Development of synthetic transcription factors to activate biosynthetic gene clusters

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The discovery and sustainable production of new natural compounds with antibiotic activity is one of the most challenging problems currently faced by the scientific community and the pharmaceutical industry.

In fungal genomes, these substances are usually produced by enzymes encoded by genes grouped together, constituting the so-called biosynthetic gene clusters (BGCs). These clusters are at least composed of a core synthase, which uses primary metabolites to form respective backbones (e.g. polyketides). Thereafter, they are further modified by tailoring enzymes resulting in secondary metabolites. Many BGCs also contain specific transcription factors that regulate the expression of the other genes in the cluster. However, as most BGCs remain silent under laboratory conditions, it is still a key question how to activate them. This obstacle strongly hampers the identification of new substances.

In recent years different approaches have been reported on how to activate silent BGCs. A commonly followed strategy is the over-expression of the transcription factor embedded in the cluster, which, as all other approaches, is only sometimes successful. When over-expressing four transcription factors in *T. reesei*, we could not detect additional metabolites in the supernatant. Consequently, we developed a novel strategy using synthetic transcription factors. We fused the DNA binding domain of some of these cluster-specific transcription factors to a synthetic, estradiol-inducible transactivation domain. This way, we investigate the usefulness of synthetic transcription factors as a tool to activate silent biosynthetic gene clusters in fungi.