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Review

Transport and transporters in the endoplasmic reticulum

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Abstract

Enzyme activities localized in the luminal compartment of the endoplasmic reticulum are integrated into the cellular metabolism by transmembrane fluxes of their substrates, products and/or cofactors. Most compounds involved are bulky, polar or even charged; hence, they cannot be expected to diffuse through lipid bilayers. Accordingly, transport processes investigated so far have been found protein-mediated. The selective and often rate-limiting transport processes greatly influence the activity, kinetic features and substrate specificity of the corresponding luminal enzymes. Therefore, the phenomenological characterization of endoplasmic reticulum transport contributes largely to the understanding of the metabolic functions of this organelle. Attempts to identify the transporter proteins have only been successful in a few cases, but recent development in molecular biology promises a better progress in this field.

Keywords: Nucleotide sugar transporters; Solute carrier family 35; Glucose 6-phosphate translocase; TAP; Translocon; Permeability

Contents

Abbreviations: ER, endoplasmic reticulum; SER, smooth ER; RER, rough ER; EST, expressed sequence tags; DIDS, 4,4′-diisothiocyanostilbene-2,2′-disulfonic acid; NEM, N-ethylmaleimide; G6Pase, glucose 6-phosphatase; PDI, protein disulfide isomerase; G6P, glucose 6-phosphate; H6PDH, hexose 6-phosphate dehydrogenase; 11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; GSD1, glycogen storage disease type 1; G6PT, G6P translocase; vG6PT, variant G6P translocase; SR, sarcoplasmic reticulum; NaPi or NPT, sodium/phosphate transporter; UDP, uridine diphosphate; UDP-Glc, UDP-glucose; UDP-GlcNAc, UDP-N-acetylglucosamine; UDP-Gal, UDP-galactose; UDP-GalNAc, UDP-N-acetylgalactosamine; UDP-Xyl, UDP-xylose; NSTs, nucleotide sugar transporters; SLC35, solute carrier family 35; Glc, glucose; Man, mannose; GlcNAc, N-acetylglucosamine; UGGT, UDP-Glc glycoprotein glucosyltransferase; UGTrel1 (SLC35B1), UDP-Gal transporter related protein 1; AtUTr1, *Arabidopsis thaliana* UDP-Gal/UDP-Glc transporter; UDP-GlcA, UDP-glucuronic acid; SITS, 4-acetamido-4′-isothiocyanostilbene-2,2′-disulfonic acid; DEPC, diethyl pyrocarbonate; UGTrel7 (SLC35D1), UDP-Gal transporter related protein 7; UGT, UDP-glucuronosyltransferase; Ero1p, endoplasmic reticulum oxidoreductin 1 protein; Erv1p, essential for respiration and viability 1 protein; Fmo1p, flavin-containing monooxygenase; Flc, flavin carrier; CoA, coenzyme-A; Ac-CoA, acetyl-CoA; AT-1, Ac-CoA transporter; STS, steroid sulfatase; ARSC, arylsulfatase C; ES, estrone sulfatase; GSH, glutathione; GSSG, glutathione disulfide; RyR1, ryanodine receptor type 1; MHC, major histocompatibility complex; TAP, transporter associated with antigen processing; HEPES, 4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid

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The endoplasmic reticulum (ER) is a membrane network [1] found in every nucleated cell. The morphologically distinct smooth and rough ER (SER and RER) are formed by the same continuous membrane as the nuclear envelope. Its internal compartment, the ER lumen, is completely separated from the cytosol. However, the luminal enzyme activities related to carbohydrate metabolism, biotransformation, steroid metabolism and protein processing [2] are integrated in the cellular metabolism, and strongly connected to the cytosolic processes. This compartmentation often narrows the specificity of luminal enzymes because several potential substrates cannot pass the barrier. The transport of selected substrates across the ER membrane is an additional point where the enzyme activity can be potentially regulated. It is, therefore, doubtless that the ER functions cannot be properly revealed without understanding the related transport processes, which, in turn, requires the identification of the participating membrane proteins. Certain proteins involved in transport processes across ER membrane have been molecularly identified. Nonetheless, for the majority of the molecules that admittedly cross the ER membrane the involved transport protein(s) are still molecularly undefined, which is probably due to technical difficulties. The classic strategy based on separation, purification and fractional reconstitution of solubilized ER membrane proteins did not lead to the expected success, with the exception of the translocon pore components. Screening cDNA libraries or EST databases for homologues of previously cloned transporters seems to be a more fruitful approach. Although some transport activities have only been characterized functionally, our knowledge about the trans-membrane traffic in the ER is growing gradually. This review focuses on the ER transport activities, which connect luminal and extraluminal metabolic processes by facilitating substrate and product fluxes. Our aim was to provide a summary of the available information in the field.

1. Transported molecules

1.1. Sugars and derivatives

1.1.1. Glucose

The assumption that glucose crosses the microsomal membrane by simple diffusion [3] proved false and it has become clear that glucose is unable to cross cellular membranes. There are two possible routes for glucose generated in the ER lumen to be exported to the blood. It has not been clarified whether glucose leaves the cell by vesicular transport or it is secreted through two consecutive transport steps through the ER and plasma membranes.

Glucose transporters known at molecular level are integral proteins of the plasma membrane. Facilitated transport of glucose across the plasma membrane is catalyzed by a family of proteins referred to as GLUTs. At least 12 GLUT isoforms are known [4], having different kinetic properties, specificity and tissue distribution.

Much less is known about glucose transport across the ER membrane. The existence of a microsomal facilitative transport system – different from GLUTs – was confirmed in several ways. Meissner and Allen [5] studied glucose transport in rat liver microsomes using rapid filtration technique. Pre-loaded microsomes released 70% of glucose within 20 s. Nevertheless, about 30% of microsomes showed a much lower glucose permeation rate ($t_{1/2}$=3 min). It was concluded that the existence of microsomal vesicles with different permeability properties could be due to the restricted number of glucose channels in the ER.

Two components of the heterogeneous glucose transport were characterized in rat liver microsomes [6]. The dominant rapid phase of glucose transport had a $t_{1/2}$ of a few seconds and it was inhibited by pentamidine, cytochalasin B and 4,4′-