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Function of polyketide synthases from the SAXS structure of a complete module

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The modular polyketide synthases (PKS), common to many bacterial antibiotic-producers, are huge multienzyme, multidomain systems which can be likened to molecular assembly lines.1 An understanding of the structural and mechanistic aspects which underpin interdomain cooperation during biosynthesis by modular PKS is crucial to ongoing efforts to re-engineer these systems for the production of novel compounds of medicinal value.2 Previous attempts to solve the structures of PKS modules by X-ray crystallography have been unsuccessful, likely due to the high, inherent flexibility of the multienzymes. Here, we have employed an alternative technique, small-angle X-ray scattering (SAXS), in combination with NMR structure elucidation and homology modelling of individual domains, to obtain the first low-resolution structural data on an entire apo PKS module. The model system comprises a multidomain region of the virginiamycin M1 PKS from Streptomyces virginiae, a target of relevance for its involvement in production of the commercial antibiotic dalfopristin. The investigated region, which comprises a ketosynthase (KS) and two consecutive acyl carrier protein (ACP) domains, interacts with a wide range of protein partners, including notably, a complex of discrete enzymes responsible for b-methylation of the polyketide, and the N-terminus of the downstream PKS protein, VirFG.3 In our solved structure (Fig. 1), the homodimeric KS, which is flanked by well-folded linker regions, occupies the center of the module. While the first ACP is located close to the KS, the second is situated at the end of a flexible linker, and mobile. Taken together, these data provide a physical explanation for the functional non-equivalence previously observed for certain tandem ACPs of this class of PKS. Furthermore, the overall open shape of the module renders the second ACP highly accessible, which may be critical for its interaction with its multiple in trans catalytic partners. Finally, our analysis redefines the function of a putative dimerization motif of tandem ACPs as a docking domain, suggesting that the module likely adopts a more closed form in order to affect transfer of the chain extension intermediate to the subsequent module.

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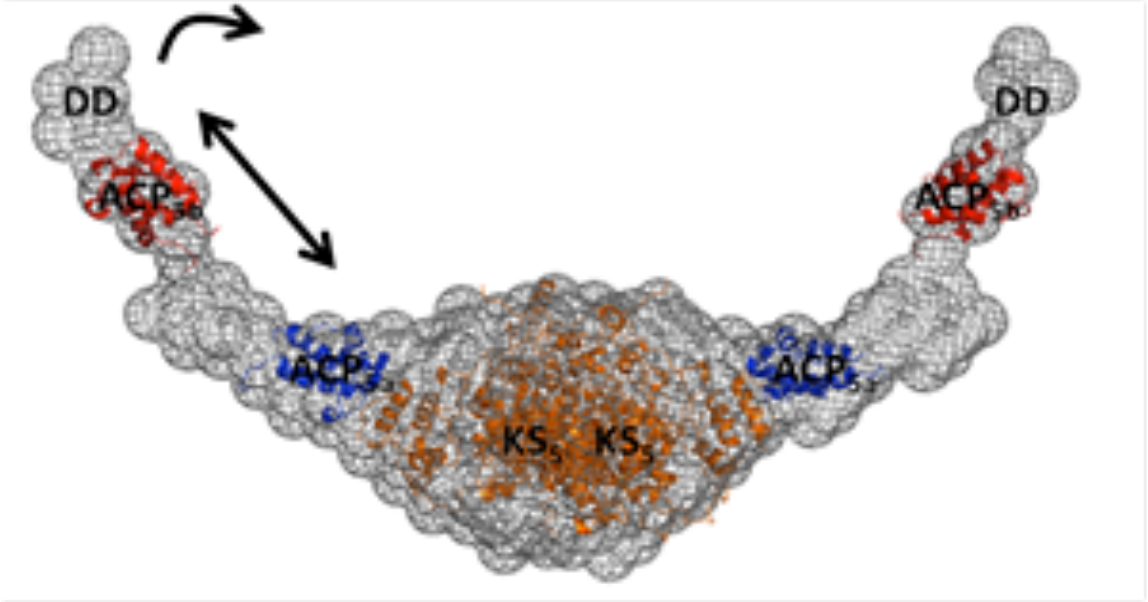

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