Chapter

Introductory Chapter: Glucose Transporters

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1. Introduction

The major source of energy for mammalian cells is glucose. Glucose derived from the diet and synthesized within the body is transported from the circulation into target cells. The transfer of glucose across the plasma membrane is necessary. Cell membrane is composed by lipid bilayer, which is hydrophobic. Glucose has hydrophilic nature. Therefore, cell membranes act as barriers to most molecules. For water molecules and a few other small molecules, such as oxygen and carbon dioxide, the lipid bilayer is permeable. These molecules move spontaneously down their concentration gradient by diffusion. For cations such as K^+, Na^+, and Ca^{2+}; anions such as Cl^- and HCO_3^-; and hydrophilic molecules and macromolecules such as proteins and RNA, lipid bilayer is impermeable. Therefore, these molecules and ions need specific transport system. There are two general classes of membrane transporters: channels and carriers.

Glucose transporters belong to the major facilitator superfamily (MFS). MFS contains 74 families of membrane transporters including more than 10,000 members. These transporters transport variety of molecules.

Glucose as well as other monosaccharides cannot penetrate the lipid bilayer because they are hydrophilic in nature; therefore, they require specific carrier proteins to undergo diffusion through the bilayer. In humans, there are three families of genes that encode for glucose transporters: *SLC2A*, *SLC5A*, and *SLC50A* [1].

Glucose is transported across the cell membranes and tissue barriers by a sodium-independent glucose transporter (facilitated transport, GLUT proteins, and *SLC2* genes), sodium-dependent glucose symporters (secondary active transport, SGLT proteins, and *SLC5* genes), and glucose uniporter—SWEET protein (*SLC50* genes). Most cells express more than one kind of glucose transporters. However, these membrane carrier proteins are called glucose transporters; they are involved in the transport of several different molecules, not just glucose.

2. Characteristics of glucose transporters

2.1 Characteristics of GLUT proteins

In humans, 14 members of GLUT proteins have been identified. They are encoded by the solute-linked carrier family 2, subfamily A gene family, and *SLC2A* [2, 3]. All GLUT proteins are predicted to contain 12 hydrophobic membrane spanning, α-helical transmembrane (TM) domains. These domains are connected by hydrophilic loop between TM6 and TM7 of the protein [4–6]. GLUTs contain a site for single glycosylation on the exofacial end, either in the large loop between TM1 and TM2 (first extracellular loop) or between TM9 and TM10 (fifth extracellular

loop) [7]. As was proposed for GLUT1, helices 1, 2, 4, 5, 7, 8, 10, and 11 form an inner bundle that is stabilized by the outer helices 3, 6, 9, and 12 [8].

Based on the phylogenetic analysis of sequence similarity and characteristic elements, the GLUT family of sugar transporters is divided into three classes [4, 5, 9, 10]: an N-linked glycosylation site for GLUTs of class I and II is positioned in the first exofacial loop between TM1 and TM2, and family members of class III contain the glycosylation site between TM9 and TM10 [5].

Class I GLUTs include GLUT1–GLUT4 and GLUT14, which are 48–63% identical in humans. Class II GLUTs comprise of GLUT5, GLUT7, GLUT9, and GLUT11. These transporters are 36–40% identical. Class III GLUTs include GLUT6, GLUT8, GLUT10, GLUT12, and GLUT13 (HMIT). GLUTs in this class are only 19–41% identical.

The human GLUTs are involved in the transport of the several hexoses in addition to myoinositol, urate, glucosamine, and ascorbate [7]. All the members of the GLUT family are facilitative transporters except for GLUT13 (HMIT), which is an H^+/myoinositol symporter [11].

2.2 Pseudogenes

To date, four pseudogenes of *SLC2A* family were described [5, 7]:

1. *SLC2A3P1* (alias GLUT6 or GLUT3 pseudogene) is located on chromosome 5q35.1 and is a retroposon of *SLC2A3*.

2. *SLC2A3P2* (alias GLUT3 pseudogene 2) is located on chromosome 1p31.3 and is a retroposon of *SLC2A3*.

3. *SLC2A3P4* (alias GLUT3 pseudogene 4) is located on chromosome 8q21.3 and is a retroposon of *SLC2A3*.

4. *SLC2AXP1* is located on chromosome 2q11.2 and contains internal stop sequences.

2.3 Characteristics of sodium-dependent glucose symporters

Crane [12] showed that active glucose absorption by hamster's small intestine required sodium ions in the bathing medium. He proposed that these symporters have two binding sites: one for glucose and one for sodium [13].

The sodium-dependent glucose cotransporters belong to the gene family (*SLC5A*), the SGLTs, or sodium/substrate symporters family (SSSF), containing over 450 members [14–16]. In humans, 12 members of sodium-dependent glucose cotransporters have been identified. Amino acid comparison of the human sodium-dependent glucose cotransporters shows the range of identity from 57 to 71% [17]. The members of the SGLT family also share considerable homology among the proteins (21–70% amino acid identity with SGLT1) [10, 16]. These proteins contain of 580–718 amino acid residues, with a predicted mass of 60–80 kDa. There is a diversity in gene structure. In eight genes, the coding sequences are found in 14–15 exons (*SLC5A1, SLC5A2, SLC5A4–SLC5A6,* and *SLC5A9–SLC5A11*), and the coding sequence for *SLC5A7* and *SLC5A3* are present in exons 8 and 1, respectively. In *SLC5A9–SLC5A11* and *SLC5A3*, there is evidence for alternative splicing. These proteins contain 14 TM α-helices (TMHs) in all but not in sodium-iodide symporter (NIS) and SMCT1, which lack TMH^{14} [18]. Both the hydrophilic N- and C-termini are located on the extracellular side of the cell membrane [1]. SGLTs are

highly glycosylated membrane proteins; however, glycosylation is not required in the functioning of the protein. The human *SLC5A* genes are expressed in different tissues, and all of them code for sodium-dependent glucose cotransporter proteins, except for SGLT3 (*SLC5A4*), which acts as a glucose sensor [19]. These carrier proteins transport substrates such as glucose, myoinositol, and iodide; one is a Na^+/Cl^-/choline cotransporter, and another is a glucose-activated ion channel [16].

2.4 Characteristics of SWEET glucose transporters

SWEETs transport mono- and disaccharides across vacuolar and plasma membranes. A new class of glucose transporters, SWEET, was first identified by expressing candidate *Arabidopsis* genes coding for polytopic membrane proteins in HEK293T cells [20]. SWEETs are ubiquitously expressed in plants. In contrast to *Arabidopsis thaliana*, in which up to two dozen SWEETs have been identified, animals usually have only one SWEET, except for *Caenorhabditis elegans*, where seven SWEET-encoding genes have been found. Homologs of the SWEETs are widespread in metazoan genomes, and there is a single homolog in human genome (SWEET1) encoded by the gene *SLC50A1* [1].

Human SWEET1 (RAG1AP1), encoded by *SLC50A1*, comprises 221 amino acids with a molecular weight of 25 kDa. Human SWEET1 did not promote glucose uptake but instead mediated a weak efflux. Human SWEET1 when expressed in HEK293T cells was predominantly found to be localized in the Golgi with minimum expression also found in the plasma membrane. Chen et al. [20] discovered the highest level of expression in the oviduct, epididymis, and intestine, and its expression was induced in mouse mammary gland during lactation. The authors suggest that the human SWEET1 serves to supply glucose for lactose synthesis in the mammary gland. Human SWEET1 glucose transporter is the missing glucose transporter in the basolateral membrane of enterocytes where it may account for the exit of glucose from the cell into the blood in patients with Fanconi-Bickel syndrome and in mice missing the GLUT2 transporter [21, 22].

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