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Glucose transporters in the 21st Century

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Thorens B, Mueckler M. Glucose transporters in the 21st Century. *Am J Physiol Endocrinol Metab* 298: E141–E145, 2010. First published December 15, 2009; doi:10.1152/ajpendo.00712.2009.—The ability to take up and metabolize glucose at the cellular level is a property shared by the vast majority of existing organisms. Most mammalian cells import glucose by a process of facilitative diffusion mediated by members of the Glut (SLC2A) family of membrane transport proteins. Fourteen Glut proteins are expressed in the human and they include transporters for substrates other than glucose, including fructose, myoinositol, and urate. The primary physiological substrates for at least half of the 14 Glut proteins are either uncertain or unknown. The well-established glucose transporter isoforms, Gluts 1–4, are known to have distinct regulatory and/or kinetic properties that reflect their specific roles in cellular and whole body glucose homeostasis. Separate review articles on many of the Glut proteins have recently appeared in this journal. Here, we provide a very brief summary of the known properties of the 14 Glut proteins and suggest some avenues of future investigation in this area.

glucose transporter proteins; myoinositol transporters; urate transporters

Glucose as a Substrate and a Regulator of Metabolic Pathways

As a major product of the carbon fixation carried out by photosynthetic organisms, glucose is undoubtedly one of the most abundant biological molecules on the earth, existing mostly in various polymerized forms such as cellulose. Mechanisms have consequently evolved to utilize glucose as a major catabolic and anabolic substrate for the great majority of extant organisms in all three kingdoms.

In higher organisms, the preservation of energetic integrity requires adaptation to external resources and extensive inter-organ communication. In this context, glucose has acquired a role as a signaling molecule to control glucose and energy homeostasis. Glucose can regulate gene transcription, enzyme activity, hormone secretion, and the activity of glucoregulatory neurons.

The transcription factor carbohydrate response element-binding protein (ChREBP) mediates the effect of glucose on glycolytic and lipogenic gene expression (32). Glucose flux through the glucosamine pathway regulates the activity of transcription factors by promoting their *O*-GlcNAcylation (16). Glycolysis, through the production of NAD^+, modulates the activity of the Sirt1 deacetylase, which has emerged as an important regulator of gene transcription (49). Glucose metabolism via the production of acetyl-CoA induces histone modifications, resulting in epigenetic control of gene expression (44).

In pancreatic β-cells, glucose is the principal regulator of insulin secretion, and, in the brain, groups of glucose-sensitive neurons are activated or inhibited by rises in glucose concentrations. These neurons are involved in the control of feeding, energy expenditure, and glucose homeostasis (27).

These various glucoregulatory functions are usually secondary to glucose uptake, a step that, in most tissues (with the notable exception of hepatocytes and pancreatic β-cells), is controlled by the level of glucose transporter expression at the cell surface. The existence of multiple glucose transporter isoforms, with different kinetic properties and regulated cell surface expression, provides the basis for the fine tuning of glucose uptake, metabolism, and signal generation in order to preserve cellular and whole body metabolic integrity.

Glucose Transporters

In an attempt to explain the isomeric specificity and saturability of glucose uptake into human red blood cells that had been observed 30 years previously, LeFevre (23) in 1948 was the first to postulate that a specific component within the cellular plasma membrane was required for the transfer of glucose across the lipid bilayer. In the early 1950s, Widdas (45) proposed a mobile carrier mechanism to explain the observed kinetics of glucose transport across sheep placenta, but it was not until the 1970s that glucose transport was demonstrated to be mediated by a protein embedded in the erythrocyte plasma membrane that could be partially purified and functionally reconstituted into proteoliposomes (2, 20). The cloning of cDNA encoding the red cell glucose transporter (Glut1) occurred in 1985 (29), and 13 related members of the SLC2A (Glut) protein family have subsequently been identified in the human (41).

The Glut protein family belongs to the Major Facilitator Superfamily (MFS) of membrane transporters (31). Well over 5,000 members of the MFS have been identified to date, encompassing all three kingdoms. Indeed, the authors are unaware of a single organism that does not appear to express

multiple members of the MFS. Most Glut proteins catalyze the facilitative (energy-independent) bidirectional transfer of their substrates across membranes, and they may exhibit either symmetric or asymmetric transport kinetics. Gluts are proteins of ~500 amino acids and are predicted to possess 12 transmembrane-spanning alpha helices and a single N-linked oligosaccharide. The Glut family members can be grouped into three different classes based on their sequence similarities (18).

A series of reviews on many of the Glut proteins has recently appeared in the *American Journal of Physiology - Endocrinology and Metabolism* (4, 5, 8, 10, 19, 25, 35, 36). In this article, we briefly summarize the key features of the 14 Glut family members and provide some subjective comments on the current status of the glucose transporter field.

Glut1

Glut1 is undoubtedly one of the most intensively studied of all membrane transport proteins. The structure, mechanism, and kinetics of transport via this protein have been the subject of many hundreds of studies conducted over the past several decades (4). Despite this attention, we still know little of the precise three-dimensional structure of Glut1 and very little concerning how this protein transports sugars across lipid bilayer membranes (30). Although the crystal structures of three bacterial members of the MFS have been published (1, 15, 48), these data are of little value in elucidating the structure of Glut proteins at the atomic level because of the lack of sequence similarity among different families that comprise the MFS (24). It is therefore imperative to obtain high-resolution crystal structures of glucose transporters in different conformational states if we are to understand their mechanism of action.

Of what value would knowledge of the structure and mechanism of Glut1 be? First, Glut1 catalyzes the rate-limiting step in supplying cells of the central nervous system with glucose, an essential fuel for these cells. The ability to acutely upregulate Glut1 activity might be a very useful strategy to counter the effect of strokes due to arterial blockage as well as the damage that occurs to cardiomyocytes during cardiac infarction (50). Although many more examples could be mentioned, a second and inverse application reflects the observation that Glut1 is frequently upregulated during oncogenesis in many different tissue types (13), a process that is probably essential for tumors to grow beyond a size limited by their glycolytic capacity (the Warburg effect). The rational design of isoform-specific inhibitors of glucose transport is of obvious interest in this regard.

Glut2

Glut2 has a uniquely high K_m for glucose (~17 mM), and it is expressed at a very high level in pancreatic β-cells and in the basolateral membranes of intestinal and kidney epithelial cells and of hepatocytes (38). This ensures fast equilibration of glucose between the extracellular space and the cell cytosol at all physiological or diabetes-associated glycemic levels. In these cells, the rate of glucose metabolism is controlled at the glucose phosphorylation step. Thus, usually, modulation of Glut2 surface expression does not regulate metabolism except if its reduction is sufficient to limit glucose access to the hexokinases, as can happen in diabetic conditions in β-cells

(39). In intestine, Glut2 may also reach the apical surface in the presence of high luminal glucose concentration to increase glucose absorption (21).

In pancreatic β-cells, rises in blood glucose concentrations trigger insulin secretion, and in hepatocytes, glucose induces the expression of glycolytic and lipogenic genes. Absence of Glut2 prevents glucose-stimulated insulin secretion by β-cells and the regulation of glucose-sensitive gene expression in hepatocytes. Studies with gene knockout mice have indicated that Glut2 is also required for the function of glucose sensors present in the hepatoportal vein area and in the central nervous system. These sensors appear to control glucagon secretion, feeding behavior, insulin secretion, and peripheral tissue glucose uptake (27).

In their review, Leturque et al. (25) propose that Glut2 is also a glucose receptor that controls diverse cellular functions. This contention is based on the observation that transgenic mice that express a fusion protein consisting of EGFP and the cytoplasmic middle loop of Glut2 is present in the nucleus and alters liver, β-cell, and renal functions. However, it is unclear how this model can be extrapolated to the function of intact Glut2 in the plasma membrane. Nevertheless, because Glut2 appears to be associated with glucose-sensitive cells in the brain and the periphery, study of these Glut2-expressing cells may lead to a better understanding of the role of glucose as a regulatory signal. In this context, a recent study in humans reported an association between a mutation in Glut2 and preference for sugar-containing food, suggesting a possible role for this transporter in glucose sensing in humans (11).

Glut3

Glut3 (see Ref. 36) is the major neuronal glucose transporter, present in both dendrites and axons, and its level of expression in different regions of the brain correlates with regional cerebral glucose utilization (rCGU). Glut3 has a high affinity for glucose (K_m ~1.5 mM) and has the highest calculated turnover number of the Glut isoforms, thus ensuring efficient glucose uptake by neurons. In mouse sperm, Glut3 is highly expressed and controls glucose uptake and metabolism necessary for motility and maturation. During embryonic development, GLUT3 is present in the trophectoderm at the blastocyst stage and, after implantation, in extra-embryonic tissues. Its expression is reduced in preimplantation embryos of diabetic mothers, which leads to increased apoptosis. Knockout of Glut3 in the mouse induces apoptosis in the embryos, which do not survive past E6.5. Interestingly, a transient exposure to glucose is required for progression of compacted embryos to the blastula stage, and this is associated with induction of Glut3 expression. As this effect is also observed with a pulse of glucosamine, this suggests that O-GlcNAcylation of transcription factors may be involved in triggering Glut3 expression and embryo development. Glut3 is also expressed in lymphocytes, monocytes/macrophages, and platelets. In these cells, it is present in intracellular vesicles that can translocate and fuse to the plasma membrane upon cellular activation to ensure increased glucose uptake and metabolism. The basis for this regulated appearance of Glut3 to the plasma membrane is unknown. Its elucidation may lead to a better understanding of immune and inflammatory cell activation.

Glut4

Since its discovery as a distinct glucose transporter isoform in the late 1980s by James et al. (17), Glut4 has perhaps received more experimental attention than any other single membrane transport protein. A recent PubMed search revealed over 1,800 publications associated with Glut4 as a keyword. This high level of interest probably reflects the importance of this protein in whole body glucose homeostasis, its complex and elusive mechanism of regulation by insulin, and the disruption of this regulation in several prevalent insulin-resistant states, including obesity and type 2 diabetes mellitus. The knowledge of insulin-induced Glut4 translocation from intracellular membrane compartments to the cell surface in adipocytes and skeletal muscle has been available since the pioneering work conducted in the laboratories of Cushman (7), Kono (37), and Jenrenaud (43) in the early 1980s. Much has been learned of the details of this regulation in the intervening three decades (22). However, the fundamental structural features of Glut4 required for its unique regulated protein trafficking, the cellular components that are directly involved in these trafficking processes, and the precise pathways by which insulin signaling components impinge on Glut4 trafficking remain matters of considerable controversy and uncertainty. It is probably not coincidental that the primary cellular defects that lead to peripheral insulin resistance in obesity and type 2 diabetes remain unknown. In order to decipher the precise role of Glut4 in insulin resistance, we must deduce the structure of the molecule, identify how specific cellular components interact with the transporter to control its subcellular distribution, and ultimately unravel the maze of signaling events, from insulin and other mediators, that directly alter the interactions among Glut4 and these regulatory components. Our understanding of the acute and chronic (19) regulation of Glut4 in intact skeletal muscle, the major site of insulin-stimulated whole body glucose disposal, is still relatively poor and needs to be a major focus of future investigations.

Glut5

Glut5 appears to be the only Glut protein with a high specificity for fructose (10). Its principal site of expression is the apical membrane of intestinal epithelial cells, where it provides a major route for the absorption of dietary fructose. Although it is present at lower levels in several other tissues, including the kidney, brain, fat, testes, and muscle, the physiological significance of its extraintestinal expression in humans is unclear given the relatively low fructose concentrations that typically exist in the peripheral circulation and in urine ($<<0.1$ mM) compared with the >10 mM K_m of Glut5 for fructose. Glut5 is regulated by diurnal rhythm, substrate availability, and other factors. Interest in fructose metabolism has been aroused by the correlation between increased fructose consumption and the rise in the incidence of obesity, metabolic syndrome, and type 2 diabetes. However, it is unclear whether fructose plays a specific role in the increased incidence of these disorders or whether excess caloric intake in general is the real culprit. Regardless, the role of Glut5 in extraintestinal tissues needs to be investigated further via the generation of tissue-specific null mice.

Glut9

The physiological substrate for the Glut9 transporter has been investigated for many years (8), with the initial suggestion that it was a glucose and/or fructose transporter (3). However, the key function of this transporter was revealed unexpectedly from human genetic studies. Several groups reported genome-wide association studies (GWAS) that identified single-nucleotide polymorphisms in the Glut9 gene that were linked with elevated plasma uric acid levels (26, 42). This led to the immediate realization that Glut9 was a urate transporter. Glut9 is present in the liver, kidney, and intestine and, at a lower level, in chondrocytes. In humans, inactivating mutations of Glut9 cause hypouricemia, suggesting a role in renal urate reabsorption (28). It is thus unclear why the single-nucleotide variants present in noncoding regions identified in GWAS are associated with hyperuricemia and gout. In mice, genetic inactivation of Glut9 indicates that it is a major regulator of uric acid levels through its expression in liver to allow urate access to its degrading enzyme uricase and in kidney where it is probably involved in urate reabsorption (33). Liver-specific Glut9 gene inactivation causes hyperuricemia with apparently no other physiological abnormalities. This mouse model should help test whether elevated plasma uric acid levels may lead to insulin resistance, hypertension, or atherosclerosis, as suggested by epidemiological studies (12).

Gluts 6–8 and 10–14

Relatively little is known about the specific functions of these more recently discovered and less well studied Glut proteins, all of which were identified as a consequence of the sequencing of the human genome. Initial studies with knockout mice indicate roles for Glut8 in hippocampal neuronal proliferation and heart atrial activity (35) and of Glut12 in the regulation of glucose homeostasis (K. Moley, personal communication). Glut7 is the most recently characterized Glut protein and has a high degree of sequence similarity to Glut5 (5). It is expressed in the apical membrane of the small and large intestine and exhibits a low level of transport activity for fructose and glucose. Its principal physiological substrate has probably not yet been identified, but Glut7 is most likely involved in the dietary absorption of one or more low-molecular-weight carbon compounds. Glut13, also called HMIT (proton-coupled myoinositol transporter), is a myoinositol transporter expressed primarily in the brain and is the only Glut protein that appears to function as a proton-coupled symporter (40). Its precise role in brain myoinositol metabolism has not yet been established, but because intraneuronal myoinositol metabolism is associated with membrane trafficking at synapses and growth cones and is a target of the bipolar disorder drug LiCl, variants of this transporter may be associated with mood disorders (14, 46). Glut14, expressed in the testes, is a class I protein with a very high degree of sequence similarity to Glut3 (47), and thus it is most likely a glucose transporter; however, its specific role in glucose metabolism in this tissue is unknown. Glut6 cDNA was originally cloned from leukocytes, and it appears to exhibit glucose transport activity, but its primary physiological substrate has not been definitively identified (9). Glut11 exists in three different forms that vary at their extreme NH_2 termini and that are expressed in different tissue types (34). It exhibits detectable glucose and fructose

transport activity, but again, its principal substrate has probably not yet been identified. Mutations in the Glut10 gene are the cause of arterial tortuosity syndrome (6); however, the precise physiological role of Glut10 and its primary transported substrate have not yet been defined. Clearly, there is still much to be learned about the fundamental roles of more than half of the Glut protein family members.

Some Major Questions and Future Directions

Why are there so many glucose transporter isoforms? Why, for example, does human skeletal muscle express at least six different Glut proteins? Studies of the "old" Gluts 1–5 have shown that each has a specific role in the control of sugar homeostasis, whether because of its tissue-restricted expression, its kinetic characteristics, its substrate specificity, or mechanisms regulating its cell surface expression and role in the control of glucose metabolism. There is thus clear evidence that each glucose transporter isoform may play a specific role related to glucose handling in different cell types to regulate metabolism, gene expression, differentiation, or oncogenesis. It is likely that the lesser-studied Glut proteins will be shown in some cases to transport novel substrates or to exhibit unique kinetic or regulatory properties that are directly related to their distinct physiological roles.

Glut proteins have proven to be extremely refractory to crystallization. Is it possible to deduce high-resolution structures of Glut proteins? What will their structures tell us about the transport mechanism, and can the structures be used to design isoform-specific inhibitors that may prove to be valuable in dissecting out their specific functions and for possible pharmacological use in the treatment of diseases such as cancer?

The pathway leading from insulin binding to its receptor to the redistribution of Glut4 to the cell surface in muscle and fat cells is still incompletely understood. What new signaling elements will be discovered to be involved in this process, and how might they impinge on Glut4 subcellular trafficking? Will the identification of novel signaling elements lead to the development of new pharmacological treatments to alleviate peripheral insulin resistance? Is the trafficking of Glut4 regulated identically in white fat, brown fat, and skeletal muscle? Are our current models for studying Glut4 regulation in immortalized cell lines truly representative of what occurs in native tissues?

Given that Glut2 is associated with glucose sensing in different cell types, can its study inform us about the defect in glucose sensing that appears during the pathogenesis of type 2 diabetes? What roles might Glut2 and Glut4 play in glucose-sensitive neurons and the regulation of satiety and whole body glucose homeostasis?

Is the consumption of high dietary fructose, relative to glucose and other simple sugars, truly deleterious to human metabolism? If so, can inhibitors of Glut5 be designed to minimize the absorption of the sugar in susceptible individuals?

How many new physiological substrates will be discovered for the more recently discovered Glut proteins? Are these Gluts directly involved in the pathogenesis of any human diseases, as is the case for Glut9 and Glut10? Can they be exploited in some manner for the treatment of any disease conditions?

These and many other questions will likely keep investigators interested in the study of glucose transporters occupied for a very long time.

DISCLOSURES

No conflicts of interest are reported by the author(s).

REFERENCES

1. **Abramson J, Smirnova I, Kasho V, Verner G, Kaback HR, Iwata S.** Structure and mechanism of the lactose permease of *Escherichia coli* [see comment]. *Science* 301: 610–615, 2003.
2. **Baldwin JM, Gorga JC, Lienhard GE.** The monosaccharide transporter of the human erythrocyte. Transport activity upon reconstitution. *J Biol Chem* 256: 3685–3689, 1981.
3. **Carayannopoulos MO, Schlein A, Wyman A, Chi M, Keembiyehetty C, Moley KH.** GLUT9 is differentially expressed and targeted in the preimplantation embryo. *Endocrinology* 145: 1435–1443, 2004.
4. **Carruthers A, Dezutter J, Ganguly A, Devaskar SU.** Will *the* original glucose transporter isoform please stand up! *Am J Physiol Endocrinol Metab* 297: E836–E848, 2009.
5. **Cheeseman C.** GLUT7: a new intestinal facilitated hexose transporter. *Am J Physiol Endocrinol Metab* 295: E238–E241, 2008.
6. **Coucke PJ, Willaert A, Wessels MW, Callewaert B, Zoppi N, De Backer J, Fox JE, Mancini GM, Kambouris M, Gardella R, Facchetti F, Willems PJ, Forsyth R, Dietz HC, Barlati S, Colombi M, Loeys B, De Paepe A.** Mutations in the facilitative glucose transporter GLUT10 alter angiogenesis and cause arterial tortuosity syndrome [see comment]. *Nat Genet* 38: 452–457, 2006.
7. **Cushman SW, Wardzala LJ.** Potential mechanism of insulin action on glucose transport in the isolated rat adipose cell. Apparent translocation of intracellular transport systems to the plasma membrane. *J Biol Chem* 255: 4758–4762, 1980.
8. **Doblado M, Moley KH.** Facilitative glucose transporter 9, a unique hexose and urate transporter. *Am J Physiol Endocrinol Metab* 297: E831–E835, 2009.
9. **Doege H, Bocianski A, Joost HG, Schurmann A.** Activity and genomic organization of human glucose transporter 9 (GLUT9), a novel member of the family of sugar-transport facilitators predominantly expressed in brain and leucocytes. *Biochem J* 350: 771–776, 2000.
10. **Douard V, Ferraris RP.** Regulation of the fructose transporter GLUT5 in health and disease. *Am J Physiol Endocrinol Metab* 295: E227–E237, 2008.
11. **Eny KM, Wolever TM, Fontaine-Bisson B, El-Sohemy A.** Genetic variant in the glucose transporter type 2 is associated with higher intakes of sugars in two distinct populations. *Physiol Genomics* 33: 355–360, 2008.
12. **Feig DI, Kang DH, Johnson RJ.** Uric acid and cardiovascular risk. *N Engl J Med* 359: 1811–1821, 2008.
13. **Ganapathy V, Thangaraju M, Prasad PD.** Nutrient transporters in cancer: relevance to Warburg hypothesis and beyond. *Pharmacol Therapeut* 121: 29–40, 2009.
14. **Hallcher LM, Sherman WR.** The effects of lithium ion and other agents on the activity of myo-inositol-1-phosphatase from bovine brain. *j Biol Chem* 255: 10896–10901, 1980.
15. **Huang Y, Lemieux MJ, Song J, Auer M, Wang DN.** Structure and mechanism of the glycerol-3-phosphate transporter from *Escherichia coli* [comment]. *Science* 301: 616–620, 2003.
16. **Issad T, Kuo M.** O-GlcNAc modification of transcription factors, glucose sensing and glucotoxicity. *Trends Endocrinol Metab* 19: 380–389, 2008.
17. **James DE, Brown R, Navarro J, Pilch PF.** Insulin-regulatable tissues express a unique insulin sensitive glucose transport protein. *Nature* 333: 183–185, 1988.
18. **Joost HG, Bell GI, Best JD, Birnbaum MJ, Charron MJ, Chen YT, Doege H, James DE, Lodish HF, Moley KH, Moley JF, Mueckler M,**

Rogers S, Schurmann A, Seino S, Thorens B. Nomenclature of the GLUT/SLC2A family of sugar/polyol transport facilitators. *Am J Physiol Endocrinol Metab* 282: E974–E976, 2002.

19. **Karnieli E, Armoni M.** Transcriptional regulation of the insulin-responsive glucose transporter GLUT4 gene: from physiology to pathology. *Am J Physiol Endocrinol Metab* 295: E38–E45, 2008.

20. **Kasahara M, Hinkle PC.** Reconstitution and purification of the D-glucose transporter from human erythrocytes. *J Biol Chem* 252: 7384–7390, 1977.

21. **Kellett GL, Brot-Laroche E, Mace OJ, Leturque A.** Sugar absorption in the intestine: the role of GLUT2. *Annu Rev Nutr* 28: 35–54, 2008.

22. **Larance M, Ramm G, James DE.** The GLUT4 code. *Mol Endocrinol* 22: 226–233, 2008.

23. **LeFevre PG.** Evidence of active transfer of certain non-electrolytes across the human red cell membrane. *J Gen Physiol* 31: 505–527, 1948.

24. **Lemieux MJ.** Eukaryotic major facilitator superfamily transporter modeling based on the prokaryotic GlpT crystal structure. *Mol Membr Biol* 24: 333–341, 2007.

25. **Leturque A, Brot-Laroche E, Le Gall M.** GLUT2 mutations, translocation, and receptor function in diet sugar managing. *Am J Physiol Endocrinol Metab* 296: E985–E992, 2009.

26. **Li S, Sanna S, Maschio A, Busonero F, Usala G, Mulas A, Lai S, Dei M, Orru M, Albai G, Bandinelli S, Schlessinger D, Lakatta E, Scuteri A, Najjar SS, Guralnik J, Naitza S, Crisponi L, Cao A, Abecasis G, Ferrucci L, Uda M, Chen WM, Nagaraja R.** The GLUT9 gene is associated with serum uric acid levels in Sardinia and Chianti cohorts. *PLoS Genet* 3: e194, 2007.

27. **Marty N, Dallaporta M, Thorens B.** Brain glucose sensing, counterregulation, and energy homeostasis. *Physiology (Bethesda)* 22: 241–251, 2007.

28. **Matsuo H, Chiba T, Nagamori S, Nakayama A, Domoto H, Phetdee K, Wiriyasermkul P, Kikuchi Y, Oda T, Nishiyama J, Nakamura T, Morimoto Y, Kamakura K, Sakurai Y, Nonoyama S, Kanai Y, Shinomiya N.** Mutations in glucose transporter 9 gene SLC2A9 cause renal hypouricemia. *Am J Hum Genet* 83: 744–751, 2008.

29. **Mueckler M, Caruso C, Baldwin SA, Panico M, Blench I, Morris HR, Allard WJ, Lienhard GE, Lodish HF.** Sequence and structure of a human glucose transporter. *Science* 229: 941–945, 1985.

30. **Mueckler M, Makepeace C.** Model of the exofacial substrate-binding site and helical folding of the human Glut1 glucose transporter based on scanning mutagenesis. *Biochemistry* 48: 5934–5942, 2009.

31. **Pao SS, Paulsen IT, Saier MH Jr.** Major facilitator superfamily. *Microbiol Mol Biol Rev (Washington, DC)* 62: 1–34, 1998.

32. **Postic C, Girard J.** Contribution of de novo fatty acid synthesis to hepatic steatosis and insulin resistance: lessons from genetically engineered mice. *J Clin Invest* 118: 829–838, 2008.

33. **Preitner F, Bonny O, Laverriere A, Rotmann S, Firsov D, da Costa A, Metref S, Thorens B.** GLUT9 is a major regulator of urate homeostasis and its genetic inactivation induces hyperuricosuria and urate nephropathy. *Proc Natl Acad Sci USA* 106: 15501–15506, 2009.

34. **Scheepers A, Schmidt S, Manolescu A, Cheeseman CI, Bell A, Zahn C, Joost HG, Schurmann A.** Characterization of the human SLC2A11 (GLUT11) gene: alternative promoter usage, function, expression, and subcellular distribution of three isoforms, and lack of mouse orthologue. *Mol Membr Biol* 22: 339–351, 2005.

35. **Schmidt S, Joost HG, Schurmann A.** GLUT8, the enigmatic intracellular hexose transporter. *Am J Physiol Endocrinol Metab* 296: E614–E618, 2009.

36. **Simpson IA, Dwyer D, Malide D, Moley KH, Travis A, Vannucci SJ.** The facilitative glucose transporter GLUT3: 20 years of distinction. *Am J Physiol Endocrinol Metab* 295: E242–E253, 2008.

37. **Suzuki I, Kono T.** Evidence that insulin causes translocation of glucose transport activity to the plasma membrane from an intracellular storage site. *Proc Natl Acad Sci USA* 77: 2542–2545, 1980.

38. **Thorens B.** Molecular and cellular physiology of GLUT2, a high-Km facilitated diffusion glucose transporter. *Int Rev Cytol* 137A: 209–238, 1992.

39. **Thorens B, Weir GC, Leahy JL, Lodish HF, Bonner-Weir S.** Reduced expression of the liver/beta-cell glucose transporter isoform in glucose-insensitive pancreatic beta cells of diabetic rats. *Proc Natl Acad Sci USA* 87: 6492–6406, 1990.

40. **Uldry M, Ibberson M, Horisberger JD, Chatton JY, Riederer BM, Thorens B.** Identification of a mammalian H(+)-myo-inositol symporter expressed predominantly in the brain. *EMBO J* 20: 4467–4477, 2001.

41. **Uldry M, Thorens B.** The SLC2 family of facilitated hexose and polyol transporters. *Pflügers Arch* 447: 480–489, 2004.

42. **Vitart V, Rudan I, Hayward C, Gray NK, Floyd J, Palmer CN, Knott SA, Kolcic I, Polasek O, Graessler J, Wilson JF, Marinaki A, Riches PL, Shu X, Janicijevic B, Smolej-Narancic N, Gorgoni B, Morgan J, Campbell S, Biloglav Z, Barac-Lauc L, Pericic M, Klaric IM, Zgaga L, Skaric-Juric T, Wild SH, Richardson WA, Hohenstein P, Kimber CH, Tenesa A, Donnelly LA, Fairbanks LD, Aringer M, McKeigue PM, Ralston SH, Morris AD, Rudan P, Hastie ND, Campbell H, Wright AF.** SLC2A9 is a newly identified urate transporter influencing serum urate concentration, urate excretion and gout. *Nat Genet* 40: 437–442, 2008.

43. **Wardzala LJ, Jeanrenaud B.** Potential mechanism of insulin action on glucose transport in the isolated rat diaphragm. *J Biol Chem* 253: 4758–4762, 1981.

44. **Wellen KE, Hatzivassiliou G, Sachdeva UM, Bui TV, Cross JR, Thompson CB.** ATP-citrate lyase links cellular metabolism to histone acetylation. *Science* 324: 1076–1080, 2009.

45. **Widdas WF.** Inability of diffusion to account for placental glucose transfer in the sheep and consideration of the kinetics of a possible carrier transfer. *J Physiol* 118: 23–39, 1952.

46. **Williams RSB, Cheng L, Mudge AW, harwood AJ.** A common mechanism of action for three mood-stabilizing drugs. *Nature* 417: 292–295, 2002.

47. **Wu X, Freeze HH.** GLUT14, a duplicon of GLUT3, is specifically expressed in testis as alternative splice forms. *Genomics* 80: 553–557, 2002.

48. **Yin Y, He X, Szewczyk P, Nguyen T, Chang G.** Structure of the multidrug transporter EmrD from *Escherichia coli*. *Science* 312: 741–744, 2006.

49. **Yu J, Auwerx J.** The role of sirtuins in the control of metabolic homeostasis. *Ann NY Acad Sci* 1173, *Suppl* 1: E10–E19, 2009.

50. **Yu S, Zhao T, Guo M, Fang H, Ma J, Ding A, Wang F, Chan P, Fan M.** Hypoxic preconditioning up-regulates glucose transport activity and glucose transporter (GLUT1 and GLUT3) gene expression after acute anoxic exposure in the cultured rat hippocampal neurons and astrocytes. *Brain Res* 1211: 22–29, 2008.