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Review

The role of nucleotide sugar transporters in development of eukaryotes

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ABSTRACT

The Golgi apparatus membrane of all eukaryotes has nucleotide sugar transporters which play essential roles in the glycosylation of glycoproteins, proteoglycans and glycolipids. Mutations of these transporters have broad developmental phenotypes across many species including diseases in humans and cattle.

Contents

Abbreviations: UDP-Gal, uridine diphosphate galactose; UDP-Glc, uridine diphosphate glucose; UDP-GlcA, uridine diphosphate glucuronic acid; UDP-GlcNAc, uridine diphosphate-*N*-acetylglucosamine; UDP-GalNAc, uridine diphosphate-*N*-acetylgalactose; GDP-Fuc, guanosine diphosphate fucose; GDP-Man, guanosine diphosphate mannose; MDCK, Madin–Darby canine kidney; LADII, leukocyte adhesion deficiency type II; SQV, squashed vulva.

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1. Introduction

Defects in glycosylation cause very diverse developmental phenotypes that are shown in Fig. 1. Panel A is of a child with growth and mental retardation and abnormal toes [1]. Panel B corresponds to a calf with a short neck, fused vertebrae and scoliosis [2]. Panel C shows a mutant *Drosophila melanogaster* that has a shorter leg and a nicked wing [3]. Panel D shows a mutant *Caenorhabditis elegans* with abnormal gonad migration [4].

These four diverse phenotypes have in common defects in glycosylated macromolecules. Specifically, there is a deficiency of covalent linkages between sugars and proteins and/or between sugars and other sugars which in turn are bound to proteins. Defects also occur in glycolipids where sugars are covalently linked to lipids. The mechanisms leading to these biochemical defects originate from mutations in specific *nucleotide sugar transporters*, membrane proteins present in the Golgi apparatus of all eukaryotes. Recent reviews, emphasizing biochemical aspects of these transporters have been published [5–7].

1.1. Why is there a need for Golgi apparatus nucleotide sugar transporters?

Approximately half of all proteins in eukaryotic cells are either membrane bound or secreted. Both groups of proteins are synthesized on membrane bound polysomes, then translocated into the lumen of the endoplasmic reticulum from where they are transported, via vesicles, to the Golgi apparatus. Thereafter, these proteins are either transported, via vesicles, to other organelles, such as the plasma membrane or lysosomes, or are secreted to the outside of cells. In the lumen of the endoplasmic reticulum and Golgi apparatus approximately 80% of secreted and membrane bound proteins undergo posttranslational modifications, principally glycosylation but also sulfation and phosphorylation.

Substrates for these modifications are activated sugars (nucleotide sugars), activated sulfate (adenosine 3′-phosphate 5′-phosphosulfate) and activated phosphate (ATP). None of these nucleotide derivatives are synthesized in the lumen of the Golgi apparatus, where the above modifications occur, but rather in the cytosol. Exceptions to this rule are ATP, most of which is

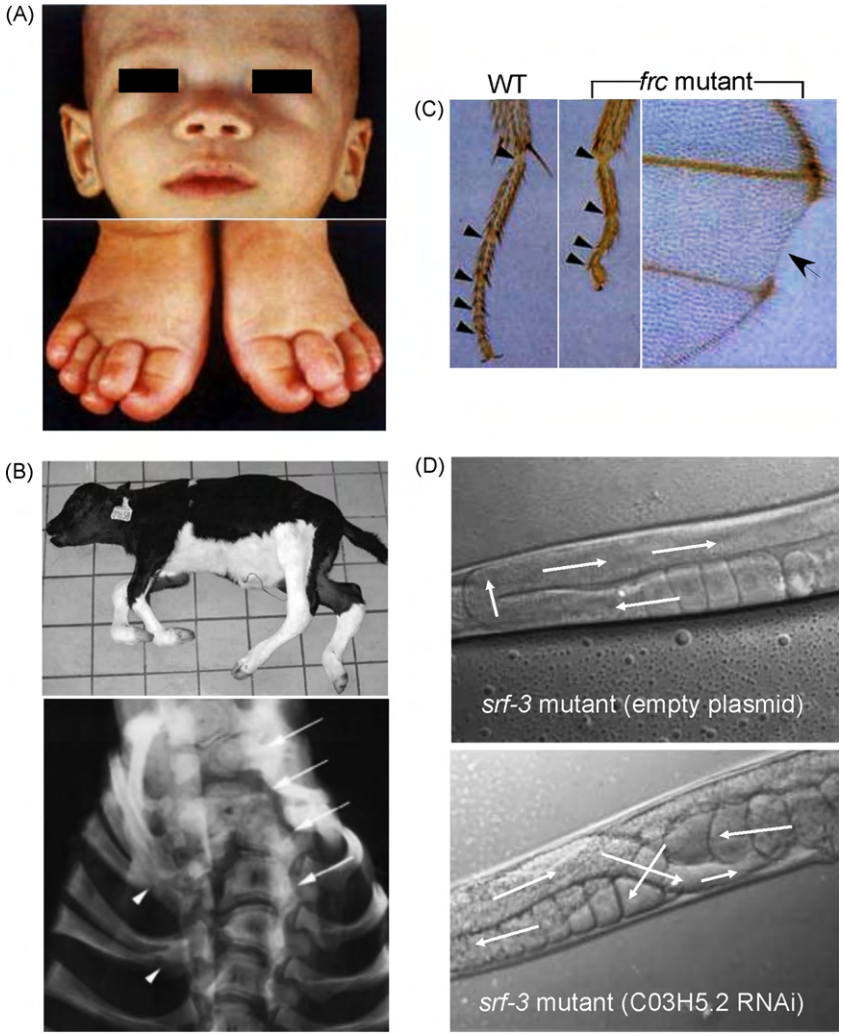

Fig. 1. The phenotypes of nucleotide sugar transporter diseases and mutations in multicellular organisms. (A) A child with leukocyte adhesion deficiency II (a mutation of the GDP-Fuc transporter), Copyright Elsevier (J Pediatrics) (1999) Ref. [1]. (B) A calf with complex vertebral malformation (a mutation in the UDP-GlcNAc transporter), Copyright Cold Spring Harbor Laboratory Press, Ref. [2]. The malformed vertebrae and scoliosis are shown by arrows, the fused ribs are shown by arrowheads. (C) *Drosophila melanogaster* with a mutation in a multisubstrate nucleotide sugar transporter, adapted by permission from Macmillan Publishers Ltd. Ref. [3]. Arrowheads show the shortened joints between tarsal segments in the *frc* mutant. Nicked wing is indicated by an arrow. (D) *Caenorhabditis elegans* nucleotide sugar transporter mutant *srf-3* in which the nucleotide sugar transporter C03H5.2 was silenced, Copyright ASBMB (2007), Ref. [4]. The migration of gonads is depicted by white arrows.