

## GLUT1: STRUCTURE, FUNCTION, AND BIOMEDICAL SIGNIFICANCES

Ika Yustisia<sup>1,2</sup>, Mutmainah Arif<sup>1</sup>

<sup>1</sup>Master Program of Biomedical Sciences, Graduate School Hasanuddin University, Makassar, Indonesia

<sup>2</sup>Department of Biochemistry, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

### ABSTRACT

**Background;** *Glucose is the main energy source for cells. To be utilized by cells, glucose enters the intracellular space facilitated by transporters. GLUT1 is one of the glucose transporters and is the most widely expressed by various tissues in the body. Not only that, cancer cells, which are known to have very high glucose requirements compared to healthy cells, have a high expression of GLUT1 as well.*

**Reviews;** *This paper reviews the structure, function, and biomedical importance of GLUT1 and specifically describes recent developments regarding GLUT1 inhibition as a novel therapeutic approach in both metabolic diseases and cancers.*

**Conclusion;** *Inhibition of GLUT1 has also been shown to increase cancer cells' sensitivity to chemotherapy agents such as cisplatin and adriamycin. GLUT1 inhibition also increases the sensitivity of cancer cells to radiotherapy.*

**Keywords:** *GLUT1, cancers, metabolic diseases.*

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**Correspondence:** Ika Yustisia, Master Program of Biomedical Sciences, Graduate School Hasanuddin University, Makassar, Indonesia; Department of Biochemistry, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia. ikayustisia@pasca.ac.id

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### INTRODUCTION

Glucose is the main energy source for eukaryotic organisms, which plays an important role in metabolism and cellular homeostasis. Catabolism of glucose through glycolysis, the citric acid cycle, and oxidative phosphorylation will produce energy in the form of adenosine-5-triphosphate (ATP). Glucose also functions as an important raw material for synthesizing the main cell biomolecules, such as lipids, non-essential amino acids, and nucleic acids. In humans and animals that are breastfeeding, glucose plays an important role in synthesizing lactose in the mammary glands, which is the main carbohydrate in milk.<sup>1,2</sup>

Glucose is mainly obtained directly from the diet through the enzymatic hydrolysis of disaccharides and polysaccharides in the digestive tract. Under certain physiological conditions, glucose can be synthesized by organs in the body such as the liver through the breakdown of glycogen (glycogenolysis) and the synthesis of glucose from non-carbohydrate substrates, namely pyruvate, lactate, glycerol, and glucogenic amino acids (gluconeogenesis).<sup>3</sup>

Brain and red blood cells require a continuous supply of glucose. Meanwhile, most of the cells in the body need glucose in moderation. An increase in the concentration of glucose in the plasma can cause glucose poisoning (glucotoxicity). Therefore, the concentration of glucose in plasma is maintained in the range of 60-110 mg/dL and involves the role of metabolic hormones, especially insulin and glucagon. Glucose homeostasis in the body is maintained through coordinated regulation of three processes: 1) absorption of glucose as a result of the enzymatic hydrolysis of carbohydrates from food by the small intestine; 2) glucose production by body organs, especially the liver; 3) consumption of glucose by almost all body tissues.<sup>1</sup> The discussion of this paper will further focus on the third regulatory process.

The glucose concentration is maintained over a narrow range by the homeostatic mechanism, as mentioned above, so that most cells obtain glucose from the interstitial fluid passively down the concentration gradient across the plasma membrane.<sup>2</sup> Meanwhile, eukaryotic cells' plasma membrane (lipid bilayer) itself is impermeable to hydrophilic polar molecules such as glucose. Thus, to facilitate the entry and exit of glucose into and from the cell, an integral membrane protein called the glucose transporter is required.<sup>1,4</sup> The exception is the brush border epithelial cells of the small intestine and the proximal renal tubule, where glucose is absorbed against the electrochemical gradient through a pump's secondary active transport mechanism.  $\text{Na}^+/\text{K}^+/\text{ATP}$ .<sup>2</sup> This also shows that the expression of glucose transporters is tissue-specific, and this expression reflects each tissue's physiological characteristics.<sup>4</sup>

Glucose transporter proteins fall into two distinct groups, structurally and functionally. The first group is the  $\text{Na}^+$ -dependent glucose cotransporter, an active glucose transport mechanism for glucose absorption in the small intestine and glucose reabsorption in the urinary tract system. As the name implies, sodium-dependent glucose transporter, this protein group is given the SGLT symbol, and its coding genes are included in the solute carrier gene group (SLC) as the solute carrier family 5A (SLC5A). The second group is glucose transporters that are not dependent on sodium ( $\text{Na}^+$ ). This group transports glucose passively across the plasma membrane by a facilitated diffusion mechanism. The protein symbol for this second group is GLUT, which stands for glucose transporter. The gene encodes this protein belongs to the solute carrier family, SLC2A.<sup>2,3,4,5</sup>

The human body has three types of glucose transporter that different in structure and transport mechanism. The first type is the  $\text{Na}^+$ -dependent glucose cotransporter, an active glucose transport mechanism for glucose absorption in the small intestine and glucose reabsorption in the urinary tract system. As the name implies, sodium-dependent glucose transporter, this protein group is given the SGLT symbol, and its coding gene is included in the solute carrier gene group (SLC) as the solute carrier family 5A (SLC5A). The second type is a glucose transporter that is not dependent on sodium ( $\text{Na}^+$ ). This transporter transports glucose passively across the plasma membrane by a facilitated diffusion mechanism. The protein symbol for this second group is GLUT, which stands for glucose transporter. The gene encoding belongs to the solute carrier family, SLC2A. The third type, SWEETs, is a recently characterized glucose transporter, a uniporter. The SLC50 family codes this transporter.<sup>2,3,4,5,6</sup>

## REVIEW

This article will further elaborate on the structure, function, characteristics, and biomedical interests of GLUT1 as a glucose transporter distributed in almost all tissues. Several recent studies regarding GLUT1, especially its prospects as a new drug target for cancer, will be explicitly discussed at the end of this review.

### **$\text{Na}^+$ -independent glucose transporter (GLUT)**

$\text{Na}^+$ -independent glucose transporter (GLUT) or facilitative glucose transporter transports glucose across cell membranes, which is hydrophobic, in a diffusion-facilitated manner without requiring energy but down the concentration gradient between glucose outside and inside the cell or vice versa. To date, fourteen members of the GLUT transporter have been identified based on the similarity in structure and sequence of amino acids in their constituents. The fourteen transporters are then grouped into three main classes based on the similarity of amino acid sequences, namely classes I, II, and III. Class I consists of four well-

characterized transporter members, GLUT1, GLUT4, and GLUT14. Class II has a specific feature that is able to facilitate fructose consisting of GLUT5, GLUT7, GLUT9, and GLUT11, also known as the "odd GLUT" group. Class III is the "even GLUT" group consisting of GLUT6, GLUT8, GLUT10, GLUT12, and HMIT. This last group has a similar feature in that they have an internalization signal that maintains these transporters at the intracellular location under a steady state.<sup>3,4,6</sup>

Based on the amino acid sequence of GLUT, a protein model was created to estimate the orientation of this transporter on the cell membrane. GLUT is estimated to have twelve hydrophobic helical domains. This arrangement shows that the amino acid GLUT sequence forms twelve loops across the plasma membrane with the amino (NH<sub>2</sub>-) and carboxyl (COOH-) ends located on the cytoplasmic side and a large intracellular loop between the 6 and 7 transmembrane domains. The transmembrane has a high homology between one GLUT and another, while the amino acid sequence of the amino ends, carboxyl ends, and loops vary. The most obvious structural difference between GLUT Class I, II, and III is the long extracellular loop position. The long extracellular loop of class I and II members is between transmembrane domains 1 and 2 and have glycosylation sites that increase the efficiency of transport of these proteins. Whereas class III members do not have a long extracellular loop between transmembrane domains 1 and 2 with potential glycosylated sites between transmembrane domains 9 and 10.<sup>3,4,6</sup>

The GLUT protein model described above explains that the transfer of glucose by GLUT is based on two conformational alternatives. In the first conformation GLUT displays the glucose binding site on the extracellular side of the plasma membrane and in the second conformation GLUT displays this binding site on the intracellular side. The binding of glucose (or other suitable monosaccharide) at one of these sites triggers a conformational change of GLUT. In this process monosaccharides can move across the plasma membrane in two directions (leaving or entering the cell). Despite their similar structure, GLUTs differ in their ability to transport monosaccharides, regulation, and distribution across tissues.

### **Molecular characteristics of GLUT1**

GLUT 1 is a class I glucose transporter isoform firstly isolated from the HepG2 cell line and then successfully cloned and characterized by Mueckler et al. in 1985. The GLUT1 coding gene is a solute carrier family 2 member 1 (SLC2A1). SLC2A1 is an official symbol created by the HUGO Gene Nomenclature Committee (HGNC). HGNC itself is a committee of the Human Genome Organization (HUGO) responsible for approving/assigning unique symbols and names for protein-coding genes, ncRNA genes, and pseudogenes to enable clear scientific communication. SLC2A1 is located on the short arm of chromosome 1 (1p34.2), consisting of 10 exons with the complete reference sequence code in the NCBI gene bank is NC\_000001.11 and the reference sequence codes for mRNA and protein are NM\_006516.2 (3687 bp) and NP\_006507.2. respectively.<sup>7,8</sup>

GLUT1 is an integral membrane protein that plays a role in the glycolysis pathway as a uniporter for glucose with several alternative names: DYT17, DYT18, GTR1, HepG2 glucose transporter, MGC141895, MGC141896, PED, SLC2A1, and solute carrier family 2 (facilitated glucose transporter), member 1.<sup>9, 10</sup> This protein has a reference sequence code from the NCBI gene bank, namely NP\_006507.2 and the UniProt reference code is P11166. Table 1 shows the molecular characteristics of GLUT1.

**Table 1.** The results of the chemical parameter analysis of GLUT1 using ProtParam Expsy

Parameter	Analysis results
<b>Molecular weight</b>	54083.78
<b>Formula</b>	C <sub>2503</sub> H <sub>3916</sub> N <sub>622</sub> O <sub>664</sub> S <sub>23</sub>
<b>Atomic composition</b>	Carbon (C) 2503 Hydrogen (H) 3916 Nitrogen (N) 622 Oxygen (O) 664 Sulfur (S) 23
<b>Total number of atoms</b>	7728
<b>Theoretical pI</b>	8.93
<b>Number of amino acids</b>	492
<b>Amino acid composition</b>	Ala (A) 34 [6.9%] Arg (R) 21 [4.3%] Asn (N) 14 [2.8%] Asp (D) 7 [1.4%] Cys (C) 6 [1.2%] Gln (Q) 21 [4.3%] Glu (E) 24 [4.9%] Gly (G) 46 [9.3%] His (H) 5 [1.0%] Ile (I) 37 [7.5%] Leu (L) 59 [12.0%] Lys (K) 16 [3.3%] Met (M) 17 [3.5%] Phe (F) 38 [7.7%] Pro (P) 23 [4.7%] Ser (S) 35 [7.1%] Thr (T) 26 [5.3%] Trp (W) 6 [1.2%] Tyr (Y) 13 [2.6%] Val (V) 44 [8.9%]
<b>The estimated half-life</b>	30 hours (mammalian reticulocytes, in vitro) >20 hours (yeast, in vivo) >10 hours (Escherichia coli, in vivo)

GLUT1 is a strong hydrophobic protein consisting of 492 amino acids. Like the class 1 GLUT structure discussed earlier, GLUT1 has a long NH<sub>2</sub> end and COOH end facing the cell's cytoplasmic site, a cytoplasmic loop connecting transmembrane domains 6 and 7, and glycosylated extracellular loop between transmembrane domains 1 and 2 10. The GLUT1 activity transport studied in the oocyte of *Xenopus laevis* frogs showed that GLUT1 transports glucose with Km ~3 mM. Under equilibrium exchange conditions, GLUT1 has Km 20 - 21 mM for 3-O-methylglucose and 5 mM for 2-deoxyglucose. Other monosaccharides that can be transported by GLUT1 are galactose, mannose, and glucosamine.<sup>2,11,12</sup> GLUT1 also transports dehydroascorbic acid, the oxidized form of vitamin C, into the brain.<sup>11</sup> This transporter is a highly conserved isoform with approximately 74 - 98% identical amino acid sequences between species (humans, cattle, rats, mice, chicken, and fish). The glycosylated part of GLUT1 is the most often part of differences in amino acid sequences between species.<sup>2,11,12</sup>

GLUT1 is expressed in the highest levels in cells actively proliferating, such as in developing embryos, cells forming the blood tissue barrier, erythrocytes, astrocytes, and heart muscle.<sup>9,10</sup> Erythrocytes and brain cells selectively express GLUT1, so it is known as erythrocyte and brain glucose transporter. This protein makes up 3-5% of the erythrocyte

membrane protein. However, further research has proven that GLUT1 is the glucose transporter most widely expressed by tissues in the body such as the eyes, peripheral nerves, placenta, and mammary glands. This protein expression is also high in cell lines that are routinely used in the laboratory but not by hepatocytes.<sup>2,10,13,14</sup>

GLUT1 has two forms based on its molecular weight, namely the 45 kDa and 55 kDa forms. These two forms are distinguished only by the length of the glycosylation chain. The 45 kDa form is found in most cells, including astrocytes, and is thought to be responsible for glucose uptake by cells. The 55 kDa form is mainly found in the endothelial cells of the brain micro blood vessels and erythrocytes as the main glucose transporter. If there is a GLUT1 deficiency, the amount of glucose from the blood that enters the brain will decrease. This, in turn, can lead to central nervous system dysfunction.<sup>2,10,13,14</sup>

### Biomedical Significances of GLUT1

The biomedical importance of GLUT1 is mainly genetic, caused by mutations of its encoding gene, SCL2A1. The manifestation of this mutation is mainly a deficiency in GLUT1's function as the brain's primary glucose transporter. Some of the syndromes associated with GLUT1 deficiency are GLUT1 deficiency type 1 syndrome (Glut-1 DS1, OMIM 606777), GLUT1 type 2 deficiency syndrome (Glut-1 DS2, OMIM 612126), dystonia, and idiopathic epilepsy. Research data on animals and humans show that the safe limit value for glucose transport across the blood-brain barrier to meet the needs of brain metabolism and cerebral function is very narrow. In the mildest clinical phenotype with intermittent symptoms of epilepsy, dyskinesia, and ataxia, it is predicted that there will be a 25-35% decrease in GLUT1 transporter function, while in the more severe phenotypes, it is estimated that there will be 40-75% decrease in function. Most SCL2A1 mutations are de novo in nature, whereas this mutation is inherited as an autosomal dominant trait in familial cases. A case of autosomal recessive transmission has also been reported. All mutations detected were heterozygous, while homozygous mutations from GLUT1 were thought to be lethal, causing death in utero.<sup>14,15</sup>

Genetic abnormalities in GLUT1 deficiency syndrome or known as De Vivo syndrome, have various clinical manifestations. Patients with the missense mutation generally show mild to moderate symptoms without a clear boundary of phenotype-genotype correlation. The results of other studies showed that mild mental retardation and movement disorders were more common in patients with a missense (type A) mutation than those with a translational initiation mutation (type B) or multiple deletions in exon (type C). It suggests additional mechanisms at work, such as modifying proteins and genes that then influence the phenotype and potentially play a role in these complex states' pathophysiology. It is also possible that secondary genes and proteins are involved in glucose transport. Patients with identical mutations exhibit phenotypic heterogeneity in terms of the range of clinical expression and disease severity.<sup>14</sup>

Cases of GLUT1 deficiency syndrome type 1 have been reported in 27 variations of protein sequences. One of them was reported by Klepper J et al.<sup>16</sup> On the UniProtKB/Swiss-Prot website, P11166 variant is recorded as p.Arg468Trp variant. The position of variation is at position 468 of the wild-type amino acid sequence GLUT1, where the amino acid arginine is replaced by tryptophan caused by a missense mutation of the protein-coding gene. This variant belongs to the type of "disease" variant, which means that the variant found in patients and related diseases has been reported in the literature. Physio-chemically, the amino acid changes that occur are large and alkaline amino acids (arginine / R) into large and aromatic amino acids (tryptophan/W). This change has a BLOSUM score of -3, which means that the chance of substitution arginine to tryptophan is quite low. The lowest score of

BLOSUM was -4, with the lowest probability interpretation of amino acid substitutions and the highest 11 with the highest probability interpretation of substitutions.<sup>17</sup> The secondary structure analysis of GLUT1 using the Psipred program showed quite clear differences in secondary structure between the wild type and the R468W variant even though the amino acid substitution location was not in that part but the range of amino acid sequence 380 - 410.<sup>17</sup> It shows that substitution in one amino acid can cause changes in the secondary structure of GLUT1, which then causes malfunctioning.

GLUT1 expression abnormalities affect a pathway that impacts the pathogenesis of diabetic nephropathy. There are indications that variations in SLC2A1 contribute to the development of microangiopathy in patients with type 2 diabetes mellitus.<sup>18,19</sup> Individuals with the XbaI (-) GLUT1 allele are more likely to develop DM that progresses to diabetic nephropathy.<sup>18</sup> Other studies have shown that GLUT1 regulates cytokines and growth factors that act as pro-sclerotic mediators that induce diabetic glomerulosclerosis.<sup>20</sup> Furthermore, GLUT1 inhibition becomes a further therapeutic approach in diabetes mellitus to prevent serious complications. Studies show GLUT1 is a promising therapeutic target for preventing diabetic retinopathy. Knockdown of GLUT1 by intraocular injection of siRNA directed at SLC2A1 significantly reduced mean retinal glucose levels in diabetic mice. Systemic treatment of diabetic mice with forskolin or genistein, which binds to GLUT1 and inhibits glucose transport, significantly reduced retinal glucose to the same level seen in non-diabetics.<sup>21</sup> Another similar study by Zhi-Peng You et al. (2017) showed similar results.<sup>22</sup>

Research by Yabo Hu et al. demonstrated that 4 mM aspirin administration could inhibit glucose uptake and metabolism in vascular endothelial cells by downregulating GLUT1 expression and suggested that vascular endothelial cell GLUT1 is a potential target for aspirin. This research certainly requires further investigation to be applicable to various new disease treatment strategies through the GLUT1 inhibition approach.<sup>23</sup>

### **GLUT1 and cancer**

Another significance of GLUT1 is its overexpression in cases of malignancy. Cells that undergo malignant transformation experience accelerated metabolism and an increase in glucose demand. In mammalian cells, glucose transport across the plasma membrane is the first step that limits GLUT-mediated glucose metabolism. Increased glucose transport in cancer cells is associated with increased and deregulated expression of glucose transporter proteins, especially in the overexpression of GLUT1 and GLUT3. Oncogenic transformations in mammalian cell cultures lead to increased glucose transport and overexpression of GLUT1 through interactions with the GLUT1 promoter-enhancing elements. Studies in humans have shown that increased expression of GLUT1 in tumors is associated with lower survival. The main regulator of GLUT1, especially HIF, also has increased expression in cancer associated with the extracellular environment of cancer, which tends to be hypoxic.<sup>24,25</sup>

Several studies have shown a relationship between GLUT1 expression and cancer. Among them, Kang SS et al. showed that GLUT1 expression was related to the invasion ability of breast cancer cell lines where cell lines with high GLUT1 expression had a tendency to be more aggressive and potentially malignant than those that did not. Krzeslak et al. reported that GLUT1 and GLUT3 expression was significantly increased in poorly differentiated breast and endometrial tumors compared with well-differentiated ones. Increased mRNA and GLUT1 protein levels have also been reported in colorectal, thyroid, lung, stomach, head and neck, bladder, kidney, and endometrial carcinomas. Carvalho KC et al. demonstrated that GLUT1 was expressed in varying degrees by tumor type. Sarcomas, melanomas, hepatoblastomas, and lymphomas do not express GLUT1, which means that there are other glucose transport mechanisms that play a role in these tumor types.<sup>26,27,28</sup>

GLUT1 also has biomedical significance in cancer stem cells. Research by Wanandi et al. showed an increase in the expression of the breast CSC GLUT1 gene CD24- / CD44 + in hypoxic conditions, which correlated with the increased expression of HIF1 . This increase in GLUT1 expression was followed by an increase in glucose consumption. Although this study did not measure the activity of the four key enzymes that regulate glycolysis (hexokinase, glucokinase, phosphofructokinase, and pyruvate kinase), it seems that most of the pyruvate formed is converted to lactate as indicated by increased LDH activity accompanied by increased production of lactate by the cells. These results show that under hypoxic conditions, HIF1 regulates the glucose metabolic state of CD24- / CD44 + breast CSCs in the form of increased anaerobic glycolytic activity.<sup>29</sup>

### GLUT1 inhibition as a novel cancer therapeutic strategy

Evidence showing increased glucose consumption in cancer cells versus healthy cells implicates the role of GLUT1 and other roles of this protein in oncogenesis, paving the way for new strategies in cancer therapy. Biomedical studies on GLUT1 inhibition in various types of cancer using natural and synthetic compounds have been carried out in the last decade with promising results. Some examples of GLUT1 inhibitor compounds that have been studied on various types of cancer cells and animal models are shown in Table 2.

**Tabel 2.** Studies of GLUT1 inhibition by synthetic and natural compounds in various types of cancer

Cancer types	Cell lines/model	Synthetic compound	Effect	References
Breast cancer (triple negative)	11 TNBC cell lines and patient-derived samples	BAY-876	BAY-876 impairs the growth of a subset of TNBC cells displaying high glycolytic, lower oxidative phosphorylation (OXPHOS) rates, and high protein level of retinoblastoma tumor suppressor (RB1).	30
Lung cancer	A549/ nude mouse	WZB117	WZB117 inhibited cell growth in cancer cell lines and cancer growth in a nude mouse model.	31
Neuroblastoma	SH-SY5Y	WZB117	WZB117-induced GLUT1 inhibition suppressed tumor cell growth, induced cell cycle arrest and reduced glycolysis metabolites.	32
Ovarian cancer	A2780 and OVCAR3/NOD-scid IL2Rgamma(null) mice	Ciglitazone	Ciglitazone induces apoptosis in ovarian cancer cells by inhibiting and decreasing expression levels of GLUT-1	33
Colon cancer	HTC-116, SW480	Metformin	Metformin inhibited Glut1 and SLC1A5 expressions leading to reduced influx of glucose and glutamine in cancer cells, which is associated with reduced tumor growth	34
Cervical cancer	HeLa			
Breast cancer	MCF-7			
Ovarian cancer	PA-1 (p53 wild type), OVCAR3, MDAH2774 (p53 mutant), and SKOV3 (p53 null)	Resveratrol	RSV induced apoptosis in ovarian cancer cells by impairing glucose uptake, involving Akt-regulated plasma membrane GLUT1 trafficking.	35

<b>Hepatocellular carcinoma</b>	HuH-7	D-Allose	D-allose inhibited cancer growth by reducing both GLUT1 expression and glucose uptake.	36
<b>Breast adenocarcinoma</b>	MDA-MB-231			
<b>Neuroblastoma</b>	SH-SY5Y			
<b>Breast cancer</b>	4T1	Epigallocatechin-3-gallate (EGCG)	EGCG decreased the expression of hypoxia-inducible factor 1 (HIF1) and glucose transporter 1 (GLUT1),	37
<b>Lung cancer</b>	A549 cells	Curcumin	These results suggested that curcumin inhibit lung cancer invasion and metastasis by attenuating GLUT1/MT1-MMP/MMP2 pathway	38

## SUMMARY

Apart from the direct effect that causes a decrease in GLUT1 expression and a decrease in glucose uptake, which then results in the suppression of tumor growth, inhibition of GLUT1 has also been shown to increase cancer cells' sensitivity to chemotherapy agents such as cisplatin and adriamycin.<sup>39,40,41</sup> GLUT1 inhibition also increases the sensitivity of cancer cells to radiotherapy.<sup>42</sup>

Inhibition of GLUT1 appears to provide new hope for cancer treatment strategies. Various compounds have been shown to be able to inhibit the expression of GLUT1, which then suppress tumor growth both in vitro and in vivo. A more detailed understanding of these compounds' specific inhibitory mechanisms against cancer cells and their delivery mechanisms is needed. Thus, the inhibitory effect does not affect healthy cells because, as stated in the beginning, GLUT1 is the most widely expressed glucose transporter in the body tissues and has a high level of expression in actively proliferating cells.

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