Glucose Transporters and Breast Cancer

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Reprogramming of cellular energy metabolism is widely accepted to be a cancer hallmark. The deviant energetic metabolism of cancer cells-known as the Warburg effect-consists in much higher rates of glucose uptake and glycolytic oxidation coupled with the production of lactic acid, even in the presence of oxygen. Consequently, cancer cells have higher glucose needs and thus display a higher sensitivity to glucose deprivation-induced death than normal cells. So, inhibitors of glucose uptake are potential therapeutic targets in cancer. Breast cancer is the most commonly diagnosed cancer and a leading cause of cancer death in women worldwide. Overexpression of facilitative glucose transporters (GLUT), mainly GLUT1, in breast cancer cells is firmly established, and the consequences of GLUT inhibition and/or knockout are under investigation.

Keywords: breast cancer ; glucose transport ; drugs ; natural compounds

1. Introduction

According to the last Global Cancer Statistics (GLOBOCAN 2018), breast cancer represented 12% of all cancers, being the second most frequent cancer worldwide, after lung cancer, and caused about 7% of the total cancer deaths in 2018 [1]. In women, breast cancer is the leading type of cancer and the leading cause of cancer death worldwide [1].

Screening programs and adjuvant chemotherapy have had a significant impact on the prognosis of breast cancer patients, having significantly improved their overall survival, disease-free survival, and death rates related to breast-cancer since the early 1990s [2][3]. Nevertheless, efforts must continue in order to reduce not only the incidence but also the mortality and treatment-associated morbidities associated with this disease. In this context, discovery of new molecular targets and the refinement of lead compounds constitute a priority in breast cancer research.

2. Upregulation of Glucose Transport in Breast Cancer Cells

Since the energetic metabolic shift in cancer cells produces less ATP per glucose molecule, the demand for glucose in these cells is higher than in normal cells. Therefore, cancer cells rely on higher rates of glucose uptake in order to support their increased energy, biosynthesis and redox needs. This increased rates of cellular uptake of glucose is met by overexpression of glucose transporters, which is observed in most cancer cells [4].

Two families of glucose transporters mediate glucose uptake in mammalian cells: the Na^+-dependent glucose co-transporters (SGLTs) and the facilitative glucose transporters (GLUTs).

The SGLT family (gene symbol *SLC5A*) are secondary active transporters that transfer glucose against its concentration gradient coupled with Na^+ transport down its concentration gradient, which is maintained by the Na^+/K^+ pump. For every glucose molecule that is transported, two Na^+ are also transported. SGLT transporters have 14 transmembrane domains and a high affinity for glucose. At physiological extracellular Na^+ concentration and membrane potential, an apparent Km of 0.5 mM of SGLT1 for glucose was described, but glucose is transported with a lower affinity when the plasma membrane is depolarized and/or the extracellular Na^+ concentration is low [5][6]. SGLT1 and SGLT2 overexpression is present in some types of cancer, such as pancreas, prostate, lung, liver, and ovarian cancer, but these transporters have not been described in breast cancer [7].

The GLUT family (gene symbol *SLC2A*) are facilitative transporters that mediate the transport of glucose down its concentration gradient. This family of transporters is composed of 14 members: GLUT1-GLUT12, GLUT14, and the H^+/myo-inositol transporter. All GLUTs are predicted to have 12 transmembrane domains connected by hydrophilic loops. Each of the GLUT transport protein possesses different affinities for glucose and other hexoses such as fructose. GLUT1, GLUT3, and GLUT4 have a high affinity for glucose (e.g., the Km of GLUT1 for glucose is 1–3 mM), allowing transport of glucose at a high rate under normal physiological conditions [8].

Increased cellular uptake of glucose in tumor cells is associated with increased and deregulated expression of GLUT transporters [4]. Among GLUT family members, overexpression of GLUT1 has been consistently observed in many different cancers, including breast, lung, renal, colorectal, and pancreatic cancers [4][9][10]. Consistent with its overexpression, GLUT1 is crucial for uptake of glucose by breast cancer cells [11][12][13] and is also the main glucose transporter in breast cancer cell lines (e.g., MCF-7 and MDA-MB-231) [12][14]. GLUT1 is a transporter ubiquitously expressed in most mammalian tissues (abundantly in brain and erythrocytes), being responsible for basal glucose cellular uptake in the majority of tissues [7][8]; it is also the predominant isoform present in human and bovine mammary glands [15][16]. Glucose uptake mediated by GLUT1 appears to be especially critical in the early stages of breast cancer development, affecting cell transformation and tumor formation [17][18]. Indeed, GLUT1 overexpression, which occurs early during the transformation process, induces a change in breast epithelial cell metabolism that precedes morphological changes in breast cancer, and thus may be a fundamental part of the neoplastic process [9]. Interestingly, the loss of even a single GLUT1 allele is sufficient to impose a strong break in breast tumor development in a mouse model [17]. A strong correlation between *GLUT1* gene expression and breast cancers of higher grade and proliferative index and lower degree of differentiation [19] and higher malignant potential, invasiveness, and consequently poorer prognosis [20] exists. GLUT1 is thus considered an oncogene [9][10][11][21].

One of the factors responsible for the upregulation of GLUT1 in breast tumor cells is hypoxia. The promoters of GLUT1 contain hypoxia-response elements, which bind the hypoxia-inducible factor (HIF-1) to facilitate transcription. Since an increase in the levels of HIF-1α protein is a phenomenon seen in most cancers, it provides a molecular mechanism for cancer-associated overexpression of GLUT1 [9][22]. Additionally, hypoxia appears to increase GLUT1 transport activity in the MCF-7 breast cancer cell line, independently of changes in transporter expression [23]. Besides HIF-1, the ovarian hormone estrogen is also known to induce GLUT1 expression in breast cancer [9][24]. Moreover, the histone deacetylase SIRT6, the cellular oncogene product c-MYC (V-Myc Avian Myelocytomatosis Viral Oncogene Homolog), the pro-survival protein kinase Akt (Protein Kinase B) and mutant p53, all of which induce the expression of GLUT1 [22][25], can also be involved in GLUT1 overexpression in breast cancer.

In addition to GLUT1, which is consistently found to be expressed in breast tumors and cell lines, other GLUT family members can also contribute to glucose uptake by breast cancer cells. More specifically, GLUT2 [10][14] and GLUT3 [9] are also expressed in several breast cancer cell lines. Additionally, GLUT4 expression [21][26][27][28] and insulin-stimulated glucose uptake were also described in some cancer cell lines [29][30][31]. Moreover, the involvement of GLUT4 in basal glucose uptake was described in two breast cancer cell lines [32]. Finally, a second insulin-stimulated transporter, GLUT12, was also described in MCF-7 cells [9][33]. Similar to GLUT1, the expression of GLUT3 and GLUT12 correlate with poor prognosis [9][10]. Importantly, increased expression of GLUT1 and GLUT3 was also associated with resistance of cancer cells to radio or chemotherapy [34][35][36], but the underlying mechanisms linking GLUT and chemo- or radio-resistance remain largely unknown.

Increased glucose uptake by cancer cells has been exploited clinically in diagnosis and follows up of cancer via the use of ^{18}fluoro-2-deoxy-D-glucose (FDG), a radiolabeled glucose analogue, in Positron Emission Tomography (PET) [37]. This radiotracer enters cells via GLUTs, being then phosphorylated by hexokinases into FDG-6-phosphate that cannot be further metabolized and thus accumulates in the cytoplasm. Importantly, the sensitivity of this technique varies depending on the type of cancer, and this heterogeneity has been particularly associated with GLUT1 or GLUT3 tumor expression [14][38].

3. Effect of Stimulation of the Interaction of Anticancer Agents with GLUT

Conjugation of anticancer agents with glucose or other sugars is a widely exploited technique to design therapeutic agents, in order to improve their uptake into highly glycolytic cancer cells overexpressing GLUTs, thus increasing efficacy while reducing side effects. One possibility is to develop sugar-conjugated agents that can be transported into cancer cells through GLUT without inhibiting GLUTs themselves [39]. Another possibility is to promote interaction of anticancer agents with GLUT by their conjugation with an anti-GLUT antibody. Some of these agents have been tested in breast cancer cell lines, as shown next.

3.1. Adriamycin

Adriamycin (doxorubicin) is effective against many types of solid tumors in clinical applications. However, its use is limited because of systemic toxicity and multidrug resistance. Adriamycin conjugated with a glucose analogue (2-amino-2-deoxy-d-glucose) and succinic acid (2DG-SUC-ADM) was designed to target tumor cells through GLUT1, thus enhancing the selectivity of doxorubicin against cancer cells while reducing its toxicity to healthy cells [40]. In a work using several cancer

cell lines, including MCF-7 and MDA-MB-231 cell lines, the complex showed better inhibition to tumor cells and lower toxicity to normal cells, and, most importantly, displayed a potential to reverse multidrug resistance. In vivo experiments also showed that this new complex could significantly decrease organ toxicity and enhance the antitumor efficacy compared with free ADM, indicating 2DG-SUC-ADM as a promising drug for targeted cancer therapy [40]. The GLUT1-mediated transport into the cells explained the specificity of 2DG-SUC-ADM, because uptake of free doxorubicin mainly occurred through diffusion, whereas the uptake of 2DG-SUC-ADM was mostly GLUT1-mediated [40].

Sztandera et al. [41] developed a glucose-modified PAMAM dendrimer for the delivery of doxorubicin (dox) to breast cancer cells, designed to specifically enter tumor cell with enhanced glucose uptake. They verified that PAMAM-dox-glucose conjugate exhibited pH-dependent drug release and an increased cytotoxic activity compared to free drug in MCF-7 cells, in the absence of glucose. They also verified that GLUT1 inhibition eliminated the toxic effect of the conjugate. So, they concluded that the cytotoxic effect of PAMAM-dox-glucose depends on presence of a functional GLUT1, suggesting specific, transporter-dependent internalization as a main route of cellular uptake of glucose-conjugated PAMAM dendrimers [41].

3.2. Paclitaxel

This drug is widely used for the treatment of breast, ovarian, and lung carcinomas, but its low water solubility severely reduces its clinical application. In this context, a new prodrug was designed to enhance its solubility and its selective delivery to cancer by a preferential uptake via GLUTs. More specifically, the glycoconjugation of paclitaxel led to a derivative in which the drug was linked to 1-methyl glucose via a short succinic acid linker. The resulting compound, whose transport was mediated at least in part by GLUT1, showed a comparable cytotoxicity against several cancer cells without toxicity on normal cells. Of note, paclitaxel linked to succinic acid resulted in a lower toxicity against MCF-7 cells than the parent compound, suggesting that the presence of glucose improved its cytotoxicity [42].

3.3. Oxiplatin

The platinum antitumor drug oxaliplatin is a commonly used chemotherapeutic agent; however, its multiple side effects severely limit its benefits. The conjugation with sugar portions was introduced as a strategy to improve the tumor-targeting ability of the drug and also to enhance its water solubility, allowing renal excretion and lower systemic toxicity. A glycosylated (trans-R,R-cyclohexane-1,2-diamine)-malonatoplatinum(II) derivative showed increased cytotoxicity compared to oxaliplatin in all the tested human carcinoma cell lines. Its potency was prevented when human colon cancer (HT29) and breast cancer (MCF-7) cells, which overexpress GLUTs, were treated with the GLUT inhibitor phlorizin, thus confirming that the uptake and the antiproliferative activity of this compound are GLUT-mediated [43].

In summary, a great potential of GLUT-mediated transport of therapeutics into cancer cells opens new roads for targeted delivery of anticancer drugs.

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