Review Article

Glucose transporter 1 in health and disease

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Abstract

Glucose, a major source of energy for all cells, is transported into cells with the help of glucose transporters (GLUTs). These transporters are of two types, namely sodium-dependent GLUTs and facilitative GLUTs. These transporters are present in a tissue-specific pattern and have substrate specificity. Among these transporters, GLUT1 (facilitative GLUT) is present ubiquitously on all tissues of the body and helps in the basal uptake of glucose. GLUT1 is known to have many physiological functions in the body from the time of implantation of an embryo and is also seen associated with pathologies, including cancers. This review mainly focuses on GLUT1 in physiological and pathological conditions and the recent advances related to its role in cancer development and applications in cancer therapeutics.

Keywords: Glucose transporter 1, GLUT 1, pathology, physiology

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Received: 02.02.2018, **Accepted:** 27.06.2019

INTRODUCTION

Carbohydrates are one of the four major classes of organic molecules in the living systems that help in energy production, long-term storage of energy, the formation of nucleic acids (ribose and deoxyribose) and in the detoxification process. They also function as signaling, recognition and adhesion molecules. Nowadays, it is known that aberrations in cell surface carbohydrates are involved in malignant cell transformation, invasion and metastasis.[1,2] The majority of carbohydrates available in the dietary food are absorbed into the bloodstream in the form of glucose. Glucose acts as a major source of energy, plays a central role in metabolism, cellular homeostasis and act as an important substrate for protein and lipid synthesis. It can also be converted into other carbohydrates which carry out specific functions in the body.[2-4] The transport of this essential hydrophilic glucose molecule across the hydrophobic plasma membrane is mediated by a group of membrane-associated carrier proteins called glucose transporters (GLUTs). There are two types of GLUTs which belong to the solute carrier gene series (SLC). They are (a) sodium-coupled carrier proteins (sodium-glucose co-transporter [SGLT]) and (b) facilitative GLUTs. SGLT (gene name SLC5A) family comprise of cotransporters that mediate transport of glucose and galactose by an active process. SGLT1 is a high-affinity, low-capacity transporter protein expressed mainly in the intestine, heart and kidney. SGLT2 is a low-affinity, high-capacity symporter which is ubiquitously present with the highest expression in the kidney. GLUT (gene name SLC2A) family comprise of facilitative transporters that transport hexose molecules down the concentration gradient in a tissue- and substrate-specific

Access this article online

Quick Response Code:

Website: www.jomfp.in

DOI: 10.4103/jomfp.JOMFP_22_18

How to cite this article: Pragallapati S, Manyam R. Glucose transporter 1 in health and disease. J Oral Maxillofac Pathol 2019;23:443-9.

manner. There are 14 members in this group are numbered according to their order of discovery and are subdivided into three subfamilies according to sequence similarities, characteristic elements and functional characteristics. Brief details of these 14 GLUTs have been described in Table 1.[3-5] Among these transporters, GLUT1 is present on all cells to provide basal glucose uptake and is known to be elevated in various physiological and pathological conditions. This review mainly focuses on GLUT1 in physiological and pathological conditions and the recent advances related to its role in cancer development and applications in cancer therapeutics.

GLUCOSE TRANSPORTER 1

GLUT1 is an integral membrane hydrophobic protein that comprises of 492 amino acids with a molecular weight of 54 kDa. It helps in the transport of glucose, galactose, mannose, glucosamine and ascorbic acid. It is also known as erythrocyte/brain; HepG2 GLUT protein. GLUT1 is made up of 12 hydrophobic transmembrane α-helices with both N and C terminal on the cytoplasm side and a glycosylated extracellular loop between 1 and 2 transmembrane helices.

GLUT1 is present in human tissues with the highest levels of expression in plasma membranes of proliferating cells in the early development of an embryo. Postnatally during suckling phase, it is localized in high concentrations in the brain, skeletal muscle and myocardium, and in post-suckling phase and beyond into adult stages, there is a decline in the expression of GLUT1 except in the brain and there is an increase in the tissue-specific isoforms. In human erythrocytes, it comprises about 5%–10% of the total membrane protein.

It is seen widely in the cells forming various blood–tissue barriers. In cells forming blood–brain barriers; endothelial cells, astrocytes and choroid plexus express GLUT1. Retinal-pigmented epithelial cells, the choroidal, iridial, paras planus, retinal Mueller cells, lens fiber cells, iridial microvasculature endothelial cells and outer segments of the photoreceptor cells (lesser extent) of the blood–retinal barrier express GLUT1. The components of the perineurium and vascular endothelium of the blood–nerve barrier express GLUT1.

It is also seen in cardiac muscle, placenta and lactating mammary gland and has an important role in the development of the vertebrate brain. In insulin-sensitive tissues, such as adipose tissue and muscle, it is present in association with GLUT4.

Glucose transporter 1 functions in physiology

It helps in the implantation of the embryo by its increased expression in the endometrium and the basolateral surface of the polarized trophectodermal cells and the inner cell mass under the influence of the hormones estrogen and progesterone. Maternal diabetes with hyperglycemia is known to reduce the expression of GLUT1 which activates Bax leading to apoptosis, thereby causing embryo death.

It plays a vital role in maternal–placental glucose transport and also regulates the placenta–fetal glucose transport by enhancing its expression in the syncytiotrophoblastic cells and microvillus surface of the trophoblastic layer. This function of GLUT1 is supported by the coordinated expression of GLUT3 in the syncytiotrophoblastic layer.

In adults, it helps in providing glucose for energy production in red blood cells and brain. In muscle and adipose tissue, it helps in the transport of glucose during

Table 1: Description of details related to subclasses of glucose transporter 1 family arranged in order of their percentage identity [HMIT full form: H+/myoinositol cotransporter]

GLUT (Gene name)	Chromosomal localisation	Tissue localisation	Substrate specificity
		CLASS I	
GLUT1 (*SLC2A1*)	1p35-31.3	Ubiquitous distribution in tissues and culture cells	Glucose/Galactose
GLUT4 (*SLC2A4*)	17p13	Muscle, fat, heart	Glucose, not Galactose
GLUT3 (*SLC2A3*)	12p13.3	Brain and nerve cells	Glucose/Galactose
GLUT14 (*SLC2A14*)		Testis	Glucose/Galactose
GLUT2 (*SLC2A2*)	3q26-1-q26.2	Liver, islets, kidney, small intestine	Glucose/Galactose/Fructose
		CLASS II	
GLUT5 (*SLC2A5*)	1p36.2	Intestine, kidney, testis	Fructose (Glucose)
GLUT7 (*SLC2A7*)	1p36.22	Small intestine, colon, testis	Glucose/Fructose, not galactose
GLUT9 (*SLC2A9*)	4p16-p15.3	Liver, Kidney	Glucose/Fructose, not galactose
GLUT11 (*SLC2A11*)	22q11.2	Heart, muscle	Glucose/Fructose, not galactose
		CLASS III	
GLUT6 (*SLC2A6*)	9q34	Spleen, leucocytes, brain	Glucose
GLUT8 (*SLC2A8*)	9q33.3	Testis, blastocyst, brain, muscle, adipocytes	Glucose/(Fructose)
GLUT10 (*SLC2A10*)	20q13.1	Liver, pancreas	Glucose/Galactose, not fructose
GLUT12 (*SLC2A12*)	6q23.2	Heart, prostrate, mammary gland	Glucose, Galactose, Fructose
HMIT (*SLC2A13*)	12q12	Brain	Myoinositol

basal state. In active state and in times of hyperglycemia, GLUT4 expression is elevated due to the translocation of GLUT4 to the cell membrane by the action of insulin.[4,6,7]

It helps in protection against insulin-resistant glucose uptake in the skeletal muscle caused by oxidative stress through regulation of the reactive oxygen species.[8] It's expression on mitochondrial membrane helps in the transport of ascorbic acid into the mitochondria where it acts as an antioxidant and protects cells from oxidative damage.[9]

Glucose transporter 1 in altered physiological conditions

During acute exercise, there is no change in the expression of GLUT1, but there is an increase in the expression of GLUT4. In exercise training, there is an increase in the expression of both GLUT1 and GLUT4 which help in increasing the insulin-stimulated glucose uptake in the trained muscles.[10]

In hypoxia conditions, hypoxia-inducible factor which is normally present in the cells undergo transformation and regulate many genes that help in angiogenesis (such as vascular endothelial growth factor (EGF), inducible nitric oxide synthase), cell proliferation and survival (such as EGF, insulin-like growth factor-2, transforming growth factor-β) and for metabolic adaptations (such as glycolytic enzymes, GLUTs) that are essential for tumor growth, invasion and metastasis. The enhanced expression and function of GLUT-1 in response to hypoxia represents a fundamental adaptation that is critical to the maintenance of cellular homeostasis. Various mechanisms such as oxygen sensors theory, reduced adenosine triphosphate (ATP) or inhibition of phosphorylation theory and duration of hypoxia theory have been proposed to explain the activation of GLUT-1 in hypoxic conditions.[11,12]

Regulation of glucose transporter 1 expression

GLUT1 expression is mainly regulated by blood glucose concentration, cell signaling mechanisms and hormones. In hypoglycaemic states, there is an upregulation of GLUT1 in tissues such as brain where it helps in providing a major source of energy.

In normal cells, PIK3 (phosphoinositide 3-kinase)/Akt signaling pathway upregulates the transcription of GLUT1 mRNA through mammalian target of rapamycin complex 1 and 4E binding protein.[13] Prolactin and hydrocortisone elevate the intracellular GLUT1 expression 15 times in mouse mammary epithelial cells. Thyroid hormones regulate the expression of GLUT1 and GLUT3 which has been studied in cerebral cortex of hypothyroid rat neonates where they have found the regulation of these proteins by T3 hormone.[4]

GLUCOSE TRANSPORTER 1 DEFICIENCY

GLUT1 deficiency syndrome occurs due to impaired glucose transport into the brain either by *de novo* mutation in SLC2A1 gene or familial inheritance through autosomal-dominant inheritance pattern with complete penetrance. Few cases have been reported with autosomal recessive pattern of inheritance.

Clinical phenotypes of this disorder include: (a) classical phenotype, which was described in 1991 as an early-onset childhood epileptic encephalopathy. The characteristic features of this phenotype include epileptic encephalopathy with different seizure types, developmental delay, acquired microcephaly, complex movement disorders (variable combinations of ataxia, dystonia and spasticity) and paroxysmal events and (b) nonclassical phenotypes which are considered as variants of the classical phenotype. These are classified by Brockmann as (i) carbohydrate-responsive symptoms, characterized by a correlation between fasting and neurological deterioration including seizure frequency; (ii) predominant ataxia or dystonia, but without seizures and (iii) paroxysmal exertion-induced dyskinesia and seizures.

Nowadays the use of terms classical and nonclassical has limited clinical utility. Hence the disorder is studied in terms of its broad clinical spectrum which include: intellectual impairment, acquired microcephaly, epilepsy, movement disorders and hemolytic anemia. The condition is diagnosed by cerebrospinal fluid analysis, molecular analysis, erythrocyte 3-O methyl glucose uptake analysis, electroencephalography findings, positron emission tomography (PET) scans and brain imaging. Treatment option for the majority of these disorders is by administration of ketogenic diet.[14,15]

GLUCOSE TRANSPORTER 1 IN PATHOLOGY

Glucose metabolism in cancers

Warburg (1956) observed that cancer cells have high rates of aerobic glycolysis, which leads to the accumulation of lactate in the cancer cells. This increase in lactate production is due to upregulation of lactate dehydrogenase enzyme. The reduced pyruvate available for citric acid cycle decreases the production of ATP for energy requirement. Hence, more glucose has to enter cells for energy production by glycolysis through enhanced expression of GLUTs. This enhanced lactate dehydrogenase has been used as a prognostic marker in lymphomas, leukemia and colon cancer.

Other glucose metabolism enzymes known to be associated with cancers are glucose 6-phosphate dehydrogenase (cervical carcinomas, breast carcinomas) and 6-phosphogluconate dehydrogenase (cervical carcinomas).[16] Modification of pyruvate kinase M2 isoform diverts the glucose flux for the production of components essential for cell proliferation and differentiation. This further mediates histone H3 phosphorylation which causes EGF-induced expression of cyclin D1 and c-myc, tumor cell proliferation, cell-cycle progression and brain tumorigenesis.[17]

Relation between oncogenes and glucose transporter 1

Ras and Src oncogenes are known to enhance elements in the GLUT1 promoter region which leads to increased GLUT1 expression. This has been studied in rat fibroblasts where the transformation of cells with Ras, Src and Fujinami sarcoma virus has been done which resulted in increased glucose transport and GLUT1 expression.[16]

c-Myc oncogene is known to be associated with upregulation of glycolysis by increasing the levels of glycolytic enzymes (lactate dehydrogenase and pyruvate kinase) and GLUT1.[17-19]

Relation between tumor suppressor genes and glucose transporter 1

The tumor suppressor gene p53 which is known to be involved in the carcinogenesis of many tumors has implication in the alteration of expression of GLUT1.

p53, which is known for its regulation of normal growth and development, also regulates glycolysis and oxidative phosphorylation by inhibiting the expression of GLUT1 and GLUT4. Alterations or mutations in p53 leads to upregulation of glucose transporters, thereby enhancing the glucose influx required for energy production, proliferation and growth of cancer cells.[17,18,20]

Relation between glucose transporter 1and apoptosis

GLUT1 is known to have an indirect relation with that of apoptosis various mechanisms have been described. This has been proved by conducting various studies on cancer cell lines of breast, colon, lung and gastric using GLUT1 antibodies increased apoptosis and reduction in tumor size due to the arrest of cell cycle in G1 phase.[21-23] This has been used in clinical trials for inhibition of cell proliferation to know the efficacy of GLUT1 inhibitors in targeted therapy, thereby bringing new insights into cancer therapeutics.

Glucose transporter 1 in oral vascular lesions

GLUT1, which is normally expressed in the vasculature of blood–tissue barriers and placenta, is known to be used as a marker for differential diagnosis of various vascular lesions. It helps in differentiating hemangiomas which show diffuse positivity to GLUT1 from vascular malformations and pyogenic granulomas which show a negative reaction with GLUT1. These are frequently confused lesions due to their overlapping histological features and have to be differentiated because of their differing treatment strategies.[24,25]

Studies related to glucose transporter 1 in cancers

Altered metabolism is one of the adaptive mechanisms adopted by tumor cells to sustain in adverse conditions. This adaptive mechanism helps the tumors cells in continuing growth, proliferation and survival. GLUT1 which is considered as a gateway for the entry of glucose required for metabolism in cancer cells various studies have been conducted on tumors of the body to know the correlation between GLUT1 and biology of various cancers.

Various studies conducted on hepatic carcinomas,[26] gastric carcinomas,[27] cervical cancers,[28,29] renal cancers,[30] colorectal cancers,[31] pancreatic cancers,[32] ovarian cancers,[33] abdominal and mesothelial carcinomas,[34] head and neck squamous cell carcinomas,[35] lung adenocarcinomas,[36] metastatic and nonmetastatic lip squamous cell carcinomas,[37] breast carcinomas,[38] endometrial carcinomas,[39] verrucous carcinoma[40] and soft-tissue sarcoma[41] showed overexpression of GLUT1 which states that aerobic glycolysis is adapted as a fundamental mechanism in almost all types of tumors in the body, and it can be used as an immunodiagnostic marker in these tumors.[42,43]

The study conducted on benign melanocytic lesions and malignant melanomas showed contrasting findings reduced expression of GLUT1 has been observed in melanomas when compared to their benign counter lesion. This shows that other mechanisms play a role in the progression of melanoma and further studies have to be conducted to know its mechanism.[44]

Studies related to prognostic applications of glucose transporter 1 in cancers

Increased expression of GLUT1 has been seen in many tumors, but few studies have correlated the expression of GLUT1 with the prognosis of the patients [Table 2].[45-49] These studies have shown that increased expression of GLUT1 has been correlated with the poor survival of the patient.[45-49]

Studies related to relation between ^{18}F-fluoro-2-deoxyglucose uptake and glucose transporter 1 in cancers

PET is a noninvasive nuclear medicine imaging technique that produces a three-dimensional image of functional

processes in the body. The use of 2-deoxy-2-18fluoro-β-D glucose, which is an analog of glucose, helps in early detection of tumors and assesses the response to cancer therapy. The use of this scan as an adjuvant in oncology helps in understanding possible mechanisms of cancer biology and to determine the aggressiveness. The use of 18F-fluoro-2-deoxyglucose (FDG)-PET scan in combination with GLUT1 helps in understanding cancer metabolism.[50,51]

Various studies have been conducted on nonsmall cell lung carcinoma,[51] cardiac myxoma,[52] neuroendocrine tumors, colorectal adenocarcinomas,[53] pancreatic tumors,[54] lymphoma[55] and salivary gland pleomorphic adenomas[56] to know the relation between the cellular uptake of ^{18}F-FDG and expression of GLUT1. In all these tumors, they have found a positive correlation between ^{18}F-FDG uptake and GLUT1 expression.

Studies conducted on inflammatory lung lesions and reactive lymph nodes in oral cancer showed no correlation between uptake of ^{18}F-FDG and GLUT1 staining. Hence, it can be hypothesized false-positive results can be seen in associated with inflammatory lesions and nonmalignant tissues.[57,58]

Studies related to glucose transporter 1 in odontogenic cysts and tumors

Odontogenic cysts and tumors are the common lesions seen in the head-and-neck region. The expression of GLUT1 in these lesions has not been reported except a case report related to ameloblastoma.

Otsuru *et al.* conducted a study to investigate the usefulness of FDG-PET in diagnosing recurrent ameloblastoma. Furthermore, as GLUT-1 expression has been found to be involved with FDG uptake in numerous malignancies, they ascertained whether this also applies to ameloblastoma. They hypothesized that FDG-PET is useful in diagnosing recurrence and metastasis of various malignant tumors. If FDG-PET is useful for identifying ameloblastoma as a locally invasive tumor with a high rate of recurrence, early diagnosis of recurrent ameloblastoma may be possible. They have studied four cases of ameloblastoma which

Table 2: Studies related to GLUT1 application in assessing prognosis of carcinomas

Study	Results
Martin Kunkel *et al*. 2003, conducted a immunohistochemical study on oral squamous cell carcinomas (OSCC)	Increase GLUT1 is associated with poor prognosis of patients. This increase in GLUT1 bypasses apoptosis causing increased survival of cells leading to aggressiveness of the lesion.
Martin Kunkel *et al*. 2007, conducted a immunohistochemical study oral squamous cell carcinoma and compared it with the resistance to radiotherapy	Increase in the expression of GLUT1 is associated with increased resistance to radiotherapy which cause poor prognosis and reduced survival rate. They have concluded that GLUT1 can be used as a marker to assess radioresistance prior to start of radiotherapy
Makoto Endo *et al*. 2007, conducted a immunohistochemical study on bone and soft tissue sarcomas	Increased expression of GLUT1 has been correlated with poor prognosis of the patient and it has been correlated with the results of other prognostic markers. The authors have suggested that this can be used to assess high risk patients prior to start of therapy.
Shinichi Ohba *et al*. 2010, conducted a immunohistochemical study on oral squamous cell carcinoma and compared the GLUT1 expression in invasive front of tumor with prognosis	Increased expression of GLUT1 has been noted in the lesions with invasive front at a depth more than 4mm which was correlated with increased aggressiveness, resistance to radio and chemo therapy, poor prognosis and overall survival rate.
Jyotsna M Harshini *et al*. 2014, conducted a immunohistochemical study on oral squamous cell carcinoma	GLUT1 expression has correlated with the staging, grading and prognosis of the patient and they suggested that increased GLUT1 can be regarded as an early event in development of OSCC

Table 3: GLUT1 inhibitors and their mechanism of action

Inhibitor	Target	Mechanism	Status of research
WZB117	GLUT1	Directly binds to GLUT1 using 3 hydrogen bonds with amino acid residues Asn34, Arg126 and Trp412. This leads to cell cycle arrest, senescence and necrosis.	Animal study
STF-31	GLUT1	Selectively targets von Hippel-Lindau (VHL)- deficient renal cell carcinoma cells.	Animal study
Fasentin	Intracellular domain of GLUT1	Enhances death receptor stimuli FAS-mediated cell death in FAS-resistant cancer cells.	*In vitro*
Apigenin	GLUT1	Natural compound that inhibits uptake of glucose in a dose dependent manner by targeting GLUT1 at both mRNA and protein levels.	Phase II
Genistein	External surface of GLUT1	Inhibits the transport of hexose and dehydroascorbic acid through GLUT1 in a dose dependent manner.	Phase II/III
Oxime-based GLUT1 inhibitors	Intracellular domain of GLUT1	Similar potency as WZB117	Animal study
Pyrrolidinone derived GLUT1 inhibitors	GLUT1	Inhibits glucose transporter mediated by erythrocyte membrane derived vesicles.	*In vitro*

have shown diffuse expression of GLUT1 that has been correlated with the FDG uptake in those tumors.[59]

USE IN CANCER THERAPEUTICS

Abnormal glucose metabolism, which is considered as one of the factors responsible for carcinogenesis, has been linked to drug resistance in cancer therapy. Research on targeting dysregulated metabolism is going on to overcome the therapeutic resistance and for improving the efficacy of cancer therapy. Targeting of glucose metabolism can be directed either toward glycolytic enzymes or GLUTs. GLUT targeting acts as a first rate-limiting step of glucose metabolism, as it prevents the entry of glucose into the cell. Various GLUT1 inhibitors available, their mechanism and site of action and its current status in research has been tabulated [Table 3].[60-62] Other GLUT1 inhibitors include cryptocoryne, thiazolidinediones, methylxanthines and resveratrol which direct their action against GLUT1. The advantage with these inhibitors is that the normal cells are spared hence causing little harm to the patients.[60-62]

FUTURE PERSPECTIVES

Further investigations related to the detailed role of GLUT1 in the carcinogenesis process and research related to selective targeting and enhanced inhibitory efficacy of inhibitors have to be considered for formulating an effective anticancer therapeutics.

CONCLUSION

Glucose is the main source of energy for all the cells, including the transformed cells. Transport of glucose is carried out by transporter proteins, among this GLUT1 is ubiquitously present and overexpressed in transformed cells. GLUT1 plays a vital role both in physiology and pathology. Knowledge related to GLUT1 helps us in understanding its role in carcinomas and help us in formulating a better treatment plan for the patients.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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