

Genomic mining for untapped biosynthetic gene clusters in entomopathogenic bacteria identifies unique natural products

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Entomopathogenic bacteria of the genera *Xenorhabdus* and *Photorhabdus* living in symbiosis with nematodes *Steinernema* and *Heterorhabditis*, respectively, are able to produce a huge diversity of toxic proteins as well as natural products (NPs) as signaling molecules and virulence factors to maintain nematode development and protect the insect cadaver from food competitors. Previous studies have shown a large number of NPs derived from NRPSs abound in both genera. However, little is known about other classes of NPs whose bioactivities might help the bacteria–nematode complex to maintain its special environmental niche. Our recent comprehensive analysis for 45 genomes by mapping their BGCs onto sequence similarity networks reveals the entomopathogenic bacteria harbor untapped potential BGCs encoding immense unknown NRPS hybrids, PKS, PKS-NRPS hybrids, RiPPs, and others. We then apply a well-established approach in the lab, promoter activation in Δhfq mutants/wild-type strains, to homologously overproduce some unique BGCs, and lead to the discovery of yersiniabactin-like, branched-NPRs, and pyrrolidine dimeric NPs.