Comprehensive in Vitro Analysis of Acyltransferase Domain Exchanges in Modular Polyketide Synthases and Its Application for Short-Chain Ketone Production - DTU Orbit (19/01/2019)

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Type I modular polyketide synthases (PKSs) are polymerases that utilize acyl-CoAs as substrates. Each polyketide elongation reaction is catalyzed by a set of protein domains called a module. Each module usually contains an acyltransferase (AT) domain, which determines the specific acyl-CoA incorporated into each condensation reaction. Although a successful exchange of individual AT domains can lead to the biosynthesis of a large variety of novel compounds, hybrid PKS modules often show significantly decreased activities. Using monomodular PKSs as models, we have systematically analyzed the segments of AT domains and associated linkers in AT exchanges in vitro and have identified the boundaries within a module that can be used to exchange AT domains while maintaining protein stability and enzyme activity. Importantly, the optimized domain boundary is highly conserved, which facilitates AT domain replacements in most type I PKS modules. To further demonstrate the utility of the optimized AT domain boundary, we have constructed hybrid PKSs to produce industrially important short-chain ketones. Our in vitro and in vivo analysis demonstrated production of predicted ketones without significant loss of activities of the hybrid enzymes. These results greatly enhance the mechanistic understanding of PKS modules and prove the benefit of using engineered PKSs as a synthetic biology tool for chemical production.

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