The Facilitative Glucose Transporter SLC2A8 Regulates Reproductive Outcomes and Growth Phenotype in Mice

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Glucose is a primary source of energy for all mammalian cells, and its uptake or exit by the cell is primarily controlled through the presence of specialized gateways, called glucose transporters. The facilitative glucose transporters (GLUTs), structurally related membrane-spanning glycoproteins encoded by a family of SLC2A genes, are responsible for the uptake of several monosaccharides, including glucose, fructose, mannose, galactose, and glucosamine [1]. To date, 14 SLC2A proteins are known to be expressed in human and mouse cells. Although SLC2A proteins possess a high degree of sequence similarity, they differ significantly in their substrate specificity and binding kinetics as well as in their tissue-specific expression and subcellular distribution [1, 2]. The more recently discovered SLC2A8 (also known as GLUT8) binds and transports glucose with a higher affinity and is expressed in human and mouse tissues including the testis, brain, heart, liver, uterus, and ovary [3]. Although the currently available data suggest that SLC2A8 may exist at the level of the plasma membrane or as an intracellular transporter, the physiological significance of SLC2A8 remains poorly understood. In this regard, an interesting study published in the current issue of *Biology of Reproduction* by Adastra et al. [4] provides novel evidence to suggest that SLC2A8 plays a major role in controlling the reproductive outcomes in both males and females and in postnatal growth in mice.

Earlier studies have strongly indicated that glucose transport and metabolism are essential not only in early embryonic development, but also for the preparation of the receptive uterine endometrium to support embryo implantation [1, 5, 6]. It has been shown that early mammalian embryos are unable to utilize glucose until the beginning of blastocyst formation, when the embryo undergoes a metabolic switch from its preferred substrate pyruvate to glucose, a transition that is presumably signaled by glucose transport proteins. Consistent with this speculation, the expression of several transporters (SLC2A1–SLC2A4) has been reported in blastocysts [7]. The hyperglycemic condition (~50 mM concentration of glucose) generally causes repression of SLC2A1–SLC2A3. Moreover, the insulin-stimulated glucose uptake is primarily insensitive to SLC2A1–SLC2A3 [8], suggesting a limitation for use of these transporters in the above effects. However, recent studies by Carayannopoulos et al. [8] have demonstrated that, during the early embryonic development in mice, SLC2A8 is expressed in blastocysts, predominantly in the trophectoderm, and is subjected to translocation from an intracellular compartment to the cell surface under insulin-stimulated conditions. Further studies employing suppression of SLC2A8 expression by antisense oligonucleotides have demonstrated an inhibition of glucose uptake by the blastocysts under the insulin-stimulated condition [9], suggesting that SLC2A8 is an insulin-stimulated glucose transporter that plays a role in early embryonic development. Several SLC2A proteins, including SLC2A8, are also expressed in the uterus during the progression of stromal cell decidualization [6, 10, 11], indicating they also participate in uterine function during early pregnancy.

Based on the homozygous mutation of the SLC2A8 gene in mice [12, 13], two independent groups have shown that null mutation can lead to altered glucose metabolism in certain tissues or cells. Specifically, one null allele showed reduction of sperm function in respect to ATP levels, mitochondrial membrane potential, and motility, and a slight deviation from the expected Mendelian frequency for heterozygous breeding [12], implicating a mild reproductive phenotype for generation of offspring. The other null allele caused an increase in hippocampal cell proliferation and cardiac P-wave duration [13]. These studies, however, are at odds with the report by Adastra et al. [4], which has established a new SLC2A8-deficient mouse model by targeted deletion of the transcriptional start site and exons 1–4 of the gene. Adastra et al. [4] have uncovered defective phenotypes in females at the level of oocyte metabolism and ATP production. In addition, they have demonstrated significant defects in respect to endometrial stromal cell decidualization during early pregnancy in SLC2A8-null mice compared to wild-type littermates. Moreover, ovarian cross-transplantation studies have elegantly demonstrated that the decidualization phenotype in SLC2A8-null mice is not a result of secondary effects from the ovary, but rather that the effects lie in both the embryo and the endometrial aspects of implantation. Overall, the authors argue that defects in uterine decidualization caused the reduction of litter size, as well as retarded growth phenotype in the offspring, as exhibited by decreased body fat and increased resistance to a high-fat and high-carbohydrate diet in the adults. The overall finding of reproductive outcome and growth phenotype in SLC2A8 knockout mice is an important and novel advance in the field.

The above decidualization defect described for the SLC2A8-null mice is particularly interesting, because a recent report shows that the decidual polyploidy cells require, at the site of implantation, high energy homeostasis through increased mitochondrial generation and ATP production during their development and survival [14]. The role of SLC2A8 in the...
development of decidual polyploid cells will be most interesting to explore in the future.

REFERENCES