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Facilitative glucose transporters: Implications for cancer detection, prognosis and treatment

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ABSTRACT

It is long recognized that cancer cells display increased glucose uptake and metabolism. In a rate-limiting step for glucose metabolism, the glucose transporter (GLUT) proteins facilitate glucose uptake across the plasma membrane. Fourteen members of the GLUT protein family have been identified in humans. This review describes the major characteristics of each member of the GLUT family and highlights evidence of abnormal expression in tumors and cancer cells. The regulation of GLUTs by key proliferation and pro-survival pathways including the phosphatidylinositol 3-kinase (PI3K)-Akt, hypoxia-inducible factor-1 (HIF-1), Ras, c-Myc and p53 pathways is discussed. The clinical utility of GLUT expression in cancer has been recognized and evidence regarding the use of GLUTs as prognostic or predictive biomarkers is presented. GLUTs represent attractive targets for cancer therapy and this review summarizes recent studies in which GLUT1, GLUT3, GLUT5 and others are inhibited to decrease cancer growth.

1. Introduction

One of the hallmarks of cancer is its uncontrolled capacity for proliferation, resulting from oncogenic mutations and epigenetic changes that deregulate signals controlling the cell growth-and-division cycle. In order to sustain enhanced proliferation, cancer cells have increased requirements for sugars, fatty acids and amino acids, which provide energy and serve as building blocks for macromolecules [1]. Although the metabolism of all nutrient substrates is altered in cancer, the role of carbohydrate metabolism has received attention because cancer cells depend on glucose metabolism for energy production.

Otto Warburg observed that, even in the presence of oxygen, human and animal tumors prefer to convert glucose into lactate instead of utilizing the mitochondrial metabolism and the oxidative phosphorylation chain for energy production [2]. His observation is supported by the elevated levels of

Abbreviations: FDG-PET, ^{18}F-deoxy-glucose positron emission tomography; 2DG, 2-deoxy-glucose; GLUT, facilitated glucose transporter; SGLT, sodium-coupled glucose co-transporter; DHA, dehydroascorbic acid; HMIT, H+/myo-inositol transporter; PI3K, phosphatidylinositol 3-kinase; EGFR, epidermal growth factor receptor; IGF-I, insulin-like growth factor-I; PTEN, phosphatase and tensin homolog; HIF-1, hypoxia-inducible factor- 1; VHL, von Hippel–Lindau tumor suppressor; mTOR, mammalian target of rapamycin; HRE, hypoxia-response element; HK2, hexokinase 2; PFKM, phosphofructokinase; LKB1, liver kinase B 1; AMPK, AMP-kinase, SUVs, standardized uptake values.

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lactate dehydrogenase that have been found in various cancers [3]. This preferred conversion of glucose to lactate in the presence of oxygen is known as aerobic glycolysis or the "Warburg effect". Readers are referred to these recent excellent reviews on the regulation of glucose metabolism in cancer cells [4–9].

Glucose uptake across the plasma membrane is considered the rate-limiting step for glucose metabolism [10]. In order to achieve a glycolytic rate that is approximately 30 fold higher than normal, cancer cells take up glucose at an elevated rate. This is the basis of diagnostic ^{18}F-deoxy-glucose positron emission tomography (FDG-PET) in which 2-deoxy-glucose (2DG), a non-metabolizable glucose analog, radiolabeled with a positron emitter 18-fluorine, is administered intravenously and concentrates preferentially in tumors allowing for their detection. At the molecular level, ^{18}FDG enters cells through facilitative glucose transporters and becomes phosphorylated by hexokinases, but ^{18}FDG-6P cannot be further metabolized by any metabolic pathway, including glycolysis, therefore it accumulates within cells. Tumor cells may achieve increased ^{18}FDG uptake by upregulating facilitative glucose transporter (GLUT) proteins or hexokinases. Importantly, higher glucose uptake on ^{18}FDG-PET scans is often correlated with more aggressive and advanced-staged tumors [11]. In light of these observations, it is well-founded that a better understanding of these two initial steps of glucose metabolism could reveal better approaches in treating many cancers. Several studies have noted increased expression of hexokinase 2 in a number of cancers and readers are referred to recent reviews on this topic [12–15].

Previous studies have demonstrated that elevated expression of glucose transporters has been observed in most cancers [16–19]. Moreover, some cancers also show abnormal transporter expression pattern compared to healthy tissues (Fig. 1). Deregulated expression of GLUTs, with different hexose affinities, may allow cancer cells to optimize their energy supply providing a fundamental advantage for growth. This review will describe the characteristics of the GLUT family, discuss studies of GLUT expression in cancer cells and tumors and examine the potential for GLUT proteins as biomarkers of malignancy and targets for cancer therapy.

2. The Mammalian Facilitative Glucose Transporter Family

Glucose, due to its hydrophilic nature, requires specific carrier proteins to cross the plasma membrane of cells. Two families of membrane-associated carriers mediate the transport of glucose into the cell: the facilitative glucose transporter proteins (Fig. 2) and the sodium-coupled glucose co-transporter (SGLT) proteins. Unlike SGLT proteins, which require energy to transport glucose, GLUT transporters move sugars down a concentration gradient [18,20,21]

Fourteen members of the GLUT protein family have been identified in humans, which exhibit different substrate specificities and tissue expression (Table 1). Nevertheless, GLUTs show a high degree of homology, share common sequence features and can be grouped into three classes (Fig. 2) which differ in the position of a predicted long extracellular loop [20]. In class I and II proteins this loop containing an N-linked glycosylation site is found between transmembrane domains 1 and 2, while in class III proteins it is between domains 9 and 10 [20]. These proteins transport glucose as well as fructose, galactose, mannose, glucosamine, xylose, dehydroascorbic acid (DHA), urate and myoinositol with variable affinities (Table 1).

2.1. *Class I*

Class I consisting of GLUT1-4, were the first described and best-characterized transporters.

2.1.1. *GLUT1*

GLUT1 (human *SLC2A1*: 1p34.2) is a highly conserved isoform that exhibits 74–98% sequence identity among fish, chicken, human, cow, rat and mouse[22]. This transporter has a high affinity for glucose (K_m 3 mmol/L), and can also transport galactose, mannose, glucosamine and DHA [23] (Table 1). GLUT1 is responsible for basal glucose uptake and it is expressed in virtually all tissues under normal conditions. It is referred to as the "Erythrocyte-Type Glucose Transporter" due to its high expression in erythrocytes where it composes 3–5% of total membrane protein [22]. High levels of GLUT1 can also be found in endothelial and epithelial cells from blood–tissue barriers in the brain, eye, peripheral nerve, placenta and lactating mammary gland [20,22,24].

Previous research has documented high levels of GLUT1 expression in a number of cancer types including lung, brain, breast, bladder, cervical, colorectal, esophageal, hepatocellular, head and neck, gastric, ovarian, renal cell, pancreatic, thyroid, penile and uterine cancers [25–27] (Table 2) suggesting an important role of this transporter in the increased glucose uptake seen in cancer. While it is widely accepted that most tumors overexpress GLUT1, mixed evidence exists in the literature in regards to its expression in breast cancer. Younes et al. (1995) found GLUT1 expression in only 42% of tumors [28] and their findings are supported by subsequent studies in which GLUT1 was detected in only a portion (47% and 51%, respectively) of breast cancer tumors [29,30]. Contrary to these reports, Godoy et al. reported positive staining in 91% of the invasive ductal carcinomas analyzed with immunohistochemistry [27] and high expression has been reported in additional studies [31,32]. While, healthy skin tissue has been shown to express GLUT1, studies have failed to detect this protein in melanoma [27,33].

2.1.2. *GLUT2*

GLUT2 (human *SLC2A2*: 3q26.1-q26.2) has a low affinity for glucose with a K_m of 17 mmol/L [34] and high-affinity for glucosamine with a K_m of 0.8 mmol/L [23]. It has been shown in Xenopus oocytes to be a low affinity transporter of galactose (K_m 92 mmol/L), mannose (K_m 125 mmol/L) and fructose (K_m 76 mmol/L) [35] (Table 1). GLUT2 is expressed in the basolateral membrane of intestinal and kidney epithelial cells [36] and is responsible for the transepithelial transport of glucose into the blood. In hepatocytes, GLUT2 is expressed in the sinusoidal membrane and functions in both taking up glucose from the blood and releasing it [37]. GLUT2 is found at