「本来の生理活性」が明らかな天然物の探索法
−自己耐性遺伝子を利用したゲノムマイニング−

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二次代謝産物の本来の役割は不明な場合が多い。この論文では、自己耐性遺伝子と生合成遺伝子がクラスターを形成する場合があることを利用して、本来の標的タンパク質が明らかな二次代謝産物の取得に成功している。この方法を適用できる遺伝子クラスターは多くは無いが、そのような遺伝子クラスターにあたればラッキーだと思うので、覚えておいて損はない論文であると思った。論文概要は以下の通り。DHAD は除草剤の標的として有望だが、現在まで天然物由来の DHAD 阻害剤は発見されていなかった。Yi Tang、Steve Jacobsen らの研究グループは、DHAD 阻害剤に対する自己耐性を示すのに必要な耐性型 DHAD が存在する糸状菌の遺伝子クラスターを探索し、そのようなクラスターとしてアスプテル酸の生合成遺伝子クラスターを見出し、実際にアスプテル酸が DHAD 阻害剤として働くことを見出した。

紹介論文

Resistance-gene-directed discovery of a natural product herbicide with a new mode of action,
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要旨

Bioactive natural products have evolved to inhibit specific cellular targets and have served as lead molecules for health and agricultural applications for the past century[1,2,3]. The post-genomics era has brought a renaissance in the discovery of natural products using synthetic-biology tools[4,5,6]. However, compared to traditional bioactivity-guided approaches, genome mining of natural products with specific and potent biological activities remains challenging[4]. Here we present the discovery and validation of a potent herbicide that targets a critical metabolic enzyme that is required for plant survival. Our approach is based on the co-clustering of a self-resistance gene in the natural-product biosynthesis gene cluster[7,8,9], which provides insight into the potential biological activity of the encoded compound. We targeted dihydroxy-acid dehydratase in the branched-chain amino acid biosynthetic pathway in plants; the last step in this pathway is often targeted for herbicide development[10]. We show that the fungal sesquiterpenoid aspterric acid, which was discovered using the method described above, is a sub-micromolar inhibitor of dihydroxy-acid dehydratase that is effective as a herbicide in spray applications. The self-resistance gene *astD* was validated to be insensitive to aspterric acid and was deployed as a transgene in the establishment of plants that are resistant to aspterric acid. This herbicide-resistance gene combination complements the urgent ongoing efforts to overcome weed resistance[11]. Our discovery demonstrates the potential of using a resistance-gene-directed approach in the discovery of bioactive natural products.