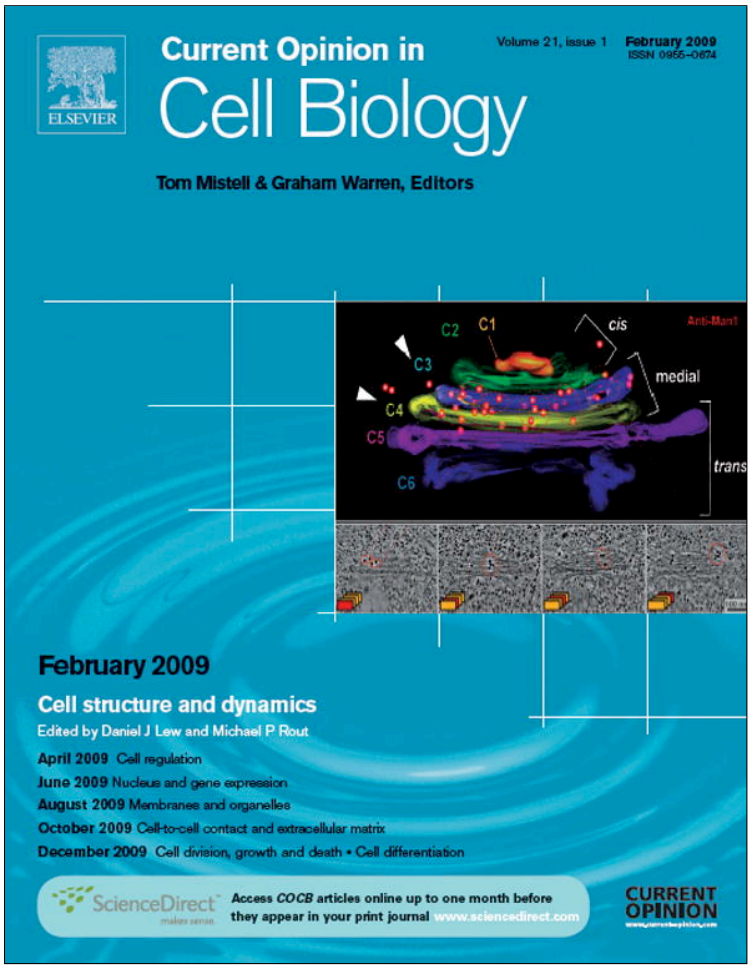
Provided for non-commercial research and education use.
Not for reproduction, distribution or commercial use.



This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

http://www.elsevier.com/copyright

Author's personal copy

Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Cell Biology

Transcriptional memory at the nuclear periphery

Jason H Brickner

A number of inducible yeast genes are targeted to the nuclear periphery upon transcriptional activation. However, when repressed again, the *INO1* and *GAL1* genes remain at the nuclear periphery for multiple generations. Retention at the nuclear periphery represents a novel type of transcriptional memory; the peripherally localized, recently repressed state of *GAL1* is activated more rapidly than the nucleoplasmically localized long-term repressed state of *GAL1*. This rapid reactivation involves localization at the nuclear periphery, the SWI/SNF chromatin remodeling complex, the histone variant H2A.Z and the Gal1 protein itself. Here, I review what we have learned about this type of transcriptional memory in yeast, what remains to be resolved and the challenges associated with understanding such epigenetic phenomena.

Address
Department of Biochemistry, Molecular Biology and Cell Biology, Northwestern University, Evanston, IL, USA

Corresponding author: Brickner, Jason H (j-brickner@northwestern.edu)

Current Opinion in Cell Biology 2009, **21**:127–133

This review comes from a themed issue on
Cell structure and dynamics
Edited by Daniel J. Lew and Michael Rout

Available online 30th January 2009

0955-0674/$ – see front matter
© 2009 Elsevier Ltd. All rights reserved.

DOI 10.1016/j.ceb.2009.01.007

Gene recruitment to the nuclear periphery

DNA is spatially organized within the nucleus. It has long been appreciated that certain parts of the genome localize at the nuclear periphery and associate with the nuclear envelope [1–4]. Peripheral localization has been proposed to promote transcriptional repression because much of the DNA at the nuclear periphery is transcriptionally repressed; heterochromatin, centromeres, telomeres and chromatin insulators (which can block enhancer function) localize at the nuclear periphery [5]. Proximity to the nuclear envelope in *Saccharomyces cerevisiae* [6] and association with the mammalian nuclear lamina [7,8] promotes transcriptional silencing of some genes.

Recent work, however, shows that peripheral localization is not always repressive. Artificially tethering of a reporter gene that lacks any silencing elements to the nuclear envelope does not promote repression [6]. Furthermore, certain inducible yeast genes were found to be targeted to the nuclear periphery upon activation [9,10,11••]. Recent work has shown that many genes undergo recruitment to the nuclear periphery [12–15] and that peripheral localization correlates with a physical association with the nuclear pore complex (NPC) [10,12,16]. Peripheral targeting promotes transcription [9,13,17,18] and may be important for post-transcriptional events such as mRNA processing, mRNA export or translation [10,12].

The mechanism of gene recruitment

Physical interaction of genes with the NPC *in vivo* has been observed using different methods [10,12,16,19]. Furthermore, targeting of genes to the nuclear periphery requires NPC components, the SAGA histone acetyltransferase complex, the transcription-mRNA export complex TREX2 and the export receptor Mex67 [14,18–20]. These observations suggest that relocalization of genes to the nuclear periphery represents a 'tethering' of genes to the NPC. Consistent with this interpretation, in mutant strains lacking in which NPCs cluster together into plaques, there is a significant increase in the colocalization of the *HXK1* gene with clustered NPCs upon transcriptional activation [13].

However, it is worth mentioning that a direct interaction with the NPC and genes has not been shown. Furthermore, the fraction of cells in which *HXK1* colocalized with clustered NPCs (17% of the cells in the population) is still much lower than the fraction of the cells in which *HXK1* is localized at the nuclear periphery (>85% of the cells in the population). Also, it is unclear if the ~150 NPCs in the typical haploid nucleus in yeast would be able to accommodate both a large number of transcriptionally active genes (as suggested by the NPC association data in refs. [11••,12,16]) and nucleo-cytoplasmic transport, without interference. Therefore, it remains possible that the site to which genes are recruited is actually the nuclear envelope, a platform of the filamentous Mlp/Tpr proteins or other, unidentified structures at the nuclear periphery that are influenced by the integrity of the NPC. That said, for the purposes of this review, I will build on the simplest model for gene recruitment that is consistent our current state of knowledge: that genes are targeted to the NPC.

Gene recruitment of one gene to the nuclear periphery requires the 3′ UTR [13]. Furthermore, the association of certain genes with NPC components, as measured by chromatin immunoprecipitation, is sensitive to RNase treatment [12]. The connection between peripheral relocalization of genes, the NPC and RNA elements important for mRNA export suggested that relocalization might represent a *consequence* of transcription. In other words,

Author's personal copy

relocalization of genes to the nuclear periphery might be mediated by a bridging interaction between chromosomal DNA, the mRNA, export factors and the NPC. If so, then relocalization to the nuclear periphery might simply represent an emergent property of highly expressed genes, rather than a specific targeting event. Several results argue against this interpretation. From experiments using a temperature-sensitive allele of RNA polymerase to block transcription, it became clear that transcription is not essential for either the interaction of *GAL1* with the NPC [16] or for relocalization of *INO1* to the nuclear periphery [11••]. Furthermore, association of the Mex67 mRNA export receptor with the *GAL2* gene was independent of RNA, suggesting that the export receptor can interact directly with DNA or chromatin [14]. Also, *INO1* and *GAL1* remain at the nuclear periphery for generations after transcription is repressed (see below; ref. [11••]). Finally, we have recently identified an eight basepair element in the *INO1* promoter that functions as a 'DNA zip code' to target an ectopic locus to the nuclear periphery [18]. Therefore, although the mRNA may play important roles in the localization of genes with the NPC after transcription is initiated (see below), transcription-independent mechanisms of gene relocalization also occur and relocalization to the nuclear periphery represents an active and specific targeting mechanism.

Transcriptional memory at the nuclear periphery

In addition to a role in transcriptional activation, we have identified a role for peripheral targeting in the rapid reactivation of recently repressed genes. When cells are shifted from activating to repressing conditions, both the *INO1* and *GAL1* genes remain at the nuclear periphery through multiple cell divisions [11••]. Retention of *GAL1* at the nuclear periphery is very stable, lasting greater than seven generations. This suggested that peripheral localization might represent a novel epigenetic state that reflects previous transcription. Furthermore, it suggested that this recently repressed 'memory' state might be functionally different from the long-term repressed state. Indeed, the reactivation of the *GAL1* gene, even after seven generations of repression, is much faster than the initial activation of the *GAL1* gene [11••]. This suggested that cells have cellular and molecular mechanisms to mark previously expressed genes and to promote their reactivation, a phenomenon I call adaptive transcriptional memory.

Concurrent work independently demonstrated that previous transcription of *GAL1*, *GAL7* and *GAL10* promoted their rapid reactivation [21••]. Rapid reactivation of *GAL1* required as little as one hour of activation and persisted through cell division. The rapid reactivation of the *GAL1* gene was not due to the lingering association of RNA polymerase II, the TATA binding protein (which binds upstream of preinitiation complex formation) or coactivators such as Mediator (which interacts with RNA Polymerase II to promote transcription), the SWI/SNF chromatin remodeling complex or the SAGA histone acetyltransferase [21••]. Therefore, recently repressed *GAL1* is not primed through a lingering association with a stalled RNA polymerase II, but through faster recruitment of RNA polymerase II upon reactivation.

Defects in mRNA processing can also lead to post-transcriptional targeting of genes to the nuclear periphery. *GAL1* promoter-driven reporter genes that produce mRNAs that are improperly polyadenylated remain associated with post-transcriptional RNA 'dots' at the nuclear periphery [22]. Localization at the nuclear periphery is maintained for approximately one hour after transcription is repressed [22,24•], increases with defects in mRNA processing [22] and requires both an mRNA export factor (TREX 2; ref. [23•]) and the nuclear exosome, an exoribonuclease complex that degrades aberrant nuclear mRNAs [24•]. Likewise, in mutants lacking the THO complex (which coordinates mRNA processing with export), an intermediate in the mRNA processing pathway accumulates associated chromatin [25•]. This intermediate is visible as an RNA dot, requires the nuclear exosome for its formation and leads to the relocalization of genes to the nuclear pore complex [25•]. It is unclear how this mechanism of peripheral retention relates to the epigenetic peripheral retention observed for the endogenous, wild type *GAL1* gene.

The mechanism of transcriptional memory

Although both *INO1* and *GAL1* are retained at the nuclear periphery after transcriptional repression, the mechanism of *GAL1* transcriptional memory is easier to study because it lasts longer [11••]. Recently repressed *GAL1* is different from long-term repressed *GAL1* in several important ways: (1) it is more rapidly reactivated, (2) it is localized at the nuclear periphery and (3) it is activated by a different mechanism (see below; refs. [11••,21••]). Therefore, I propose that cells have molecular and cellular mechanisms to mark recently repressed genes and that this creates a novel epigenetic 'memory' form of the gene.

Many epigenetic phenomena require post-translational histone modifications or alterations in nucleosome composition [26–29]. Adaptive transcriptional memory requires two chromatin-based factors: the histone variant H2A.Z [11••] and the SWI/SNF chromatin remodeling complex [21••] play essential roles in either the establishment of transcriptional memory or the rapid reactivation of the memory state.

H2A.Z nucleosomes have several functions. They are found in subtelomeric regions, where they prevent the spread of transcriptional silencing from telomeres [30].

Author's personal copy

They are found in the promoters of many eukaryotic genes, where they promote transcriptional activation [31–36]. H2A.Z is also essential both for the retention of *INO1* and *GAL1* at the nuclear periphery after repression and for the rapid reactivation of these genes [11••]. Importantly, the initial targeting of *INO1* or *GAL1* to the nuclear periphery and the initial activation of these genes is not dependent on H2A.Z. Thus, H2A.Z plays a specific, essential role in the peripheral retention and reactivation of certain recently repressed genes.

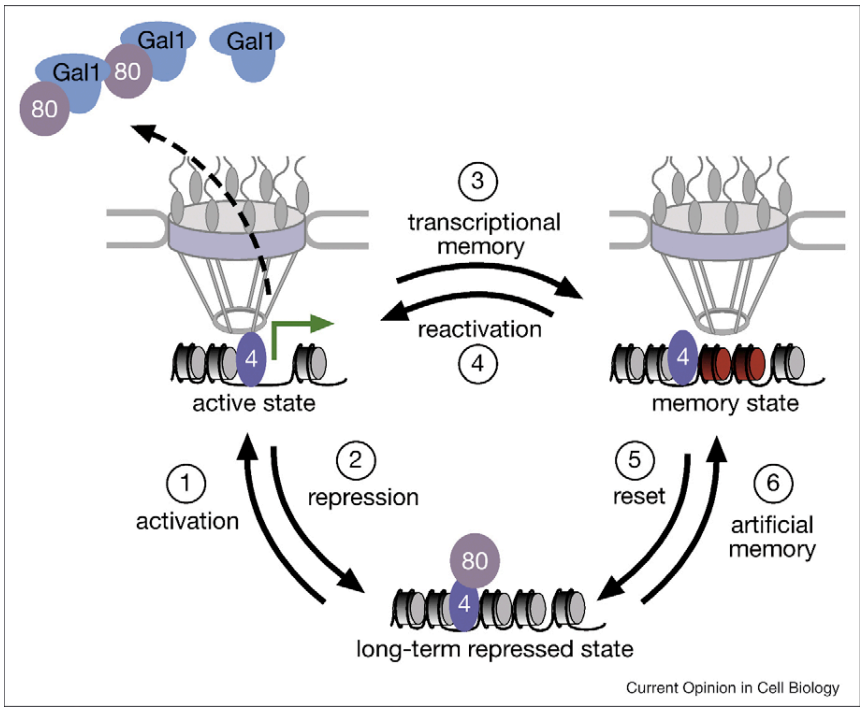
The reactivation of *GAL1* does not require histone modifications that are associated with transcriptional activation [21••]. This is important because previous work had shown that immediately after *GAL1* transcription is repressed, the trimethylation of lysine 4 on histone H3, which is associated with transcription, persists [37]. However, rapid reactivation of *GAL1* does require the SWI/SNF chromatin-remodeling complex. In the absence of the Swi2 protein, the reactivation of *GAL1* is no faster than its initial activation. The initial activation of *GAL1* was normal in the *swi2*Δ mutant, indicating that, like H2A.Z, the role of SWI/SNF was specific to the reactivation of the memory state.

The role of SWI/SNF appears to be to counteract the repressive effects of either Isw1 or Isw2 remodeling complexes, two related chromatin-remodeling complexes implicated in transcriptional repression. The requirement for SWI/SNF in *GAL1* reactivation was bypassed in strains lacking either Isw1 of Isw2 [21••]. When the *swi2*Δ mutation was combined with either *isw1*Δ or *isw2*Δ, the double mutant exhibited normal transcriptional memory, reactivating *GAL1* more rapidly.

The role of DNA localization in transcriptional memory

The correlation of rapid reactivation with peripheral localization suggests that localization may be important for transcriptional memory. Loss of H2A.Z causes both a dramatic decrease in the reactivation rate and loss of peripheral localization of *INO1* and *GAL1* after repression, suggesting that peripheral localization is coupled to reactivation and both are dependent on H2A.Z. Intriguingly, H2A.Z physically associates with the NPC-associated protein Nup2 [38]. Also, tethering silenced genes to the NPC creates a boundary that prevents the spread of silencing [39] and loss of Nup2 causes a spread of silencing from telomeres, similar to the effect of loss of

Figure 1



Three distinct states of the *GAL* genes. Initial activation of the *GAL1*, *GAL2*, *GAL7* and *GAL10* genes (step 1) through the Gal3 galactose sensor, leads to relocalization to the nuclear periphery through association with the NPC and the production of the Gal1 protein. Gal1 binds and inhibits the repressor Gal80. After repressing transcription (via the glucose repression system), the genes remain at the nuclear periphery in a memory state that can be rapidly reactivated. The establishment of the memory state requires chromatin changes (indicated as red nucleosomes). Eventually, transcriptional memory is lost (reset, step 5). The memory state differs from the long-term repressed state in its localization, its chromatin requirements for activation and its rate of reactivation.

Author's personal copy

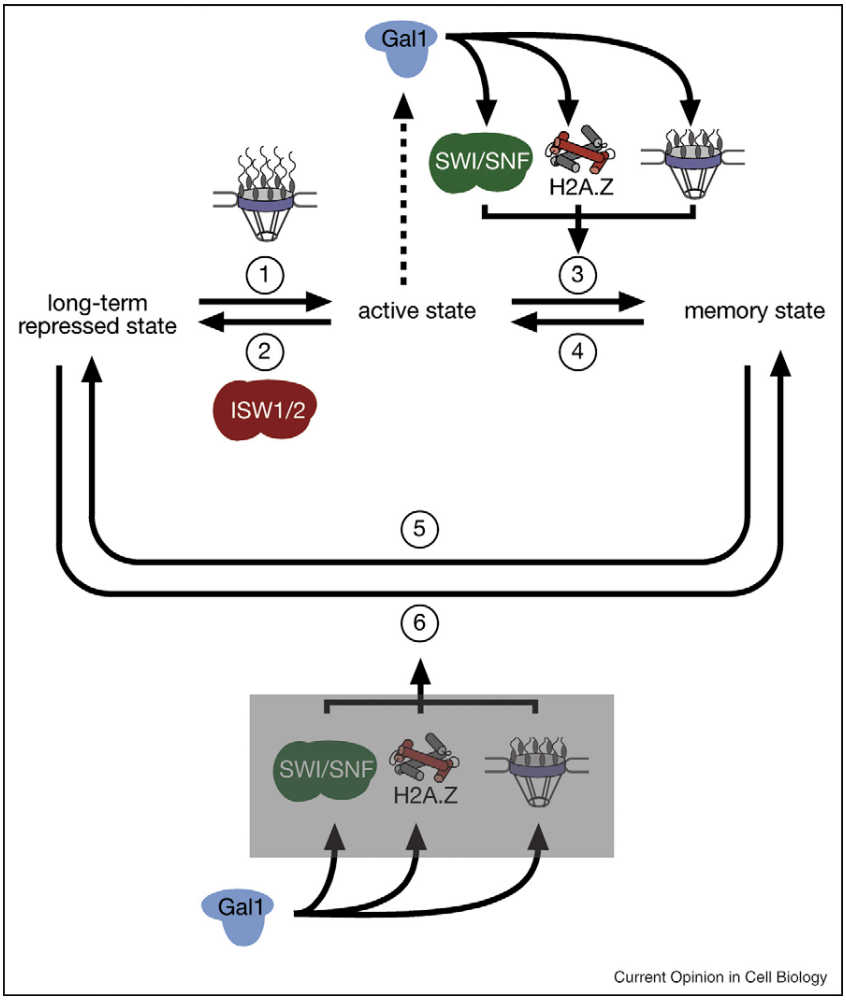
H2A.Z [30,38]. Therefore, perhaps the memory state and boundary activity represent mechanistically related chromatin states that both require H2A.Z nucleosomes and interaction with the NPC.

Artificially tethering the *INO1* gene to the nuclear periphery leads to more rapid transcriptional activation [9,11••]. This effect may represent a type of artificial memory. Like genuine transcriptional memory, tethering does not affect the ultimate steady-state activation of *INO1* [11••]. However, unlike genuine memory, tethering to the nuclear envelope induces rapid activation in the absence of previous transcription.

The mechanism of epigenetic inheritance

SWI/SNF is required for rapid reactivation of *GAL1*. H2A.Z is required for rapid reactivation of both *GAL1* and *INO1* and for their retention at the nuclear periphery after repression. The requirement for chromatin factors for rapid reactivation and post-transcriptional peripheral localization raised the possibility that transcriptional memory might represent a self-perpetuating chromatin state and that this might explain its epigenetic inheritance. In other words, a change in the chromatin state that reflects the history of the gene might 'bookmark' a gene and, if it persists until DNA replication, this bookmark might somehow promote its own inheritance. The concept that

Figure 2



Regulation of transcriptional memory. The states and the interconversion between them are the same as in Figure 1. Conversion between the three states is regulated by the production of a cytoplasmic regulator (the Gal1 protein in the case of the *GAL* genes). The cytoplasmic regulator functions upstream of the SWI/SNF chromatin-remodeling complex, the H2A.Z histone variant and peripheral localization (indicated as the NPC) to promote transcriptional memory (step 3). Because we cannot order these events relative to each other currently, I represent them as parallel inputs. SWI/SNF is necessary to counteract the conversion of the active state into the long-term repressed state by the ISW1 and ISW2 complexes. The memory state can be generated directly from the long-term repressed state by expression of the cytoplasmic regulator (artificial memory; step 6). Grey box: possible role for SWI/SNF, H2A.Z and peripheral localization in the generation of artificial memory.

Author's personal copy

chromatin might promote its own inheritance to produce stable epigenetic changes in gene expression has been broadly endorsed and has even been proposed as a modern definition of epigenetics [40]. However, the perpetuation of epigenetic states through chromatin alone, without input from *trans*-acting factors, is still controversial and has been greeted with skepticism [41].

To directly test the hypothesis that chromatin alone is the source of epigenetic inheritance of *GAL* transcriptional memory, a recent study used heterokaryon analysis, in which cells fuse, but nuclei do not [42••]. This study showed that rapid reactivation of *GAL1* could be transferred from one cell to another via cytoplasmic mixing. Therefore, *GAL* transcriptional memory is a *cytoplasmically* inherited phenomenon. The cytoplasmic factor was identified as the Gal1 protein itself; a *gal1*Δ mutant is unable to rapidly reactivate the *GAL7* gene. Furthermore, constitutive expression of *GAL1* was sufficient to confer rapid reactivation of *GAL7* [42••]. *GAL1* encodes the galactokinase enzyme. Galactokinase is 70% identical to the galactose sensor Gal3, which senses galactose and inactivates the Gal80 transcriptional repressor [43]. Therefore, Gal1 may directly inhibit Gal80, priming the *GAL* genes for reactivation. The ~100 fold induction of the *GAL1* gene, coupled with an extremely long half-life, provides a plausible mechanism for the inheritance of transcriptional memory for >7 generations [11••,42••]. Thus, although *GAL* transcriptional memory requires chromatin-based mechanisms, the inheritance of memory is mediated by a cytoplasmic factor.

Based on what we have learned from the regulation of the *GAL* genes, I propose a model for adaptive transcriptional memory (Figure 1). For genes that utilize this type of transcriptional memory, three qualitatively distinct states can exist: a long-term repressed state, an active state and an epigenetic memory state. Each state is distinguished from the other two by its subnuclear localization, its transcriptional activity and its mechanism of regulation (Figures 1 and 2). Furthermore, I propose that it is possible to convert between any state and any other state. Conversion from the active state to the memory state requires a cytoplasmic effector (Gal1 in the case of the *GAL* genes). I propose that the cytoplasmic effector functions upstream of peripheral localization, SWI/SNF and H2A.Z (Figure 2). The long-term repressed state can also be converted directly into the memory state (i.e. artificial memory) by expression of the cytoplasmic regulator and, perhaps, by tethering to the nuclear periphery (Figure 2).

Two observations indicate that the memory state is qualitatively different from the long-term repressed state and that reactivation occurs by a novel mechanism that is not simply due to titration of a negative regulator. First, the long-term repressed state and the memory state localize to different parts of the nucleus (Figure 1). Second, the requirement for H2A.Z and SWI/SNF in rapid reactivation of recently repressed *INO1* and *GAL1* is specific; loss of these proteins has no significant effect on the activation of long-term repressed *INO1* and *GAL1* [11••,21••]. This, too, is not simply due to a change in the rate-limiting step because SWI/SNF and H2A.Z are not required for the rapid activation of *GAL1* when cells are shifted from non-repressing raffinose medium to activating galactose medium (our unpublished data; ref. [21••]). Finally, if the tethering of *INO1* truly generates artificial memory and if cytoplasmic regulators are a general feature of transcriptional memory, this suggests that their role can be bypassed by tethering *INO1* to the nuclear envelope. If so, then the transient expression of a cytoplasmic regulator (like Gal1) generates a transcriptional memory through downstream chromatin modifications mediated by peripheral localization, SWI/SNF and H2A.Z (Figures 1 and 2).

Future directions

Future work will integrate what we have learned to create a coherent model of transcriptional memory and to answer a number of important questions. How do cytoplasmic factors, chromatin-based changes and gene localization work together to create a marked promoter that can be activated more rapidly? What cytoplasmic factors, if any, are involved in *INO1* transcriptional memory? How many genes utilize this type of transcriptional memory? What are the selective advantages of this system? Finally, do metazoan cells utilize this type of transcriptional memory? SWI/SNF and H2A.Z are conserved among eukaryotes and peripheral targeting of genes has been observed in flies [44•] and mammalian cells [45•]. If metazoan cells utilize adaptive transcriptional memory, it might provide a mechanism by which environmental or physiological inputs can produce short-term to long-term changes in gene expression.

Acknowledgements

I thank the members of the lab, as well as Andreas Matouschek, Rick Gaber, Jonathan Widom, Sandy Westerheide and Jacklyn Jansen for their helpful comments on the manuscript. JHB is supported by grant GM080484 from the National Institute of General Medical Sciences and the Baldwin Fund for Biomedical Research at Northwestern University.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Rabl C: **Über Zelltheilung**. In *Morphol. Jahrbuch*. Edited by Gegenbaur C. 1885:214-330.

2. Boveri T: **Die blastermerenkerne von *Ascaris megalocephala* und die theorie der chromosomenindividualität**. *Arch. Zellforschung* 1909, **3**:181.

3. Marshall WF, Dernburg AF, Harmon B, Agard DA, Sedat JW: **Specific interactions of chromatin with the nuclear envelope: positional determination within the nucleus in *Drosophila melanogaster***. *Mol Biol Cell* 1996, **7**:825-842.

Author's personal copy

4. Gasser SM: **Visualizing chromatin dynamics in interphase nuclei**. *Science* 2002, **296**:1412-1416.

5. Cockell M, Gasser SM: **Nuclear compartments and gene regulation**. *Curr Opin Genet Dev* 1999, **9**:199-205.

6. Andrulis ED, Neiman AM, Zappulla DC, Sternglanz R: **Perinuclear localization of chromatin facilitates transcriptional silencing**. *Nature* 1998, **394**:592-595.

7. Reddy KL, Zullo JM, Bertolino E, Singh H: **Transcriptional repression mediated by repositioning of genes to the nuclear lamina**. *Nature* 2008, **452**:243-247.

8. Finlan LE, Sproul D, Thomson I, Boyle S, Kerr E, Perry P, Ylstra B, Chubb JR, Bickmore WA: **Recruitment to the nuclear periphery can alter expression of genes in human cells**. *PLoS Genet* 2008, **4**:e1000039.

9. Brickner JH, Walter P: **Gene recruitment of the activated *INO1* locus to the nuclear membrane**. *PLoS Biol* 2004, **2**:e342.

10. Casolari JM, Brown CR, Komili S, West J, Hieronymus H, Silver PA: **Genome-wide localization of the nuclear transport machinery couples transcriptional status and nuclear organization**. *Cell* 2004, **117**:427-439.

11. •• Brickner DG, Cajigas IC, Fondufe-Mittendorf Y, Ahmed S, Lee P-C, Widom J, Brickner JH: **H2A.Z-mediated localization of genes at the nuclear periphery confers epigenetic memory of previous transcriptional state**. *PLoS Biol* 2007, **5**:e81.

This paper describes the discovery that *INO1* and *GAL1* remain at the nuclear periphery after repression and that this promotes more rapid reactivation. The authors also show that the histone variant H2A.Z is essential for both retention at the nuclear periphery and rapid reactivation.

12. Casolari JM, Brown CR, Drubin DA, Rando OJ, Silver PA: **Developmentally induced changes in transcriptional program alter spatial organization across chromosomes**. *Genes Dev* 2005, **19**:1188-1198.

13. Taddei A, Van Houwe G, Hediger F, Kalck V, Cubizolles F, Schober H, Gasser SM: **Nuclear pore association confers optimal expression levels for an inducible yeast gene**. *Nature* 2006, **441**:774-778.

14. Dieppois G, Iglesias N, Stutz F: **Cotranscriptional recruitment to the mRNA export receptor Mex67p contributes to nuclear pore anchoring of activated genes**. *Mol Cell Biol* 2006, **26**:7858-7870.

15. Sarma NJ, Haley TM, Barbara KE, Buford TD, Willis KA, Santangelo GM: **Glucose-responsive regulators of gene expression in *Saccharomyces cerevisiae* function at the nuclear periphery via a reverse recruitment mechanism**. *Genetics* 2007, **175**:1127-1135.

16. Schmid M, Arib G, Laemmli C, Nishikawa J, Durussel T, Laemmli UK: **Nup-PI: the nucleopore-promoter interaction of genes in yeast**. *Mol Cell* 2006, **21**:379-391.

17. Menon BB, Sarma NJ, Pasula S, Deminoff SJ, Willis KA, Barbara KE, Andrews B, Santangelo GM: **Reverse recruitment: the Nup84 nuclear pore subcomplex mediates Rap1/Gcr1/Gcr2 transcriptional activation**. *Proc Natl Acad Sci U S A* 2005, **102**:5749-5754.

18. Ahmed S, Brickner DG, McDonough M, Light WH, Volpe T, Brickner JH: **DNA zip codes: an ancient mechanism for targeting genes to the nuclear periphery**. Manuscript under revision.

19. Luthra R, Kerr SC, Harreman MT, Apponi LH, Fasken MB, Ramineni S, Chaurasia S, Valentini SR, Corbett AH: **Actively transcribed *GAL* genes can be physically linked to the nuclear pore by the SAGA chromatin modifying complex**. *J Biol Chem* 2007, **282**:3042-3049.

20. Cabal GG, Genovesio A, Rodriguez-Navarro S, Zimmer C, Gadal O, Lesne A, Buc H, Feuerbach-Fournier F, Olivo-Marin JC, Hurt EC *et al.*: **SAGA interacting factors confine sub-diffusion of transcribed genes to the nuclear envelope**. *Nature* 2006, **441**:770-773.

21. •• Kundu S, Horn PJ, Peterson CL: **SWI/SNF is required for transcriptional memory at the yeast *GAL* gene cluster**. *Genes Dev* 2007, **21**:997-1004.

This paper describes the discovery that *GAL1, GAL2, GAL7* and *GAL10* are more rapidly activated if they have previously been expressed. This transcriptional memory persists through cell division. Memory does not require histone acetylation or methylation but does require the SWI/SNF chromatin-remodeling complex. SWI/SNF functions to overcome ISW1/2-mediated repression.

22. Abruzzi KC, Belostotsky DA, Chekanova JA, Dower K, Rosbash M: **3′-end formation signals modulate the association of genes with the nuclear periphery as well as mRNP dot formation**. *EMBO J* 2006, **25**:4253-4262.

23. • Chekanova JA, Abruzzi KC, Rosbash M, Belostotsky DA: **Sus1, Sac3, and Thp1 mediate post-transcriptional tethering of active genes to the nuclear rim as well as to non-nascent mRNP**. *RNA* 2008, **14**:66-77.

This paper shows that proteins involved in mRNA export are essential for the accumulation of mRNA 'dots' in association with *GAL1* promoter-driven reporter genes and for their post-transcriptional localization at the nuclear periphery.

24. • Vodala S, Abruzzi KC, Rosbash M: **The nuclear exosome and adenylation regulate posttranscriptional tethering of yeast *GAL* genes to the nuclear periphery**. *Mol Cell* 2008, **31**:104-113.

Using both *GAL1* promoter-driven reporter genes and the endogenous *GAL1* gene, this paper argues that the nuclear exosome normally generates unpolyadenylated RNAs that accumulate in gene-associated 'dots'. These RNA dots and the associated reporter genes are localized at the nuclear periphery.

25. • Rougemaille M, Dieppois G, Kisseleva-Romanova E, Kanth Gudipati R, Lemoine S, Blugeon C, Boulay J, Heick Jensen T, Stutz F, Devaux F *et al.*: **THO/Sub2p functions to coordinate 3′-end processing with gene-nuclear pore association**. *Cell* 2008, **135**:308-321.

This paper describes the accumulation of a stalled mRNA processing/export intermediate in mutants lacking THO components. This intermediate, which may correspond to RNA 'dots' observed in refs [22,23•,24•] is associated with chromatin and interacts with the NPC. The accumulation of this intermediate and its targeting to the NPC requires the nuclear exosome.

26. Andersen AA, Panning B: **Epigenetic gene regulation by noncoding RNAs**. *Curr Opin Cell Biol* 2003, **15**:281-289.

27. Rusche LN, Kirchmaier AL, Rine J: **The establishment, inheritance, and function of silenced chromatin in *Saccharomyces cerevisiae***. *Annu Rev Biochem* 2003, **72**:481-516.

28. Lawrence RJ, Earley K, Pontes O, Silva M, Chen ZJ, Neves N, Viegas W, Pikaard CS: **A concerted DNA methylation/histone methylation switch regulates rRNA gene dosage control and nucleolar dominance**. *Mol Cell* 2004, **13**:599-609.

29. Henikoff S: **Nucleosome destabilization in the epigenetic regulation of gene expression**. *Nat Rev Genet* 2008, **9**:15-26.

30. Meneghini MD, Wu M, Madhani HD: **Conserved histone variant H2A.Z protects euchromatin from the ectopic spread of silent heterochromatin**. *Cell* 2003, **112**:725-736.

31. Raisner RM, Hartley PD, Meneghini MD, Bao MZ, Liu CL, Schreiber SL, Rando OJ, Madhani HD: **Histone variant H2A.Z marks the 5′ ends of both active and inactive genes in euchromatin**. *Cell* 2005, **123**:233-248.

32. Zhang H, Roberts DN, Cairns BR: **Genome-wide dynamics of Htz1, a histone H2A variant that poises repressed/basal promoters for activation through histone loss**. *Cell* 2005, **123**:219-231.

33. Guillemette B, Bataille AR, Gevry N, Adam M, Blanchette M, Robert F, Gaudreau L: **Variant histone H2A.Z is globally localized to the promoters of inactive yeast genes and regulates nucleosome positioning**. *PLoS Biol* 2005, **3**:e384.

34. Barski A, Cuddapah S, Cui K, Roh TY, Schones DE, Wang Z, Wei G, Chepelev I, Zhao K: **High-resolution profiling of histone methylations in the human genome**. *Cell* 2007, **129**:823-837.

35. Mavrich TN, Jiang C, Ioshikhes IP, Li X, Venters BJ, Zanton SJ, Tomsho LP, Qi J, Glaser RL, Schuster SC *et al.*: **Nucleosome organization in the *Drosophila* genome**. *Nature* 2008, **453**:358-362.

Author's personal copy

36. Whittle CM, McClinic KN, Ercan S, Zhang X, Green RD, Kelly WG, Lieb JD: **The genomic distribution and function of histone variant HTZ-1 during *C. elegans* embryogenesis**. *PLoS Genet* 2008, **4**:e1000187.

37. Ng HH, Robert F, Young RA, Struhl K: **Targeted recruitment of Set1 histone methylase by elongating Pol II provides a localized mark and memory of recent transcriptional activity**. *Mol Cell* 2003, **11**:709-719.

38. Dilworth DJ, Tackett AJ, Rogers RS, Yi EC, Christmas RH, Smith JJ, Siegel AF, Chait BT, Wozniak RW, Aitchison JD: **The mobile nucleoporin Nup2p and chromatin-bound Prp20p function in endogenous NPC-mediated transcriptional control**. *J Cell Biol* 2005, **171**:955-965.

39. Ishii K, Arib G, Lin C, Van Houwe G, Laemmli UK: **Chromatin boundaries in budding yeast: the nuclear pore connection**. *Cell* 2002, **109**:551-562.

40. Bird A: **Perceptions of epigenetics**. *Nature* 2007, **447**:396-398.

41. Ptashne M: **On the use of the word 'epigenetic'**. *Curr Biol* 2007, **17**:R233-236.

42. •• Zacharioudakis I, Gligoris T, Tzamarias D: **A yeast catabolic enzyme controls transcriptional memory**. *Curr Biol* 2007, **17**:2041-2046.

Using heterokaryon analysis, the authors show that *GAL* gene transcriptional memory is conferred by a cytoplasmic factor. They identify the Gal1 protein as the cytoplasmic factor. Constitutive expression of Gal1 leads to more rapid transcriptional activation of *GAL7*, suggesting that this is sufficient to generate artificial memory.

43. Peng G, Hopper JE: **Gene activation by interaction of an inhibitor with a cytoplasmic signaling protein**. *Proc Natl Acad Sci U S A* 2002, **99**:8548-8553.

44. • Kurshakova MM, Krasnov AN, Kopytova DV, Shidlovskii YV, Nikolenko JV, Nabirochkina EN, Spehner D, Schultz P, Tora L, Georgieva SG: **SAGA and a novel *Drosophila* export complex anchor efficient transcription and mRNA export to NPC**. *EMBO J* 2007, **26**:4956-4965.

The *hsp70* locus in *Drosophila* localizes at the nuclear periphery, in association with the nuclear pore complex (NPC). Full transcription and the localization at the nuclear periphery require the same NPC components that have been shown to function in gene recruitment to the nuclear periphery in yeast.

45. • Brown CR, Kennedy CJ, Delmar VA, Forbes DJ, Silver PA: **Global histone acetylation induces functional genomic reorganization at mammalian nuclear pore complexes**. *Genes Dev* 2008, **22**:627-639.

In mammalian cells, certain genes associate with the NPC and relocalize from the nucleoplasm to the nuclear periphery upon treatment with histone deacetylase inhibitors. This suggests that peripheral targeting of active genes can also occur in mammalian cells.