An Integrated Metabolomic and Genomic Mining Workflow to Uncover the Biosynthetic Potential of Bacteria

Microorganisms are a rich source of bioactives; however, chemical identification is a major bottleneck. Strategies that can prioritize the most prolific microbial strains and novel compounds are of great interest. Here, we present an integrated approach to evaluate the biosynthetic richness in bacteria and mine the associated chemical diversity. Thirteen strains closely related to *Pseudoalteromonas luteoviolacea* isolated from all over the Earth were analyzed using an untargeted metabolomics strategy, and metabolomic profiles were correlated with whole-genome sequences of the strains. We found considerable diversity: only 2% of the chemical features and 7% of the biosynthetic genes were common to all strains, while 30% of all features and 24% of the genes were unique to single strains. The list of chemical features was reduced to 50 discriminating features using a genetic algorithm and support vector machines. Features were dereplicated by tandem mass spectrometry (MS/MS) networking to identify molecular families of the same biosynthetic origin, and the associated pathways were probed using comparative genomics. Most of the discriminating features were related to antibacterial compounds, including the thiomarinols that were reported from *P. luteoviolacea* here for the first time. By comparative genomics, we identified the biosynthetic cluster responsible for the production of the antibiotic indolmycin, which could not be predicted with standard methods. In conclusion, we present an efficient, integrative strategy for elucidating the chemical richness of a given set of bacteria and link the chemistry to biosynthetic genes.

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