ABSTRACT

Congenital disorders of glycosylation (CDG) represent a rapidly growing group of rare inherited metabolic diseases with estimated prevalence as high as 1:20 000, which are caused by genetic defects that impair the process of glycosylation, i.e. the enzymatic addition of a specific saccharide structure onto a protein or lipid backbone. Due to non-specificity and variability of clinical symptoms in the patients, the medical diagnosis of CDG remains extremely challenging and significantly relies on accurate biochemical and genetic analyses.

The overall goal of the present dissertation thesis was to study CDG at the biochemical and molecular genetic level in the context of the Czech and Slovak Republic, which involved three specific aims: A.) to introduce and optimize laboratory screening methods for CDG detection in a group of clinically suspected patients, B.) to determine the corresponding genetic defect in the positive patients selected via CDG screening and to study the pathobiochemical aspects of specific CDG types at the cellular level, and C.) to analyze glycosylation disturbances of non-CDG etiology.

Contributions of this work include optimization of isoelectric focusing of apolipoprotein C-III (ApoC-III) as a screening method for O-glycosylation abnormalities, as well as the description of practical implications for using CDG screening methods (e.g., the detection of a specific transferrin polymorphism that hampers N-glycosylation screening, or the finding of hyposialylated ApoC-III in glycogen storage diseases). Moreover, while studying the subcellular structure and various pathobiochemical aspects in fibroblasts from CDG patients, we made observations that had not been previously reported (e.g., the cellular accumulation of reactive oxygen species in CDG). We accomplished biochemical characterization and genetic diagnosis in more than 20 patients, and selected cases (RFT1-CDG, PGM1-CDG, MAN1B1-CDG, NgBR defect) were published, bringing novel phenotype and genotype findings.

Keywords: congenital disorders of glycosylation, CDG, screening, apolipoprotein C-III, transferrin