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Choose your own adventure: The role of histone modifications in yeast cell fate

Deepika Jaiswal[a,b], **Rashi Turniansky**[a,c], and **Erin M. Green**[a,d]

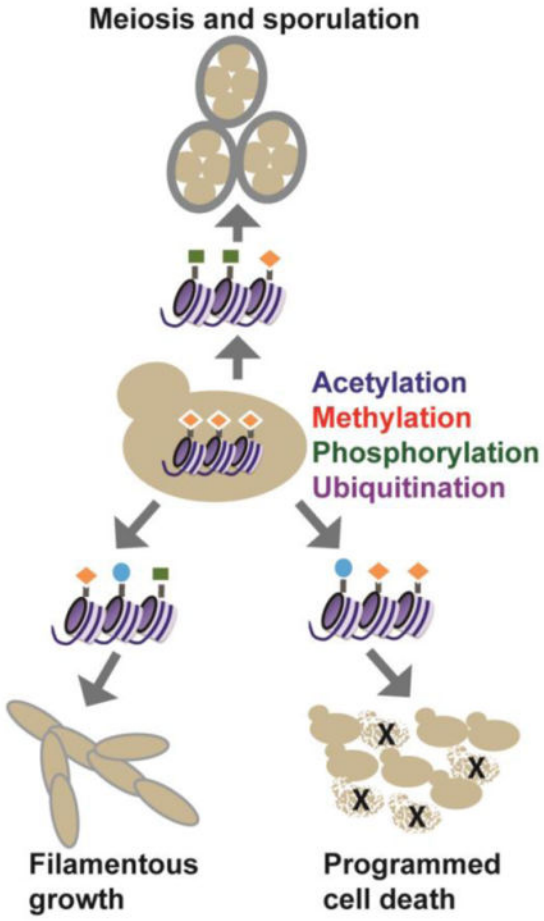
[a]Department of Biological Sciences, University of Maryland Baltimore County, 1000 Hilltop Circle, Baltimore, MD, USA, 21250

Abstract

When yeast cells are challenged by a fluctuating environment, signaling networks activate differentiation programs that promote their individual or collective survival. These programs include the initiation of meiotic sporulation, the formation of filamentous growth structures and the activation of programmed cell death pathways. The establishment and maintenance of these distinct cell fates are driven by massive gene expression programs that promote the necessary changes in morphology and physiology. While these genomic reprogramming events depend on a specialized network of transcription factors, a diverse set of chromatin regulators, including histone-modifying enzymes, chromatin remodelers and histone variants, also play essential roles. Here, we review the broad functions of histone modifications in initiating cell fate transitions, with particular focus on their contribution to the control of expression of key genes required for the differentiation programs and chromatin reorganization that accompanies these cell fates.

Graphical Abstract

[d]Corresponding author: egreen@umbc.edu; 410-455-1189.
[b]deej@umbc.edu
[c]iu26299@umbc.edu



Keywords

chromatin; post-translational modifications; meiosis; pseudohyphal growth; programmed cell death

In yeast cells, a series of intrinsic and extrinsic signals initiate cell fate changes in a fluctuating environment. The signals are transduced through integrated networks that ultimately converge on highly-regulated gene expression programs, which are orchestrated by transcription factors, chromatin-modifying enzymes, chromatin remodelers and regulatory RNAs, such as long non-coding RNAs (lncRNAs) [1–3]. The well-characterized genome and tractable genetics of *Sacchromyces cereviasie* has yielded numerous insights into the genomic reprogramming that occurs in response to diverse environmental signals, and the key mechanisms discovered parallel similar reprogramming events in metazoan systems [4]. Here, we discuss our current understanding of histone modifications and modifying enzymes in *S. cerevisiae* and review the role of chromatin dynamics during key cell fate decisions, including the differentiation of diploids into haploid spores (meiosis and sporulation), the formation of filamentous growth structures and the initiation of programmed cell death pathways. Nutrient availability dictates the cell's decision to enter

either the sporulation or filamentous growth program [5, 6], and reprogramming depends on the tightly-executed activation of key genes, such as *IME1* and *FLO11*, respectively, to drive the required cell cycle and morphological changes. Likewise, activation of programmed cell death pathways occurs in response to diverse cellular stresses in yeast and is accompanied by both transcriptional changes and massive changes to chromatin structure [7]. While these cell fate changes are orchestrated by a dedicated set of sequence-specific transcription factors, histone-modifying enzymes are critical to the reorganization of the chromatin landscape required for full execution of these fates.

Histone Modifications of *Saccharomyces cerevisiae*

The packaging of DNA into nucleosomes provides the structural foundation for genomic reprogramming events that underlie cell fate transitions. Nucleosomes are comprised of the four core histones H3, H4, H2A and H2B, and may also have one of two variant histones in budding yeast, Htz1 (H2A.Z), which marks heterochromatin-euchromatin boundaries and poised promoters [8, 9], or the centromere-specific H3 variant Cse4 (CENP-A) [10]. The role of individual nucleosomes in defining transcriptional states is determined by their level of histone modification, their position relative to defined sequence elements, the presence of histone variants and their interaction with the transcriptional machinery, all of which are regulated by the coordinated activity of chromatin-associated protein complexes and modifying enzymes [11, 12].

Histone-modifying enzymes, in particular, play a key role in integrating signals at chromatin through the dynamic process of post-translational modification (PTM), including methylation, acetylation, phosphorylation, and ubiquitination [1–3]. The enzymes that add histone PTMs are often referred to as writers and include histone methyltransferases (HMTs), histone acetyltransferases (HATs), kinases, and ubiquitin-protein transferases (UbTs). The marks are removed by erasers- histone demethylases (HDMs), histone deacetylases (HDACs), phosphatases, and deubiquitinases (DUbs)- allowing for dynamic regulation. Effector proteins, known as readers, are recruited to or stabilized at chromatin by these marks and act to transduce signals received at chromatin, governing such pathways as transcription and DNA repair. Reader proteins contain well-defined domains, such as bromodomains, chromodomains and PHD fingers, that recognize specific PTMs on histones [13–15]. Importantly, these domains are often found in writers and erasers, allowing for crosstalk between modifications and integrated signaling networks at chromatin.

As summarized in Table 1, a number of marks on the core histones have been extensively studied using proteomic and molecular techniques, and have well-characterized writers, erasers and readers. These marks, such as H3 and H4 acetylation, H3K4 and H3K36 methylation, are relatively abundant and have been implicated in diverse roles throughout the genome, especially in the realm of gene expression regulation. However, recent advances in proteomic techniques and other methods have revealed the presence of several previously unknown histone PTMs [16–20] that may act in a context-dependent manner. For example, newly-discovered acetylation at H4K44 has been identified in pre-meiotic and meiotic cells and is required for proper double strand break formation and recombination during meiosis [21]. Also, H4K5, K8 and K12 mono-methyl marks, catalyzed by Set5, which are present in

approximately 1% of nucleosomes genome-wide [22], are likely to function in a context-dependent manner. Set5's activity has been linked to stress responses and gene repression in coordination with Set1 [23], however the mechanism by which these methyl marks interpret and transduce signals at chromatin remains unclear.

The genome reprogramming events underlying cell fate decisions rely on both widespread changes to the epigenome, as well as targeted events that may be specific to environmental stimuli or the regulation of individual genomic regions. Marks that appear to be lowly abundant or present only during specialized cellular programs or stress responses may have unique, context-dependent roles in the genome. Additionally, increasing evidence indicates an extensive role for so-called histone-modifying enzymes in the post-translational modification of non-histone proteins, which has been linked to critical signaling pathways [24–28]. The kinetochore protein Dam1 is methylated by Set1, supporting a role for Set1 in chromosome segregation independent of H3K4 methylation [29]. As another example, phosphoenolpyruvate carboxykinase Pck1 is acetylated by the HAT Esa1 and deacetylated by the HDAC Sir2 to dynamically regulate its activity in gluconeogenesis [30]. Furthermore, there are numerous potential histone-modifying enzymes for which no substrates have been identified, such as the candidate methyltransfersases Set4 and Set6, and demethylase Ecm5, and also novel modifications, such as glutamate methylation and lysine succinylation [19, 31], for which the functional consequences are largely unclear. Altogether, these observations suggest that we have only begun to scratch the surface regarding the potential roles of histone modifications and histone-modifying enzymes in signaling networks that govern cell fate decisions and genomic reprogramming. Further investigation of these pathways in yeast is expected to reveal principles common to similar events in metazoan systems.

Nutrient-responsive signaling and chromatin states

Changes to nutrient availability trigger multiple responses that promote survival of yeast cells under fluctuating environmental conditions (Figure 1). For example, nitrogen depletion, the absence of glucose and the presence of a nonfermentable carbon source, such as acetate, stimulates entry into sporulation [5, 32], a specialized cell fate in which *MATa/α* diploid cells undergo a meiotic division to produce haploid progeny (spores), which are packaged into a protective ascus. Sporulation is characterized by a genetic reprogramming event in which hundreds of genes are induced or repressed in a precisely timed synchrony that controls the progression of meiosis and the morphological changes required for spore formation [33, 34]. Alternatively, a change in environmental conditions in which glucose is abundant, but nitrogen is still limiting, promotes the dimorphic transition of diploid cells from the yeast state to a pseudohyphal state, in which filamentous structures (pseudohyphae) form, adhere to other cells and solid surfaces, such as agar [35]. Similar to sporulation, the filamentous state is also driven by a signaling cascade that activates a gene expression program required for the morphological and physiological changes associated with the new polarized growth structures. In both cases, the nutrient-responsive signaling pathways converge on genes that underlie these cell fate transitions, *IME1* and *FLO11*, respectively. Below, we review the specific role of histone modifications in expression control of *IME1*

and *FLO11*, and highlight how the disruption of chromatin homeostasis alters the maintenance of the acquired cell fates.

Chromatin-based control of *IME1* expression, the meiotic master regulator

Sporulation occurs in three primary phases, defined as early, middle and late, which are each characterized by discrete events in meiosis and spore formation [5, 33, 36]. When the cell receives the necessary intrinsic (mating type and ploidy) and extrinsic (nutrient availability) signals (Figure 1), the transition from vegetative growth to the early phase of sporulation is marked by the rapid induction of *IME1*, the transcription factor which drives early gene expression required for entry into meiotic S phase [37–39]. The promoter of *IME1* consists of four upstream control sequences *(UCS*) which serve as the integration platform for the positive and negative signals regulating sporulation (Figure 2) [40, 41]. The action of the transcription factor Rme1, which is uniquely expressed in haploids, establishes the chromatin landscape regulating *IME1* expression. In haploid cells, *IME1* is strongly repressed by the binding of Rme1 to the *UCS* elements to prevent the aberrant activation of the sporulation program [42–44]. The mechanism by which Rme1 repressed *IME1* remained unknown for some time, however a breakthrough revealed that Rme1 promotes transcription of a long non-coding RNA (lncRNA). The transcription of this lncRNA, *IRT1*, from the upstream control sequences of *IME1* generates a repressive environment by interfering with activator recruitment to the *IME1* promoter and by the co-transcriptional recruitment of HMT and HDAC complexes (Figure 2) [45]. Specifically, *IRT1* transcription promotes recruitment of Set2 and Set3, each of which generate repressive environments through interactions of histone methyl marks and chromatin reader domains [46–48]. vanWerven [45] and colleagues propose that co-transcriptional recruitment of Set1 during *IRT1* induction deposits H3K4me2 at the 5′ end of the *IME1* promoter, which stabilizes the Set3 complex and its HDAC activity [48], causing local repression. Likewise, co-transcriptional recruitment of Set2, which deposits H3K36me3, is postulated to promote association of the Rpd3(S) HDAC complex (as distinguished from Rpd3(L), a larger complex with distinct interactions) over the *IRT1* coding region [45–47]. This work therefore uncovered a key mechanism of the combinatorial role of histone modifications in the control of a critical cell fate regulator.

A second pathway reported to repress *IME1* in vegetatively-growing cells involves the Tup1/Ssn6 co-repressor complex [49, 50]. Cells lacking *TUP1* show decreased nucleosome occupancy of the *IME1* promoter, and increased recruitment of RNA pol II, consistent with constitutive expression of *IME1* [50]. However, the mechanism by which Tup1 associates with *IME1* is unclear, and whether it recruits other chromatin factors has not yet been investigated. Tup1 has been shown to play diverse roles at other nutrient-responsive promoters, such as driving the association of HDACs with *FLO1* [51, 52] and cooperating with the SWR1 complex for deposition of H2A.Z (Htz1) at the *GAL1* and *SUC2* promoters [53]. As a repressor of *IME1*, Tup1 has been linked to nutrient-sensing through PKA and TOR complex signaling networks [50], whereas Rme1 levels are responsive to mating type and ploidy [42, 54, 55]. These two DNA-binding proteins therefore represent different nodes of signal integration which promote the required chromatin state at the *IME1* promoter in response to both extrinsic and intrinsic signals.

Histone modifications and meiotic progression

With the onset of the sporulation program, Ime1 activates a plethora of genes involved in meiotic DNA replication, chromosome remodeling and homologous recombination [5, 32]. A number of other chromatin-dependent mechanisms control the transcriptional dynamics of this cascade. Early and middle genes are also repressed by Ume6, a DNA binding protein that tethers Rpd3 and the chromatin remodeler Isw2 to promoter regions, resulting in histone deacetylation, chromatin compaction and occlusion of the TATA box [56, 57]. As Ime1 levels increase, Ume6 is targeted for degradation by the anaphase-promoting complex/cyclosome (APC/C) ubiquitin ligase activity, in a manner partially dependent on Ime1, and early gene transcription is initiated [58]. Intriguingly, Ume6 is targeted by the HAT Gcn5 for acetylation, and can be deacetylated by Rpd3 [59]. Lysine acetylation of Ume6 appears to promote its destruction, revealing that a non-histone target of Gcn5 may be a critical substrate determining its role in early gene expression, and that Rpd3 has an additional role in stabilizing Ume6 prior to the onset of the meiotic program [59]. Acetylation at additional lysines of Ume6 also appears to release it from its DNA binding sites, providing another mechanism for the rapid inactivation of Ume6 and ensuring proper timing of the transcriptional cascade [60]. These observations highlight the potential contribution of non-histone targets of chromatin-modifying enzymes to the regulation of reprogramming events.

Middle genes are repressed by the Sum1 transcriptional repressor, which binds DNA and tethers the HDAC Hst1 to middle gene promoters through an interaction with the adaptor protein Rfm1 [61–63]. Sum1-Rfm1-Hst1 and Ume6-mediated mechanisms have been reported to repress the middle sporulation gene *NDT80* [64], which encodes a master regulator transcription factor that activates a series of middle genes required for nuclear division and spore formation [63, 65]. Beyond this, we still have relatively little knowledge regarding the role of chromatin modifiers during middle, and also late-stage, gene expression. As an example, the methyltransferase Set1 has been implicated in repressing middle gene expression [66], however the mechanism by which it specifically represses this gene set has not been reported. While Set1's activity promotes meiotic progression, this is primarily thought to be due to the role of H3K4 methylation in recombination and double strand break repair [67, 68], whereas the function or Set1 in meiotic gene expression control is unclear.

In addition to the large-scale changes in gene expression that accompany the sporulation program, massive chromosomal rearrangements, which rely on critical genome integrity pathways, also occur during meiosis. While the role of chromatin in these processes has been reviewed elsewhere [69], genetic and proteomic screens focused on meiotic chromatin and sporulation have uncovered previously-unknown modifications. These approaches have revealed that phosphorylation at H4S1 is required for post-meiotic chromatin compaction and spore maturation [70], H3T11ph has been implicated in meiotic progression [71] and H4K44ac is associated with meiotic recombination [21]. These studies not only elucidate key mechanisms of meiotic chromosomal reorganization, but also underscore the notion that novel, context-dependent histone modifications may be discovered through analysis of specialized cell fates.

Chromatin-based regulation of *FLO11*, initiator of filamentous growth

High expression levels of *FLO11*, a cell surface glycoprotein that mediates cell-cell and cell-surface adhesion, causes flocculation, haploid invasion, biofilm formation and diploid pseudohyphal, or filamentous, growth [6, 72, 73]. In *S. cerevisiae*, a family of related genes that encode adhesion proteins, *FLO1*, *FLO5*, *FLO9* and *FLO10*, are not expressed due to their proximity to telomeres and position-dependent gene silencing [74]. This gene family is similar to the *ALS* and *EPA* adhesin gene families in the human pathogens *Candida albicans* and *Candida glibrata*, respectively. In particular, the *EPA* genes of *C. glibrata* are also adjacent to telomeres and subject to metastable gene silencing, with activation of individual *EPA* genes occurring in different host environments and generating cell surface variation for the pathogen [75]. Understanding the regulatory mechanisms controlling expression of these gene families is therefore of high clinical relevance due to their role in promoting adherence to host cells, such as human epithelial cells, and biofilm formation on abiotic surfaces, including implanted medical devices [76].

Similar to *IME1*, *FLO11* expression is controlled by a very large, complex promoter that receives input from multiple nutrient-responsive signaling pathways, including the MAPK, SNF, TOR and RAS/cAMP-PKA pathways [6, 77]. Its expression levels are modulated through the coordinated activity of transcription factors, such as Flo8, which govern the contributions of histone-modifying enzymes, chromatin remodelers and lncRNAs to *FLO11* expression (Figure 3). While genetic screens have revealed potential involvement of the HAT Gcn5, the histone variant Htz1 and chromatin remodelers RSC and SWI/SNF in *FLO11* expression [78, 79], HDACs have the most well-documented roles in both repressing and activating *FLO11* expression. Epigenetic silencing of *FLO11* was first linked to the HDAC Hda1 [80], however other HDACs including Hos2 and Rpd3 have been implicated in its expression control. Interestingly, mutations of components of the Rpd3(L) complex (a larger Rpd3 complex than Rpd3(S) with unique interactions at chromatin) further repress *FLO11* [79], and combined deletion of Rpd3(L) and Hda1 demonstrates their partially overlapping functions in nucleosome depletion at the promoter and *FLO11* activation [81]. The paradoxical function of Rpd3(L) in *FLO11* activation was found to be due to the upstream expression of the lncRNA *ICR1*, in a manner dependent on the competing activity of two transcription factors [82, 83] (Figure 3). In the absence of the repressive chromatin environment generated by Rpd3(L), *ICR1* is transcribed and prevents expression of *FLO11* by occluding key *trans*-acting factors, such as TBP and the Flo8 transcriptional activator, from the promoter region [82, 83]. While these studies revealed a critical link between histone deacetylation and lncRNA-mediated repression of *FLO11*, there remain many open questions regarding the roles of other HDACs in this regulatory network. As one example, the Set3 complex, of which the HDAC Hos2 is a member, promotes filamentous growth in *Candida albicans* [84] and is required for lncRNA-mediated repression of *IME1*, yet its potential role in *FLO11* expression control is unclear.

Recent genetic studies have implicated other types of chromatin-modifying enzymes in regulating *FLO11* expression. The HAT Gcn5 has been reported to negatively regulate *ICR1* expression, thereby promoting *FLO11* transcriptional activation [85], most likely through regulation of a second ncRNA. Additionally, deletion of the demethylase *JHD2* or a

component of the CDK8 submodule of RNA pol II, *SSN8*, results in elevated H3K4me3 near the *FLO11* transcription start site (TSS) and constitutive activation of *FLO11* [86]. These data suggest a direct role for H3K4me3 in *FLO11* activation, although its potential contribution to lncRNA-dependent regulation of *FLO11* has not yet been investigated.

Chromatin dynamics during programmed cell death

Programmed cell death (PCD) in metazoans has key developmental roles, such as promoting proper tissue architecture and the destruction of damaged cells, and aberrant regulation of PCD pathways is implicated in diseases including cancer and neurodegenerative disorders [7, 87]. Based on the lack of some of the cell death machinery, it was not clear that *S. cerevisiae* exhibited PCD until apoptosis-related phenotypes were observed in a *CDC48* mutant. Observed phenotypes included DNA fragmentation, chromatin compaction, increased reactive oxygen species and phosphatidylserine externalization [88]. It is now appreciated that budding yeast undergo multiple types of cell death, including caspase-dependent and caspase-independent intrinsic apoptosis, autophagic cell death and regulated necrosis [89]. These pathways are activated in response to a multitude of intrinsic and extrinsic signals, including oxidative and osmotic stress, acetic acid and aging, among others [7]. While PCD is clearly not required for tissue architecture in unicellular yeasts, it may act to eliminate old, damaged or nonreplicative cells, releasing nutrients to younger, replicative cells and promoting their survival [7, 89]. Interestingly, many filamentous fungi have more similar PCD mechanisms to animal cells than budding yeast, and PCD has frequently been observed to be important for pathogenic life cycles and the formation of multicellular-like structures in these organisms [90].

Histone modifications have the potential to be important for multiple components of PCD, including gene expression associated with stress responses, transcription of apoptotic regulators and the processes of chromatin condensation and DNA fragmentation. The Ste20 kinase phosphorylates H2BS10 in apoptotic chromatin in yeast [91], which is analogous to human H2BS14ph, catalyzed by the caspase-activated kinase Mst1 [92]. It was also found that deacetylation at H2BK11 by the HDAC Hos3 is a prerequisite for Ste20-mediated phosphorylation at H2BS10 [93]. This crosstalk between histone modifications appears to promote peroxide-mediated apoptosis, with H2BS10ph proposed to have a role in chromatin condensation [91, 93]. However, this mechanism has been debated [94], and it is unclear whether other substrates of Mst1 (or Ste20) may promote PCD-associated chromatin compaction [94, 95].

In a similar example of modification cross-talk, H2BK123Ub by Bre1 was reported to be an anti-apoptotic mark, with loss of the mark suspected to promote DNA damage or transcriptional deregulation of apoptotic factors [96]. H2BK123Ub precedes Set1-dependent H3K4 methylation, as well as H3K79 methylation catalyzed by Dot1 [97]. Subsequent investigation revealed that *BRE1* mutants lacking H2BK123Ub undergo PCD due to the loss of H3K4 methylation by Set1 [98]. The loss of Set1 promotes PCD in a manner dependent on both Dot1/H3K79me and the checkpoint kinase Rad9. Increased PCD in *SET1* mutants can be rescued by simultaneous inactivation of Nuc1, the yeast ortholog of enodonuclease G associated with DNA fragmentation [98]. Although further experiments are required, these

data suggest that Set1 and H3K4 methylation may play a global role in promoting proper chromatin structure to prevent PCD-mediated condensation and fragmentation of DNA.

The studies conducted to date on histone modifications linked to yeast PCD have revealed that both program-specific (H2BS10ph) and general (H2BK123Ub, H3K4me) modifications make contributions to this developmental pathway and that cross-talk between modifications may serve to integrate multiple inputs from the signaling networks activating PCD. This highlights the need to comprehensively investigate the full complement of histone modifications participating in PCD. Additionally, acetylation of the autophagic protein Atg3 by the HAT Esa1 has been linked to the control of autophagy [99], indicating that there may be more diverse roles for typical chromatin-modifying enzymes that remain to be discovered in cell death pathways.

Concluding Remarks

We have reviewed a number of significant advances in our understanding of chromatin modifications critical to yeast cell fates. In the representative cases cited here, key themes emerge and areas for further exploration are highlighted. First, while chromatin-modifying enzymes such as Rpd3, Gcn5, Set1 and Set2 have broad functions throughout the genome, they also have critical context-dependent roles, responding to specific cues and acting within distinct genomic regions to advance cell fate programs. It is also evident that chromatin modifiers integrate signals from multiple sources, and their activity is governed by complex networks that signal to transcription factors, lncRNAs, and likely other factors, to promote the appropriate changes in the local chromatin landscape.

While substantial progress has been made in understanding the functions of diverse histone modifications in meiosis and sporulation, pseudohyphal differentiation and programmed cell death pathways in yeast, it is clear that there are still many open questions. Continued investigation into the new modifications revealed by high-resolution proteomics may elucidate state-specific roles for these marks, particularly for those that are lowly abundant or enriched in certain environmental conditions. Moreover, further understanding of the role of non-histone PTMs catalyzed by enzymes classified as chromatin modifiers may uncover additional regulatory nodes critical to these cell fate programs and diversify the biological functions of these enzymes. And finally, given the role of nutritional cues in these cell fate signaling networks, it will be critical to delineate how metabolic changes within the cell affect chromatin-modifying enzymes. There is increasing evidence that metabolic changes can signal directly to these enzymes, potentially regulating their activity, localization or co-factor availability to drive cell fate changes [100, 101]. The high conservation of chromatin-modifying pathways and the breadth of knowledge regarding the genome and epigenome suggest that continued investigation of histone modifications in yeast will yield key insights into cell fate decisions in diverse organisms.

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Abbreviations

lncRNA	long non-coding ribonucleic acid
DNA	deoxyribonucleic acid
PTM	post-translational modification
HAT	histone acetyltransferase
HDAC	histone deacteylase
HMT	histone methyltransferase
HDM	histone demethylase
UbT	ubiquitin-protein transferase
DUB	deubiquinase
me	methylation
ac	acetylation
ph	phosphorylation
MAPK	mitogen activated protein kinase
TOR	target of rapamycin
PKA	protein kinase A
UCS	upstream control sequence
APC/C	anaphase-promoting complex/cyclosome
PCD	programmed cell death
kb	kilobases

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Highlights

- Diverse histone modifications in *S. cerevisiae* regulate cell fate decisions
- Histone modifying enzymes are targeted by intrinsic and extrinsic signaling cues to regulate transcription and chromatin reorganization
- Histone modifications play critical roles in genomic reprogramming during meiotic sporulation, filamentous growth and programmed cell death

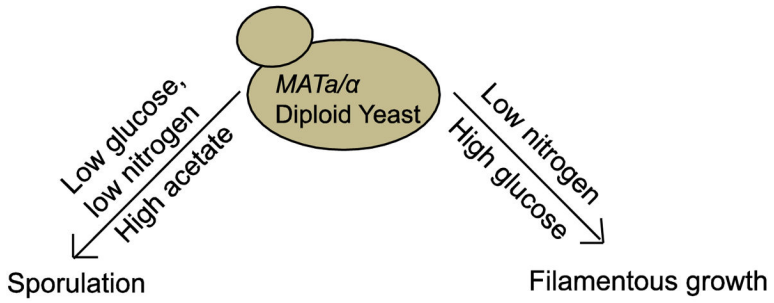

Figure 1. Changes in nutrient availability promote alternative differentiation pathways in diploid yeast

Low levels of nitrogen and glucose in the presence of a nonfermentable carbon source such as acetate promote meiotic division and sporulation. When glucose levels are high but nitrogen is limiting, filamentous growth is initiated, in which pseudohyphae form and can become invasive.

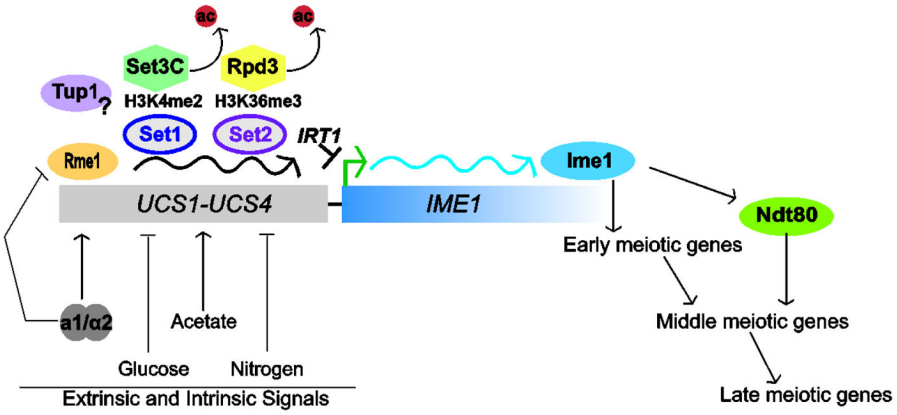

Figure 2. Regulation of *IME1* by signaling to chromatin modifiers

Intrinsic and extrinsic signals received by the upstream control sequences 1 through 4 (*UCS1-4*) of the *IME1* regulatory region. Nutrient signaling and the transcriptional regulators a1/α2 and Rme1 are essential to maintaining expression patterns of *IME1*. In diploids, the a1/α2 heterodimer, encoded by the *MATa/MATα* locus releases Rme1-mediated repression of *IME1*. In haploid cells, Rme1 promotes the expression of the lncRNA *IRT1* from this region. Histone methyltransferases Set1 and Set2 are recruited co-transcriptionally and their respective methyl marks promote HDAC containing complexes Set3C and Rpd3C(L) chromatin association, repressing *IME1* expression. Tup1 is also postulated to repress *IME1*, potentially as a parallel pathway promoting HDAC recruitment, however its precise role is unknown. *IME1* expression initiates a transcriptional cascade, including inducing *NDT80*, which leads to the sporulation-specific gene expression program required for the meiotic divisions and spore formation.

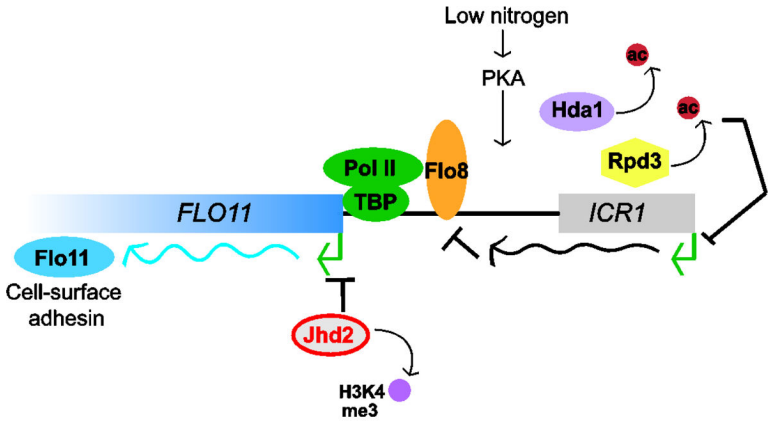

Figure 3. Chromatin-based regulation of *FLO11*

Low nitrogen availability regulates the *FLO11* promoter through PKA-mediated signaling to multiple transcription factors, including Flo8 (extensive signaling network regulation of *FLO11* is reviewed elsewhere [6, 77]). Transcription of the lncRNA *ICR1* approximately 3kb upstream of the *FLO11* transcription start site (TSS) occludes binding of the activator Flo8 and TBP. *ICR1* expression is repressed by Rpd3C(S) deacetylation, promoting *FLO11* activation. Deacetylation by Hda1 also promotes *FLO11* expression and dynamic regulation of H3K4me3 at the TSS by demethylase Jhd2 has been linked to *FLO11* activation.

Table 1

Histone modifications of *Saccharomyces cerevisiae*. Acetylation, methylation, phosphorylation and ubiquitination of the core histones from budding yeast are shown. For methylation, the extent of methylation is indicated in parentheses. All modifications listed have been detected using mass spectrometry and/or antibody-based methods and known writers and erasers are indicated.

Histone	Residue	Modification	Writer	Eraser	References
H3	K4	Methylation (me1-3)	Set1	Jhd2	[102–107]
H3	K4	Acetylation	Gcn5, Rtt109	Hst1, Sir2	[108]
H3	K9	Acetylation	Gcn5 Rtt109	Rpd3	[109–112]
H3	S10	Phosphorylation	Snf1, Ipl1	Glc7	[113, 114]
H3	T11	Phosphorylation	Mek1, Pkm2	?	[71, 100]
H3	K14	Acetylation	Gcn5	Rpd3	[115]
H3	K18	Acetylation	Gcn5	Rpd3	[111, 115]
H3	K23	Acetylation	Gcn5	Rpd3	[109, 111]
H3	K27	Acetylation	Gcn5	Rpd3	[111]
H3	K36	Methylation (me1-3)	Set2	Rph1, Jhd1	[116–118]
H3	K36	Acetylation	Gcn5	?	[119]
H3	T45	Phosphorylation	Cdc7	?	[120]
H3	K56	Acetylation	Rtt109	Hst3, Hst4	[121–124]
H3	K79	Methylation (me1-3)	Dot1	?	[125–128]
H3	Y99	Phosphorylation	Rad53	?	[129]
H4	S1	Phosphorylation	Cka1	?	[130]
H4	R3	Methylation (me1)	Rmt1	?	[127]
H4	K5	Methylation (me1)	Set5	?	[22]
H4	K5	Acetylation	Esa1, Hat1	Hos2, Rpd3	[111, 131–134]
H4	K8	Methylation (me1)	Set5	?	[22]
H4	K8	Acetylation	Esa1	Hos2, Rpd3	[111] [131, 132, 134]
H4	K12	Methylation (me1)	Set5	?	[22]
H4	K12	Acetylation	Esa1, Hat1	Hos2, Rpd3	[111, 131, 132, 134]
H4	K16	Acetylation	Sas2	Sir2	[135–138]

Histone	Residue	Modification	Writer	Eraser	References
H4	K20	Methylation (me1)	?	?	[139]
H4	K20	Acetylation	?	?	[16]
H4	K44	Acetylation	?	?	[21]
H2A	K7	Acetylation	Esa1	Rpd3	[111]
H2A	Y58	Phosphorylation	Cka1	?	[140]
H2A	Q105	Methylation	Nop1	?	[31]
H2A	S121	Phosphorylation	?	?	[141]
H2A	S128	Phosphorylation	Mec1	?	[142]
H2B	S10	Phosphorylation	Ste20	?	[91, 92]
H2B	K11	Acetylation	Gcn5	Hda1, Hos3	[93, 111]
H2B	K16	Acetylation	Gcn5, Esa1	Hda1, Rpd3	[111, 143]
H2B	K37	Methylation (me2)	?	?	[144]
H2B	K123	Ubiquitination	Rad6, Bre1	Ubp8, Ubp10	[145–148]