REVIEW ARTICLE

The expression and regulation of glucose transporters in tumor cells

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Abstract: Glucose transporter proteins are involved in many physiological and biochemical processes. In particular, the high expressions of sodium-glucose cotransporter and glucose transporter proteins in tumor cells show that these two transporters play a key role in tumor cell metabolism. Studying the crystal structure and conformation of human glucose transporter proteins has enabled the development of drugs based on specific binding sites, opening up a new path towards more effective cancer treatments. This mini review serves to summarize our existing understanding of the metabolic pathways of tumor cells, focusing on the roles of glucose transporter proteins.

Keywords: glucose transporter proteins; lactate transporters; metabolic pathways; tumor cells


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Introduction

The glucose transporter (GLUT) protein is a membrane protein that facilitates glucose absorption in most mammals. In 1952, Widdas discovered a type of saturated carrier on the red blood cell membrane[1]. This carrier is also widely found in fetal tissues. Using the Michaelis-Menten model[2], he successfully predicted the dynamics of glucose transporters within red blood cells and other types of tissues. In 1977, Kasahara and Hinkle[3] laid the foundation for future studies on glucose transporter proteins by successfully extracting GLUT1 protein from human red blood cell membranes.

Mueckler et al. cloned the human GLUT1 gene successfully in 1985, leading to more in-depth studies on glucose transporters[4]. Several studies have shown that an increased expression of glucose transporters in tumor cells is closely linked to the development of tumors[5-8]. In 2014, Yan et al. elucidated the crystal structure of human glucose transporter. Based on the crystal structure and other relevant biochemical data, they proposed a mechanistic model for GLUT1, giving rise to another major breakthrough in glucose transporter research[9].

Tissue distribution and biological functions of glucose transporters

Glucose is an essential nutrient in in vivo metabolism. The absorption of glucose in human body occurs mainly via three distinct pathways. These pathways include: (1) passive absorption along a concentration gradient, (2) active transport by the intestinal sodium-glucose co-transporter (SGLT) proteins, and (3) active transport by GLUT proteins. Currently, SGLTs and GLUTs are the two known integral families of glucose transporter proteins.

SGLT proteins

The SGLT protein family (also known as the Na'/solute symporter (SSF) family) consists of more than 450 members including SGLTs (Table 1) and sodium-myoinositol co-transporters (SMIT). There are about 230 SGLTs, many of which are similar in structure.

SGLT2 is a high-capacity, low-affinity glucose transporter protein responsible for the movement of glucose molecules across the basolateral membrane of epithelial cells. In kidneys, it also plays a critical role in the
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**Table 1. Members of the SGLT protein family and their respective functions**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT1</td>
<td>A high-affinity transporter responsible for D-glucose and D-galactose absorption. It is primarily expressed in the brush border membrane of the small intestine villi[^8].</td>
</tr>
<tr>
<td>SGLT2</td>
<td>It is mainly present in liver cells, pancreatic β cells, small intestines, and the proximal convoluted tubules of the kidneys. It is responsible for D-glucose reabsorption and has a relatively low affinity towards glucose[^11].</td>
</tr>
<tr>
<td>SGLT3</td>
<td>Originally thought to be responsible for the transport of amino acids in pig kidneys but was later reclassified to the SGLT family. However, its function needs further investigation as human SGLT3 does not seem to transport glucose[^12].</td>
</tr>
<tr>
<td>SGLT4 &amp; SGLT6</td>
<td>While the SGLT4 and SGLT6 subtypes are expressed in many tissues, their functions are still not fully understood[^13,14].</td>
</tr>
<tr>
<td>SGLT5</td>
<td>SGLT5 is expressed exclusively in the kidneys[^15].</td>
</tr>
</tbody>
</table>

**Table 2. Members of the GLUT protein family and their respective functions**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLUT1</td>
<td>Have been found in brain tissues, red blood cells, testicular germ cells, renal tubules, peripheral nerve cells, placental endothelial cells (capillaries and trophoblast cells), and in the blood-brain barrier. The highest expression of GLUT1 has been found in the brain capillary. It is a membrane glycoprotein made up of 492 amino acids and has a large number of transmembrane domains[^16].</td>
</tr>
<tr>
<td>GLUT2</td>
<td>Mainly distributed in liver and pancreatic β cells, as well as on the kidney basolateral surface and intestinal epithelial cells. May be involved in the occurrence of diabetes[^19].</td>
</tr>
<tr>
<td>GLUT3</td>
<td>Found in many body tissues, but mainly in the brain. Plays an important protective role in the maintenance of penumbra functionality and neuronal viability[^20].</td>
</tr>
<tr>
<td>GLUT5</td>
<td>Mainly found in the brush border of intestinal epithelial cells. While it is actually a fructose transporter, it can also transport glucose. It is highly expressed at the free surface of the small intestines, and it may be a major pathway for absorbing fructose that originates from food intake[^21-23].</td>
</tr>
<tr>
<td>GLUT6</td>
<td>Mostly expressed in the brain, spleen and peripheral leukocytes[^24].</td>
</tr>
</tbody>
</table>

absorption of glucose, thereby maintaining the body's glucose homeostasis. Studies found that SGLT2 inhibitors could be utilized as a new class of anti-diabetic drug, thus providing a new drug target for the treatment of diabetes[^8,11,16].

**GLUT proteins**

While the expression of GLUT proteins and their regulation mechanisms are tissue-specific, all of them exhibit a highly conserved transmembrane topology. However, they are less conserved in the cytoplasm and extracellular matrix structures. Currently, 14 subtypes of the GLUT protein have been identified (GLUT1–14)[^17], with most research focusing on GLUT1–6 (Table 2).

**Relationship between glucose transporters and tumor cell metabolism**

**Metabolic characteristics of tumor cells**

Tumor cells rely on glucose as an energy and carbon source. The high rate of growth observed in cancer cells corresponds to an increased demand for nutrients and oxygen. Low oxygen availability triggers hypoxia-inducible factors (HIF) that regulate angiogenesis, leading to tumor cells being starved of oxygen and other essential nutrients[^24]. To overcome this limitation, tumor cells mainly use anaerobic respiration (glycolytic) pathways to obtain the energy needed for their growth[^25]. Even under aerobic conditions, aerobic respiration is not carried out and the glycolytic pathway remains as the preferred pathway to acquire energy; this preference is known as the Warburg effect[^26].

The glycolytic pathway has a higher rate of adenosine triphosphate (ATP) production compared to aerobic respiration[^27], resulting in the formation of a large number of ATPs. ATP molecules are then used to drive the rapid growth of tumor cells and to synthesize biological macromolecules needed for metastasis. The aerobic respiration of 1 mole of glucose produces 36 moles of ATP without generating any lactic acid. However, in order to produce 36 moles of ATP via glycolysis, 18 moles of glucose are needed and this process yields 36 moles of lactic acid. The large amount of lactic acid generated has to be removed from the cell in order to prevent acidosis-induced cell apoptosis, and the lactic acid excreted by the cells creates an acidic microenvironment around the tumor tissues[^28]. In response to the acidic and hypoxic environments, the tumor cells increase the expression and activity of the glucose and lactate transporters accordingly as a mechanism of survival.

**Expression of glucose transporters in tumor cells**

Some studies have shown that there is a significant in-
crease in the expression of glucose transporter in lung cancer and thymic epithelial tumors\[18, 29]. A higher expression of SGLT1 has also been found in ovarian, colorectal, and lung cancer tissues compared to healthy tissues, indicating a positive correlation between the activity of glucose transporters and tumor development\[30]. Kato et al. have pointed out that the differential level of expression of GLUT1 may be used to distinguish between benign and malignant mesothelioma during diagnosis\[31].

Based on these findings, new diagnostic and therapeutic methods could be devised against cancer cells. One of these methods involves the administration of axitinib, a receptor tyrosine kinase inhibitor (RTKI), to patients with metastatic pancreatic adenocarcinoma (PDAC). Tyrosine kinase inhibitors (TKI) are anti-cancer drugs used to inhibit aberrant-activated tyrosine kinase signaling pathways in cancer cells. Hudson et al. have observed the translocation of GLUT1 transporters from cytosolic pools to the cell surface membrane and a twofold increase in glycolysis rates in axitinib-resistant mouse PDAC cell lines. By blocking phosphorylated protein kinase B (pAkt) with a phosphatidylinositol-3 kinase (PI3K) inhibitor, they successfully reversed GLUT1 translocation and restored tumor sensitivity to axitinib treatment\[5, 32].

**Regulation of glucose transporters in tumor cells**

Under hypoxic or anoxic environmental conditions, tumor cells accumulate hypoxia-inducible factors (HIF) which regulate cancer metabolism by activating the transcription of genes that encode for glucose transporters and glycolytic enzymes\[24, 33]. In addition, the activation of oncoproteins and inactivation of tumor suppressor genes in cancer cells can cause the glycolytic pathway to be selected as the primary source of energy supply. Through the phosphoinositide 3-kinases/protein kinase B/mechanistic target of rapamycin (PI3K/Akt/mTOR) pathway, the proto-oncogene Ras induces the expression of HIFs to promote glycolysis\[34].

Myc is a ubiquitously expressed factor, affecting about 15% of human genes including GLUT1 and glycolytic enzymes\[35]. The p53 gene is an important tumor suppressor gene and has been shown to suppress the expression of GLUT1 and GLUT4 in healthy cells. Puzio et al. have found that the p53 mutant HCT116 colon cancer cells have an increased level of glycolysis (by ~26%) compared to the corresponding wild-type\[36]. In normal tissues, the expression of p53-mediated cytochrome C oxidase II (SCO2) promotes the synthesis of cyclooxygenase 2 (COX2), thereby inhibiting glycolysis while raising mitochondrial activity\[37]. In summary, Ras, Myc, and p53 affect the glycolysis process and regulate the growth of tumor cells, making them prime candidates for the development of targeted cancer treatments.

**Lactic acid and glucose transporter**

Tumor cells are dependent on the glycolytic pathway for energy. During this process, glucose transporters are needed to transport a large amount of glucose into these cells, while lactate transporters are necessary to facilitate the excretion of the accumulated lactic acid. Thus, glucose and lactate transporters are two key molecules that are associated with tumor cell metabolism. Monocarboxylate transporters (MCT) play an important role in cellular metabolism by rapidly transporting monocarboxylates such as pyruvate, lactate, and ketone across the plasma membrane and maintaining cellular homeostasis\[38]. To date, at least 16 members of the MCT family have been identified and among these, MCT1 to MCT4 are located on the cell membrane and regulate lactic acid concentrations in the cells. Studies have shown that the inhibition of MCT4 results in excessive accumulation of lactic acid in tumor cells, leading to acidosis-induced tumor cell death\[39]. When the glycolysis process of tumor cells is compromised, the expression of MCT1 will increase, thereby causing MCT1-dependent cell migration.

MCT1 inhibitors have been evaluated in clinical trials as a potential target for cancer treatment\[40]. In order for tumor cells to survive, the expression of glucose and lactate transporters needs to be enhanced. Both transporters are up-regulated and they perform mutually dependent functions in the metabolism of tumor cells. As shown in Figure 1, Akt promotes glycolysis by transcrib- ing the glycolysis-associated genes using the mTOR/HIF pathway. Meanwhile, Myc and HIF promote glycolysis by transcribing the expression of the MCT1 and boosting the expression of the MCT4 genes, respectively\[32, 33, 37, 41]. p53 inhibits glycolysis using the phosphatase and tensin homolog (PTEN) and TP53-induced glycolysis and apoptosis regulator (TIGAR) molecules. It also inhibits MCT1 expression\[42]. Hence, the inactivation of p53 in cancer cells results in the upregulation of glycolytic pathways and MCTs. However, the biomolecule(s) responsible for coordinating the actions of glucose and lactate transporters is still unclear.

**Conflict of interest**

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.
Figure 1. The molecular mechanism of tumor cell metabolism[13]

References


