

Through the advancement of sequencing technology, the genome-based discovery of natural products is becoming mainstream. This strategy was applied by Dittmann and colleagues to the filamentous cyanobacterium *Nostoc punctiforme* by using RNA sequencing and fluorescence reporter analysis. Their efforts led to a better understanding of secondary metabolism regulation in *N. punctiforme* and the discovery of new microviridins. I have little experience in this area and I hope that I can learn something from their work and use it in my own study.

**Unlocking the Spatial Control of Secondary Metabolism Uncovers Hidden Natural Product Diversity in *Nostoc punctiforme***

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**Abstract**

Filamentous cyanobacteria belong to the most prolific producers of structurally unique and biologically active natural products, yet the majority of biosynthetic gene clusters predicted for these multicellular collectives are currently orphan. Here, we present a systems analysis of secondary metabolite gene expression in the model strain *Nostoc punctiforme* PCC73102 using RNA-seq and fluorescence reporter analysis. Our data demonstrate that the majority of the cryptic gene clusters are not silent but are expressed with regular or sporadic pattern. Cultivation of *N. punctiforme* using high-density fermentation overrules the spatial control and leads to a pronounced upregulation of more than 50% of biosynthetic gene clusters. Our data suggest that a combination of autocrine factors, a high CO<sub>2</sub> level, and high light account for the upregulation of individual pathways. Our overarching study not only sheds light on the strategies of filamentous cyanobacteria to share the enormous metabolic burden connected with the production of specialized molecules but provides an avenue for the genome-based discovery of natural products in multicellular cyanobacteria as exemplified by the discovery of highly unusual variants of the tricyclic peptide microviridin.