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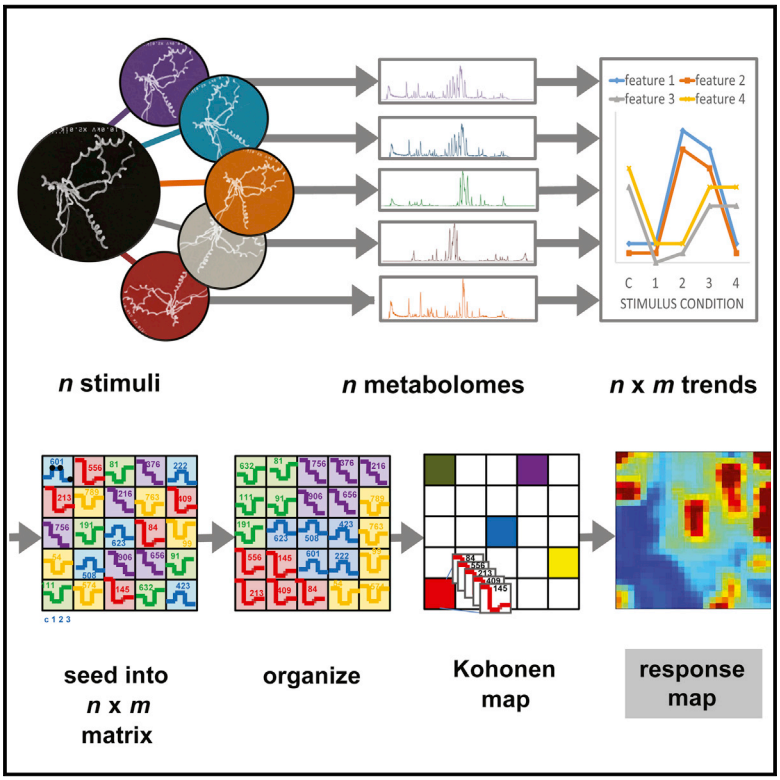
Structuring Microbial Metabolic Responses to Multiplexed Stimuli via Self-Organizing Metabolomics Maps

Graphical Abstract



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In Brief

Microbial genome sequencing reveals a large untapped potential for the discovery of new natural products drugs from microorganisms. Here Goodwin et al. use a combination of discrete chemical and biological stimuli and a big data approach to stimulate and identify natural products in a model organism producer.

Highlights

- Secondary metabolite expression is triggered by environmental stimuli
- Using stimuli and self-organizing maps, we identify a response metabolome
- Mapping responses to multiplexed stimuli reveal secondary metabolites
- In *S. coelicolor*, this revealed a large fraction of its biosynthetic potential

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Structuring Microbial Metabolic Responses to Multiplexed Stimuli via Self-Organizing Metabolomics Maps

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SUMMARY

Secondary metabolite biosynthesis in microorganisms responds to discrete chemical and biological stimuli; however, untargeted identification of these responses presents a significant challenge. Herein we apply multiplexed stimuli to *Streptomyces coelicolor* and collect the resulting response metabolomes via ion mobility-mass spectrometric analysis. Self-organizing map (SOM) analytics adapted for metabolomic data demonstrate efficient characterization of the subsets of primary and secondary metabolites that respond similarly across stimuli. Over 60% of all metabolic features inventoried from responses are either not observed under control conditions or produced at greater than 2-fold increase in abundance in response to at least one of the multiplexing conditions, reflecting how metabolites encode phenotypic changes in an organism responding to multiplexed challenges. Using abundance as an additional filter, each of 16 known *S. coelicolor* secondary metabolites is prioritized via SOM and observed at increased levels (1.2- to 22-fold compared with unperturbed) in response to one or more challenge conditions.

INTRODUCTION

Microbial producers of secondary metabolites typically contain gene clusters encoding dozens of secondary metabolite families (Zerikly and Challis, 2009), the expression of which appears to be tightly regulated in response to discrete chemical and/or biological stimulus. For example, exposure of actinomycetes to mixed fermentation conditions has demonstrated that secondary metabolite families are produced selectively via intergeneric (Onaka et al., 2011; Traxler et al., 2013) and interkingdom (Moree et al., 2012) microbial interactions. Similarly, the acquisition of antibiotic resistance via point mutations (Hosaka et al., 2009; Tanaka et al., 2013), exposure to rare earth metals (Tanaka et al., 2010; Ochi et al., 2014), exposure to small molecules (Craney et al., 2012; Seyedsayamdost, 2014), and the formulation of production media (Bode et al., 2002) have also been linked to gene-cluster-specific upregulation of secondary metabolites in actinomycetes. These data are consistent with secondary metabolites governing adaptive organismal responses to environmental stimuli. Identifying secondary metabolites and associating them to gene clusters that are linked to discrete chemical and biological stimuli can provide insight into the chemical ecological role of secondary metabolites. Moreover, the ability to selectively stimulate native expression of secondary metabolic gene clusters via chemical or biological stimuli and detect their corresponding products without resorting to genetic recombinant methods would greatly expedite microbial secondary metabolite discovery.

If secondary and primary metabolite regulation has adapted to selectively respond to chemical and biological stimuli, then metabolites possessing selective responses may be identifiable within metabolomes by possessing characteristic abundance trends across multiplexed stimulus conditions. To investigate this hypothesis and enable secondary metabolite discovery, we herein assess the potential for stimulus-mediated production of secondary metabolites in the native microbe by multiplexed chemical and biological stimulation. To access a broad spectrum of responses, a battery of 23 perturbations in a single growth medium was utilized from three reported categories of activating conditions for *Streptomyces coelicolor A3(2)*. The resulting collected sum of detectable metabolomic response inventories was analyzed by ultra-performance liquid chromatography-ion mobility-mass spectrometric (UPLC-IM-MS) analysis. To structure and categorize the response specificity of metabolic features within these data, we developed and implemented a self-organizing map (SOM)-based analysis (Goodwin et al., 2014; Eichler et al., 2003) for the identification and prioritization of increased metabolite production resulting from the multiplexed perturbations. SOM analysis converted the collected metabolomes into a navigable topological response phenotype map and efficiently identified specific primary and secondary