5th International Conference on
GLYCOBIOLOGY & GLYCOPROTEOMICS
&
3rd International Conference on
MOLECULAR BIOLOGY & NUCLEIC ACIDS
August 27-28, 2018 | Toronto, Canada

Structure and engineering of plant uridine diphosphate glycosyltransferase toward drug development and metabolism

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A large number of uridine diphosphate glycosyltransferase (UGT) genes have evolved in plants for the biosynthesis and glycosylation of a large variety of plant natural products which are important for plant defense and may also have significant health benefits for animals and humans. Glycosylation is a key modification of plant natural products during their biosynthesis for enhancing their solubility and stability and facilitating their storage and accumulation in plant cells. Glycosylation is also one of the major factors determining natural product bioactivity and bioavailability. UGTs are members of family 1 glycosyltransferases (GTs), transfer a sugar from an activated donor such as a nucleoside diphosphate (NDP)-sugar to various acceptors, and are responsible for the glycosylation of plant secondary metabolites. We determined the first crystal structures of plant UGTs, providing structural insights into the glycosylation mechanisms of plant natural products. The structures of three UGTs revealed the detailed structural features and interactions between enzymes and substrates which define the substrate specificity of the individual enzymes. Mutagenesis studies enabled us to manipulate the regio-selectivity of glycosylation and to improve the enzyme activity. We are further performing both structural and functional studies of UGTs for understanding the complex glycosylation mechanisms and facilitating UGT engineering and synthetic biology approaches to natural product synthesis toward drug development and discovery. We also found that plant UGT71G1 could efficiently metabolize typical human UGT1A1 substrates including SN-38 and estradiol in vitro. We, therefore, are developing novel UGT mutants to mimic human UGTs for detoxification of the anticancer drugs with significant implications in human health.

Biography

Dr Xiaoqiang Wang has his expertise in glycosyltransferase structure and engineering research. His research group determined structures of three UGTs from Medicago truncatula, performed extensive mutagenesis studies, and revealed their structural basis of glycosylation mechanisms. He is developing a detoxification system of anticancer drugs with UGTs. He is also working on rational design and engineering of glycosyltransferases for the biosynthesis of glycosides of various bioactive compounds and drugs with enhanced bioactivity and bioavailability, facilitating the development of drugs and treatment strategies for various diseases.

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