ABSTRACT

Inherited disorders of glycosylation (CDG) are a large group of more than 160 types of metabolic disorders caused by genetic defects that lead to impaired glycan biosynthesis and modification. The lipid dolichol plays an essential role in glycan biosynthesis. Glycans play a key role in the function and structure of proteins and lipids and their deficiency leads to severe clinical symptoms. CDG usually manifests in childhood as a multisystem disorder. Families thus face a serious health problem due to the progressive and highly variable nature of the disease, the unfavorable prognosis and, with few exceptions, the unavailability of treatment. Currently, we still do not have a sufficient range of methods to recognize rare types of CDG and our knowledge of the pathophysiology of CDG is still limited.

The first aim of this work was to optimize the method of determination of dolichol isoforms and to study them in physiology and pathology. The second aim of the work was to investigate the bioenergetic status and overall metabolism in the most common type of CDG – deficiency of phosphomannomutase 2 (PMM2-CDG), and in CDG caused by a defect in dolichol biosynthesis.

The distribution of urinary dolichol isoforms in the population was characterized using an optimized method. The dolichol isoforms profile varied with age, suggesting possible changes in the physical properties of membranes during aging due to proportional changes in dolichol isoforms.

The present work also reveals a possible chronic stress in the endoplasmic reticulum in PMM2-CDG fibroblasts that leads to an activated response to misfolded proteins, which likely cause changes in cellular metabolism.

The study of bioenergetic parameters in fibroblasts in selected CDG types (PMM2-CDG, NUS1-CDG, SRD5A3-CDG and DHRSX-CDG) revealed a number of changes in biochemical pathways. Reduced glycolytic function was observed in all CDG types analyzed, providing a novel explanation for the disease manifestations and suggesting possible therapeutic targets.

Key words: Congenital disorders of glycosylation, bioenergy, dolichol, endoplasmic reticulum stress