI, and positive correlations with hemoglobin, low-density lipoprotein cholesterol, and cerebrovascular event frequency [13]. Analysis of SNP databases revealed that the AG genotype of GLCE rs3865014 exhibits high racial specificity, serving as a risk factor for breast cancer susceptibility in the Siberian population and correlating with aggressive ER-negative and triple-negative breast cancer, thereby promoting disease incidence and progression [14].

Furthermore, studies by Mostovich et al. and Prudnikova et al. revealed multi-level regulatory mechanisms of GLCE expression [15,16]. Unlike in prostate cancer, where promoter methylation participates in GLCE regulation [17], methylation is not the primary mechanism in breast cancer. Instead, chromatin activation (e.g., H3K9ac and H3K4Me3 modifications) significantly upregulates GLCE expression. This difference suggests that the regulatory mechanisms of GLCE are tissue-specific. Exogenous TCF4/β-catenin expression alone failed to activate GLCE, but its synergistic effect with chromatin activation drove GLCE transcription, highlighting the importance of cooperative regulation. miRNA-218 showed a positive correlation with GLCE mRNA but a negative correlation with GLCE protein. This seemingly contradictory observation may reflect a feedback regulatory mechanism: when GLCE transcription is active, cells upregulate miRNA-218 to limit its translation, suggesting that measuring mRNA levels alone may not accurately reflect the functional status of GLCE.

2.2. GLCE and endometrial cancer

Endometrial cancer is the second most common gynecological malignancy worldwide, after cervical cancer, with over 90% of uterine cancers being endometrial cancer [18]. Its incidence continues to rise in developed countries. Numerous studies have shown that aberrant expression of Long non-coding RNAs is associated with tumor development and progression. One study reported that GLCE inhibits epithelial-mesenchymal transition (EMT) in endometrial cancer stem cells via the MONC/miR-636/GLCE axis [19], providing new perspectives on the pathogenesis and therapeutic intervention of endometrial cancer. Unlike in breast and lung cancers, where GLCE directly functions as a tumor suppressor, the role of GLCE in endometrial cancer is indirectly regulated via the lncRNA-miRNA axis. This difference suggests that GLCE may serve as a “common downstream effector” of

multiple upstream regulatory signals, with its function depending on tumor type-specific upstream regulatory networks. The expression levels of lncRNA Monc and miR-636 can be detected in both tissue and body fluids, offering clinical accessibility. Future studies, such as collecting endometrial cancer tissue microarrays to examine the expression correlations among MONC, miR-636, and GLCE and their associations with patient prognosis, are warranted.

2.3. GLCE and prostate cancer

Prostate cancer is the most common malignancy of the male reproductive system. Statistical analysis revealed that increased GLCE expression in prostate tumors positively correlates with Gleason score, TNM stage, and prostate-specific antigen (PSA) levels. However, GLCE expression was decreased in 10% of benign prostatic hyperplasia (BPH) tissues and 53% of prostate tumors, while increased expression was observed in 49% of BPH tissues and 21% of tumors [17]. Prostate cancer is a highly heterogeneous tumor, and different molecular subtypes may exhibit distinct regulatory mechanisms for GLCE. The coexistence of increased and decreased expression suggests that GLCE may play different roles across subtypes. The simultaneous presence of increased (49%) and decreased (10%) GLCE expression in BPH tissues indicates that GLCE dysregulation may occur at early stages of malignant transformation, though its functional direction may shift with disease progression.

Rosenberg et al. compared differentially expressed genes among several prostate cancer cell lines (LNCaP, PC3, and DU145) and normal prostate epithelial cells (PNT2). Transcriptomic analysis revealed that GLCE primarily affects angiogenesis-related genes (e.g., *ANGPT1, SERPINE1, IL8, PDGFB*), suggesting that it may promote prostate cancer progression by activating angiogenesis [20].

The co-culture model of BjTERT fibroblasts with normal PNT2 human prostate epithelial cells, established by Elvira V. Grigorieva et al., revealed the regulatory effect of the tumor microenvironment on GLCE and HS metabolism-related genes [21]. When co-cultured with normal prostate epithelial cells (PNT2), HS metabolism-related genes were significantly downregulated in fibroblasts. However, this downregulation was attenuated or abolished when co-cultured with prostate cancer cells. This suggests that normal epithelial cells may maintain microenvironmental homeostasis by secreting factors that suppress GLCE expression in fibroblasts, whereas cancer cells may “reprogram” fibroblasts to reverse this inhibitory effect, maintaining higher expression levels of HS metabolism-related genes and thereby creating a favorable microenvironment for the tumor. These findings provide a basis for GLCE as a prognostic marker and potential target for anti-angiogenic therapy in prostate cancer.

3. GLCE and digestive system cancers

3.1. GLCE and colorectal cancer

Hyperactivation of the Wnt/β-catenin pathway is a core driving event in the development and progression of colorectal cancer, with approximately 90% of cases harboring APC mutations or β-catenin mutations that lead to constitutive activation of the β-catenin/TCF4 complex [22]. Studies have shown that in the human colorectal cancer cell line HCT116, GLCE expression correlates with the degree of β-catenin/TCF4 complex activation, and enhanced GLCE expression increases the conversion rate of GlcA to IdoA in HS chains [23]. GLCE is regulated by TCF4/β-catenin in breast cancer research [15], and this regulatory relationship was further validated in colorectal cancer, suggesting that GLCE is a conserved downstream target gene of the Wnt signaling pathway. When Wnt

signaling is aberrantly activated, GLCE expression is upregulated and participates in HS structural remodeling. Inhibitors targeting Wnt signaling (e.g., Porcupine inhibitors, TCF4 inhibitors) are currently under clinical development for colorectal cancer. As a downstream effector of Wnt signaling, changes in GLCE expression may serve as a pharmacodynamic biomarker to assess the efficacy of Wnt inhibitors. Given the close association between Wnt signaling activation and chemotherapy resistance in colorectal cancer, whether GLCE influences drug sensitivity through HS structural remodeling warrants further investigation.

3.2. GLCE and pancreatic cancer

Pancreatic cancer is the fourth leading cause of cancer-related death worldwide, with its incidence doubling over the past 25 years and projected to become the second leading cause of cancer death by 2030 [24]. The extremely poor prognosis of pancreatic cancer (5-year survival rate of approximately 10%) is largely attributed to difficulties in early diagnosis, high tumor aggressiveness, and resistance to chemotherapy and immunotherapy. Therefore, identifying novel risk markers and therapeutic targets holds significant clinical value. Currently, no functional studies of GLCE in pancreatic cancer have been reported. However, the TCGA database shows significantly higher GLCE expression in pancreatic cancer tissues compared to adjacent normal tissues. Furthermore, a prospective cohort study by Tanxin Liu et al. validated a positive correlation between GLCE and pancreatic cancer risk [25]. GLCE participates in metabolic regulation by stabilizing GDF15 in the liver, and obesity is an important risk factor for pancreatic cancer. Whether high GLCE expression synergizes with obesity-related metabolic dysregulation warrants further investigation.

4. GLCE and other cancers

4.1. GLCE and small cell lung cancer

Small-cell lung cancer accounts for approximately 15% of all lung cancers and is characterized by extremely high proliferative rates, early metastasis, and poor prognosis [26]. Based on the phenomenon that targeted disruption of GLCE leads to lung defects, Grigorieva et al. [27] found that ectopic re-expression of GLCE in the SCLC cell line U2020 affected cell morphology and inhibited both in vitro cancer cell proliferation and in vivo tumor formation, indicating a potential tumor-suppressive role for GLCE in small cell lung cancer. This effect is mediated through downregulation of several pro-angiogenic growth factors (e.g., VEGF-A, TGFβ1) and their receptors. SCLC is a highly vascularized tumor, and GLCE-mediated downregulation of angiogenic factors may not only affect tumor cell proliferation but also remodel the tumor microenvironment, reduce vascular permeability, and decrease metastatic potential.

4.2. GLCE and osteosarcoma

Osteosarcoma is the most common primary malignant bone tumor in adolescents, accounting for approximately 20–34% of all primary malignant bone tumors [28]. Its clinical characteristics include high aggressiveness, early pulmonary metastasis, and significant heterogeneity in chemotherapy sensitivity. Although neoadjuvant chemotherapy combined with surgical resection has increased the 5-year survival rate to 60-70%, the prognosis for patients with recurrence or metastasis remains extremely poor. Wei Huang et al. performed gene set enrichment analysis (GSEA) using osteosarcoma datasets from the TARGET database and constructed a risk model using TCGA data, revealing that GLCE is positively correlated with poor prognosis in osteosarcoma [29]. The prognosis

of osteosarcoma is largely determined by metastatic status. Whether GLCE affects patient survival by promoting invasion and metastasis requires further validation through in vitro and in vivo experiments.

4.3. GLCE and medulloblastoma

Medulloblastoma is the most common malignant brain tumor in children [30]. Its treatment includes surgical resection, craniospinal radiotherapy, and multi-agent chemotherapy, but patient prognosis exhibits significant heterogeneity. Identifying molecular prognostic markers is crucial for guiding risk stratification and treatment intensity adjustment. Through univariate Cox regression analysis, GLCE was identified as one of the top 10 genes significantly associated with survival in medulloblastoma, with high expression correlating with better prognosis [31]. Univariate Cox regression analysis only assesses the independent association between GLCE and prognosis without adjusting for other clinical variables, such as molecular subtype, MYC amplification status, and metastatic status. Therefore, whether the prognostic value of GLCE is independent of known risk factors remains to be validated.

4.4. GLCE and glioma

A study reported that analysis of HS biosynthesis-related genes in human gliomas of different grades revealed significantly decreased GLCE expression in glioma tissues [32]. Glioblastoma (GB) is the most common and aggressive primary malignant tumor of the central nervous system. Even with maximal safe resection, temozolomide (TMZ) chemoradiotherapy, and tumor-treating fields, the median survival of patients remains less than 15 months, with extremely high recurrence rates [33]. Dexamethasone (DXM), a glucocorticoid, is widely used in GB patients to control cerebral edema and alleviate radiotherapy-related inflammatory reactions, but its effects on tumor biology have long been overlooked. In an animal model of GB recurrence, DXM pretreatment resulted in significantly decreased GLCE expression and overall attenuation of HS biosynthesis [34]. This finding provides new molecular insights into how glucocorticoids influence the tumor microenvironment and therapy resistance.

4.5. GLCE and Ewing sarcoma

Ewing sarcoma is an aggressive malignancy characterized by non-random chromosomal translocations that generate fusion genes, making gene therapy a promising treatment approach [35], with GLCE potentially serving as a therapeutic target. Current research on GLCE in Ewing sarcoma has primarily focused on prognostic assessment through risk model construction. Fusen Jia et al. integrated multiple datasets to construct a risk scoring model and found that GLCE correlates with better prognosis in Ewing sarcoma [36]. Cross-validation across multiple datasets, including GSE17679, GSE17674, ICGC, GSE63155, and GSE63156, strengthened the credibility of the association between GLCE and favorable prognosis. Jian Wen et al. validated this finding through Kaplan-Meier analysis and discovered upregulation of the glycosaminoglycan biosynthesis-heparan sulfate/heparin pathway in Ewing sarcoma. Functional enrichment analysis suggested that GLCE may regulate tumor proliferation, angiogenesis, and metastasis by influencing heparan sulfate synthesis [37]. **Table 1** shows the summary of GLCE research evidence.

Table 1. Summary of GLCE research evidence in different cancers

Cancer type	GLCE expression	ValidationSamples /Models	Clinical Association	Molecular Mechanism/Regulatory Axis
Breast cancer	Downregulation of mRNA and protein expression (82-84% of tumors)	Human breast cancer tissues, MCF7 cells	Correlated with ER-negative and triple-negative breast cancer; AG genotype associated with breast cancer susceptibility	Regulated by TCF4/β-catenin and chromatin structure; post-transcriptionally regulated by miRNA-218; upregulates p53, BRCA1, and SYK expression
Endometrial Cancer	Indirectly regulated via the ceRNA axis	Endometrial cancer cell lines	Unknown	Inhibits EMT in cancer stem cells via the MONC/miR-636/GLCE axis
Prostate Cancer	Bidirectional changes (decreased in 53%, increased in 21%)	Human prostate tissues, LNCaP, PC3, DU145 cells, PNT2 cells	Increased expression positively correlated with Gleason score, TNM stage, and PSA level	Affects angiogenesis-related genes, including ANGPT1 and SERPINE1; HS metabolism genes (including GLCE) downregulated during fibroblast co-culture
Colorectal Cancer	Expression correlates with β-catenin/TCF4 activation	HCT116 cells	Unknown	Regulated by β-catenin/TCF4 complex; enhances conversion rate of GlcA to IdoA in HS chains
Pancreatic Cancer	Significantly higher expression in tumor tissues compared to adjacent normal tissues	TCGA database, prospective cohort of 10,355 participants	Positively correlated with pancreatic cancer risk	Unknown
Small Cell Lung Cancer	Ectopic re-expression in U2020 cells	U2020 small cell lung cancer cells, mouse xenograft model	Ectopic re-expression inhibits tumor formation	Downregulates pro-angiogenic growth factors and their receptors including VEGF-A, TGFβ1, FGFR2, PDGF-A/B, and MMP2
Osteosarcoma	High expression	TARGET database, TCGA database	Positively correlated with poor prognosis	Unknown
Medulloblastoma	High expression	Medulloblastoma clinical samples	Correlated with better prognosis	Unknown
Glioma	Significantly decreased expression	Human glioma tissues of different grades	Unknown	Dexamethasone pretreatment reduces GLCE expression and attenuates HS biosynthesis
Ewing Sarcoma	Correlated with better prognosis	GSE17679, GSE17674, ICGC, GSE63155, GSE63156 datasets	High expression is associated with better prognosis	Glycosaminoglycan biosynthesis-heparan sulfate/heparin pathway upregulated; may regulate proliferation, angiogenesis, and metastasis via HS synthesis

5. Discussion

As a key modifying enzyme in heparan sulfate biosynthesis, GLCE exhibits expression patterns that are not uniformly increased or decreased across different cancers, but rather demonstrate significant heterogeneity and racial specificity. This presents unique opportunities and challenges for its translational application.

By generating IdoA, GLCE regulates HS structure and growth factor signaling, thereby influencing tumor angiogenesis, invasion, and the immune microenvironment. Therefore, targeting GLCE enzymatic activity may represent a strategy for intervening in HS-related signaling pathways. In cancers where GLCE is highly expressed

and promotes tumor progression (e.g., certain prostate cancers), small-molecule inhibitors of GLCE could be developed to block IdoA generation and disrupt the activation of pro-angiogenic signals. In cancers where GLCE is underexpressed and functions as a tumor suppressor (e.g., breast and lung cancers), GLCE expression could be restored through recombinant GLCE protein, gene therapy, or miRNA-218 inhibitors to re-establish tumor-suppressive functions [12,16].

Recent studies have revealed that GLCE protein can directly bind to EGFR, inhibit the EGFR/ERK signaling pathway, and exert anti-fibrotic and anti-tumor effects independent of its enzymatic activity [38]. This provides a new avenue for developing GLCE-derived peptides or mimetics, particularly for tumors with active EGFR signaling. The expression of GLCE is regulated by TCF4/β-catenin and miRNA-218 [12,25], suggesting that combination strategies with Wnt signaling inhibitors or miRNA mimics could achieve multi-target synergistic intervention.

GLCE not only affects tumor cells themselves but also regulates immune cell function, it deficiency impairs B cell maturation and plasma cell survival, altering APRIL-mediated immune responses [39]. In Ewing sarcoma, GLCE expression positively correlates with mast cell infiltration, influencing the composition of the immune microenvironment [37]. These findings suggest that GLCE may serve as an immunomodulatory target and could be combined with immune checkpoint inhibitors to enhance anti-tumor immune responses.

Although the functions of GLCE in tumors are becoming increasingly clear, the following issues warrant further investigation: The expression profiles and clinical correlations of GLCE in most tumors remain incomplete; understanding of the functions and molecular mechanisms of GLCE is still superficial, with most studies limited to prognostic assessment using databases or expression level determination, lacking animal models and in vivo validation. Tissue-specific knockout/knock-in mouse models could be developed to mimic GLCE function in tumor contexts. Large-scale multicenter clinical cohort studies are needed to establish databases correlating GLCE expression with staging, prognosis, and treatment response. The relative contributions of GLCE's enzymatic and non-enzymatic functions across different tumors remain unclear; comparative models using enzyme activity mutants versus wild-type should be constructed to elucidate the mechanisms. The lack of specific small-molecule tools targeting GLCE calls for virtual screening and medicinal chemistry optimization based on GLCE crystal structures [40] to develop highly selective inhibitors or activators.

6. Conclusion

This article reviews the research progress on GLCE expression changes, mechanisms, and targets in different cancers. GLCE is a unique molecule that exhibits both enzyme activity-dependent and -independent functions and displays bidirectional regulatory roles in tumors. In the future, systematic functional mechanism studies, large-scale clinical validation, and the development of targeted intervention strategies will lay a solid foundation for the clinical translation of GLCE.

Disclosure statement

The authors declare no conflict of interest.

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