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REVIEW

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Strategies for mining fungal natural products

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Abstract Fungi are well known for their ability to produce a multitude of natural products. On the one hand their potential to provide beneficial antibiotics and immunosuppressants has been maximized by the pharmaceutical industry to service the market with cost-efficient drugs. On the other hand identification of trace amounts of known mycotoxins in food and feed samples is of major importance to ensure consumer health and safety. Although several fungal natural products, their biosynthesis and regulation are known today, recent genome sequences of hundreds of fungal species illustrate that the secondary metabolite potential of fungi has been substantially underestimated. Since expression of genes and subsequent production of the encoded metabolites are frequently cryptic or silent under standard laboratory conditions, strategies for activating these hidden new compounds are essential. This review will cover the latest advances in fungal genome mining undertaken to unlock novel products.

Keywords Secondary metabolism · Gene clusters · Polyketide · Non-ribosomal peptide · LaeA

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Introduction

Microorganisms, including prokaryotic actinobacteria and eukaryotic ascomycetes, are prominent producers of a variety of biologically active natural products [17, 18]. As the topic of bacterial natural products is covered elsewhere in this JIMB Special Issue on Microbial Genome Mining, we are focusing on natural products produced by filamentous fungi belonging to the phylum Ascomycota. These compounds are also termed secondary metabolites because they are not essential for the organism's growth under laboratory conditions [30, 79]. However, the maintenance of the genetic information allowing fungi to produce secondary metabolites suggests that these small molecules provide essential benefits, e.g. against predation [139] and hostile environmental conditions [55]. Apart from providing evolutionary fitness to the producing organism in their natural habitat, many secondary metabolites are of major importance to humankind owing to their beneficial and deleterious effects as drugs and toxins. Beneficial fungal secondary metabolites have a wide range of applications, including antibiotics (penicillin and cephalosporin [52]), immunosuppressants (cyclosporins [140]), cholesterol-lowering drugs (statins [115]), angiogenesis inhibitors (fumagillin derivatives and pseurotin derivatives [5, 15]), anti-osteoporosis agents (orsellinic acid derivatives F-9557 A and B [23]), anti-migraine and hypertension-lowering medications (ergot alkaloids [73]), plant growth hormones (gibberellins [27]) and food additives (carotenoids [7]). Deleterious effects of fungal secondary metabolites are most often attributed to their carcinogenic (aflatoxins, fumonisins [107, 170]), apoptotic (gliotoxin, deoxynivalenol [97, 172]) and mutagenic (fusarins [157]) activities as well as ability to cause plant disease (e.g. T-toxin and cercosporin [9, 47]) thereby contributing to reduced harvest yields.

This review will focus on the latest advances that contribute to our current understanding of the genetic basis for production and regulation of these heterogeneous small molecular weight substances and how this knowledge can help to identify and activate cryptic secondary metabolites in fungal genomes efficiently. We also direct the reader to other recent reviews on this topic for additional insights into fungal secondary metabolism [30, 184].

Chemical classes of secondary metabolites

The heterogeneous secondary metabolites produced by fungi can generally be classified into four distinct chemical categories: polyketides (e.g. aflatoxins), non-ribosomal peptides (e.g. penicillin), terpenes (e.g. gibberellins) and prenylated tryptophan derivatives (e.g. ergot and indole alkaloids) [79]. Additionally, hybrids between these classes have been identified in several fungal species (e.g. fumagillin, pseurotin [104, 114]). Production of each class of secondary metabolite requires specific backbone enzymes providing the chemical scaffold, hence named polyketide synthases (PKSs), non-ribosomal peptide synthetases (NRPSs), terpene synthases/cyclases (TCs) and dimethylallyl tryptophan synthases (DMATSs), respectively. In contrast to actinomycetes which were shown to harbour modular type I PKS, type II PKS and type III PKS in their genomes, in ascomycetes iterative type I PKS and type III PKS have been identified so far [6, 82, 86, 154, 173]. In filamentous fungi, production of polyketide/non-ribosomal peptide hybrids involves one respective chimeric PKS/NRPS enzyme if only a single amino acid is incorporated into the final product [21]. In cases where the hybrid molecule contains more than one amino acid moiety, two distinct enzymes, one PKS and one NRPS, are involved in the biosynthesis [44]. Similarly, meroterpenoids (polyketide/terpene hybrids) are assembled by two distinct enzymes [46, 84, 104, 108]. Some secondary metabolites like loline alkaloids do not involve any of the backbone enzymes mentioned above despite their structural relatedness to non-ribosomal peptides [160]. Examples of prominent fungal secondary metabolites of each chemical class are given in Fig. 1.

Secondary metabolite gene clusters

A hallmark trait of fungal secondary metabolites is that the genes required for modification of the chemical scaffold, transport of substrates and/or products, specific regulatory functions and resistance are usually contiguously aligned in the genome leading to the concept of secondary metabolite gene clusters [79, 90]. The first fungal gene cluster to be identified was the penicillin cluster in *Penicillium chrysogenum* and *Aspergillus nidulans* [54, 111, 156]. Before genome sequences became readily available for fungal species, evidence for contiguous aligned genes responsible for the aflatoxin precursor sterigmatocystin [35], melanins [95], trichothecenes [80], gibberellins [168] and fumonisins [53] consolidated the view of secondary metabolite gene clusters in fungi as a common trait. Interestingly, filamentous fungi share this hallmark trait with Gram-positive bacteria belonging to the phylum Actinobacteria [16, 83, 119, 126, 128]. Advances in fungal secondary metabolism have shown deviations of this strict motif. Genes responsible for production of the *A. nidulans* spore pigment and trichothecenes in *Fusarium* spp. are present in two distinct genomic positions [94]. Recent observations in *A. nidulans* showed that prenylation of PKS- and NRPS-derived products can be executed by prenyltransferases (PTs) distantly located in the genome [4, 108, 144], whereas similar prenylations are carried out by PTs encoded within the core cluster in *P. aethiopicum*, *Neosartorya fischeri* and *A. fumigatus* [46, 96]. Also the genes required for T-toxin production in *Cochliobolus heterostrophus* are located at least in two unlinked loci in the genome [9] and in one extreme example, the genes required for dothistromin synthesis are scattered throughout the genome [29]. Another feature that adds to a more complex view of the secondary metabolite gene cluster is the recent finding that some clusters can be intertwined leading to production of two distinct products [177]. Nevertheless, the canonical cluster hallmark is still a very useful motif to look for in mining new fungal genomes.

In silico identification of backbone enzymes and gene clusters by genome sequencing

The fact that the backbone enzymes involved in secondary metabolite production have specific protein sequence signatures facilitates the identification of their encoding genes in available genome sequences. Pioneering work in the first available filamentous fungal genome sequences of *C. heterostrophus*, *Botrytis cinerea*, *Neurospora crassa*, *Fusarium verticillioides* and *F. graminearum* showed the existence of 7–25 PKS-encoding genes in these Pezizomycotina [98]. Later genome sequences of other Ascomycota showed a similar high number of genes encoding PKS, NRPS, TC and DMATS [3, 49, 65, 66, 99, 109, 116, 120, 124, 133, 146, 169, 178]. More recently, the genome sequences of Basidiomycota have revealed the presence of several PKS-encoding genes [100] and additional large-scale fungal genome projects carried out at the Joint Genome Institute will most certainly reveal more backbone genes in the sequenced species [70]. Prediction of the gene

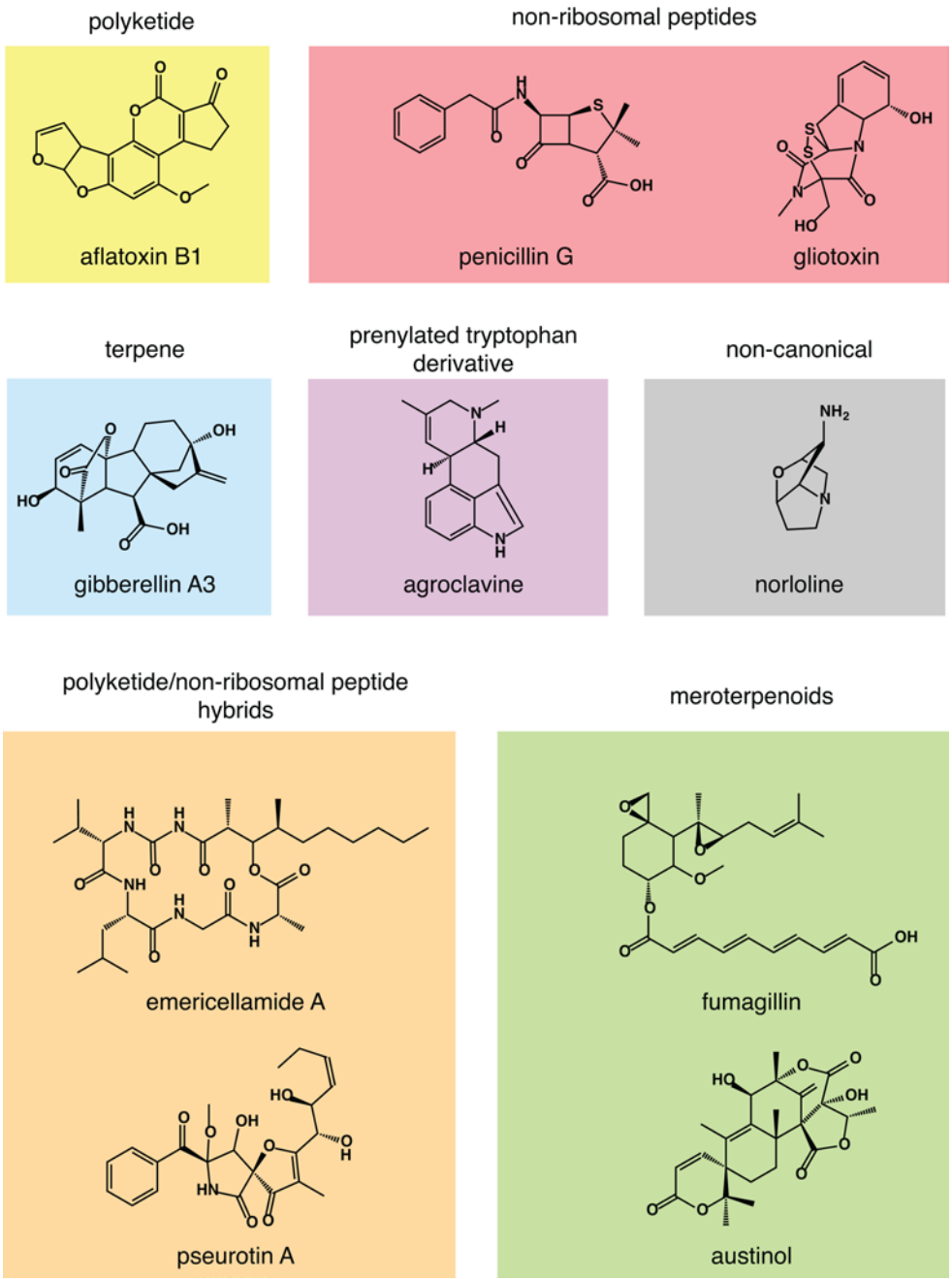

Fig. 1 Select fungal secondary metabolites of various chemical classes derived by different biosynthetic routes. *Top left* (*yellow*) Structure of aflatoxin B1 as an example of a polyketide derived by a PKS. *Top right* (*red*) NRPS-derived non-ribosomal peptides, penicillin G and gliotoxin. *Middle left* (*blue*) Gibberellin A3 belonging to the class of terpenes, produced by TCs as the scaffold enzymes. *Center* (*purple*) Prenylated tryptophan derivative, agroclavine; a DMATS-derived natural product also referred to as the class of alkaloids. *Note* Some prenylated tryptophan derivatives can be fused to non-ribosomal peptides, e.g. ergotamine (not depicted). *Middle right* (*grey*) Structure of norloline. Its biosynthesis involves a pyridoxal-phosphate-containing enzyme and thereby differs from canonical non-ribosomal peptide assembly routes. *Bottom left* (*orange*) polyketide/non-ribosomal peptide hybrid compounds, emericellamide A and pseurotin A. *Bottom right* (*green*) Meroterpenoid (chimeric polyketide/terpene) natural products, fumagillin and austinol (color figure online)

clusters corresponding to each backbone-enzyme-encoding gene has been eased by bioinformatics programs that identify cluster genes on the basis of genomic distance and predicted protein functions [20, 56, 92, 118]. However, given the complexity of some clusters as mentioned earlier, these programs can only hint at the potential secondary metabolome of each fungal species. Additional genetic studies are pertinent for an accurate prediction of the extent and functionality of each cluster, which is the prerequisite for an efficient mining of the metabolites produced by each cluster. The following paragraphs will highlight the latest advances in prediction and activation of clusters by genetic means in the natural host and expression of putative clusters in non-natural hosts. Comparable strategies have been successfully applied for actinomycetes as described elsewhere in this JIMB Special Issue on Microbial Genome Mining and in other reviews [10, 11].

Activation of gene clusters in the natural host

Regulation of secondary metabolism occurs on multiple levels intimately linked to specific environmental cues. These complex regulatory networks are not surprising,

given that these natural compounds often have evolved to secure ecological niches [66, 146, 178], avoid predation [138] and defend against environmental stresses [55]. Expression of some clusters is therefore cryptic under standard laboratory growth conditions and needs to be triggered to enable activation of the corresponding metabolite.

Cluster-specific activation

Since the discovery of the sterigmatocystin/aflatoxin gene cluster-specific zinc binuclear cluster (Zn(II)2Cys6) transcription factor AflR that binds palindromic promoter sequences and is responsible for activation of all genes within the cluster [35, 39, 57, 182] several Zn(II)2Cys6 narrow domain proteins have been identified within other secondary metabolite gene clusters [38, 151]. Prominent examples apart from AflR are GliZ responsible for activation of all but one gene in the gliotoxin cluster in *A. fumigatus* and its homologue, SirZ, in *Leptosphaeria maculans* responsible for sirodesmin production [24, 61], the fumonisin activator Fum21 in *F. verticillioides* [33], Ctb8 responsible for cercosporin cluster activation in *Cercospora nicotianae* [40], LovE in *A. terreus* needed for lovastatin gene expression [81], AzaR responsible for azanigerones production in *A. niger* [187] and Gip2, Bik5 and Fsr6 in *F. graminearum* and *F. fujikuroi* controlling respective pigment production [93, 164, 179]. Deletion of the encoding genes has been successfully applied to localize cluster borders of the respective secondary metabolite clusters, establishing Zn(II)2Cys6 proteins as specific secondary metabolite cluster activators. Hence, several labs have utilized cluster Zn(II)2Cys6 genes to activate otherwise cryptic clusters in a natural host. For example, induced expression of *A. nidulans apdR*—encoding a Zn(II)2Cys6 protein and located in the subsequently characterized aspyridone cluster—led to activation of the aspyridone cluster and concomitant production of the PKS/NRPS hybrid metabolite [19]. Following this example, asperfuranone, monodictyphenone and *ent*-pimara-8(14),15-diene were discovered as products of the otherwise silent gene clusters in *A. nidulans* which are all activated by inducing the cluster-embedded Zn(II)2Cys6 gene [32, 42, 43]. Similar approaches were successful in other fungal species, i.e. for the discovery of fusarielins in *F. graminearum* [158], the virulence enhancer hexadehydroastechrome in *A. fumigatus* [185], neosartoricin/fumicycline B in *A. fumigatus* and *Neosartorya fischeri*, respectively [45, 96], and two novel metabolites of *F. fujikuroi* [178] (Table 1).

Global regulators

In addition to the narrow domain Zn(II)2Cys6 cluster activators described, global regulatory proteins represent another higher level of regulatory modulation of secondary metabolism. The signature hallmark of global regulation of fungal secondary metabolism was the discovery of the nuclear protein LaeA in *Aspergillus* spp. [2, 22, 26]. LaeA was found to be part of a protein complex with the fungal developmental regulatory protein VeA in *A. nidulans* [14], and subsequently in other filamentous fungi [78, 87, 176, 183], thereby connecting fungal development to secondary metabolism [13]. No other global regulatory protein has been used as successfully as LaeA and its orthologues to activate cryptic secondary metabolite gene clusters and increment their borders [85]. Deletion and overexpression in *A. nidulans* led to prediction and demarcation of several clusters and identification of the novel anti-tumour compound terrequinone A [25, 28]. In other genera similar approaches were implemented that led to discovery of the novel product ML-236B in *P. citrinum* [8, 25] and the discovery of several new secondary metabolites and gene clusters in *A. fumigatus*, *A. flavus*, *F. verticillioides* and *Monascus pilosus* [36, 67, 102, 134], some of which were later attributed to production of endocrocin, hexadehydroastechrome, fusaric acid and a duplicated set of tyrosine-derived alkaloids, respectively [34, 59, 103, 185] (Table 1).

Although LaeA is the most famous regulator regarding secondary metabolism, its mode of action remains enigmatic. The nuclear protein, which has homology to methyltransferases, was shown to perform automethylation at a methionine residue that is dispensable for biological function [132]. There is evidence that LaeA counteracts silencing heterochromatic marks in the *aflR* promoter region [136] as well as being required for full establishment of activating euchromatic marks at several secondary metabolite gene clusters in *A. nidulans* [159] making a connection to chromatin remodelling feasible. Furthermore, a recent study in *A. orzyae* has demonstrated that some histone deacetylases may impact secondary metabolism through regulation of *laeA* expression [88].

Histone and protein modification

A variety of modifications are known to act on proteins thereby affecting gene expression globally. For example, gene expression has been associated with acetylation of histone H3 lysine 9 (H3K9ac) and dimethylation of histone H3 lysine 4 (H3K4me2), whereas gene silencing has been associated with trimethylation of histone H3 lysine 9 (H3K9me3) [12, 48, 130, 163]. Additionally, sumoylation of histones and histone-modifying enzymes affects gene expression globally [162, 167] and the overall protein turnover is mediated by ubiquitination [175]. In several filamentous fungi chromatin modifications were shown to influence the production of different secondary metabolites and helped to demarcate known and orphan clusters

Table 1 Methods used to identify secondary metabolite clusters and their products in fungi

Metabolite	Organism	Reference
Cluster-specific activation		
Apicidin-like	*F. fujikuroi*	[178]
Asperfuranone	*A. nidulans*	[43]
Aspyridone	*A. nidulans*	[19]
Azanigerones	*A. niger*	[187]
ent-Pimara-8(14),15-diene	*A. nidulans*	[32]
Fumicycline A and B	*A. fumigatus*	[96]
Fusarielins	*F. graminearum*	[158]
Hexadehydroasterchrome	*A. fumigatus*	[185]
Monodictyphenone	*A. nidulans*	[42]
Neosartoricin	*N. fischeri*	[45]
Global regulator activation		
Endocrocin	*A. fumigatus*	[103]
Fusaric acid	*F. verticillioides*	[34, 36]
Hexadehydroasterchrome	*A. fumigatus*	[185]
ML-236B	*P. citrinum*	[8]
Terrequinone A	*A. nidulans*	[25, 28]
Tyrosine-derived alkaloids	*A. flavus*	[59]
Histone and protein modification		
2,4-Dihydroxy-3-methyl-6-(2-oxopropyl)benzaldehyde	*A. nidulans*	[68]
Asperthecin	*A. nidulans*	[165]
Atlantinones A and B	*P. citreonigrum*	[171]
Chladochromes F and G	*Cladosporium cladosporioides*	[180]
Lunalides A and B	*Diatrype disciformis*	[180]
Monodictyphenone	*A. nidulans*	[23, 42, 144]
NRPS9- and NRPS11-derived metabolites	*A. nidulans*	[101]
Nygerone A	*A. niger*	[77]
Orsellinic acid/F9775	*A. nidulans*	[23, 42, 144]
Culture conditions		
Aspernidine A and B	*A. nidulans*	[150]
Aspoquinolone A–D	*A. nidulans*	[148]
Bikaverin	*F. fujikuroi*	[179]
Fumicycline A and B	*A. nidulans*	[96]
Fusarubins	*F. fujikuroi*	[164]
Gibberellins	*F. fujikuroi*	[27]
Isoflavipucines	*A. flavus*	[69]
Monodictyphenone	*A. nidulans*	[149]
Nidulanin A	*A. nidulans*	[4]
Orsellinic acid	*A. nidulans*	[145, 152]
Penicillin/cephalosporin	*A. nidulans/P. chrysogenum*	[31]
Heterologous expression		

	Donor organism	Heterologous host	
6-Methylsalicylic acid	*A. terreus/P. patulum*	*A. nidulans*, *E.coli*, *S. cerevisiae*	[63, 89]
Asperfuranone	*A. terreus*	*A. nidulans*	[41]
Citrinin	*Monascus purpureus*	*A. oryzae*	[143]
Fumitremorgin	*A. fumigatus*	*E. coli*, *S. cerevisiae*	[71, 72, 112, 161]
Mycophenolic acid	*P. brevicompactum*	*A. nidulans*	[74]
Neosartoricin C	*Trichophyton tonsurans*	*A. nidulans*	[186]
Pyripyropenes	*A. fumigatus*	*A. oryzae*	[84]
SMA76a/pre-bikaverin	*F. fujikuroi*	*E. coli*	[110]
Squalestatin	*Phoma* sp.	*A. oryzae*	[50]

[101, 121, 123, 131, 135, 171, 180]. Specifically, deletion of a component of the complex involved in H3K4 methylation resulted in the identification of the monodictyphenone [23, 42, 144] and orsellinic acid/F9775 [23, 42, 144] gene clusters, respectively. In conjunction with these results, applying a chemical inhibitor of histone deacetylases to *A. niger* cultures led to the identification of the novel secondary metabolite nygerone A, but identification of the corresponding gene cluster awaits experimental proof [77] (Table 1).

Similarly, deletion of *sumO* encoding the only sumoylation gene in *A. nidulans* enabled the identification of the asperthecin gene cluster [165] and deletion of *csnE* encoding a protein of the COP9 proteasome resulted in identification of the *dba* gene cluster and its respective PKS-derived natural product [68] (Table 1).

Culture conditions

It has long been known that culture conditions, including nutrient source, ambient pH, redox status, co-cultivation with other organisms, light and temperature conditions, can alter the metabolome significantly [184]. The best understood examples of the impact of environmental conditions that affect secondary metabolism are the pH-dependent expression of the penicillin/cephalosporin genes clusters [31] and the nitrogen-dependent expression of the gibberellin gene cluster [27]. Change of culture conditions resulted in activation of aspoquinolones and aspernidine in *A. nidulans*, but no responsible cluster could be identified, respectively [148, 150]. Specific approaches where the promoter of the backbone gene of interest was fused to a reporter gene led to identification of producing culture conditions for isoflavipucines in *A. terreus* [69] and phylogenetic analysis in conjunction with modifying culture conditions enabled the identification of the fusarubin gene cluster in *F. fuikuroi* [164] (Table 1).

The coupling of growth on different media with genome-wide expression and/or protein data has been exploited to identify optimal culture conditions for activation of orsellinic acid and monodictyphenone pathways [145, 149] that had previously been identified through chromatin remodelling mutants [23]. Similar genomic approaches were used to accurately demarcate known gene clusters and identify the previously cryptic two-loci gene cluster responsible for nidulanin A production in *A. nidulans* [4] and also led to demarcation of known and novel gene clusters in *F. fujikuroi* [178]. Co-cultivation of *A. nidulans* with a bacterial species in combination with expression and histone profiling showed that expression of the orsellinic acid pathway is triggered by co-cultivation most likely through histone modifications [23, 122, 152]. A similar approach in *A. fumigatus* led to induction of neosartoricin/fumicycline B production [96] which had previously been activated by overexpressing the pathway-specific Zn(II)2Cys6 transcription factor [45] (Table 1).

Expression of gene clusters in non-natural hosts

Another method to elucidate the identity of a fungal natural product is to express the desired gene cluster in a different host. This synthetic biology approach was first established for expressing single cluster genes in order to assess their enzymatic functions during the biosynthetic process. For example, genes have been expressed for assessment of enzymatic function in *A. nidulans*, *A. oryzae*, *Saccharomyces cerevisiae* or *Escherichia coli* [50, 63, 71, 72, 74, 89, 91, 110, 112, 141–143, 153, 161]. The first complete reconstructions of whole secondary metabolite pathways were achieved by subsequently introducing the genes of the tenellin, penicillin, pyripyropene and aphidicolin pathways, respectively, in *A. oryzae* [64, 76, 84, 117]. Yeast recombinational cloning methodology [127] has recently been utilized to clone entire gene clusters (including activation of specific Zn(II)2Cys6 transcription factors by promoter replacement) and to transform *A. nidulans* with these [186]. Another approach complementary to that of yeast cloning was the use of fusion PCR [125, 166] to express an entire heterologous gene cluster in *A. nidulans* strain [41] (Table 1). This latter work was particularly productive as the heterologous cluster was placed in an engineered *A. nidulans* strain deficient of its own secondary metabolite gene clusters in order to avoid interfering chemical compounds thereby easing the structure elucidation of the heterologous natural product.

Modification of gene clusters leading to unnatural products

Mining of fungal genomes and activation of cryptic secondary metabolite gene clusters by applying the strategies previously outlined will aid the identification of novel natural products. However, not every end product that can be found has the desired bioactivity. Therefore engineering of the novel metabolic pathway can improve the accumulation of either naturally occurring intermediates or additionally modified molecules. The first successful application was the manipulation of the penicillin/cephalosporin pathway by additionally integrating bacterial-derived enzyme-encoding genes in order to modify product spectrum [37, 75, 137, 174]. Modification of the fumitremorgin pathway of *A. fumigatus* by either overexpressing the backbone enzyme in the natural host [112] or by expressing partial pathway genes in *A. nidulans* increased yields of biological active intermediates [113]. A genome-wide approach was recently conducted by individually overexpressing each non-reducing PKS in *A. nidulans*, leading to identification of their putative products that in most cases will be pathway intermediates [1]. Similar pathway disruption approaches

of several pathways in different filamentous fungi lead to accumulation of previously unobserved intermediates [27, 51, 60, 62, 103, 147, 164].

Additionally, the modular nature of PKS and NRPS enzymes can be exploited by exchanging specific domains between these backbone enzymes that will result in new "unnatural" chemical scaffolds thereby increasing chemical and putatively bioactive diversity. The first successful example of such a engineered backbone enzyme was reported by swapping domains of the backbone genes responsible for tenellin and desmethylbassianin production in *Beauveria bassiana*, respectively, and expressing the engineered enzymes in *A. oryzae* [58]. In *A. nidulans* swapping domains of the asperfuranone and sterigmatocystin backbone enzymes resulted in production of new metabolites [106]. Engineering of the PKS responsible for hypothemycin production in *Hypomyces subiculosus* and subsequent expression in *S. cerevisiae* produced an unnatural diastereomer of the natural product [188].

Future perspectives

The improvements in genome sequencing, particularly next-generation sequencing, ensure a massive increase in the availability of fungal genomes. For example, the 1,000 fungal genomes undertaken by the Department of Energy (DOE) Joint Genome Institute (JGI) is just one example of a large-scale sequencing effort [70]. Undoubtedly, these genomes will fuel concomitant research efforts in elucidating the bioactive natural products produced by these fungi. Not only do we expect efforts to continue as reviewed in this article but likely novel and quicker ways to unlock the fungal treasure chest. It is hard to predict future developments but three approaches which we speculate will emerge in fungal biology are to express artificial gene clusters in fungi, as has been recently shown for actinomycetes [129, 155], to express entire heterologous clusters in one cloning step, for example using bacterial artificial chromosomal (BAC) technology [105] and to engineer the precursor pool availability [181].

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