Facilitative Sugar Transporters

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Contributor: Abdelrahman Ismail , Marina Tanasova

Facilitative sugar transporters (GLUTs) are passive membrane transporters that are responsible for nearly all of our cells' sugar uptake. They mainly pass glucose and other similar substrates like fructose, mannose, ascorbate, and urate ions. They have been classified into three classes based on structure similarity and substrate affinity.

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1. Overview of Facilitative Sugar Transporters (GLUTs)

In total, there are 14 GLUT transporters, divided into three classes. They all have different but mostly overlapping functions and structures. **Table 1** [1] shows an overview of the GLUT family, their currently known substrates, and their expression sites. The Class I GLUTs (1–4 and 14) facilitate the uptake of glucose and other hexoses, but not fructose. The Class II GLUTs (5, 7, 9 and 11) are fructose transporters, and Class III GLUTs (6, 8, 10, 12, and 13 (HMIT1)) are structurally atypical members. The affinity of each transporter for glucose ranges from 0.2 to 17 mM.

Table 1. Classification, expression, and substrate preference of the 14 known GLUTs.

Expression Tissues	Main Substrates		
GLUT1	Erythrocytes, blood-tissue barriers	Glucose, 2-DG	
GLUT2	Liver, pancreas, small intestine	Glucose, Glucosamine	
GLUT3	Neurons	Glucose, 2-DG	Class I
GLUT4	Adipocytes, muscle, heart	Glucose, Glucosamine	
GLUT14	Testis	Unknown	
GLUT5	Testis, intestine, muscle	Fructose	
GLUT7	Testis, intestine, prostate	Fructose, glucose	Class II
GLUT9	Liver, kidney	Urate	
GLUT11	Pancreas, kidney, placenta, muscle	Fructose, glucose	
GLUT6	Brain, spleen, leukocytes	Glucose	Class III
GLUT8	Testis, neurons, adipocytes	Glucose, trehalose	

Expression Tissues	Main Substrates	
GLUT10	Liver, pancreas	2-DG
GLUT12	Heart, prostate	Glucose

Only GLUTs 1–5 have been studied in depth, and relatively little is known about the other, more recently discovered GLUTs. This section provides an overview of the transport efficiencies, tissue expression, and links to different disorders of all 14 GLUTs.

2. Class I

GLUT1 was the first GLUT to be identified. It is ubiquitously found in all tissues of the body. GLUT1 also transports glucose through the blood-brain barrier [2][3], and is expressed in other barrier structures in the brain [4]. Its main substrate is glucose (K_m = 3 mM [5]), and other known substrates include galactose, mannose, and glucosamine [6]. GLUT1 is overexpressed in many different types of cancers including brain [7], breast [8], cervix [9], colon [10], kidney [11], lung [12], ovary [13], prostate [14], skin [15], and thyroid [16]. Cancers that express more GLUT1 have been shown to be more aggressive and invasive [17]. Due to its widespread prevalence, many different therapies have attempted to target it, but the same widespread prevalence makes it difficult to achieve specificity.

GLUT2 has a sequence similarity of 55% to GLUT1. It is primarily expressed in the liver, kidney, insulin-secreting pancreatic beta cells, and absorptive epithelial cells of the intestinal mucosa. Its main function is regulating the uptake of glucose in the gastrointestinal tract [18][19]. GLUT2 partakes in glucose uptake (K_m = 17 mM), but its main substrate is glucosamine (K_m = 0.8 mM) [6]. It also transports fructose, galactose, and mannose (K_m = 76 mM, 92 mM and 125 mM, respectively) [20][21][22]. Since it plays a significant role in carbohydrate uptake in the intestines, it has become a target of interest for diabetes prevention and treatment by inhibiting glucose absorption in the intestine and thereby lowering blood glucose levels [23].

GLUT3 is the second most prevalent transporter in the brain, but unlike GLUT1, it is widely distributed in the neurons [24][25], particularly in the pre- and post-synaptic nerve terminals and small neuronal processes [26]. It is also expressed in embryos, sperm, and white blood cells [27]. It has the highest affinity to glucose of all class I transporters (K_m = 1.4 mM) [28]. It was also shown to transport mannose, galactose, and xylose [28]. GLUT3 is overexpressed in many cancers including breast, colon, endometrial, kidney, lung, and renal cancers [8][29][30]. This overexpression is also associated with the aggressiveness of glioblastomas and recurrent brain tumors [31].

GLUT4 is the dominant glucose transporter in striated muscle and adipose tissues, and is the second most abundant transporter in cardiovascular tissue [32]. Its main substrate is glucose ($K_m \approx 5$ mM [33]) and it also transports mannose, galactose, dehydroascorbic acid, and glucosamine [34]. Unlike other glucose transporters, GLUT4 is regulated by insulin as insulin binding receptors translocate GLUT4 to the cell surface [27]. GLUT4 has been linked to obesity, type-2 diabetes, and heart disease, making inhibition of GLUT4 a promising therapeutic approach [35][36]. In fact, GLUT4 inhibition has been shown to cause cardioprotective effects and aided affected individuals to return to normal heart/body weight ratios [35].

GLUT14 is the most recently identified member of the GLUT family. It is a duplicon of GLUT3 but it is only expressed in the testis [37]. Not much else is known about this transporter.

In addition to the expression regulation by their substrates, the expression of GLUTs 1–4 was also found to be regulated by hormones. Estrogen and progesterone have been linked to GLUT expression in the endometrium [38]. Data suggests that high glucose uptake and metabolism are necessary for endometrial proliferation and differentiation. Abnormal GLUT expression has been found in a wide range of endometrial cancers, and steroid hormones have been linked to the genesis of endometrial cancer [39].

3. Class II

While fructose is a rare substrate for the class I GLUTs, it is one of the main substrates of class II GLUTs. Class II GLUTs also have significantly higher affinities for their substrates in general, including glucose. Among all GLUTs, GLUT5 is a unique transporter, as its only substrate is fructose (K*i* = 5–15 mM [40]). It is primarily expressed in the small intestine [41] and has been strongly linked to cancer development, progression and metastasis, making it an attractive target for cancer therapeutics [42]. This, along with its unique substrate specificity, prompted several structural activity relationship (SAR) studies into its H-bonding requirements for fructose uptake in order to design GLUT5-specific probes as cancer diagnostic tools [43][44][45]. Furthermore, the heightened consumption of fructose in cancers lead to the development of GLUT5-specific inhibitors of fructose uptake [42][46].

GLUT7 is primarily expressed in the small intestine and colon, although its mRNA has been detected in the prostate and testis. It has a sequence identity of 44% to GLUT5 [47]. GLUTs 9 and 11 share 58.1% and 41.7% sequence identity with GLUT5, respectively [40][48]. All three transporters have high affinities (<0.5 mM) for both glucose and fructose [47][49]. GLUT9 is mainly expressed in the liver and kidney [49], and GLUT11 has been found in various organs, including the heart, skeletal muscle, kidney and pancreas [50]. GLUTs 7 and 9 are also expressed in the apical membrane of the small intestine and colon. The abundance of GLUTs 7 and 9 in the small intestine changes according to dietary carbohydrate intake. However, the distribution of transporters along the small intestine does not entirely match the availability of glucose and fructose, which might indicate the presence of another substrate for those transporters that has yet to be identified.

4. Class III

The members of this class share a limited sequence homology with class I (~25% identity) and are considered structurally atypical [51]. GLUT10 has a 35% similarity to GLUT2 and it can also transport glucose (K_m = 2 mM). GLUT12 has a number of similar features to GLUT4, but a much higher affinity for glucose (K_m = 0.3 mM) [52].

GLUT8 is predominantly expressed in the testes [53] and is thought to play a major role in providing glucose to mature spermatozoa, in addition to being able to transport fructose [54]. It is also expressed in a number of other tissues such as the liver, spleen, brown adipose and blastocysts, albeit in significantly lower quantities [55]. The expression of GLUT8 was suggested to be regulated by insulin in a similar manner to GLUT4. However, this claim

has been disputed [56][57]. There is some evidence that glucose itself may influence the location and expression of GLUT8, as glucose induces GLUT8 translocation from an intracellular compartment to the endocyclic reticulum in rat hippocampal cells [58]. GLUT8 knock-out mice reportedly displayed normal embryonic and postnatal development and glucose homeostasis, but had mild defects in hippocampal neurogenesis and cardiac function.

GLUT12, like GLUT8, is also able to transport both glucose and fructose. Insulin-regulated expression has also been suggested for GLUT12, as it is predominantly expressed in the insulin-sensitive skeletal muscle, heart and fat tissues [52]. GLUT12 was originally cloned from the human breast cancer cell line, MCF7, and its expression was found to be stronger in ductal cell carcinoma than in benign ducts of breast cancer tissues [59], indicating a possible role in glucose uptake in breast cancer tissue.

HMIT, formerly known as GLUT13, is an H^+/myo-inositol cotransporter and is the last of the GLUTs. Unlike the other 13 transporters, HMIT does not transport either glucose or fructose. Its only substrate is myo-inositol ($K_m \approx$ 100 mM), and this uptake is pH-dependent [60]. HMIT is largely expressed in the brain, particularly in neuron intracellular vesicles, and its transition to the cell surface can be triggered by cell depolarization.

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