DIRECTED EVOLUTION OF GLYCOSYLTRANSFERASE FOR THE ARTIFICIAL BIOSYNTHESIS OF NATURAL PRODUCT GLYCOSIDES

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Over one fifth natural product drugs (including protein biopharmaceuticals), cosmetics, and nutraceuticals have a diverse set of sugars in their structures. These glycosylations dramatically influence the physicochemical and pharmacological properties of these compounds. Glycosyltransferases (GTs) offer very attractive approaches to the biosynthesis of complex glycosylated natural products. However, the limited number of available GTs, together with their instability and strict substrate specificity, have severely hampered the broad application of these enzymes. In the past few years, we have used directed evolution as a tool to tailor the GTs with desired substrate specificity and higher catalytic activity. Here I will introduce some of our efforts in 1) the semi-rational design of a glucosyltransferase UGT51 from *S. cerevisiae* to repurposing its promiscuous activity towards the biosynthesis of rare ginsenoside Rh2; and 2) the directed evolution of an α1,3-fucosyltransferase using a single-cell ultrahigh-throughput screening method. I will also discuss the development of new tools for the high-throughput screening method for GTs and the mechanistic insight we found during the evolution of these enzymes.