Cyclodipeptide synthase-dependent pathways: an efficient tool to incorporate non-canonical amino acids into 2,5-diketopiperazines

Nicolas Canu,[1] Mireille Moutiez,[1] Pascal Belin,[1] Muriel Gondry[1]

[1] *Institute for Integrative Biology of the Cell (I2BC), CEA, CNRS Univ.Paris-Sud,Université Paris-Saclay 91198 Gif-sur-Yvette Cedex (France)*

muriel.gondry@i2bc.paris-saclay.fr

Cyclodipeptide synthases (CDPSs) constitute a family of bacterial enzymes that divert aminoacyl-tRNAs (AA-tRNAs) from the ribosomal machinery to synthesize 2,5-diketopiperazines (2,5-DKPs)[1], a class of natural products containing many therapeutically promising compounds[2].

CDPSs utilize two AA-tRNAs as substrates for catalysing formation of two peptide bonds between aminoacyl moieties to yield the DKP scaffold[1], which is often equipped with different chemical groups by 2,5-DKP-tailoring enzymes found associated to CDPSs in dedicated biosynthetic pathways (Figure 1)[3,4].

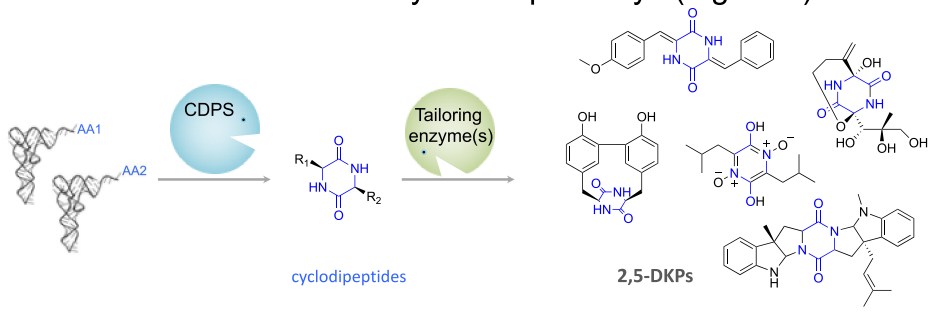

Figure 1: CDPS-dependent pathways

The recent characterization of large sets of CDPSs has revealed that they can produce highly diverse products[5,6], and therefore have great potential for use in the production of different 2,5-DKPs. Several strategies for further increasing the diversity accessible with these enzymes will be discussed, including the incorporation of non-canonical amino acids by CDPSs[7] and use of the remarkable diversity of 2,5 DKP-tailoring enzymes discovered in recent years[8–10].

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