# Solution structure of the type I polyketide synthase Pks13 from Mycobacterium tuberculosis

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Type I polyketide synthases (PKSs) are multifunctional enzymes responsible for the biosynthesis of a group of diverse natural compounds with biotechnological and pharmaceutical interest called polyketides. The diversity of polyketides is impressive despite the limited set of catalytic domains used by PKSs for biosynthesis, leading to considerable interest in deciphering their structure-function relationships, which is challenging due to high intrinsic flexibility. Among nineteen polyketide synthases encoded by the genome of *Mycobacterium tuberculosis*, Pks13 is the condensase required for the final condensation step of two long acyl chains in the biosynthetic pathway of mycolic acids, essential components of the cell envelope of *Corynebacterineae* species. It has been validated as a promising druggable target and knowledge of its structure is essential to speed up drug discovery to fight against tuberculosis.

We report here a quasi-atomic model of Pks13 obtained using small angle X-ray scattering of the entire protein and various molecular subspecies combined with known high-resolution structures of Pks13 domains or structural homologues. As a comparison, the low-resolution structures of two other mycobacterial polyketide synthases, Mas and PpsA from *Mycobacterium bovis* BCG, are also presented. This study highlights a monomeric and elongated state of the enzyme with the apo and holo forms being identical at the resolution probed. Interestingly, dimerization of the enzyme occurs following the loading of a C16-CoA substrate analogue onto the acyltransferase domain. Catalytic domains are segregated into two parts, which correspond to the condensation reaction per se and to the release of the product, a pivot for the enzyme flexibility being at the interface. The two acyl carrier protein domains are found at opposite sides of the ketosynthase domain and display distinct characteristics in terms of flexibility.

The Pks13 model reported here provides the first structural information on the molecular mechanism of this complex enzyme and opens up new perspectives to develop inhibitors that target the interactions with its enzymatic partners or between catalytic domains within Pks13 itself.

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