

Glucose transporters as markers of diagnosis and prognosis in cancer diseases

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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 over-expression 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 through.

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

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

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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 diseases¹⁹, 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 (¹⁸F-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 somatostatinoma⁴⁴ 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 1) Overexpression of GLUT1. Its expression increases from low-grade dysplasia toward carcinoma, and from benign toward malignant lesions.
Biliary intraepithelial neoplasia	<ol style="list-style-type: none"> 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 (BillN). Its expression with cholangiocarcinogenesis of the large bile duct, may be a marker for the presence of high-grade BillN lesions and atypical bile ducts. Expression of GLUT2 is correlated with early stage of carcinogenesis from high-grade neoplasia to invasive cholangiocarcinoma.
Pancreatic tumors	<ol style="list-style-type: none"> 1) The level of GLUT1 expression depends on the stage of neoplasia; in stage pancreatic intraepithelial neoplasms (PanIN)-IA 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 1) GLUT1 and GLUT3 are detected in the adrenocortical carcinoma samples but not in normal adrenal glands or adenomas.
Thymic carcinomas	<ol style="list-style-type: none"> 1) GLUT1 is upregulated and its overexpression depends on the subtype of thymic carcinoma.
Skin cancer	<ol style="list-style-type: none"> 1) GLUT1 is downregulated in nonmelanoma skin cancer; 2) In melanoma samples, expression of GLUT1 depends on the explants of melanoma.
Laryngeal cancer	<ol style="list-style-type: none"> 1) GLUT1 mRNA and protein levels positively correlate with tumor grade.
Bone cancer	<ol style="list-style-type: none"> 1) GLUT1 is overexpressed in osteosarcoma cells and its level is significantly associated with tumor node metastasis.
Multiple myeloma	<ol style="list-style-type: none"> 1) Overexpression of GLUT1, GLUT4, GLUT8, and GLUT11 is observed in cancer cell lines; 2) GLUT3 is downregulated in these cancer cell lines.
Lymphomas	<ol style="list-style-type: none"> 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 lines⁵⁶ 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, oncocytoma, 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-1 α (hypoxia-inducible factor-1 α),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 anti-cancer 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 RCC⁸⁹ 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), prostatitis 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 neuropilin) 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 endometrioid 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 ¹⁸F-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 ¹⁸F-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 ¹⁸F-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 NSCLC¹³⁹ 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 ¹⁸F-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 can-

cer 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.

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