

## バクテリア由来の繰り返し型ポリケチド合成酵素の立体構造

加藤直樹

ポリケチド合成酵素 (PKS) の機能を自在に操り、望みの天然物誘導体を創出することは天然物生合成研究のゴールの1つである。それには、PKS の各触媒ドメインがどのように協調して働いているのか理解する必要がある、立体構造の解明はその鍵となる。従来、ドメインごとに切り分け解析されてきたが、最近になり、cryo-EM や SAXS といった新たな技術を組み合わせることで、モジュールの全体像が動的なモデルとして示されるようになった。今回は、バクテリア由来の繰り返し型 PKS の立体構造が明らかにされたので紹介する。

### 紹介論文

“Mycocerosic acid synthase exemplifies the architecture of reducing polyketide synthases”

Herbst, DA\*, Jakob, RP\*, Zähringer, F & Maier, T (Univ. of Basel, Switzerland)

*Nature* **531**, 533–537 (2016)

### 要旨

Polyketide synthases (PKSs) are biosynthetic factories that produce natural products with important biological and pharmacological activities. Their exceptional product diversity is encoded in a modular architecture. Modular PKSs (modPKSs) catalyse reactions colinear to the order of modules in an assembly line, whereas iterative PKSs (iPKSs) use a single module iteratively as exemplified by fungal iPKSs (fiPKSs). However, in some cases non-colinear iterative action is also observed for modPKSs modules and is controlled by the assembly line environment. PKSs feature a structural and functional separation into a condensing and a modifying region as observed for fatty acid synthases. Despite the outstanding relevance of PKSs, the detailed organization of PKSs with complete fully reducing modifying regions remains elusive. Here we report a hybrid crystal structure of *Mycobacterium smegmatis* mycocerosic acid synthase based on structures of its condensing and modifying regions. Mycocerosic acid synthase is a fully reducing iPKS, closely related to modPKSs, and the prototype of mycobacterial mycocerosic acid synthase-like PKSs. It is involved in the biosynthesis of C<sub>20</sub>–C<sub>28</sub> branched-chain fatty acids, which are important virulence factors of mycobacteria. Our structural data reveal a dimeric linker-based organization of the modifying region and visualize dynamics and conformational coupling in PKSs. On the basis of comparative small-angle X-ray scattering, the observed modifying region architecture may be common also in modPKSs. The linker-based organization provides a rationale for the characteristic variability of PKS modules as a main contributor to product diversity. The comprehensive architectural model enables functional dissection and re-engineering of PKSs.