Glucose transporters as markers of diagnosis and prognosis in cancer diseases

Leszek Szablewski

Chair and Department of General Biology and Parasitology, Medical University of Warsaw, Poland

Abstract

The primary metabolic substrate for cells is glucose, which acts as both a source of energy and a substrate in several processes. However, being lipophilic, the cell membrane is impermeable to glucose and specific carrier proteins are needed to allow transport. In contrast to normal cells, cancer cells are more likely to generate energy by glycolysis; as this process generates fewer molecules of adenosine triphosphate (ATP) than complete oxidative breakdown, more glucose molecules are needed. The increased demand for glucose in cancer cells is satisfied by overexpression of a number of glucose transporters, and decreased levels of others. As specific correlations have been observed between the occurrence of cancer and the expression of glucose carrier proteins, the presence of changes in expression of glucose transporters may be treated as a marker of diagnosis and/or prognosis for cancer patients.

Introduction

Mammalian cells are heavily reliant on glucose as both a source of energy and a substrate in protein and lipid biosynthesis. Glucose itself can be obtained directly from the diet, following the hydrolysis of ingested di- and polysaccharides, or can be synthesized in organs such as the liver and kidney. Following ingestion or synthesis, together with other monosaccharides, glucose must be transported through the blood circulation to the target cells, and then across the plasma membrane. However, as these monosaccharides are hydrophilic, and the plasma membrane presents an impermeable barrier, specific carrier proteins known as glucose transporters are required to allow them to pass though.

Despite their name, these proteins can also transport a range of molecules, including fructose, galactose, mannose, myo-inositol, D-chiro-inositol, iodide, pyruvate, lactate and nicotinate, among others; they can also act as glucose sensors. Glucose transporters themselves belong to the major facilitator superfamily (MFS), which consists of 74 families of carrier membrane proteins, more than 10.000 of which have been sequenced to date.[1]

In humans, glucose transporters are encoded by three families of genes: sodium-independent glucose uniporters (facilitated transport, GLUT proteins, SLC2A genes), sodium-dependent glucose symporters (secondary active transport, SGLT proteins, SLC5A genes), and a new class of glucose uniporters, SWEET proteins (SLC50A genes).[2]

Correspondence: Leszek Szablewski, Medical University of Warsaw, Ul. Chalubinskiego 5, 02-004, Warsaw, Poland.
E-mail: leszek.szablewski@wum.edu.pl.
Tel. +48 22 621-26-07.

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Characteristics of human glucose transporters

The human SLC2A family of glucose transporters

The *SLC2A* gene family codes sodium-independent glucose transporters, named GLUTs. Fourteen GLUT proteins, GLUT1–GLUT14, have been identified in humans. All contain 12 hydrophobic membranes spanning α-helical transmembrane (TM) domains. They also contain a short intracellular N-terminal segment, a large C-terminal segment and a single site for glycosylation on the exofacial end, which is located in the large loop between transmembranes 1 and 2 or between transmembranes 9 and 10.[3,4] All GLUT proteins are facilitative transporters, except for GLUT13 (HMIT), which is an H^+ myo-inositol symporter.[5,6]

The human SLC5A family of glucose transporters

The sodium-dependent glucose cotransporters are the members of the SLC5A gene family. The sodium/substrate symporters family (SSSF) contains over 450 members.[7,8] In humans, 12 members of proteins encoded by SLC5A genes, SGLT1–SGLT6, SMIT1, NIS, SMVT, CHT1, SMCT1, and SMCT2 have been identified. Ten contain 14 TM α-helices, and two (NIS and SMCT1) lack TM-14.[9] Both the N- and C-termini are located on the extracellular side of the cell membrane.[2] Although sodium-dependent cotransporters are highly glycosylated proteins, glycosylation is not required for their functions. All act as cotransporter proteins, transporting a range of substrates, such as glucose, myo-inositol and iodide;[8] however, SGLT3 acts as a glucose sensor.[10]

The human SLC50A family of glucose transporters

SLC50A genes code glucose transporters named SWEETs. These proteins have seven predicted transmembrane domains with

two internal-helix-bundles connected by an inversion linker helix, resulting in a 3+1+3 construction translocation pathway. This class of glucose transporters was first identified by expressing candidate *Arabidopsis thaliana* genes coding for polytopic membrane proteins in HEK293T cells. In plants, SWEET proteins supply carbohydrates to a variety of tissues throughout the organism, and approximately two dozen plant SWEETs have been identified in comparison to only one SWEET in animals. Several dozen SWEETs have been recorded in *Caenorhabditis elegans* alone.[6] In contrast, the only SWEET protein identified in humans is SWEET1 (RAG1AP1), encoded by the SLC50A1 gene.

Glucose metabolism in cancer cells

In the 1920s, Otto Warburg observed that cancer cells secrete lactate, which is an end-product of glycolysis. This process generates only two molecules of adenosine triphosphate (ATP) from one molecule of glucose, whereas the complete oxidative breakdown of one molecule of glucose in the presence of oxygen generates 36 molecules of ATP. The author suggested that cancer cells favor the process of glycolysis in the presence of oxygen, a phenomenon known as the Warburg effect or Aerobic glycolysis.[11,12] Several possible explanations have been proposed for this phenomenon.[13,14] Hypoxic tumors are more invasive and metastatic.[15] As the glycolytic rate of cancer cells is approximately 30 times higher than that of normal cells,[16] cancer cells need much greater amounts of glucose to provide energy. To accommodate this extra demand, many cancer cells express higher levels of glucose transporters than normal "healthy" cells.[17,18] Hence, it has been proposed that glucose transporter expression may serve as a diagnostic and/or prognostic marker in cancer diseases[19], and that these membrane carrier proteins may play a role in anticancer therapy.[16,20]

Glucose transporter proteins in cancer cells

Several human tissues and organs have been found to demonstrate unspecific expression of glucose transporters during tumor development (Table 1). For example, GLUT1 is overexpressed to a high degree in cells experiencing hypoxia,[21] especially in the peri-necrotic regions of a tumor. Its overexpression is an important part of the neoplastic process.

Cancers of the human digestive system

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) patients with high GLUT1 expression demonstrate poorer differentiation in comparison to those with low GLUT1 expression. In patients who underwent FDG-PET (^{18}F-deoxy-glucose positron emission tomography), a high standardized uptake value (SUV) was correlated with larger tumor size, more frequent vascular invasion and poorer differentiation; the high SUV patients also demonstrated significantly higher GLUT1 expression and poor prognosis.[22] High GLUT1 expression promotes tumorigenesis, and is associated with increased malignancy and potential for invasion.[23]

The expression of GLUT1 on the tumor endothelium is altered in hepatocellular carcinoma, and this may be an important prognostic and diagnostic marker.[24,25] As its cytoplasmic expression is variable, it has been proposed that this may allow differentiation between cholangiocarcinomas and hepatocellular carcinoma.[26] GLUT1 overexpression has been found in both primary and metastatic hepatic tumors,[27] but not in hepatoblastomas;[28] in the case of the latter, other GLUT proteins play the role of glucose transporters.

GLUT2 expression also is increased in HCC.[25] The presence of GLUT2 in tissue samples from HCC patients, and its upregulation, correlate with poor prognosis.[29] In contrast, GLUT2 expression is decreased in preneoplastic and neoplastic hepatic lesions.[30] It has also been observed in human cell lines, and those subjected to hypoxia.[31] Otherwise, GLUT5 expression is significantly higher in the liver metastatic lesions than primary lung tumors,[27] and elevated in liver carcinoma.[32] GLUT6 mRNA was detected only in hepatoma cell lines,[33] whereas GLUT9 was detected in the cytoplasm of pericentral hepatocytes in HCC.[32] SGLT1 overexpression has also been described in HCC.[34]

Gallbladder carcinoma

In 95% of cases, this is classified as adenocarcinoma. The cells demonstrate GLUT1 overexpression,[35] with the level correlating with the stage of carcinoma; the expression increases from low-grade dysplasia toward carcinoma, and from benign toward malignant lesions.[36] The level of GLUT1 expression in patients with gallbladder carcinoma may be a marker of poor prognosis.

Cholangiocellular carcinoma

Of the glucose transporters, GLUT1 predominates in cholangiocellular carcinoma (CCC) patients, being detected in 81% of cases. This is followed by GLUT2, which was detected in 54% of CCC patients, and GLUT3 in 19%. Neither GLUT4 and GLUT5 were detected.[37]

Biliary intraepithelial neoplasia

GLUT 1 is expressed in all grades of biliary intraepithelial neoplasia (BilIN), and its expression correlates with aggressiveness and poor prognosis.[38] In contrast, GLUT2 is detected only in high-grade BilINs, and its presence may be a marker for the presence of high-grade BilIN lesions on atypical bile ducts; its expression may be associated with cholangiocarcinogenesis of the large bile duct, and with an early stage of carcinogenesis from high-grade neoplasia to invasive cholangiocarcinoma.[38]

Pancreatic neoplasia

Several forms of pancreatic neoplasia are known, including pancreatic ductal adenocarcinomas (PDACs), pancreatic intraepithelial neoplasms (PanINs), intraductal papillary mucinous neoplasms (IPMNs) and serous cystadenomas.[39] In addition, about 70% of all neuroendocrine tumors (NETs) are gastroenteropancreatic neuroendocrine tumors (GEP-NETs).[40-43] In contrast, pancreatic NETs are rarer, and are characterized by slow growth, low proliferation index, indolent behavior and a good prognosis.[44] These cancers, such as glucagonoma, insulinoma and somatostatinoma[44] are often accompanied by distant metastases.[45]

The expression of GLUT1 in pancreatic cancer is dependent on cancer type, stage and size. It is detected in about 73.6% of pancreatic cancers, of which 47.2% are strongly positive, but only in 20.8% of samples from healthy controls.[46] Its expression does not correlate with cancer location, cancer differentiation or vascular invasion, but its overexpression is associated with poor prognosis.[46] GLUT1 overexpression has been detected in most metastatic lesions; however, in primary pancreatic tumors (metastatic PDAC), no significant overexpression was noted in primary tumor and lung metastatic lesions compared with metastatic ones.[47,48] In the normal pancreas, GLUT1 is not expressed in the acini and ducts but it has been noted in the islets, perineurial cells and endothelial cells.

Table 1. Expression of glucose transporters in cancer cells.

Cancer	Changes in expression of glucose transporters
Hepatocellular carcinoma	1) Overexpression of GLUT1 in both primary and metastatic hepatic tumors; 2) Lack of GLUT1 expression in hepatoblastomas; 3) Overexpression of GLUT2; 4) Decreased levels of GLUT2 in preneoplastic and neoplastic hepatic lesions; 5) Significantly higher expression of GLUT5 in the liver metastatic lesions tumors. Higher level of GLUT5 in the liver carcinoma; 6) Overexpression of SGLT1.
Gallbladder carcinoma	1) Overexpression of GLUT1. Its expression increases from low-grade dysplasia toward carcinoma, and from benign toward malignant lesions.
Biliary intraepitheliala neoplasi	1) Expression of GLUT1 is correlated with aggressiveness of neoplasia and poor prognosis; 2) GLUT2 is detected only in the high-grade biliary intraepithelial neoplasia (BilIN). Its expression with cholangiocarcinogenesis of the large bile duct, may be a marker for the presence of high-grade BilIN lesions and atypical bile ducts. Expression of GLUT2 is correlated with early stage of carcinogenesis from high-grade neoplasia to invasive cholangiocarcinoma.
Pancreatic tumors	1) The level of GLUT1 expression depends on the stage of neoplasia; in stage pancreatic intraepithelial neoplasms (PanIN)-1A GLUT1 is not expressed in cancer cells, whereas in stage PanIN-3, its expression is significantly higher. No such expression was detected in pancreatic neuroendocrine tumors; 2) GLUT2 is expressed in malignant tumors, but not in benign tumors. Its overexpression is detected in liver metastases, but not other metastases. Its expression in neuroendocrine tumors is downregulated; 3) Expression of GLUT4 is detected in the malignant pancreatic tumors, but not benign tumors. Studies suggest that GLUT4 expression is decreased in pancreatic tumors; 4) SGLT1 levels is correlated with Bcl-2 expression in pancreatic cancer patients.
Gastric cancer	1) Expression of GLUT1 is detected in late carcinogenesis and increases with disease progression; 2) GLUT2 and GLUT3 are overexpressed in gastric tumors.
Colorectal cancer	1) Level of GLUT1 is correlated with cancer stage; 2) Some studies revealed overexpression of GLUT2 in colorectal cancer; 3) GLUT4 is overexpressed in colon adenocarcinoma and in colon cancer; 4) SGLT1 is overexpressed in colorectal cancer, and its expression is correlated with the clinical stage of cancer.
Kidney cancer	1) GLUT1 is upregulated in renal cell carcinoma; 2) GLUT2 is downregulated in renal cell carcinoma; 3) Level of GLUT3 mRNA is increased; 4) GLUT4 expression may be downregulated, or upregulated depending on the type of renal cancer; 5) GLUT5 is overexpressed in renal cell carcinoma; 6) GLUT9 and GLUT12 are downregulated in kidney cancer.
Prostate cancer	1) GLUT1 is overexpressed and its expression depends on the malignancy grade; 2) GLUT3 and GLUT5 are expressed in normal prostate gland tissue, but not prostate carcinoma; 3) GLUT5 expression is observed in the high-grade prostatic intraepithelial neoplasia; 4) Level of GLUT7 mRNA is higher in benign tissue than in prostate cancer; 5) The level of GLUT9 mRNA in prostate cancer is decreased in comparison with benign tissue; 6) Level of GLUT11 mRNA in prostate cancer is higher as compared to benign prostate cancer; 7) GLUT12 expression is detected in malignant prostate tissue, but not in benign prostate hyperplasia; 8) Level of SGLT1 is increased in prostate cancer cells; 9) SGLT2 is expressed in prostate adenocarcinoma, but not in the normal prostate gland.
Cervical cancer	1) GLUT1 is overexpressed and its expression is correlated with the histologic grade of a tumor; 2) The SLC2A6 gene is the most highly expressed gene of 40 genes investigated in endometrial cancer.
Ovarian cancer	1) Normal ovarian epithelial cells are negative or weakly positive for GLUT1, whereas epithelial ovarian cancer cells are positive for GLUT1. Expression is correlated with the grade of tumor; 2) GLUT3 is not detected in normal ovarian tissue, whereas high immunostaining is detected in ovarian cancer; 3) GLUT4 is not detected in normal ovarian tissue or malignant tumors; however, in some studies its expression was detected in ovarian tumor cells; 4) Expression of SGLT1 increases with tumor grade.
Breast cancer	1) GLUT1 is overexpressed in breast cancer, whereas healthy breast cells are negative or slightly positive for this glucose transporter; 2) GLUT5 expression is observed in human breast cancer cells, but not in normal human breast tissue; 3) NIS expression is observed in 13% of normal breast tissue samples, and in 76-89% of breast cancer samples.
Lung cancer	1) Expression of GLUT1–GLUT5 depends on the histological subtype of lung cancer; 2) SGLT1 is overexpressed in lung cancer; 3) SGLT2 expression is significantly higher in metastatic areas than primary tumors; 4) NIS is detected in lung carcinoma samples but not in healthy human lung tissue.
Brain cancer	1) GLUT1 mRNA level correlates with astrocytoma grade, whereas GLUT1 protein is not detected in human brain tumors; 2) GLUT3 level correlates with glioma grade, and is the predominant glucose transporter in highly malignant cells of the human brain; 3) The level of GLUT4 mRNA correlates with glioma tumor grade. 4) Level of GLUT4 mRNA correlates with glioma tumor grade.
Thyroid cancer	1) GLUT1, GLUT3, and GLUT14 are upregulated, and their expression correlates with advanced tumor stage, tumor aggressiveness, and poor prognosis; 2) GLUT9 is not detected in normal thyroid tissue, whereas its expression is detected in papillary thyroid carcinoma; 3) High NIS expression is observed in thyroid cancers, but its activity depends on its cellular localization.
Adrenocortical carcinoma	1) GLUT1 and GLUT3 are detected in the adrenocortical carcinoma samples but not in normal adrenal glands or adenomas.
Thymic carcinomas	1) GLUT1 is upregulated and its overexpression depends on the subtype of thymic carcinoma.
Skin cancer	1) GLUT1 is downregulated in nonmelanoma skin cancer; 2) In melanoma samples, expression of GLUT1 depends on the explants of melanoma.
Laryngeal cancer	1) GLUT1 mRNA and protein levels positively correlate with tumor grade.
Bone cancer	1) GLUT1 is overexpressed in osteosarcoma cells and its level is significantly associated with tumor node metastasis.
Multiple myeloma	1) Overexpression of GLUT1, GLUT4, GLUT8, and GLUT11 is observed in cancer cell lines; 2) GLUT3 is downregulated in these cancer cell lines.
Lymphomas	1) GLUT1 is not detected in cancer cells; 2) Level of GLUT3 is higher in non-Hodgkin's lymphoma than in normal cells; 3) GLUT4 is overexpressed in chronic lymphoblastic leukemia in comparison with normal B-cells.

In PanIN, the level of GLUT1 expression depends on the stage of neoplasia: while it is not observed in PanIN-1A, all samples, its expression is significantly higher in stage PanIN-3. A similar trend is observed in IPMNs and PDAC, where GLUT1 expression is correlated with histological grade and tumor size of PDAC. Significant expression of GLUT1 is observed in 100% of serous cystadenomas.[39]

GLUT1 expression is also correlated with survival among patients with pancreatic tumors,[49,50] and its overexpression is associated with poorly-differentiated tumors, positive lymph node metastasis, and larger tumor size. Therefore, GLUT1 may be a prognostic biomarker and potential therapeutic target for pancreatic cancer.[46,51-54] In addition, in patients undergoing pancreaticoduodenectomy for PDAC, GLUT1 may also be a predictor of worse prognosis in pancreatic adenocarcinoma, and is indicative of higher aggressiveness in PDAC.[50] GLUT1 overexpression is also detected in pancreatic NETs, including mixed adenoneuroendocrine carcinoma.[40,44,55] GLUT1 expression has been found to correlate with pancreatic cancer invasiveness in experiments with human pancreatic cell lines[56] and in human studies.[40]

GLUT2 is predominantly expressed in pancreatic islet cells. However, its expression in pancreatic cancers remains a point of controversy. GLUT2 protein and mRNA levels were found to be downregulated in NETs, [32] and that the number of positive cases depended on tumor stage.[55] Elsewhere GLUT2 expression was noted in 46% of tested malignant tumors, with no such expression observed in benign tumors.[57] GLUT2 expression was also observed in 75% of human PanIN cases, with very extensive expression observed in samples of grade 1B and higher.[58] Overexpression was also reported in liver metastases, but not those of other organs.[47]

Interestingly, while malignant and benign pancreatic tumors were found to be negative for GLUT3 based on immunohistochemical testing,[57] GLUT3 mRNA was found in all positive samples by Northern blot and reverse transcriptase polymerase chain reaction (PCR).[59] GLUT4 expression was detected only in 36% of malignant pancreatic tumors, and not in any tested benign tumors,[57] and was found to be reduced in pancreatic tumor patients.[60] In addition, while normal GLUT4 protein and mRNA levels were observed in pancreatic cancer patients and healthy subjects,[61] high expression of GLUT4 was detected in muscle metastatic lesions.[47] Finally, GLUT5 was detected in 46% of malignant pancreatic tumors and in 50% of benign tumors.[57]

Pancreatic adenocarcinomas are also known to express SGLT1, which is restricted to the nuclei of malignant cells, and SGLT2, which is detected in the cytoplasm. SGLT2 is responsible for the accumulation of the tracer Me4FDG, which is specific for SGLT; as such, it may be a therapeutic target in anticancer therapy.[62] Furthermore, as SGLT1 expression is correlated with Bcl-2 expression, the two may serve as prognostic biomarkers of pancreatic cancers.[63] Another study revealed a strong correlation between the SGLT1, Bcl-2 and p53 expression, and found that SGLT1 overexpression in primary pancreatic cancer is correlated with disease-free survival.[64]

Gastric cancer

In cases of gastric cancer, GLUT1 expression varies between cancer type, tumor stage and state of nodal metastasis. A relationship may exist between GLUT1 expression and the intestinal type of gastric cancer, as expression was detected in 33.3% of patients with intestinal type carcinoma, but not in normal gastric tissue or in early gastric carcinoma.[65] In another study, GLUT1 expression was observed in 10% of patients with gastric carcinoma.[28] Elsewhere, GLUT1 was detected in 29.5% of gastric carcinoma, but not in tubular gastric adenomas.[66]

In gastric cancer, GLUT1 expression is detected in late carcinogenesis, and increases with disease progression. Its expression depends also on the stage of carcinoma, as well as its depth and type of invasion, be it lymphatic or venous invasion, lymph node or hepatic metastasis. Patients with gastric carcinoma who demonstrate GLUT1 expression also have significantly shorter survival than those in whom GLUT1 is not expressed.[66] In gastric adenocarcinoma patients, GLUT1-positive patients demonstrate a significant decrease in survival compared to GLUT1-negative patients.[67] While GLUT1 mRNA is not detected in the normal gastric mucosa, it is detected in 95% of patients with gastric carcinomas.[68]

GLUT2 is overexpressed in gastric carcinomas, and is associated with metastasis and poor prognosis of gastric cancer. In one study, GLUT2 mRNA was found to be present in all samples of gastric carcinoma, but in 80% of normal gastric mucosa samples.[68] GLUT3 protein and its mRNA also are overexpressed in gastric tumors, but no data exists regarding the relationship between GLUT3 expression and the metastasis and prognosis of gastric cancer.[68] Finally, while GLUT4 is expressed in gastric carcinomas, the correlation between expression and metastasis and/or prognosis of cancer has not yet been described.[69]

Colorectal cancer or bowel cancer

GLUT1 mRNA was detected in the cellular membranes from all investigated samples of colon muscle cancer, but not in normal colon muscle.[70] GLUT1 was also found in 70% of specimens taken from patients with rectal carcinoma who underwent preoperative and postoperative radiotherapy/chemoradiotherapy, and the level of expression was correlated with cancer stage.[71] In these patients, a high level of GLUT1 expression is significantly correlated with overall survival (OS)[71] and with high postoperative stage, as well as the presence of lymph node metastasis and distant recurrence.[72] Therefore, the level of GLUT1 expression may be a prognostic marker in rectal carcinoma.[71,72]

In patients with colon cancer, GLUT1 is primarily expressed in the peri-necrotic regions,[73] and is observed in peri-necrotic and peri-ulcerative regions of rectal carcinoma. In addition, its expression at the deepest site of cancer invasion is associated with poorer prognosis.[74] GLUT1 expression is also correlated with tumor progression and poorer prognosis in colon cancer;[75] indeed, patients with high GLUT1 expression demonstrate a 2.3-times higher risk of death due to colon carcinoma than those with low expression.[76] High levels of GLUT1 are observed more frequently in colorectal cancer (CRC) than in adenomas.[77]

While similar amounts of GLUT2 mRNA have been observed in normal mucosa and colon cancer samples,[70] other studies have indicated elevated GLUT2 expression in CRCs compared to healthy controls.[32] No differences in GLUT3 protein and mRNA expression have been noted between normal colon cells and colon cancer cells.[70] However, the data regarding GLUT4 is ambiguous: one study did not detect GLUT4 mRNA in normal mucosa or colon cancer samples,[70] while another reported GLUT4 overexpression in colon adenocarcinoma and colon cancer tissue.[32] Finally, GLUT5 expression may be a good marker of malignancy or high proliferation rate, as indicated by studies on intestinal Caco-2 cells.[78]

SGLT1 is overexpressed in colorectal cancer, and SGLT1 expression has been reported to be positively correlated with clinical stage and prognosis, particularly at the higher clinical stage. No expression is observed in normal tissue.[79] SGLT1 expression was also detected in CRC cell lines.[80]

Cancers of the human urogenital system

Kidney cancer

Renal cell carcinoma (RCC) has several subtypes, including clear cell RCC (ccRCC), papillary RCC, chromophobe RCC, oncocystoma, and collecting duct carcinoma. Recently, this list was supplemented with rare subtypes to form the Vancouver classification: translocation-linked, mucinous tubular, spindle-type RCC, and tubule-cyst carcinoma.[81,82] Another RCC classification comprises the following types: sporadic, nonfamilial kidney cancer, clear cell kidney cancer, type 1 papillary kidney cancer, type 2 papillary kidney cancer (it includes collecting duct carcinoma, and medullary RCC), the microphthalmia-associated transcription (MiT), family translocation RCC (tRCC), chromophobe kidney cancer, and oncocytoma.[83] The inherited forms include von Hippel-Lindau (VHL), heredity papillary renal carcinoma (HPRC), Birt-Hogg-Dubé (BHD), hereditary leiomyomatosis RCC (HLRCC), succinate dehydrogenase kidney cancer (SHD-RCC), tuberous sclerosis complex (TSC), and Cowden's disease.[83,84]

The expression of glucose transporters depends on the type of RCC and type of glucose transporter.[85,86] It is possible that the SLC2A1 gene influences the development of ccRCC, as indicated by the effect of an SNP in the gene.[87] CcRCC demonstrated higher GLUT1 expression in comparison with chromophobe RCC, papillary RCC, and normal kidney tissue.[63] In normal kidney tissue, GLUT1 is primarily expressed in the cytoplasm; in contrast, 86.2% of patients with ccRCC demonstrated membranous expression as did 100% of those with transitional cell carcinomas. However, no such expression was detected in other subtypes. Cytoplasmic expression of GLUT1 was detected in 55.2% of the patients with ccRCC, 38% of patients with papillary RCC, 13% of patients with chromophobe RCC, 22% of patients with oncocytomas, and in 82% of patients with transitional cell carcinoma.[88] In 72.7% of ccRCC patients, the expression of GLUT1 was increased 12.7±2.2-fold.[89] Lower GLUT1 expression has been observed in CD8+ cells,[90] while positive correlations have been noted between GLUT1 and HIF-1α (hypoxia-inducible factor-1α),[91] and between GLUT1 levels and expression of the *VHL* gene, which codes the von Hippel-Lindau tumor suppressor protein (pVHL),[92] which is a regulator of HIF. The relationship between GLUT1 level and renal cell carcinoma is an ambiguous one, and it appears to be an unlikely prognostic marker for RCC; however, it may be a target for anticancer therapy in most ccRCC.[88]

GLUT2 is downregulated in ccRCC,[93] and was found to be decreased around nine-fold in tested samples.[89,92] However, while downregulation is observed in chromophobe RCC, no change of expression was observed in oncocytoma RCC.[93] GLUT3 mRNA expression was 8-fold higher in patients with RCC[89] and GLUT3 protein expression was elevated in 36.6% of the RCC samples.[91] In contrast, GLUT4 was downregulated in ccRCC patients and upregulated in chromophobe RCC patients;[93] however, GLUT4 overexpression was observed only in patients with stage 4 of RCC.[91] GLUT5 expression was elevated in patients with ccRCC, particularly in patients with the chromophobe and papillary subtypes,[91] it was lowered in patients with ccRCC, and was unchanged from normal kidney levels in samples of oncocytoma RCC.[93] In addition, increased GLUT5 expression was noted in patients with pelvic invasion and capsule breakage during diagnosis. As its expression is correlated with grade II differentiation and aggressiveness, it may play a role in the development of RCC.[91] GLUT9 and GLUT12 are downregulated in ccRCC patients.[93]

Bladder cancer

GLUT1 is not expressed in normal bladder urothelium tissue or in benign bladder papillomas.[94,95] Urothelial papilloma of the bladder has low malignancy potential. While GLUT1 expression is selective in urothelial tissue, it is unspecific in neoplastic urothelial tissue.[96] In bladder cancer (BC), its level of expression is correlated with progression.[94,96] Its expression also correlates with malignancy potential in non-invasive urothelial carcinomas,[97] and may serve as a prognostic marker in BC, with overexpression significantly correlating with worse overall survival.[94,98,99] In superficial bladder transitional cell carcinoma, no correlation is seen between GLUT1 expression and recurrence rate.[96] GLUT1 may be a helpful marker for differentiating between benign urothelial lesions and the rare, but aggressive, nested urothelial carcinoma variant.[100]

Otherwise, GLUT3 demonstrated stronger cytoplasmic expression in advanced bladder cancers than those in earlier stages.[101] Expression of GLUT3 mRNA significantly correlates with disease survival, and a high level predicts poor prognosis in human bladder urothelial carcinoma. Its expression is also significantly correlated with the epithelial-mesenchymal transition of cancer cells in urothelial cancer.[101]

Prostate cancer

Prostate cancer (PCa) develops in two different regions of the gland: in the peripheral zone (80% of cases), and in periurethral region (20% of cases).[102] The expression of GLUT proteins depends on the stage of PCa.[103] While GLUT1 is localized to the basolateral membrane of the secretory epithelial cells in benign prostate tissue, it is undetectable immunohistochemically in high-grade prostatic intraepithelial neoplasia (HGPIN) and in PCa; however, overexpression has been noted in some specimens of highly-proliferative intraductal PCa.[104,105] GLUT1 expression also increases with malignancy grade. Its expression increases significantly in moderately- to poorly-differentiated PCa, while it is just above the detection limit in primary well-differentiated PCa.[106] The cytoplasmic localization of GLUT1 may be used as a prognostic marker in prostate cancer.[107]

GLUT3 and GLUT5 are expressed in the normal prostate gland, but not in prostate carcinoma.[32] GLUT5 expression was detected in high-grade prostatic intraepithelial neoplasia, but not in PCa samples.[104] Fructose may be a source of energy for HGPIN, but not for PCa. GLUT4 is not detected in human cancer biopsies;[32] however, its cytoplasmic expression has been observed in PCa cell lines.[108] GLUT7 mRNA is more highly expressed in benign tissue than in PCa, while GLUT9 expression is decreased in benign prostatic hyperplasia (BPH), prostatis and high-grade PCa.[109] In one study, GLUT9 mRNA levels were generally reduced in PCa compared to benign tissue; however, the opposite was observed in one specimen.[104] GLUT11 mRNA is more strongly expressed in PCa specimens as compared to benign prostate cancer.[104] GLUT12 mRNA is detected in the normal prostate gland, whereas GLUT12 protein is not; this protein is detected in several cell lines,[110] with immunohistochemical staining confirming GLUT12 expression in malignant prostate tissue, but not in benign prostatic hyperplasia.[110]

SGLT1 is weakly, but exclusively, expressed in the epithelium of normal prostate tissue.[111] PCa cells demonstrated a strong positive reaction for SGLT1. Increased levels of SGLT1 were detected in the basal and stromal cells of benign prostatic hyperplasia and in the epithelial cells of prostatic intraepithelial neoplasia. In the cells of low-grade cancers, it is localized to the cytoplasm and the plasma membrane, whereas in high-grade cancers, its expression is detected in the nuclear envelope.[111] SGLT2 is expressed in prostate adenocarcinoma but not in the normal prostate gland.[62] SGLT2

may be involved in the growth of PCa and affects survival of patients.[62]

Cancers of the uterus

All samples of squamous cell carcinoma (SCC) are positive for GLUT1, its expression is higher as compared to healthy controls.[112] GLUT1 expression has also been found to correlate with histological grade, progressing from normal or dysplastic lesions to invasive cancer. GLUT1 expression was absent or weakly positive in normal cervical squamous epithelium, in 100% of low-grade cervical intraepithelial neoplasia and in 73% of high-grade cervical intraepithelial neoplasia. Moderate to strong staining for GLUT1 was observed in 68% of samples of primary squamous cervical cancers.[112] Its expression is also correlated with radiation resistance and poor prognosis in cervical SCC.[113]

CD147 (extracellular matrix metalloproteinase inducer, basigin, and neurotelin) plays an important role in processes involved with tumor progression, such as invasiveness, metastasis, proliferation and angiogenesis. Patients with higher expression of CD147 and GLUT1 show greater resistance to radiotherapy and shorter progression-free survival than those with lower expression.[113] GLUT1 expression is also correlated with metastasis-free survival in advanced carcinoma of the cervix. Increased GLUT1 immunostaining intensity is associated with decreased disease-free survival and decreased metastasis-free survival.[114] GLUT1 expression is also correlated with neoplastic progression of endometrial carcinoma.[115]

Significant correlations were also observed between strong staining of GLUT1 in malignant epithelial cells and tumor stage, and between high GLUT1 staining score and location of expression in the transformed epithelium: all investigated samples (100%) with cytoplasmic and membranous expression showed high GLUT1 staining scores. GLUT1-positive endometroid adenocarcinoma patients demonstrate considerably healthier survival estimates with low grades, low stage and no recurrence. Immunohistochemical staining for GLUT1 may therefore be used to support prognoses and survival estimates.[116]

Ishikawa endometrial cancer cells demonstrate GLUT1-GLUT4, but no information exists on the relationship between their levels of expression, and cancer progression. Among 40 genes believed to be associated with endometrial cancer, SLC2A6, coding for GLUT6, was the most highly expressed.[117]

Ovarian cancer

A previous study found normal human ovarian epithelial cells to be negative or weakly positive for GLUT1, whereas, samples of the epithelial ovarian cancers were positive in 98.8% of cases.[118] GLUT1 expression is significantly correlated with tumor grade; immunostaining for GLUT1 is significantly stronger in borderline neoplasms and carcinomas than in borderline tumors. GLUT1 expression also increases from borderline tumors to high-grade carcinomas. In addition, significantly stronger immunostaining is detected in the serous tumors than in the mucinous or other histologic subtypes, such as endometrioid, clear cell, and transitional cells.[118,119]

Patients positive for GLUT1 are more likely to demonstrate complete responses to chemotherapy than those who are negative or weakly positive for GLUT1. However, GLUT1 overexpression in patients with stage III-IV ovarian carcinoma is associated with shorter disease-free survival.[119] GLUT1 expression increases from the benign serous cystadenomas, through borderline cystadenomas, to cystadenocarcinomas.[120] While it is undetectable in the benign ovarian surface epithelium and in ovarian cystadenomas, it is present in 95% of ovarian adenocarcinoma samples. In addition, GLUT1 is present in primary borderline ovarian tumors, and in invasive borderline tumors, but not in noninvasive borderline tumors.[121] GLUT1 also demonstrates more extensive immunostaining in primary ovarian adenocarcinomas than in primary fallopian tube cancers.[122]

Patients with advanced stage cancer, in which GLUT1 is overexpressed, have less chance for optimal cytoreduction,[123] and GLUT1 overexpression has been found to predict poor prognosis in EOC;[124] however, GLUT1 inhibition may be used for the treatment of ovarian cancer.[125] Other GLUTs have been detected by immunostaining in all types of ovarian lesions, borderline tumors, and invasive ovarian cancer tissues, at similar intensities. No GLUT2 or GLUT4 expression was detected in malignant or benign tumors.[126] GLUT3 has not been detected in the normal ovarian tissue, but high immunostaining was reported in ovarian cancer. Again, GLUT4 expression is unclear: while it was not detected in the normal or malignant tumors in one study, it was identified in 84% of ovarian tumor cells elsewhere.[127]

SGLT1 expression is elevated in ovarian cancer,[128] and this level correlates positively with tumor grade and negatively with prognosis. In one study, no expression was reported in normal ovarian tissues, but was noted in 39.7% of invasive carcinomas. SGLT1 expression correlates with tumor aggressiveness.[128]

Lung cancers

Approximately 85% of diagnosed lung cancer is non-small cell lung cancer (NSCLC).[129] In one study, all samples obtained from NSCLC patients were GLUT1-positive; the same result was observed in samples of adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma.[130] Although the highest expression was detected in the cell membrane, GLUT1-positive granules were also observed in the cytoplasm of adenocarcinomas and large cell carcinomas. GLUT1 was found to demonstrate significantly higher expression than transporters GLUT2-GLUT5.[130] GLUT1 expression has been found to be significantly correlated with ^{18}F-FDG uptake and tumor size.

GLUT2 showed diffuse staining in the cytoplasm of SCC cells, whereas neither GLUT3 nor GLUT5 were detected. GLUT4 was expressed in cancer cells; however, its level of expression was found to be much lower than that of GLUT1.[130] Interestingly, contradictory results were obtained in another study:[131] GLUT1 expression was observed in 83% of adenocarcinoma and SCC samples, whereas GLUT3 was detected in 97%. No significant differences were found between individual patients regarding the immunostaining intensity. GLUT1 expression was lower in adenocarcinoma than in SCC; however, no differences between subtypes were detected for GLUT3. In adenocarcinoma, GLUT1 and GLUT3 expression correlate with maximum standardized uptake value (SUV max), but no such correlation was observed for SCC. Neither GLUT1 or GLUT3 expression was correlated with tumor size or ^{18}F-FDG uptake.[131]

RNA-seq and FDG of lung squamous cell carcinoma (LUSC) from patients who underwent surgical resection in correlation to glucose transporters by RNA-seq and immune cell enrichment score (ImmuneScore).[132] The ImmuneScore was negatively correlated with GLUT1 and positively with GLUT3. The single cell RNA-seq analysis found that GLUT1 was mostly expressed in cancer cells and GLUT3 in immune cells. Positive correlations were found between FDG uptake and GLUT1 expression in immune-poor lung squamous cell carcinoma, and between FDG uptake and GLUT3 expression in immune-rich LUSC.[132] In the tumor microenvironment, cancer cells and immune cells compete for uptake of glucose, and this may be associated with the differential expression of glucose transporters between the cells.

The results on the prognostic role of GLUT1 are ambiguous. Some suggested that it may be a prognostic factor for poor survival,[133,134] which correlates with an aggressive phenotype of lung carcinoma,[135] whereas others indicate no significant correlation between GLUT1 expression and OS in non-small cell lung cancer.[136] However, a correlation was observed between expression and SUV max value in NSCLC patients in all investigated tumor-cell types (SCC, adenocarcinoma, SCC, and large cell carcinoma).[137] GLUT1 expression was also found to correlate with ^{18}F-FDG uptake by malignant lymph nodes in NSCLC, but not in benign nodes in lymphoid hyperplasia.[138] Other investigations of NSCLC patients indicate an association between GLUT1 overexpression, poor overall survival and disease-free survival. GLUT1 appears to promote a malignant phenotype in NSCLC[139] and upregulation of GLUT1 was also correlated with sex, advanced tumor stage, histology, and large tumor size.[140]

GLUT1, GLUT3 and GLUT4 may be targets for the treatment of NSCLC [141,142] and other lung cancers.[143] Some studies indicate the expression of GLUT2-GLUT5 in histological subtypes such as adenocarcinoma, small-cell carcinoma and large cell carcinoma.[144] These observations have been confirmed on cancer cell lines.[86,145,146]

A distinct subtype of pulmonary neoplasms are neuroendocrine carcinomas of the lung, *i.e.* typical carcinoids, atypical carcinoids, large cell neuroendocrine carcinomas, and small-cell carcinomas.[147,148] Among patients with limited-disease small-cell lung cancer, a higher percentage of GLUT1-positive tumor cells was associated with better tumor response to chemoradiation therapy; however, the researchers suggest that may be due to the influence of GLUT1 on metabolic activity.[149] GLUT1 expression depends also on the subtype of neuroendocrine carcinoma. It has been proposed that its expression is correlated with neuroendocrine differentiation and tumor type, but not with tumor size and stage. GLUT1 expression also appears to strongly correlate with the risk of death due to neuroendocrine carcinomas.[147] A correlation has also been noted between ^{18}F-FDG uptake and GLUT1 expression in neuroendocrine tumors of the lung.[148] Small-cell lung cancer cells demonstrate higher expression of GLUT1 than GLUT3 and GLUT4.[150]

Lung cancer cells have been found to overexpress SGLT1;[151] however, in another study, SGLT1 and SGLT2 expression was unchanged in lung cancer cells compared to healthy controls.[152] Investigations of early-stage lung adenocarcinoma, a subtype of NSCLC, indicated, that SGLT2 may be used as diagnostic marker and therapeutic target for this form of lung cancer.[153] More precise investigations of metastatic lesions from the liver and lymph nodes revealed significantly higher expression of SGLT2 in metastatic areas in comparison with primary tumors, whereas the expression of SGLT1 was not changed.[152] NIS expression was also detected in 66% of the lung carcinoma samples,[154] but not in healthy human lungs.

Other glucose transporter expression profiles have also been reported for cancers of other organs and tissues, such as breast,[155] brain,[156] endocrine glands,[157,158] and bones,[159] as well as cancers of the human head and neck,[160] blood cells and lymphoid tissues.[161] These are given in more detail in Table 1 and Szablewski, 2019.[86]

Cancer cells favor glycolysis as a means of energy generation, even in the presence of oxygen. As this process generates fewer molecules of ATP in comparison to complete oxidative breakdown of glucose, cancer cells need more molecules of glucose than normal cells. This increase is facilitated by changes in the expression of glucose transporters: increased levels of glucose transporters and/or their mRNA, especially GLUT1, have been reported in cancer cells, as well as other glucose transporters, such as GLUT3 and NIS. In addition, some glucose transporters demonstrate lower expression in cancer cells. As such, the immunostaining intensity profiles of glucose transporters may be used to characterize the development, stage and type of cancer. In many cancers, the overexpression of GLUT1 or GLUT3 may be treated as a marker of stage of carcinogenesis, aggressiveness of cancer, prognosis, and OS for patients. It has also been proposed that glucose transporters may be targets for anticancer therapy.

References

1. Saier MH Jr. Families of transmembrane sugar transport proteins. Mol Microbiol 2000;35:699-710.
2. Wright EM. Glucose transport families SLC5 and SLC50. Mol Asp Med 2013;34:183-96.
3. Mueckler M, Thorens B. The SLC2 (GLUT) family of membrane transporters. Mol Asp Med 2013;34:121-38.
4. Szablewski L. Expression of glucose transporters in health. In: Human glucose transporters in health and diseases, L. Szablewski (Ed.), Cambridge Scholars Publ. 2019:5-61.
5. Uldry M, Ibberson M, Horisberger J-D, et al. Identification of a mammalian H^+-myo-inositol symporter expressed predominantly in the brain. EMBO 2001;20:4467-77.
6. Deng D, Yan N. GLUT, SGLT, and SWEET: structure and mechanistic investigations of the glucose transporters. Prot Sci 2016;25:546-58.
7. Wright EM. Renal Na^+/glucose cotransporters. Am J Physiol 2001;280:F10-F8.
8. Wright EM, Turk E. The sodium/glucose cotransport family SLC5. Pflügers Arch – Eur J Physiol 2004;447:510-8.
9. Turk E, Wright EM. Membrane topology motifs in the SGLT cotransporter family. J Membr Biol 1997;159:1-20.
10. Bianchi L, Diez-Sampedro A. A single amino acid change converts the sugar sensor SGLT3 into a sugar transporter. PLoS ONE 2010;5:e10241.
11. Warburg O. The chemical constitution of respiratory ferment. Science. 1928:68;437-443.
12. Warburg, O. On the origin of cancer cells. Science 1956;123:309-14.
13. Vander Heiden MG, DeBerardinis RJ. Understanding the intersections between metabolism and cancer biology. Cell 2017;168:657-69.
14. Fan C, Tang Y, Xiong F, et al. Role of long non-coding RNAs in glucose metabolism in cancer. Mol Canc 2017;16:130.
15. Cairns RA, Kalliomaki T, Hill RP. Acute (cyclic) hypoxia enhances spontaneous metastasis of KHT murine tumors. Canc Res 2001;61:8903-8.
16. Barron CC, Bilan PJ, Tsakiridis T, Tsiani E. Facilitative glucose transporters: Implications for cancer detection, prognosis and treatment. Metabolism 2016;65:124-39.
17. Szablewski L. Expression of glucose transporters in cancers. Biochim Biophys Acta Rev Canc 2013;1835:164-9.
18. Nowak N, Kulma A, Gutowicz J. Up-regulation of key glycolysis proteins in cancer development. Open Life Sci 2018;13:569-81.
19. Zhao ZX, Lu LW, Qiu J, et al. Glucose transporter-1 as an independent prognostic marker for cancer: A meta-analysis. Oncotarget 2018;9:2728-38.
20. Pliszka M, Szablewski L. Glucose transporters as a target for anticancer therapy. Cancers 2021;13:4184.
21. Airley RE, Mobasheri A. Hypoxic regulation of glucose transport anaerobic metabolism and angiogenesis in cancer: novel pathways and targets for anticancer therapeutics.

Chemotherapy 2007;53:233-56.
22. Mano Y, Aishima S, Kubo Y, et al. Correlation between biological marker expression and fluorine-18 fluorodeoxyglucose uptake in hepatocellular carcinoma. Am J Clin Pathol 2014;142:391-7.
23. Mohd Abdul Rashid MB, Toh TB, Silva A, et al. Identification and optimization of combinatorial glucose metabolism inhibitors in hepatocellular carcinomas. J Lab Autom 2015;20:423-37.
24. Amann T, Maegdefrau U, Hartmann A, et al. GLUT1 expression is increased in hepatocellularly carcinoma and promotes tumorigenesis. Am J Pathol 2009;174:1544-52.
25. Daskalow K, Pfander D, Weichert W, et al. Distinct temporospatial expression patterns of glycolysis-related proteins in human hepatocellular carcinoma. Histochem Cell Biol 2009;132:21-31.
26. Roh MS, Jeong JS, Kim YH, et al. Diagnostic utility of GLUT1 in the differential diagnosis of liver carcinoma. Hepatogastroenterology 2004;51:1315-8.
27. Kurata T, Oguri T, Isobe T, et al. Differential expression of facilitative glucose transporter (GLUT) genes in primary lung cancers and their liver metastases. Jpn J Canc Res 1999;90:1238-43.
28. Carvalho KC, Cunha IW, Roch RM, et al. GLUT1 expression in malignant tumors and its use as an immunodiagnostic marker. Clinics 2011;66:965-72.
29. Paudyal B, Paudyal P, Oriuchi N, et al. Clinical implication of glucose transport and metabolism evaluated by 18F-FDG PET in hepatocellular carcinoma. Int J Oncol 2008;33:1047-54.
30. Grobholz R, Hacker HJ, Thorens B, Bannasch P. Reduction in the expression of glucose transporter protein GLUT2 in preneoplastic and neoplastic hepatic lesions and reexpression of GLUT1 in late stages of hepatocarcinogenesis. Canc Res 1993;53:4204-11.
31. Ebert BL, Gleadle JM, O'Rourke JF, et al. Isoenzyme-specific regulation of genes involved in energy metabolism by hypoxia: similarity with the regulation of erythropoietin. Biochem J 1996;313:809-14.
32. Godoy A, Ulloa V, Rodŕiquez F, et al. Differential subcellular distribution of glucose transporters GLUT1-6 and GLUT9 in human cancer: ultrastructural localization of GLUT1 and GLUT5 in breast tumor tissues. J Cell Physiol 2006;207:614-27.
33. Kayano T, Burant CF, Fukumoto H, et al. Human facilitative glucose transporters. Isolation, functional characterization, and gene localization of cDNA encoding an isoform (GLUT5) expressed in small intestine, kidney, muscle, and adipose tissue an unusual glucose transporter pseudogene-like sequence (GLUT6). J Biol Chem 1990;265:13276-82.
34. Lei S, Yang J, Chen C, et al. $FLIP_L$ is critical for aerobic glycolysis in hepatocellular carcinoma. J Exp Clin Canc Res 2016;35:79.
35. Kim, Y.W.; Park, Y.K.; Yoon, T.; Lee, S.M. Expression of GLUT-1 glucose transporter in gallbladder carcinoma. Hepato-Gastroenterology 2002;49:907-11.
36. Legan M, Tevzić S, Tolar A, et al. Glucose transporter-1 (GLUT-1) immunoreactivity in benign, premalignant and malignant lesions of the gallbladder. Pathol Oncol Res 2011;17:61-66.
37. Paudyal B, Oriuchi N, Paudyal P, et al. Expression of glucose transporters and hexokinase II in cholangiocellular carcinoma compared using [18F]-2fluoro-2-deoxy-D-glucose positron emission tomography. Canc Sci 2008;99:260-6.
38. Kubo Y, Aishima S, Tanaka Y, et al. Different expression of glucose transporters in the progression of intrahepatic cholangiocarcinoma. Hum Pathol 2014;45:1610-7.
39. Basturk IO, Singh R, Kaygusuz E, et al. GLUT-1 expression in pancreatic neoplasia: implications in pathogenesis, diagnosis, and prognosis. Pancreas 2011;40:187-92.
40. Sampedro-Núñez M, Bouthelier A, Serran-Somavilla A, et al. LAT-1 and GLUT-1 carrier expression and its prognostic value in gastroenteropancreatic neuroendocrine tumors. Cancers 2020;12:2968.
41. Low SK, Giannis D, Bahaie NS, et al. Competing mortality in patients with neuroendocrine tumors. Am J Clin Oncol 2019;42:668-74.
42. Pavel M, Oberg K, Falconi M, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMS Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annu Oncol 2020;31:844-60.
43. Chai SM, Brown IS, Kumarasinghe MP. Gastroenteropancreatic neuroendocrine neoplasms: Selected pathology review and molecular updates. Histopathology 2018;72:153-67.
44. Binderup T, Knigge UP, Federspiel B, et al. Gene expression of glucose transporter 1 (GLUT1), hexokinase 1 and hexokinase 2 in gastroentero-pancreatic neuroendocrine tumors: correlation with F-18-fluoro-deoxy-glucose positron emission tomography and cellular proliferation. Diagnostic 2013;3:372-84.
45. Panzuto F, Baoninsegna L, Fazio N, et al. Metastatic and locally advances pancreatic endocrine carcinomas: Analysis of factors associated with disease progression. J Clin Oncol 2011;29:2372-7.
46. Lu K, Yang J, Li D-C, et al. Expression of clinical significance of glucose transporter-1 in pancreatic cancer. Oncol Lett 2016;12:243-9.
47. Chaika N, Yu F, Purohit V, et al. Differential expression of metabolic genes in tumor and stromal components of primary and metastatic loci in pancreatic adenocarcinoma. PLOS ONE 2012;7:e32996.
48. Yang H-J, Xu W-J, Guan Y-H, et al. Expression of Glut-1 and HK-II in pancreatic cancer and their impact on prognosis and FDFG accumulation. Transl Oncol 2016;9:583-91.
49. Chikamoto A, Inoue R, Komohara Y, et al.; Preoperative high maximum standardized uptake value in association with glucose transporter 1 predicts poor prognosis in pancreatic cancer. Ann Surg Oncol 2017;24:2040-60.
50. Boira MA, Di Martino M, Gordillo C, et al. GLUT-1 as a predictor of worse prognosis in pancreatic adenocarcinoma: immunohistochemistry study showing the correlation between expression and survival. BMC Cancer 2020;20:909.
51. Chen X, Lu P, Zhou S, et al. Predicted value of glucose transporter-1 and glucose transporter-3 for survival of cancer patients: A meta-analysis. Oncotarget 2017;8:13206-13.
52. Yu M, Yongzhi H, Chen S, et al. The prognostic value of GLUT1 in cancers: a systematic review and meta-analysis. Oncotarget 2017;8:43356-67.
53. Pizzi S, Porzionato A, Pasquali C, et al. Glucose transporter-1 expression and prognostic significance in pancreatic carcinogenesis. Histol Histopathol 2009;24:175-85.
54. Kurahara H, Maemura K, Mataki, Y, et al. Significance of glucose transporter type 1 (GLUT-1) expression in the therapeutic strategy for pancreatic ductal adenocarcinoma. Ann Surg Oncol 2018;25:1432-9.
55. Fujino M, Aishima S, Shindo K, et al. Expression of glucose transporter-1 is correlated with hypoxia-inducible factor 1α and malignant potential in pancreatic neuroendocrine tumors.

Oncol Lett 2016;12:3337-43.
56. Ito H, Duxbury M, Zinner MJ, et al. Glucose transporter-1 gene expression is associated with pancreatic cancer invasiveness and MMP-2 activity. Surgery 2004;136:548-56.
57. Higashi T, Tamaki N, Honda T, et al. Expression of glucose transporters in human pancreatic tumors compared with increased FDG accumulation in PET study. J Nucl Med 1997;38:1337-44.
58. Fendrich V, Schneider R, Maitra A, et al. Detection of precursor lesions of pancreatic adenocarcinoma in PET-CT in a genetically engineered mouse model of pancreatic cancer. Neoplasia 2011;13:180-6.
59. Seino Y, Yamamoto T, Inoue K, et al. Abnormal facilitative glucose transporter gene expression in human islet cell tumors. J Clin Endocrinol Metab 1993;76:75-8.
60. Reske SN, Grillenberger KG, Glatting G, et al. Overexpression of glucose transporter 1 and increased FDG uptake in pancreatic carcinoma. J Nucl Med 1997;38:1344-8.
61. Liu J, Knezetic A, Strömmer L, et al. The intracellular mechanism of insulin resistance in pancreatic cancer patients. J Clin Endocrinol Metab 2000:85;1232-1238.
62. Scafoglio C, Hiaryama BA, Kepe V, et al. Functional expression of sodium-glucose transporters in cancer. PNAS 2015;112:E4111-E9.
63. Calco MB, Figurea A, Pulido EG, et al. Potential role of sugar transporters and their relationship with anticancer therapy. Int J Endocrinol 2010;205357.
64. Casneuf VF, Fonteyne P, Van Damme N, et al. Expression of SGLT1, Bcl-2 and p53 in primary pancreatic cancer related to survival. Canc Invest 2008;26:852-9.
65. Kim WS, Kim YY, Jang SJ, Jung MH. Glucose transporter 1 (GLUT1) expression is associated with intestinal type of gastric carcinoma. J Korean Med Sci 2000;15:420-4.
66. Kawamura T, Kusakabe T, Sugino T. Expression of glucose transporter-1 in human gastric carcinoma. Cancer 2001;92:634-41.
67. Zhou D, Jiang L, Jin L, et al. Glucose transporter-1 cooperating with AKT signaling promote gastric cancer progression. Canc Manag Res 2020;12:4151-60.
68. Noguchi Y, Marat D, Saito A, et al. Expression of facilitative glucose transporters in gastric tumors. Hepatogastroenterology 1999;46:2683-9.
69. Medina RA, Owen GI. Glucose transporters: expression, regulation and cancer. Biol Res 2002;72:113-7.
70. Noguchi Y, Okamoto T, Marat D, et al. Expression of facilitative glucose transporter 1 mRNA in colon cancer was not regulated by k-ras. Canc Lett 2000;154:137-42.
71. Cooper R, Sarioğlu S, Sökmen S, et al. Glucose transporter-1 (GLUT-1): a potential marker of prognosis in rectal carcinoma. Br J Canc 2003;89:870-6.
72. Saigusa S, Toiyama Y, Tanaka K, et al. Prognostic significance of glucose transporter-1 (GLUT1) gene expression in rectal cancer after preoperative chemoradiotherapy. Surg Today 2012;42:460-9.
73. Airley R, Evans A, Mobasheri A, Hewit SM. Glucose transporter Glut-1 is detectable in peri-necrotic regions in many tumor types but not normal tissues: Study using tissue microarrays. Ann Anat 2010;192:133-8.
74. Furudoi A, Tanaka S, Haruma K, et al. Clinical significance of human erythrocyte glucose transporter 1 expression at the deepest invasive site of advanced colorectal carcinoma. Oncology 2001;60:162-9.
75. Winiewicz A, Sulkowska M, Koda M, et al. Significant expression of GLUT-1, Bcl-XL, and Bax in colorectal cancer. Ann NY Acad Sci 2007;1095:53-61.
76. Haber RS, Rathan A, Weiser KR, et al. GLUT1 glucose transporter expression in colorectal carcinoma: a marker for poor prognosis. Cancer 1998;83:34-40.
77. De Wit M, Jimenez CR, Carvalho B, et al. Cell surface proteomics identifies glucose transporter type 1 and prion protein as candidate biomarkers for colorectal adenoma-to-carcinoma progression. Gut 2012;61:855-64.
78. Douard V, Ferraris RP. Regulation of the fructose transporter GLUT5 in health and disease. Am J Physiol Endocrinol 2008;295:E227-E37.
79. Bissonnette P, Gagné H, Coady MJ, et al. Kinetic separation and characterization of three sugar transport models in CaCo-2 cells. Am J Physiol 1996;270:G833-G43.
80. Guo GF, Cai YC, Zhang B, et al. Overexpressing of SGLT1 and EGFR in colorectal cancer showing a correlation with the prognosis. Med Oncol 2011;28:S197-S203.
81. Gnjidić M, Fucak IK. Renal cell carcinoma: molecular pathways and targeted therapy. Period Biol 2014;116:393-8.
82. Sringley JR, Delahunt B, Eble JN. The International Society of Urological Pathology (ISUP) Vancouver classification of renal neoplasia. Ann J Surg Pathol 2013;37:1469-89.
83. Linehan WM. Genetic basis of kidney cancer: Role of genomics for the development of disease-based therapeutics. Gen Res 2012;22:2089-100.
84. Inamura K. Translational renal cell carcinoma: an update on clinicopathological and molecular features. Cancer 2017;9:111.
85. Szablewski L. Distribution of glucose transporters in renal diseases. J Biomed Sci 2017;24:64.
86. Szablewski L. Expression of glucose transporters in diseases. In: Human glucose transporters in health and diseases. L. Szablewski (Ed.), Cambridge Scholars Publ 2019;63-227.
87. Page T, Hodgkinson AD, Ollerenshow M, et al. Glucose transporter polymorphisms are associated with clear-cell renal carcinoma. Canc Genet Cytogenet 2005;163:151-5.
88. Ozcan A, Shen SS, Zhai QJ, Truong LD. Expression of GLUT in primary renal tumors. Morphologic and biologic implications. Am J Clin Pathol 2007;128:245-54.
89. Soltysova A, Breza J, Takacova M, et al. Deregulation of energetic metabolism in the clear cell renal cell carcinoma: A multiple pathway profiling. Int J Oncol 2015;47:287-95.
90. Singer K, Kastenberger M, Gottfried E, et al. Warburg phenotype in renal cell carcinoma: a high expression of glucose transporter-1 (GLUT-1) correlates with low $CD8^+$ T-cell infiltration in the tumor. Int J Canc 2011;128:2085-95.
91. Aparicio LMA, Villaamil VM, Calvo MB, et al. Glucose transporter expression and the potential role of fructose in renal cell carcinoma: A correlation with pathological parameters. Mol Med Rep 2010;3:575-80.
92. Chan DA, Sutphin PD, Nguyen P, et al. Targeting GLUT1 and the Warburg effect in renal cell carcinoma by chemical synthetic lethality. Sci Transl Med 2011;3:94ra70.
93. Suganuma N, Segade F, Matsuzu K, Bowden DW. Differential expression of facilitative glucose transporters in normal and tumour kidney tissues. BJU Inter 2007;99:1143-9.
94. Massari F, Ciccarese C, Santoni M, et al. Metabolic phenotype of bladder cancer. Canc Treat Rev 2016;45:46-57.
95. Lee J-H, Kim Y-W, Chang S-G. Glucose transporter-1 expression in urothelial papilloma of the bladder. Urol Int 2005;74:268-71.
96. Chang S, Lee S, Lee C, et al. Expression of the human erythrocyte glucose transporter in transitional cell carcinoma of the bladder. Urology 2000;55:448-52.

97. Reis H, Tschirdewahn S, Szarvas T, et al. Expression of GLUT1 is associated with increasing grade of malignancy in non-invasive and invasive urothelial carcinomas of the bladder. Oncol Lett 2011;2:1149-53.
98. Wang J, Ye C, Chen C, et al. Glucose transporter GLUT1 expression and clinical outcome in solid tumors: a systematic review and meta-analysis. Oncotarget 2017;8:16886.
99. Zhao Z-X, Lu L-W, Qiu J, et al.Glucose transporter-1 as an independent prognostic marker for cancer: a meta-analysis. Oncotarget 2018;9:2728-38.
100. Boyaci C, Behzatoglu K. Diagnostic value of glucose transporter 1 (glut-1) expression in nested variant of urothelial carcinoma. Turk J Pathol 2018;1:2-7.
101. Ou Y-C, Tsai Y-S, Liv C-J, et al. Glucose transporter-3 expression predicts poor prognosis in human bladder urothelial carcinoma and is associated with epithelial mesenchymal transition. Eur Urol Suppl 2015;14/2:e233.
102. Mc Neal JE. Normal histology of the prostate. Am J Surg Pathol 1998;12:619-33.
103. Gonzalez-Menendez P, Hevia D, Mayo JC, Sainz RM. The dark side of glucose transporters in prostate cancer: Are they a new future to characterize carcinomas? Int J Canc 2018;42:2414-24.
104. Reinicke K, Sotomayor P, Cisterna P, et al. Cellular distribution of Glut-1 and Glut-5 in benign and malignant human prostate tissue. J Biol Biochem 2012;113:553-62.
105. Gasinska A, Jaszczyński J, Rychlik U, et al. Prognostic significance of serum PSA level and telomerase, VEGF and GLUT-1 protein expression for the biochemical recurrence in prostate cancer patients after radical prostatectomy. Pathol Oncol 2020;26:1049-56.
106. Effert P, Beniers AJ, Tamimi Y, et al. Expression of glucose transporter 1 (Glut-1) in cell lines and clinical specimens from human prostate adenocarcinoma. Anticanc Res 2004;24:3057-64.
107 Khandani AH, Funkhouser WK, Feins R, Socinski MA. Simultaneous FDG PET+/Glut1+ lung and FDG PET-/Glut1- subcranial lymph node metastases from prostate cancer. Ann Nucl Med 2009;23:595-7.
108. Gonzalez-Mendez P, Hevia D, Rodriquez-Garcia A, et al. Regulation of GLUT transporters by flavonoids in androgen-sensitive and –insensitive prostate cancer cells. Endocrinology 2014;155:3238-50.
109. Sangkop F, Singh G, Rodrigues E, et al. Changes in cellular uric acid homeostasis facilitated by Glucose Transporter (GLUT9) drive activing sensitivity and prostate cancer behavior. Physiol Proc Physiol Soc 2016;37:PCB129.
110. Chandler JD, Williams ED, Slavin JL, et al. Expression and localization of GLUT1 and GLUT12 in prostate carcinoma. Cancer 2003;97:2035-42.
111. Blessing A, Xu L, Gao G, et al. Sodium/glucose co-transporter 1 expression increases in human diseased prostate. J Canc Sci Ther 2012;4:306-12.
112. Mendez LE, Manci N, Cantuaria G, et al. Expression of glucose transporter-1 in cervical cancer and its precursors. Gynecol Oncol 2002;86:138-43.
113. Huang X-O, Chen X, Xie X-X, et al. Co-expression of CD147 and GLUT-1 induces radiation resistance and poor prognosis in cervical squamous cell carcinoma. Int J Clin Exp Pathol 2014;7:1651-66.
114. Airlay R, Lancaster J, Davidson S, et al. Glucose transporter Glut-1 expression correlates with tumor hypoxia and predicts metastasis-free survival in advanced carcinoma of the cervix. Clin Canc Res 2001;7:928-34.
115. Wang BY, Kalir T, Sabo E, et al. Immunohistochemical staining of GLUT-1 in benign, hyperplastic and malignant endometrial epithelia. Cancer 2000;88:2774-81.
116. Khabaz MN, Qureshi IA, Al-Magrabi JA. GLUT1 expression is a supportive mean in predicting prognosis and survival estimates of endometrial carcinoma. Ginekol Pol 2019;90:582-8.
117. Andrade J, Choi Y, Baker W, et al. Estrogens rapidly stimulate expression of GLUT6, a glucose transporter overexpressed in obesity-linked endometrial cancer. Endocrine Societ's 97th Ann Meet Expo San Diego. 2015;SAT-322.
118. Cantuaria G, Magalhaes A, Penalver M, et al. Expression of GLUT-1 glucose transporter in borderline and malignant tumors of the ovary. Gynecol Oncol 2000;79:33-7.
119. Cantuaria G, Fagotti A, Ferrandina G, et al. GLUT-1 expression in ovarian carcinoma. Association with survival and response to chemotherapy. Cancer 2001;92:1144-50.
120. Cai Y, Zhai J, Feng B, et al. Expression of glucose transporter protein 1 and p63 in serous ovarian tumor. J Obstet Gynecol Res 2014;40:1925-30.
121. Kalir T, Wang BY, Goldfischer M, et al. Immunohistochemical staining of GLUT1 in benign, borderline, and malignant ovarian epithelia. Cancer 2002;94:1078-82.
122. Kalir T, Rahaman J, Hagopian G, et al. Immunohistochemical detection of glucose transporter in benign and malignant fallopian tube epithelia, with comparison to ovarian carcinomas. Arch Pathol Lab Med 2005;129:651-4.
123. Semaan A, Munkarah AR, Arabi H, et al. Expression of GLUT1 in epithelial ovarian carcinoma: Correlation with tumor proliferation, angiogenesis, survival and ability to predict optimal cytoreduction. Gynecol Oncol 2011;121:181-6.
124. Cho H, Lee YS, Kim J, et al. Overexpression of glucose transporter-1 (GLUT-1) predicts poor prognosis in epithelial ovarian cancer. Canc Invest 2013;31:607-15.
125. Shin SJ, Kim JY, Kwon SY, et al. Ciglitazone enhances ovarian cancer cell death *via* inhibition of glucose transporter-1. Eur J Pharmacol 2014;743:17-23.
126. Rudlowski C, Moser M, Becker AJ, et al. GLUT1 mRNA and protein expression in ovarian borderline tumors and cancer. Oncology 2004;66:404-10.
127. Kellenberger LD, Bruin JE, Greenway J, et al. The role of dysregulated glucose metabolism in epithelial ovarian cancer. J Oncol 2010;514310.
128. Lai B, Xiao Y, Pu H, et al. Overexpression of SGLT1 is correlated with tumor development and poor prognosis of ovarian carcinoma. Arch Gynecol Obstet 2012;285:1455-61.
129. Molina JR, Yang P, Cassivi SD, et al. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc 2008;83:584-94.
130. Brown RS, Leung JY, Kison PV, et al. Glucose transporters and FDG uptake in untreated primary human non-small cell lung cancer. J Nucl Med 1999;40:556-65.
131. Choi WH, Yoo IR, O JH, et al. Is the Glut expression related to FDG uptake in PET/CT of non-small cell lung cancer patients? Technol Health Care 2015;23:S311-S8.
132. Na KJ, Choi H, Oh HR, et al. Reciprocal change in glucose metabolism of cancer and immune cells mediated by different glucose transporters predicts immunotherapy response. Theranostatics 2020;10:9579-90.
133. Minami JI, Saito Y, Immamura H, Okamura A. Prognostic significance of p53 VEGF and Glut-1 in resected stage 1 adenocarcinoma of the lung. Lung Canc 2002;38:51-7.
134. Zhang B, Xie Z, Li B. The clinicopathological impacts and prognostic significance of GLUT1 expression in patients with

lung cancer: A meta-analysis. Gene 2019;689:76-83.
135. Sasaki H, Shitara M, Yokota K, et al. Overexpression of GLUT1 correlates with *Kras* mutations in lung carcinomas. Mol Med Rep 2012;5:559-62.
136. Osugi J, Yamaura T, Muto S, et al. Prognostic impact of the combination of glucose transporter 1 and ATP citrate lyase in node-negative patients with non-small lung cancer. Lung Canc 2015;88:310-8.
137. Nguyen XC, Lee WW, Chung J-H, et al. FDG uptake, glucose transporter type 1, and Ki-67 expression in non-small-cell lung cancer: Correlations and prognostic values. Eur J Radiol 2007;62:214-9.
138. Chuang J-H, Lee WW, Park SY, et al. FDG uptake and glucose transporter type 1 expression in lymph nodes of non-small cell lung cancer. EJSO 2006;32:989-95.
139. Zhao H, Sun J, Shao J, et al. Glucose transporter 1 promotes the malignant phenotype of non-small cell lung cancer through integrin β1/Src/FAK signaling. J Canc 2019;10:4989-97.
140. Tan Z, Yang C, Zhang X, et al. Expression of glucose transporter 1 and prognostic in non-small cell lung cancer: a pooled analysis of 1665 patients. Oncotarget 2017;8:60954-61.
141. Masin M, Vazquez J, Rossi S, et al. GLUT3 is induced during epithelial-mesenchymal transition and promotes tumor cell proliferation in non-small cell lung cancer. Canc Metab 2014;2:11.
142. Tuccinardi T, Granchi C, Iegre J, et al. Oxime-based inhibitors of glucose transporter 1 (GLUT1) displaying antiproliferative effects in cancer cells. Bioorg Med Chem Let 2013;23:6923-7.
143. Granchi C, Qian Y, Lee HY, et al. Salicyloketoximes targeting glucose transporter 1 restrict energy supply to lung cancer cells. Chem Med Chem 2015;10:1892-900.
144. Ito T, Noguchi Y, Udaka N, et al. Glucose transporter expression in developing fetal lungs and lung neoplasma. Histol Histopathol 1999;14:895-904.
145. Ito T, Noguchi Y, Satoh S, et al. Expression of facilitative glucose transporters isoforms in lung carcinomas: its relation to histologic type, differentiation grade and tumor stage. Mod Pathol 1998;11:437-443.
146. Barron C, Tsiani E, Tsakiridis T. Expression of glucose transporters GLUT1, GLUT3, GLUT4, and GLUT12 in human cancer cells. BMC Proc 2012;6:Suppl.3,P4.
147. Ozbudak IH, Shilo K, Tavora F, et al. Glucose transporter-1 in pulmonary neuroendocrine carcinomas: expression and survival analysis. Mod Pathol 2009;22:633-8.
148. Song YS, Lee WW, Chung J-H, et al. Correlation between FDG uptake and glucose transporter type 1 expression in neuroendocrine tumors of the lung. Lung Canc 2008;61:54-60.
149. Lee J, Kim JO, Jung CK, et al. Metabolic activity on [^{18}F]-fluorodeoxyglucose-positron emission tomography/computed tomography and glucose transporter-1 expression might predict clinical outcomes in patients with limited disease small-cell lung cancer who receive concurrent chemoradiation. Clin Lung Canc 2014;15:e13-21.
150. Pedersen MWB, Holm S, Lund EL, et al. Correlation of glucose uptake and vascular endothelial growth factor (VEGF) in two small-lung cancer (SCLC) sublines *in vivo* and *in vitro.* Neoplasia 2001;3:80-7.
151. Zhao P, Wang W, Yang L, Gaole A. The expression and regulation of glucose transporters in tumor cells. Adv Med Oncol Res 2016;2:6.
152. Ishikawa N, Oguri T, Isobe T, et al. SGLT gene expression in primary lung cancers and their metastatic lesions. Jap J Canc Res 2001;92:874-9.
153. Scafoglio CR, Villegas B, Abdelhady G, et al. Sodium-glucose transporter 2 is a diagnostic and therapeutic target for early-stage lung adenocarcinoma. Sci Transl Med 2018;10:eaat5933.
154. Wapnir IL, Van de Rijn M, Nowels K, et al. Immunohistochemical profile of the sodium/iodide symporter in thyroid, breast, and other carcinomas using high density tissue microarrays and conventional sections. J Clin Endocrinol Metab 2003;88:1880-8.
155. Mo L, Chen Q, Yang Y, et al. High expression of GLUT1 and GLUT3 correlate with neoadjuvant chemotherapy infectiveness breast cancer patients. Int J Clin Path 2016;9:9555-6.
156. Zheng C, Yang K, Zhang M, et al. Specific protein 1 depletion attenuates glucose uptake and proliferation of human glioma cells by regulating GLUT3 expression. Oncol Lett 2016;12:125-31.
157. Coelho RG, Fortunato RS, Carvalho DP. Metabolic reprogramming in thyroid carcinoma. Front Oncol 2018;8:82.
158. Chai YJ, Wook J, Oh SW, et al. Upregulation of *SLC2* (GLUT) family genes is related to poor survival outcomes in papillary thyroid carcinoma: Analysis of data from The Center Genome Atlas. Surgery 2017;161:188-94.
159. Fan J, Mei J, Zhang M-Z, et al. Clinicopathological significance of glucose transporter protein-1 overexpression in human osteosarcoma. Oncol Lett 2017;14:2439-45.
160. Bandyopadhyay A, Panda A, Behura A, et al. Glucose transporter 1 expression in odontogenic keratynocyst, dentigerous cyst, and ameloblastoma. An immunohistochemical study. J Contemp Dent Pract 2017;18:366-70.
161. Liu T, Kishton RJ, Macintyre AN, et al. Glucose transporter 1-mediated glucose uptake is limiting for B-cell acute lymphoblastic leukemia anabolic metabolism and resistance to apoptosis. Cell Death Dis 2014;5:e1516.