Activation of fungal silent gene clusters: a new avenue to drug discovery.

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Abstract

The ongoing exponential growth of DNA sequence data will lead to the discovery of many natural-product biosynthesis pathways by genome mining for which no actual product has been characterised. In many cases, these clusters remain silent under laboratory conditions. New technologies based on genetic engineering are available to induce silent genes. Heterologous expression of a silent gene cluster under the control of defined promoters can be applied. Alternatively, promoters of biosynthesis genes within the genome can be exchanged by defined promoters. Most promising, however, is the activation of pathway-specific regulatory genes, which was recently demonstrated. Such regulatory genes are present in many secondary metabolite gene clusters. This approach is rendered feasible by the fact that all of the genes encoding the large number of enzymes required for the synthesis of a typical secondary metabolite are clustered and that in some cases, a single regulator controls the expression of all members of a gene cluster to a certain extent. The advantage of this technique is that only a small gene needs to be handled, and that an ectopic integration is sufficient, bypassing all limitations of homologous recombination.

Most conveniently, this strategy can trigger the concerted expression of all pathway genes. The vast amount of DNA sequences in the public database represents only the beginning of this new genomics era. The activation of these gene clusters by genetic engineering will lead to the discovery of many so far unknown products and therefore represents a novel avenue to drug discovery.

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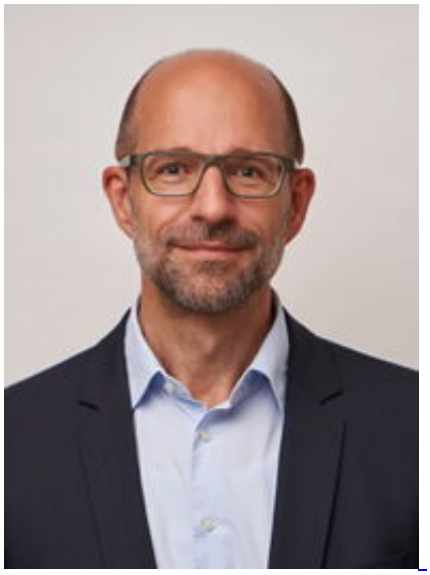
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