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SYNZIP ドッキングドメインを用いたキメラ PKS のエンジニアリング

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新規生物活性化合物を創出するためのポリケチドシンターゼ(PKS)エンジニアリングは 20 年以上前から研究されており、これまでにドメインの交換・モジュールの交換・活性部位の変異などが行われてきた。今回筆者らは、新しい合成生物学のツールとして SYNZIP と呼ばれる異種特異的合成コイルドコイルペプチドを PKS のモジュール内に組み込んだキメラモジュールを作製した。また、これらを用いて PKS のドメイン間相互作用について検討を行い、SYNZIP の有用性を示した。今後、SYNZIP が PKS エンジニアリングの新しいツールとして利用できるのではないかと期待される。

紹介論文

Engineering of Chimeric Polyketide Synthases Using SYNZIP Docking Domains
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要約

Engineering of assembly line polyketide synthases (PKSs) to produce novel bioactive compounds has been a goal for over 20 years. The apparent modularity of PKSs has inspired many engineering attempts in which entire modules or single domains were exchanged. In recent years, it has become evident that certain domain–domain interactions are evolutionarily optimized and, if disrupted, cause a decrease of the overall turnover rate of the chimeric PKS. In this study, we compared different types of chimeric PKSs in order to define the least invasive interface and to expand the toolbox for PKS engineering. We generated bimodular chimeric PKSs in which entire modules were exchanged, while either retaining a covalent linker between heterologous modules or introducing a noncovalent docking domain, or SYNZIP domain, mediated interface. These chimeric systems exhibited non-native domain–domain interactions during intermodular polyketide chain translocation. They were compared to otherwise equivalent bimodular PKSs in which a noncovalent interface was introduced between the condensing and processing parts of a module, resulting in non-native domain interactions during the extender unit acylation and polyketide chain elongation steps of their catalytic cycles. We show that the natural PKS docking domains can be efficiently substituted with SYNZIP domains and that the newly introduced noncovalent interface between the condensing and processing parts of a module can be harnessed for PKS engineering. Additionally, we established SYNZIP domains as a new tool for engineering PKSs by efficiently bridging non-native interfaces without perturbing PKS activity.