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Bioengineering of metabolic pathways of pyrrocidines for the generation of chemical diversity in this family of compounds.

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PURPOSE OF THE ABSTRACT
Pyrrocidines are secondary metabolites isolated from diverse fungi and characterized by antimicrobial1 and apoptosis-inducing activities2, as well as potential inhibitory effects of SARS-CoV2 RNA-dependent RNA polymerase3. These molecules belong to a growing family of fungal natural products sharing a decahydrofluorene core connected to a highly strained paracyclophane moiety. Each member possesses different combinations of configuration at the chiral centers present in the paracyclophane-decahydrofluorene motif such as in hirsutellone B and xenoacremone C.

In order to understand the steps leading to this unique polycyclic structure, we investigated pyrrocidine biosynthesis in the fungal producing strain Sarocladium zeae by gene knock-out and thorough metabolic analysis. Thus, a biosynthetic gene cluster encoding a hybrid polyketide synthase – non-ribosomal peptide synthetase (PKS-NRPS) and its auxiliary enzymes was identified. This work reveals an intrinsic plasticity of the pyrrocidine pathway and leads to the generation of complex metabolites with new cyclic backbones in the mutants. In this process, the megaenzyme PKS-NRPS forms a linear precursor which then undergoes diverse cyclisation and redox steps catalyzed by the auxiliary enzymes. Among them, several enzymes are attractive tools for biocatalytical approaches like the α,β-hydrolase PrcH catalyzing the formation of pyrrolidinone ring by a Knoevenagel reaction and PrcI performing the reduction of this five-member ring, or the lipocalin-like protein PrcX controlling a Diels-Alder cycloaddition. Our work also focuses on the reprogramming of the PKS-NRPS by reassembling this multi-domain protein to generate a chemical diversity of linear precursors and integrates it in synthetic biology approaches. The latest results will be presented.

FIGURES

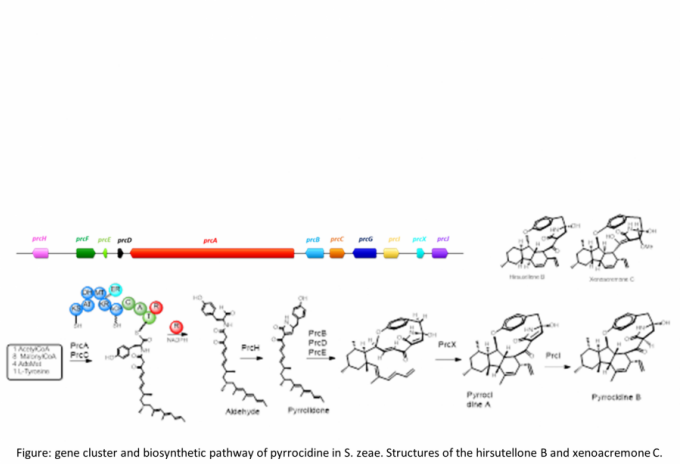

Figure: gene cluster and biosynthetic pathway of pyrrocidine in S. zeae. Structures of the hirsutellone B and xenoacremone C.

FIGURE 1

Figure

gene cluster and biosynthetic pathway of pyrrocidine in S. zeae. Structures of the hirsutellone B and xenoacremone C.

FIGURE 2

KEYWORDS

Pyrrodicidines | Metabolic engineering | PKS-NRPS | Secondary metabolites

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