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Review Article

Glycolysis in gastrointestinal stromal tumor: a brief overview

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ABSTRACT

Gastrointestinal stromal tumor (GIST) is the most prevalent mesenchymal tumor of the digestive tract. Its growth is primarily influenced by mutations in *KIT* or *PDGFRA*. Surgery is the primary treatment option for GIST; however, KIT inhibitors, such as imatinib, are used for inoperable cases. Resistance to imatinib is an upcoming challenge, especially because the effectiveness of alternative drugs is limited. Enhancement of the glycolysis pathway in cancer cells has been identified as a key feature in cancer. This unique metabolic activity has implications on tumor growth, prognosis, and resistance to therapy, even in GIST. Members of the glucose transporter (GLUT) family (particularly GLUT-1) play a significant role in GIST progression and response to treatment. Diagnostic imaging using 18F-fluorodeoxyglucose positron emission tomography/computed tomography, which enables visualization of glucose metabolism, can aid in GIST diagnosis and risk assessment. The interplay between glycolysis and GIST can lead to the development of various therapeutic strategies, especially those involving glycolysis-related molecules, such as hexokinase and lactate dehydrogenase. However, further research is required to understand the full spectrum of glycolysis in GIST and its therapeutic potential. Herein, we present an exhaustive overview and analysis of the role of glycolysis in GIST, especially as a therapeutic target.

Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the digestive tract [1]. GIST primarily develops due to the constitutive activation of the receptor tyrosine kinase *KIT* or *PDGFRA*, with approximately 75 % of GISTs harboring gain-of-function mutations in *KIT* [2,3].

Surgical resection is the primary treatment option for GISTs that can be removed. However, for GISTs that are unresectable, metastatic, or recurrent, KIT inhibitors, such as imatinib mesylate (also known as imatinib), are administered [4-6]. Drug resistance represents a major obstacle to the treatment of GISTs. Typically, resistance to imatinib develops after a median duration of 18–24 months of therapy [7,8]. While sunitinib and regorafenib are considered effective for treating imatinib-resistant GIST, the median progression-free survival is 8.5 months for sunitinib and 4.8 months for regorafenib [9-11]. A recent study has highlighted the potential of TAS-116, a heat shock protein 90 inhibitor, in the treatment of treatment-resistant advanced GISTs [12]. Nonetheless, only a few chemotherapy regimens are available for GIST, and no chemotherapy regimens are available for imatinib-resistant GIST.

Tumor cells favor aerobic glycolysis, a phenomenon observed when sufficient oxygen is available. This pathway generates less energy than mitochondrial oxidative phosphorylation, which occurs in healthy cells. Tumor cells facilitate nucleic acid synthesis and promote rapid growth using the pentose phosphate pathway [13,14]. Several studies have reported on the association between this distinct metabolic fingerprint and various hallmarks, including tumor cells' progression and resistance to chemotherapy [15-17].

In the context of GIST, there is a growing body of evidence suggesting that this cancer-specific metabolic paradigm influences tumor malignancy, tumor risk stratification, and resistance to imatinib [18-20]. However, the relationship between glycolysis and GIST remains unclear.

Here, we provide a brief overview and analysis of the role of glycolysis in GIST, laying special emphasis on potential avenues for metabolic research and underscoring its merit as an intriguing

List of abbreviations: GLUT: Glucose transporter; GIST: Gastrointestinal stromal tumor; MTV:Metabolic tumor volume; PK: Pyruvate kinase; TLG: Total lesion glycolysis

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therapeutic target.

Glucose transporter (GLUT)

GLUT serves as the initial rate-limiting step in cellular glucose metabolism. Within the GLUT family, GLUT-1 predominantly regulates basal glucose uptake, ensuring the maintenance of foundational cellular glucose metabolism. Thus, this transporter is essential in the modulation of cellular energy production [21,22].

In the context of GIST, it has been demonstrated that elevated GLUT-1 expression corresponds to an increased tumor risk grade [19]. In a study assessing CD63 (a significant protein of the transmembrane 4 superfamily and an exosomal marker) expression in conjunction with GLUT-1 expression, a significant correlation was found between GLUT-1 expression and CD63 expression in tumor cells among 54 patients with CD117(c-kit)-positive gastric GIST who had not undergone prior treatment with imatinib or other chemotherapy agents, and high levels of GLUT-1 and CD63 were associated with a substantial decrease in disease-free survival [18]. Conversely, another study examining the characteristics of small extracellular vesicles derived from GIST cells in the plasma of patients with GIST suggested a correlation between an unfavorable prognosis and elevated carcinoembryonic antigen levels and/or diminished GLUT-1 levels [23]. Notably, direct comparisons between the expression levels of GLUT-1 and the levels of GLUT-1 in small extracellular vesicles may not be feasible, possibly accounting for the discrepancy observed in the abovementioned two studies [23]. Here, we conducted a comparative analysis between GIST cell lines with secondary mutations in *PDGFRA* exon 12 and the GIST-T1 cell line. Interestingly, our findings revealed that imatinib treatment led to the downregulation of GLUT-1 and other components of the glycolysis pathway in parental GIST-T1 cells, even at low concentrations. In contrast, imatinib treatment increased the expression of these components in imatinib-resistant cells [20]. Therefore, we considered that the glycolysis pathway is essential for the acquisition of imatinib resistance by GIST cells and for cell survival.

GLUT-2 is predominantly localized in pancreatic beta cells, hepatocytes, and renal tubular cells, whereas GLUT-3 is mainly expressed in nervous tissues [24]. In a study that assessed the potential advantages of continuous versus intermittent imatinib administration in mice implanted with an imatinib-resistant GIST cell line harboring a secondary mutation in *KIT* exon 17, cytoplasmic GLUT-2 expression was significantly elevated in the treated group compared with the untreated group. Moreover, the cytoplasmic and membrane-bound GLUT-3 levels were significantly higher in the intermittent treatment group than in the continuous treatment group [25]. However, the significance of these findings and their underlying mechanisms are yet to be fully elucidated.

GLUT-4 is a high-capacity glucose transporter primarily found in nondividing cells, such as those in adipose tissue, skeletal muscle, and the myocardium [26]. In a study conducted on 57 patients with GIST receiving neoadjuvant chemotherapy with imatinib, all patients exhibited detectable GLUT-4 levels before imatinib therapy. However, among 22 patients whose tumor samples were obtained during surgery after neoadjuvant chemotherapy, 19 showed decreased GLUT-4 expression [27]. Based on these data, imatinib was considered to interact with glycolysis and GLUT-4 expression.

Overall, these findings suggest that a multitude of GLUT subtypes are involved in the pathogenesis of imatinib resistance in GIST. The upregulation of GLUT expression can play a vital role in the acquisition of imatinib resistance by GIST and cell survival.

Glycolysis-related molecules besides GLUT

In addition to GLUT, hexokinase (HK), phosphofructokinase 1 (PFK1), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), pyruvate kinase (PK), lactate dehydrogenase (LDH), and monocarboxylate transporters (MCT) are recognized to be associated with glycolysis [28]. A previous study demonstrated increased activity of HK1 (one of the HK isoforms), PKM2 (one of the PK isoforms), and LDH in high-risk grade tumors, suggesting their potential in the preoperative prediction of malignancy [19]. Furthermore, research into the association between MCT and GIST has unveiled the pronounced expression of MCT1, MCT2, and MCT4 [29]. The coexpression of MCT1 and its chaperone, CD147, has been implicated in the aggressiveness of GIST and correlated with reduced patient survival [29]. While numerous studies have reported on the association between glycolysis-related molecules and various types of cancer, there has been a paucity of research focusing solely on GIST [15-17]. A summary of glycolysis-related molecules in GIST is shown in Table 1.

Diagnostic imaging

^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is one of the most commonly used functional imaging modalities in clinical practice. This technique uses a radioisotope to trace glucose and is recommended for GIST imaging [30,31]. The imaging diagnosis using ^{18}F-FDG PET/CT is based on glucose metabolism *in vivo* [32,33]. The accumulation of the tracer is primarily mediated by GLUT [34,35]. Notably, FDG PET/CT has been demonstrated to have a high predictive prognostic value for recurrence-free survival in patients with localized primary GIST through assessment of preoperative metabolic tumor volume (MTV) and total lesion glycolysis (TLG) [36]. Regarding GIST patients with *KIT* exon 11 mutations, FDG PET/CT demonstrated that imatinib treatment reduces FDG uptake levels within 1–7 days post treatment [27]. Immunohistochemical findings have suggested the involvement of GLUT-4 in FDG uptake in GIST, which is confirmed by the decrease in GLUT-4 levels following imatinib therapy [27]. Additionally, *in vitro* treatment of GIST cells with imatinib caused translocation of GLUT-4 from the plasma membrane to the cytosol via endocytosis as shown by lower plasma membrane-bound GLUT-4 levels [37]. Imatinib directly affects glycolysis and GLUT-4 expression, thereby resulting in decreased FDG uptake [27,37]. FDG uptake evaluations on preoperative PET/CT of 40 patients with GIST revealed positive correlations between FDG uptake and tumor size; tumor risk grade per the Fletcher classification; and GLUT-1, HK1, and LDHA expression levels [19]. Analyses were conducted on several metabolic parameters, including maximum standardized uptake value

Table 1
Role of glycolytic molecules in gastrointestinal stromal tumor.

Molecules	Associations and functions	References
GLUT-1	Elevated GLUT-1 expression corresponds to heightened tumor risk grade	19
	GLUT-1 expression positively correlates with CD63 expression	18
	High GLUT-1 and CD63 levels in GIST cells correlate with lower disease-free survival	18
	High carcinoembryonic antigen or low GLUT-1 in plasma small extracellular vesicles indicates poor prognosis	23
	Imatinib reduced GLUT-1 in GIST-T1 cells but increased glycolysis in imatinib-resistant cells	20
GLUT-2	In imatinib-treated mice with resistant GIST, GLUT-2 expression was higher than in untreated mice	25
GLUT-3	Intermittent imatinib treatment increased GLUT-3 levels compared to continuous treatment in mice	25
GLUT-4	Neoadjuvant imatinib therapy reduced GLUT-4 expression	27
HK, PK, LDH	HK1, PKM2, and LDH activity elevated in high-risk grade	19
MCT	MCT1 and CD147 coexpression are associated with GIST aggressiveness and reduced patient survival	29

GIST: gastrointestinal stromal tumor; GLUT: glucose transporter; HK: hexokinase; LDH: lactate dehydrogenase; MCT: monocarboxylate transporters; PK: pyruvate kinase

corrected for body weight (SUVbw), lean body mass (SUVlbm), and body surface area (SUVbsa), as well as MTV and TLG in 35 patients with GIST [38]. The study, which included 35 patients with GIST, aimed to assess the predictive capability of preoperative FDG PET/CT in determining the malignancy risk of GIST and the likelihood of recurrence and mortality. Although there were no statistically significant associations between PET/CT metabolic parameters (SUVbw, SUVlbm, SUVbsa, MTV, and TLG) and patient demographics, tumor size, mitotic index, Ki-67, and tumor location, these parameters were positively correlated with the tumor risk grade per the Fletcher classification. Moreover, MTV and TLG were identified as independent outcome predictors for progression-free survival [38]. The report of the aforementioned study suggests the profound involvement of molecules associated with glycolysis, including GLUT, in the risk of GIST malignancy and recurrence. However, the clinical utility of PET/CT in GIST remains unclear, and there is lack of direct evidence to show the extent of the effect of imatinib treatment on FDG uptake via downregulation of GLUT contributing to the risk of malignancy and recurrence of GIST. A summary of FDG PET/CT in GIST is shown in Table 2.

Oxidative phosphorylation

Using GIST cell lines, validation studies revealed differences in the metabolic activity of glycolysis and oxidative phosphorylation (OXPHOS) between imatinib-sensitive GIST and imatinib-resistant GIST. However, these varied depending on the specific cell line examined. For instance, imatinib-resistant GIST 882 cells showed a distinct metabolic profile with increased levels of glycolysis and OXPHOS compared with their original parent cells. In contrast, imatinib-resistant cells derived from the GIST-T1 cell line had glycolytic activity that was comparable to that of their parent cells; however, their mitochondrial respiration was decreased. Moreover, imatinib-resistant GIST 882 cells were more vulnerable to glycolysis inhibition than GIST 882 cells, whereas imatinib-resistant GIST-T1 cells were more resistant to OXPHOS inhibition than GIST-T1 cells [39,40].

The intertumor heterogeneity in the metabolic phenotype of imatinib-resistant GIST needs to further investigated. Imatinib can influence the metabolic phenotype of GIST, potentially contributing to imatinib resistance. We also speculate that the observed differences in metabolic activity levels could be attributed to a process known as the reverse Warburg effect. In this mechanism, metabolites such as lactate and pyruvate are produced by oxidative stressed cancer-associated fibroblasts and are used by cancer cells for ATP synthesis within the mitochondria [41]. However, no studies have confirmed the presence of this phenomenon in GIST.

Table 2
Overview of ^{18}F-Fluorodeoxyglucose positron emission tomography/computed.

Associations and functions	References
FDG PET/CT, using preoperative MTV and TLG assessments, strongly predicts RFS in localized primary GIST patients	36
Imatinib treatment lowers FDG uptake within 1–7 days	27
Imatinib downregulates glycolysis and GLUT-4 expression, leading to reduced FDG uptake	27, 37
FDG uptake positive correlates with tumor size, Fletcher risk grade, and the expression of GLUT-1, HK1, and LDHA	19
PET/CT metabolic parameters (SUVbw, SUVlbm, SUVbsa, MTV, and TLG) positive correlate with Fletcher risk grade but not with patient background, tumor size, mitotic index, Ki-67, or location	38
MTV and TLG independently predict PFS outcomes	38

FDG: F-Fluorodeoxyglucose; GIST: gastrointestinal stromal tumor; GLUT: glucose transporter; HK: hexokinase; LDHA: lactate dehydrogenase; MTV: metabolic tumor volume; PET/CT: positron emission tomography/computed tomography; PFS: progression-free survival; RFS: recurrence-free survival; SUVbsa: standardized uptake value corrected for body surface area; SUVbw: standardized uptake value corrected for body weight; SUVlbm: standardized uptake value corrected for lean body mass; TLG: total lesion glycolysis

Biomarkers

Recent studies have highlighted the potential prognostic significance of various DNAs (*KIT, PDGFRA, BRAF, SDH, SETD2*, and *ROR2*) and microRNAs (miR-221, miR-222, miR-494, miR-196a, miR-320a, miR-218, miR-125a-5p, and miR-518a-5p) in GIST [42]. However, only a few molecular markers have been developed for GIST prognosis. At present, there are no established circulating biomarkers associated with glycolysis [42]. Fig. 1 illustrates the relationship among GIST, glycolysis, and oxidative phosphorylation.

EVs: extracellular vesicles; GLUT: glucose transporter; HK1: hexokinase 1; PKM2: pyruvate kinase M2; LDH: lactate dehydrogenase; MCT: monocarboxylate transporter; MTV: metabolic tumor volume; PFS: progression-free survival: RFS: recurrence-free survival; SUVbsa: standardized uptake value corrected for body surface area; SUVbw: standardized uptake value corrected for body weight; SUVlbm: standardized uptake value corrected for lean body mass; TLG: total lesion glycolysis

Therapeutics targeting metabolic pathways

Considering substantial evidence regarding lactate and altered cellular metabolism in various cancers, targeting these aspects is now a major focus for pharmaceutical drug development [28]. While research has highlighted the effectiveness of glycolysis pathway inhibitors in various cancer types and their anti-GIST potential is being explored, several aspects remain unclear [20,28].

GLUT inhibitors have started being increasingly recognized for their potential to target glucose dependency in cancer and other diseases, thereby opening new avenues for future drug development [43]. Our research indicated that WZB117 induced apoptosis in imatinib-resistant GIST cells [20]. To the best of our knowledge, no other studies have reported on the association between GLUT inhibitors and GIST.

Gossypol, a recognized LDHA inhibitor, and 3-bromopyruvate (3-BP), an inhibitor of HK2, have demonstrated efficacy against specific imatinib-resistant GIST cell lines. However, the mechanism underlying these cell growth suppressions is yet to be elucidated [40,44]. 2-deoxyglucose (2DG), an HK inhibitor, has been identified as a potential agent for treating tumors [45]. While an *in vitro* study has demonstrated that 2DG possesses significant disease-specific effects, its primary action in GIST is not the disruption of energy production through glycolysis inhibition. 2DG primarily functions by inhibiting KIT through suppression of KIT glycosylation [46]. Targeting MCT has emerged as a potential therapeutic strategy in cancer. Pharmacological and genetic suppression of MCT1 or MCT4 lead to reduced tumor cell proliferation *in vitro* and *in vivo*, making them promising therapeutic targets [47,48]. While the efficacy of MCT inhibitors has been indicated in several types of tumors [49,50], there is currently no evidence supporting their anti-GIST efficacy. As shown in Fig. 2, it is noteworthy that very few reports have demonstrated the efficacy of drugs targeting the glycolytic system in GIST.

2PG: 2-phosphoglycerate; 3-BP: 3-bromopyruvate; ENO: enolase; Fructose 6-P: fructose-6-phosphate; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; Glucose 6-P: glucose-6-phosphate; LDH: lactate dehydrogenase; MCT: monocarboxylate transporter; PEP: phosphoenolpyruvate; PFK: phosphofructokinase; PK: pyruvate kinase

Discussion and future perspectives

As discussed in this review, the critical association between GIST and glycolysis is yet to be fully elucidated. Given the rarity of GIST and the limited treatment options currently available, there is a compelling need for further exploration of the association between GIST and glycolysis. Such investigations can potentially unveil novel anti-GIST therapeutic strategies in the future. Furthermore, the mechanism of imatinib resistance should be clarified from the perspective of the glycolytic system and strategies to overcome imatinib resistance should be developed.

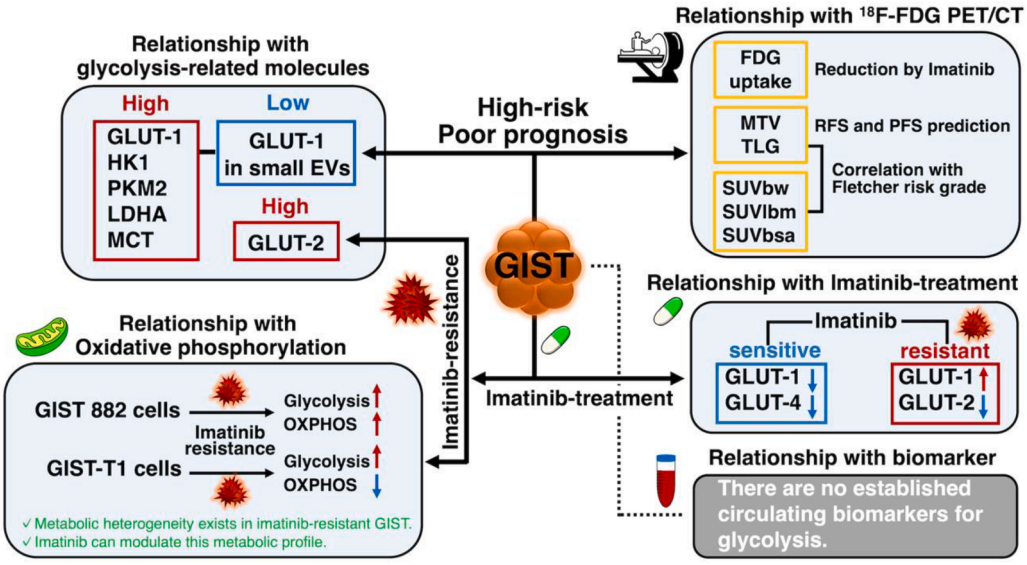

Fig. 1. A schematic illustration of the relationship between gastrointestinal stromal tumor (GIST) and glycolysis and oxidative phosphorylation (OXPHS). Particularly, we focused on the relationship bwtween GIST and imatinib, a representative drug for treating GIST. Moreover, the usefulness of ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) and findings about the glycolytic system as a biomarker in GIST are presented. For details, please refer to sections from Glucose transporter (GLUT) to Biomarkers.

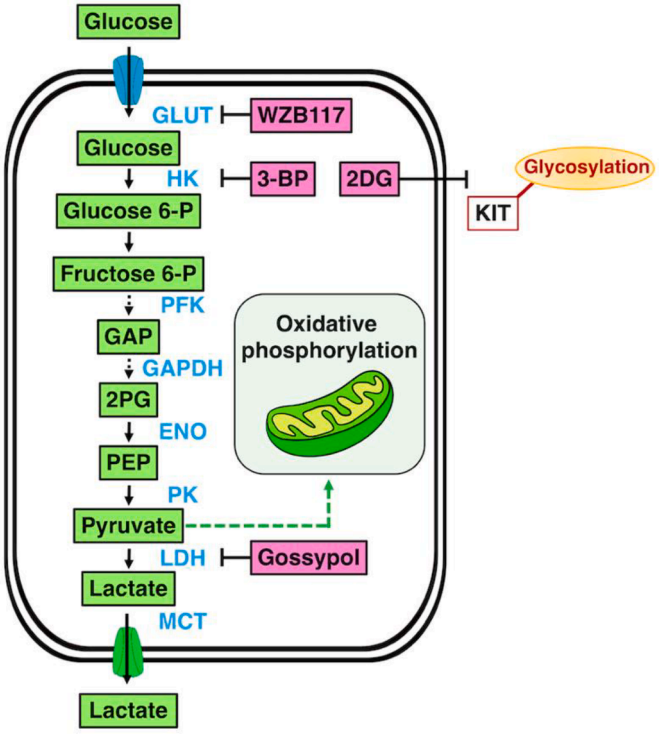

Fig. 2. A schematic representation of aerobic glycolysis and its inhibitors in gastrointestinal stromal tumor (GIST) cells. The three drugs (WZB117, 3-BP, and Gossypol) inhibit glucose transporter (GLUT), hexokinase 2 (HK2), and lactate dehydrogenase (LDH), respectively. Only these three glycolytic inhibitors are potentially effective against GISTs. Note: 2-Deoxyglucose (2DG) serves as an HK inhibitor; however, its principal action within GIST does not primarily involve the curtailment of energy generation through inhibition of glycolysis. Instead, it mainly operates through repression of KIT by suppressing KIT glycosylation.

Glycolysis inhibition represents a promising target for therapeutic development. Despite several key molecules in the glycolysis pathway, only three glycolytic inhibitors exhibit potential anti-GIST efficacy. Furthermore, differences exist among effective inhibitors depending on the metabolic phenotype of the cell lines. Further studies are required to substantiate these findings and establish the effectiveness of glycolysis inhibitors as potential anti-GIST therapeutic targets.

Conclusion

This review discusses the involvement of glycolysis-related molecules in the pathogenesis of GIST and their potential as therapeutic targets. It also explores prospects for GIST research within glycolysis. Targeting glycolysis as a therapeutic approach shows significant promise as a novel strategy for GIST treatment. The insights gained from the reviewed reports hold the potential to lead to significant advancements in the field of GIST treatment.

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Takafumi Shima: Data curation, Investigation, Writing – original draft. **Kohei Taniguchi:** Writing – review & editing. **Yosuke Inomata:** Writing – review & editing. **Jun Arima:** Writing – review & editing. **Sang-Woong Lee:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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