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Review

Metabolic manipulation of glycosylation disorders in humans and animal models

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ABSTRACT

In the last decade, over 40 inherited human glycosylation disorders were identified. Most patients have hypomorphic, rather than null alleles. The phenotypic spectrum is broad and most of the disorders affect embryonic and early post-natal development; a few appear in adult life. Some deficiencies can be treated with simple dietary sugar (monosaccharide) supplements. Here we focus on four glycosylation disorders that have been treated with supplements in patients or in model systems, primarily the mouse. Surprisingly, small differences in the amount of exogenous sugar have a major impact on the diseases in specific cells or organs while others are unaffected. The underlying mechanisms are mostly unknown, but changes in the contributions of the de novo, salvage and dietary pathways may contribute to the beneficial outcome. Clearly, the metabolic chart is not flat; all arrows are not equally robust at all points of time and space. This metabolic perspective may help explain some of these observations and guide the development of other vertebrate models of glycosylation disorders that can respond to dietary manipulation.

Contents

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1. Introduction

The metabolic chart is not flat since all metabolites in various pathways are not equally represented in time and space within an organism. For the most part, we do not know the sources or flux rates of metabolites. Patients with metabolic defects are sometimes treated by dietary manipulations [1–3], because they have hypomorphic alleles, allowing for direct or indirect stimulation of an injured pathway. Here, we focus on a few Congenital Disorders of Glycosylation (CDG) and related diseases that impair sugar chain (glycan) synthesis with specific reference to the expectations, and surprises when monosaccharide supplements are given to patients or animals with inherited glycosylation deficiencies (Table 1). These examples provide insights and cautions for studies covering the four-dimensional metabolic chart.

2. Biosynthetic pathways and glycans

2.1. Sources of precursors

De novo and salvage metabolic pathways for monosaccharides are shown in Fig. 1 [4]. Monosaccharides can be derived from the diet, or salvaged (reutilized) from degraded endogenous glycans.

Animal cell glycans made within the ER/Golgi contain nine precursor sugars: glucose, mannose, galactose, N-acetylglucosamine, N-acetylgalactosamine, sialic acid(s), fucose, xylose and glucuronic acid. All can be derived exclusively from glucose. Some occur in the diet or are indirectly salvaged from glycans degraded within lysosomes [4]. The relative contributions of de novo, salvage and dietary pathways are quite variable but mostly unknown [5,6]. How the preferences translate into physiology/pathology probably depends on the relative biosynthetic loads of different tissues. For instance, during embryonic development chondrocytes carry a heavy glycosylation burden [7], and in postnatal growth, hepatocytes make most plasma glycoproteins.

2.2. Glycosylation pathways

The N-glycan precursor is assembled on a carrier lipid (dolichol-P-P) into a 14-sugar unit containing 9 mannose, 3 glucose and 2 N-acetylglucosamine residues which is transferred to Asn within a Asn-X-Thr/Ser sequence of newly synthesized proteins in the ER. The protein-bound chains are trimmed, processed and extended within the Golgi. Membrane-associated proteins in the ER, Golgi, lysosome and on the cell surface contain N-glycans as do extracellular matrix and secreted proteins. O-GalNAc linked glycans are usually found in large clusters on secreted and cell surface mucins typically produced by epithelial cells. Some of the O-GalNAc containing proteins also function as ligands for lectins such as the selectins, which are important for trafficking of leukocytes [8]. Glycophospholipid anchors and glycosphingolipids, often occur in lipid rafts [9]. Proteoglycans are made on a limited number of core proteins. They begin with xylose linked to Ser and are extended with glycosaminoglycan chains, e.g., heparan sulfate, chondroitin- and dermatan-sulfate, which influence morphogen and growth factor distribution [10]. Quantitatively smaller, more recently appreciated important glycosylation pathways include O-fucose (on Notch receptors and ligands) [11], O-glucose (Notch receptors/igands) [12], and O-mannose (primarily on α-dystroglycan at neuromuscular junctions) [13,14]. The occurrence of monosaccharides in these pathways is shown in Table 2.

3. Glycosylation disorders

An estimated 2–3% of the genome encodes proteins used for biosynthesis and/or recognition of glycans. In just over a decade, >40 different human genetic disorders were discovered that affect one or more glycosylation pathways [15]. Below we focus on several disorders where the patients' pathology results from a limited supply of biosynthetic precursors.

3.1. CDG-Ia

3.1.1. Metabolic steps

CDG-Ia and Ib involve the earliest steps of mannose metabolism. Mannose-6-P can be made from fructose-6-P using phosphomannose isomerase (MPI) or from mannose imported directly from an extracellular source (diet or turnover) via a hexose transporter. It is then converted into Man-1-P using phosphomannomutase 2 (PMM2, Man-6-P → Man-1-P) which then leads to GDP-Man.

3.1.2. Patients

This disorder is caused by deficiency in PMM2 (<25% normal), which limits the amount of mannose flux into the glycosylation pathway resulting in sub-optimal occupancy of N-linked sites [16]. It is unknown whether other glycosylation pathways are also affected.

CDG-Ia patients are usually born at a normal weight, but are often symptomatic at birth and therefore show evidence of developmental abnormalities [17]. The babies often have an unusual distribution of fat above their buttocks along with inverted nipples. Symptoms which appear early after birth include stunted growth, crossed eyes, hypotonia (floppiness at the trunk) and highly variable developmental delay. They usually fail to develop a normal-sized, functional cerebellum. It is unknown whether this

Table 1
Disease names, genes, and enzymatic defects, and typical symptoms.

Disease name	Gene	Enzymatic defect	Symptoms
CDG-Ia (PMM2-CDG)	*PMM2*	Man-6-P → Man-1-P	Psychomotor retardation, hypotonia, esotropia, lipodystrophy, cerebellar hypoplasia, stroke-like episodes, seizures
CDG-Ib (MPI-CDG)	*MPI*	Man-6-P ↔ Fru-6-P	Hepatic fibrosis, protein-losing enteropathy, coagulopathy, hypoglycemia
CDG-IIc (SLC35C-CDG)	*SLC35C1*	GDP-Fuc(c) → GDP-Fuc(g)	Recurrent infections, persistent neutrophilia, psychomotor retardation, microcephaly, hypotonia
HIBM/DMRV	*GNE*	UDP-GlcNAc → ManNAc-6-P	Adult onset with progressive distal and proximal muscle weakness; spares quadriceps