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REVIEW

The Role of Chromatin and Transcriptional Control in the Formation of Sexual Fruiting Bodies in Fungi

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SUMMARY Fungal fruiting bodies are complex, three-dimensional structures that arise from a less complex vegetative mycelium. Their formation requires the coordinated action of many genes and their gene products, and fruiting body formation is accompanied by major changes in the transcriptome. In recent years, numerous transcription factor genes as well as chromatin modifier genes that play a role in fruiting body morphogenesis were identified, and through research on several model organisms, the underlying regulatory networks that integrate chromatin structure, gene expression, and cell differentiation are becoming clearer. This review gives a summary of the current state of research on the role of transcriptional control and chromatin structure in fruiting body development. In the first part, insights from transcriptomics analyses are described, with a focus on comparative transcriptomics. In the second part, examples of more detailed functional characterizations of the role of chromatin modifiers and/or transcription factors in several model organisms (*Neurospora crassa*, *Aspergillus nidulans*, *Sordaria macrospora*, *Coprinopsis cinerea*, and *Schizophyllum commune*) that have led to a better understanding of regulatory networks at the level of chromatin structure and transcription are discussed.

KEYWORDS ascomycetes, basidiomycetes, chromatin, fruiting body formation, multicellular development, transcription factors, transcriptome

INTRODUCTION

The formation of complex multicellular structures has evolved independently several times in eukaryotes (1, 2). Within fungi (Eumycota), the most complex multicellular structures are sexual fruiting bodies of filamentous fungi, which most likely evolved independently at least twice, in ascomycetes and basidiomycetes (3). Fruiting body formation in these groups progresses from a vegetative mycelium and requires the differentiation of multiple specialized cell types that form three-dimensional structures that are unique to sexual development and play a role in the production, protection, and

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dispersal of sexual spores (4–11). Even though ascomycete and basidiomycete fruiting bodies evolved independently, they probably arose from the same "toolbox" of eukaryotic genes in their last common ancestor that allowed the evolution of complex multicellular structures (not all of which are sexual fruiting bodies) (3, 12). Understanding the molecular processes that underlie fruiting body formation is of interest in developmental biology because the production of three-dimensional structures from a mycelium (as opposed to true tissues in animals, the closest fungal relatives with complex multicellular structures) might unravel novel molecular principles. It is also of interest for applied research, e.g., for the use of fruiting bodies as food and sources of medicinal drugs, the formation of sexual spores as infective agents of pathogenic fungi, and an improved understanding of the life cycles of pathogenic or biotechnologically relevant fungi (13–15). Two reviews that give an overview of sexual reproduction and fruiting body formation in asco- and basidiomycetes have already been published as part of this *Microbiology and Molecular Biology Reviews* special collection (7, 16). Here, I focus on the role of transcriptional control and the regulation of chromatin in fruiting body development.

An important role for transcriptional control in fungal sexual development was first discovered through the analysis of developmental mutants that turned out to carry causative mutations in transcription factor genes. The mating type genes of *Neurospora crassa* were the first transcription factor genes with a role in fruiting body formation to be identified in a filamentous fungus (17, 18), and many (putative) transcription factor genes have been identified since then (Table 1). In addition to the analysis of developmental mutants, reverse genetic analyses were instrumental in identifying developmental roles for transcription factor genes, either through the large-scale generation of deletion mutants for transcription factor genes of selected model organisms (e.g., see references 19–22) or through transcriptome analyses that led to the identification of developmentally regulated target genes for functional characterization, as described in the next section. In addition to transcription factors, transcription is also regulated by other proteins that modify chromatin, and a number of genes encoding chromatin modifiers that are involved in fruiting body differentiation have been identified in both asco- and basidiomycetes (Table 2).

This review is intended to give an overview in tabular form of the already large number of transcription factors and chromatin modifiers that were shown to be involved in fruiting body formation (Tables 1 and 2) since a discussion of each gene would be outside the scope of this review. Instead, the following sections focus on examples of studies that resulted in conceptual insights by using new methods or conducting in-depths analyses of selected model organisms.

The next section gives an overview of studies in which global changes in chromatin or transcriptomes during fruiting body development were analyzed to identify evolutionary trends in gene expression, and the four subsequent sections discuss results about the roles of chromatin modifications and transcriptional control in five model organisms for fruiting body development, the ascomycetes *N. crassa*, *Aspergillus nidulans*, and *Sordaria macrospora* and the basidiomycetes *Coprinopsis cinerea* and *Schizophyllum commune*.

CHANGES IN CHROMATIN STRUCTURE AND TRANSCRIPTOMES DURING FRUITING BODY DEVELOPMENT

Studies in asco- and basidiomycetes have shown that differentiation processes are accompanied by the massive restructuring of the transcriptome in the developing fruiting bodies compared to the vegetative mycelium. This became clear early on in the first expressed sequence tag (EST) study of different developmental stages in *N. crassa* (23), and many analyses of different fungal species using different transcriptomics methods have confirmed this finding (reviewed in references 3 and 24–26). Genes that are differentially expressed under certain conditions might be involved in the corresponding biological processes and therefore make suitable candidates for functional studies. However, in most species, the large number of genes that change their expression during fruiting body formation makes targeting genes for further characterization

TABLE 1 Transcription factor genes involved in fruiting body development[e]

Gene name(s)	Species and mutant or overexpression phenotype(s)[a]	Class[b]	Reference(s)
Transcription factors encoded by mating type genes			
MAT-1-1-1	*Neurospora crassa* and *Podospora anserina*, no fertilization; *Cochliobolus heterostrophus*, sterile; *Aspergillus nidulans*, cleistothecia without spores; *Aspergillus fumigatus*, no cleistothecia; *Fusarium graminearum*, perithecia without asci; *Didymella zeae-maydis*, only a few ascospores produced; *Sclerotinia sclerotiorum*, sclerotia but no apothecia; *Botrytis cinerea*, no primordia (male and female sterile)	α domain	17, 103, 144–153
MAT-1-1-3	*Fusarium graminearum*, perithecia without asci; *Podospora anserina*, strongly reduced ascospore production	HMG	146, 154, 155
MAT-1-2-1	*Neurospora crassa*, no mature perithecia; *Podospora anserina*, no fertilization; *Cochliobolus heterostrophus*, sterile; *Sordaria macrospora*, only protoperithecia; *Aspergillus nidulans*, cleistothecia without ascospores; *Aspergillus fumigatus*, no cleistothecia; *Fusarium graminearum*, perithecia without asci; *Didymella zeae-maydis*, no ascospores; *Sclerotinia sclerotiorum*, sclerotia but no apothecia; *Botrytis cinerea*, no primordia (male and female sterile)	HMG	18, 103, 145–152, 156–158
HD1, *HD2*[c]	*Coprinopsis cinerea* and *Schizophyllum commune*, double mutants of HD and P/R[f] mating type loci show monokaryotic fruiting	HD	125–127, 159, 160
Other transcription factors			
stuA, *asm-1*	*Aspergillus nidulans*, no cleistothecia and Hülle cells; *Neurospora crassa*, no protoperithecia; *Fusarium graminearum*, no perithecia; *Arthroderma benhamiae*, pseudocleistothecia without asci	APSES domain	161–166
fgswi6, *GlSwi6*	*Fusarium graminearum*, fewer and smaller perithecia without asci; *Ganoderma lucidum*, no fruiting bodies in RNAi knockdown strains	APSES domain	167, 168
bri1	*Schizophyllum commune*, no fruiting bodies	BRIGHT domain	130
devR	*Aspergillus nidulans*, no cleistothecia and Hülle cells	bHLH	169
urdA	*Aspergillus nidulans*, increased cleistothecium formation	bHLH	170
atfA	*Aspergillus nidulans*, increased cleistothecium formation	bZIP	171
flbB	*Aspergillus nidulans*, increased cleistothecium formation	bZIP	170
cpcA	*Aspergillus nidulans*, overexpression leads to a block at the microcleistothecium stage	bZIP	172
napA	*Aspergillus nidulans*, overexpression leads to fewer ascospores	bZIP	173
rsmA	*Aspergillus nidulans*, overexpression leads to fewer ascospores	bZIP	173
zipA	*Aspergillus nidulans*, overexpression leads to fewer ascospores	bZIP	173
fpo1	*Fusarium graminearum*, increased and earlier production of perithecia	bZIP	174
zif1	*Fusarium graminearum* and *Magnaporthe oryzae*, no asci	bZIP	175
asl-2, *ts*	*Neurospora crassa*, ascospores do not germinate	bZIP	20, 176
Smjlb1	*Sordaria macrospora*, no ascospores	bZIP	177
c2h2	*Agaricus bisporus*, overexpression leads to accelerated mushroom production; *Schizophyllum commune*, only fruiting body precursors (aggregate stage)	C_2H_2	130, 178
flbC, *flb-3*	*Aspergillus nidulans*, increased cleistothecium formation; *Neurospora crassa*, female and male sterile	C_2H_2	179, 180
mtfA	*Aspergillus nidulans*, fewer cleistothecia and Hülle cells	C_2H_2	181
nsdC	*Aspergillus nidulans*, no cleistothecia; *Aspergillus fumigatus*, no cleistothecia in crosses of two *nsdC* mutant strains	C_2H_2	182, 183
sltA	*Aspergillus nidulans*, no cleistothecia and Hülle cells, rescued by the addition of potassium ions	C_2H_2	184
vidA	*Aspergillus nidulans*, smaller cleistothecia	C_2H_2	185
pcs1	*Fusarium graminearum*, no perithecia	C_2H_2	186
pacC, *GlPacC*	*Neurospora crassa*, no protoperithecia; *Ganoderma lucidum*, no primordia or fruiting bodies	C_2H_2	187, 188
zfc7	*Schizophyllum commune*, only fruiting body precursors (aggregate stage)	C_2H_2	60

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TABLE 1 (Continued)

Gene name(s)	Species and mutant or overexpression phenotype(s)[a]	Class[b]	Reference(s)
fhpA	*Aspergillus nidulans*, no cleistothecia	FKH box	189
FoxE2	*Sclerotinia sclerotiorum*, no apothecia	FKH box	190
SsFKH1	*Sclerotinia sclerotiorum*, no sclerotia (female sterile)	FKH box	191
nsdD, *sub-1*, *pro44*, *bcltf1*, *Ssnsd1*, *PaNsdD*, *CcNsdD1*/*CcNsdD2*	*Aspergillus nidulans*, no cleistothecia; *Neurospora crassa* and *Sordaria macrospora*, only protoperithecia (these are submerged in agar); *Aspergillus fumigatus*, no mating; *Botrytis cinerea*, no sclerotia (female sterile); *Sclerotinia sclerotiorum*, no apothecia; *Trichoderma reesei*, female sterile; *Podospora anserina*, female sterile but more spermatia; *Coprinopsis cinerea*, defects in fruiting body formation in double knockdown of *NsdD1*/*NdsD2* under a dark/light regime	GATA	20, 96–103
wc-1, *lreA*, *Cmwc-1*, *FgWc-1*, *Sfwc-1*, *dst1*	*Neurospora crassa*, reduced protoperithecial production, no phototropism of the perithecial beak; *Aspergillus nidulans*, light-dependent reduction/inhibition of fruiting body formation; *Cordyceps militaris*, no fruiting bodies in a homozygous cross; *Fusarium graminearum*, fruiting bodies under unfavorable conditions; *Sordaria fimicola*, perithecium formation delayed, no light-dependent zonation pattern and beak phototropism; *Coprinopsis cinerea*,[d] only stipes; *Schizophyllum commune*,[d] no fruiting bodies	GATA	90, 128, 192–198
wc-2, *lreB*, *FgWc-2*	*Neurospora crassa*, reduced protoperithecial production, no phototropism of the perithecial beak; *Aspergillus nidulans*, light-dependent reduction/inhibition of fruiting body formation; *Fusarium graminearum*, fruiting bodies under unfavorable conditions; *Schizophyllum commune*, no fruiting bodies	GATA	90, 128, 194, 196, 197, 199
asd4	*Neurospora crassa*, no asci when crossed as a male or female parent	GATA	200
gat1	*Schizophyllum commune*, more but smaller fruiting bodies; *Pleurotus ostreatus*, no fruiting bodies in a cross with a compatible wild type	GATA	130, 201
steA, *pp-1*, *ste12*, *cpst12*, *CfSte12*	*Aspergillus nidulans*, no cleistothecia; *Neurospora crassa*, no protoperithecia; *Sordaria macrospora*, impaired ascus and ascospore development; *Cryphonectria parasitica*, female sterile; *Fusarium graminearum*, fewer perithecia; *Arthroderma benhamiae*, pseudocleistothecia without asci; *Colletotrichum fructicola*, perithecia without asci	HD	165, 202–206
pah2	*Podospora anserina*, perithecial neck formation is delayed or lacking	HD	207
pah5	*Podospora anserina*, perithecia without necks, reduced ascospore pigmentation	HD	207
hom1	*Schizophyllum commune*, more but smaller fruiting bodies	HD	130
hom2	*Schizophyllum commune*, no fruiting bodies	HD	130
hmbC	*Aspergillus nidulans*, reduced ascospore viability	HMG	208
exp1	*Coprinopsis cinerea*, no pileus expansion and autolysis	HMG	209
pcc1	*Coprinopsis cinerea*, monokaryotic fruiting	HMG	210
pdd1	*Flammulina velutipes*, few to no fruiting bodies in RNAi knockdown strains	HMG	133
Fvhmg1	*Flammulina velutipes*, increased fruiting in RNAi knockdown strains	HMG	132
fmf-1	*Neurospora crassa*, no mature perithecia when crossed as a male or female parent	HMG	211, 212
PaHMG5, *FGSG_01366*	*Podospora anserina*, male and female sterile; *Fusarium graminearum*, smaller perithecia, no asci	HMG	213, 214
PaHMG6, *hmbA*	*Podospora anserina*, reduced female fertility; *Aspergillus nidulans*, cleistothecia with few ascospores	HMG	208, 214
PaHMG8	*Podospora anserina*, female sterile	HMG	214
PaHMG9	*Podospora anserina*, female sterile	HMG	214
fsd-1	*Neurospora crassa*, defective in female sexual development and ascospore maturation	Ig fold	215
vib-1	*Neurospora crassa*, reduced no. of protoperithecia	Ig fold	215
Fvmads2, *Bcmads1*	*Fusarium verticillioides*, no mating when in the *MAT1-2* background; *Botrytis cinerea*, no sclerotia (female sterile)	MADS box	216, 217

(Continued on next page)

TABLE 1 (Continued)

Gene name(s)	Species and mutant or overexpression phenotype(s)[a]	Class[b]	Reference(s)
mcm1, *Fvmads1*, *Fgmcm1*, *mcmA*, *CfMcm1*	*Sordaria macrospora*, only protoperithecia; *Fusarium verticillioides*, no mating when in the *MAT1-2* background; *Fusarium graminearum*, no perithecia; *Aspergillus nidulans*, no cleistothecia; *Colletotrichum fructicola*, no ascospores	MADS box	217–221
flbD	*Aspergillus nidulans*, viable naked ascospores produced (no peridium)	Myb domain	222
myt1	*Fusarium graminearum*, female sterile	Myb domain	223
myt2	*Fusarium graminearum*, increased perithecium size	Myb domain	224
myt3	*Fusarium graminearum*, male and female sterile	Myb domain	225
tea1	*Schizophyllum commune*, strongly reduced fruiting body formation	TEA/ATTS domain	129
rcm-1	*Neurospora crassa*, no protoperithecia	Tetratricopeptide repeat	226, 227
rco-1, *cag1*	*Neurospora crassa*, no protoperithecia; *Coprinopsis cinerea*, fruiting body primordia but no gills	Tup N-terminal domain	227–229
veA, *vel1*, *bcvel1*, *ve-1*	*Aspergillus nidulans*, no cleistothecia; *Cochliobolus heterostrophus*, female sterile; *Trichoderma reesei*, no mating in darkness, female sterile in light; *Botrytis cinerea*, no sclerotia (female sterile); *Neurospora crassa*, fewer protoperithecia	Velvet domain	78, 83, 230–233
velB, *vel2*, *ve-2*	*Aspergillus nidulans*, no cleistothecia; *Cochliobolus heterostrophus*, female sterile; *Neurospora crassa*, fewer protoperithecia	Velvet domain	83, 232, 234
velC	*Aspergillus nidulans*, deletion leads to reduced and overexpression leads to increased no. of cleistothecia	Velvet domain	92
vosA, *vos1*	*Aspergillus nidulans*, defects in ascospore maturation; *Cochliobolus heterostrophus*, deletion or overexpression results in reduced no. of pseudothecia	Velvet domain	80, 91, 94, 234
rosA	*Aspergillus nidulans*, cleistothecia produced in normally unfavorable conditions (low glucose and high osmolarity)	$Zn(II)_2Cys_6$	235
vadZ	*Aspergillus nidulans*, increased cleistothecium formation	$Zn(II)_2Cys_6$	236
zcfA	*Aspergillus nidulans*, decreased cleistothecium formation	$Zn(II)_2Cys_6$	237
lfc1	*Flammulina velutipes*, earlier and more basidiomata in RNAi knockdown strains	$Zn(II)_2Cys_6$	134
hada-1, *ada-6*	*Hypsizygus marmoreus*, fewer fruiting bodies in RNAi knockdown strains; *Neurospora crassa*, few protoperithecia, no perithecia (female sterile)	$Zn(II)_2Cys_6$	238, 239
asm2	*Sordaria macrospora*, defects in ascospore maturation	$Zn(II)_2Cys_6$	59, 117
pro1, *adv-1*, *nosA*	*Sordaria macrospora* and *Aspergillus nidulans*, only fruiting body precursors; *Neurospora crassa*, no fruiting body precursors; *Cryphonectria parasitica*, female sterile	$Zn(II)_2Cys_6$	20, 109, 112, 113
fst1	*Schizophyllum commune*, only immature mushrooms are produced	$Zn(II)_2Cys_6$	60
fst3, *Pofst3*	*Schizophyllum commune* and *Pleurotus ostreatus*, more but smaller fruiting bodies	$Zn(II)_2Cys_6$	31, 240
fst4	*Schizophyllum commune*, no fruiting bodies	$Zn(II)_2Cys_6$	31

[a]Only phenotypes related to fruiting body development are given.
[b]bHLH, basic helix-loop-helix; C_2H_2, C_2H_2 zinc finger; FKH box, forkhead box; HD, homeodomain; HMG, high mobility group.
[c]Two homeodomain genes, *HD1* and *HD2*, usually form a divergently transcribed gene pair at the basidiomycete *HD* mating type locus. The resulting proteins belong to two different classes of homeodomain transcription factors (241).
[d]The *Coprinopsis cinerea dst1* gene and the *Schizophyllum commune wc-1* gene do not encode a GATA zinc finger domain, in contrast to their homologs in ascomycetes (128, 193). The lack of the zinc finger domain appears to be a feature of basidiomycete WC-1 homologs (242). Nevertheless, the genes were included in this list since the WC-1 protein likely forms a transcription factor complex with the GATA factor WC-2, and both genes are required for fruiting body formation in *S. commune* (128).
[e]Genes are sorted according to the encoded transcription factor class and within class according to the species name. This table does not contain transcription factor genes that were identified in large-scale screens of *N. crassa* (19, 20) and *F. graminearum* (21, 213) deletion strains.
[f]P/R, pheromone precursors and pheromone receptors.

difficult. Furthermore, as was shown in early studies of genes chosen for their expression profiles, not all genes that are differentially expressed under a certain condition are absolutely required under that condition (24). One way to improve the identification of potential developmental genes via transcriptomics as well as to gain insights into the evolutionary trajectory of gene expression during development is the use of comparative transcriptomics to identify evolutionarily conserved expression patterns by comparing transcriptomes across species at the same developmental stages. The

TABLE 2 Genes encoding chromatin modifiers or transcriptional coactivators involved in fruiting body development[d]

Gene name(s)	Species and mutant or overexpression phenotype(s)[a]	Function or class[b]	Reference(s)
snt-2, *sntB*	*Neurospora crassa*, no perithecia; *Aspergillus flavus*, no sclerotia	BAH/PHD domain protein	243, 244
crc1	*Sordaria macrospora*, single mutant fertile, only protoperithecia in a Δcrc1 Δcac2 Δrtt106 Δscm1 quadruple mutant	CRC domain protein	32, 59
dmtA	*Aspergillus nidulans*, immature cleistothecia without ascospores	(Putative) DNA methyltransferase	245
asf1	*Sordaria macrospora*, only protoperithecia	H3/H4 histone chaperone	28, 59
rtt106	*Sordaria macrospora*, single mutant fertile, only protoperithecia in a Δcrc1 Δcac2 Δrtt106 Δscm1 quadruple mutant	H3/H4 histone chaperone	28, 32, 59
cac2	*Sordaria macrospora*, single mutant fertile, only protoperithecia in a Δcrc1 Δcac2 Δrtt106 Δscm1 quadruple mutant	H3/H4 histone chaperone (CAF-1 complex subunit)	28, 32, 59
AflGcnE, *FgGCN5*	*Aspergillus flavus*, no sclerotia; *Fusarium graminearum*, no perithecia	HAT	246, 247
FgRTT109	*Fusarium graminearum*, smaller perithecia with a few ascospores	HAT	246
FgSAS3	*Fusarium graminearum*, fewer perithecia	HAT	246
SNT2	*Colletotrichum fructicola*, smaller perithecia without spores	HDAC Rpd3 complex subunit	248
HOS2	*Colletotrichum fructicola*, smaller perithecia without spores	HDAC Set3 complex subunit	248
FTL1	*Fusarium graminearum*, female sterile	HDAC Set3 complex subunit	249
HDF1	*Fusarium graminearum*, female sterile	HDAC Set3 complex subunit	250
dim-3	*Neurospora crassa*, homozygous sterile	Importin subunit α	251
FfJmhy	*Flammulina filiformis*, reduced stipe elongation in RNAi knockdown strains	JmjC domain protein	131
rtfA	*Aspergillus nidulans*, no cleistothecia and Hülle cells	(Putative) Paf1 complex subunit	252
fscA	*Aspergillus nidulans*, no cleistothecia	RcLS2F complex subunit	253
scrC	*Aspergillus nidulans*, no cleistothecia	RcLS2F complex subunit	253
spt3	*Sordaria macrospora*, only protoperithecia	SAGA complex subunit	32, 117
ich1	*Coprinopsis cinerea*, no pileus differentiation	SAM-dependent methyltransferase domain[c]	254
laeA, *bclaea*, *lae-1*	*Aspergillus nidulans*, fewer Hülle cells and more but smaller cleistothecia with fewer ascospores, cleistothecia produced in light; *Botrytis cinerea*, no sclerotia (female sterile); *Neurospora crassa*, fewer protoperithecia	SAM-dependent methyltransferase domain[c]	82, 93, 232, 233
vapB	*Aspergillus nidulans*, cleistothecia produced in light	SAM-dependent methyltransferase domain[c]	85
vipC	*Aspergillus nidulans*, cleistothecia produced in light	SAM-dependent methyltransferase domain[c]	85
scm1	*Sordaria macrospora*, single mutant fertile, only protoperithecia in a Δcrc1 Δcac2 Δrtt106 Δscm1 quadruple mutant	(Putative) SAS complex subunit	32
kmt6	*Fusarium graminearum*, sterile (no fruiting body precursors)	SET domain protein (H3K27 methyltransferase)	73
dim-5	*Neurospora crassa*, few spores in homozygous crosses	SET domain protein (H3K9 methyltransferase)	58, 69
Cc.arp9	*Coprinopsis cinerea*, no fruiting body formation	(Putatively) associated with SWI/SNF and RSC complexes	255
Cc.snf5	*Coprinopsis cinerea*, no fruiting body formation	(Putative) SWI/SNF complex subunit	256

[a]Only phenotypes related to fruiting body development are given.
[b]BAH, bromo-adjacent domain; CAF-1, chromatin assembly factor 1; CRC, chromatin remodeling complex; HAT, histone acetyltransferase; JmjC, Jumonji C (putative histone H3 demethylase domain); HDAC, histone deacetylase; PHD, plant homeodomain zinc finger; RcLS2F complex, RpdA core/LafA/SdsC/ScrC/FscA complex (a histone lysine deacetylase complex); RSC, remodels the structure of chromatin (a member of the SWI/SNF chromatin remodeling complex family); SAGA, Spt-Ada-Gcn5 acetyltransferase (a transcriptional coactivator); SAM, *S*-adenosylmethionine; SAS, something about silencing; SET domain, Su(var)3-9, enhancer-of-zeste, trithorax domain (a lysine methyltransferase family); SWI/SNF, switch/sucrose nonfermentable (a class of ATP-dependent chromatin remodeling complexes).
[c]The methyltransferase proteins LaeA, VapB, and VipC from *A. nidulans* have not yet been shown to directly modify chromatin components but are included here because they are nuclear proteins with (at least) an indirect role in mediating the chromatin structure. The putative methyltransferase protein Ich1 from *C. cinerea* has not yet been shown to be involved in regulating the chromatin structure but was included because of its predicted methyltransferase domain and nuclear localization.
[d]Genes are sorted according to (predicted) function and within group according to the species name.

idea behind this is that the evolutionary conservation of gene expression, i.e., of a gene being active as opposed to just being present in a genome, is a strong indicator of functional significance (27). The first comparative transcriptomics studies of fruiting body development were conducted based on EST sequencing or microarray hybridization (28–31), but since the advent of next-generation sequencing techniques, comparative transcriptomics analyses were done mostly using RNA sequencing (RNA-seq) data in studies focusing on ascomycetes (32–36), basidiomycetes (37–40), or both (12).

Comparative transcriptomics can be used to identify not only conserved expression patterns across species but also expression patterns that diverged between species after a split of lineages from a common ancestor. Such patterns can be used to identify group- or species-specific expression patterns that might help to explain morphological or physiological differences between species and identify genes that might mediate these differences (41, 42). In fungi, this was demonstrated in two studies using species from the Sordariomycetes (35, 36). RNA-seq data from several stages of fruiting body formation for all analyzed species were used to infer expression profiles from the last common ancestors at the nodes of the corresponding phylogenetic species tree. This allowed those authors to identify genes that had significantly changed expression in certain species/lineages for all analyzed developmental stages. The analysis of deletion mutants for some of the identified genes revealed a high proportion of cases where the mutant phenotypes in a species deviated from the wild type at the developmental stage corresponding to the highest expression levels in this species. Taken together, these data highlight the regulatory complexity of fruiting body development and the rapid evolution of regulatory networks that control this process, even within closely related species (35, 36).

Apart from comparative transcriptomics, transcriptomics analyses of developmental mutants, especially mutants of transcription factor or chromatin modifier genes, can also be extremely informative for analyzing gene functions and identifying target genes for further characterization (reviewed in references 4, 24, and 25). For genes encoding transcription factors, it is informative not only to analyze mutant transcriptomes, which can reveal direct as well as indirect target genes of the corresponding transcription factors, but also to perform ChIP-seq (chromatin immunoprecipitation sequencing) experiments that identify genomic DNA binding sites of the transcription factor proteins, thereby distinguishing between direct and indirect target genes. ChIP-seq analyses were used to identify DNA binding sites and, thereby, direct target genes for the transcription factor PRO1 in *S. macrospora* and its ortholog ADV-1 in *N. crassa* (43, 44).

RNA-seq data not only can be used to infer transcript levels but also allow the analysis of other biological features, e.g., RNA editing, the presence of antisense transcripts, or allele-specific expression in dikaryons. In recent years, it was shown that A-to-I (adenosine-to-inosine) RNA editing is widespread and plays a role in fruiting body morphogenesis in filamentous ascomycetes (45–51). This was first discovered in *Fusarium graminearum*, where it was shown that A-to-I editing occurs in a high number of mRNAs in perithecia but not in the vegetative mycelium and that RNA editing of two sites in the coding region is essential for the function of the developmental gene *PUK1* (49). In coding regions, the change from A to I is equivalent to a change to guanosine (G) since the ribosome interprets I as G during translation (45). A-to-I RNA editing in coding regions of transcripts was subsequently shown to be widespread in filamentous ascomycetes (47–51), whereas in basidiomycetes, it does not appear to be prevalent during mushroom formation (39). Antisense transcripts as well as allele-specific expression in dikaryons were found during mushroom formation in basidiomycetes (31, 39, 52), but it is not yet clear if these phenomena are mostly transcriptional noise or sources of functional transcripts that might play a role in the regulation of fruiting body morphogenesis.

Since there are global transcriptome changes during fruiting body formation, one might hypothesize that they are mediated by or result in concomitant large-scale changes in the chromatin structure, e.g., through modifications of DNA or histones,

changes in nucleosome occupancy, or changes in the three-dimensional structure and, thus, the accessibility of chromatin domains. However, even though DNA methylation as well as histone modifications have been studied in great detail in the ascomycete model organism *N. crassa* as well as the phytopathogenic fungi *Fusarium graminearum* and *Zymoseptoria tritici*, these studies have focused mostly on the analyses of molecular mechanisms in vegetative tissues, not on the effects of chromatin modifications on fruiting body development (53–57). Nevertheless, some studies also looked at fruiting body formation: an analysis of the developmental consequences of the mislocalization of histone H3 trimethylation at lysine 27 (H3K27me3) in *N. crassa* (58) and an analysis of the nucleosome distribution and DNA methylation in a developmental mutant of *S. macrospora* (59) are described in the next sections. In basidiomycetes, a recent analysis of the dimethylation of histone H3 at lysine 4 (H3K4me2) during mushroom formation in *Schizophyllum commune* was the first ChIP-seq analysis of mushroom formation (60). Those authors identified about 800 sites of differential enrichment of H3K4me2 during monokaryotic (vegetative) or dikaryotic (fruiting body) development, associated with about 960 genes. Two transcription factor genes with genomic H3K4me2 enrichment during fruiting body development, *fst1* and *zfc7*, were functionally characterized by generating deletion mutants, and both genes were shown to be required for fruiting body formation (60) (Table 1).

Analyses of potential changes in the three-dimensional chromatin structure during fruiting body development have not yet been performed for fungi. One technique that can be used to infer contacts between genomic regions and, thus, map the three-dimensional structure of chromatin is Hi-C (chromosome conformation capture coupled with high-throughput sequencing) (61). Hi-C was used in *N. crassa* to study the chromosome organization in the wild type and mutants of genes involved in the establishment of heterochromatin, but the strains were grown only vegetatively (62, 63). Hi-C was also used to improve the assemblies of several fungal genomes (e.g., see references 64 and 65), but studies using Hi-C to analyze structural changes in chromatin during development have yet to be performed.

Overall, there has already been much progress in the analysis of mechanisms of fruiting body development at the chromatin and transcriptome levels, and large numbers of transcription factor genes as well as chromatin modifier genes involved in this process have been identified in ascomycetes and basidiomycetes (Tables 1 and 2). However, we still lack critical information regarding the role of chromatin modifications, interactions between specific transcription factors and chromatin modifiers, and the spatiotemporal control of these processes at different stages of development. Techniques that have been developed for other systems or that were applied to fungi in the vegetative state, e.g., Hi-C, single-cell transcriptomics (scRNA-seq), or spatial transcriptomics (63, 66, 67), could be applied in future studies of fruiting body development to address these open questions.

NEUROSPORA CRASSA: A ROLE FOR HISTONE METHYLATION IN DEVELOPMENT

Much of our knowledge of the molecular mechanisms of heterochromatin formation and maintenance in fungi has been gained through analyses of *N. crassa* (53–55, 68). The corresponding studies concentrated mostly on the molecular mechanisms at the levels of DNA, histones, and chromatin modifiers, and connections to morphogenetic events were not usually the focus of these analyses. However, intriguing insights into a connection among histone methylation, heterochromatin, and fruiting body development were revealed in a study by Basenko and coworkers (58). Those authors found that the developmental phenotype of a Δdim-5 mutant, which produces only a few, mostly inviable ascospores (69), can be rescued in a Δdim-5 Δset-7 double mutant (58) (Fig. 1). *dim-5* encodes the catalytic subunit of the histone methyltransferase complex DCDC (DIM-5/DIM-7/DIM-9/CUL4/DDB1 complex), which is required for histone H3 lysine 9 methylation (H3K9me3) (70), whereas *set-7* encodes the catalytic subunit of the histone H3 lysine 27 (H3K27) methyltransferase complex PRC2 (polycomb

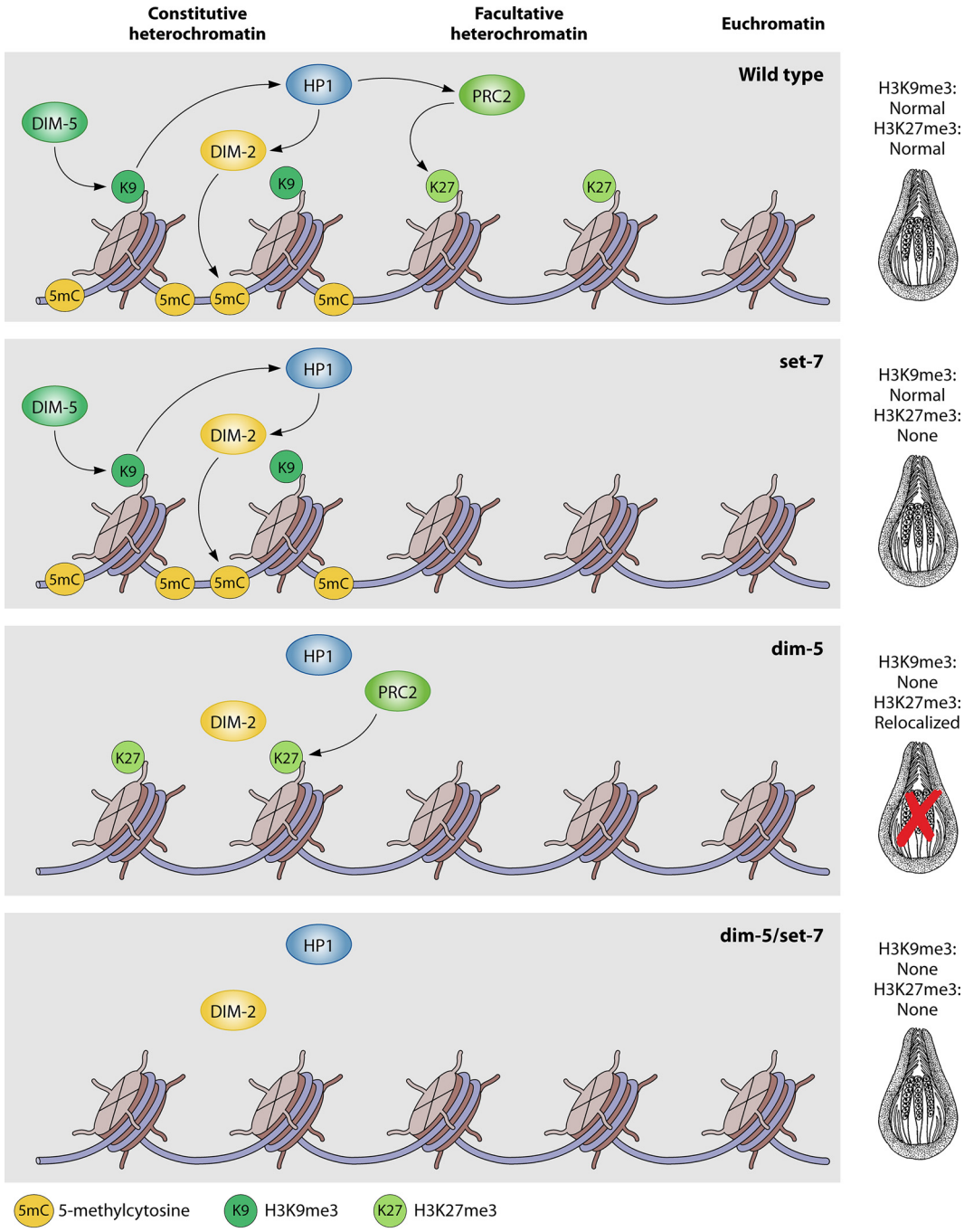

FIG 1 Role of histone modifications in the development of *Neurospora crassa*. Shown are models of DNA (gray line) wrapped around histone octamers (purple cylinders) with different DNA and histone modifications in the wild-type and several mutant strains (strains are indicated in each panel; histone H3 at lysine 9 [H3K9me3] and H3K27me3 status and the development of mature fruiting bodies are indicated in separate panels on the right). Arrows indicate steps that occur during the methylation of histones and DNA: in constitutive heterochromatin regions, the methyltransferase DIM-5 methylates H3K9me3, and H3K9-methylated histone H3 is recognized by heterochromatin protein 1 (HP1), which recruits the DNA methyltransferase DIM-2, which is responsible for all cytosine methylation in *N. crassa* (69, 139–141). The PRC2 complex, of which SET-7 is an essential subunit, methylates histone H3 at lysine 27 in facultative heterochromatin (55, 71, 142). Mutation of *dim-5* results in the relocalization of H3K27me3 marks to constitutive heterochromatin regions that are no longer marked by H3K9me3. The *dim-5* mutant does not form mature spores, in contrast to a *set-7* mutant and the *dim-5 set-7* double mutant, both of which lack H3K27me3 (58). Thus, neither H3K9me3 nor H3K27me3 is essential for fruiting body formation, but the mislocalization of H3K27me3 causes developmental defects. HP1 is required for the formation of H3K27me3 marks in facultative heterochromatin, and the lack of HP1 leads to the relocalization of H3K27me3 to constitutive heterochromatin, similar to the loss of DIM-5 (not depicted), but sexual development was not tested in an HP1 mutant strain (58).

repressive complex 2) (71). In the wild type, H3K9 methylation by DIM-5 is present in constitutive heterochromatin, whereas H3K27 methylation by PRC2 is found in facultative heterochromatin (58) (Fig. 1). In a Δdim-5 mutant, H3K9me3 is no longer present, and H3K27me3 marks are shifted from facultative to constitutive heterochromatin regions (58) (Fig. 1). Based on these findings, three possible explanations for the developmental phenotype of the Δdim-5 mutant might be hypothesized: (i) it is caused by the lack of H3K9me3, (ii) it is caused by the lack of H3K27me3 in facultative heterochromatin, or (iii) it is caused by the presence of H3K27me3 in constitutive heterochromatin. The finding that the developmental phenotype is rescued in a Δdim-5 Δset-7 double mutant, whereas a Δset-7 single mutant is fertile, indicates that neither the lack of H3K9me3 (which is missing in the fertile double mutant) nor the lack of H3K27me3 in facultative heterochromatin (which is missing in the double mutant and the Δset-7 mutant) leads to a sterile phenotype (Fig. 1). Therefore, the mislocalization of H3K27me3 to constitutive heterochromatin regions is responsible for the developmental phenotype of the Δdim-5 mutant (58). Interestingly, the Δset-7 mutant, while fertile in homozygous crosses (58), forms high numbers of false perithecia when incubated without a mating partner, a phenotype that it shares with a mutant in the *epr-1* gene that mediates H3K27 methylation-mediated silencing (72). These data suggest that H3K27 methylation and its downstream effects have a repressive function in sexual development. The Δepr-1 mutant does not show a mislocalization of H3K27 methylation (72); however, whether the deletion of *epr-1* is able to rescue the sterile phenotype of the Δdim-5 mutant similarly to the deletion of *set-7* has not yet been tested.

Similar to the rapid evolution of transcription patterns and the corresponding regulatory networks mentioned above (35, 36), the regulation of fruiting body development by chromatin modifications might undergo rapid evolutionary changes, as evidenced by the finding that in *F. graminearum*, the *set-7* homolog *kmt6* is required for fruiting body formation (73) (Table 2). Thus, the elucidation of the conserved versus lineage-specific effects of the chromatin structure on fungal multicellular development will be an important topic of future investigations.

ASPERGILLUS NIDULANS: VELVET PROTEINS AND A FAMILY OF METHYLTRANSFERASES BALANCE SECONDARY METABOLISM AND DEVELOPMENT

The filamentous ascomycete *A. nidulans* is able to form sexual fruiting bodies (cleistothecia) that contain ascospores and also asexual conidiophores that produce mitotic spores (conidia), and a network of dynamic protein complexes orchestrates the balance between sexual and asexual development as well as secondary metabolism through the regulation of gene expression (74) (Fig. 2). Major components of these protein complexes are four velvet domain proteins (VeA, VelB, VelC, and VosA), four proteins with methyltransferase domains (LaeA, VapB, VipC, and LlmF), the red-light photoreceptor FphA, and the blue-light photoreceptor LreA and its interaction partner LreB (75, 76). The first of the corresponding genes to be discovered was *veA*, based on the veA1 mutant, in which development is biased toward conidiation even under unfavorable conditions like the absence of light (74, 77). This mutant has been used as a laboratory strain since the 1960s, but it was not until nearly 4 decades later that the *veA* gene was cloned in 2002 (78). However, the molecular role of the corresponding VeA protein could not be identified at that time since VeA did not have any homologs with known functions. A characteristic domain present in VeA was named the velvet domain, and it turned out that gene families encoding velvet domain proteins exist not only in *A. nidulans* but also in other filamentous fungi (74, 79). In 2013, it was shown through an analysis of crystal structures and electrophoretic mobility shift assays that the velvet domain of the VosA protein from *A. nidulans* is a DNA binding domain with structural homology to the mammalian transcription factor NF-κB, indicating that the velvet proteins constitute a family of transcription factors (80).

Another group of genes involved in regulating the balance between sexual and

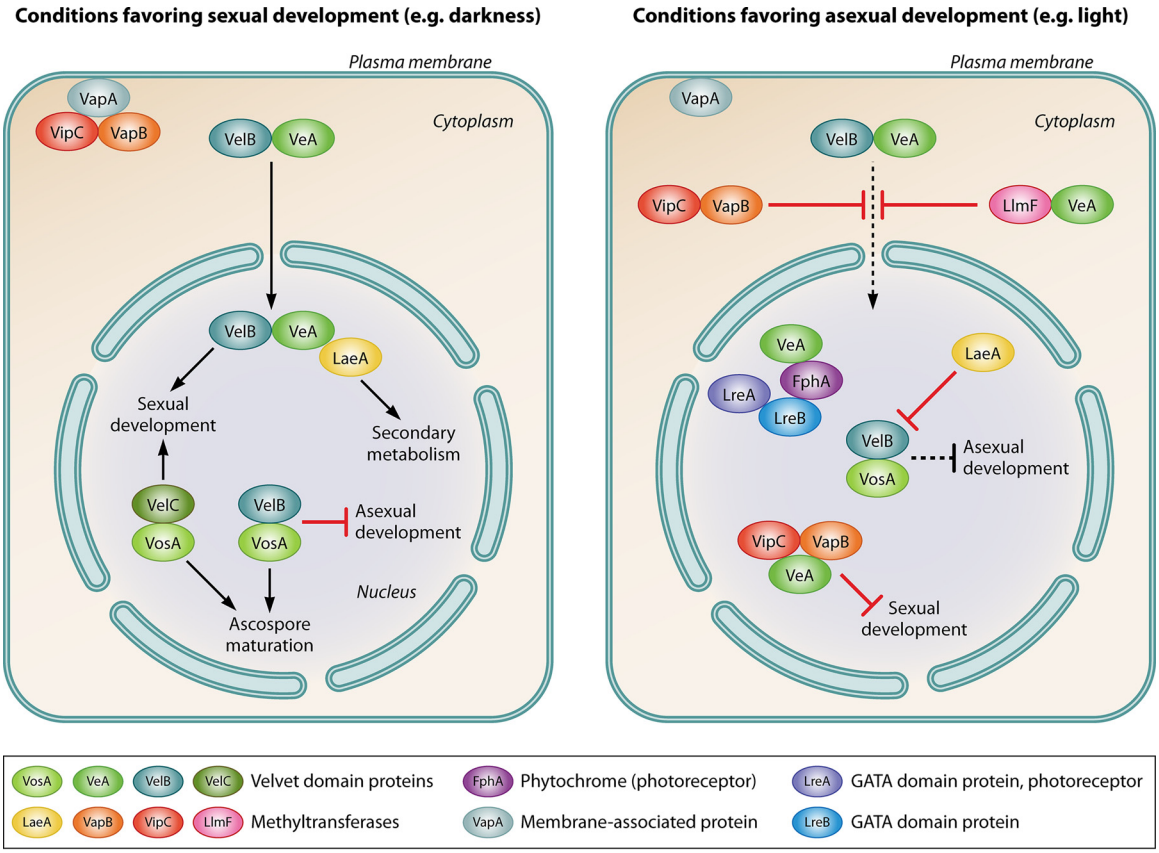

FIG 2 Balancing development and secondary metabolism in *Aspergillus nidulans*. Four velvet domain proteins and four methyltransferase domain proteins balance sexual development, asexual development, and secondary metabolism in *Aspergillus nidulans*. Depending on the growth conditions, the velvet domain proteins form different protein complexes with each other, the methyltransferase proteins, and red-light and blue-light photoreceptors (see the text). Different complexes support either sexual or asexual development (Based on references 74, 75, and 143).

asexual development and secondary metabolism is a family of methyltransferase genes. The first member to be discovered was *laeA*, for which the corresponding mutant was identified in a screen for mutants defective in sterigmatocystin gene cluster activity (81). One of the mutants was complemented through transformation with a cosmid library, and the complementing gene was named *laeA* (for loss of *aflR* expression since *aflR*, the main regulator gene within the sterigmatocystin gene cluster, is no longer expressed in the *laeA* mutant) (82). Subsequent analyses identified *laeA* as not only a regulator of the sterigmatocystin gene cluster but also a global regulator of secondary metabolism (82). The LaeA protein contains a conserved *S*-adenosylmethionine (SAM) binding site found in methyltransferases, and based on the fact that LaeA localizes to the nucleus and influences the transcriptional activity of secondary metabolite gene clusters (82, 83), it was hypothesized that it might methylate chromatin components. Studies on histone modifications in genomic regions of some secondary metabolism genes showed that H3K9me3 levels that mark inactive genes are increased in a ΔlaeA mutant, and the overexpression of the methyltransferase protein VapB resulted in a reduction in overall H3K9me3 levels (84, 85). However, despite significant efforts, no direct targets of methylation by LaeA or the other related methyltransferases VapB, VipC, and LlmF have been identified so far (75, 86). Furthermore, ChIP-seq analyses of *A. nidulans* under conditions of primary or secondary metabolism did not show an enrichment of histone modifications, including H3K9me3, in secondary metabolism gene clusters, suggesting that the relationship between these methyltransferases and histone modifications in secondary metabolism gene clusters may be indirect (87).

Thus, any direct targets of the methyltransferases LaeA, VapB, VipC, and LlmF remain to be elucidated.

Nevertheless, much progress has been made in unraveling the composition and subcellular localization of protein complexes containing velvet proteins, methyltransferases, and photoreceptors in various combinations that mediate different developmental and metabolic stages (Fig. 2). The velvet domain proteins VeA and VelB are required for fruiting body formation, which is mediated by a VeA-VelB dimer in the nucleus (78, 83, 88). Both proteins are also part of different protein complexes within the nucleus depending on the growth conditions or extracellular signals that favor either sexual or asexual development (74, 75). The nuclear entry of VeA is modulated by the methyltransferase domain proteins VipC, VapB, and LlmF (85, 89). Within the nucleus, VeA can interact with the methyltransferase protein LaeA and the phytochrome FphA, which in turn interacts with the photoreceptor complex formed by LreA and LreB (83, 90). The exact function of this complex with respect to fruiting body development has yet to be determined. Protein complexes of the velvet protein VosA with VelB or VelC are involved in ascospore maturation (80, 91–95).

In addition to velvet proteins and methyltransferase domain proteins, the balance between sexual and asexual development in *A. nidulans* is also mediated by the transcription factor NsdD. The *nsdD* gene encodes a GATA transcription factor, and homologs of *nsdD* were shown to be involved in fruiting body formation in a number of ascomycetes as well as the basidiomycete *C. cinerea* (Table 1) (20, 96–103); thus, NsdD is a conserved developmental regulator in fungi. In *A. nidulans*, not only is the *nsdD* gene required for the formation of fruiting bodies, but also the deletion of *nsdD* leads to the formation of asexual spores under conditions that are not conducive to this developmental pathway in the wild type (97, 104). In the wild type, NsdD and VosA act cooperatively to repress the expression of the *brlA* gene that is required for asexual spore formation (105).

Thus, the picture of a highly dynamic network of nuclear protein complexes emerges that balances developmental and metabolic outcomes depending on internal and external signals. Among the open questions for further research are the molecular functions of LaeA and related methyltransferases and the downstream targets of different protein complexes that mediate different developmental pathways.

TRANSCRIPTION FACTORS AND CHROMATIN MODIFIERS AT DIFFERENT DEVELOPMENTAL STAGES IN *SORDARIA MACROSPORA*

The homothallic ascomycete *S. macrospora* has been a model organism for the analysis of fruiting body (perithecium) formation as well as meiosis for decades (106–108), and the first developmental gene required for fruiting body formation that was identified in *S. macrospora* was the transcription factor gene *pro1* (109) (Fig. 3). *pro1* was identified by the complementation of a sterile mutant from a screen for strains that were blocked at different stages of development. Mutants designated "pro" were blocked at the stage of protoperithecium (immature fruiting body) formation (109, 110). PRO1 was shown to have transcriptional activation and DNA binding activities, and it contains a $Zn(II)_2Cys_6$ DNA binding domain that is required for fruiting body formation (44, 111). Several *pro1* orthologs in other ascomycetes were also shown to be required for fruiting body development, indicating that PRO1 is a conserved developmental transcription factor (20, 112, 113) (Table 1).

Transcriptome analyses of the pro1 mutant compared to the wild type revealed a number of genes that are differentially regulated in the pro1 mutant (114–116). Among the genes that are upregulated in young fruiting bodies of the wild type but not the pro1 mutant is *pro44*, which also encodes a transcription factor (116). *pro44* was originally discovered through genome sequencing of the sterile pro44 mutant, and it encodes a GATA domain protein that is most strongly expressed in the outer layer of young fruiting bodies (59, 100). *pro44* is the ortholog of the *A. nidulans nsdD* gene described above. Mutants of *pro44* orthologs have been analyzed in several ascomycetes and the basidiomycete *C. cinerea* and have

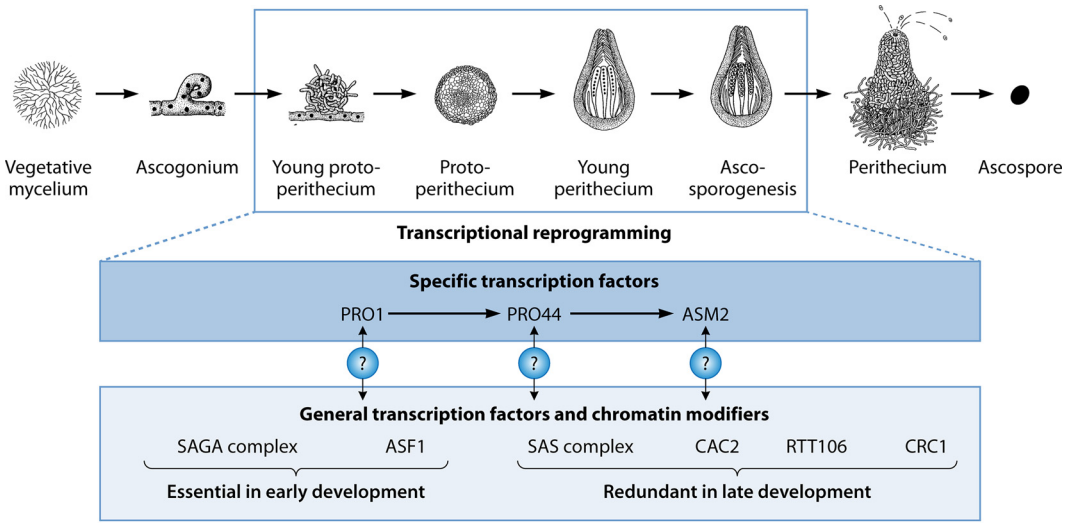

FIG 3 Transcriptional and chromatin control during fruiting body development in *Sordaria macrospora*. The top row shows the life cycle of *S. macrospora*, which is completed in 7 days under laboratory conditions. The transcription factors PRO1, PRO44, and ASM2 have been shown to be involved in fruiting body formation, with *pro44* transcript levels depending on *pro1* and *asm2* transcript levels depending on *pro44* (see the text). (Subunits of) chromatin modifiers and general transcription factors in the bottom row are involved in fruiting body formation at different developmental stages (see the text). Blue circles indicate as-yet-unknown factors connecting the activities of specific transcription factors and chromatin modifiers. (Pictures of life cycle stages republished from *Applied Microbiology and Biotechnology* [107]).

blocks mostly at the early stages of fruiting body development (20, 96–103) (Table 1). Thus, similar to *pro1*, *pro44* encodes a conserved developmental transcription factor, and the expression of *pro44* in young fruiting bodies is dependent on *pro1* (Fig. 3). Transcriptome analysis of a Δpro44 mutant identified the transcription factor gene *asm2* among genes that are dependent on *pro44* for upregulation in young fruiting bodies (59). Similar to *pro1*, *asm2* encodes a $Zn(II)_2Cys_6$ zinc cluster transcription factor, but in contrast to *pro1*, it is not required for early fruiting body development but is involved in ascospore maturation (59, 117). Thus, a transcription factor cascade including PRO1, PRO44, and ASM2 is involved in fruiting body development, although it is not yet clear if the activation of the more downstream-acting transcription factors is achieved directly or indirectly (Fig. 3).

Through comparative transcriptomics analyses, two chromatin modifiers that are essential for sexual development in *S. macrospora* were identified (28, 32, 117) (Table 2). The histone chaperone ASF1 and the SAGA complex subunit SPT3 are involved in the early steps of fruiting body development (Fig. 3), similar to PRO1 and PRO44. However, a transcriptomics analysis of Δasf1 and Δpro44 mutants showed distinct expression patterns in the mutant strains, pointing to the involvement of ASF1 and PRO44 in different aspects of development (59).

ASF1 is a conserved eukaryotic histone chaperone that binds to histones H3 and H4 and is involved in the assembly and disassembly of nucleosomes (118, 119). In addition, it can interact with nonhistone proteins and mediate their chromatin-related functions, e.g., histone acetylation through interaction with the histone acetyltransferase Rtt109 from *Saccharomyces cerevisiae* (120). However, the connection between the molecular function of ASF1 and its role in fruiting body development is not yet clear. It was hypothesized that the lack of *asf1* might lead to changes in nucleosome positioning, thereby preventing the chromatin changes required for correct gene expression during development. However, micrococcal nuclease sequencing to determine nucleosome positions in the wild type and the Δasf1 mutant showed no significant differences in nucleosome spacing and positioning around transcriptional start sites, making this hypothesis unlikely (59). Through bisulfite sequencing, reduced cytosine methylation levels were identified in the Δasf1 mutant, but whether these have any functional consequences remains to be elucidated (59).

In addition to the early-acting chromatin modifiers ASF1 and SPT3, four chromatin modifiers that have redundant functions later in sexual development were identified in

S. macrospora (Fig. 3 and Table 2). Single mutants of the histone chaperone genes *cac2* and *rtt106* as well as the chromatin modifier genes *crc1* and *scm1* are fertile, as are all combinations of double mutants (28, 59). However, triple mutants show reduced fruiting body formation, and the corresponding quadruple mutant is completely sterile (32). Thus, it seems likely that there are certain requirements for chromatin structure and modifications that allow fruiting body formation to proceed. This might include the possibility that the establishment and maintenance of distinct cell types and stages within the fruiting body require cell type-specific chromatin occupancy and accessibility landscapes, as found for multicellular plants and animals (121–124). One might also hypothesize that the activities of specific transcription factors and chromatin modifiers have to be coordinated, but the molecular basis of these putative interactions is not yet clear (Fig. 3). Future experiments to prove or disprove these hypotheses could include analyses of DNA and histone modifications as well as three-dimensional chromatin structures in the wild type and mutants under conditions of fruiting body development. It would also be important to generate data at high spatial and temporal resolutions, ideally at the single-cell level for different cell types during different stages of development.

TRANSCRIPTION FACTOR NETWORKS THAT REGULATE MUSHROOM FORMATION IN AGARICOMYCETES

Similar to ascomycetes, the first transcription factors with a role in fruiting body formation that were identified in basidiomycetes were mating type genes, in this case, the homeodomain protein-encoding genes of the *HD* mating type locus that were analyzed in the agaricomycetes *Coprinopsis cinerea* and *Schizophyllum commune* (125–127). However, even though transcription factor networks in basidiomycete development are less well known than those for ascomycetes, in the last 2 decades, a number of other transcription factors as well as chromatin modifiers involved in mushroom formation were identified in the two model species *C. cinerea* and *S. commune* (Fig. 4) (11). In *S. commune*, a network of transcription factors acting at different stages of development could be established based on transcriptome data of wild-type and mutant strains (128–130) (Fig. 4). While several transcription factor genes, for example, *wc-2*, *ada1*, *nsdD*, *pacC*, *rco-1*, and *swi6* (Table 1), are involved in fruiting body formation in both ascomycetes and basidiomycetes, the majority of the developmental transcription factors identified in *S. commune* do not have direct orthologs in ascomycetes (130). This is consistent with the hypothesis that fruiting body formation evolved independently in asco- and basidiomycetes based on the gene repertoire of a common ancestor with a predisposition for the evolution of multicellular development (3, 12).

In addition to the established model organisms *S. commune* and *C. cinerea*, a number of other mushroom-forming basidiomycetes have been used to analyze the role of transcription factors and chromatin modifiers in fruiting body development, for example, in several studies using RNA interference (RNAi) to knock down genes in *Flammulina* species (131–134) (Tables 1 and 2). For the edible mushroom *Cyclocybe aegerita*, transcriptomics data suggest that a transcription factor network similar to that in *S. commune* might be active during fruiting body morphogenesis (135), and a recently developed transformation system for this fungus will make functional studies feasible (136).

CONCLUSIONS

Through a combination of forward and reverse genetics coupled with genome-wide analyses of gene expression or chromatin modifications, the developmental roles and molecular functions of many transcription factors and chromatin modifiers that play a role in fungal fruiting body development have been revealed. However, for none of the fungi studied so far do we have a complete picture where spatiotemporal events at the molecular level can explain developmental effects at the morphological level, e.g., transcription factor and/or chromatin modifier cascades in different cell

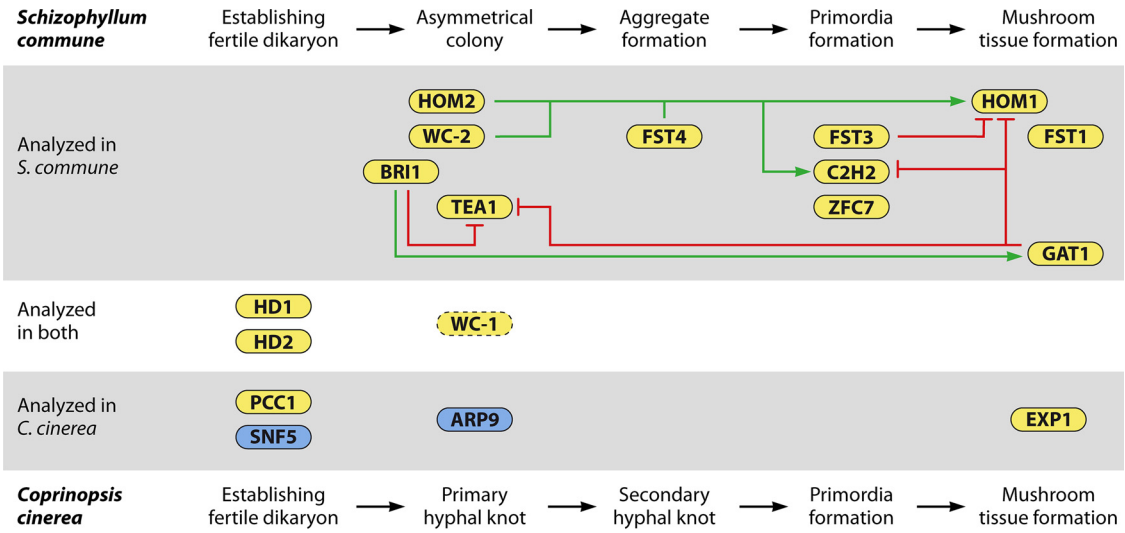

FIG 4 Transcription factors and chromatin modifiers in mushroom formation of *Schizophyllum commune* and *Coprinopsis cinerea*. Developmental stages of *S. commune* and *C. cinerea* are given at the top and bottom, respectively, according to previous studies (7, 10, 128). It is not yet clear if the differently named stages of development in *S. commune* and *C. cinerea* correspond to completely homologous structures (10). Proteins are given at the stages where mutant phenotypes occurred in the corresponding mutants. A yellow background denotes transcription factors, and a blue background denotes chromatin modifiers. The dashed outline around WC-1 indicates the lack of a GATA domain in the WC-1 homolog of basidiomycetes (Table 1). Green and red lines indicate (directly or indirectly) activating and repressing functions of transcription factors, as described previously (128–130).

types and at different developmental time points. But there is cause for optimism since method developments in a number of areas will now allow us to better address these questions. Techniques that might be especially helpful when applied to fruiting body differentiation are, for example, spatial transcriptomics (137) and novel microscopy techniques like light sheet microscopy, which can be used to study fluorescent molecules within intact three-dimensional structures and was recently applied to fruiting bodies of *S. macrospora* (138).

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