

CONGENITAL DISORDERS OF GLYCOSYLATION: FROM YEAST TO MAN

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Glycosylation of proteins is the most complex and costly type of protein modification and is conserved during evolution to a large extent from yeast to man. Glycoconjugate biosynthesis occupies some 2-3% of human genes. However the role of this modification is still largely an enigma and only few examples of functional implications are known. Since about ten years it is now well established that defects in glycosylation cause a severe neurologic and multisystemic, frequently lethal disease, designated "Congenital Disorders of Glycosylation" (CDG). Biochemically, two groups with several subtypes have been defined. CDG-I types contain deficiencies in the biosynthesis and transfer of the lipid-linked oligosaccharide precursor chain onto nascent proteins in the ER lumen. CDG-II types cover broadly all other genes including defects in the processing steps of the carbohydrate moiety in the ER and Golgi, the supply of glycosyl donors, disorders in O-glycosylation, and most recently also genes involved in shuttling proteins between the ER and Golgi. It seems clear now that protein-linked glycans, play a fundamental role in embryonic and postembryonic development.

The lecture will give an overview on this rapidly expanding family of genetic diseases and will focus more specifically how yeast has been an invaluable model in elucidating the molecular basis of novel CDG-I types. Owing to the high conservation of the pathway, occurring in the ER, determining the phenotypes and the underlying gene sequences of various yeast glycosylation mutants (*alg*-mutants), it was possible to characterize corresponding human defects. For example, we could characterize CDG-Ii as a deficiency in *ALG2*. An *alg2* yeast *ts* mutant was shown earlier to accumulate Man₂GlcNAc₂-PP-Dol and Man₁GlcNAc₂-PP-Dol at the restrictive temperature, as it occurred in fibroblasts from a CDG-Ii patient, pointing to a defect in the corresponding human gene. However the precise biochemical defect of *ALG2* was not known. Incubation of CDG-Ii patient fibroblasts with Man₁GlcNAc₂-PP-Dol and GDP-Man revealed a severely reduced mannosyltransfer activity. Elongation of Man₁GlcNAc₂-PP-Dol could occur either by addition of an α 1,3- or an α 1,6-mannose residue. Since also elongation of Man α 1,6Man₁GlcNAc₂-PP-Dol was affected in the patient, the mannosyltransferase encoded by *ALG2* must be specific for the α 1,3-linkage and the biosynthetic route of mannose elongation in LLO formation must be α 1,3- followed by α 1,6-mannose. Heterologous expression of the human *ALG2* gene in *alg2* cells complemented the *ts* growth phenotype, normalized LLO formation as well protein glycosylation. This indicates that human *ALG2* is indeed the ortholog of yeast *ALG2*. Similar approaches were used to identify CDG-1c (*ALG6* glucosyltransferase), CDG-1g (*ALG12* mannosyltransferase) or CDG-1d (*ALG3* mannosyltransferase).

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