



Glucose transporters in the mammalian blood cells

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List of unusual abbreviations:

AA – ascorbic acid
BBM – brush border membrane
BLM – basolateral membrane
CRS – cardiorenal metabolic syndrome
DHA – dehydroascorbic acid
PT – proximal tubules

Key words: GLUT, red blood cells, leukocytes, macrophages, SGLT, CD68

Abstract

Glucose is the main source of metabolic energy for various cellular functions, and thus plays a central role in supporting intermediary metabolism and cellular homeostasis. Since plasma membrane is impermeable to glucose, its cellular uptake is mediated by two distinct processes via specific glucose transporter proteins that belong to the family of solute carriers (SLC); the SLC2 family members, GLUTs (glucose transporters), are sodium-independent facilitators of the glucose transport, whereas the SLC5 family members, SGLTs (sodium and glucose transporters) mediate the secondary-active sodium-glucose cotransport. Until now, 14 GLUTs and 12 SGLTs isoforms have been identified in humans of which 5 GLUTs and none SGLTs were detected in the mammalian blood cells. Detailed physiological function, precise mechanism of transport, substrates affinity, exact three-dimensional structures, and a precise tissue distribution of most GLUTs in various mammalian organs, including blood, have been poorly explored. In this review we will focus on GLUTs in the mammalian blood cells, where the data on their expression and functional roles are contradictory or largely missing. Since many GLUTs are associated with diabetes, and are up-regulated in cancers, it is undoubtedly important to further investigate GLUTs expression in different organs/tissues, including the blood cells. Understanding the complexity of glucose homeostasis that includes knowledge about tissue distribution and function of GLUTs, as well as the signaling pathways that regulate glucose metabolism, may help to develop new therapeutic strategies to target specific diseases, such as diabetes mellitus, some autoimmunity diseases, and cancer.

INTRODUCTION

In the mammalian cells, glucose is the key source of metabolic energy used in various functions. Metabolic energy that was stored in ATP is generated by degradation of glucose through the processes of glycolysis and citric acid cycle. As a metabolic substrate, glucose is also used for synthesis of glycerol and non-essential amino acids, which represent precursors in synthesis of lipids and proteins (1). Because of the prevalent role of glucose in cellular metabolism, one can ask the following question: why is glucose, and not some other monosaccharide, such as fructose, a preferred source of energy in the most of living organisms? The answer could be partially attributed to widespread availability of glucose in the environment, and partially could be explained by the evolutionary-developed protection from the toxicity of other hexoses; in comparison to other hexoses, glucose has a lower tendency to react nonspecifically with amino groups in proteins and form the advanced glycation end products (AGEs) through the process of glycation. Glycation is non-enzymatic post-translational modification of proteins which is ini-

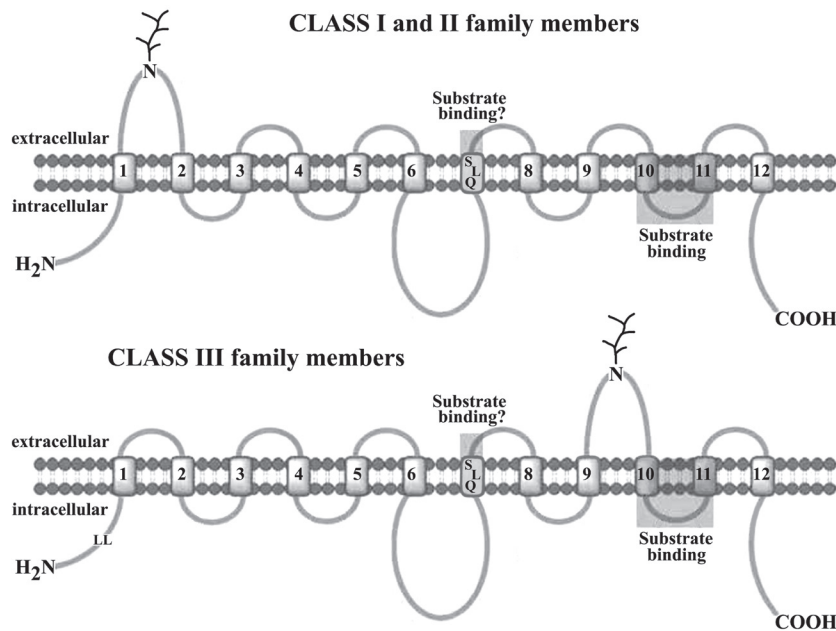


Figure 1. Schematic models for the GLUT (SLC2) family members of class I, II, and III, with their specific characteristics: **1)** Twelve transmembrane domain that form six extracellular and five intracellular loops having N- and C-termini located intracellularly, **2)** Proposed substrate binding sites are located in the 7th transmembrane domain (containing QLS amino acid sequence) and in the 5th intracellular loop between 10th and 11th transmembrane domains (indicated by shadowed regions), **3)** N-linked glycosylation sites are located on the 1st (class I and II) or 5th (class III) extracellular loops; **4)** Dileucine signal, located on the N-terminus, is present exclusively in the class III members. Class I group is comprised of GLUTs 1-4 and 14, Class II group is comprised of GLUTs 5, 7, 9 and 11, whereas Class III group is comprised of GLUTs 6, 8, 10, and 12 (29, 31). The scheme was adapted after Augustin (31).

tiated by the binding of carbohydrates to amino groups of the amino acid residues. By disrupting the molecular conformation of proteins, glycation alters their biological activity and degradation, and contributes to various diabetic-related complications such as retinopathy, nephropathy, neuropathy, and cardiomyopathy, as well as to development of physiological aging and neurodegenerative diseases such as Alzheimer's and Parkinson's (2-6). Contrary to glycation, glycosylation is another post-translational, but regulated modification of the proteins that occurs at the specific amino acid residues and enables specific functions of such proteins.

The mammalian cells are supplied with glucose mainly from two sources, from the ingested disaccharides and polysaccharides, and *via* the synthesis from various precursors (gluconeogenesis) in the liver and kidneys. Some amount of glucose can also be released from the stored glycogen in skeletal muscle. Following absorption in gastrointestinal tract, or release from the body glycogen stores (liver, kidneys, skeletal muscles), glucose is delivered to the cells by the circulating blood. In order to maintain the body homeostasis, the concentration of blood glucose should be kept constant. According to American Diabetes Association, normal blood glucose concentration (normoglycemia) is kept in the range from 4.4 to 6.1 mmol/L; concentrations below and above this range are known as

a hypoglycemia and hyperglycemia, respectively (7). Blood glucose is regulated by the negative feedback loop that predominantly involves two hormones secreted by the specific cells of pancreatic Langerhans islets, insulin and glucagon. When blood glucose rises, β -cells of the Langerhans islets secrete insulin, which then stimulates the transporters-mediated glucose uptake into the cells, and enhances the rate of glucose utilization in the most body cells. It also accelerates the formation of glycogen from glucose in the liver and skeletal muscle, and stimulates the fat synthesis in the liver and adipose tissue (8, 9). Overall, these processes decrease blood glucose back to the normal values. On the other side, if blood glucose decreases below the normal range, insulin secretion is inhibited, and α -cells of the Langerhans islets secrete glucagon (10, 11). This hormone accelerates the breakdown of glycogen to glucose in the liver and skeletal muscle cells, and breakdown of fats to fatty acids and glycerol in adipose tissue. Glucagon also stimulates gluconeogenesis, i.e. *de novo* synthesis of glucose from glycerol and some amino acids in the liver and kidney cells, and stimulates release of the synthesized glucose into the blood (12, 13). In summary, these processes increase blood glucose back to the normoglycemic values. In addition to insulin and glucagon, there are several other hormones such as epinephrine, cortisol, and growth hormone, whose actions increase blood glucose (14-16). Long-termed hyperglyce-

mia causes excessive glycation of proteins that change their structure and function, thus affecting the physiology of various organs such as eyes, kidneys, heart, blood vessels, and brain (17). Hypoglycemia also affects the brain functions, causing cognitive dysfunction, anxiety and depression (18). Therefore, coordinated regulation of pancreas, liver, kidneys, adipose tissue, muscle and brain is of great importance in maintaining the normoglycemic range necessary for keeping the body homeostasis.

GLUCOSE TRANSPORTERS

Plasma membrane of the mammalian cells is more or less permeable to nonpolar molecules (O_2 , CO_2), weakly permeable to small polar but uncharged molecules (water), and largely impermeable to ions and other charged or larger uncharged molecules such as glucose, amino acids, and organic anions and cations. To enter the cell, the latter molecules need specific transporters localized in the cell membrane.

Transporters of glucose belong to the large SLC/Slc (solute carriers) family (19, 20). According to the HUGO Gene Nomenclature Committee, the names of human *genes/proteins* are written in capital letters (*SLC/SLC*) (21), while the respective rodent *genes/proteins* are written in small letters (*Slc/Slc*) (<http://www.informatics.jax.org/mgihome/nomen/> and <http://rgd.mcw.edu/nomen/nomen.shtml>). The names of *genes/proteins* from other animal species are written following the recommendation of the respective nomenclature committees (<http://www.thearkdb.org/arkdb/>). Up to now, two functionally and structurally distinct families of glucose transporters have been cloned, and their biochemical structure, kinetic/transport properties, tissue distribution, transcriptional/translational regulation, as well as physiological and pathophysiological functions have been recently reviewed in details (19, 20). In mammalian cells, glucose is transported across the plasma membrane by two distinct processes: 1) Sodium-independent facilitated diffusion is mediated by glucose transporters (GLUT/Glut) that belong to the SLC2/Slc2 family, and 2) Sodium-driven secondary-active transport is mediated by sodium-glucose cotransporters (SGLT/Sglt) that belong to the SLC5/Slc5 family (1, 19, 20, 22, 23).

Thus far 26 various glucose transporters have been cloned in humans and animals. The physiological reason for so many glucose transporters in mammalian cells is unclear, and may be based on the nature of glucose as main circulating fuel and need for multiple, cell type-specific glucose transporters with different kinetic and regulatory properties (19, 20). Regarding SGLTs/Sglt, thus far 12 members of the SLC5/Slc5 family have been cloned and their tissue distribution and features in various mammalian cells have been characterized (20, 22). The founding member of this family, SGLT1/Sglt1 (SLC5A1/Slc5a1) is primarily expressed in the epithelial cells of small intestine

and kidneys, and was also detected in some other organs such as heart, brain, lung, testes and prostate. In the kidneys and small intestine it is localized to the brush border membrane (BBM) of proximal tubules (PT) and enterocytes, respectively (20, 24). Our detailed immunochemical data in rat kidneys, performed with specific non-commercial antibody, immunolocalized the Sglt1 protein to the BBM and intracellular organelles of PT, the expression being highest in the S3 segments and lower in the S1 and S2 segments. A limited expression was detected also in the apical membrane of thick ascending limb of Henle (TALH) and Macula densa cells. In the intestine, Sglt1 was localized strongly to the BBM of absorptive cells (enterocytes) along the entire small intestine, the expression being highest in jejunum. In addition, some enteroendocrine cells and myenteric plexus in the small intestine, bile ducts in the liver, initial ducts in the submandibular gland, pyramid cells in the brain cortex, and ependymal epithelium of the brain ventricles were also positive for Sglt1, indicating a widespread localization and importance of this glucose transporter in a variety of cell types (25). The second important member of the SLC5 family, SGLT2 (SLC5A2), was in humans detected in various tissues, including kidneys, liver, brain, heart, thyroid and skeletal muscle (20, 24), whereas in rodents (rats and mice), Sglt2 was localized exclusively in the kidneys (26), where it is localized in the BBM of cortical PT segments (S1/S2). Being present in small intestine (SGLT1/Sglt1) and renal PT (SGLT1/Sglt1 and SGLT2/Sglt2), these two sodium-glucose cotransporters represent the key factors in maintaining normoglycemia in the body - they mediate absorption of glucose in the intestine, and reabsorption of the filtered glucose in the kidneys (20, 24, 27, 28). The presence, tissue distribution, and functional roles of other members of the SLC5 family have been reviewed elsewhere (1, 20, 24). However, although there are many studies showing the SGLTs expression in various organs, many of them are contradictory due to absence of specific antibodies on the market (20, 24).

Thus far 14 various facilitative glucose transporters of the SLC2 family (GLUTs/Gluts) have been cloned in humans (19). According to their sequence similarity and intrinsic or inducible transport characteristics, various GLUT isoforms within the SLC2 family have been grouped in three classes (I, II and III). GLUTs of all three classes have several common characteristics, such as 12 putative transmembrane domains with N- and C-termini located in the cytoplasm, ~500 amino acid residues, and one N-linked glycosylation site located on the first (class I and II) or fifth (class III) extracellular loop. They all have putative substrate binding sites located in the 7th transmembrane domain containing QLS amino acid motif and between 10th and 11th transmembrane domains (1, 29-31). Schematic presentation of the basic properties of all three GLUT classes is depicted in Fig. 1, whereas a scheme of GLUT distribution in major human organs/

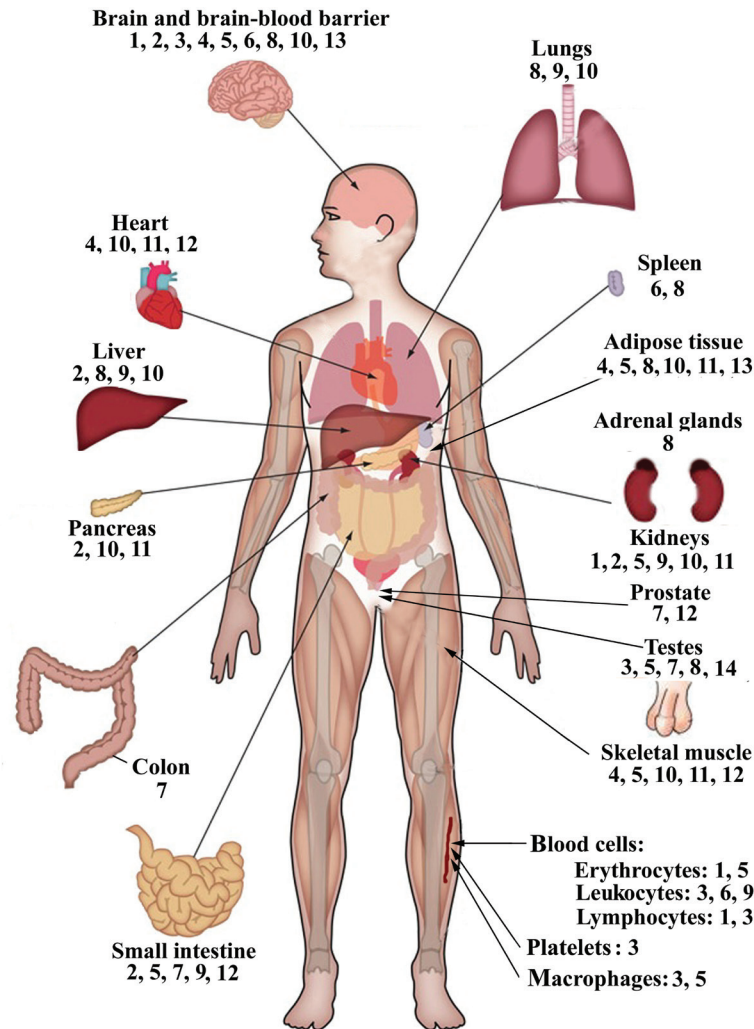


Figure 2. Schematic representation of various GLUTs (SLC2) distribution in the tissues/organs of the human body. Data have been collected from the available literature (19, 29, 31).

tissues is presented in Fig. 2. A more detailed distribution of GLUTs/Gluts in almost every mammalian cell has been reported (19, 30). Specific GLUT/Glut isoforms reside in the basolateral membrane (BLM) of a) enterocytes in the small intestine (GLUT2/Glut2), b) PT S1 and S2 segments in the renal cortex (GLUT2/Glut2), and c) PT S3 segments in the renal outer stripe (GLUT1/Glut1), where they mediate glucose exit following its accumulation mediated by SGLTs in the BBM (19, 20, 24). In the following sections we shall focus our description on glucose transporters in the mammalian blood cells.

GLUCOSE TRANSPORTERS IN BLOOD CELLS

The expression of SGLTs/Sglts at either mRNA and/or protein levels has not been clearly detected in the human or animal (rats and mice) blood cells (20, 24; *our unpublished data*). A number of studies, however, have

demonstrated the blood cell type-specific presence of one or more GLUT/Glut isoforms, as listed in Fig. 2. The GLUTs 1, 3, 5, 6, and 9 in human blood cells have been localized and characterized in more details, and the respective selected data are described *in extenso*.

Glucose transporter 1 (GLUT1)

GLUT1 (gene *SLC2A1*) was the first facilitative sugar transporter to be identified, purified and cloned from the HepG2 cell line (32), but the real research on this transporter began when GLUT1 was purified from the human erythrocyte (red blood cell/RBC) membrane (33). Primary physiological function of GLUT1 is mediation of glucose uptake in order to maintain cellular respiration. Except glucose, GLUT1 also transports other sugars such as mannose, galactose, glucosamine, and reduced ascorbate (19, 34). Human RBC express the highest level of GLUT1 (> 200.000 molecules/cell), comprising 10% of total integral membrane protein (35, 36, 37). The reason

for high GLUT1 expression in RBC may be to effectively increase the blood capacity to carry glucose, since glucose freely equilibrates between the serum and RBC cytoplasm through their plasma membrane. Study of Montel-Hagen et al. (38) has demonstrated that expression of GLUT1 in RBC is species-specific; its expression is unique feature of those mammalian species such as humans, other higher primates, guinea pigs and fruit bats, that are unable to synthesize ascorbic acid (AA) from glucose. GLUT1 preferentially transports L-dehydroascorbic acid (DHA), rather than glucose. DHA and glucose have structural similarities, but GLUT1-mediated DHA uptake is not competed with glucose (38). It was further identified that stomatin, an integral membrane protein in RBC, regulates a switch from glucose to DHA transport. In patients with a rare genetic disorder of the RBC membrane permeability (overhydrated hereditary stomatocytosis), where the expression of stomatin is very low, DHA transport is decreased by 50%, while glucose uptake is significantly increased (38). In the mammalian species that naturally synthesize AA, such as mice, GLUT1 is expressed during perinatal period but is rapidly lost following birth, and GLUT4 becomes the unique glucose transporter in RBC of adult mice. In contrast, humans maintain the GLUT1 expression in their RBC during the whole life (39, 40). However, a recent study by Sage and Carruthers (41) argues against the above mentioned stomatin-regulated pool of GLUT1 that preferentially transports DHA rather than glucose in mature RBC; their data suggest that human RBC transport glucose and DHA *via* the same GLUT1-dependent mechanism. Besides in RBC, GLUT1 is expressed in lymphocytes as a key player in the adaptive immune response; metabolism of glucose in lymphocytes is a tightly regulated process having significant effects on the immune cell function (42). Activated T-lymphocytes demand a high glucose uptake that is necessary for their growth, proliferation, and cytokine production. If glucose uptake is insufficient, activated T-lymphocytes undergo apoptosis (43-45). On the other hand, excessive glucose uptake can promote hyperactive immune responses and possible immune pathology (42). Therefore, a precise regulation of glucose metabolism in lymphocytes is necessary for maintaining immune homeostasis and avoiding immune pathology, such as autoimmune and inflammatory diseases, and cancer.

Glucose transporter 3 (GLUT3)

GLUT3 (gene *SLC2A3*) has the highest affinity for glucose, but can also accept galactose, mannose, maltose, xylose, and DHA, but not fructose. It has been cloned from the human fetal skeletal muscle cell line (46). It shows 64% identity with GLUT1. Its higher affinity, and a higher turn-over number for glucose, as compared to GLUT1, explains its primary expression in the tissues with the high metabolic activity such as brain (47). GLUT3 has been found in other cells with high glucose

demand and energy consumption, including sperm, pre-implanting embryos, human white-blood cells (lymphocytes, monocytes/macrophages, neutrophils) and platelets (48). In the blood cells, GLUT3 is localized in intracellular vesicles that can be translocated to and fused with the plasma membrane upon cellular activation to ensure increased glucose uptake (49). However, the mechanism that promotes translocation, as well as the nature of GLUT3-positive intracellular vesicles, have not been defined. The only known data concerning the GLUT3 translocation indicate that insulin may induce its translocation in monocytes and B-lymphocytes, but not in neutrophils and T-lymphocytes (50-53). The activation of neutrophils, monocytes and lymphocytes includes various changes related to their function: phagocytosis and bacteria elimination, immunoglobulin production, and antigen presentation (51, 54). Lymphocytes divide rapidly, and during activation they alter their metabolism in order to increase the rates of oxidative phosphorylation and glycolysis. Therefore, glucose is a very important energy source for these cells. Besides leukocytes, human platelets also express GLUT3 in their plasma membrane (15%) and in the membranes of secretory granules (85%). Upon platelet activation, GLUT3 is recruited from the secretory granules (α -granules) to the plasma membrane. This translocation, which is triggered by thrombin, is followed by various energy-dependent changes such as actin polymerization, platelet shape and aggregation, and clot formation. These cellular processes demand a lot of energy from ATP, which is generated/replenished by glycolytic degradation of glucose (55). Similar phenomenon, i.e., translocation of GLUT3 from intracellular stores was detected in neutrophils; upon activation with bacteria, GLUT3 is not only recruited to the plasma membrane, but also appears to concentrate in the phagosome-like structures. A glycolysis-generated high energy from glucose is needed here as well, to eliminate bacteria by phagocytosis through the production of superoxide radicals and function of lysosomal hydrolases (49).

Glucose transporter 5 (GLUT5)

Among all the members of SLC2 family, GLUT5 (gene *SLC2A5*) is the only transporter with high specificity for fructose; it can not transport glucose or galactose (19). GLUT5 was cloned from the human small intestine and sperm (56, 57). Primary physiological functions of GLUT5 is absorption of fructose across the BBM of small intestinal enterocytes. It also participates in the transfer of fructose across the BLM of jejunal enterocytes (19, 58). In blood cells, GLUT5 is the primary transporter of fructose in the human RBC, as confirmed in immunoblotting, immunolocalization, and transport studies (59). The consumption of fructose as a natural sweetener (corn syrup) has dramatically increased in human diet, and high dietary intake of fructose may be an important factor in development of cardiorenal metabolic syndrome (CRS)-

associated insulin resistance, type 2 diabetes mellitus, and high blood pressure (60-62). It is unclear whether fructose plays a specific role in the increased incidence of these disorders or whether an excessive caloric intake is responsible for these diseases. It is, therefore, very important to understand the metabolic pathways involved in the metabolism of fructose in human RBC. Although some studies showed lower expressions of GLUT5 in several tissues such as kidneys, testes, sperm, muscle, and fat (1), the physiological significance of these extra-intestinal expression in humans remains unclear. An animal model of *GLUT5* knockout mice may be a suitable experimental model to resolve these questions. GLUT5 is also expressed in immune cells; in the fully differentiated resting macrophages GLUT5 was localized in intracellular organelles by immunoblotting and immunofluorescence, but similar expression was not detected in the monocyte-like cells (52, 63). Activation of fully differentiated cultured macrophages by phorbol myristate acetate (PMA) resulted in redistribution of GLUT5 from the cell surface to an intracellular compartment (54). Since the concentrations of fructose in peripheral blood and other extra-intestinal tissues are very low, the physiological role(s) of GLUT5 expression in these tissues is unclear (63). It is possible that GLUT5 transports one or more substrates other than fructose, which may explain its wider tissue distribution and response to diabetes.

Glucose transporter 6 (GLUT6)

GLUT6 (gene *SLC2A6*) is a low-affinity glucose transporter whose primary physiological substrate has not yet been identified (64). Its mRNA is mainly expressed in the brain, spleen, and peripheral leukocytes. GLUT6 was originally cloned from the human leukocyte cDNA (31). In general, little is known about GLUT6 isoform, as well as the whole class III of facilitative sugar transporters. However, it has been clearly established that GLUT6 contains a dileucine (LL) motif in N-terminus, functioning as a signal for translocation of the protein to the membrane-derived organelles, including endosomes, lysosomes or endoplasmic reticulum (65). It displays low glucose transport activity when reconstituted into proteoliposomes, indicating that the physiological function of GLUT6 protein may be the glucose transport across the membrane of intracellular organelles. A clear function of this transporter in healthy human leukocytes is not known. Also a significant change of GLUT6 expression in chronic lymphocytic leukemia was not found (66).

Glucose transporter 9 (GLUT 9)

GLUT9 (gene *SLC2A9*) has been initially considered as a glucose and fructose transporter (67), but several later studies showed that it transports glucose or fructose very weakly compared with a high urate transport activity (68, 69). GLUT9 exists in two alternatively spliced variants of the *SLC2A9* gene that encode for long (GLUT9A) and

short (GLUT9B) isoforms due to different length of their N-terminal tails (70-72). In humans and mice, the isoform GLUT9A is expressed in the basolateral domain of various epithelial cells (sinusoidal membrane of hepatocytes, BLM of PT cells and enterocytes, placental syncytiotrophoblast), as well as in chondrocytes and leukocytes, whereas the isoform GLUT9B is expressed in the apical domain of various cells (canalicular membrane of hepatocytes, BBM of PT, placental syncytiotrophoblast) (73). In humans, uric acid is the end product of purine metabolism, which is in other mammals further degraded to allantoin by uricase (urate oxidase) in the liver. During evolution, humans have lost the uricase, and thus contain an elevated level of uric acid in their plasma (74). Higher serum levels of uric acid may represent a selective advantage in the evolution of hominids because of its strong antioxidant activity. However, hyperuricemia and formation of urate crystals is correlated with multiple diseases in humans, such as gout, hypertension, atherosclerosis, insulin resistance, and diabetes. It has been established that GLUT9 represents a major regulator of urate homeostasis in dogs, mice, and men. However it is still unknown whether uric acid causes hypertension, atherosclerosis or insulin resistance (19). Although there are many published studies focused on molecular mechanisms of the renal urate transport, it would be interesting to reveal the function(s) of GLUT9 in other organs or tissues. There is a good evidence that GLUT9 is expressed in leukocytes, but so far there is no indication whether this transporter is required for any specific uptake or secretion (75).

In conclusion, 14 different isoforms of the thus far identified GLUTs indicate a complexity of handling and regulation of glucose homeostasis in the mammalian cells. However, their physiological function, precise mechanism of transport, substrates affinity, exact three-dimensional structures as well precise tissue distribution, are poorly explored. Since the expression of some GLUTs may be associated with diabetes, several degenerative diseases and cancers, it is undoubtedly important to investigate their expression in healthy and diseased organs. We have noticed a very few data in the literature concerning the expression of GLUTs in the mammalian blood cells. There is a need for wider and deeper investigations of cellular localization, tissue distribution, function and other characteristics of GLUTs in blood cells in order to better understand their possible association with specific diseases in humans and develop possible therapeutic strategies. The related studies in experimental animals and experimental models of diseases are also deficient.

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