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REVIEW

Epigenetic transcriptional memory

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Abstract Organisms alter gene expression to adapt to changes in environmental conditions such as temperature, nutrients, inflammatory signals, and stress (Gialitakis et al. in Mol Cell Biol 30:2046–2056, 2010; Conrath in Trends Plant Sci 16:524–531, 2011; Avramova in Plant J 83:149–159, 2015; Solé et al. in Curr Genet 61:299–308, 2015; Ho and Gasch in Curr Genet 61:503–511, 2015; Bevington et al. in EMBO J 35:515–535, 2016; Hilker et al. in Biol Rev Camb Philos Soc 91:1118–1133, 2016). In some cases, organisms can "remember" a previous environmental condition and adapt to that condition more rapidly in the future (Gems and Partridge 2008). Epigenetic transcriptional memory in response to a previous stimulus can produce heritable changes in the response of an organism to the same stimulus, quantitatively or qualitatively altering changes in gene expression (Brickner et al. in PLoS Biol, 5:e81, 2007; Light et al. in Mol Cell 40:112–125, 2010; in PLoS Biol, 11:e1001524, 2013; D'Urso and Brickner in Trends Genet 30:230–236, 2014; Avramova in Plant J 83:149–159, 2015; D'Urso et al. in Elife. doi: 10.7554/eLife.16691, 2016). The role of chromatin changes in controlling binding of poised RNAPII during memory is conserved from yeast to humans. Here, we discuss epigenetic transcriptional memory in different systems and our current understanding of its molecular basis. Our recent work with a well-characterized model for transcriptional memory demonstrated that memory is initiated by binding of a transcription factor, leading to essential changes in chromatin structure and allowing binding of a poised form of RNA polymerase II to promote the rate of future reactivation (D'Urso et al. in Elife. doi: 10.7554/eLife.16691, 2016).

Keywords Epigenetics · Chromatin · Transcription · Memory · Environmental response · Nuclear pore complex · Mediator · Histone methylation · Transcription factor

Epigenetic memory of environmental stimuli

Transcriptional responses to environmental changes play a critical role in allowing organisms to adapt to their environment. Epigenetic regulation of gene expression is both essential for proper development and survival (Pigliucci 2005) and can impact the response of organisms to environmental stimuli. Epigenetic transcriptional memory, whereby the rate or strength of the expression of genes in response to a stimulus is enhanced by previous exposure to that stimulus, has been observed in evolutionary divergent organisms in response to a variety of environmental stimuli (D'Urso and Brickner 2014). For example, in *Arabidopsis*, for several days following heat shock, the transcriptional responsiveness of certain genes to heat stress is stronger or faster (Ding et al. 2012, 2013; Sani et al. 2013; Liu et al. 2014; Lämke et al. 2016). In HeLa cells, hundreds of Interferon-γ-inducible genes exhibit faster/stronger induction in cells that have been previously exposed to Interferon-γ (IFN-γ; Gialitakis et al. 2010; Light et al. 2013). This effect persists for up to seven cell divisions (Light et al. 2013). In budding yeast, one of the first systems in which epigenetic transcriptional memory was described, several conditions induce memory: previous

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inositol starvation induces memory for *INO1* reactivation (encoding inositol-1-phosphate synthase), growth in galactose leads to memory for galactose-inducible *GAL* genes (Brickner et al. 2007; Kundu et al. 2007; Zacharioudakis et al. 2007; Tan-Wong et al. 2009), and previous treatment with high salt induces memory for ~75 genes induced by oxidative stress (Gasch et al. 2000; Berry and Gasch 2008; Guan et al. 2012). In every case, memory leads to heritable changes in the responsiveness of a subset of the genes that are induced by that stimulus. Thus, memory is likely an adaptive system that permits a faster response of cells to episodic challenges such as heat stress, nutritional deprivation or infection.

Molecular mechanisms of epigenetic transcriptional memory

Recent results suggest that epigenetic transcriptional memory is initiated by specific transcription factors that bind to the promoters of genes upon repressing transcription (D'Urso et al. 2016; Lämke et al. 2016). These factors promote changes in chromatin structure and binding of RNA polymerase II (RNAPII) to promote future transcriptional reactivation (D'Urso et al. 2016). For instance, heat shock in *Arabidopsis* leads to "acquired thermolerance" (heat stress memory), whereby some of the induced genes are expressed for days after heat shock and other genes exhibit faster induction in response to a subsequent heat stress. The binding of the heat shock factor-like transcription factor HSFA2 regulates genes that exhibit these behaviors. This factor specifically promotes the response to the second heat shock treatment and not the initial heat shock. Moreover, the effects of HSFA2 persist longer than the binding of HSFA2, suggesting that it stimulates downstream events important for memory (Lämke et al. 2016).

The yeast transcription factor Sfl1 plays an essential role in regulating *INO1* transcriptional memory. *INO1* memory requires a *cis*-acting memory recruitment sequence (MRS) in the promoter, to which Sfl1 binds specifically during memory (D'Urso et al. 2016). Sfl1 has a heat shock factor-like DNA binding domain but has been characterized as a transcriptional repressor (Fujita et al. 1989; Robertson and Fink 1998; Song and Carlson 1998). Loss of Sfl1 disrupts all aspect of *INO1* memory. Interestingly, although Sfl1 binds to the *INO1* promoter specifically during memory, Sfl1 recognizes other sites in the genome constitutively (i.e, the MRS inserted at an ectopic site in the genome or within the *SUC2* promoter), suggesting that Sfl1 binding to the *INO1* promoter is regulated by its promoter context (Song and Carlson 1998; D'Urso et al. 2016). This regulation might be due to the function of other transcription factors or to changes in chromatin structure.

Many genes that are induced by oxidative stress show memory in cells that have previously experienced high salt (Guan et al. 2012). Although these genes also have MRS-like elements in their promoters, they do not require Sfl1 suggesting that other transcription factor(s) may be involved in promoting this memory (Guan et al. 2012; D'Urso et al. 2016). These results suggest that cis-acting DNA elements and transcription factors can play essential roles in transcriptional memory. Furthermore, the downstream outputs of memory are universal and highly conserved (Fig. 1a, b).

Chromatin changes are required for transcriptional memory

Chromatin changes such as histone H3 lysine 4 methylation and the incorporation of histone variants (i.e., the histone variant H2A.Z) are essential for transcriptional memory (Brickner et al. 2007; Light et al. 2010). Loss of H3K4 methylation or H2A.Z disrupts the binding of RNAPII to the promoter and transcriptional memory. Our recent work has revealed how such chromatin changes are specified and how they promote the persistence/inheritance of memory.

A conserved and apparently universal chromatin change associated with transcriptional memory is dimethylation of histone H3 on lysine 4 (H3K4me2) (Fig. 1a). This histone mark has also been implicated in epigenetic phenomena that impact for germ-line development in *C. elegans* and *Drosophila* (Schaner et al. 2003). Genes in plants, plasmodium, yeast, and human that show memory have persistent H3K4me2 in their promoters specifically following previous expression (Santos-Rosa et al. 2002; Gialitakis et al. 2010; Light et al. 2013; Lämke et al. 2016; Bevington et al. 2016). This histone mark is inherited through cell division and is required for memory. Mutants lacking the histone methyltransferase that methylates H3K4 or expressing a mutant histone H3 with lysine 4 replaced with alanine or arginine are disrupted for *INO1* memory (D'Urso et al. 2016). Thus, H3K4me2 is essential for transcriptional memory.

In yeast, the *SET1/COMPASS* complex is the sole methyltransferase responsible for H3K4 methylation (Briggs et al. 2001; Roguev et al. 2001; Krogan et al. 2002). However, this complex has diversified in higher metazoans and different complexes produce H3K4me1, H3K4me2, and H3K4me3. For instance, flies have up to three COMPASS-related complexes and humans express up to six COMPASS-related complexes (Petruk et al. 2001; Hughes et al. 2004; Lee et al. 2007; Shilatifard 2008; Wu et al. 2008; Ardehali et al. 2011; Mohan et al. 2011). The diversity of the functions of these COMPASS-related complexes might explain how during memory dimethylation

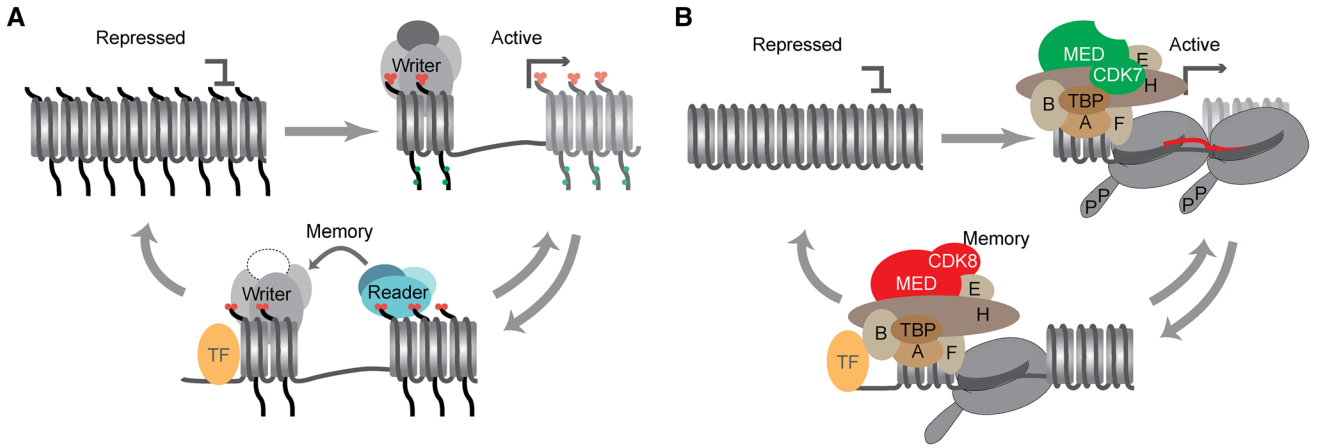

Fig. 1 Conserved and universal features of epigenetic transcriptional memory. **a** Chromatin changes during memory. Histones within the repressed promoter are hypoacetylated and unmethylated. Upon transcriptional activation, nucleosomes become acetylated (*green circles*) and tri-methylated (*red circles*) on histone H3, lysine 4 by the Set1/COMPASS writer. Upon repression, memory is initiated by the binding of a specific transcription factor (TF), leading to remodeling of the writer to generate H3K4me2. This mark recruits the SET3C reader complex, which promotes the persistence of H3K4me2 possibly by a positive feedback with the remodeled writer complex. **b** Mediator-dependent poising. Active transcription is associated with the preinitiation complex, including Mediator lacking Cdk8 and the Cdk7/TFIIK kinase, which phosphorylates serine 5 of the RNAPII CTD to stimulate initiation. Upon repression, memory is initiated by the specific binding of a transcription factor (TF), leading to remodeling of Mediator to recruit Cdk8 and potentially excluding Cdk7/TFIIK. Cdk8^{+} Mediator promotes recruitment of poised RNAPII during memory, bypassing the rate-limiting step in future activation

of H3K4 is produced, but not mono- or tri-methylation of H3K4. We discovered that yeast COMPASS can be remodeled to achieve the same purpose. During *INO1* memory, the COMPASS complex is remodeled upon repression to remove Spp1, a subunit that is required for COMPASS to catalyze tri-methylation of H3K4 but is dispensable for dimethylation of H3K4 (D'Urso et al. 2016) (Fig. 1a). This results in loss of H3K4me3 and formation of H3K4me2 during memory. Thus, although higher metazoans have evolved several complexes that can catalyze mono-, di-, or tri-methylation of H3K4, yeast remodels a single COMPASS complex to generate different outputs at the same locus (Fig. 1a).

To date, dimethylation of H3K4 has been associated with all genes that exhibit memory (Gialitakis et al. 2010; Light et al. 2013; D'Urso et al. 2016; Lämke et al. 2016). What is its function? H3K4 dimethylation recruits the SET3/HDAC Complex through binding of the PHD finger of Set3 (Kim and Buratowski 2009; Kim et al. 2012). SET3C is essential for both *INO1* memory and salt stress memory (D'Urso et al. 2016). Inactivation of a conditional allele of Set3 leads to rapid loss of poised RNA polymerase II (Light et al. 2013; D'Urso et al. 2016). Surprisingly, inactivation of SET3C also led to rapid loss of the H3K4me2 mark itself (D'Urso et al. 2016). Therefore, Set3 both recognizes the H3K4me2 modification and is essential for maintaining the mark. It is possible that SET3C either protects H3 lysine 4 from demethylases or promotes recruitment of remodeled COMPASS during memory, creating a positive feedback-loop that promotes the persistence or inheritance of this chromatin modification (Ragunathan et al. 2015; D'Urso et al. 2016). Set3 is similar to mammalian MLL5 and SET3C is related to NCoR/SMRT in metazoan organisms. The Trithorax H3K4 methyl transferase complex in flies interacts directly with the nucleoporin Nup98, which is essential for transcriptional memory (Capelson et al. 2010; Light et al. 2013). In addition, the NCoR/SMRT complex is required for RNAPII poising at human PARP gene (Pavri et al. 2005). Thus, homologous proteins may play a similar role in higher metazoans.

How does memory lead to faster transcriptional reactivation?

The critical output of memory is to allow recruitment of a poised form of RNAPII to the promoter, bypassing the rate-limiting step during future transcriptional activation (Fig. 1b). Memory in yeast and human cells is associated with a poised form of RNAPII that it is unphosphorylated on serine 5 of the carboxy terminal domain (CTD), suggesting that it has not initiated transcription (Light et al. 2010, 2013). Such a poised RNAPII can been found binding to many inactive genes in yeast and humans (Pavri et al. 2005; Light et al. 2013; D'Urso et al. 2016). For instance, the human retinoic acid receptor β promoter is bound by RNAPII and a poised form of the PIC in the absence of retinoic acid (Pavri et al. 2005). Likewise, in *C. elegans,*

starvation of L1 larvae leads to RNAPII "docking" over the promoters of genes involved in growth and development (Maxwell et al. 2014). This form of RNAPII is neither active nor paused, suggesting that it may be similar to the poised RNAPII associated with genes that exhibit transcriptional memory. Therefore, three distinct steps in transcription can be regulated: (1) PIC assembly and recruitment, (2) transcription initiation and (3) transcription elongation.

We now have a model for the molecular basis of transcriptional poising during transcriptional memory. Both active *INO1* and recently repressed *INO1* bind to the PIC components TATA binding protein (TBP), TFIIA, TFIIB, TFIIE, TFIIF, TFIIH, and Mediator (Light et al. 2013; D'Urso et al. 2016). However, there are several critical differences. Whereas active *INO1* recruits the Cdk7 kinase (a.k.a. TFIIK/Kin28), which phosphorylates RNAPII on serine 5 of the CTD, this kinase and the resulting phosphorylation are absent during memory (Fig. 1b; Light et al. 2013; D'Urso et al. 2016). RNAPII phosphorylation by Cdk7 disrupts the interaction of Mediator with the preinitiation complex (PIC), allowing promoter escape (Wong et al. 2014; Jeronimo and Robert 2014). This suggests that initiation is prevented under memory conditions by the absence of Cdk7. Inactivation of PIC components reveals the same pattern. Recruitment of poised PIC during *INO1* transcriptional memory requires TBP, Mediator and TFIIH, but it is independent of Cdk7. Thus, the molecular requirements for assembly of poised PIC are distinct from the molecular requirements for assembly of active PIC (Fig. 1b).

Likewise, two different types of Mediator are recruited to promoters under activating and memory conditions: Mediator lacking Cdk8 under activating conditions and Cdk8$^+$ Mediator under memory conditions (D'Urso et al. 2016). Inactivation of Cdk8 had no effect on the binding of RNAPII under activating conditions or on the rate of initial activation. Cdk8$^+$ Mediator binding correlates with memory for a number of yeast and human genes, suggesting that Cdk8 plays a universal and conserved role during memory (D'Urso et al. 2016). Because Cdk7 is not present during memory, Cdk8$^+$ Mediator may allow assembly of the preinitiation complex, but prevent recruitment of Cdk7 (Fig. 1b). In this way, Cdk8$^+$ Mediator could facilitate transcriptional poising without allowing initiation.

Conclusions

Previous experiences can induce transcriptional memory for certain genes through a deeply conserved molecular mechanism. From studies of several model genes, it seems reasonable to propose that memory is initiated by binding of transcription factors that both alter promoter chromatin structure and recruit Cdk8$^+$ Mediator, leading to binding of poised RNAPII (Fig. 1b). The duration and epigenetic inheritance of memory requires transcription factors, changes in chromatin structure, and recognition of that chromatin state by a reader protein. It is unclear if the epigenetic inheritance of memory is mediated simply by the regulating binding of transcription factors or if the chromatin changes associated with memory can be self-propagating. The examples highlighted in this review show that transcriptional memory can quantitatively or qualitatively alter the phenotype of an organism over significant time scales, potentially impacting fitness. Quantifying this benefit will be an important challenge for the future.

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