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Insights into the combinatorial biosynthesis and tailoring of fungal polyketides

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Combinatorial biosynthesis aspires to exploit the incorporation of different microbial anabolic pathways to engineer the synthesis of new chemical entities. The modular enzymes composed by functionally independent domains, e.g., polyketide synthases (PKS), are suitable test cases for the modularization of secondary metabolic pathways into "build–couple–pair" synthetic schemes. Fungal benzenediol lactones (BDLs) polyketides provide an opportunity for combinatorial biosynthesis. Fungal BDLs are important pharmacophores with wide-ranging bioactivities, and their biosynthesis involves a pair of collaborating iterative polyketide synthases (iPKSs): A highly reducing iPKS (hrPKS) with product that is further elaborated by a non-reducing iPKS (nrPKS) to yield a 1,3-benzenediol moiety bridged by a macrolactone. Co-expressing random heterocombinations of hrPKSs and nrPKSs from different BDL biosynthetic pathways in *Saccharomyces cerevisiae* lead to the one-pot, one-step combinatorial biosynthesis of structurally diverse polyketides. In addition, the chemical diversity was further increased using heterologous tailoring enzymes such as glycosyltransferase and methyltransferase. Through heterologous expression and domain recombination to create hybrid enzymes, the product template (PT) domains in fungal nrPKSs that catalyze the first-ring cyclization of the benzenediol moiety can be used heterologously to create unnatural products with different polyketide folding modes. This folding mode difference can be programed by reshaping the cyclization chamber of a PT domain by only three selected point mutations. In addition, unnatural products can be generated via shuffling the nrPKS subunit if carefully tune the selectivity of the starter unit (SAT) and the TE domain. Our work provides a biosynthetic tool to generate unnatural polyketides as an unexplored source of chemical diversity and novelty, ready to be exploited for drug discovery, and these results demonstrated the potentials of combinatorial biosynthesis to produce new product with structure variety while considering the rules of enzyme activity and selectivity, shedding lights to further engineer the metabolic pathways in fungi.

Biography

Yuquan Xu has completed his PhD from China Agricultural University and Post-doctoral studies from the University of Arizona and University of California, San Diego. His research focuses on combinatorial biosynthesis of fungal polyketides. He has published more than 23 papers in reputed journals.

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