Integrated structural biology of enacyloxin polyketide synthase

S. Kosol[1], A. Gallo[1], D. Griffiths[1], T.R. Valentic[2], J.L. Masschelein[2], M. Jenner[1], E.de los Santos[3], L. Manzi[4], D. Rea[3], V. Fülöp,[3], N.J. Oldham[4], S.-C. Tsai[2], G.L. Challis[1] and J.R. Lewandowski[1]

[1]Department of Chemistry, University of Warwick, Coventry, UK, [2]Departments of Molecular Biology and Biochemistry, Chemistry, and Pharmaceutical Sciences, University of California Irvine, Irvine, USA, [3]Department of Life Sciences, University of Warwick, Coventry, UK, [4]School of Chemistry, University of Nottingham, Nottingham, UK, **j.r.lewandowski@warwick.ac.uk**

Many structurally complex antibiotics are synthesized inside bacterial cells by large modular multienzymatic assembly lines such as polyketide synthases (PKS) or non-ribosomal peptide synthases (NRPS). Because the components of these assembly lines that are responsible for a single synthesis step are often not encoded in one polypeptide, the quality of the product relies on the flawless interplay between different modules and enzymes [1,2]. The interactions between different proteins require a high degree of specificity and molecular recognition must be fast and efficient [3]. One example of a system relying on such principles for biosynthetic control is a hybrid PKS/NRPS that produces an antibiotic enacyloxin IIa shown to be active against a common hospital-acquired multidrug resistant pathogen *A. baumannii*. Here we use an integrated structural biology approach combining solution and solid state NMR, carbene foot printing and X-ray crystallography and molecular dynamics to elucidate the atomic details of interactions between a peptidyl carrier protein (PCP; 11 kDa) and a stand-alone condensation domain (C; 57 kDa) in a pivotal chain termination step of enacyloxin biosynthesis [4]. We show that intrinsically disordered docking domain located on the C-terminus of PCP is essential for initiation of the interaction and consequently successful substrate transfer to the condensation domain. Solid-state NMR helps us to tease out the atomic resolution details of PCP in the richly dynamic complex with C domain. Our findings suggest an intriguing dynamically regulated allosteric mechanism for condensation domain activity and provide a basis for rational engineering approaches of biosynthetic pathways to yield novel antibiotics.

References

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