

Daughter-specific repression of *Saccharomyces cerevisiae* *HO*: Ash1 is the commander

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The GATA-1-like factor Ash1 is a repressor of the *HO* gene, which encodes an endonuclease that is responsible for mating-type switching in the yeast *Saccharomyces cerevisiae*. A multi-step programme, which involves a macromolecular protein complex, the secondary structure of *ASH1* mRNA and the cell cytoskeleton, enables Ash1 to asymmetrically localize to the daughter cell nucleus in late anaphase and to repress *HO* transcription. The resulting Ash1 activity prevents the daughter cell from switching mating type. How does Ash1 inhibit transcription of *HO* exclusively in the daughter cell? In this review, a speculative model is proposed and discussed. Through its action as a daughter-specific repressor, Ash1 can be considered to be an ancestral regulator of cell fate in eukaryotes.

Keywords: Ash1; repression; transcription; asymmetry; yeast

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Introduction

The yeast *Saccharomyces cerevisiae* propagates as haploid **a**, haploid α or diploid **a/α** cell types. During its vegetative cycle, the diploid **a/α** cells undergo meiosis and sporulation to produce an ascus that contains four haploid spores. After germination, two of these spores become cell type **a** and the other two α . These new **a** and α spores divide to produce a mother and a daughter cell that have the same mating type as the original spore (Fig 1). During the second mitotic division, the mother switches mating type before S phase, whereas the daughter undergoes DNA duplication, budding and division without switching mating type. Four cells are then generated after two mitotic divisions of the original spore: two with the **a** mating type and two with the α .

The cell mating type is determined by the *MAT* locus. The interconversion between *MATa* and *MATα* in homothallic strains is due to the protein product of the *HO* gene, which is an endonuclease that causes mating-type switching in *S. cerevisiae* (Herskowitz, 1988; Nasmyth, 1982). Mating-type interconversion occurs exclusively in mother cells, and never in daughters or in spores; indeed, *HO* is expressed exclusively in mother cells, and only during late G1. Mother/daughter asymmetric *HO* expression is due to the protein product of the *HO*-specific repressor gene, known as the asymmetric synthesis of *HO* (Ash1).

Asymmetric *HO* expression: the discovery of *ASH1* and *SHE*

How *HO* is expressed exclusively in mother cells was an intriguing question until the discovery of the *ASH1* and the Swi5p-dependent *HO* expression (*SHE*) genes by genetic screening. Indeed, these discoveries were a milestone in the study of asymmetry and cell-fate determination in eukaryotic cells. Even in a simple organism such as *S. cerevisiae*, the fate of the two newborn cells is controlled at each mitotic division by a tight programme, which is orchestrated by the gene products of *ASH1* and *SHE*.

ASH1 was identified through the isolation of mutants, the daughter cells of which were defective in *HO* repression and so were able to switch mating type. Ash1 is a repressor that inhibits *HO* transcription through its asymmetric accumulation in the daughter nucleus in late anaphase (Bobola *et al*, 1996; Sil & Herskowitz, 1996). It is also required for pseudohyphal growth (Chandarlapaty & Errede, 1998). Ash1 contains a region that is highly homologous to the zinc-finger domain of the erythroid cell nuclear protein GATA-1 (Bobola *et al*, 1996; Sil & Herskowitz, 1996). The GATA motif is a *cis* regulatory element that is located in enhancers, insulators and the 5' and 3' regions of genes. It was first found in globin gene promoters and in other erythroid-expressed non-globin genes (Orkin, 1992). All the GATA-like factors bind to the GATA motif and either activate or repress transcription. Recently, the Ash1-binding consensus sequence, YTGAT, was identified within the *HO* promoter. This consensus, which is related to the canonical (A/T)GATA(A/G) sequence bound by most GATA factors, is present at least 20 times within the upstream repression sequence 1 (URS1) region of the *HO* promoter (Maxon & Herskowitz, 2001). The *HO* promoter can be divided into two *cis* regulatory regions, URS1 and URS2, which are bound by many regulatory factors and which determine the expression of *HO* in late G1, exclusively in the mother cell (Nasmyth, 1993). Ash1 has two principal domains: the C-terminal DNA-binding domain, which binds to the YTGAT consensus within URS1 of *HO*; and the amino-terminal domain, which is devoted to the repression of *HO* transcription (Maxon & Herskowitz, 2001). Remarkably, the YTGAT consensus of *HO* is located within a chromosomal region that is highly regulated by nucleosome modifications (Cosma *et al*, 1999; Krebs *et al*, 1999); similarly, the GATA motifs of human α - and β -globin gene clusters are found in the locus control regions within nucleosome-modified regions (Orkin, 1992).

The asymmetric accumulation of Ash1 in late anaphase is due to the products of five genes, *SHE1–SHE5*, each of which has a specific function (Jansen *et al*, 1996). *SHE* mutants fail to restrict Ash1 to the

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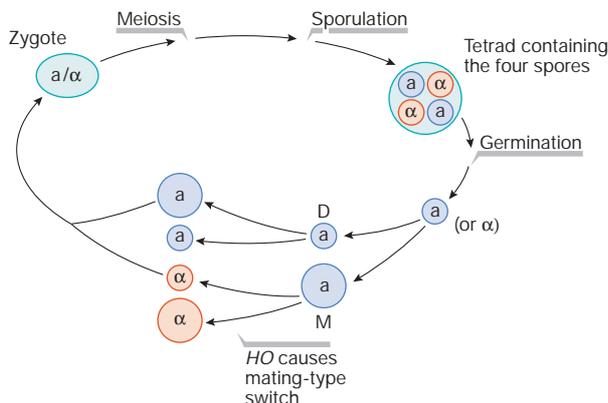


Fig 1 | The budding yeast life cycle. The zygote undergoes meiosis and sporulation. Four spores germinate from the ascus. Each spore divides, producing a mother (M) and a daughter (D) cell without changing mating type. During the second mitotic division, only the mother cell can switch mating type before division.

daughters therefore *HO* transcription is repressed in both mother and daughter cells. The She proteins are cytoplasmic, with She1 and She3 accumulating preferentially in the bud. *SHE1* encodes the actin-based myosin motor protein She1/Myo4, and *SHE5* encodes the septin protein Bni1, which is required for cytokinesis. *SHE4* encodes a protein that binds to some motor myosins, including She1/Myo4 (Toi *et al*, 2003; Wesche *et al*, 2003), and *she4* mutants show defects in endocytosis and in the polarization of the actin cytoskeleton (Wendland *et al*, 1996). Finally, *SHE2* and *SHE3* were originally classified as unknown open reading frames (Jansen *et al*, 1996).

The identification of *ASH1* and the *SHE* genes by genetic screening and the initial studies on the functions of their protein products raised many questions as to how the asymmetric localization of Ash1 is achieved. Many other cases of regulation of gene expression through the asymmetric localization of mRNA are known; to ensure cellular or developmental-stage specificity, the mRNA is actively transported to where the gene product is needed. This is a post-transcriptional level of regulation of gene transcription that occurs in a large variety of organisms (Kloc *et al*, 2002). The key elements that cooperate in the asymmetric localization of Ash1 have been identified as follows: the *cis*-acting sequences within *ASH1* mRNA; the secondary structure of the *ASH1* mRNA; the cell cytoskeleton; a macromolecular complex that includes the She1–3 proteins; and finally, factors that are required for the recognition of *ASH1* mRNA in the nucleus and for *ASH1* mRNA anchoring and translation at the bud tip.

Localization elements of *ASH1* mRNA and the cytoskeleton

Ash1 localizes to the nucleus in the bud in late anaphase. It soon became clear that this asymmetric localization of Ash1 is due to the asymmetric localization of the *ASH1* mRNA. The latter is assembled into particles that associate with the cell cortex of the distal tip in late anaphase (Long *et al*, 1997; Takizawa *et al*, 1997). Initially, it was observed that the 3'-untranslated region (UTR) of *ASH1* mRNA was able to localize a hybrid mRNA (formed by the *ASH1* 3'-UTR fused either to the *LacZ* coding sequence or to green fluorescent protein (GFP)) to the bud in uninucleate cells and to the daughters in

binucleate cells. This localization was dependent on *SHE1* (Long *et al*, 1997; Takizawa *et al*, 1997).

Further studies have shown that there are four minimal localization sequences within the *ASH1* mRNA. In addition to the minimal 3'-UTR region, known as E3 or *ASH1* U, which spans seven nucleotides before and 67 after the stop codon, there are three elements within the *ASH1* mRNA that are present within the carboxy- and N-terminal domains of Ash1. The minimum size of these additional localization elements has been determined, and they have been named as E1 (spanning between nucleotides 598 and 750) in the N-domain, and E2A (between 1044 and 1196) and E2B (between 1175 and 1447) in the C-domain (Fig 2A). When fused to *LacZ* or GFP reporter genes, all of these elements are equally able to localize the hybrid mRNA in a *SHE1*-dependent manner (Chartrand *et al*, 1999; Gonzalez *et al*, 1999).

The secondary structure within such localization elements is important for their function (Kloc *et al*, 2002), and the ability of the E3 element to fold into stem-loop-containing double-stranded regions has been studied in detail. This secondary structure is crucial for *ASH1* mRNA localization (Bertrand *et al*, 1998) and mutations in the stem loop of the E3 element can affect the localization of *ASH1* mRNA (Chartrand *et al*, 1999).

The cytoskeleton has a role in the transport of different mRNAs in many organisms. There are two classes of cytoskeletal elements that are involved in cargo functions: actin microfilaments and microtubules (Kloc *et al*, 2002). The localization of *ASH1* mRNA was not affected in the *tub2-401* mutant, which causes the disruption of astral microtubules. However, disruption of actin-dependent motor proteins, such as She1/Myo4, tropomyosin, profilin and actin, abolished *ASH1* mRNA localization to the bud (Long *et al*, 1997). In addition, disruption of the cytoskeleton by latrunculin A, but not of microtubules by nocodazole, affected *ASH1* mRNA localization and Ash1 asymmetry (Takizawa *et al*, 1997). The She proteins regulate various functions of the cytoskeleton (Jansen *et al*, 1996) and indeed, in *she1*, *she2*, *she3* and *she4* mutants, not only Ash1, but also *ASH1* mRNA were equally distributed in mothers and daughters (Long *et al*, 1997).

A ribonucleoprotein complex localizes *ASH1* mRNA

Another step in the regulation of the asymmetric distribution of Ash1 is the activity of a ribonucleoprotein (RNP) complex formed by the She proteins and *ASH1* mRNA. Numerous studies from many groups have suggested the following model of RNP assembly: She2, an RNA-binding protein, binds to *ASH1* mRNA first, which allows the association of a pre-assembled She1/Myo4/She3 complex. Significantly, She2 associates with *ASH1* mRNA independent of the other She proteins. She3 is an adaptor protein that binds She1/Myo4 through its N-terminal domain and the *ASH1* E1 and E3 elements via its C-terminal domain (Fig 2B). The assembled RNP, and therefore *ASH1* mRNA, is transported by She1/Myo4 to the distal tip along the actin filaments (Bohl *et al*, 2000; Long *et al*, 2000; Takizawa & Vale, 2000).

In the RNP complex, She2 was proposed to be the cargo of the *ASH1* mRNA as it moves into and out of the nucleus. Kruse and colleagues demonstrated that a small fraction of She2 shuttles into the nucleus, and can be exported into the cytoplasm in an mRNA-dependent manner (Kruse *et al*, 2002). In a *mex67-5ts* mutant, in which mRNA export is blocked, She2 was sequestered in the nucleus and the cells failed to localize She1/Myo4, which is one of the components of the RNP, to the bud. Similarly, She1/Myo4 is mislocalized in a *she2ΔN70* mutant (which encodes a truncated She2 that lacks

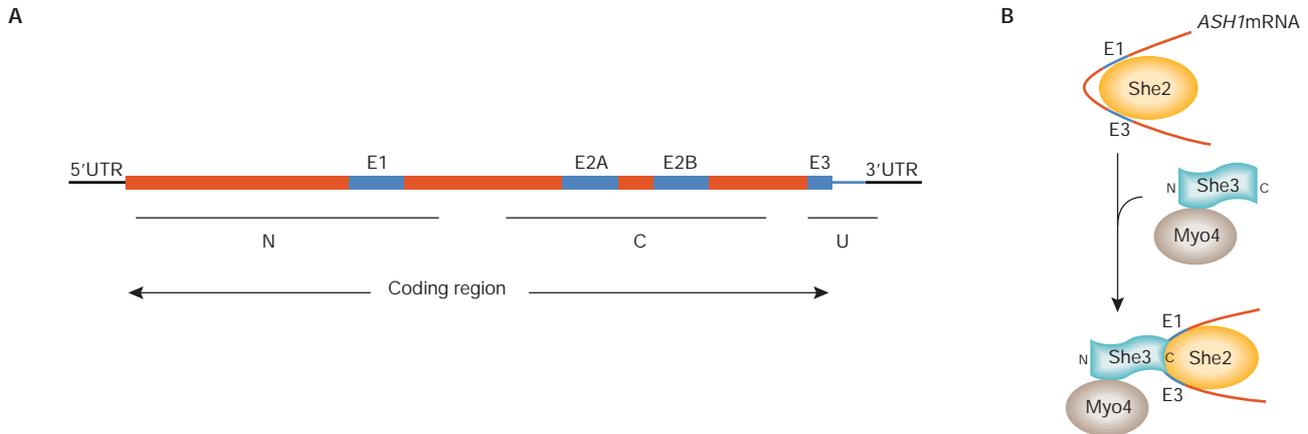


Fig 2 | *ASH1* mRNA localization domains and RNP complex formation. **(A)** *ASH1* mRNA has four localization domains: E1, E2A, E2B and E3. **(B)** The RNA-binding protein She2 binds first to *ASH1* mRNA, thus allowing the association of the pre-assembled She1/Myo4/She3 complex. C, carboxy-terminal domain; N, amino-terminal domain; U, untranslated region.

the 70 N-terminal amino acids): the truncated she2 Δ N70 failed to co-precipitate *ASH1* mRNA and accumulated in the nucleus (Kruse *et al*, 2002). These results, however, remain controversial, as Gonsalvez and colleagues reported that the nuclear export of She2 was independent of both mRNA transport and the ability of She2 to bind mRNA (Gonsalvez *et al*, 2003).

In terms of *ASH1* mRNA recognition, She2 is not unique; another key factor, Loc1, resides strictly in the nucleus and contributes to the asymmetric localization of *ASH1* mRNA. Loc1 has a high affinity for double-stranded RNAs, and can interact non-specifically with RNA-containing stem loops. However, it interacts specifically (with higher affinity) with the E3 domain and with full-length *ASH1* mRNA; these interactions are dependent on the structural integrity of the stem-loop elements. In a *loc1* mutant, *ASH1* mRNA and Ash1 itself are symmetrically localized in mother and daughter cells, which implies that Loc1 is important for the correct localization of *ASH1* mRNA (Long *et al*, 2001).

Anchoring and translation of *ASH1* mRNA

The anchoring of *ASH1* mRNA to the bud tip and its consequent translation are additional control steps in its asymmetric localization. Khd1 is involved in this process owing to its co-localization and physical binding to *ASH1* mRNA. A genetic interaction has been demonstrated between the *KHD1* and *SHE* genes; indeed, over-expression of *KHD1* suppressed the effects of *she* mutations on *HO* expression by reducing the concentration of Ash1. This was due to the decreased anchoring of *ASH1* mRNA. Therefore, *KHD1* is involved in the translational control of *ASH1* mRNA, through its role in anchoring *ASH1* mRNA at the distal cortex (Irie *et al*, 2002). Furthermore, a stop codon inserted immediately after the AUG of the *ASH1* coding region did not affect the stability of the mRNA, but instead impaired the localization of the untranslated mRNA (Gonzalez *et al*, 1999). As *ASH1* mRNA is highly mobile within the bud, it is possible that although the untranslatable mRNA reaches the distal cortex of the daughter, it does not remain there because it is not properly anchored. Thus, the concentration of Ash1 is essential for efficient anchoring of its mRNA; indeed, a hybrid mRNA encoded by a *GFP-STOP-ASH1* construct, which only translates GFP, was symmetrically distributed in mother and daughter cells (Gonzalez *et al*, 1999).

The rate of translation is also important for the efficient localization of Ash1; a decreased rate of *ASH1* mRNA translation was observed following the introduction of a short stem loop in the 5'-UTR, which resulted in an increase in Ash1 localization (Chartrand *et al*, 1999). The 5'-UTR of mRNA is a fundamental regulatory element during the initial steps of protein synthesis in eukaryotes as it facilitates start-codon recognition by ribosomes (Preiss & Hentze, 2003). The introduction of a stem loop in the 5'-UTR interferes with the correct assembly of the translational machinery, which leads to a slowing down, or even a block, of translation. Remarkably, a temperature-sensitive translational control mechanism was described for *prfA* mRNA, the *Listeria monocytogene* virulence-activating transcription factor. At 30°C, the 5'-UTR of the *prfA* mRNA formed a stem-loop structure that blocked ribosome binding, whereas at 37°C the loop melted, thus allowing translation (Johansson *et al*, 2002).

Chartrand and colleagues demonstrated that the disruption of all four localization elements resulted in the de-localization of the *ASH1* mRNA and its protein product. Additionally, the four elements were functionally redundant in their ability to localize *ASH1* mRNA, and their effects were independent of their positions within the *ASH1* mRNA. By contrast, their positions were essential for localization of the Ash1 protein to the bud (Chartrand *et al*, 2002). This mechanism was shown to be correlated to the rate of translation; the faster *ASH1* mRNA is translated, the more likely that Ash1 enters the mother-cell nucleus and thus loses its asymmetric localization. Chartrand and colleagues suggested that the position of the localization elements interferes with ribosome elongation and thus with the rate of translation. Indeed, when the elements were moved to the 3'-UTR of *ASH1* mRNA, this was asymmetrically localized, but the protein itself was not because of an increased rate of translation (Chartrand *et al*, 2002).

Movement of *ASH1* mRNA within the bud

Once transported to the bud, *ASH1* mRNA is mobile. It moves within the cortical region of the bud tip and from the cortical cap to the neck. The path of this movement and its rate have been measured by visualizing a fluorescent 'particle' (formed by the bacteriophage coat protein MS2 fused to GFP and the 3'-UTR of *ASH1*) in the bud. However, particle formation and localization were

inhibited in *she* mutants (Beach & Bloom, 2001; Beach *et al*, 1999; Bertrand *et al*, 1998).

Living cell time-lapse experiments revealed cell-cycle-dependent movements of the particle. From late anaphase to cytokinesis, the particle moved from the cortical region of large budded cells to the bud neck, and finally from there to the newly forming bud site. Therefore, the emerging bud contained the particle at the cortical cap. The particle moved with different velocities within the bud. In cells that lack Bud6/Aip3 or She5, which are involved in polarity establishment and actin organization, the particle migrated to the bud but did not remain stably localized at the bud cup. In these mutants, the movement and the rate of excursions out of the cortical cup were much higher than in wild-type cells. This observation led to the conclusion that Bud6/Aip3 or She5 are required for the anchoring of *ASH1* mRNA at the cortical bud cup (Beach & Bloom, 2001; Beach *et al*, 1999).

The goal: Ash1 represses *HO* transcription in daughters

All the events described above lead to the final goal: the repression of *HO* transcription in daughter cells. This results in the inhibition of mating-type switching, as follows (Fig 3).

In late anaphase, cyclinB/Cdk1 degradation and Cdc14 activity lead to the de-phosphorylation of the Swi5 nuclear localization signal, which allows Swi5 to enter both mother and daughter nuclei (Visintin *et al*, 1998). Swi5 binds the *ASH1* and *HO* promoters in both cells with similar kinetics, but although *ASH1* is immediately transcribed to start the *HO* repression program, the transcription of *HO* is delayed until late G1.

ASH1 mRNA is recognised in both mother and daughter nuclei by the nuclear RNA-binding proteins Loc1 and She2. It is then transported through nuclear pores into the cytoplasm, where it is coupled to other She proteins to form the RNP. This macromolecular complex is transported through the bud neck along actin cables and is asymmetrically localized to the distal tip of the bud, where it is anchored by factors such as Khd1 and/or Bud6/Aip3 and/or She5. *ASH1* mRNA is finally translated and Ash1 enters the daughter nucleus, where it binds its consensus sequences within URS1 and represses *HO* transcription by aborting all of the events following Swi5 association (Gonzalez *et al*, 1999; Irie *et al*, 2002; Long *et al*, 2001; Maxon & Herskowitz, 2001; Munchow *et al*, 1999).

Meanwhile, at the *HO* promoter in the mother cell, *ASH1* transcription has already been accomplished and the following occurs: after Swi5 association, the recruitment of SWI/SNF and SAGA results in the binding of SBF—an *HO*-specific activator—to the *HO* promoter, which then recruits the mediator complex. Finally, following the activation of the cyclin kinase Cdk1, RNA PolII and the basal transcription factors can associate with the *HO* promoter and commence transcription (Cosma, 2002).

Concluding remarks and speculations

What is remarkable about the regulation of *ASH1* transcription, translation and Ash1 repression is the temporal window during which all of these events occur. In late anaphase, Swi5 recruits chromatin remodelling and acetylation complexes to the *HO* promoter in the mother cell, but not in the daughter. However, there have been indications that Swi5 recruits these proteins to the *ASH1* promoter in both mother and daughter cells (Krebs *et al*, 2000). How are these nucleosome-modifying complexes recruited by Swi5 in mother and daughter at *ASH1*, but only in the mother at *HO*? It is the time that it takes from Swi5 binding to both promoters

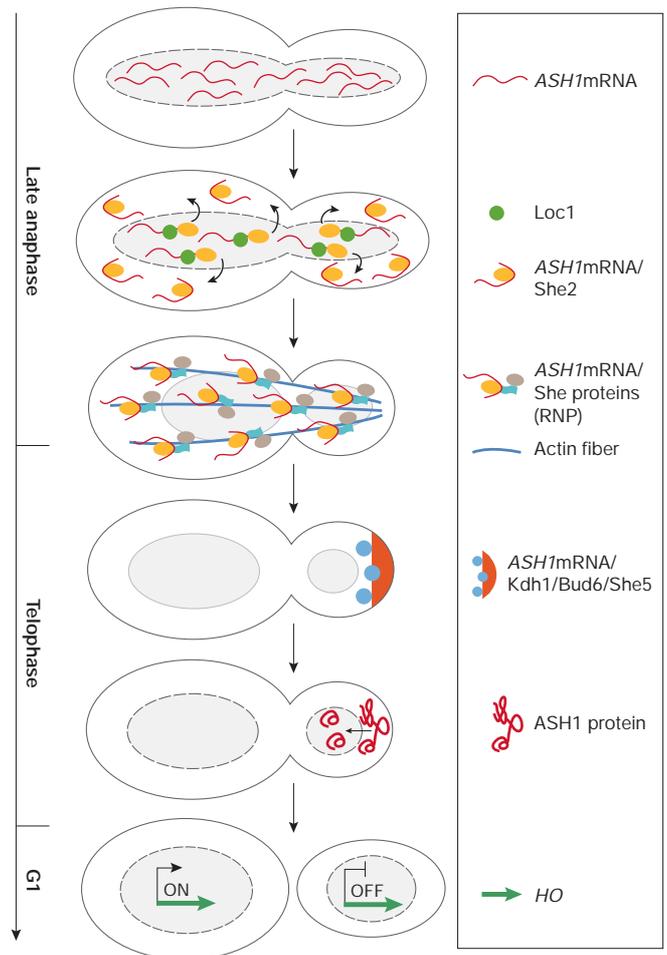


Fig 3 | The asymmetric accumulation of Ash1 represses *HO* in daughters. *ASH1* mRNA is recognized by Loc1 and She2 and transported in the cytoplasm, where it is coupled to the other She proteins to form the ribonucleoprotein (RNP; *ASH1*mRNA/She2/She3/Myo4). The RNP is transported along the actin cables to the distal tip, where the anchoring and translation of *ASH1* mRNA occurs. Finally, Ash1 enters the daughter nucleus, where it represses *HO*.

to Ash1 synthesis and localization that results in this mother-specific recruitment of SWI/SNF and differential mother/daughter *HO* expression. Five minutes elapse between Swi5 and Ash1 association with the *HO* promoter (Cosma *et al*, 1999). During this time window, the scenario on the *HO* promoter is frozen in both mother and daughter until all of the factors that regulate *ASH1* mRNA nuclear recognition, asymmetric localization, anchoring and translation complete their activities.

The big issue here is what happens at *HO* during those five minutes that the transcriptional programme continues at *ASH1*. An explanation could be that because SWI/SNF binds first to the URS1 region and then five minutes later, at the time of Ash1 association, to the URS2 region of the *HO* promoter (Cosma *et al*, 1999), Ash1 might impair binding of SWI/SNF to URS2 in daughters, which would ultimately induce the release of the complex from the URS1 region. In the case of *ASH1* activation, SWI/SNF might associate at once upon Swi5 recruitment and the transcriptional programme would thus be committed to a rapid progression. Furthermore, all of

the events following Swi5 association can occur efficiently at *ASH1* because Ash1 specifically represses *HO* and not the *ASH1* gene.

However, once on the promoter, how does Ash1 prevent Swi5 from recruiting SWI/SNF in the daughter cell? It is possible that Ash1 has a role in the control of the affinity and specificity of the DNA, such that the association of the SWI/SNF remodelling complex becomes unstable. Alternatively, Ash1 might itself occupy putative SWI/SNF association sites, or it might even mask a Swi5-binding domain that is responsible for the recruitment of the SWI/SNF remodelling complex, particularly as a physical interaction between Swi5 and SWI/SNF has been detected by co-immunoprecipitation (Neely *et al.*, 1999).

The temporal association of factors is a regulation mechanism of eukaryotic genes, and the activity of Ash1 is clearly modulated by time-dependent events. Moreover, Ash1 itself regulates transcription of *HO* in a time-dependent manner. The targeting of *ASH1* mRNA to the bud is a post-transcriptional mechanism of gene regulation that specifies the cell mating type through *HO* repression. The asymmetric localization of Ash1 can, therefore, be considered to be a stunning mechanism of cell lineage determination.

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