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REVIEW

Epigenetic manipulation of filamentous fungi for biotechnological applications: a systematic review

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Abstract The study of the epigenetic regulation of gene function has reached pivotal importance in life sciences in the last decades. The mechanisms and effects of processes such as DNA methylation, histone posttranslational modifications and non-coding RNAs, as well as their impact on chromatin structure and dynamics, are clearly involved in physiology homeostasis in plants, animals and microorganisms. In the fungal kingdom, studies on the model yeasts *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe* contributed enormously to the elucidation of the eukaryote epigenetic landscape. Epigenetic regulation plays a central role in the expression of virulence attributes of human pathogens such as *Candida albicans*. In this article, we review the most recent studies on the effects of drugs capable of altering epigenetic states and on the impact of chromatin structure-related genes deletion in filamentous fungi. Emphasis is given on plant and insect pathogens, endophytes, secondary metabolites and cellulases/xylanases producing species.

Keywords Epigenetics · Filamentous fungi · Dnmts and HDACs inhibitors · Gene deletion · Biotechnology applications

Abbreviations

5-AZA	5-Azacytidine
CHART-PCR	Chromatin accessibility real-time PCR
ChIP	Chromatin immunoprecipitation
Cre1	Carbon catabolite repressor 1
DNMTi	DNA-methyltransferases inhibitor(s)
DNMTs	DNA-methyltransferases
GlcNAc	N-acetyl-D-glucosamine
HATs	Histone acetyltransferases
HDACi	Histone deacetylases inhibitor(s)
HDACs	Histone deacetylases
HP1	Heterochromatin protein 1
HPLC	High performance liquid chromatography
HPTMs	Histone posttranslational modifications
KMTs	Histone lysine methyltransferases
NaBut	Sodium butyrate
ncRNAs	Non-coding RNAs
PKE	Polyketides
PKS	Polyketides synthase

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SAHA	Suberoylanilide hydroxamic acid
SMRT	Single molecule real-time sequencing
SMs	Secondary metabolites
TEs	Transposable elements
TSA	Trichostatin A
VOCs	Volatile organic compounds
VPA	Valproic acid
Xyr1	Xylanase regulator 1

Introduction

The term epigenetics normally refers to "the study of changes in gene function that are mitotic and/or meiotically inherited and that do not involve alteration in the DNA sequence"; in other words, which do not involve mutation. Another common definition is "the study of inheritance components not fully explained or interpretable by the Mendelian principles of heredity" (Jablonka and Lamb 2002; Holliday 2006).

Epigenetic mechanisms have been extensively studied in both normal as in pathological processes such as cell differentiation and senescence, embryonic development, neuronal plasticity, transposon silencing, plant flowering, eye color variegation in *Drosophila melanogaster*, phenotypic differences between monozygotic twins, oncogenesis, autoimmune diseases, obesity, behavioral disorders such as schizophrenia and depression. In this view, epigenetic regulation seems to correspond to a universal strategy of gene expression control, although it is not completely understood.

Filamentous fungi are essential microorganisms to modern biotechnology due to the ubiquity, diversity and versatile metabolism. Since the antibiotics discovery era, fungi are not only seen as possible pathogens, but mainly as "microbial cell factories, source of enzymes, chemicals, and pharmaceuticals", as pointed out by Ghimire and Jin (2017). As alternatives for chemical or physical processes, filamentous fungi govern the White and Red Biotechnological field. As an example, the production of plant biomass degrading enzymes by filamentous fungi, which alone corresponds to a €4.7 billion market, is expected to double in the next 10 years (Meyer et al. 2016).

Currently, the obtainment of products by the simple cultivation of microorganisms has reached the upper limit. The genomic era and the technical approaches developed thereafter revealed how much more complex the metabolic regulation can be. In this view, epigenetics, initially seen as a mere additional gene regulation strategy, can now be engineered as a biotechnological tool. Despite considerable advances in recent years, information on epigenetic mechanisms in filamentous fungi is still much limited to model (e.g. *Saccharomyces cerevisiae*, *Schizosacharomyces pombe*) and pathogenic (*Candida albicans*, *Cryptococcus neoformans*) organisms. Nonetheless, the studies of epigenetic mechanisms involved in the regulation of secondary metabolites (SMs) production by fungi are gaining importance (reviewed by Strauss and Reyes-Dominguez 2011; Gacek and Strauss 2012; Aghcheh and Kubicek, 2015).

In this work, we present a comprehensive review of the most recent findings on the employment of epigenetic drugs for the increase of fungi-derived bioproducts, and on the characterization of filamentous fungi mutant strains for genes involved in epigenetic regulation and chromatin remodeling processes. Our aim is to highlight the main results and the potential biotechnological applications of such findings.

For the bibliometric analysis, a detailed literature survey was conducted using the Web of Science (Wos) Core Collection database (Clarivate Analytics, Philadelphia, USA, https://clarivate.com/webofsciencegroup/). Multiple strings were used aiming results that would contribute to the scope of this review. The survey employed the "advanced search" area using Boolean operators and combined research. This methodology demonstrated the distribution of the key words in literature. The string TS = ("filamentous fungi" AND epi*) resulted in publications mentioning the words epigenetics, epigenome, epidrugs or their derivatives, thus completely covering the topics we wanted to address. As illustrated in Table 1 and in Fig. 1, the literature on epigenetic aspects of fungal morphogenesis, reproduction and virulence has been increasing exponentially.

Table 1 Search strings used on Web od science database

Research string	Number of results	Time interval
ALL = (Filamentous fungi epigenetic)	82	1992–2019
ALL = (Fungi epigenetics AND biotechnology)	17	All years
ALL = (epigenetic mechanism AND Biotechnology)	830	2009–2019
TS = ("Filamentous fungi" AND "epigenetic")	50	All years
TS = ("filamentous fungi" AND epi*)	720	All years

ALL all fields, *TS* topic

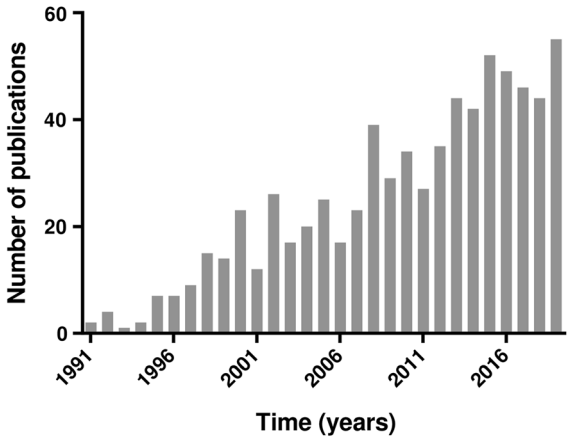

Fig. 1 Number of publications retrieved from the Web of Science by using the search string TS = ("filamentous fungi" AND epi*) (Jan/2020)

DNA methylation

In eukaryotes, DNA methylation usually occurs in cytosines followed by guanines and it has been studied especially in the context of gene promoter regions, where hypermethylation is normally related to gene repression and hypomethylation is associated to gene transcription activation. The enzymes that catalyze the methylation of the cytosines 5′ carbon atom are called DNA-methyltransferases (DNMTs) and are particularly well characterized in mammals. In general, DNA methylation in 5′ regulatory regions of genes hinders (or even prevents) the access of the transcription machinery. DNA methylation also recruits enzyme complexes involved in histone modifications leading to changes in chromatin structure (relaxation or compaction), thus promoting the activation or repression of transcription (Fig. 2). Zheng et al. (2013) demonstrated that the RNA methylation/demethylation dynamics also influences the mRNA synthesis and translocation, indicating that epigenetic interactions in gene regulation are even more complex than previously believed.

Histone posttranslational modifications and chromatin structure

Histone core hyperacetylation, catalyzed by acetyltransferases (HATs) is generally associated with gene expression due to decreased DNA-histone interaction, leading to a more open chromatin conformation (reviewed by Hyndman and Knepper 2017; Javaid and Choi 2017). On the other hand, removal of acetyl groups from histone and other proteins is performed by a class of ubiquitous enzymes referred as histone deacetylases (HDACs) (Fig. 3). The histone methylation/demethylation dynamics has also been drawing attention as an important gene regulation process in several different models (Eglen and Reisine 2011; Hirst 2013; Huang et al. 2013).

Unlike DNA methylation and histone acetylation, histone methylation is associated with both activation and repression of gene transcription (Fig. 3). Methyl groups may be added at three different sites of lysine (mono-, di- or trimethylation) and at two different sites of arginine (mono- or dimethylation) residues. The number of methyl groups and the specific sites result on different effects on chromatin structure and gene regulation.

Epigenetic drugs

Epidrugs are described as synthetic or natural compounds that are able to alter the epigenetic landscape of the cell. Most of them act by inhibiting the enzyme machinery responsible for transferring methyl, acetyl or alkyl groups, either to DNA or to histones. DNMTs, HATs and HDACs inhibitors are widely employed in studies of cancer therapy and in animal models for

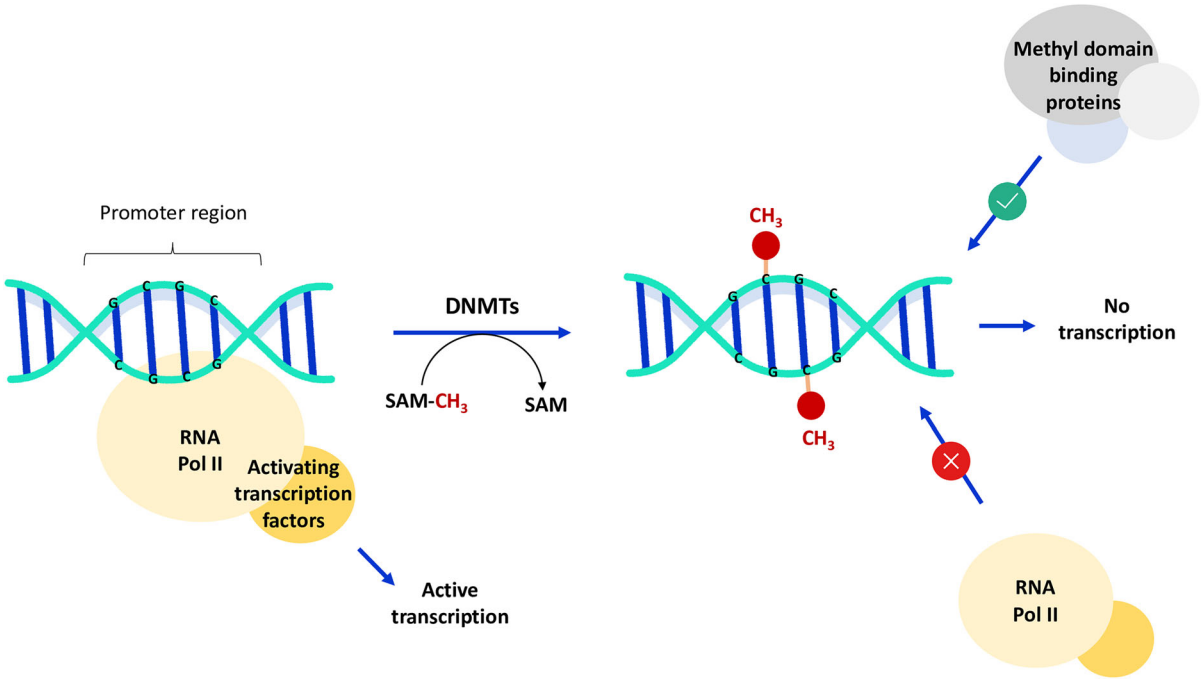

Fig. 2 DNA Methylation. CpG sites are often located on promoter regions, where RNA pol II and transcription factors can bind to start transcription. The DNA methyltransferases (DNMTs) catalyze the transferring of a methyl group from S-adenosylmethionine (SAM) to the cytosine fifth carbon, generating 5-methylcytosine. DNA methylation impairs the binding of the transcription machinery and recruit repressive complexes via Methyl Domain Biding proteins, resulting in the inhibition transcription

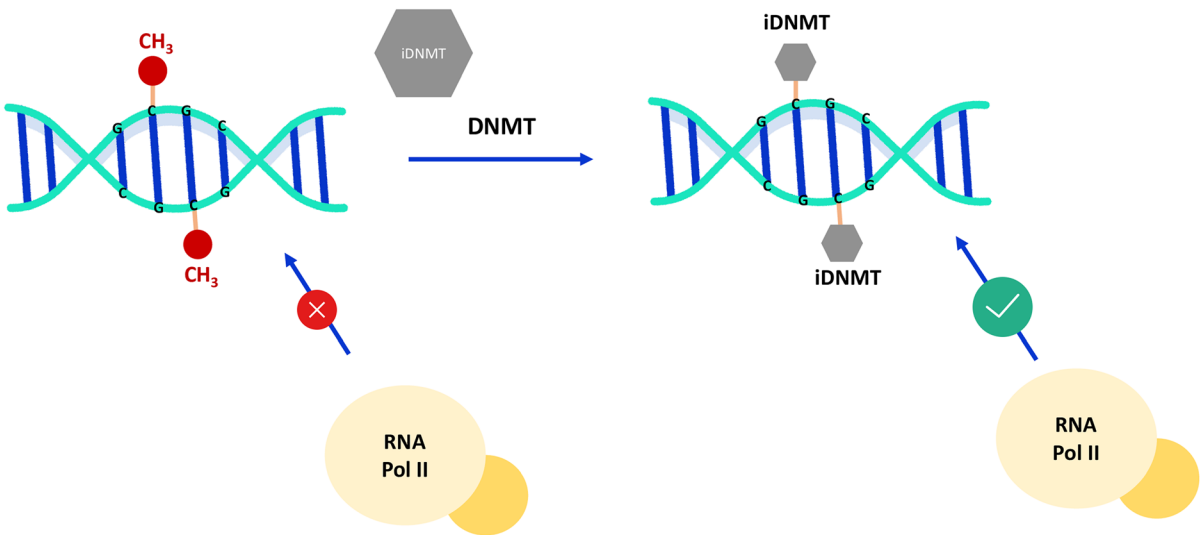

Fig. 3 Chromatin remodeling by histone post-translation modifications. DNA methylation recruits histone methyltransferases (HMTs) which establish repressive marks, such as the methylation of the histone 3 lysine 9 residue (H3K9me), resulting in chromatin condensation. Histone Acetyl Transferases (HATs) acetylate histone lysines residues, which diminishes the interaction with DNA and leads to an open chromatin state poised to transcription. Lysine acetylation also recruits different HMTs, which establish gene activation marks, such as the methylation of the histone 3 lysine 4 residue (H3K4me)

neurodegenerative and behavioral diseases. Some epidrugs have been approved by the USA Food and Drug Administration (FDA) for the therapeutic use in humans aiming, for instance, the reactivation of tumor suppressor genes, such as p53 and p16, in different types of leukemia and other myeloblastic syndromes (Heerboth et al. 2014; Dunne et al. 2015).

It is important to note that, so far, it is not possible to target epigenetic drugs to precise regions of the genome or even to specific cell types. In this view, their effects can represent an overall impact on cell physiology or in the metabolism. It is widely known that HDACi, for instance, interfere in the deacetylation of many other proteins apart from histones. As in other drugs interventions, studies employing molecular probes, monoclonal antibodies or nanotechnology shall be conducted in an attempt to achieve specific responses.

In this work, we focus on the effect of drugs and gene deletions in the production of biotechnological products or applications. Mechanistic approaches are discussed in reviews such as Aghcheh and Kubicek (2015).

DNMTs inhibitors

DNMTs were reported for several filamentous fungi such as *Neurospora crassa*, as reviewed by Aramayo and Selker (2013) and Aghcheh and Kubicek (2015). 5-azacytidine (5-AZA) and Decitabine (5-aza-2′-deoxycytidine) are frequently employed as DNMTi in studies aiming to elucidate the impact of DNA methylation on fungal physiology. These synthetic drugs are analogs of cytidine, presenting a nitrogen atom instead of a carbon in the position 5 of the pyrimidine ring. Thus, the molecule is incorporated in the DNA and prevents the proper transferring of the methyl group by the DNMT (Fig. 4). This results in passive demethylation through consecutive DNA replication cycles (Santi et al. 1984). In the presence of the DNMTi, DNMTs remain bound to the DNA and then are degraded by the proteasome pathway. 5-AZA, a ribonucleoside analog, is incorporated in the RNA molecule and, to a lesser extent, in the DNA. Decitabine, as a deoxyribose analog, is incorporated only in DNA (Gnyszka et al. 2013).

HDACs inhibitors

HDACs inhibitors (HDACi) can be structurally grouped into at least four classes: hydroxamates, cyclic peptides, aliphatic acids and benzamides. Trichostatin A (TSA), suberoylanilide hydroxamic acid (SAHA) and sodium butyrate (NaBut) are frequently used in the most recent studies with filamentous fungi. These HDACi alter gene expression patterns and promote changes in non-histone proteins at the post-translational level (Kim and Bae 2011).

TSA was initially isolated from a *Streptomyces hygroscopicus* strain and presents a specific inhibitory effect on HDACs in vitro and in vivo. SAHA is a synthetic bishydroxamic-acid-based molecule. Both TSA and SAHA present a hydroxamic acid group which binds to the Zn^{++} ion of Class I and II HDACs active sites, thus preventing their activity (Yoshidas and Kijima 1990; Mark and Breslow 2007) (Fig. 5).

NaBut is a naturally occurring molecule that, even at millimolar concentrations, inhibits the histone deacetylases activity. The precise action mechanism remains unknown, but it has been proposed that NaBut can occupy the enzyme hydrophobic pocket and act as a noncompetitive inhibitor of HDACs (Candido et al. 1978; Davie 2003).

Biological effects of epigenetic drugs on filamentous fungi

The employment of epidrugs during filamentous fungi growth is contributing to the elucidation of epigenetic mechanisms related to morphology, physiology and metabolism in these organisms. Several studies were conducted in the last two decades, leading to the obtainment of *epivariants* after the treatment with one, two or even more epidrugs in combination. Some of the species, epidrugs, concentrations and the most remarkable physiological impacts are presented in Table 2.

Furthermore, these drugs can optimize the production of biotechnologically relevant molecules and lead to the discovery of cryptic bioactive compounds (Table 3).

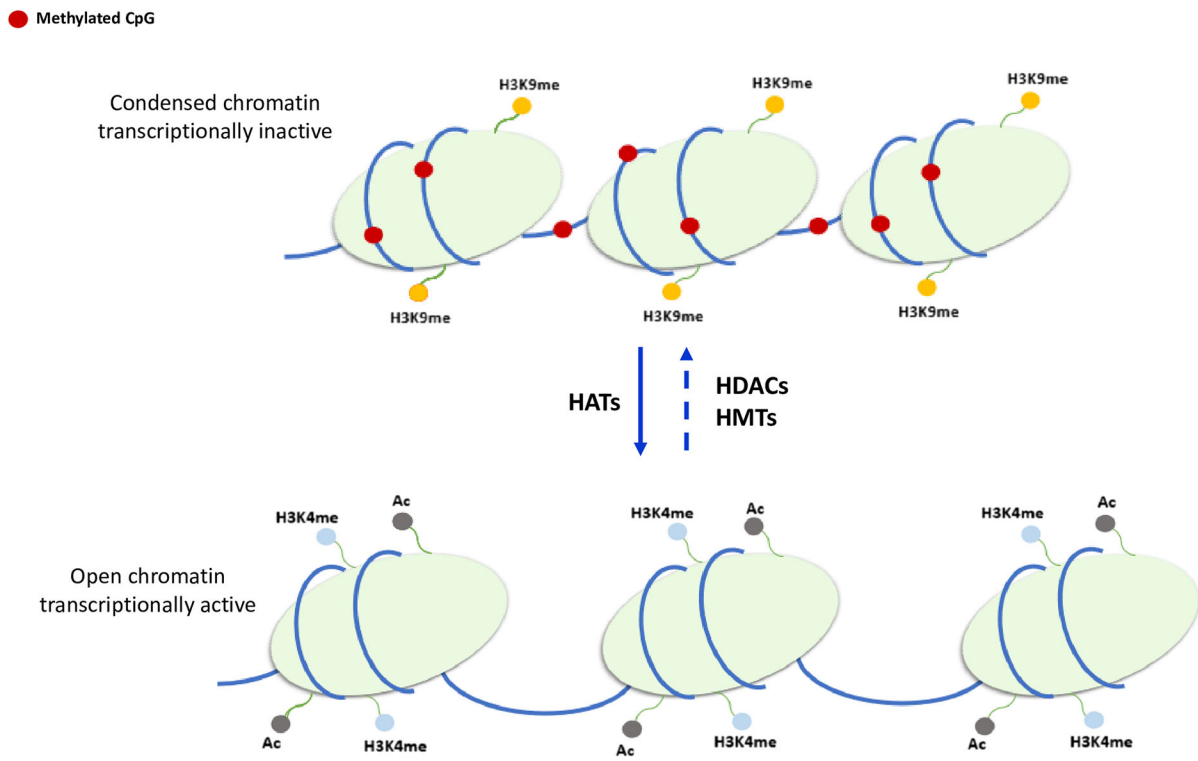

Fig. 4 DNMTs inhibition. DNMTs inhibitory drugs, such as azacytidine or decitabine, are base analogs which are incorporated into the nucleic acids and prevent the transference of the methyl group to cytosine by the DNMTs. The inhibitors remain covalently linked to the RNA or DNA, leading to a hypomethylated status and to the activation of previously repressed genes

Biomass degrading fungus

Doratomyces microspores is a fungus normally isolated from feces, decaying plant biomass and soil. Besides the production of an extracellular keratinase and the capacity of degrading the antifungal alkaloid sampangine, little was previously known about this fungus metabolism. This fact motivated Zutz et al. (2016) to investigate it upon growth on minimal medium supplemented with valproic acid (VPA), a HDAC inhibitor. High performance liquid chromatography (HPLC) analyses of the fungal extract revealed seven compounds derived from primary and secondary metabolism. These compounds were able to inhibit the growth of *Staphylococcus aureus*, including two antibiotic-resistant clinical isolates. Cyclo-(L-proline-L-methionine) (cPM), was isolated from a fungus for the first time. cPM, (cFP) and phenylacetic acid (PAA) presented low cytotoxicity against human cell lines and marked synergic effect with ampicillin against *S. aureus* and *Escherichia coli* ampicillin-resistant strains.

Marine fungi

Upon cultivation in the presence of 5-AZA, the marine-derived fungus *Cochliobolus lunatus* (TA26–46) produced seven new diethylene glycol phthalate ester monomers and oligomers, along with four known analogues (Chen et al. 2016). The treatment of another marine fungus (the *Aspergillus* sp. SCIOW2 strain) with 5-AZA and SAHA led to the description of three new eremophilane-type sesquiterpenes (dihydrobipolaroxin B, C and D) and also of a new dihydrobipolaroxin analogue. None of these compounds were previously produced in untreated cultures (Wang et al. 2016). Such studies clearly demonstrate the potential of epigenetic modulators to induce the expression of compounds which are not obtained during regular culture conditions and also to enhance the production of known metabolites.

The growth of *Penicillium brevicompactum* in the presence of nicotinamide or NaBut resulted in a two to tenfold increase in the production of phenolic

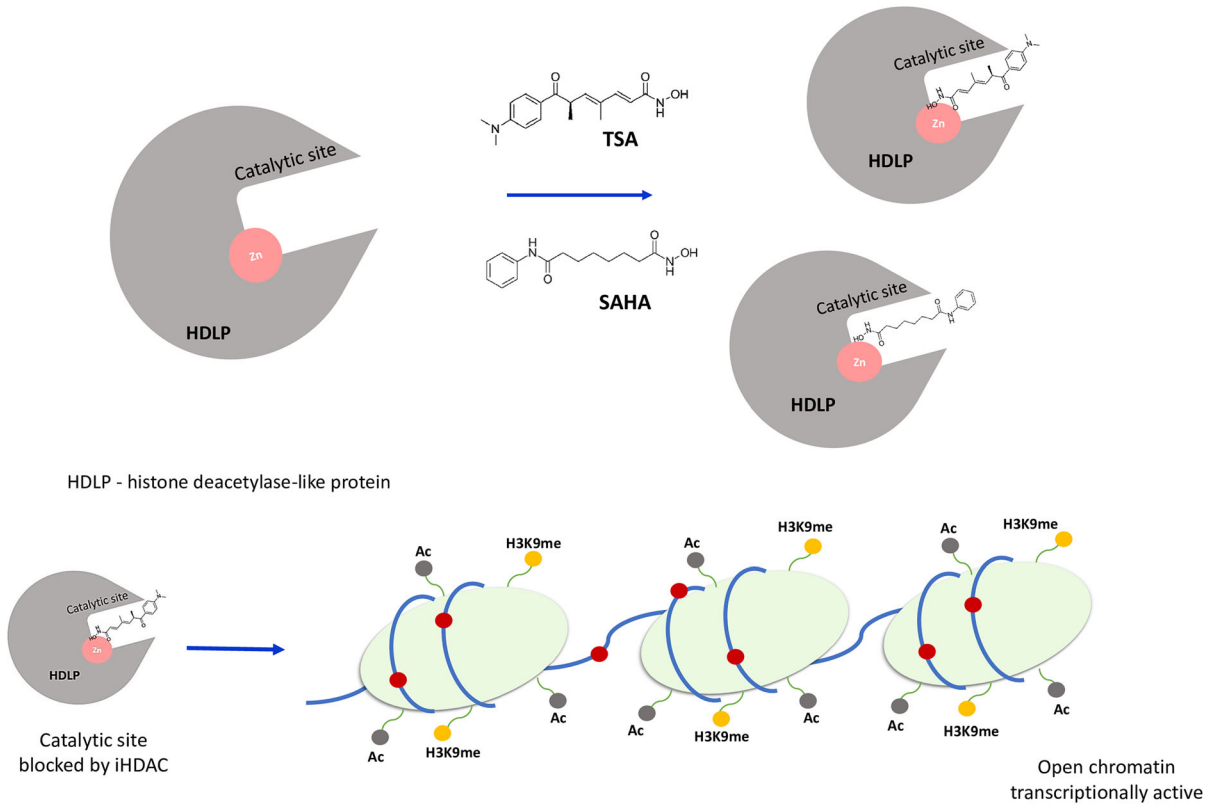

Fig. 5 Inhibition of histone deacetylase enzymes (HDACs). The catalytic site of HDACs presents a pocket containing a Zinc atom that operates as cofactor. TSA and SAHA block this pocket by insertion of the aliphatic chain. Once the deacetylation is inhibited, the chromatin structure remains favorable to transcription

compounds, some of them presenting cytotoxic activity against liver carcinoma cells (El-Hawary et al. 2018).

Endophytes and plant pathogen fungi

When *Pestalotiopsis crassiuscula*, isolated from the leaves of *Fragaria chiloensis*, was grown in culture medium supplemented with 5-AZA, one new coumarin was isolated and structurally elucidated (Yang et al. 2014). As recently reviewed by Sarker and Nahar (2017), naturally occurring coumarins draw the scientific attention due to the structural diversity and therapeutic properties they present as analgesic, anticoagulant, anti-HIV, anti-inflammatory, antimicrobial, antineoplastic, antioxidant and immunomodulatory compounds.

Polyketides constitute a relevant class of bioactive compounds employed as antibiotics, antiparasitic, insecticides, antineoplastic, as immunosuppressants (reviewed by Hussain et al. 2017), in the production of biofuels and industrial chemicals (reviewed by Cai and Zhang 2017). Qadri et al. (2016) treated the endophyte *Muscodor yucatanensis* Ni30 with 5-AZA and with SAHA in order to obtain putative epivariants for the production of volatile organic compounds (VOCs). When compared to the control strain, epivariants presented differences in the growth rate, mycelia morphology, pigmentation and in the production of distinct VOCs. The authors attributed these differences to the transcription activation of polyketides synthase (PKS) genes. An increased accumulation of different PKE transcripts was indeed verified for epivariant 1 (EV-1) in comparison to the control.

The treatment of *Eupenicillium* sp. Lg41 with different concentrations of nicotinamide revealed the production of two new decalin-containing compounds. One of them inhibited *Staphylococcus aureus* growth with a MIC of 0.1 µg/mL and presented

Table 2 General effects of the exposure of filamentous fungi to epidrugs

Species	Epigenetic modulator/concentration	Effect(s)	References
Aspergillus niger (ATCC1015)	SAHA 10 μM	Production of a new fungal metabolite (nygerone A), presenting a unique 1-phenylpyridin-4(1H)-one core not previously reported from any natural source	Henrikson et al. (2009)
Aspergillus nidulans	SAHA 4 mM; Anacardic acid 100 μM	Activation of the *orsA* gene transcription by SAHA and repression by anacardic acid	Nützmann et al. (2011)
Alternaria sp.	5-AZA, SAHA	Induced production of mycotoxins (alternariol, alternariol-5-O-methyl ether, 30—hydroxyalternariol-5-O-methyl ether, altenusin, tenuazonic acid and altertoxin II)	Sun et al. (2012)
Hypoxylon sp. CI-4	5-AZA 100 μM; SAHA 50 μM	Induced production of VOCs, terpenes, primary and secondary alkanes, alkenes, organic acids and benzene derivatives	Ul-Hassan et al. (2012)
Chaetomium indicum	SBHA	Production of structurally diverse chaetophenols, some presenting new polycyclic skeletons	Asai et al. (2013)
Aspergillus clavatus	VPA, TSA, NaBut, 5-AZA, GlcNAc, 5 μM each	Modulation of the secondary metabolites production, depending on the culture medium and time of growth	Zutz et al. (2013)
Aspergillus flavus	5-AZA 1 mM	Impairment of fungal development; modulation of secondary metabolism	Lin et al. (2013)
Pestalotiopsis crassiuscula	5-AZA	Isolation and structural characterization of a new coumarin	Yang et al. (2014)
Chaetomium cancroideum	Nicotinamide 50 μM	Increased production of aromatic and branched aliphatic polyketides; production of new secondary metabolites (chaetophenol G and cancrolides A and B)	Asai et al. (2016)
C. lunatus (TA26–46)	5-AZA 10 μM	Increased production of diethylene glycol phthalate ester monomers and oligomers	Chen et al. (2016)
Muscodor yucatanensis Ni30	5-AZA, SAHA 50 μM each	Defects in growth rate, mycelia morphology, pigmentation; enhanced production of VOCs, ergosterol and xylaguaianol C were reported for the epivariant 1	Qadri et al. (2016)
Aspergillus sp.	5-AZA, SAHA 1 mM each	Production of three new eremophilane-type sesquiterpenes, (dihydrobipolaroxin B, C and D) and of a new dihydrobipolaroxin analogue	Wang et al. (2016)
Doratomyces microspora	VPA 50uM	Increased production of seven antimicrobial compounds. Isolation of cyclo-L-proline-L-methionine from fungi for the first time	Zutz et al. (2016)
Phoma sp. *nov. LG0217*	SAHA 500 μM	Alteration of the SM profile. Production of (10'S)-verruculide B, vermistatin and dihydrovermistatin	Gubiani et al. (2017)
Eupenicillium sp. LG41	Nicotinamide	Production of two new decalin-containing compounds (eupenicinicols C and D) and of two related compounds previously described (eujavanicol A and eupenicinicol A)	Li G. et al. (2017a)
Aspergillus sp. SCSIOW3	SBHA and 5-AZA 1 mM each	Production of a new diphenylether-O-glycoside (1, diorcinol 3-O-α-D-ribofuranoside)	Li et al. (2017a, b, c)
Humicola grisea	5-AZA 25 μM	Derepression of cellulase and xylanase genes transcription upon growth on glucose	Manfrão-Netto et al. (2017)
5 species of *Talaromyces* and *Penicillium janthinellum*	Different combinations of SBHA, Procainamide and Hydralazine 0,1 mM each	Crude extract increased antibacterial activity against *L. monocytogenes*. Inhibition of the acetylcholinesterase activity	Lima et al. (2018)

Table 2 continued

Species	Epigenetic modulator/concentration	Effect(s)	References
Lachnum palmae	SAHA 500 μM	Production of 18 dihydroisocoumarins, including five unkown brominated and two chlorinated compounds	Zhao et al. (2018)
Aspergillus versicolor	SAHA 20 mg/L	Production of a new biphenyl derivative (Versiperol A) and of two known compounds (2,4-dimethoxyphenol and diorcinol)	Zhu et al. (2018)
Penicillium brevicompactum	Nicotinamide 100 μM; NaBut 100 mM	Production of 11 new phenolic compounds, some presenting cytotoxic activity against cancer cell lines	El-Hawary et al. (2018)
Drechslera sp.	SAHA, VPA, OHA	Increased production of benzophenone	Siless et al. (2018)

nd not described, *SBHA* suberohydroxamic acid, *OHA* octanoylhydroxamic acid

Table 3 Biological activity of metabolites obtained from the exposure of filamentous fungi to epidrugs

Metabolite	Activity/effect/employment	References
Cytochalasins	Mycotoxin; actin polymerization inhibitor	Cooper (1987)
Tenuazonic acid	Mycotoxin; protective effect against induced skin tumors in mice	Antony et al. (2002)
Altenusina	Biphenyl derivative; antifugal and trypanothione reductase inhibition activity	Cota et al. (2008) and Johann et al. (2012)
Nygerone A	Not described	Herinkson et al. (2009)
Pseurutin A	SM; antibiotic and immunosuppressive activities	Molla et al (2010)
Vermistatin	Inhibition of caspase-1 and of IL-1beta production in human THP1 cells	Stierle et al. (2013)
Alternariol (alternariol methyl ether)	Mycotoxin; cytotoxic effects	Sun et al. (2012) and Solhaug et al (2016)
Altertoxin II	Perylene quinone mycotoxin; mutagenic effect on mammalian cells	Fleck et al. (2012)
Verruculide B	Tyrosine phosphatase inhibitor	Yamazaki et al (2015)
chaetophenol G and cancrolides A and B	Not described	Asai et al. (2016)
Diethylene glycol phthalate	Plasticizer for industrial products; it causes environment pollution	Chen et al. (2016)
Patulin	Tetraketide; antibiotic	Reviewed by Siddiquee (2018)
Benzophenone compounds	Cosmetic industry; anti-inflammatory, anticancer, antiviral and antimicrobial activities	Reviewed by Surana et al. (2018)
Aurofusarin	Pigment; cytotoxic activity against the colon adenocarcinoma HT29 cell line and the non-tumorigenic HCEC-1CT colon cells	Jarolim et al (2018)

cytotoxicity against a human acute monocytic leukemia cell line (Li et al. 2017a, b, c).

Dreschslera sp. is a member of the dark septate endophytes. The cultivation of this fungus in the presence of non-toxic concentrations of SAHA, VPA and octanoylhydroxamic acid (a SAHA analogue) led to the emergence of 6 epivariants. SAHA, in particular, enhanced the production of benzophenone (Siless et al. 2018).

Shiraia bambusicola is a pathogenic fungus of bamboo trees whose fruiting bodies are used in traditional Chinese medicine and present high content of the red pigments hypocrellins. These pigments have been studied as photosensitizer agents for the photodynamic therapy of skin diseases. Aiming to initiate epigenetic studies in *S. bambusicola* and to gain information on hyprocrellins regulation, Ma and collaborators (2018) evaluated this fungus global DNA methylation profile in control conditions and upon exposure to 5-AZA. Even though genome digestion with the McrBC endonuclease followed by HPLC analysis indicated low level of DNA methylation, growth of *S. bambusicola* in the presence of 5-AZA resulted in morphological alterations such as fluffy white substrate mycelia, instead of the homogenous red color of the control, sever reduction of the number of conidia and in the content of hypocrellins. RNA-seq and qRT-PCR data indicated downregulation of polyketide synthase and redox pathway genes. ROS production, as revealed by fluorescence microscopy, was diminished despite no alteration in CAT, SOD and GSH-Px activities. The authors argued that the impact of 5-AZA in the hyprocrellins production could represent an effect of the redox metabolism alteration, rather than the DNA methylation inhibition.

Mutant strains for epigenetic regulation- and chromatin remodeling-related genes

Several studies aiming to elucidate the impact of chromatin structure-related genes on the fungal development, physiology and metabolism, as well as on the production of specific compounds, have been conducted. Gene replacement or inactivation by recombination with dominant selection markers resulted in relevant information. Some of the most remarkable studies are summarized below.

Endophytes

Calcarisporium arbuscular

Calcarisporium arbuscular is a mushroom-endophytic fungus pointed out as a potential producer of PKEs. The deletion of a *C. arbuscular* HDAC encoding gene (*hdaA*) resulted in altered growth, hyphae morphology and sporulation. Liquid chromatography/mass spectrometry analysis of the mutant strain crude extract revealed several new natural products of different chemical structure and biosynthetic pathways (Mao et al. 2015).

Pestalotiopsis microspore and P. fici

Pestalotiopsis microspore is an endophytic fungus which is able to degrade polyester polyurethane, thus presenting the potential to be employed in the biodegradation of plastics (Russell et al. 2011). The deletion of this fungus histone acetyltransferase *hat1* gene impaired the conidiation, melanin pigmentation and SMs production (Zhang et al. 2016a, b).

Pestalotiopsis fici is another endophyte whose production of SMs is regulated at the epigenetic level. Wu et al. (2016) identified and disrupted a histone methylation (PfCcla) and a histone deacetylase (PfHdaA) gene. The mutant strains crude extracts HPLC profiles revealed 15 new polyketides when compared to the wild type one.

Plant pathogens

Fusarium graminearum

The gene for the putative histone methyltransferase KMT6 from the cereal pathogen *F. graminearum* was deleted by Connolly et al. (2013). The absence of the histone 3 lysine 27 tri-methylation (H3K27me3) was verified by western blot with different antibodies. Mutant strains presented a twofold slower linear growth, as revealed by long-term experiments on Ryan race test tubes, an intense orange pigmentation and showed to be sterile in crossing experiments. The deletion of the *kmt6* gene resulted in the depression of 15–30% of the *F. graminearum* genes. Most of these genes corresponded to SM clusters, such as those required to produce the pigments aurofurasin, neurosporaxanthin and torulene, and the mycotoxin fusarin C. The abolishment of the H3K27me3 mark revealed more cryptic gene clusters than changes in the level of nitrogen, a well-known regulator of SM production in *Fusarium* species. The expression of genes for secreted putative virulence factors and for plant cell wall degradation was also upregulated, although the *kmt6* mutant strain proved to be hypovirulent in a wounded tomato infection assay. Most of the

wild type phenotypes were restored in a reconstituted strain.

In *F. graminearum*, the deletion of the *Set1* gene, which encodes a histone methyltransferase capable of promoting mono-, di- and trimethylation of H3K4, provoked defects in virulence upon flowering wheat heads and in the production of aurofusarin and deoxynivalenol. On the other hand, an increased resistance to cell wall-damaging agents was reported. (Liu et al. 2015).

Fusarium fujikuroi

Fusarium fujikuroi causes the rice *bakanae* disease and it is potent producer of plant hormones, pigments and mycotoxins. The effect of the deletion of *F. fujikuroi* HDAC genes on the production of SM and on virulence was investigated by Studt et al. (2013). Initially, the authors demonstrated that growth of the wild type strain in the presence of 1 µM TSA provoked a 75% reduction in the production of gibberellins. Four HDAC genes were identified in the fungus genome (*ffhda1*, *ffhda2*, *ffhda3* and *ffhda4*) and gene deletions were conducted in order to evaluate the impact of histone deacetylation on fungal growth and SM production. No mutant strain could be obtained for the *ffhda3* gene, suggesting that this is essential for the fungus.

In vitro deacetylation activity assays with nuclear extracts from mutant strains pointed out to FfHda1 as the major *F. fujikuroi* histone deacetylase. Expression analyses by microarray were conducted after growth of the wild type and the Δ*ffhda1* strain on low and high nitrogen conditions. The mutant strain displayed downregulation of genes involved in the synthesis of gibberellins, of the red pigments bikaverin and fusarubin, and of the mycotoxin fusaric acid on inducing conditions. Interestingly, the same result was observed in a mutant that overexpressed FfHda1. Deletion of the *ffhda2* gene also reduced the production of gibberellins, bikaverin and mycotoxins, but resulted in increased production of fusarubin. The ΔΔ*ffhda1*/*ffhda2* double mutant revealed that both genes exert a distinct effect concerning the fusarubin regulation, but an additive effect on the downregulation of the other SM. Deletion of the *ffhda4* gene did not impact the SM production but resulted in reduced growth and microconidia formation. Furthermore, Studt et al. (2013) demonstrated that both FfHda1 and FfHda2 are required for virulence in the rice seedlings infection model.

Unlike as in *F. graminearum*, the deletion of the *F. fujikuroi KMT6* gene was not viable. Therefore, Studt et al. (2016) employed the iRNA approach to knock-down this gene expression to 9–12% of the wild type. Western blot analysis revealed that H3K27me3 levels were reduced in *KMT6*^{kd} mutants. KMT6 presented pleiotropic effects in *F. fujikuroi*, since knock-down mutants displayed impaired radial growth and conidia formation, apart from the alteration in the gene expression pattern of about one third of the genome. Among several SM key enzyme-encoding genes whose expression was modified, *STC5* was the most upregulated. Heterologous expression of the *STC5*cDNA in *Escherichia coli*, followed by protein purification, incubation with farnesyl pyrophosphate and gas chromatography coupled mass spectrometry (GC–MS) revealed the new sesquiterpene hydrocarbon [(1R,4R,5S)-guaia-6,10(14)-diene].

Magnaporthe oryzae

Magnaporthe oryzae is the ascomycete which causes blast, the most damaging rice disease (Saleh et al. 2014). In the past few years, the analyses of epigenetic mechanisms revealed significant roles in the development, reproduction and pathogenicity of this species of economic importance. BLAST analyses indicated two putatives DNMTs (MoDIM-2 and MoRID) (Jeon et al. 2015). Mutant strains for the respective genes presented defects in the vegetative growth. Furthermore, RNA-seq studies demonstrated differences in Transposable Elements (TEs) transcripts abundance between the wild-type and the Δ*Modim-2* strains, according to the genomic location. These results indicate that DNA methylation is crucial for the life cycle and genome defense in *M. oryzae*, even though loss-of-function mutations in another DNMT gene (MoDMT1), identified in different isolates, had previously suggested otherwise (Ikeda et al. 2013).

Pham et al. (2015) analyzed the effect of histone methylation on *M. oryzae* plant infection process by the generation and analysis of lysine methyltransferases (KMTs) genes mutants. All mutants showed some degree of alteration in the infection process, and Δ*moset1* (deletion of the MoSET1 H3K4 methyltransferase gene) presented the most pronounced defects in

infection-related morphogenesis, particularly in conidiation and appressorium formation.

Ustilago maydis

Ustilago maydis is a basidiomycete that causes smut in maize and represents a model organism for plant-pathogen interactions, extensively studied during the twentieth century (Snetselaar and McCann 2017). Martínez et al. (2015) performed transcriptomic analyses with an *U. maydis* strain defective for a HAT encoding gene (*GCN5*), since they had previously demonstrated that Δ*Umgcn5* mutant strains were avirulent and did not produce teliospores (González-Prieto et al. 2014). A striking difference in the global transcription profile between the wild type and the Δ*Umgcn5* strains was reported: 1203 genes were differently expressed in the wild type in comparison to GCN5 mutant strains. Most of these genes were associated with mycelial growth and pathogenesis.

Mycotoxins producers

Aspergillus flavus

Yang et al. (2016) identified and deleted the DNMT gene *dmtA* in the human opportunist pathogen *A. flavus* genome. The Δ*dmtA* mutant strain displayed morphological alterations and reduction in conidiation, indicating that DNA methylation is important for fungal development and could represent a target for biocontrol. *A. flavus* is a food contaminant, affecting mainly grains, and produces aflatoxins, which are toxic secondary metabolites associated with the development of cancers. DNA methylation was also shown to be crucial for mycotoxins biosynthesis pathways.

Histone methylation was likewise studied in *A. flavus* by the deletion of the *dot1* gene, which encodes a putative H3K79 methyltransferase (Liang et al. 2017). The Δ*dot1* mutant presented colony diameter, conidia production and aflatoxin biosynthesis reduction and impaired ability in infecting corn seeds. On the other hand, the mutant strain demonstrated increased sclerotia formation and higher resistance to stress agents (methylmercuric sulfate, hydroxyurea and sodium dodecyl sulfate).

Arginine methylation is relevant to *A. flavus* biology as well. The deletion of the arginine methyltransferase *RmtA* gene provoked hyperconidiation during the vegetative growth, impaired formation of sclerotia and of aflatoxin B1. The transcription profile of genes of the aflatoxin biosynthesis was altered in the Δ*rmtA* mutant. Interestingly, this mutant was more resistant to menadione-induced oxidative stress (Satterlee et al. 2016).

Aspergillus fumigatus

In order to elucidate the interaction between vegetative growth and SM production on certain tissues, like in conidia, of the human pathogen *Aspergillus fumigatus*, Lind et al. (2018) have deleted the genes encoding for the "loss of *aflR* expression" regulator (LaeA) and for the asexual cycle regulators BrlA, AbaA and WetA. RNAseq analysis was performed upon growth of the wild type and mutant strains in conditions that favor the asexual cycle and the SM production. The absence of BrlA provoked the most significant impact on the global gene expression profile in comparison to wild type. Genes related to SM, stress response and development were among those downregulated in the Δ*brlA* mutant. Nonetheless, BrlA regulated a broader range (about 96%) of the contiguous biosynthetic gene clusters which presented differential expression. Ultrahigh-performance liquid chromatography-mass spectrometry analyses confirmed that the levels of different conidium-associated siderophores, antibacterial alkaloids and mycotoxins were diminished in the Δ*brlA* and Δ*abaA* strains.

Microarray analysis demonstrated that most of the SM clusters regulated by BrlA were jointly regulated by LaeA. Northern blot experiments showed that *laeA* transcription is not much affected in the Δ*brlA* genetic background; on the other hand, *brlA* transcript level is profoundly diminished in Δ*laeA*. By ChIP revealed that the *laeA* deletion provoked a decreased level of the activating H3K4me3 epigenetic mark, and enrichment of the H3K9me3 repressive mark, in the *brlA* gene promoter.

Among the cellular processes not related to SM that are positively regulated by both BrlA and LaeA, hypoxia response associated with the SrbA transcription factor was highlighted. Apart from hypoxia, genes related to the ergosterol biosynthesis and nitrate assimilation were shown to be coregulated by BrlA and SrbA. In conclusion, Lind et al. (2018)

demonstrated an elaborate BrlA-LaeA regulatory network for processes as diverse like SM production, conidiation and stress response.

LaeA has also been implicated in the regulation of development and of secondary metabolism in other fungi, such as *Aspergillus terreus* (Palonen et al. 2017), *Penicillium expansum* (Kumar et al. 2018), *Pestalotiopsis microspora* (Akhberdi et al. 2018), *A. flavus* (Zhi et al. 2019), *Aspergillus ochraceus* (Wang et al. 2019) and *Penicillium dipodomyis* (Yu et al. 2019). Nonetheless, histone methyltransferase activity or chromatin remodeling were not addressed in these studies.

Insect pathogens

Entomopathogenic fungi represent a relevant source of innovative biotechnological products, particular secondary metabolites, with potential applications in human therapy, including anti-cancer treatment (reviewed by Gibson et al. 2014).

Metarhizium robertsii

Metarhizium robertsii is an entomopathogenic fungus that infects a variety of arthropods, thus presenting a considerable potential for pest biocontrol (Kryukov et al. 2017).

Wanzhen et al. (2017) demonstrated that *M. robertsii* global genome presents higher methylation in mycelia than in conidia. This difference is particularly evident in genes related to metabolic pathways. In this view, the authors propose that a DNA methylation reprograming occurs during *M. robertsii* development. The same research group had previously demonstrated a global DNA methylation reprograming during the sexual reproduction of another insect pathogenic fungus, *Cordyceps militaris* (Wang et al. 2015).

Decreased radial growth, conidia production and spore viability under stress conditions (UV irradiation and heat) were reported for the ΔMrDIM-2 and ΔRID/ΔDIM-2 DNMT genes mutant strains. These strains were hypovirulent in the *Galleria mellonella* larvae infection model (Wang et al. 2016).

Still in *M. robertsii*, the disruption of a putative HAT encoding gene (MAA_02282) led to alterations in growth and pigmentation. HPLC analyses demonstrated differences in the biochemical profile between Δ*Hat1* and the wild type strain. The production of new secondary metabolites was reported when the histone acetylation enzyme activity was absent (Fan et al. 2017).

The first study on fungal mitochondrial genome epigenetic modifications was reported by Kang et al. (2017) for the ghost moth larvae pathogen *Ophiocordyceps sinensis*, which is endemic to the Tibetan Plateau and whose parasitic complex is employed in traditional Chinese medicine for several purposes. Single molecule real-time sequencing (SMRT) revealed 1604 sites for DNA modification in *O. sinensis* mitogenome, such as 5-methylcytosine, 5-hydroxymethylcytosine, 4-methylcytosine and 6-methyladenine. The function of such modifications is yet unknown.

Epigenetic regulation for lignocellulolytic enzymes production

Filamentous fungi capacity to degrade the plant cell-wall and generate inputs for diverse biotechnological applications has been studied for decades. Nonetheless, while considerable efforts have been made in exploiting epigenetic mechanisms to increase the production of secondary metabolites, the knowledge of the impact of such mechanisms on the production of enzymes such as cellulases and xylanases is still limited.

Humicola grisea var. *thermoidea*

Our research group evaluated the effects of the DNMTi 5-aza-2-deoxycytidine, a 5-AZA analog, on the secreted enzymes activities and on the transcription of genes encoding cellulases and xylanases in the thermophilic fungus *H. grisea* var. *thermoidea* upon growth on different agricultural wastes or on glucose (Manfrão-Netto et al. 2017). Concentrations ranging from 10 to 100 μM of 5-aza-2-deoxycytidine did not affect growth or sporulation on potato-dextrose agar medium.

Humicola grisea was then grown up to 96 h in liquid minimal medium supplemented with 25 μM of the DNMTi and with wheat bran, sugar cane bagasse or ground hay, as enzyme-inducing carbon sources, or with glucose, as repression condition. Although, in general, secreted cellulase and xylanase activities were lower than for the control condition upon growth

on inducing conditions, a striking increase of transcript accumulation for *cbh1.1* and *cbh1.2* (cellobiohydrolase), and *xyn2* (xylanase) genes was observed upon growth on glucose. This study indicates that DNA methylation inhibition overcomes the glucose-mediated transcription repression mechanism we previously observed for these genes (Mello-de-Sousa et al. 2011) and that an epigenetic approach can be used to improve *H. grisea* potential as a producer of biotechnology inputs.

Penicillium oxalicum

The heterochromatic protein 1 (HP1) is associated with heterochromatin formation and transcription repression in fission yeast (Haldar et al. 2011). Zhang et al. (2016) investigated the effects of the deletion and of the overexpression of the heterochromatic protein 1 gene (*hep*A) in *P. oxalicum*. Comparative transcriptome analyses with the wild type strain revealed downregulation of cellulase genes in the Δ*hep*A mutant. On the other hand, these genes were upregulated in a *hep*A-overexpressing strain. In this view, epigenetic approaches can be envisaged to enhance cellulases production in this industrial fungus.

The impact of the "loss of *aflR* expression" regulator (LaeA) on glycoside hydrolases regulation was studied in *Penicillium oxalicum* (Li et al. 2017a, b, c). The authors created mutant strains for deletion and/or overexpression of the *laeA*, *clrB*, *xlnR* and *creA* genes, individually or in different combinations. The mutant colonies presented lighter color than the typical dark-green displayed by the wild type. In the absence of LaeA, conidia formation and active cellulases production were severely reduced. RNAseq and qRT-PCR analyses of the wild type and Δ*laeA* strains grown on cellulose and wheat bran medium indicated the downregulation of several SM and glycoside hydrolase genes, including the main amylase, cellobiohydrolase, endoglucanase and xylanase, particularly for the longer cultivation period (60 h). A cross-talk for the regulatory genes was observed: *creA, clrB* and *xlnR* were downregulated in the Δ*laeA* genetic background after 60-h growth, even though physical interaction between LaeA and ClrB or XlrR was not detected in a yeast two-hybrid assay. Furthermore, data suggested that LaeA is required for the activation of most cellulase and xylanase genes by ClrB and XlnR. On the other hand, the *xyl3A* β-xylosidase gene expression was increased in the absence of LaeA, particularly when XlnR was overexpressed. It is important to note that, even though LaeA is a putative methyltransferase, no evaluation of histone post-translation modification or chromatin structure was performed in this study.

Li et al. (2019) have recently identified the *P. oxalicum* gene encoding the *disruptor of telomeric silencing 1* protein (PoDot1), which methylates specifically the H3K79 residue. Since glycoside hydrolase genes in *P. oxalicum* are mostly grouped near telomeric regions, the authors hypothesized whether the *Po*Dot1 gene disruption could affect these genes regulation. *Po*Dot1 was microscopically located mostly in the nucleus. The Δ*Podot1* mutant colony diameter was smaller than for the wild-type strain, presented a lighter green color and wrinkled surface. Delayed conidiation, abnormal hyphae morphology, altered septa formation, defective conidiophores and spores were also observed. The transcription of genes important to the regulation of *P. oxalicum* asexual cycle was reduced in the mutant strain. Interestingly, *Po*Dot1 overexpression resulted in similar effects on conidiation, indicating that an appropriate protein level is required for this process.

Trancriptome analyses revealed that the expression of amylase, cellulase, polysaccharide monooxigenases, xylanases and chitinases was downregulated in the Δ*Podot1* strain. Also, the cellulase and amylase activity was diminished both in solid medium and broth cultures. Curiously, the accumulation of transcripts for genes encoding positive (XlnR and ClrB) or negative (CreA and AmyR) factors involved in glycoside hydrolases regulation was not altered in the mutant strain. On the other hand, the H3K79 dimethylation in particular regions of the *amy15A* (amylase), *cel7A*/*cbh1* and *cel7B*/*eg1* (cellulase) and *cel61A*/*LPMO* (cellulase-related polysaccharide monooxigenase) genes was diminished, indicating that the reduction of this epigenetic mark was the main responsible for the downregulation of the glycoside hydrolase genes. Tandem Affinity Purification–Mass Spectrometry analyses revealed that *Po*Dot1 does not interact directly with RNA Pol II subunits, but with proteins related to methylation, translation, energy transfer, redox reactions, heat shock proteins and chaperones.

Trichoderma reesei

The effect of the LAE1 putative methyltransferase on glycoside hydrolases production by *T. reesei* was studied by Seiboth et al. (2012). The *lae1* gene null mutants (Δ*lae1*) did not form pigment, presented impaired conidiation, biomass formation and secreted cellulases production upon growth on lactose as inducing agent. Microarray analyses demonstrated that, in Δ*lae1* transformants, genes encoding for cellulases, xylanases and for most of the accessory proteins for cellulose degradation, such as swollenin, were downregulated by at least twofold in comparison to the *T. reesei* QM 9414 parental strain. The requirement of LAE1 for cellulases production did not depend on the nature of the inducer, since it was also verified upon growth on sophorose, a potent inducer for cellulases in *T. reesei*. Overexpression of LAE1 led to increased levels of secreted proteins and cellulase activity upon growth on lactose or cellulose.

Furthermore, the aforementioned authors demonstrated that the effect of LAE1 on the production of cellulases is related to the function of the Transactivator Xylanase Regulator (XYR1), and that the XYR1 function itself depends on LAE1. Since the deletion of the *lae1* gene did not significantly affect the level of methylation of histone 3 lysine 4 or lysine 9 residues associated with the glycoside hydrolase genes, the mechanism by which LAE1 regulates *T. reesei* enzymes production is yet to be determined.

Xin et al. (2013) identified and characterized the *T. reesei* Gcn5 acetyltransferase gene (*TrGcn5*) that was able to restore a *S. cerevisiae gcn*5Δ mutant strain impaired phenotypes, namely the ability to grow on minimal medium with glucose, at elevated temperatures or under salt and oxidative stress. The analysis of a TrGcn5 mutant strain revealed that the phenotypes recovery was dependent on the Gcn5 histone acetyltransferase activity.

Gene disruption of *TrGcn5* in the homologous system resulted in decreased growth on different carbon sources, absence of conidiation on solid medium, increased pigment production and hyphae morphology alterations. Even upon induction by lactose or Avicel, the *TrGcn5*Δ mutant strain was not able to hydrolase amorphous or crystalline cellulose, and transcript accumulation for cellobiohydrolase 1 (*cbh*1), β-mannosidase and α-D-galactosidase genes was impacted. A correlation between cellulases regulation and the histone acetyltransferase activity was established by demonstrating that the level of histone 3 K9 and K14 residues acetylation was reduced in the *cbh*1 gene promoter of the *TrGcn5*Δ mutant strain.

Mello-de-Sousa et al. (2014) demonstrated that an open chromatin state in the *T. reseei* cellulase-hyperproducing Rut-C30 strain was related to higher transcript levels of cellulase-encoding genes and to increased enzyme activity.

By chromatin accessibility real-time PCR (CHART-PCR) analyses, Mello-de-Sousa et al. (2015) revealed that, in the wild type *T. reesei* strain, chromatin opens up for the *cbh*1 and *cbh*2 (cellobiohydrolase) and *xyn*1 and *xyn*2 (xylanase) genes sophorose-induced expression. Diversely, a compact chromatin structure is associated with the glucose-mediated gene repression. Interestingly, unlike the cellulase genes, xylanase genes repression in glucose occurs independently of the chromatin status.

Chromatin is globally denser when the major regulator *xyr1* gene is deleted (Mello-de-Sousa et al. 2016). The Δ*xyr*1 strain is not subject to sophorose induction and chromatin access is drastically reduced. In vivo footprinting studies with the *cbh*1 gene promoter demonstrated that Xyr-1 sites are less methylated than the Carbon Repressor 1 (Cre1) sites when Xyr1 is absent.

Remodeling of the chromatin conformation was also shown to be involved in the *xyr1* gene regulation itself during growth in sophorose. The promoter is more accessible upon cellulases induction, particularly when Cre1 is absent (Mello-de-Sousa et al. 2016).

The *T. reesei* data clearly demonstrate how chromatin structure can be engineered aiming an optimized production of cellulases and xylanases.

Conclusions

The studies of mechanisms associated with epigenetic regulation of gene function are emerging as an additional tool for fungal biotechnology. The employment of drugs that target epigenetic mechanisms and the generation of mutant strains for key genes in chromatin remodeling allow the elucidation of biological processes. These processes can be manipulated aiming more efficient biological control approaches,

the increase of the production of useful metabolites, such as the ones already employed as antibiotic and antineoplastic drugs, and the discovery of new bioactive compounds.

Apart from the impact on the control of the widely studied human pathogenic fungi, epigenetic engineering is emerging as a powerful strategy for the management of mycotoxin-producing and plant pathogen species. Furthermore, *epiengineering* can target the optimization of strains already utilized for plant biomass conversion into fertilizers, biofuels or food additives, amongst other products, namely the hydrolytic enzymes producers.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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