

Chemogenomics, An Advanced Tool for the Dereplication of Polyketide Anti-Infective Drugs from Microbial Endosymbionts

“In order to discover polyketide anti-infective metabolites from microbial endosymbionts, it is crucial to look into their genomes to recognize its significant constraints in the biosynthesis of anti-infective potentials”



HC Yashavantha Rao
University of Mysore
India

COLUMN ARTICLE

Microbial endosymbionts are an eclectic group of microorganisms (fungi, bacteria and actinomycetes) having the capability to chemically colligate the bridge between microbes and associated medicinal plants due to their relatively high metabolic versatility [1]. They strongly establish endophyte–endophyte and plant-endophyte interactions, which constitute stress condition within the host and play a vital role in the biosynthesis of anti-infective drugs (Figure 1) [2]. Microbial endosymbionts are extremely considered as underexplored drug resources having the capacity to produce novel anti-infective compounds [3].

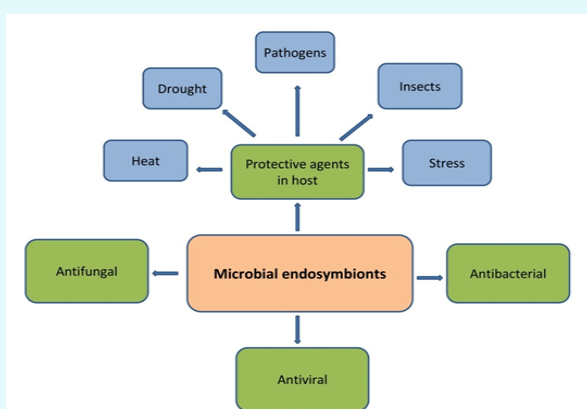


Figure 1: Microbial endosymbiont biome: As a part of endosymbiont community, microbial endosymbionts may have one or multiple functional roles during their life cycles or in response to plant or environmental cues.

Polyketides constitute a large family of structurally diverse group of natural secondary metabolites found in fungi, bacteria and plants, which play a significant role in the biodiscovery of anti-infective metabolites from natural resources [4]. They are governed by multi-domain enzymes which catalyze iterative events to frame a polyketide molecule [5]. Scads of anti-infective drugs in the market are of polyketide origin including anticholesterol drug lovastatin, antibiotics tetracycline, erythromycin, anticancer drug epothilone B and immunosuppressant rapamycin. Novel antimicrobial drugs deduced from microbial endosymbionts with unique and targeted mode of action are crucially rudimentary to combat multi-drug resistance. Biodiscovery of polyketide antimicrobial natural drugs are time and resource consuming processes [6]. Advanced approaches in searching for rapid prediction of polyketide antimicrobial compounds from microbial endosymbionts require novel genomics and chemical investigation. The use chemogenomics strategy may enlightens to predict the nature of antimicrobial metabolites during the bioprospecting of microbial endosymbionts for new polyketide anti-infective drugs. Indeed, microbial genome mining reveals the bearing of numerous secondary metabolite gene clusters, exhibiting the numbers of putative genes involved in the biosynthesis of secondary metabolism [7].

The study of polyketide synthase (PKS) genes in natural environments may provide an important ecological insight for anti-infective drug development [8]. Indeed, microbial endosymbionts have been genetically screened for the de-

tection of PKS genes as indicators of anti-infective potential [9]. Biosynthetic gene clusters encoding PKS type-I gene domains were detected using different sets of degenerate primers [10-13]. Potential endosymbiont strains which exhibit biosynthetic PKS gene clusters are the promising source for the discovery of novel anti-infective polyketide metabolites. Simultaneously from these potent endosymbiont strains, isolation and purification of secondary metabolites can be carried out using high performance liquid chromatography, column chromatography or preparative thin layer chromatography. The isolated anti-infective metabolites can be characterized using suitable hyphenated techniques like liquid chromatography mass spectroscopy, nuclear magnetic resonance and other related studies.

Taking all the above into account, PKS gene is a functional gene of microbial endosymbionts which might perform an important role in endosymbiotic secondary metabolite production. We have come a long way to find a suitable holistic strategy for the rapid discovery of polyketide anti-infective drugs from microbial endosymbionts.

ACKNOWLEDGEMENT

I am grateful to Dr. Sreedharamurthy Satish (University of Mysore, India) for his valuable guidance and I also thank University Grants Commission (UGC), India for the funding.

BIBLIOGRAPHY

1. Deepika VB, *et al.* "Modulation of genetic clusters for synthesis of bioactive molecules in fungal endophytes: a review". *Microbiological Research* 182 (2016):125-140.
2. Kusari P, *et al.* "Cross-species biosynthesis of maytansine in *Maytenus serrata*". *RSC Advances* 6.12 (2016): 10011-10016.
3. Rao HCY and Satish S. "Intra-specific differentiation of fungal endosymbiont *Alternaria longissima* CLB44 using RNA secondary structure analysis and their anti-infective potential". *The Science of Nature* 103.7-8 (2016): 69.
4. Schumann J and Hertweck C. "Advances in cloning, functional analysis and heterologous expression of fungal polyketide synthase genes". *Journal of Biotechnology* 124.4 (2006): 690-703.
5. Fujii I, *et al.* "Identification of a Claisen cyclase domain in fungal polyketide synthase WA, a naphthopyrone synthase of *Aspergillus nidulans*". *Cell Chemical Biology* 8.2 (2001):189-197.
6. Kapetanovic IM. "Computer-aided drug discovery and development (CADDD): In silico-chemico-biological approach". *Chemico Biological Interactions* 171.2 (2008): 165-176.
7. Craney A, *et al.* "Towards a new science of secondary metabolism". *Journal of Antibiotics* 66.7 (2013): 387-400.
8. Zhao J, *et al.* "Phylogenetic analysis of type I polyketide synthase and non-ribosomal peptide synthetase genes in Antarctic sediment". *Extremophiles* 12.1 (2008): 97-105.
9. Rao HCY, *et al.* "Implication of PKS type I gene and chromatographic strategy for the biodiscovery of antimicrobial polyketide metabolites from endosymbiotic *Nocardiosis prasina* CLA68". *The Science of Nature* 103.5-6 (2016): 45.
10. Ayuso-Sacido A and Genilloud O. "New PCR primers for the screening of NRPS and PKS-I systems in actinomycetes: detection and distribution of these biosynthetic gene sequences in major taxonomic groups". *Microbial Ecology* 49.1 (2005): 10-24.
11. Metsa-Ketela M, *et al.* "An efficient approach for screening minimal PKS genes from *Streptomyces*". *FEMS Microbiology Letters* 180.1 (1999): 1-6.
12. Bingle LE, *et al.* "Ketosynthase domain probes identify two subclasses of fungal polyketide synthase genes". *Fungal Genetics and Biology* 26.3 (1999): 209-223.
13. Nicholson TP, *et al.* "Design and utility of oligo nucleotide gene probes for fungal polyketide synthases". *Chemical Biology* 8.2 (2001): 157-178.

©All rights reserved by HC Yashavantha Rao.