

## 新規二次代謝産物の発見と遺伝子クラスターの同定のための拡張基盤

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二次代謝産物生合成遺伝子クラスターの解析手法の一つとして異種発現が挙げられるが、一度に発現させられる遺伝子の長さには限界があり、糸状菌の遺伝子クラスター全体を確実に別の糸状菌で異種発現させるという手法は今まで存在しなかった。そこで著者らは、先行研究において、糸状菌の遺伝子クラスター全体をまとめて別の糸状菌で異種発現させることのできる FAC (fungal artificial chromosome) を開発した。今回著者らは、FAC を用いて *Aspergillus* 属のゲノムライブラリーを作製し、*Aspergillus nidulans* で異種発現させることで、糸状菌の未知の二次代謝産物をハイスループットに探索する FAC-MS (fungal artificial chromosome – metabolomic scoring) という実験系を考案した。FAC-MS によるスクリーニングの結果、生産物が未知の 56 個の遺伝子クラスターの内、15 個の遺伝子クラスターが生産する化合物の発見に成功した。その内の 1 つの化合物をさらに解析した結果、新規化合物である valactamide A の発見にも成功した。

## 紹介論文

**A scalable platform to identify fungal secondary metabolites and their gene clusters**

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## 要旨

The genomes of filamentous fungi contain up to 90 biosynthetic gene clusters (BGCs) encoding diverse secondary metabolites—an enormous reservoir of untapped chemical potential. However, the recalcitrant genetics, cryptic expression, and unculturability of these fungi prevent scientists from systematically exploiting these gene clusters and harvesting their products. As heterologous expression of fungal BGCs is largely limited to the expression of single or partial clusters, we established a scalable process for the expression of large numbers of full-length gene clusters, called FAC-MS. Using fungal artificial chromosomes (FACs) and metabolomic scoring (MS), we screened 56 secondary metabolite BGCs from diverse fungal species for expression in *Aspergillus nidulans*. We discovered 15 new metabolites and assigned them with confidence to their BGCs. Using the FAC-MS platform, we extensively characterized a new macrolactone, valactamide A, and its hybrid nonribosomal peptide synthetase–polyketide synthase (NRPS–PKS). The ability to regularize access to fungal secondary metabolites at an unprecedented scale stands to revitalize drug discovery platforms with renewable sources of natural products.