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Engineering the biosynthesis of artemisinin

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Abstrcat

Terpenoids represent the largest class of natural products with a diverse array of structures and functions. Many terpenoids have reported therapeutic properties such as antimicrobial, anti-inflammatory, immunomodulatory and chemotherapeutic properties making them of great interest in the medical field. Terpenoids suffer from low natural yields and complicated chemical synthesis; hence there is a need for a more sustainable production method. Metabolic engineering using biosynthetic mevalonate and non-mevalonate pathways provides an excellent opportunity to construct microbial cell factories producing terpenoids. The complexity and diversity of terpenoid structures depends mainly on the action of the terpene synthases responsible for their synthesis. Amorpha- 4, 11-diene synthase (ADS) cyclizes the substrate farnesyl pyrophosphate to produce amorpha- 4, 11-diene as major product. This is considered the first committed and rate-limiting step in the biosynthesis of the antimalarial artemisinin. Here, we utilize a reported 3D model of ADS to perform mutability landscape guided enzyme engineering. A mutant library of 258 variants along sixteen active site residues was created and then screened for catalytic activity and product profile. This allowed for identification of the role of some of these residues in the mechanism. The mutability landscape also helped to identify variants with improved catalytic activity. H448A showed ~4 fold increase in catalytic efficiency and the double mutation T399S/H448A showed that kcat has improved by ~5 times. This variant can be used to enhance amorphadiene production and in turn artemisinin biosynthesis. Our findings provide the basis for the first step in improving industrial production of artemisinin and they open up possibilities for further engineering and understanding of ADS.

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