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Review

Expression of glucose transporters in cancers

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ABSTRACT

It has been known for 80 years that cancer cell growth in an energy-related process supported by an increased glucose metabolism. This phenomenon suggests a need for a corresponding increased uptake of glucose across the plasma membrane through an enhancement in the glucose transporter proteins, SGLT proteins as well as GLUT proteins. The results of many studies have demonstrated that the expression of glucose transporters, especially GLUT1, is increased in a variety of malignancies. GLUT1 overexpression has been found to be associated with tumor progression. It was found that GLUT1 overexpression is associated with poor overall survival in various malignant tumors.

Contents

1. Introduction

Glucose is an essential metabolic substrate of all mammalian cells. It is not only as a precursor of glycoproteins, triglycerides, and glycogen. Glucose metabolism governs many functions, because the oxidation of glucose generates a major source of metabolic energy in eukaryotic cells. These functions are secondary to glucose uptake. Glucose is a hydrophilic compound. It cannot pass through the lipid bilayer by simple diffusion, and therefore requires specific carrier proteins to mediate its specific carrier proteins to mediate its specific transport into the cytosol. Glucose is transported into cells via two classes of hexose transporters: the SGLT (sodium-dependent glucose transporter) family and GLUT family. The SGLT family of transporters transports sugars against the concentration gradient utilizing the sodium-electrochemical gradient. The GLUT family are facilitative transporters that transport sugars along the concentration gradient [1]. After glucose enters normal cells, it is converted into pyruvate through glycolysis. Subsequently, pyruvate is transformed into acetyl-CoA, which is used as substrate in mitochondria to generate ATP.

Tumor cells exhibit an altered metabolism. Increased need for glycolysis, known as Warburg effect, and glucose uptake for ATP production and also lactate secretion is observed in tumor cells, particularly in cells lacking of oxygen supply. Hypoxia is a hallmark of cancer, upregulating GLUT expression [2].

2. Glucose metabolism in cancer

Tumor cells require a host vasculature for their supply of nutrients and oxygen, but oxygen cannot diffuse further than around 150 μm through tissues. As tumor growth outstrips its vasculature, the cells become hypoxic [3]. Although tumors induce formation of new blood vessels to deliver nutrients and oxygen to the growing tumor, angiogenesis does not keep pace with the growth of the neoplastic cells. A high level of hypoxia in solid tumors is an adverse prognostic factor for the poor outcome of cancer patients following treatment [4]. Hypoxic tumors are known to be more malignant, to be more likely to metastasize, and to

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have a poor prognosis. They are also radio- and chemoresistant [5]. There are different cellular adaptations to hypoxia and acidosis during carcinogenesis [6]. Due to their inherently hypoxic environment, cancer cells often resort to glycolysis, or the anaerobic breakdown of glucose to form ATP to provide for their energy needs. The oxidative catabolism, which is more efficient in energy production, is impaired in cancer cells. The fermentation pathway carried out by cancer cells implies the consumption of more sugar to fulfil their energy requirements. In cancer cells it has been also proposed an enhanced activity of glycolytic enzymes, especially the activity of the enzyme hexokinase. The changed activity of lactate dehydrogenase was observed in lymphoma, leukaemia, and colon cancer [7]. Activities of the pentose phosphate pathway enzymes glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase have been reported to be higher in human cervical carcinomas [8], and glucose-6-phosphate dehydrogenase also in human breast cancer [9] compared to normal tissue.

3. Human sodium glucose transporters (SGLT)

Sodium glucose transporters are also known as Na^+/glucose transporters or symporters (SGLTs). Glucose transport is driven by the inward Na^+ gradient maintained by the Na^+ pump. There are 12 members of the human family (encoded by genes *SLC5A1–SLC5A12*), and they include Na^+ cotransporters for sugars, *myo*-inositol, iodide, short fatty acids, and choline [10]. The human genome project ultimately led to the gene mapping of all six SGLTs beginning with SGLT1 on chromosome 22, SGLT2 16p12-p11, SGLT3 21q22.12, SGLT4 1p32, SGLT5 17p11.2 and SGLT6 on chromosome 16p12.1 [10]. The organization of all *SLC5A* genes is quite similar, in having 15 exons, although they span from 8 to 72 kb. In other members of the *SLC5A* gene family the coding sequences are found in 14, 8, or only 1 exon(s). In SGLT 4–6 there are some indications of alternative splicing, and this may account for the difficulty in expressing these clones in heterologous expression systems [11]. All members of the *SLC5A* family code for 60 to 80 kDa proteins containing 580–718 amino acids. Human SGLT3 is not a transporter but a glucosensor [12]. Relative to human SGLT1, it is between 50 and 70% identity and 67–84% similarity in the sequence for SGLT2–6. The greatest divergence in sequence occurs at the extracellular NH_2- terminal domain and the COOH– terminal third of the proteins [10].

Analysis of the gene expression in human tissues has been carried out using different methods, such as Northern blots, real-time PCR, and PCR. A comprehensive study of *SLC5A* gene expression has been published [13]. In the PCR experiments, SGLT1 was found in the small intestine, trachea, kidney, heart, and colon; SGLT2 in kidney; SGLT3 in small intestine; SGLT4 in small intestine and kidney; SGLT5 in kidney; SGLT6 in spinal cord, kidney, and brain [11]. In the RNAase protection assays, SGLT1 mRNA was found in testis; SGLT2 mRNA in cerebellum, heart, salivary gland, liver, and thyroid; SGLT3 in testis, spleen, uterus, brain, and lung; SGLT4 in liver, brain, and lung; SGLT5 in kidney cortex; SGLT6 in brain, kidney, and small intestine [11].

The demand for glucose in cancer is even higher than normal cells. SGLT1 is expressed in colorectal, head and neck, and prostate tumors, in primary tumors, and metastatic lesions of lung, pancreatic adenocarcinomas, and head and neck cancers [14–16]. Weihua et al. [17] find epidermal growth factor receptor (EGFR) associates with and stabilizes the SGLT1 to promote glucose uptake into cancer cells. According to authors, in human cancer cells, the function of kinase-independent EGFR is to prevent autophagic cell death by maintaining intracellular glucose level through interaction and stabilization of the SGLT1 [17]. These studies suggest that EGFR functions not only as an important instigator of signal transduction cascades, but also as an integral component of an active glucose transport system [18]. This may explain the resistance of tumor cells to chemotherapeutic agents and tyrosine kinase inhibitors. A novel strategy has been proposed to deliver chemotherapeutic agents into tumor cells through SGLTs [11].

SGLT2 is expressed in colorectal, gastrointestinal, head and neck, and kidney tumors as well as in carcinomas and leukaemia. It was found in primary tumors and metastatic lesions of lung, pancreatic adenocarcinomas, and head and neck cancers [14–16].

By analyzing the metastatic lesions (from liver and lymph nodes) of lung tumors, it was found that the expression of SGLT2 was significantly higher in metastasis areas than in primary tumors, whereas SGLT1 expression did not display changes [16]. In the other study, the expression of SGLT1, together with Bcl-2 and p53, was analyzed in pancreatic cancer to relate the data obtained with different survival parameters [14]. It was found that overexpression was significantly correlated with disease-free survival in pancreatic adenocarcinomas, and high SGLT1 expression in pancreatic primary tumors was correlated with high Bcl-2 expression. Therefore, it is suggestion that SGLT1 and Bcl-2 may be as potential prognostic biomarkers for pancreatic cancer [19].

4. Facilitative glucose transport

A ubiquitous glucose transport also exists. LeFevre in 1948 was the first to postulate that a specific component within the cellular plasma membrane was required for the transfer of glucose across the lipid bilayer [20]. Facilitative glucose transporters (GLUTs) allow the energy independent transport of glucose across the hydrophobic cell membrane down its concentration gradient. The GLUT protein family belongs to the Major Facilitator Superfamily (MFS) of membrane transporters [21]. Well over 5 000 members of the MFS have been identified to date, encompassing all three kingdoms [22]. GLUTs are proteins of ~500 amino acids and are predicted to possess 12 transmembrane-spanning alpha helices and a single N-linked oligosaccharide. Fourteen members of the mammalian facilitative glucose transporter have been identified (GLUT1–GLUT12, GLUT14, and HMIT; H^+/*myo*-inositol transporter). The genes belong to the solute carrier 2A family, with the symbol *SLC2A* (*SLC2A1–SLC2A14*). Recently three groups have been classified, based on their sequence similarities, within the family [23]. Each of the glucose transporter proteins possesses different affinities for glucose and the other hexoses such as fructose. The GLUTs are intrinsic membrane proteins which differ in tissue-specific expression and responds to metabolic and hormonal regulation. It is to note that GLUT1 is frequently upregulated during oncogenesis in many different tissue types [24]. It is probably essential process for tumors to grow beyond a size limited by their glycolytic capacity (the Warburg effect) [22].

5. Expression of GLUT proteins in cancers

GLUT1 is a representative of the GLUT family and is widely distributed in normal tissues. This transporter is overexpressed in many tumors, including hepatic, pancreatic, breast, esophageal, brain, renal, lung, cutaneous, colorectal, endometrial, ovarian, and cervical cancers [25]. Several studies have shown a close relationship between GLUT1 expression, tumor development, and unfavourable prognosis of several tumors. The level of GLUT1 expression might be a suitable marker of hypoxia and glucose metabolism, which could be measured simply and inexpensively as part of the routine histologic assessment of tumors [5]. Increased levels of GLUT mRNA [26] and GLUT transporter [27] have been found in extracts of human cancer cells of diverse origin. It is hypothesis that is a selective overexpression of different GLUT transporters in various tumors [28]. The patterns of GLUT1 expression in adenocarcinomas and squamous cell carcinomas differed in location and frequency in tumor compartments. Burstein et al. [30] examined GLUT1 expression in 80% of case studied. In prostate and thyroid tumors, frequencies of GLUT1 expression were 47 and 29%, respectively [29]. Brown and Wahl [27] showed that primary breast cancer was positive for GLUT1. This transporter was expressed on the cell membrane and in cytoplasm of the tumor cells, but exhibited marked intratumoral and intertumoral variability in the proportions of positive cells and the intensity of staining. In the other study, in untreated primary human breast cancers,