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REVIEW

Molecular regulation of fungal secondary metabolism

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Abstract

Many bioactive secondary metabolites synthesized by fungi have important applications in many fields, such as agriculture, food, medical and others. The biosynthesis of secondary metabolites is a complex process involving a variety of enzymes and transcription factors, which are regulated at different levels. In this review, we describe our current understanding on molecular regulation of fungal secondary metabolite biosynthesis, such as environmental signal regulation, transcriptional regulation and epigenetic regulation. The effects of transcription factors on the secondary metabolites produced by fungi were mainly introduced. It was also discussed that new secondary metabolites could be found in fungi and the production of secondary metabolites could be improved. We also highlight the importance of understanding the molecular regulation mechanisms to activate silent secondary metabolites and uncover their physiological and ecological functions. By comprehensively understanding the regulatory mechanisms involved in secondary metabolite biosynthesis, we can develop strategies to improve the production of these compounds and maximize their potential benefits.

Keywords Fungi · Secondary metabolism · Molecular regulation · Epigenetic

Abbreviations

SMs	Secondary metabolites
BGCs	Biosynthetic gene clusters
PKSs	Polyketide synthases
NRPSs	Non-ribosomal peptide synthetases
SMURF	Specially used for prediction of fungal SMs
antiSMASH	Mainly used for the analysis of antibiotics and secondary metabolite gene clusters
HS	Heat stress
ROS	Reactive oxygen species
HSPs	Heat shock proteins
HSFs	Heat shock transcription factors
HAT	Histone acetyltransferas
HDAC	Histone deacetylase
H3K9me3	Histone 3 lysine 9 trimethylation
H3K14	Histone 3 at position 14

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Introduction

Fungal secondary metabolites (SMs) are low molecular weight compounds produced by primary metabolism (Brakhage 2013). They have the survival functions of self-protection, defense against pathogens and inhibition of competitive microorganisms, even more interaction with their biological environment (Demain and Fang 2000). SMs are critical sources of drug molecules for decades. These compounds are synthesized by enzymes encoded by genes that are clustered in the genome. The vast majority of SM biosynthetic gene clusters (BGCs) are not expressed under normal growth conditions (Grau et al. 2018). Hence, activation of these silent BGCs is essential to current natural products discovery research. It is well known that the SMs of fungi include penicillin, cephalosporin, lysergate and statins. Although the chemical composition is different, all SMs are produced by some common biosynthetic pathways, usually related to morphological development. The SMs in fungi can be mainly divided into terpenoids, indole alkaloids, polyketides and nonribosomal peptides (Kuhnert and Collemare 2022). Studies have shown that half of the last SMs

are used for antibiotics, immunosuppressants or antitumor agents, while others are involved in disease interactions with plants or animals (Macheleidt et al. 2016). For example, the antifungal bacterial metabolite polaramycin B can leads to the production of antibacterial defence chemicals (Berger et al. 2022). The terpenoid paclitaxel produced by the endophytic fungus *Taxomyces andreanae* is recognized today as the broad-spectrum antitumor drug (Cheng et al. 2022). Penicillin, a widely-used antibiotic produced by *Penicillium* fungi (Charu et al. 2023). Cyclosporin A, an immunosuppressant produced by *Tolypocladium inflatum* (Yang et al. 2018). With the completion of genome sequencing of more and more filamentous fungi, genetic manipulation methods and techniques to affect fungal SMs through molecular regulation have gradually developed. In this review, we summarized the research progress in molecular regulation of fungal secondary metabolism, with the addition of proposing research challenges in related fields.

Secondary metabolism gene clusters

SMs are generally controlled by multiple genes. With the advancements of SMs genes in molecular biology as well as bioinformatics, it has been observed that genes involved in primary metabolism are usually dispersed throughout the fungal genome, while most secondary metabolic genes involved in the production of a specific SM are arranged continuously in clusters known as (BGCs) (Brakhage 2013). Further, genes present in a SM biosynthetic cluster are typically co-regulated via a complex process involving multiple layers of regulation, such as transcriptional, epigenetic, and environmental regulation (Pfannenstiel and Keller 2019). It is found that the genes encoding fungal SMs are usually clustered near the telomere (Chu et al. 2011). Additionally, their number is far more than the SMs species that have been isolated and identified from a fungus (Brakhage and Schroeckh 2010). The number of genes in the gene cluster of SMs of different fungal species is diverse. For example, the kojic acid biosynthesis cluster composed of three genes (Tamano et al. 2019), while the aflatoxin cluster in *Aspergillus flavus* (*A. flavus*) cluster contains approximately 30 different genes (Fig. 1) (Amaike and Keller 2011). Usually, the fungal secondary metabolic gene clusters have one or more transcription factors, which are necessary for the expression of related enzyme genes in the gene clusters (Krause et al. 2018). Biosynthetic genes in the secondary metabolism gene cluster are usually regulated by transcription factors, and the genes encoding these transcription factors are not necessarily in the cluster.

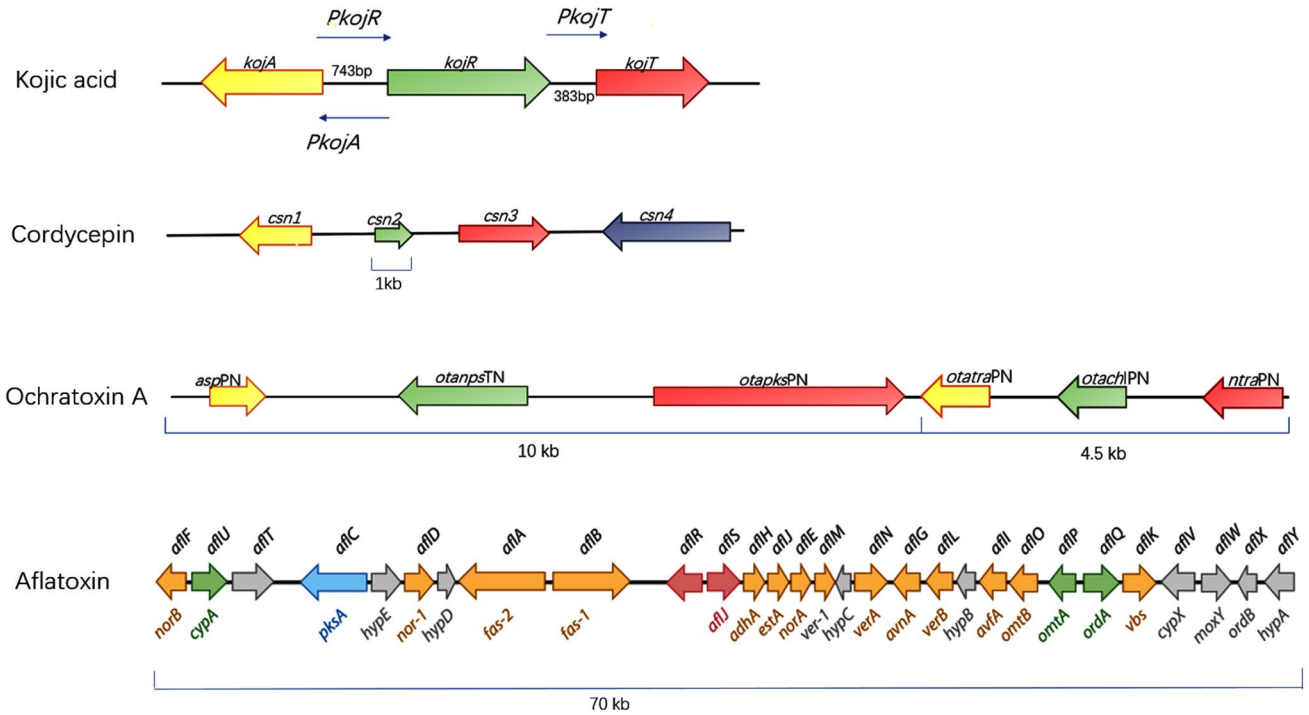

Fig. 1 Maps of some secondary metabolites biosynthesis genes clusters. The different colored arrows represent the direction of gene transcription in each of the gene clusters. Cordycepin gene clusters are found in *Cordyceps sinensis*, *Cordyceps militaris*, etc. Aflatoxin gene clusters are found in *Streptomyces roseolus*, *A. flavus*, etc. *Aspergillus oryzae* is a well-known producer of kojic acid. Ochratoxin A gene clusters are found in some fungi, such as *Aspergillus, Penicillium,* and/or *Monascus species.,* etc.

Genome sequencing showed that *Aspergillus* contains more than 30 secondary metabolic gene clusters, and many reports have reported that the regulatory protein LaeA can regulate these clusters. For example, the deletion of *laeA* in *Aspergillus* blocks the gene clusters required for the synthesis of some SMs (sterigmatocystin, penicillin and lovastatin) (Bok and Keller 2004). Additionally, an LaeA ortholog (AnLaeA) has been shown to positively play a role in regulating the ochratoxin A cluster in *Aspergillus niger (A. niger)* (Zhang et al. 2022). The itaconic acid biosynthetic gene clusters are regulated by LaeA in *Aspergillus pseudoterreus* (Pomraning et al. 2022). In general, the BGCs encoding antibiotics, toxins and pigments are silent under laboratory conditions. Therefore, the mechanisms of artificially turning on silent gene clusters in the laboratory can only be explained by activating metabolic pathways. There are many successful methods, such as promoter exchange and epigenetic regulation (Motoyama 2020). For example, the expression of the gliotoxin synthesis gene clusters in *Aspergillus fumigatus (A. fumigatus)* require the activation of GliZ transcription factor (Bok et al. 2006a). Eleven different biosynthetic genes from aflatoxin clusters were well characterized after the activation of *aflR* (Price et al. 2006). In addition, heterologous expression of secondary metabolite genes in fungi has been found to activate silent gene clusters in fungi, which is a new method for directly converting waste materials into SMs. For example, developing *Trichoderma reesei (T. reesei)* as a heterologous host for SMs production is one such approach (Shenouda et al. 2022). However, it may be cumbersome for promoter exchanging in fungal secondary metabolic gene clusters (Kennedy and Turner 1996). Because all genes required for the biosynthesis of typical SMs are clustered, in some cases, a single regulator controls the expression of all members of the cluster to a certain extent (McAlpine et al. 2005). Therefore, the overexpressing of pathway-specific regulatory genes that exist in many secondary metabolite gene clusters is easier than overexpressing all the many genes in the cluster.

Most clusters contain one or several key biosynthetic genes, which encode enzymes belonging to larger domains or multiple modules of polyketide synthases (PKSs) or nonribosomal peptide synthetases (NRPSs), as well as other key enzymes (Strieker et al. 2010), such as sterigmatocystin and aflatoxin (Brown et al. 1996). The prediction of the secondary metabolic gene clusters is based on the homology comparison of the core genes encoding PKS and NRPS. Because of the characteristics of the secondary metabolic gene cluster, the genes around the core genes are also predicted, then forming predicted gene clusters (Sanchez et al. 2011; Bergmann et al. 2007). At present, there are three commonly used prediction tools for secondary metabolite synthesis gene clusters, including SMURF (specially used for prediction of fungal SMs) (Clevenger et al. 2017), antiSMASH (mainly used for the analysis of antibiotics and secondary metabolite gene clusters) (Medema et al. 2011), and FungiFun (mainly used for functional annotations to fungal genes or proteins) (Priebe et al. 2010). CusProSe is a new application that has been developed to aid users in searching for specific proteins based on their domain composition. This application has been successfully utilized in identifying and characterizing various enzyme families, including polyketide synthases (PKS), non-ribosomal peptide synthetases (NRPS), hybrid PKS-NRPS, dimethylallyl tryptophan synthases (DMATS), and distinct terpene synthases (TS) sub-families, in fungal genomes (Oliveira et al. 2023). Overall, these and other recent studies have greatly advanced our understanding of the molecular mechanisms underlying the regulation of fungal SMs.

Environmental signals regulation

Secondary metabolism is related to fungal development. With the innovation in the field of science as well as technology, it has been observed that fungi have complex signal transmission pathways to respond to various biological and abiotic external triggers, such as nutrients, pH, light, stress (Fig. 2). Moreover, fungi also use environmental signals to regulate development and metabolism (Cerdá-Olmedo 2001). For example, the light conditions and diurnal changes caused by the rotation of the earth lead to significant changes in the physiological processes of fungi (Monroy et al. 2017). When receiving signals from light (Corrochano and Garre 2010), the development of reproductive structures of *Mucor circinelloides* will be regulated. Transcription and epigenetic activation of BGCs are the result of environmental stimulation (Lind et al. 2016). Moreover, the responding to environmental signals is crucial to the lifestyle of filamentous fungi (Kalinina et al. 2017). Understanding how fungi respond to environmental signals can provide insights into fungal signal transduction mechanisms (Lei and Shengying 2021). Environmental signals affecting secondary metabolism can be divided into three factors: physical factors, nutritional conditions and single chemical/biological/biochemical signals.

Physical factors usually exist in nature. Researchers found that light is an important environmental signal for fungi, and it have been found to have a significant impact on the production of certain SMs (Zhang et al. 2021). For example, light has been shown to activate carotenoid biosynthesis in *Neurospora crassa* (*N. crassa*) (Bayram et al. 2019), however, the potential molecular mechanism of light regulation is largely unknown (Shakya and Idnurm 2017). In addition, a considerable number of studies have identified the role of photoreceptors and their respective signal transduction pathways in fungal secondary metabolic synthesis (Bazafkan et al. 2017a). Some studies have analyzed the photoreaction

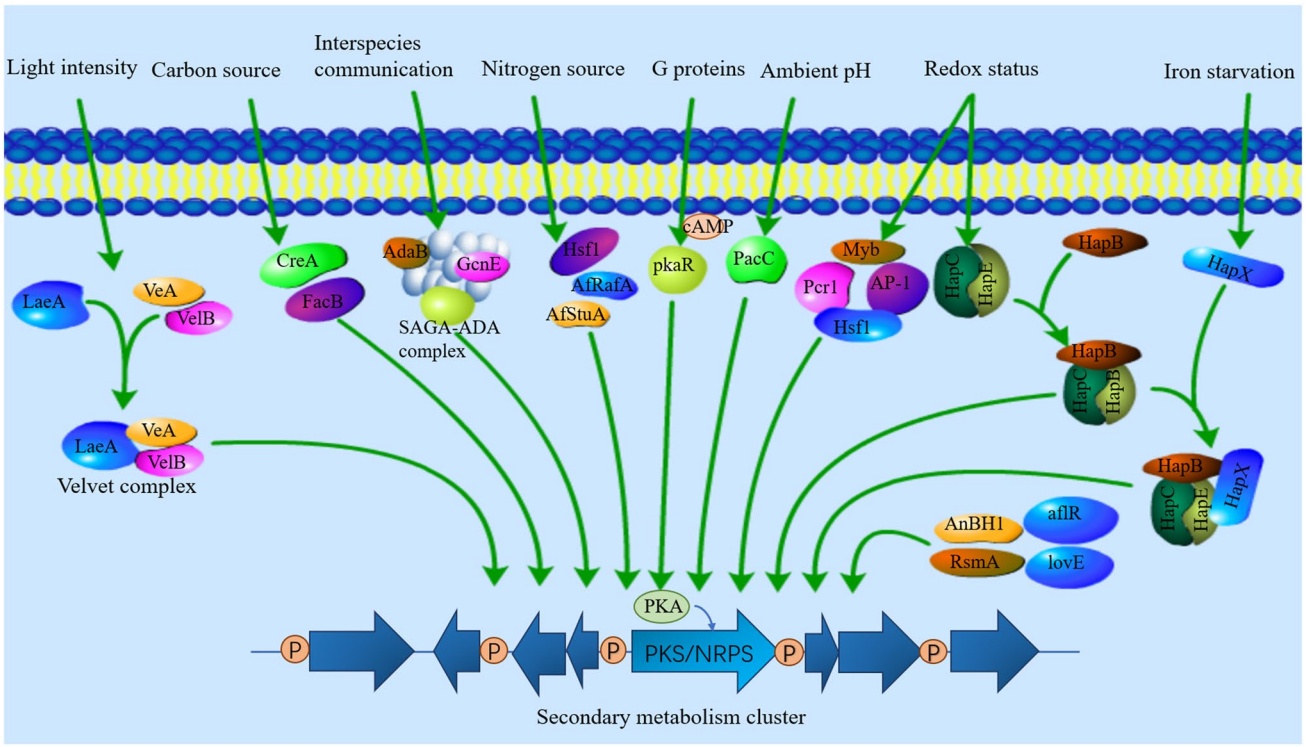

Fig. 2 Regulation of the fungal secondary metabolism biosynthetic gene cluster. Each environmental factor may influence the expression of multiple genes and proteins within the biosynthetic gene cluster. Each arrow represents the general regulatory effect of the environmental factor on the biosynthetic gene cluster as a whole. *cAMP will be regulating cAMP-dependent protein kinase (PKA) as an intracellular molecule*

pathway and its physiological correlation with *T. reesei*, and found that photoreceptors, as the expression regulators of cellulase genes, have an impact on the regulatory factors of secondary metabolism (Schmoll 2018). In addition, G protein coupled receptor GPR8 can be used to adjust the production of SMs, so as to adjust the chemical communication with signals from the environment. GPR8 has a photo dependent effect on secondary metabolism, which is partly mediated by the function of transcription factors (Hinterdobler et al. 2020). Heterotrimeric G proteins are involved in a variety of cellular responses to extracellular stimuli, including the regulation of secondary metabolism and stress response pathways (Yao et al. 2016). The alpha subunit of heterotrimeric G proteins has been shown to play an important role in the biosynthesis of SMs in fungi, including the industrial penicillin producer *Penicillium chrysogenum*, for example, the alpha subunit of the heterotrimeric G protein is involved in regulating the activity of several enzymes that are needed for penicillin biosynthesis (García-Rico et al. 2017). This makes it an important target for genetic engineering efforts aimed at improving penicillin production. The light response pathway can be associated with light dependent global transcription factors (such as VelB) to regulate the synthesis of a variety of SMs (Nadia et al. 2022). Velvet family protein VEL1 and its effect on secondary metabolism mediated photoresponse effects on sexual development (Bazafkan et al. 2017b). The global regulatory proteins can control the timing of developmental processes, such as hyphal differentiation, spore formation and pigment generation, ensuring that the cells differentiate in the correct order so that the SMs are produced at the right time. In order to elucidate the relationship between light dependent morphology and secondary metabolism, the complex protein LaeA/VeA/VelB in fungi was studied under dark conditions, among them Δ*laeA* almost lost the ability to produce conidia (Wang et al. 2019a, b). Some studies have shown that light and temperature can affect the spore activity level of the strain (Kher et al. 2021), in which temperature plays an important role in the composition of SMs (such as phenolic compounds) (Karppinen et al. 2016). For example, temperature during conidiation has been shown to impact stress tolerance, pigmentation, and trypacidin accumulation in the conidia of airborne pathogen *A. fumigatus* (Hagiwara et al. 2017), or the physiological state and germination time of fungi such as *A. flavus*, *Aspergillus ochraceus*, *Aspergillus carbonarius*, *Penicillium nordicum* and *Penicillium verrucosum*have also been found to be affected by temperature (Nguyen Van Long et al. 2016; Beier et al. 2020).

Velvet protein complexes are generally temperature dependent when regulating certain SMs gene clusters (Lind et al. 2016). In addition, solid/liquid medium is also one of the physical factors. Some studies have shown that solid medium culture can significantly increase the yield of SMs compared with deep culture (You et al. 2012). pH, as a physical factor, can affect the development and secondary metabolism of many fungi (Wu et al. 2016). Heat stress (HS), as a physical means, can affect the growth and metabolism of fungi in their growth environment (Calvo et al. 2002). For example, HS induces a significant increase in cytosolic reactive oxygen species (ROS) concentration, thereby regulating the biosynthesis of ganoderic acid (Liu et al. 2018b). HS can also significantly enhance the concentration of cytosolic $Ca^{2+}$and improve the content of SMs (Zhang et al. 2016). It has been found that there are many calcium ion transporters that affect the SMs in fungi, but it is still necessary to study the calcium signal synthesis function at the molecular level (Martín, 2022).

Secondly, nutritional conditions are also important for the synthesis of SMs (Ren et al. 2019), which are used for mining metabolites of single strain multi compound (Hewage et al. 2014). Studies have shown that distinct transcription factors can be induced by different nutritional conditions if secondary metabolism needs to be regulated (Przylucka et al. 2017). Many nutritional conditions are able to regulate secondary metabolism, including carbon sources (microcrystalline cellulose, D-galactose, sucrose, glucose and maltose) (Hu et al. 2017), nitrogen sources (sodium nitrate, ammonium sulfate, ammonium chloride and asparagine) (Hossain et al. 2019; Ding et al. 2018; Zhao et al. 2011), amino acids (alanine, histidine) (Wang et al. 2017), minerals and inorganic ions (Beier et al. 2020), and the proportion between different nutrients (Shariati et al. 2019; Ling et al. 2016). Changes in salinity affect the biosynthesis and signal transduction process of SMs (such as terpenoids and polyketides) (Elferink et al. 2020). For example, our research team found that the production of cordycepin increased significantly with the increment of salt concentration (Lv et al. 2021). The available extracellular carbon source such as glucose and acetate, significantly affected the secondary metabolite secretion of *A. fumigatus* (Ries et al. 2021). At the same time, the researchers found that the use of growth medium supplements would expand the diversity of compounds accumulated outside cells. For example, compared with the control extract without supplementary culture, the extract using organic salt ionic liquid as the supplement of *N. crassa* culture medium shows greater toxicity potential (Sequeira et al. 2022).

Thirdly, a single chemical/biological or biochemical signal can impact the physiological factors of SMs synthesis or directly affect the gene expression or enzyme activity in this pathway, such as methyl jasmonate (Wei et al. 2022), salicylic acid (Cao et al. 2017), engineered silver nanoparticles (Mitra et al. 2019), quercetin (Li et al. 2019a), phenylpropionic acid (Li et al. 2019a, b), aspirin (You et al. 2013), flavonoids (Wang et al. 2019a, b), alkaloids (Mabrouk and El-Shayeb 1992; Buchanan et al. 1983), cAMP/PKA (You et al. 2017; Hu et al. 2018), Cu^{2+} (Tang and Zhu 2009), Ca^{2+} (Silverman-Gavrila and Lew 2001; Kim et al. 2017), phosphatidic acid (Liu et al. 2018c). In addition, biochemical signals can also regulate the biosynthesis of SMs, such as kinases and cellulases (Darzian Rostami et al. 2020). Among them, kinase USK1 also regulates the expression of cellulase gene in *T. reesei* (Beier et al. 2020). Some studies have shown that jasmonate and salicylic acid may affect hormone biosynthesis and signal transduction in *Ganoderma boninense* treated oil palm roots in an antagonistic manner. In addition, ethylene biosynthesis can promote the ability of *G. boninense* to control oil palm mycosis (Ho et al. 2016). These research data clearly show that the environmental signals affecting the synthesis of SMs are interdependent, which not only provides a new method for further improving the genetic algorithm, but also provides new insights for studying the response of fungi to the environment (Fountain et al. 2016). In addition, secondary metabolism usually involves multiple signal pathways, which may act synergistically. Therefore, it is necessary to understand the relationship between different signals, such as upstream/downstream relationship and mutual promotion/antagonism relationship, in order to unveil the signal network that responds to the environmental regulation of SMs synthesis.

In addition, secondary metabolism usually involves crosstalk between multiple signal pathways (Macheleidt et al. 2016). For example, crosstalk between NO and Ca^{2+} has been observed under HS (Liu et al. 2018a). HS causes an increase in ganodermic acid production and NO accumulation in *Ganoderma*, whereas the NO accumulation attenuates the increase in ganoderic acid production (Liu et al. 2022). At the same time, HS promotes mutual promotion between NO and Ca^{2+}. However, under HS, Ca^{2+} promoted the synthesis of SMs more directly and significantly than NO. Enhancing the efficiency of epigenetic modification and the yield of fungal SMs requires exploring the physiological process and signal transduction pathways regulating the synthesis of SMs. Therefore, it is essential to identify the signals involved in SMs synthesis regulation. ROS is a notable example, as it is not only intracellular substance, but also a signal. Common ROS include superoxide anion, hydrogen peroxide, and hydroxyl (Segal and Wilson 2017), which plays an important role in the synthesis of SMs. Under different environmental conditions, these signals with crosstalk may have different functions in SMs synthesis. For example, the interaction between ROS and Ca^{2+} in regulating the synthesis of SMs varies under different conditions. For certain conditions, the ROS signal is positively correlated with the

synthesis of SMs. Studies have shown that there was important cross talk between cytosolic ROS and Ca^{2+} levels in the regulation of hyphal growth and biosynthesis of ganoderic acid induced by Cu^{2+} in *Ganoderma lucidum* (Gao et al. 2018). Penicillin, lovastatin and cephalosporin biosyntheses are also regulated by ROS in *Pencillium chrysogenum* and in *Acremonium chrysogenum* (Bibián et al. 2020). In addition, cytoplasmic Ca is involved in heat shock signal transduction and regulates the biosynthesis and accumulation of heat shock proteins (HSPs) in filamentous fungi (Zhang et al. 2016). Heat shock transcription factors (HSFs) are responsible for regulating the expression of HSPs. Though all HSFs play a fundamental role in coordinating the transcriptional response to temperature, they exhibit considerable complexity in regulating diverse environmental signals (Gomez-Pastor et al. 2017). Meanwhile, SMs may also affect the signals reciprocally, for example, the activation of biosynthesis of SMs (such as aflatoxin) have effect on the yield of ROS in *Aspergillus parasiticus* (*A. parasiticus*) (Kenne et al. 2018). Exploring the crosstalk between signals will provide a deeper conception into the impact of environmental factors on the regulation of SMs synthesis, but there are few studies on the regulation mode of signals interaction and the mechanism of signals transduction in SMs synthesis (Ren et al. 2016). It is very important to conduct in-depth research on the regulation methods of different signals in the process of SMs synthesis regulation, which will provide more effective regulation targets for improving the synthesis of SMs.

Transcriptional regulation

In the biosynthesis of microbial natural products, regulatory factors are generally divided into two categories: one is pathway-specific regulatory factors, which are basically located in specific BGCs and affect genes expression in clusters. The other is a global regulatory protein, which is basically located outside BGCs, controlling a variety of metabolic pathways. These transcription factors mediate fungal responses to environmental signals.

Pathway-specific regulators

According to genome information obtained, more than half of fungal secondary metabolism gene clusters contain pathway-specific transcription regulators (Bergmann et al. 2010). Pathway-specific regulators are a diverse set of transcription factors that are specific to a particular gene cluster involved in secondary metabolism. One of the most common types of pathway-specific regulators is Zn2Cys6, which is found in many fungal secondary metabolism gene clusters. These Zn2Cys6 regulators include AflR, which is specific for the biosynthesis pathway within the gene cluster of sterigmatocystin and aflatoxin (Buitimea-Cantúa et al. 2020), and LovE, which is specific for the regulation of gene expression within the gene cluster of lovastatin in *Aspergillus terreus* (*A. terreus*) (Huang and Li 2009). Additionally, PoxCxrA, a transcription factor, has been identified as necessary for the production of cellulase and xylanase in *Penicillium oxalicum*. It can not only directly regulate its expression by combining cellulase genes and promoters of regulatory genes on different nucleic acid sequences, but also automatically regulate its own gene expression (Liao et al. 2019). In addition to Zn2Cys6 regulators, other types of pathway-specific regulators have also been identified, such as Cys2His2 zinc finger proteins like AreA, CreA, and PacC (de Araújo et al. 2019). For example, VRF1 in *Magnaporthe oryzae*, a Cys2His2 zinc finger protein, is required for pathogenicity, specifically affecting the expression of genes related to appressorial structure and function, including melanin biosynthesis (Cao et al. 2016). While these regulators have different specificities, they all play a similar role in controlling the expression of genes within secondary metabolism gene clusters. By understanding the mechanisms by which these regulators control gene expression, researchers can develop strategies to manipulate gene expression patterns to optimize SM production.

Global regulatory proteins

In addition to pathway-specific regulators, global regulatory proteins are able to regulate secondary metabolism at higher level, mainly regulating mycelial differentiation, spore formation, pigment production and other growth forms. Such regulatory factors can not only sense the changes of nutrient components in the culture medium, but also the changes of environmental signals such as physical factors, and they are capable of associating with other regulatory factors for transmission (Bibb 2005), ultimately regulating multiple secondary metabolic reactions in cells to adapt to environmental changes, including antibiotic synthesis (Rigali et al. 2008). Global regulatory proteins are regulated by single proteins, such as AreA, WblA, DasR. The *areA* gene is a global nitrogen regulatory gene of GATA transcription factor family, which is important for the growth of *A. flavus*, and the production and pathogenicity of aflatoxin (Fasoyin et al. 2019). AreA could also interact Velvet to affect the secondary metabolism and virulence function of *Fusarium oxysporum* (López-Berges et al. 2013). Sometimes the biosynthesis of SMs is co-regulated by pathway-specific regulators and global regulatory proteins. For example, the biosynthesis of aflatoxin is not only regulated by pathway-specific regulators *aflR* and *aflS* in *A. flavus* or *A. parasiticus* strains, but also by the *laeA* gene (Kale et al. 2008). In addition, pathway-specific regulators could be regulated by global regulatory proteins. For example, VeA and LaeA regulate

the output of ML-236B by controlling the pathway-specific regulator *mlcR* in *Penicillium citrinum* (Baba et al. 2011).

The global regulation of fungal secondary metabolism gene cluster is characterized by the discovery of nuclear protein LaeA in *Aspergillus nidulans* (*A. nidulans*) (Bok and Keller 2004). LaeA (*aflR* expression deletion A) is a methyltransferase found in *Aspergillus*, which affected the biosynthesis of many SMs in fungi, such as *A. fumigatus* (Jain et al. 2018), *A. niger* and *A. terreus* (Zhgun et al. 2019; Zhang et al. 2022). Among them, LaeA has the ability to regulate more than half of the secondary metabolic BGCs in filamentous fungi. For example, overexpression of the *laeA* gene will promote the expression of penicillin and lovastatin gene clusters (Palonen et al. 2017). Additionally, overexpression of the *laeA* gene increases the production of chaetoglobosin A in *Chaetomium globosum* (Cheng et al. 2020), and promotes the accumulation of patulin in *Penicillium expansum* (*P. expansum*) (Kumar et al. 2018). Furthermore, LaeA regulates the expression of many unknown secondary metabolic gene clusters, such as the anti-tumor compound hydroquinone A in *A. nidulans* (Bok et al. 2006b). However, the specific molecular mechanism of LaeA is still unclear. The speculated mechanism of LaeA action in fungi can be roughly divided into the following three aspects: first, because LaeA contains a conservative SAM domain (Bok et al. 2006b), the protein regulates the synthesis of SMs through interaction with synthetase (Son et al. 2020), and there is a certain correlation between its regulatory principle and histone genetic modification (Song et al. 2019). Second, sequence analysis has shown that many BGCs contain pathway-specific regulatory factors (such as the *aflR* gene). It is hypothesized that LaeA can regulate the synthesis of SMs by regulating transcription factors (Ehrlich et al. 2011). Third, it is speculated that the *laeA* gene may be associated with signal transduction pathway (Bok and Keller 2004).

There are also some global regulatory proteins that are regulated by forming complexes, such as Velvet complex and VapA-VipC-VapB trimers. VeA bridges VelB and LaeA to form a heterotrimer complex called Velvet complex (Park et al. 2012). Studies have shown that they play different roles in fungal mycelial growth, asexual production and secondary metabolism, such as producing Taxol in *Pestalotiopsis microspora* (Akhberdi et al. 2018). The distribution of this complex in vivo is affected by the light dependent protein VeA. Under light conditions, the synthesis of VeA is reduced and the content of LaeA, VeA and VelB trimers is small, leading that the synthesis of SMs sterigmatocystin and ascus is inhibited. Under dark conditions, the VelB-VeA dimer in the cytoplasm is transported to the nucleus via interacting with the protein KapA, forming the LaeA-VeA-VelB trimer with the nucleoprotein LaeA and promoting the synthesis of stegomycin and asexual reproduction. In some filamentous fungi, including *Aspergillus* and *Penicillium* species, the pheromone module has been shown to regulate secondary metabolite biosynthesis by modulating the activity of global regulatory proteins such as the Velvet complex (Frawley et al. 2018). In particular, studies have suggested that the MAPK protein MpkB (a Fus3 ortholog) plays a crucial role in regulating secondary metabolism by phosphorylating VeA in the nucleus (Frawley et al. 2020). This phosphorylation event is thought to alter the conformation of the Velvet complex and modulate its activity, leading to changes in secondary metabolite production. At present, the members of the Velvet family proteins found include VeA, VelB, VosA and VelC, which play an important role in the growth and development of many fungi and the regulation of secondary metabolism (Bayram et al. 2008), such as the absence of the *veA* gene greatly reduces the production of patulin and citrinin in *P. expansum* (Hajj Assaf et al. 2018). The deletion of *laeA* and *veA* genes can reduce the toxin production of *Alternaria alternata* in wheat (Estiarte et al. 2016), and can reduce economic losses when applied to the food industry. The light dependent global transcription factor VelB plays a key role in the regulation of SMs citrinin and chaetoglobulin A in *P. expansum* (Nadia et al. 2022). Proteins VeA, VelC and VosA have the ability to interact with methyltransferases LaeA and LlmF (Palmer et al. 2013b). The expression, interaction and modification of Velvet regulatory factors can be controlled by LaeA (Sarikaya Bayram et al. 2010).

One recent study showed that a gene CsgA in *A. nidulans* plays a key role in regulating the production of the sterigmatocystin. The study demonstrated that CsgA acts as a molecular sensor that responds to cellular redox status and regulates the transcription of genes involved in sterigmatocystin biosynthesis (Cho and Park 2022). Another recent study, showed that the protein GliZ plays a key role in coordinating the expression of pseurotin A biosynthetic genes in the fungus *A. fumigatus*. The study demonstrated that a zinc-responsive transcriptional activator ZafA sequentially regulates pseurotin A biosynthesis through GliZ (Seo et al. 2023). According to research findings in recent years, there are VapA-VipC-VapB trimers on the cell membrane (VipC and LaeA have 52% homology). They activate the transcription of the global regulatory protein VelB-VeA-LaeA complex through physical interaction with VeA to regulate growth and development as well as secondary metabolism. Among them, VapA will depolymerize under the stimulation of external signal light, the methyltransferase VapB can reduce regulatory genes *brlA* and *abaA* of histone 3 lysine 9 trimethylation (H3K9me3) to promote asexual development (Sarikaya-Bayram et al. 2014). There are researches finding that VosA related to fungal sexual reproduction can also form dimers with VelB to participate in the regulation of reproductive process beyond that (Sarikaya Bayram et al. 2010). Evidence from other studies suggests that there

are so many global regulatory proteins (such as Spo0A, CcpA, CodY and AbrB) using genetic engineering (mutation, deletion or overexpression) to modify them, which will provide advantages for the synthesis or development of SMs (Tolibia et al. 2022), and it is important for the commercial interests of industrial production. The coordination between the growth stage dependent concentration gradient of the global regulators and the dynamics of chromosome configuration determines the spatio-temporal pattern of genome expression (Muskhelishvili et al. 2021).

Epigenetic regulation

Epigenetics refers to changes in the level of gene transcription caused by non-gene sequence changes, including chemical epigenetic modification and molecular genetic modification. The molecular genetic modification mechanisms usually include DNA methylation, histone methylation, acetylation, phosphorylation and ubiquitination. Epigenetic modification has an impact on fungal SMs. Examples of epigenetic regulation reported so far are summarized in Table 1. Histone genetic modifications are interrelated and jointly control gene expression, thus ultimately affecting the synthesis of fungal SMs. The histone methylation and acetylation are the most thorough among them. Lysine 2-hydroxyisobutyrylation, a recently discovered post-translational modification (PTM), plays a crucial role in regulating various cellular metabolic processes, including cell development and aflatoxin biosynthesis in *A. flavus*. The study of epigenetics has opened up a new way to clarify the regulation of the formation of SMs. However, many BGCs are silent in the laboratory environment, so researchers manipulate epigenetic stimulants and histone genetic modification to turn the heterochromatin covering BGCs into euchromatin.

The KERS complex, composed of KdmB, EcoA, RpdA, and SntB, has been discovered to regulate the epigenetic mechanisms that control secondary metabolism in the fungus *A. nidulans*. In particular, the KERS complex is responsible for the assembly of cohesin acetyltransferase (EcoA) and H3K4 histone demethylase KdmB into a heterodimer, along with the histone reader/E3 ligase protein SntB and the histone deacetylase RpdA. This complex is able to regulate the transcriptional activity of genes, exerting promoter-specific transcriptional effects. Deletion of any one of these subunits results in a negative impact on the production of SMs, including sterigmatocystin (Karahoda et al. 2022). Thus, the KERS complex plays a critical role in regulating secondary metabolism and asexual development in filamentous fungi, and provides important insight into the epigenetic mechanisms that control these processes.

Histone methylation

Histone provides binding sites for DNA binding as an essential component of nucleosome. It can also be used as a modified substrate to regulate the transcription of related genes and play an important role in the exercise of cell functions (Biel et al. 2005). Studies on the mechanisms of histone modification mainly focused on *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe* and *N. crassa* (Freitag 2017). Both histone methylation and histone acetylation have an impact on the synthesis of SMs. Histone methylation is the most stable epigenetic modification with extensive biological functions. For example, the histone methylation regulates aflatoxin in *A. flavus* (Liang et al. 2017; Liu et al. 2020). The common forms of histone methylation are lysine 4 (H3K4), lysine 9 (H3K9) and lysine 27 (H3K27), among which H3K4 me3 plays a key role in regulating the secondary metabolism of the fungus of *Colletotrichum higginsianum* (Dallery et al. 2019). Regulation of histone H3 demethylase is necessary to enrich for genes with known or predicted functions in secondary metabolite biosynthesis of *A. nidulans* (Gacek-Matthews et al. 2016). Methylation of H3K9 is usually a marker of the heterochromatin formation and leads to gene silencing (Stewart et al. 2005). Methylation of histones H3K9 and H3K27 regulates the alkaloid biosynthesis of *Epichloë festucae* in fungal endophytic symbiosis endophytic (Chujo and Scott 2014). It was also found that the production of SMs in wheat pathogenic fungus *Zymoseptoria tritici* was regulated by the facultative heterochromatin H3K27me3 (Amine Hassani et al. 2021), which plays a role in the development, virulence and production of SMs of rice pathogenic fungus *Ustilaginoidea virens* (Meng et al. 2021). Furthermore, the absence of H3K27me3 plays an important role in derepression of genes predominantly involved in secondary metabolite pathways in *Fusarium graminearum* (Connolly et al. 2013).

The relatively conservative lysine residues in the N-terminal tails of histones H3 and H4 are the sites of histone methylation and acetylation in fungi. Histone H3 methylation is at two sites related to active transcription, namely H3K4, H3K36, the constitutive heterochromatin H3K9 and facultative heterochromatin H3K27 (Freitag 2017). The methylation of H3K4 is established by COMPASS complex, some data have shown that the histone methylation gene plays a decisive role in the activation or inhibition of SMs gene cluster, for example, monocarboxylone, emodin and their derivatives are produced by mutants that lack *cclA* gene (one of the eight COMPASS proteins encoding *A. nidulans*) (Bok et al. 2009). In agreement with these findings, deletion of the COMPASS components *cclA* and CCL1(homologous tobre2) in *Aspergillus spp*. and *Fusarium spp.* respectively, resulted in increased expression of several SM cluster genes and the subsequent production of additional SMs in these

Table 1 Examples of epigenetic regulation

Species	Epigenetic type	Secondary metabolites affected	Key enzyme	Other physiological functions affected	References
Aspergillus flavus	Histone methylation	Aflatoxin	Histone methyltransferase DOT1	Virulence, Formation of conidiation and sclerotia	(Liang et al. 2017)
Aspergillus flavus	Histone methylation	Aflatoxin	Histone methyltransferase AflSet1	Fungal development, Virulence, Fungal resistance against osmotic, oxidative and cell membrane stress	(Liu et al. 2020)
Colletotrichum higginsianum	Histone methylation	Colletochlorins, higginsianins and sclerosporide	H3K4 methyltransferase	Regulating fungal growth, development, pathogenicity	(Dallery et al. 2019)
Aspergillus nidulans	Histone methylation	Austinol, dehydroaustinol, sterigmatocystin, emericellamide, orsellinic acid and emodin	Jumonji Histone H3 Demethylase KdmB	Gene activation	(Matthews et al. 2016)
Epichloë festucae	Histone methylation	Alkaloid	H3K9- (ClrD) or H3K27- (EzhB) methyltransferases	Forming a mutualistic interaction with its host	(Chujo and Scott 2014)
Zymoseptoria tritici	Histone methylation	Melanin,liotoxin, fusaridione, and echinocandin	H3K27 methyltransferase	Regulating fungal growth	(Amine Hassani et al. 2021)
Ustilaginoidea virens	Histone methylation	PKS, NRPS, and Cytochrome	H3K27 methyltransferase	Growth, conidiation and pathogenicity,response to various stresses	(Meng et al. 2021)
Fusarium graminearum	Histone methylation	Carotenoid, fusarin	H3K27 methyltransferase KMT6	Germination patterns, Pigment production	(Connolly et al. 2013)
Aspergillus fumigatus	Histone methylation	Gliotoxin	H3K4 demethylase	Pathogenicity	(Palmer et al. 2013a)
Fusarium fujikuroi and Fusarium graminearum	Histone methylation	Gibberellic acid and deoxynivalenol	H3K4 demethylase	Virulence	(Studt et al. 2017)
Aspergillus parasiticus	Histone acetylation and methylation	Aflatoxin B1	Histone H4 deacetylase	Regulating fungal growth	(Roze et al. 2007)
Calcarisporium arbuscula	Histone acetylation	Arbumycin and arbumelin, the diterpenoid arbuscullic acid A, and the meroterpenoid arbusculic acid B	Histone H3 deacetylase	Pleiotropic activation	(Xu-Ming et al. 2015)
Aspergillus flavus	Histone acetylation	Aflatoxin	HDAC SirE	Genetic information process and oxidation–reduction	(Wen et al. 2022)
Aspergillus nidulans	Histone acetylation	Archetypal polyketide orsellinic acid and its derivatives	HDACs	Regulating fungal growth	(Nützmann et al. 2011)
Aspergillus fumigatus	Histone acetylation	Niacin	HAT GcnE	Conidiation and biofilm formation	(Lin et al. 2020)
Aspergillus fumigatus	Histone acetylation	Gliotoxin,sterigmatocystin and penicillin	HDAC HdaA	Germination	(Pidroni et al. 2018)
Aspergillus niger	Histone acetylation	Fumonisin, kojic acid	HATs and HDACs	Growth, pigment production, sporulation and stress resistance	(Li et al. 2019b)

H3K4, histone 3 lysine 4; H3K9, histone H3 lysine 9 H3K27, histone H3lysine 27; PKS, polyketide synthases; NRPS, nonribosomal peptide synthases; HAT, histone acetyltransferase; HDAC, histone deacetylas

fungi (Bok et al. 2009; Palmer et al. 2013a; Studt et al. 2017). The molecular mechanism behind the effect of this effect on the formation of several SMs has not been clarified (Szewczyk et al. 2008).

Histone acetylation

Studies have detected that histone acetylation and methylation are correlated with up-regulation of aflatoxin B1 gene clusters in *A. parasiticus*, further confirming that epigenetic modification markers are involved in the synthesis of SMs (Roze et al. 2007). Among them, the acetylation modification can flexibly affect the structure and function of chromatin. Multiple silent gene clusters can be activated simultaneously and rapidly through histone acetylation modification, providing a powerful tool for genome mining. For example, the removal of histone deacetylase from *Calcarisporium arbuscula* increases the expression level of three quarters of the secondary metabolism gene cluster in the cell, and half of the compounds isolated from the mutant have new structures (Xu-Ming et al. 2015). Histone acetylation allows the mutual transformation between transcription and inhibition of chromatin domains. Its expression has a direct impact on the stability of nucleosome arrays and controls the generation of docking sites of regulatory proteins (Gujral et al. 2020).

The modification and regulation of histone acetylation is one of the clearest histone modification mechanisms studied in fungi at present, which mainly occurs on the relatively conserved lysine residues at the N-terminal tail of histone H3 and H4. Histone acetyltransferase (HAT) and histone deacetylase (HDAC) regulate the acetylation level of lysine residues in the N-terminal tail of histones (Song et al. 2022). With the acetylation of lysine residues, the enhancement of negative charges contained in histones reduces the binding force between histones and DNA, which is conducive to the binding of various proteins such as transcription factors with DNA (Nakayama and Takami 2001), it further affects transcription and expression of related genes. Some researchers have shown that the production of SMs is due to the activation of histone modification of fungi. For example, histone deacetylase SirE was crucial for secondary metabolism production as well as genetic information process in *A. flavus* (Wen et al. 2022). The co-culture of *Streptomyces rapamycinicus* and *A. nidulans* can activate the secondary metabolism genes of fungi then produce SMs (Nützmann et al. 2011). Both the gene *gcnE* with HAT activity and the Saga/Ada protein complex encoded by AdaB play an important role in the activation of the SMs gene clusters (niacin, penicillin) (Lin et al. 2020). Chromatin immunoprecipitation analysis showed that the Saga/Ada increased the acetylation level of histone 3 at position 9 (H3K9) and position 14 (H3K14) in the gene clusters (Kassem et al. 2017). Knockout results of deacetylase gene *hdaA* in *A. terreus* has a positive impact on the production of butyrolactone and the biosynthesis of new azaphilone derivatives. This suggests that HdaA plays a negative regulatory role in both conidiation and secondary metabolism, and its absence can lead to an increase in the production of these compounds (Pidroni et al. 2018). Further study has shown that the histone deacetylases HosA and HdaA are crucial to the development and SM biosynthesis in *A. niger* (Li et al. 2019b).

Conclusion and challenges

This review introduces the molecular regulation of fungal secondary metabolism, including environmental signal regulation, transcriptional regulation and epigenetic regulation, which converge to form a regulatory network (Fig. 3). These three regulation modes have been proved to affect the synthesis of SMs, but the definite roles of many regulatory factors and environmental signals in fungi are still unknown. Improving the production of SMs is an essential aspect of pharmaceutical and biotechnological research as these compounds have numerous potential applications in the fields of medicine, agriculture, and industry. To improve the production of SMs, various methodologies have been employed. One commonly used methodology is metabolic engineering, which involves the manipulation of a host cell's metabolic pathways to enhance the production of a desired secondary metabolite. This can be achieved through the overexpression of key enzymes or genes involved in the biosynthesis of the compound, as well as the deletion of genes that divert metabolic flux away from the desired pathway. Another methodology is the optimization of culture conditions, such as temperature, pH, and nutrient availability, to improve the growth and metabolic activity of the microorganism. This can increase the yield of SMs produced by the organism. Additionally, the use of genetic modification, such as the introduction of plasmids or incorporation of CRISPR-Cas9 technology, can also improve the production of SMs by enabling precise genetic modifications and controlling gene expression. Overall, these methodologies represent powerful tools for improving the production of SMs and are essential for the advancement of numerous fields, including medicine and biotechnology. However, it is important to consider the ethical implications and potential risks associated with genetic modification and ensure that appropriate safety measures are taken.

In the future, the molecular regulation of fungal secondary metabolism has broad development prospects. By in-depth study of the molecular regulation mechanism of fungal secondary metabolism, the yield and quality of fungal SMs can be improved and their application fields can be expanded. At the same time, the development of new fungal

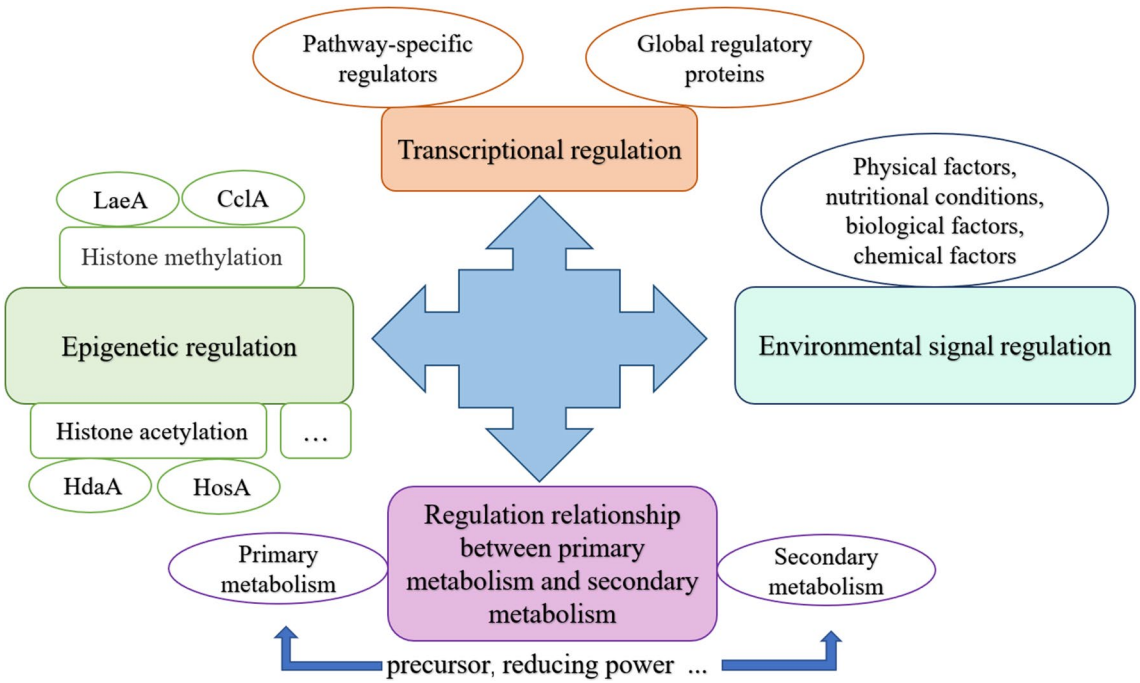

Fig. 3 Regulation network of fungal secondary metabolism

secondary metabolism regulators can provide more options for the production of fungal SMs. The future research directions of molecular regulation of fungal secondary metabolism mainly include the following aspects: deeply study the molecular regulatory mechanisms of fungal secondary metabolism, explore key genes, signaling pathways and regulators, and their interactions. New technologies, such as gene editing and single-cell sequencing, are used to study the molecular regulatory mechanism of fungal secondary metabolism and reveal the regulatory network of fungal secondary metabolism. The methods of synthetic biology are used to design new fungal SMs to improve the yield and stability of products. Development of new fungal secondary metabolism regulators for regulating the yield and quality of fungal SMs.

The future challenge is to explore the secondary metabolic pathways and regulatory patterns of fungi through gene transcriptomics and molecular biology. The goal is activating silent secondary metabolite gene clusters and expanding epigenetic tools to tap the fungal metabolome. The expression of precious fungal SMs was further enhanced through rational biosynthetic regulation. How to use these SMs of fungi to solve important social problems has aroused widespread concern. Some studies have explored the host fungus interaction to enable the SMs of anti-fungal to resist plant fungal diseases. It has also been studied to formulate the optimal culture conditions for fungal SMs through single factor analysis, with a view to large-scale production of fungal SMs in industry. Some studies have developed strategies to control mycotoxin pollution through understanding the gene regulations of SMs (Atanasoff-Kardjalieff and Studt 2022). Understanding the regulation mechanisms of fungal SMs biosynthesis and formulating an effective design to apply fungal SMs to plants, food and other aspects is the hot issue for future research. Recommendations for future development include: enhance the molecular regulation mechanism of fungal secondary metabolism, explore key genes, signaling pathways and regulators, and their interactions. New technologies, such as gene editing and single-cell sequencing, are used to study the molecular regulatory mechanism of fungal secondary metabolism and reveal the regulatory network of fungal secondary metabolism. Strengthen the synthetic biology research of fungal SMs, design new fungal SMs, and improve the yield and stability of products. Develop new fungal secondary metabolism regulators for regulating the yield and quality of fungal SMs.

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Declarations

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Consent to participate Not applicable.

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