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High-throughput platform for the discovery of elicitors of silent bacterial gene clusters

Panthee Suresh

Activation of gene clusters that are not expressed by themselves can lead to the identification of natural products with diverse structure and biological function. Most clinically used antibiotics are derived from bacterial small molecules produced by dedicated biosynthetic gene clusters. Genome sequence analyses and further investigations have indicated that the majority of these biosynthetic genes are inactive or “silent.” This paper focuses on the identification of the triggers that lead to activation of silent. A high-throughput approach for identifying activators of silent gene clusters was developed in this paper. Application of this method to two bacterial clusters revealed that both could be efficiently activated and uncovered a new metabolite. Surprisingly, almost all elicitors discovered were antibiotics, suggesting they play an important role in modulating silent biosynthetic pathways. This approach promises to reveal useful small molecules and the biological regulatory mechanisms underlying silent gene clusters.

紹介論文

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Over the past decade, bacterial genome sequences have revealed an immense reservoir of biosynthetic gene clusters, sets of contiguous genes that have the potential to produce drugs or drug-like molecules. However, the majority of these gene clusters appear to be inactive for unknown reasons prompting terms such as “cryptic” or “silent” to describe them. Because natural products have been a major source of therapeutic molecules, methods that rationally activate these silent clusters would have a profound impact on drug discovery. Herein, a new strategy is outlined for awakening silent gene clusters using small molecule elicitors. In this method, a genetic reporter construct affords a facile read-out for activation of the silent cluster of interest, while high-throughput screening of small molecule libraries provides potential inducers. This approach was applied to two cryptic gene clusters in the pathogenic model *Burkholderia thailandensis*. The results not only demonstrate a prominent activation of these two clusters, but also reveal that the majority of elicitors are themselves antibiotics, most in common clinical use. Antibiotics, which kill *B. thailandensis* at high concentrations, act as inducers of secondary metabolism at low concentrations. One of these antibiotics, trimethoprim, served as a global activator of secondary metabolism by inducing at least five biosynthetic pathways. Further application of this strategy promises to uncover the regulatory networks that activate silent gene clusters while at the same time providing access to the vast array of cryptic molecules found in bacteria.