Review

cAMP Signalling Pathway in Biocontrol Fungi

Zhan-Bin Sun 1,*†, Shu-Fan Yu 1,†, Chu-Lun Wang 1 and Ling Wang 2,*

1 School of Light Industry, Beijing Technology and Business University, Beijing 100048, China; ys18437906517@163.com (S.-F.Y.); wcl20010424@163.com (C.-L.W.)
2 Key Laboratory of Integrated Pest Management on Crops in Central China, Ministry of Agriculture and Rural Affairs, Hubei Key Laboratory of Crop Disease, Insect Pests and Weeds Control, Institute of Plant Protection and Soil Fertilizer, Hubei Academy of Agricultural Sciences, Wuhan 430064, China
* Correspondence: gilbertsun@btbu.edu.cn (Z.-B.S.); wangl@hbaas.com (L.W.)
† These authors contributed equally to this work.

Abstract: Biocontrol is a complex process, in which a variety of physiological and biochemical characteristics are altered. The cAMP signalling pathway is an important signal transduction pathway in biocontrol fungi and consists of several key components. The G-protein system contains G-protein coupled receptors (GPCRs), heterotrimeric G-proteins, adenylate cyclase (AC), cAMP-dependent protein kinase (PKA), and downstream transcription factors (TFs). The cAMP signalling pathway can regulate fungal growth, development, differentiation, sporulation, morphology, secondary metabolite production, environmental stress tolerance, and the biocontrol of pathogens. However, few reviews of the cAMP signalling pathway in comprehensive biocontrol processes have been reported. This work reviews and discusses the functions and applications of genes encoding each component in the cAMP signalling pathway from biocontrol fungi, including the G-protein system components, AC, PKA, and TFs, in biocontrol behaviour. Finally, future suggestions are provided for constructing a complete cAMP signalling pathway in biocontrol fungi containing all the components and downstream effectors involved in biocontrol behavior. This review provides useful information for the understanding the biocontrol mechanism of biocontrol fungi by utilising the cAMP signalling pathway.

Keywords: cAMP signalling pathway; biocontrol; G-protein system; adenylate cyclase; cAMP-dependent protein kinase; transcription factor

1. Introduction

Biological control is a complex process, including the recognition of pathogens by biocontrol agents, biocontrol-related signal transduction by different cell signal transduction pathways, and finally, biocontrol effects through the relevant response of biocontrol-related signals by biocontrol agents, including the secretion of cell wall degradation enzymes to destroy the cell walls of pathogens or the production of antibiotics and toxins to inhibit or kill pathogens [1–4]. Among these processes, signal transduction plays crucial roles in biocontrol. Signal transduction pathways in cells mainly include the heterotrimeric G protein signalling pathway, mitogen-activated protein kinase (MAPK) signalling pathway, and cAMP signalling pathway [1,5,6]. The G protein and MAPK signalling pathways in biocontrol agents have been well reviewed; however, seldom reviews of the cAMP signalling pathway in comprehensive biocontrol agents have been reported.

Cyclic adenosine 3’5’ monophosphate (cAMP) is a second messenger in both prokaryotes and eukaryotes and is involved in a variety of biological processes [7]. The activity of cAMP is regulated by two enzymes, adenylate cyclase (AC) and phosphodiesterase (PDE). AC catalyses ATP-synthesised cAMP, while PDE degrades cAMP [8]. The cAMP signalling pathway consists of several key components: the G-protein system contains G-protein coupled receptors (GPCRs) and heterotrimeric G-proteins, AC and cAMP-dependent protein kinase (PKA), and downstream effectors such as transcription factors [9]. Extracellular
signal transduction undergoes the following processes in the cAMP signalling pathway: extracellular signals are transmitted into cells through GPCRs, and activated heterotrimeric G-proteins stimulate AC, leading to the production of cAMP. Then, PKA is triggered by cAMP stimulation, and finally, the activated PKA regulates the expression activities by phosphorylation of downstream proteins, such as transcription factors, resulting in the modulation of multiple biological processes [10] (Figure 1).

![Diagram of cAMP signalling pathway](image)

Figure 1. cAMP signalling pathway in biological control. GRCRs: G-protein coupled receptors; AC: Adenylate cyclase; PDE: Phosphodiesterase; PKA: cAMP-dependent protein kinase A; TFs: Transcription factors; CWDES: Cell-wall-degrading enzymes. Pathogen-related signals are transmitted into cells through GPCRs, activate G-proteins, and then stimulate AC. The activated AC converts ATP to cAMP, then, cAMP stimulates PKA, and finally, the activated PKA regulates the expression activities of downstream proteins, such as transcription factors, resulting in the biocontrol of pathogens.

The cAMP signalling pathway has been widely reported in medicine. The cAMP signalling pathway is involved in neurobiology, affecting astrocyte morphology, regulating learning ability, memory formation, numerous neuronal functions, and ultimately behaviours, and participating in psychiatric and neurodegenerative illness [11–17]. The cAMP signalling pathway is critical in adjusting the development of cardiac fibrosis and the functions of cardiac fibroblasts and is closely related to the contraction rate and force of the heart [18–22]. Moreover, the cAMP signalling pathway could influence hypertrophy and hyperplasia of the pituitary gland and insulin resistance in obesity [23–27]. Therefore, the cAMP signalling pathway is generally used as a therapeutic target for the treatment of numerous illnesses, such as alcohol-associated liver disease [28–33].

In addition to its crucial roles in human health and medicine, the cAMP signalling pathway can regulate fungal growth, differentiation, development, conidiation, biofilm formation, sexual mating, and white-opaque switching in some specific fungi [34–38]. The cAMP signalling pathway is also closely related to the virulence of fungal plant pathogens, animal pathogens and malaria parasites [39–43]. Additionally, the cAMP signalling pathway plays important roles in biocontrol agents, such as Trichoderma spp.,
*Metarhizium anisopliae*, and *Beauveria bassiana*, by influencing the formation of appressoria or secretion of cell-wall-degrading enzymes and secondary metabolites [44-47].

In this review, the roles and applications of each component in the cAMP signalling pathway of biocontrol fungi are interpreted and discussed in detail. The review provides useful insights for further application of biocontrol by utilisation of the cAMP signalling pathway.

2. G Protein System

The G protein system is an upstream element of the cAMP signalling pathway. The G protein system mainly contains two components, GPCRs and heterotrimeric G protein. GPCRs contain seven transmembrane domains, which can recognise external signals [48]. Heterotrimeric G protein is highly conserved among organisms and is composed of α, β, and γ subunits [49,50]. Among the three components, the G protein α subunit (Gα) is closely involved in the cAMP signalling pathway. Three subgroups exist in Gα, and subgroups I and III can inhibit and stimulate AC, respectively [51,52]. Extracellular signals are recognised by GPCRs, and ligand-binding GPCRs exchange GDP–GTP on Gα and release the G protein βγ complex. Then, the activated Gα stimulates AC and catalyses ATP synthesis of cAMP [53]. G proteins are critical for morphogenesis, growth, development, mating, virulence, and secondary metabolism [54-57].

The G protein system was also shown to be involved in the biocontrol ability of a number of fungi, such as *Trichoderma* spp., *Clonostachys* spp., *Coniothyrium* spp., *Metarhizium* spp., and *Beauveria* spp. (Table 1). *Trichoderma* spp., *Clonostachys* spp., and *Coniothyrium* spp. are typical mycoparasitism biocontrol agents, with the main targets being pathogenic fungi. *Metarhizium* spp. and *Beauveria* spp. are commonly known as entomopathogenic biocontrol agents, with the main targets being pathogenic insects. Among these biocontrol agents, *Trichoderma* is the most widely studied in terms of the function of the G protein system. The absence of some GPCR genes reduced the biocontrol ability of *Trichoderma* against pathogens. Silencing of the seven-transmembrane GPCR-encoding gene gpr1 in *T. atroviride* resulted in the mutant losing the ability to attack and parasite the pathogens *Rhizoctonia solani*, *Botrytis cinerea*, and *Sclerotium sclerotiorum*. A study found that the quantity of some important antifungal metabolites, such as 6-pentyl-α-pyrene, was significantly reduced in the mutant, and the expression levels of some cell-wall-degrading enzyme encoding genes that are very important for *T. atroviride* mycoparasitism were also dramatically altered in the mutant [58].

Gα can directly activate AC to synthesise cAMP. Gα-encoding genes in different *Trichoderma* species, which exhibits mycoparasitism ability. Reithner et al. [59] deleted the Gα subunit-encoding gene tga1 in *T. atroviride* and found that the mycoparasitic abilities of the mutant against the pathogens *R. solani*, *B. cinerea*, and *S. sclerotiorum* were lost, and the chitinase activities and 6-pentyl-α-pyrene production capacity were reduced when compared with those of the wild-type strain. A mutant of *T. reesei* carried a constitutively activated version of gna3, which encodes for the Gα subunit, and exhibited an improved antagonistic ability to *Pythium ultimum* [60]. Overexpression of tga1 in *T. atroviride* could enhance the mycoparasitism activity of the transformant to *R. solani* [61]. Similar results were found with the disruption of another Gα subunit-encoding gene, tga3, in *T. atroviride*, and the mycoparasitic abilities of the mutant against *R. solani* and *B. cinerea* were lost. Moreover, the chitinase activity in the mutant was reduced, and the infection structures in the mutant were not formed [62]. The biocontrol roles of Gα-encoding genes in other *Trichoderma* species have also been clarified. The absence of the Gα-encoding gene tgaA in *T. virens* resulted in the mutant having a reduced ability to antagonise *S. rolfsii* and losing the ability to parasitise the sclerotia of *S. rolfsii* [63]. In *T. harzianum*, the deletion of two Gα subunit-encoding genes, thga1 and thga3, resulted in significantly altered mycoparasitic abilities of Δthga1 and Δthga3 against *R. solani*, and chitinase activity was markedly reduced in Δthga3 [64,65].
In addition to mycoparasitism agents, the role of the G protein system in entomopathogenic fungal agents has also been deeply studied. GPCRs and G protein are vital for the virulence of entomopathogenic fungal agents. Shang et al. [66] deleted ten GPCR-encoding genes in *M. robertsii* and found that the mutant ΔMrGpr8 lost the ability to form appressoria and infect insects. Disruption of the Ga subunit-encoding gene MrGPA1 in *M. robertsii* could affect the formation of appressoria and the expression level of cuticle-penetration-related genes and reduce the virulence of the mutant to *Galleria mellonella* larvae [67]. In *B. bassiana*, GPCRs also play crucial roles in virulence to insects. Knockout of BbGPCR3, which encodes a GPCR in *B. bassiana*, could lead to a reduced virulence in topical insect assays [68].

Moreover, the expression levels of some important G protein system genes are differentially expressed during the biological control process. GCCPR- and Ga-encoded genes were upregulated in *C. rosea* controlling *Helminthosporium solani* [69]. The gene encoding the PTH11-like GPCR was preferentially expressed in *C. minitans* when parasitising sclerotia of *S. sclerotiorum* [70]. The Pth11-like GPCR-encoding gene was upregulated in *B. bassiana* infecting *Anopheles stephensi* adult mosquitoes [71].

### Table 1. Biocontrol related genes involved in the cAMP signalling pathway of biocontrol fungi.

| Protein                      | Gene     | Biocontrol Fungi | Pathogens                          |
|------------------------------|----------|------------------|------------------------------------|
| G-protein alpha subunit      | tgaA     | *Trichoderma virens* | *Sclerotium rolfsii* [63]          |
| G-protein alpha subunit      | thga1    | T. harzianum     | *Rhizoctonia solani* [65]          |
| G-protein alpha subunit      | thga3    | T. harzianum     | *R. solani* [64]                  |
| G-protein alpha subunit      | tga3     | *T. atroviride*   | *Botrytis cinerea, R. solani* [62] |
| G-protein alpha subunit      | tga1     | *T. atroviride*   | *R. solani, B. cinerea, S. sclerotiorum* [59] |
| Seven-transmembrane receptor Gpr1 | gpr1     | *T. atroviride*   | *R. solani, B. cinerea, S. sclerotiorum* [58] |
| G-protein alpha subunit      | gna3     | *T. reesei*       | *Pythium ultimum* [60]            |
| G-protein alpha subunit      | MrGpa1   | *Metarhizium robertsi* | *Galleria mellonella* [67]         |
| G-protein coupled receptor   | MrGpr8   | *M. robertsii*    | *G. mellonella*, *Tenebrio molitor*, *Bombyx mori* [66] |
| G-protein coupled receptor   | BbGPCR3  | *Beauveria bassiana* | *G. mellonella* [68]              |
| G-protein coupled receptor   | BBA_00828 | *B. bassiana*     | *Anophele stephensi* [71]         |
| G-protein coupled receptor   | CmEST-463 | *Coniothyrium minitans* | *S. sclerotiorum* [70]            |
| G-protein coupled receptor   | BN869_T00001016_1 | *Clonostachys rosea* | *Helminthosporium solani* [69]    |
| Adenylate cyclase            | tac1     | *T. virens*       | *S. rolfsii, R. solani, Pythium sp.* [72] |
| Adenylate cyclase            | MaAC     | *M. acridum*      | *Locusta migratoria* [73]          |
| Adenylate cyclase            | MrAC     | *M. robertsii*    | *T. molitor* [74]                |
| Adenylate cyclase            | BcAC     | *B. bassiana*     | *G. mellonella* [74]              |
| Phosphodiesterase            | AopdeH   | *Arthrobys oligospora* | *Caenorhabditis elegans* [75]      |
| Protein kinase A             | MaPKA1   | *M. anisoplae*    | *G. mellonella* [76]              |
| Protein kinase A             | CMZSB_03553 | *C. minitans*     | *S. sclerotiorum* [77]            |
| Transcription factor         | MrStuA   | *M. rileyi*       | Spodoptera littoralis [78]         |
| Transcription factor         | MaSom1   | *M. acridum*      | *L. migratoria manilensis* [79]    |

### 3. Adenylate Cyclases

Adenylate cyclases (ACs) are highly conserved among organisms. In vertebrates, ACs commonly contain nine transmembrane and one soluble isoforms [33,80]. Several functional domains, including leucine-rich repeat domains, cyclase catalytic domains,
Adenylate cyclases have been reported to be involved in the biocontrol ability of mycoparasitic fungi, such as *Trichoderma* spp. (Table 1). Deletion of the adenylate cyclase-encoding gene *tac1* in *T. virens* reduced the cAMP level. The absence of *tac1* influenced the growth rate, morphology, sporulation, conidial germination, and secondary metabolite production ability of *T. virens*, as well as its confrontation ability against *S. rolfsii*, *R. solani*, and *Pythium* sp. [72]. The cAMP level and coil number of *T. harzianum* were dramatically increased when *T. harzianum* was in close contact with *R. solani* [94]. The deletion of *G* protein-encoding genes in *T. atroviride* or *T. harzianum* could decrease the cAMP levels and led to a weak mycoparasitic ability of *T. atroviride* against *R. solani*, *B. cinerea*, *S. sclerotiorum*, and *T. harzianum* against *R. solani* when compared with the wild strains [62,65].

In entomopathogenic fungi, ACs can influence the biocontrol ability of insects. Silencing the AC-encoding gene *MaAC* in *M. acridum* reduced cAMP levels and influenced growth and tolerance to environmental stresses, including heat shock, UV-B radiation, and oxidative and osmotic stress, in addition to reducing virulence in *Locusta migratoria* adults [73]. Deletion of the AC-encoding genes *BcAC* in *B. bassiana* and *MrAC* in *M. robertsii* affected the conidiation and response to multiple environmental stresses of the two strains and influenced the biocontrol ability of *M. robertsii* to *Tenebrio molitor* third-instar larvae and *B. bassiana* to *Galleria mellonella* larvae [74].

Phosphodiesterase (PDE) could catalyse the hydrolysis of cAMP [18]. PDEs have been reported to be involved in biocontrol behavior. Ma et al. [75] deleted a PDE-encoding gene *AopdeH* in the nematode-trapping fungus *Arthrobotrys oligospora* and found that the mutant had defect in biocontrol ability against nematodes and stress response, and its morphological characteristics included conidiation, mycelial growth and trap formation.

### 4. cAMP-Dependent Protein Kinase A

The exchange protein activated by cAMP (EPAC) and PKA are effectors of cAMP in mammalian cells [32]. Between the two effectors, PKA has been wildly studied. PKA is a serine/threonine kinase that consists of two regulatory subunits and two catalytic subunits, with the anchoring protein being A-kinase anchoring proteins (AKAPs) [18,95]. All the subunits are conserved among organisms. Without cAMP binding, the regulatory subunits are combined with catalytic subunits and do not have kinase activity. When signals are transduced through the cAMP signalling pathway, cAMP binding leads to conformational changes in PKA. Regulatory subunits of PKA bind to cAMP, and the catalytic subunits are dissociated. The activated catalytic subunits regulate the expression levels of downstream genes through phosphorylation and ultimately regulate biological behaviours [96]. PKA could influence the growth, development, metabolism, and morphological characteristics of microorganisms, as well as the virulence or invasion ability of pathogens to the host [97,98]. However, few studies of the biocontrol functions of PKA have been reported (Table 1).

Disruption of the class I PKA catalytic subunit gene *MaPKA1* in *M. anisopliae* resulted in a series of changes. The growth, tolerance to oxidative stress, conidial adhesion, and appressorium formation ability were influenced in the mutant compared with those in the wild-type strain. Moreover, the virulence of the mutant to *G. mellonella* was significantly reduced. This study found that deletion of *MaPKA1* influenced the expression levels of numerous pathogenicity genes, including sterol synthesis, tetraspanin-like protein, subtilisin-like protease, and squalene epoxydase 1 genes, which are involved in the biocontrol processes of appressorium and penetration peg formation, insect cuticle degradation and resistance to antifungal compounds [76]. In addition, the gene encoding
cAMP-dependent protein kinase was dramatically differentially expressed in C. minitans, infecting S. sclerotiorum at different time points [77].

5. Transcription Factors

Transcription factors (TFs) are downstream components of the cAMP signalling pathway. TFs are activated through phosphorylation by catalytic subunits of PKA and combine with the related cis-acting elements to regulate the expression of target genes. To date, 61 TF families have been found in Fungal Transcription Factor Database (http://ftfd.snu.ac.kr/index.php?a=view, accessed on 1 January 2022). The Zn2Cys6 family has the highest numbers of TFs, and the bZIP, C2H2 zinc finger, Forkhead, GATA type zinc finger, heteromeric CCAAT factors, HMG, homeobox, homeodomain-like, Myb, winged helix repressor DNA-binding and zinc finger (CCHC-type) TF families are the most abundant in fungal species. Among the reported fungi, Fusarium oxysporum f. sp. lycopersici had the highest number of TFs.

TFs are involved in numerous fungal physiological processes. TFs influence the growth, development, morphological characteristics, production of secondary metabolites, and environmental stress tolerance of fungi [99,100]. Moreover, TFs play crucial roles in biocontrol behavior. Although TFs have been widely reported to be involved in the biocontrol against pathogens in different fungal species, only a few biocontrol-related TF-encoding genes were reported as the downstream effector in the cAMP signalling pathway (Table 1). The APSES-type transcription factor gene StuA homologs targets of the cAMP signalling pathway in fungi. Deletion of MrStuA in M. rileyi influenced the virulence of the mutant to Spodoptera litura larvae [78]. Disruption of a downstream transcriptional factor of cAMP signalling pathway gene MaSom1 could influence M. acridum infection of L. migratoria manilensis [79].

Besides the above TF-encoding genes that are clearly involved in the cAMP signalling pathway, there are still many TF-encoding genes that belong to different TF families and exhibit biocontrol activity, and they might participate in cAMP signalling pathway. TFs that belong to the bZIP family have been reported to be activated through the cAMP signalling pathway [101]. The bZIP transcription factor gene Mrap1 null mutant of M. rileyi altered the virulence to Spodoptera litura larvae [102]. In M. robertsii, the absence of bZIP transcription factor gene MBZ1 also affected the virulence of M. robertsii to silkworm and wax moth larvae [103]. Deletion of the bZIP TF gene BbHapX affected the virulence of B. bassiana to G. mellonella larvae [104]. Moreover, bZIP transcription factor-encoding genes were involved in different mycoparasitism stages of C. minitans, and were differentially expressed during the process of T. koningii against S. rolfsii [105].

Additionally, zinc finger TF-encoding genes were also reported to be involved in the cAMP signalling pathway [106]. Absence of the C2H2 transcription factor gene Mns2 and GATA-type transcription factor gene MrNsdD would affect the virulence of M. rileyi to Spodoptera litura larvae [107,108]. In M. robertsii, disruption of PacC homologue transcription factor gene MrpacC could influence the virulence of M. robertsii to silkworm larvae [109]. In addition, deletion of the PacC gene MaPacC could affect M. acridum infection of Locusta migratoria manilensis [110]. In B. bassiana, zinc finger TFs also play vital roles in biocontrol. Deletion of the Zn(II)2Cys6 TF genes BbTpc1 and BbThm1, Far/CTF1-type zinc finger TF genes Bbctf1α and Bbctf1β in B. bassiana would influence the virulence of the mutant to G. mellonella larvae [111]. The biocontrol ability of B. bassiana’s infection of Tenebrio molitor larvae and adults and G. mellonella larvae was influenced after the PacC TF gene pacC was disrupted [112]. The Zn(2)-C6-type transcription factor-encoding gene was upregulated in Duddingtonia flagrans, infecting nematodes at different trapping stages [113]. In C. minitans, deletion of the PacC TF gene CmpacC reduced the mycoparasitic activity of C. minitans against S. sclerotiorum and the activities of the cell-wall-degrading enzymes chitinase and β-1,3-glucanase [114]. Similar results have been found in Trichoderma and Clonostachys. Deletion of a TF gene pacC in T. virens would affect the overgrowth and...
parasitism ability of *R. solani* and *S. rolfsii* to pathogens, respectively [115]. Disruption of the TF genes *pacC* in *C. rosea* attenuated their virulence to nematodes [116].

The cAMP signalling pathway could also regulate the expression of heat-shock TF-encoding genes [117]. Heat-shock TFs play important roles in the virulence of *B. bassiana*. Deletion of three heat-shock TFs encoding genes *Hsf1*, *Sfl1*, and *Skn7* in *B. bassiana* could influence the virulence to *G. mellonella* larvae [118]. In *M. robertsi*, the absence of the heat-shock TF-encoding gene *MrSkn7*, would affect the virulence of *M. robertsi* to wax moth larvae [119]. Similar phenomenon was found in *Hirsutella minnesota*; the disruption of the heat-shock TF gene *SKN7* could attenuate the virulence of *H. minnesota* to nematodes [120]. Moreover, the expression of MADS-box TFs could be regulated by the cAMP signalling pathway [121]. In *B. bassiana*, absence of the MADS-box TF gene *Bbncm1* could influence the virulence of the mutant to *G. mellonella* larvae [122]. The MADS-box TF gene *Rm1* was verified to play important roles in the *Candida oleophila* control of *B. cinerea* by gene deletion, and the mutant showed a reduced biocontrol efficacy against postharvest grey mould of kiwifruit [123].

### 6. Conclusions and Perspectives

The cAMP signalling pathway is an important signal transduction pathway. The cAMP signalling pathway can regulate the physiological characteristics of fungi, including growth, development, differentiation, sporulation, morphology, and secondary metabolite production. The cAMP signalling pathway could influence the tolerance of fungi to environmental stress through external signals, affect the pathogenicity of pathogens to the host, or affect the biocontrol ability of biocontrol fungi against different kinds of pathogens. When compared with reviews of other signal transduction pathways, reviews of cAMP signalling pathways in biological control are rare. Therefore, this review focuses on the function of each component of the cAMP signalling pathway in biocontrol fungi in the biocontrol process. This review provides a basis for understanding the mechanism of the cAMP signalling pathway involved in biological control.

Currently, studies of cAMP signalling pathways in biocontrol mainly focus on the function of individual components, such as the G protein system, AC, PKA, and transcription factors in biocontrol. However, the complete cAMP signalling pathway in comprehensive biocontrol fungi has seldom been studied. Because numerous genes encoding cAMP signalling pathway components exist in the genomes of biocontrol fungi, it is critical to understand how all cAMP signalling pathway components are connected. Studies of the cAMP signalling pathway in biocontrol could be conducted with the following steps.

1. The expression levels of cAMP signalling pathway upstream genes, such as the G protein system components (GPCRs and G protein), should be investigated in biocontrol-fungi-infecting pathogens. The expression levels could be detected through transcriptome sequencing or proteomic analysis or directly monitored by RT-qPCR. Among all the G protein system-encoding genes, those genes with significant differential expression would be selected for gene knockout or silencing to clarify their functions in biocontrol.

2. The expression levels of all AC-encoding genes should be investigated in the wild-type strain and G protein system null-mutant-infecting pathogens. AC genes that are dramatically differentially expressed after G protein system-encoding gene deletion would be chosen for the gene functional analysis. Gene knockout or silencing was used to investigate the functions of AC-encoding genes in biocontrol. Thus, genes encoding the G protein system and AC in the same cAMP signalling pathway would be connected.

3. Accordingly, PKA-encoding genes involved in the consistent cAMP signalling pathway would be selected using the above strategy through the process of comparison of the wild strain with the AC null mutant against pathogens. Hence, genes encoding the G protein system, AC, and PKA in the same cAMP signalling pathway would be connected.
The most important components in the cAMP signalling pathway are the downstream TFs. Because a variety of TF families exist, identifying TF-encoding genes consistent with the same cAMP signalling pathway using the above strategy is very important. Thus far, a complete cAMP signalling pathway involved in biocontrol behaviour has been constructed.

Finally, the expression levels of some downstream effector protein genes, such as genes encoding cell-wall-degrading enzymes or secondary metabolite production, should be investigated through comparison of the wild-type strain with the TF null mutant against pathogens. Future work is vital to deeply clear the mechanism of the biocontrol signals transduced through the cAMP signalling pathway in biocontrol fungi.

**Author Contributions:** Conceptualisation: Z.-B.S.; Writing Original Draft Preparation: Z.-B.S., S.-F.Y., C.-L.W. and L.W.; Writing—Review & Editing: Z.-B.S. and L.W.; Funding acquisition, Z.-B.S. and L.W. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by Science and Technology general project of Beijing municipal education commission [KM202110011002]. Open fund project in Key laboratory of integrated pest management of the ministry of agriculture/Key laboratory of major crop disease management of Hubei Province [2021ZTSJ09].

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

**References**

1. Karlsson, M.; Atanasova, L.; Jensen, D.F.; Zeilinger, S. Necrotrophic Mycoparasites and Their Genomes. *Microbiol. Spectr.* 2017, 5. FUNK-0016-2016. [CrossRef] [PubMed]
2. Qualhato, T.F.; Lopes, F.A.; Steindorff, A.S.; Brandão, R.S.; Jesuino, R.S.; Ulhoa, C.J. Mycoparasitism studies of *Trichoderma* species against three phytopathogenic fungi: Evaluation of antagonism and hydrolytic enzyme production. *Biotechnol. Lett.* 2013, 35, 1461–1468. [CrossRef] [PubMed]
3. Reino, J.L.; Guerriero, R.F.; Hernandez-Gala, R.; Collado, I.G. Secondary metabolites from species of the biocontrol agent *Trichoderma*. *Phytochem. Rev.* 2008, 7, 89–123. [CrossRef]
4. Vinale, F.; Sivasithamparam, K.; Ghisalberti, E.L.; Marra, R.; Barbetti, M.J.; Li, H.; Woo, S.L.; Lorito, M. A novel role for *Trichoderma* secondary metabolites in the interactions with plants. *Physiol. Mol. Plant Pathol.* 2008, 72, 80–86. [CrossRef]
5. Zeilinger, S.; Omann, M. *Trichoderma* biocontrol: Signal transduction pathways involved in host sensing and mycoparasitism. *Gene Regul. Syst. Biol.* 2007, 1, 227–234. [CrossRef]
6. Schmoll, M. Assessing the relevance of light for fungi: Implications and insights into the network of signal transmission. *Adv. Appl. Microbiol.* 2011, 76, 27–78.
7. Blanco, E.; Fortunato, S.; Viggiano, L.; de Pinto, M.C. Cyclic AMP: A polyhedral signalling molecule in plants. *Int. J. Mol. Sci.* 2020, 21, 4862. [CrossRef]
8. Lin, C.J.; Chen, Y.L. Conserved and divergent functions of the cAMP/PKA signaling pathway in *Candida albicans* and *Candida tropicalis*. *J. Fungi* 2018, 4, 68. [CrossRef]
9. Huang, G.H.; Huang, Q.; Wei, Y.J.; Wang, Y.; Du, H. Multiple roles and diverse regulation of the Ras/cAMP/protein kinase A pathway in *Candida albicans*. *Mol. Microbiol.* 2019, 111, 6–16. [CrossRef]
10. Arumugham, V.B.; Baldari, C.T. cAMP: A multifaceted modulator of immune synapse assembly and T cell activation. *J. Leukoc. Biol.* 2017, 101, 1301–1316. [CrossRef]
11. Horvat, A.; Vardjan, N. Astroglial cAMP signalling in space and time. *Neurosci. Lett.* 2019, 689, 5–10. [CrossRef] [PubMed]
12. Abel, T.; Nguyen, P.V. Regulation of hippocampus-dependent memory by cyclic AMP-dependent protein kinase. *Prog. Brain Res.* 2008, 169, 97–115. [PubMed]
13. Yao, H.; Gu, L.J.; Guo, J.Y. Study on effect of Astragali Radix polysaccharides in improving learning and memory functions in aged rats and its mechanism. *China J. Chin. Mater. Med.* 2014, 39, 2071–2075.
14. Zhou, Z.; Ikegaya, Y.; Koyama, R. The Astrocytic cAMP Pathway in Health and Disease. *Int. J. Mol. Sci.* 2019, 20, 779. [CrossRef]
15. Dwivedi, Y.; Pandey, G.N. Adenylyl cyclase-cyclicAMP signaling in mood disorders: Role of the crucial phosphorylating enzyme protein kinase A. *Neuropsychiatr. Dis. Treat.* 2008, 4, 161–176. [CrossRef]
16. Nestler, E.J. Cellular responses to chronic treatment with drugs of abuse. *Crit. Rev. Neurobiol.* 1993, 7, 23–39.
17. Lee, E.H.; Seo, S.R. Neuroprotective roles of pituitary adenylate cyclase-activating polypeptide in neurodegenerative diseases. 
BMB Rep. 2014, 47, 369–375. [CrossRef]
18. Delaunay, M.; Osman, H.; Kaiser, S.; Diviani, D. The role of cyclic AMP signaling in cardiac fibrosis. 
Cells 2019, 9, 69. [CrossRef]
19. Lv, T.T.; Du, Y.H.; Cao, N.; Zhang, S.L.; Gong, Y.L.; Bai, Y.; Wang, W.; Liu, H.R. Proliferation in cardiac fibroblasts induced by 
beta(1)-adrenoceptor autoantibody and the underlying mechanisms. Sci. Rep. 2016, 6, 32430. [CrossRef]
20. Yokoyama, U.; Patel, H.H.; Lai, N.C.; Aroonsakool, N.; Roth, D.M.; Insel, P.A. The cyclic AMP effector Epac integrates pro- and 
anti-fibrotic signals. Proc. Natl. Acad. Sci. USA 2008, 105, 6836–6839. [CrossRef]
21. Ghigo, A.; Mika, D. cAMP/PAK signaling compartmentalization in cardiomyocytes: Lessons from FRET-based biosensors. 
J. Mol. Cell Cardiol. 2019, 131, 112–121. [CrossRef] [PubMed]
22. Buxton, I.L.; Brunton, L.L. Compartments of cyclic AMP and protein kinase in mammalian cardiomyocytes. 
Handb. Exp. Pharmacol. 2016, 233, 29–49. [PubMed]
23. Ravnskjaer, K.; Madiraju, A.; Montminy, M. Role of the cAMP pathway in glucose and lipid metabolism. 
Endocrinol. Metab. 2018, 258, 10233–10239. [CrossRef]
24. Peverelli, E.; Busnelli, M.; Vitali, E.; Giardino, E.; Gales, C.; Lania, A.G.; Beck-Peccoz, P.; Chini, B.; Mantovani, G.; Spada, A. Specific roles of Gi(i) protein family members revealed by dissecting SST5 coupling in human pituitary cells. 
J. Cell Sci. 2013, 126, 638–644. [CrossRef]
25. Pertuit, M.; Barlier, A.; Enjalbert, A.; Gerard, C. Signalling pathway alterations in pituitary adenomas: Involvement of Gsalpha, 
cAMP and mitogen-activated protein kinases. J. Neuroendocrinol. 2009, 21, 869–877. [CrossRef]
26. Vortmeyer, A.O.; Glasker, S.; Mehta, G.U.; Abu-Asab, M.S.; Smith, J.H.; Zhuang, Z.; Collins, M.T.; Oldfield, E.H. Somatic GNAS 
mutation causes widespread and diffuse pituitary disease in acromegalic patients with McCune-Albright syndrome. J. Clin. Endocrinol. Metab. 2012, 97, 2404–2413. [CrossRef]
27. Hernández-Ramírez, L.C.; Trivellin, G.; Stratakis, C.A. Cyclic 3′,5′-adenosine monophosphate (cAMP) signaling in the anterior 
pituitary gland in health and disease. Mol. Cell Endocrinol. 2018, 463, 72–86. [CrossRef]
28. Musheshe, N.; Schmidt, M.; Zaccolo, M. cAMP: From long-range second messenger to nanodomain signalling. 
Trends Pharmacol. Sci. 2018, 39, 209–222. [CrossRef]
29. Okumura, S.; Takagi, G.; Kawabe, J.; Yang, G.P.; Lee, M.C.; Liu, J.; Vatner, D.E.; Sadoshima, J.; Vatner, S.F.; et al. Disruption of type 5 adenyl cyclase gene preserves cardiac function against pressure overload. 
Proc. Natl. Acad. Sci. USA 2003, 100, 9986–9990. [CrossRef]
30. Sprenger, J.U.; Perera, R.K.; Steinbrecher, J.H.; Lehnaat, S.E.; Maier, L.S.; Hasenfuss, G.; Nikolaev, V.O. In vivo model with targeted 
cAMP biosensor reveals changes in receptor-microdomain communication in cardiac disease. Nat. Commun. 2015, 6, 6965. [CrossRef]
31. Surdo, N.C.; Berrera, M.; Koschinski, A.; Brescia, M.; Machado, M.R.; Carr, C.; Wright, P.; Gorelik, J.; Morotti, S.; Grandi, E.; et al. FRET biosensor uncovers cAMP nano-domains at beta-adrenergic targets that dictate precise tuning of cardiac contractility. 
Nat. Commun. 2017, 8, 15031. [CrossRef] [PubMed]
32. El Nagdy, M.; Barve, S.; McClain, C.; Gobeishvili, L. cAMP signaling in pathobiology of alcohol associated liver disease. 
Biomolecules 2020, 10, 1433. [CrossRef] [PubMed]
33. Raker, V.K.; Becker, C.; Steinbrink, K. The cAMP pathway as therapeutic target in autoimmune and inflammatory diseases. 
Front. Immunol. 2016, 7, 123. [CrossRef] [PubMed]
34. Ding, X.; Cao, C.; Zheng, Q.; Huang, G. The regulatory subunit of protein kinase A (Bcy1) in 
cAMP-dependent signaling pathway and its role in conidial germination, growth, and virulence of the gray mold 
Botrytis cinerea. Mol. Plant Microbe Interact. 2008, 21, 1443–1459. [CrossRef]
35. Lee, N.; D’Souza, C.A.; Kronstad, J.W. Of smuts, blasts, mildews, and blights: cAMP signaling in phytopathogenic fungi. 
Annu. Rev. Phytopathol. 2003, 41, 399–427. [CrossRef]
36. Kayikci, O.; Magwene, P.M. Divergent roles for cAMP-PKA signaling in the regulation of filamentous growth in Saccharomyces cerevisiae and Saccharomyces bayanus. G3: Genes Genomes Genet. 2018, 8, 3529–3538. [CrossRef]
37. Reinton, N.; Haugen, T.B.; Orstavik, S.; Skalhegg, B.S.; Hansson, V.; Jahnsten, T.; Tasken, K. The gene encoding the C gamma 
catalytic subunit of cAMP-dependent protein kinase is a transcribed retroponon. Genomics 1998, 297, 290–297. [CrossRef]
38. Portela, P.; Rossi, S. cAMP-PKA signal transduction specificity in Saccharomyces cerevisiae. Curr. Genet. 2020, 66, 1093–1099. [CrossRef]
39. Perrin, A.J.; Patel, A.; Flueck, C.; Blackman, M.J.; Baker, D.A. cAMP signalling and its role in host cell invasion by malaria 
parasites. Curr. Opin. Microbiol. 2020, 58, 69–74. [CrossRef]
40. Schumacher, J.; Kokkelink, L.; Huesmann, C.; Jimenez-Teja, D.; Collado, J.G.; Barakat, R.; Tuzdysyni, P.; Tuzdysyni, B. The 
cAMP-dependent signalling pathway and its role in conidal germination, growth, and virulence of the gray mold 
Botrytis cinerea. Mol. Plant Microbe Interact. 2008, 21, 1443–1459. [CrossRef]
41. Choi, Y.E.; Xu, J.R. The cAMP signaling pathway in Fusarium verticillioides is important for conidiation, plant infection, and stress 
responses but not fusonomin production. Mol. Plant Microbe Interact. 2010, 23, 522–533. [CrossRef] [PubMed]
42. Caza, M.; Kronstad, J.W. The cAMP/Protein kinase A pathway regulates virulence and adaptation to host conditions in 
Cryptococcus neoformsans. Front. Cell Infect. Microbiol. 2019, 9, 212. [CrossRef] [PubMed]
43. Tzima, A.; Papломatas, E.J.; Rauyaree, P.; Kang, S. Roles of the catalytic subunit of cAMP-dependent protein kinase A in virulence 
and development of the soilborne plant pathogen Verticillium dahliae. Fungal Genet. Biol. 2010, 47, 406–415. [CrossRef] [PubMed]
70. Muthumeenakshi, S.; Sreenivasaprasad, S.; Rogers, C.W.; Challen, M.P.; Whipps, J.M. Analysis of cDNA transcripts from *Coniothyrium minitans* reveals a diverse array of genes involved in key processes during sclerotial mycoparasitism. *Fungal Genet. Biol.* 2007, 44, 1262–1284. [CrossRef] [PubMed]

71. Lai, Y.L.; Chen, H.; Wei, G.; Wang, G.D.; Li, F.; Wang, S.B. In vivo gene expression profiling of the entomopathogenic fungus *Bacillus bassiana* elucidates its infection strategies in *Anopheles* mosquito. *Sci. China Life Sci.* 2017, 60, 839–851. [CrossRef] [PubMed]

72. Mukherjee, M.; Mukherjee, P.K.; Kale, S.P. cAMP signalling is involved in growth, germination, mycoparasitism and secondary metabolism in *Trichoderma viride*. *Microbiology* 2007, 153 Pt 6, 1734–1742. [CrossRef]

73. Liu, S.Y.; Peng, G.X.; Xia, Y.X. The adenylyl cyclase gene MaAC is required for virulence and multi-stress tolerance of *Metarhizium anisopliae*. *BMC Microbiol.* 2012, 12, 163. [CrossRef] [PubMed]

74. Wang, J.; Zhou, M.G.; Yang, S.H.; Feng, M.G. Adenylate cyclase orthologues in two filamentous entomopathogens contribute differentially to growth, conidiation, pathogenesis, and multistress responses. *Fungal Biol.* 2014, 118, 422–431. [CrossRef] [PubMed]

75. Ma, N.; Jiang, K.X.; Bai, N.; Li, D.N.; Zhang, K.Q.; Yang, J.K. Functional analysis of two affinity cAMP phosphodiesterases in the nematode-trapping fungus *Arthrobotrys oligospora*. *Pathogens* 2022, 11, 405. [CrossRef]

76. Fang, W.G.; Pava-riollo, M.; Wang, S.B.; Leger, R.S. Protein kinase A regulates production of virulence determinants by the entomopathogenic fungus, *Metarhizium anisopliae*. *Fungal Genet. Biol.* 2009, 46, 277–285. [CrossRef]

77. Zhao, H.Z.; Zhou, T.; Xie, J.T.; Cheng, J.S.; Chen, T.; Jiang, D.H.; Fu, Y.P. Mycoparasitism illuminated by genome and transcriptome sequencing of *Coniothyrium minitans*, an important biocontrol fungus of the plant pathogen *Sclerotinia sclerotiorum*. *Microb. Genom.* 2020, 6, e000345. [CrossRef] [PubMed]

78. Xin, C.Y.; Zhang, J.P.; Nian, S.J.; Wang, G.X.; Wang, Z.K.; Song, Z.Y.; Ren, G.W. Analogous and diverse functions of APSES-type transcription factors in the morphogenesis of the entomopathogenic fungus *Metarhizium rileyi*. *Appl. Environ. Microbiol.* 2020, 86, e02928–19. [CrossRef] [PubMed]

79. Ma, N.; Jiang, K.X.; Bai, N.; Li, D.N.; Zhang, K.; Yang, J.K. Functional analysis of two affinity cAMP phosphodiesterases in the nematode-trapping fungus *Arthrobotrys oligospora*. *Pathogens* 2022, 11, 405. [CrossRef]

80. Zhang, F.; Zhang, L.P.; Qi, Y.; Xu, H. Mitochondrial cAMP signaling. *Cell. Mol. Life Sci.* 2016, 73, 4577–4590. [CrossRef]

81. Shapiro, R.S.; Uppuluri, P.; Zaas, A.K.; Collins, C.; Senn, H.; Perfect, J.R.; Heitman, J.; Coven, L.E. Hsp90 orchestrates temperature-stress tolerances, and virulence in *Metarhizium anisopliae*. *Microbiology* 2009, 155, 528–545. [CrossRef] [PubMed]

82. Fang, H.M.; Wang, Y. RA domain-mediated interaction of Cdc35 with Ras1 is essential for increasing cellular cAMP level for hyphal development. *Eukaryot. Cell.* 2002, 1, 634–642. [CrossRef] [PubMed]

83. Slominski, A.; Slominska, M.; Skrzypek, M.; Slominska, M.; Skrzypek, M. Analogous and diverse functions of APSES-type transcription factors in the morphogenesis of the entomopathogenic fungus *Metarhizium rileyi*. *Appl. Environ. Microbiol.* 2020, 86, e02928–19. [CrossRef] [PubMed]

84. Zhang, F.; Zhang, L.P.; Qi, Y.; Xu, H. Mitochondrial cAMP signaling. *Cell. Mol. Life Sci.* 2016, 73, 4577–4590. [CrossRef]

85. Ivey, F.D.; Borkovich, K.A. Shared and independent roles for a G alpha(i) protein and adenylyl cyclase in regulating *Aspergillus* development and stress responses in *Aspergillus fumigatus*. *Appl. Environ. Microbiol.* 2012, 78, 3978–3991. [CrossRef] [PubMed]

86. Zhang, Q.; Tao, L.; Guan, G.; Yue, H.; Liang, W.; Cao, C.; Dai, Y.; Huang, G. Regulation of filamentation in the human fungal pathogen *Candida albicans* by a Ras1-PAK signaling pathway. *Appl. Environ. Microbiol.* 2009, 75, 277–285. [PubMed]

87. García-Martínez, J.; Ávila, J.; Hernández, J.; Adán, A.L.; Avalos, J. Adenylyl cyclase plays a regulatory role in development, stress resistance and secondary metabolism in *Fusarium fujikuroi*. *PLoS ONE* 2012, 7, e28849. [CrossRef] [PubMed]

88. Choi, W.; Dean, R.A. The adenylate cyclase gene *MaC1* of *Magnaporthe oryzae* controls appressorium formation and other aspects of growth and development. *Plant Cell* 1997, 9, 1973–1983. [CrossRef] [PubMed]

89. Chen, X.; Zhang, X.; Zhu, P.; Wang, Y.; Na, Y.; Guo, H.; Cai, Y.; Nie, H.; Jiang, Y.; Xu, L. A single nucleotide mutation in adenylyl cyclase affects vegetative growth, sclerotial formation and virulence of *Botrytis cinerea*. *Int. J. Mol. Sci.* 2020, 21, 2912. [CrossRef] [PubMed]

90. Yang, K.L.; Qin, Q.P.; Liu, Y.H.; Zhang, L.M.; Liang, L.L.; Lan, H.H.; Chen, C.H.; You, Y.C.; Zhang, F.; Wang, S.H. Adenylate cyclase *AcyA* regulates development, afor biosynthesis and fungal virulence in *Aspergillus flavus*. *Front. Cell Infect. Microbiol.* 2016, 6, 190. [CrossRef] [PubMed]

91. Swaney, J.S.; Roth, D.M.; Olson, E.R.; Naugle, J.E.; Meszaros, J.G.; Insel, P.A. Inhibition of cardiac myofibril formation and collagen synthesis by activation and overexpression of adenylate cyclase. *Proc. Natl. Acad. Sci. USA* 2005, 102, 437–442. [CrossRef] [PubMed]

92. Swaney, J.S.; Patel, H.H.; Yokoyama, U.; Head, B.P.; Roth, D.M.; Insel, P.A. Focal adhesions in (myo) fibrils scaffolds adenylyl cyclase with phosphorylated caveolin. *J. Biol. Chem.* 2006, 281, 17173–17179. [CrossRef] [PubMed]

93. Lee, S.; Lee, H.C.; Kwon, Y.W.; Lee, S.E.; Cho, Y.; Kim, J.; Lee, S.; Kim, J.Y.; Lee, J.; Yang, H.M.; et al. Adenyl cyclase-associated protein 1 is a receptor for human resistin and mediates inflammatory actions of human monocytes. *Cell Metab.* 2014, 19, 484–497. [CrossRef] [PubMed]

94. Lin, Y.R.; Lo, C.T.; Liu, S.Y.; Feng, K.C. Involvement of pachybasin and emodin in self-regulation of *Trichoderma harzianum* mycoparasitic coiling. *J. Agric. Food Chem.* 2012, 60, 2123–2128. [CrossRef] [PubMed]
95. Dickman, M.; Yarden, O. Serine/Threonine protein kinases and phosphatases in filamentous fungi. *Fungal Genet. Biol.* **1999**, *26*, 99–117. [CrossRef]

96. Taylor, S.S.; Ilouz, R.; Zhang, P.; Kornev, A.P. Assembly of allosteric macromolecular switches: Lessons from PKA. *Rev. Mol. Cell Biol.* **2012**, *13*, 646–658. [CrossRef]

97. Zhu, W.J.; Zhou, M.; Xiong, Z.Y.; Peng, F.; Wei, W. The cAMP-PKA signaling pathway regulates pathogenicity, hyphal growth, appressorium formation, conidiation, and stress tolerance in *Colletotrichum higginsianum*. *Front. Microbiol.* **2017**, *8*, 1416. [CrossRef]

98. Luo, Z.B.; Ren, H.; Mousa, J.J.; Rangel, D.E.N.; Zhang, Y.J.; Bruner, S.D.; Keyhani, N.O. The PacC transcription factor regulates *Verticillium dahliae* conidiation and virulence. *Environ. Microbiol.* **2020**, *22*, 208–216.

99. Schoberle, T.J.; Nguyen-Coleman, C.K.; Herold, J.; Yang, A.; Weirauch, M.; Hughes, T.R.; MuMurray, J.S.; May, G.S. A novel C2H2 transcription factor that regulates gliA expression interdependently with GliZ in Aspergillus fumigatus. *PLoS Genet.* **2014**, *10*, e1004336. [CrossRef]

100. Matheis, S.; Yemelin, A.; Scheps, D.; Andresen, K.; Jacob, S.; Thines, E.; Foster, A.J. Functions of the *Magnaporthe oryzae* FliH3p and Flb4p transcription factors in the regulation of conidiation. *Microbiol. Res.* **2017**, *190*, 106–117. [CrossRef]

101. Thiel, G.; Al Sarraj, J.; Vison, C.; Stefano, L.; Bach, K. Role of basic region leucine zipper transcription factors cyclic AMP response element binding protein (CREB), CREB2, activating transcription factor 2 and CAAT/enhancer binding protein alpha in cyclic AMP response element-mediated transcription. *J. Neurochem.* **2005**, *92*, 321–336. [CrossRef] [PubMed]

102. Song, Z.Y.; Yin, Y.P.; Lin, Y.L.; Du, F.; Ren, G.W.; Wang, Z.K. The bZIP transcriptional factor activator protein-1 regulates *Verticillium dahliae* conidiation and virulence. *Appl. Microbiol. Biotechnol.* **2018**, *102*, 4577–4588. [CrossRef] [PubMed]

103. Huang, W.; Shang, Y.F.; Chen, P.L.; Chen, K.; Wang, C.S. Basic leucine zipper (bZIP) domain transcription factor MBZ1 regulates cell wall integrity, spore adherence, and virulence in *Metarhizium robertsii*. *J. Biol. Chem.* **2015**, *290*, 8218–8231. [CrossRef] [PubMed]

104. Peng, Y.J.; Wang, J.J.; Lin, H.Y.; Ding, J.L.; Feng, M.G.; Ying, S.H. HapX, an indispensable bZIP transcription factor for iron acquisition, regulates infection initiation by orchestrating conidial oleic acid homeostasis and cytomembrane in mycopathogen *Beauveria bassiana*. *Mystyens* **2020**, *5*, e00695-20. [CrossRef]

105. Xu, Y.P.; Wang, Y.C.; Zhao, H.Z.; Wu, M.D.; Zhang, J.; Chen, W.D.; Li, G.Q.; Yang, L. Genome-wide identification and expression analysis of the bZIP transcription factors in the mycoparasite *Coniothyrium minitans*. *Microorganisms* **2020**, *8*, 1045. [CrossRef]

106. Luo, X.; Mao, H.; Wei, Y.; Cai, J.; Xie, C.; Sui, A.; Yang, X.; Dong, J. The fungal-specific transcription factor Vdpf influences conidia production, melanized microsclerotia formation and pathogenicity in *Verticillium dahliae*. *Mol. Plant. Pathol.* **2016**, *17*, 1364–1381. [CrossRef]

107. Song, Z.Y.; Yang, J.; Xin, C.Y.; Xing, X.R.; Yuan, Q.; Yin, Y.P.; Wang, Z.K. A transcription factor, MrMsn2, in the dimorphic fungus *Metarhizium rileyi* is essential for dimorphism transition, aggravated pigmentation, conidiation and microsclerotia formation. *Microbiot. Biotechnol.* **2018**, *13*, 1157–1169. [CrossRef]

108. Xie, C.; Yang, J.; Mao, Y.Y.; Chen, W.B.; Wang, Z.K.; Song, Z.Y. GATA-type transcription factor MrNsdD regulates dimorphic transition, conidiation, virulence and the entomopathogenic fungus *Metarhizium rileyi*. *Microbiob. Biotechnol.* **2020**, *13*, 1489–1501. [CrossRef]

109. Huang, W.; Shang, Y.F.; Chen, P.L.; Gao, Q.; Wang, C.S. MrPacC regulates sporulation, insect cuticle penetration and immune evasion in *Metarhizium robertsii*. *Microbiol. Res.* **2015**, *185*, 994–1008. [CrossRef]

110. Zhang, M.G.; Wei, Q.L.; Xia, Y.X.; Jin, K. MaPacC, a pH-responsive transcription factor, negatively regulates thermotolerance and contributes to conidiation and virulence in *Metarhizium acridum*. *Curr. Genet.* **2020**, *66*, 397–408. [CrossRef]

111. Wang, Z.L.; Pan, H.B.; Huang, J.; Yu, X.P. The zinc finger transcription factors Bbctf1alpha and Bbctf1beta regulate the expression of genes involved in lipid degradation and contribute to stress tolerance and virulence in a fungal insect pathogen. *Pest. Manag. Sci.* **2020**, *76*, 2589–2600. [CrossRef] [PubMed]

112. Luo, Z.B.; Ren, H.; Mousa, J.J.; Rangel, D.E.N.; Zhang, Y.J.; Bruner, S.D.; Keyhani, N.O. The PacC transcription factor regulates secondary metabolite production and stress response, but has only minor effects on virulence in the insect pathogenic fungus *Beauveria bassiana*. *Environ. Microbiol.* **2017**, *19*, 788–802. [CrossRef] [PubMed]

113. Zhang, W.; Liu, D.; Yu, Z.; Hou, B.; Fan, Y.; Li, Z.; Shang, S.; Qiao, Y.; Fu, J.; Niu, J.; et al. Comparative genome and transcriptome analysis of the bZIP transcription factors in the mycoparasite *Coniothyrium minitans*. *Microorganisms* **2018**, *6*, 1416. [CrossRef]

114. Luo, Y.; Han, Y.C.; Yang, L.; Wu, M.D.; Zhang, J.; Cheng, J.S.; Wang, M.Y.; Jiang, D.H.; Chen, W.D.; Li, G.Q. CmpacC regulates mycoparasitism, oxalate degradation and antifungal activity in the mycoparasitic fungus *Coniothyrium minitans*. *Environ. Microbiol.* **2015**, *17*, 4711–4729.

115. Trushina, N.; Levin, M.; Mukherjee, P.K.; Horwitz, B.A. PacC and pH-dependent transcription of the mycotoxigenic fungus *Trichoderma virens*. *BMC Genom.* **2013**, *14*, 138. [CrossRef] [PubMed]

116. Zou, C.G.; Tu, H.H.; Liu, X.Y.; Tao, N.; Zhang, K.Q. PacC in the nematophagous fungus *Clonostachys rosea* controls virulence to nematodes. *Environ. Microbiol.* **2010**, *12*, 1868–1877. [CrossRef]

117. Ferguson, S.B.; Anderson, E.S.; Harshaw, R.B.; Thate, T.; Craig, N.L.; Nelson, H.C. Protein kinase A regulates constitutive expression of small heat-shock genes in an Msn2/4p-independent and Hsf1p-dependent manner in *Saccharomyces cerevisiae*. *Genetics* **2005**, *169*, 1203–1214. [CrossRef]
118. Zhou, G.; Ying, S.H.; Hu, Y.; Fang, X.; Feng, M.G.; Wang, J. Roles of three HSF domain-containing proteins in mediating heat-shock protein genes and sustaining asexual cycle, stress tolerance, and virulence in *Beauveria bassiana*. *Front. Microbiol.* **2018**, *9*, 1677. [CrossRef]

119. Shang, Y.F.; Chen, P.L.; Chen, Y.X.; Lu, Y.Z.; Wang, C.S. MrSkn7 controls sporulation, cell wall integrity, autolysis, and virulence in *Metarhizium robertsi*. *Eukaryot. Cell* **2015**, *14*, 396–405. [CrossRef]

120. Hussain, M.; Hamid, M.I.; Wang, N.N.; Bin, L.; Xiang, M.C.; Liu, X.Z. The transcription factor SKN7 regulates conidiation, thermotolerance, apoptotic-like cell death and parasitism in the nematode endoparasitic fungus *Hirsutella minnesotensis*. *Sci. Rep.* **2016**, *6*, 30047. [CrossRef]

121. Escalante, R.; Sastre, L. cAMP and DIF-1 repress the expression of the *Dictyostelium* MADS-box gene srfA at early stages of development. *Biochem. Biophys. Res. Commun.* **2001**, *285*, 820–824. [CrossRef] [PubMed]

122. Zhao, X.; Yang, X.; Lu, Z.; Wang, H.; He, Z.; Zhou, G.; Luo, Z.; Zhang, Y. MADS-box transcription factor Mcm1 controls cell cycle, fungal development, cell integrity and virulence in the filamentous insect pathogenic fungus *Beauveria bassiana*. *Environ. Microbiol.* **2019**, *21*, 3392–3416. [CrossRef] [PubMed]

123. Sui, Y.; Sun, Z.Q.; Zou, Y.P.; Li, W.H.; Jiang, M.G.; Luo, Y.Z.; Liao, W.J.; Wang, Y.H.; Gao, X.W.; Liu, J.; et al. The Rlm1 transcription factor in *Candida oleophila* contributes to abiotic stress resistance and biocontrol efficacy against postharvest gray mold of kiwifruit. *Postharvest Biol. Tec.* **2020**, *166*, 111222. [CrossRef]