UNRAVELLING THE RELATIONSHIP BETWEEN SUBSTRATE SELECTIVITY AND PRIMARY SEQUENCE OF UDP-GLYCOSYLTRANSFERASES

Tiia Kittilä, Novo Nordisk Foundation Center for Biosustainability, Technical University of Denmark
tiiaki@biosustain.dtu.dk
Ditte Hededam Welner, Novo Nordisk Foundation Center for Biosustainability, Technical University of Denmark

Key Words: Natural products, selectivity, glycosyltransferase

Plant natural products (NPs) are widely utilized in biotechnology, for example as fragrances, aromas, dyes and medicine. Although nature provides thousands of different NPs, only a small fraction of them is currently used in applications, partly because of problems in solubility and stability. These properties can be enhanced through glycosylation, but synthesis of glycosylated natural products is challenging. Enzymatic route to NP glycosylation is therefore of high interest. In plants, the enzymes responsible for NP glycosylation are called UDP-glycosyltransferases (UGTs) since they use UDP activated sugars as sugar donors. A single plant can have hundreds of UGTs allowing glycosylation of different compound groups. Understanding the bases of substrate selectivity would be important in allowing efficient engineering of UGTs for specific substrates and/or higher catalytic activities. Although UGTs have conserved tertiary structures, the relationship between UGT primary sequence and acceptor substrate is not well understood making enzyme engineering challenging. Main obstacles in creating a predictive model for substrate selectivity is the lag of UGT structures (currently nine plant UGT structures are available through PDB) and the lag of comparable information of UGT selectivity. Interestingly, it has been shown that UGT substrate selectivity is not related to phylogeny. Therefore, we wondered if more insights would be gained from comparing different phylogenetic groups to each other rather than trying to create a common predictive model for the whole enzyme group. By comparing structural information and sequence alignments, we indeed observed differences in substrate binding pocket folding when comparing UGTs from different phylogenetic groups. We hypothesize that this variation has led to difficulties in predicting substrate selectivity from UGT primary sequence, since some residues lining the binding pocket vary from one phylogenetic group to another. Therefore, it might be more feasible to predict substrate selectivity for each UGT phylogenetic group independently instead of the whole enzyme family.