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Mini Review

Structure and function of nucleotide sugar transporters: Current progress

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ABSTRACT

The proteomes of eukaryotes, bacteria and archaea are highly diverse due, in part, to the complex post-translational modification of protein glycosylation. The diversity of glycosylation in eukaryotes is reliant on nucleotide sugar transporters to translocate specific nucleotide sugars that are synthesised in the cytosol and nucleus, into the endoplasmic reticulum and Golgi apparatus where glycosylation reactions occur. Thirty years of research utilising multidisciplinary approaches has contributed to our current understanding of NST function and structure. In this review, the structure and function, with reference to various disease states, of several NSTs including the UDP-galactose, UDP-*N*-acetylglucosamine, UDP-*N*-acetylgalactosamine, GDP-fucose, UDP-*N*-acetylglucosamine/UDP-glucose/GDP-mannose and CMP-sialic acid transporters will be described. Little is known regarding the exact structure of NSTs due to difficulties associated with crystallising membrane proteins. To date, no three-dimensional structure of any NST has been elucidated. What is known is based on computer predictions, mutagenesis experiments, epitope-tagging studies, in-vitro assays and phylogenetic analysis. In this regard the best-characterised NST to date is the CMP-sialic acid transporter (CST). Therefore in this review we will provide the current state-of-play with respect to the structure–function relationship of the (CST). In particular we have summarised work performed by a number groups detailing the affect of various mutations on CST transport activity, efficiency, and substrate specificity.

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1. Introduction

Protein glycosylation, which in eukaryotes occurs predominantly in endoplasmic reticulum (ER) and the Golgi apparatus, is the most prevalent and complex post-translational modification. It was originally believed that only eukaryotic membrane-bound or secreted proteins were glycosylated, however it is now known that this process occurs in a range of eukaryotic nuclear and cytoplasmic proteins, as well as in bacteria and archaea. The process of glycosylation covalently attaches a glycan, a reaction catalysed by glycosyltransferases, to the growing end of a carbohydrate chain on a nascent protein or lipid. These complex modifications modulate the properties of the proteins they decorate. These modifications play a crucial role in every aspect of biology including increasing protein solubility [1]; increasing structural stability and

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Table 1
Selected members of the SLC35 nucleotide sugar transporter family.

SLC nomenclature	NCBI preferred name	Substrate	Sub-cellular localisation	Link to disease	Ensembl ID
SLC35A1	CMP-Sia transporter (CST)	CMP-Sia	Exclusively Golgi	Congenital disorder of glycosylation (CDG2F) (OMIM #603585) [15,16]	ENSG00000164414
SLC35A2	UDP-Gal transporter (UGT)	UDP-Gal; UDP-GlcNAc	Golgi and/or ER	Colon cancer [17]; Wiskott-Aldrich syndrome [18] CDG2M (OMIM #300896) [19,20]	ENSG00000102100
SLC35A3	UDP-GlcNAc transporter (NGT)	UDP-GlcNAc	Predominantly Golgi	Possible link to malaria through UDP-GlcNAc transporter homolog [21] Musculoskeletal abnormalities in cattle [22] Arthrogryposis, mental retardation, and seizures (OMIM #615553) [23]	ENSG00000117620
SLC35A4	Probable UDP-sugar transporter; MGC2541	Putative UDP-Gal			ENSG00000176087
SLC35A5	Probable UDP-sugar transporter	Putative UDP-sugar			ENSG00000138459
SLC35B1	UGTREL1	Putative sugar transporter			ENSG00000121073
SLC35B2	PAPS transporter 1	PAPS	Exclusively Golgi	Colorectal cancer [24]; Dysplasia [25]	ENSG00000157593
SLC35B3	PAPS transporter 2	PAPS	Exclusively Golgi	Overexpression in hepatocarcinoma cell line [26]; Colon cancer [27] Dysplasia [25]	ENSG00000124786
SLC35B4	UDP-Xyl transporter (YEA)	UDP-Xyl; UDP-GlcNAc	Golgi and/or ER	Regulation of obesity & glucose homeostasis in mice [28] PHACE syndrome [29]	ENSG00000205060
SLC35C1	GDP-Fuc transporter (GFT)	GDP-Fuc	Predominantly Golgi	Leukocyte adhesion deficiency (CDG2C) (OMIM #266265) [30,31]; hepatocellular carcinoma [32].	ENSG00000181830
SLC35C2	OVCOV1	Putative GDP-Fuc transporter. Promotes Notch1 fucosylation [33]		Ovarian cancer [34]	ENSG00000080189
SLC35D1	UDP-GlcA/UDP-GalNAc dual transporter	UDP-GlcA; UDP-GalNAc	Exclusively ER	Schneckenbecken dysplasia (OMIM #269250) [35]	ENSG00000116704
SLC35D2	UDP-GlcNAc/UDP-Glc/ GDP-Man transporter (HFRC1)	UDP-GlcNAc; UDP-Glc; GDP-Man (not humans)	Exclusively Golgi		ENSG00000130958
SLC35D3	FRCL1	Substrate unknown		Chediak-Higashi syndrome [36]; Hermansky-Pudlak syndrome [36].	ENSG00000182747

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