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Dissecting functional importance of polyketide modifying enzymes in mycobacterial biology

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Corynebacterineae includes some of the deadliest human pathogens such as, *Mycobacterium tuberculosis* (*Mtb*) and *Mycobacterium leprae*. In Recent years have seen a remarkable increase in our understanding of secondary metabolic networks that impart these potentials to this order of organisms. One of the major secondary metabolites is polyketides. Comparative genomics of closely related genera from this family have revealed unusual polyketide biosynthetic potentials with the existence of genes homologous to type III *pkss*. Type III polyketide products in recent years have been remarkably associated with cell wall modifications. Long-chain alkylresorcinols and alkylpyrones replace membrane phospholipids in *Azotobacter* cells differentiating into dormant cells. Alkyl phloroglucinols are key signaling factors required for differentiation and development of *Dictyostelium* molds. These phenolic lipids in Streptomyces confer resistance to β-lactam antibiotics by altering properties of the cytoplasmic membrane. Although, resorcinolic/phloroglucinolic lipids are not known in *Mtb*, our functional characterization of PKS18 identified alkylpyrones as major polyketide products *in vitro*. These metabolites are crucial components of pollen exine in *Arabidopsis thaliana* and could be synthesized by PKSIIINc from *Neurospora crassa*. Type III polyketide quinones have been recently identified to be key molecules required for anaerobic respiration in mycobacterial biofilms. Interestingly, many of the type III polyketides require modifying enzymes in order to become fully functional. These modifying enzymes are generally cytochrome P450s, desaturases, methyltransferases, sulfotransferases, oxidoreductases and others. Often these modifying enzymes are present in cluster with type III pks genes and transcriptionally expressed together. In this study, we have identified two unique polyketide clusters in *Mycobacterium marinum*. Our biochemical, mutational and structural studies provide evidence for an unanticipated potential of these proteins to cyclize a common biosynthetic intermediate to generate chemically and structurally distinct metabolic entities utilizing a single catalytic site and a limited pool of precursor molecules. These metabolites are variously modified to become biologically active. These observations not only provide interesting clues to the possible role of these small molecules in Corynebacterineae physiology and virulence but can be further exploited for generating a reservoir of structurally and chemically distinct unnatural bioactive scaffolds.

Biography

Priti Saxena completed her PhD in Chemical Biology from National Institute of Immunology, New Delhi. She worked as a Scientist Fellow at Institute ofGenomics and Integrative Biology, Delhi and has published several articles in reputed high impact journals. She has been awarded with the premier fellowship of Innovative Young Biotechnologist Award (IYBA) of DBT, India and SAU Intramural Grant of South Asian University, India. Her research interests focus on delineating molecular mechanisms underlying mycobacterial pathogenesis in the capacity of an Assistant Professor at South Asian University, India.

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