Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Genetics & Development

Inheritance of epigenetic transcriptional memory

Tiffany Ge and Jason H Brickner*

Epigenetic memory allows organisms to stably alter their transcriptional program in response to developmental or environmental stimuli. Such transcriptional programs are mediated by heritable regulation of the function of enhancers and promoters. Memory involves read–write systems that enable self-propagation and mitotic inheritance of *cis*-acting epigenetic marks to induce stable changes in transcription. Also, in response to environmental cues, cells can induce epigenetic transcriptional memory to poise inducible genes for faster induction in the future. Here, we discuss modes of epigenetic inheritance and the molecular basis of epigenetic transcriptional memory.

Address
Department of Molecular Biosciences, Northwestern University, Evanston, IL, USA

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

Current Opinion in Genetics & Development 2024, **85**:102174

This review comes from a themed issue on **Genome Architecture and Expression**

Edited by **Maya Capelson** and **Eda Yildirim**

Available online xxxx

https://doi.org/10.1016/j.gde.2024.102174

Introduction

An improved understanding of nuclear architecture has begun to reveal how genome organization affects transcription and other biological functions. Changes in chromatin conformation and composition influence gene expression [1]. These epigenetically heritable alterations are one of the ways in which cells respond to, and *remember*, developmental or environmental stimuli. Epigenetic regulation and memory involve mitotically — and sometimes trans-generationally — heritable mechanisms [2]. For example, in worms, fruit flies, mice, and humans, changes in paternal or maternal diet can reprogram the metabolism of offspring in future generations to cause a predisposition toward obesity or associated conditions [3–7]. Stable changes in transcription are associated with changes in DNA methylation, posttranslational histone modifications [8], transcription factor (TF) activity, noncoding RNA expression, or mRNA stability [9]. Recent experiences can also be remembered for several mitotic cell divisions; some inducible genes exhibit heritable epigenetic transcriptional memory following exposure to a transient stimulus [10]. Transcriptional memory poises genes for faster reactivation, allowing cells to better adapt to a previously encountered condition [11–15]. Stable transcriptional states and less-stable transcriptional memory both involve heritable regulation of promoter and enhancer functions in *cis*. In this review, we will discuss both general molecular mechanisms of heritable epigenetic regulation and, more specifically, epigenetic transcriptional memory.

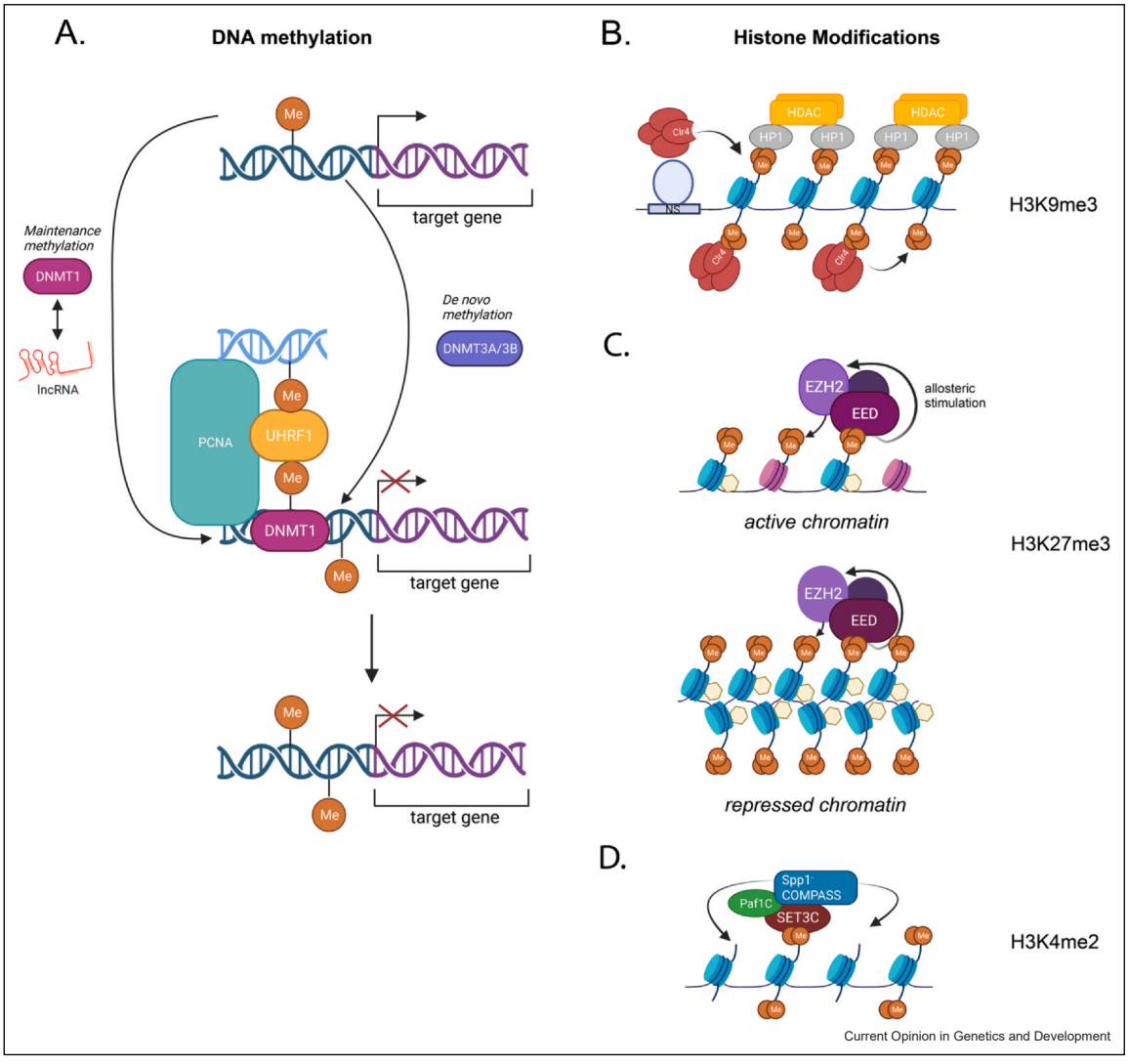
DNA methylation as an epigenetic regulator of transcription

One of the best-understood mechanisms of heritable transcriptional regulation is the methylation of DNA. The amino group on adenosine is methylated in bacteria, and the C5 position of cytosine is methylated in plants, mammals, and certain fungi such as *Neurospora crassa* [16]. However, DNA methylation is not universal; *Drosophila* has very low levels of cytosine methylation, *C. elegans* has low levels of adenosine methylation but not cytosine methylation [17], and budding and fission yeasts lack DNA methylation [18].

In mammals, methylation of cytosine in cytosine–guanine dinucleotides (CpG) can be inherited during mitosis because it is re-established following DNA replication. Unmethylated cytosine nucleotides are incorporated into newly synthesized strands during DNA replication, producing hemimethylated CpGs. These hemimethylated CpGs are recognized by maintenance DNMT1, which methylates the cytosines on the daughter strand to re-establish methylation patterns. DNMT1 interacts with replication cofactor Proliferating Cell Nuclear Antigen to couple replication to DNA methylation [19] (Figure 1a). The *de novo* DNA methyltransferases DMNT3A, DNMT3B, and DNMT3C establish new cytosine methylation on unmethylated sites (Figure 1a). DNMT3A/B/C can be recruited to sites in the genome by TFs [20], histone modifications [21], and other mechanisms [20].

CpG methylation impacts transcription by promoting stable silencing of many genes, intergenic regions, repeat elements, and transposons during cell differentiation, embryonic development, and X-inactivation [22,23]. In mammals, abnormal CpG methylation profiles can result in abnormal gene expression and phenotype [6]. Cytosine methylation can lead to different outcomes based on its context. Methylation near promoters often facilitates

Figure 1



Epigenetic inheritance mediated by DNA methylation, lncRNAs, and histone modifications. **(a)** DNMT1 is required for recognizing hemimethylated CpGs and maintaining DNA methylation after replication in organisms with DNA methylation. It interacts with PCNA and is recruited by ubiquitination of histone H3 and PAF15 by UHRF1. LncRNAs can also recruit DNMT1 to chromosomal loci to promote DNA methylation [44,49]. DNMT3A/3B establish *de novo* DNA methylation, particularly during embryogenesis and establishing imprinting. These methyltransferases are important in establishing epigenetic memory via DNA methylation. **(b)** In propagating H3K9me3 in fission yeast, HDAC Clr3 (yellow) is recruited by HP1 and sequence-specific DNA-binding factors (light-blue circle) at silencer elements or nucleation sites (NS) to deacetylate histones and reduce histone turnover, thus maintaining the H3K9me3 mark. A certain level of chromatin-bound Clr3 and high H3K9me3 density is required to keep the H3K9me3 mark and promote the dual read–write activity of $Clr4^{Suv39h}$ (red), which can bind methylated H3K4 via its chromodomain and catalyze methylation of H3K9 to promote the propagation of heterochromatin [60]. **(c)** For H3K27me3 mark in mouse embryonic stem cells, self-propagation involves H3K27me3 marks on parental histones, PRC2 complex, and linker histone H1. The EED reader component of PRC2 complex binds H3K27me3 and the EZH2 writer component of PRC2 catalyzes methylation of H3K27 on adjacent nucleosomes. In mESCs, after H3K27me3 is diluted during DNA replication due to newly incorporated histones (pink), linker histone H1 (yellow) compacts chromatin at heterochromatic regions to promote restoration of H3K27me3 on repressive genes [65]. Repressed chromatin with higher levels of H1 experience rapid re-establishment of H3K27me3 after replication, while active chromatin with lower levels of H1 experience slower rates [65]. **(d)** Establishment of epigenetic memory in yeast and humans requires RNAPII-independent H3K4me2, which promotes SWR1-dependent incorporation of histone variant H2A.Z upstream of poised gene promoters as well as recruitment of poised RNAPII, and interaction with the nuclear pore. This histone mark can be transmitted through mitosis by a proposed mechanism whereby the SET3C reader recognizes H3K4me2, interacts with Leo1, a subunit of Paf1 complex, to recruit a Spp1-deficient version of COMPASS that re-establishes H3K4me2 [14]. DNMT1; DNA Methyltransferase 1, PCNA; Proliferating Cell Nuclear Antigen, UHRF1; Ubiquitin-like with PHD and Ring Finger domains 1, HDAC; Histone Deacetylase, EED; Embryonic Ectroderm Development, mESCs; mouse Embryonic Stem Cells, SWR1; Swi2/Snf2-Related ATPase, COMPASS; Complex of proteins associated with Set1, PHD; Plant Homeodomain, RNAPII; RNA polymerase II.

transcriptional repression by inhibiting binding of transcriptional activators or methylation-sensitive TFs [24] and recruiting repressive methyl-binding proteins. Furthermore, DNA methylation over promoters is anticorrelated with expression of genes associated with differentiation during eye development in mammals [23]. In contrast, DNA methylation in the gene body is associated with gene expression in mammals [19], but has an unclear functional significance in plants [25].

Despite the stability and conservation of DNA methylation patterns, aging [26], DNA damage [27], spaceflight [28], or drought stress [29] can alter CpG methylation, leading to new, stable methylation profiles and transcriptional patterns. Stress-induced changes in DNA methylation can even prime the future offspring to better tolerate or effectively respond to such stresses [30] in a manner reminiscent of epigenetic transcriptional memory (see below). It should be noted, however, that stable transgenerational epigenetic inheritance of DNA methylation, while relatively common in plants, is rare in mammals because of erasure during early embryonic development [31].

Noncoding RNAs as epigenetic regulators of transcription

Most of the transcriptional output in plants and animals are long noncoding RNAs (lncRNAs) [32]. LncRNAs are short-lived, > 200-bp-long, nuclear [33] RNAs that facilitate transcriptional regulation. These transcripts are cell-type-specific, transcribed from sequences overlapping or upstream of coding genes. Dysregulated expression of lncRNAs has been implicated in cancer [34–36] and neurodegenerative diseases [37–42]. LncRNAs influence transcription by associating with chromatin and influencing the recruitment of enzymes that mark either DNA or histones. Their effects can produce long-term changes in the transcription of the genome (Figure 1a) [43–46]. For example, the *Xist* lncRNA coats the inactive X chromosome, stimulating recruitment of polycomb-repressive complex 1 (PRC1) and 2 (PRC2), which methylates histone H3 on lysine 27 and ubiquitinates H2A [44,47], repressing transcription [48]. Likewise, the *TINCR* lncRNA recruits DNA methyltransferase 1 (DNMT1) to chromosomal loci to promote DNA methylation and inhibit transcription (Figure 1a) [44,49]. However, lncRNAs can also promote transcription; in response to a stimulus eliciting an immune response, immune gene promoters associate with immune gene-priming lncRNA *Upstream Master lncRNA of the Inflammatory cytokine Locus* [50]. *Upstream Master lncRNA of the Inflammatory cytokine Locus* recruits the histone methyltransferase complex WDR5–MLL1, promoting trimethylation of H3K4, which primes them for enhanced response upon subsequent exposure, a form of transcriptional memory [50]. Although there is still much to uncover on the specifics of these mechanisms, it is evident that lncRNAs can function in *trans* to alter the chromatin landscape to induce heritable changes in transcription.

Histone modifications as epigenetic regulators of transcription

Posttranslational modification (PTM) of histones is associated with shorter-term, less-stable epigenetic regulation than CpG methylation. DNA is wrapped around histone octamers, which comprise two copies of each core histone proteins H2A, H2B, H3, and H4. At the amino terminus of each of these proteins are unstructured, positively charged tails. Chemical modifications of histones within nucleosomes are associated with — and required for — proper transcriptional regulation in *cis* [51]. Transcription is associated with acetylation of histone tails. Histone acetyltransferases are generally recruited to active genes by sequence-specific TFs [52]. Histone acetylation neutralizes the net positive charge of histones, reducing their affinity for negatively charged DNA [51], increasing access to DNA, and allowing sequence-specific TFs to bind. Acetylated lysines on histones also recruit factors and protein complexes with chromatin-modifying or chromatin-remodeling activities [51]. Acetyltransferases and deacetylases play critical roles in transcriptional activation and repression, respectively.

Methylation of histones enables binding by proteins bearing at least ten distinct reader domains, such as chromodomains (for histone H3 lysine-9 methylation), Plant Homeodomain domains (for H3 lysine-4 methylation), and specialized WD40 domains (for H3 lysine-27 methylation). Transcriptional repression is associated with methylation of H3 lysine 9 (H3K9me) over constitutively silenced heterochromatin and H3 lysine 27 (H3K27me) over conditionally silenced facultative heterochromatin [53]. Meanwhile, active regions are associated with methylation of H3 lysine 4 (H3K4me) and H3 lysine 36 (H3K36me). Thus, histone methylation demarcates different parts of the genome: H3K4me1 at enhancers [54], H3K4me3 at gene promoters, and H3K36me3 over gene bodies [54]. H3K4me2 marks are found at promoters and gene bodies at both active and poised genes in yeast [55,56]. The effects of each of these histone methylation marks reflect their ability to recruit co-repressors such as Heterochromatin Protein 1 (HP1) (in the case of H3K9me3), histone deacetylases (in the case of H3K27me3), or co-activators histone acetyltransferases (in the case of H3K4me3).

Based on contact frequency between chromosomal regions, chromatin can be organized into at least two distinct compartments called A and B [57]. The A compartment contains active chromatin — nearly all active promoters, distal enhancer elements, and active transcription start sites — while

the B compartment contains inactive, quiescent chromatin, and most transcription termination sites [57]. The A compartment comprises two subcompartments, A1 and A2, which are enriched for genes and active chromatin marks such as H3K4me1, H3K27ac, H3K36me3, and H3K79me2 [58]. While both are gene-rich, A2 associates more with H3K9me3, contains longer genes, is replicated later than A1, and is farther from nuclear speckles than A1 [58]. The B compartment is made up of subcompartments B1, B2, B3, and B4, of which B1 correlates with features of facultative heterochromatin (i.e. higher levels of repressive mark H3K27me3, lower levels of active mark H3K36me3), B4 with heterochromatin-associated repressive marks (H3K9me3 and H4K20me3), while B2 and B3 do not contain commonly known histone marks [57,58]. Thus, histone modifications also reflect genome compartmentalization.

Parental histones and their PTMs can be reincorporated near their original location following DNA replication [59]. Reincorporation, followed by recognition of these marks by 'reader' proteins, which recruit 'writer' enzymes, can lead to heritable histone modifications. Such read–write inheritance has been demonstrated for H3K9 [60,61] and H3K27 [62–66] methylation (Figure 1b, c) and facilitates inheritance of long-term silencing.

Are the histone marks associated with active transcription heritable? Unlike repressive chromatin marks, most histone modifications associated with transcription are not heritable, partially due to the continuous displacement of parental nucleosomes by transcription [59]. Furthermore, erasers such as histone deacetylases and demethylases actively remove marks such as H3K27ac and H3K4me3 [11,55] upon repression of inducible genes. Likewise, whereas nucleosomes over repressed chromatin domains are reincorporated through many replication cycles, nucleosomes at active genes are poorly retained through DNA replication [59,65]. Thus, in general, histone modifications associated with active transcription are reflective of current transcription and are lost quickly, making them poor sources of heritable epigenetic regulation.

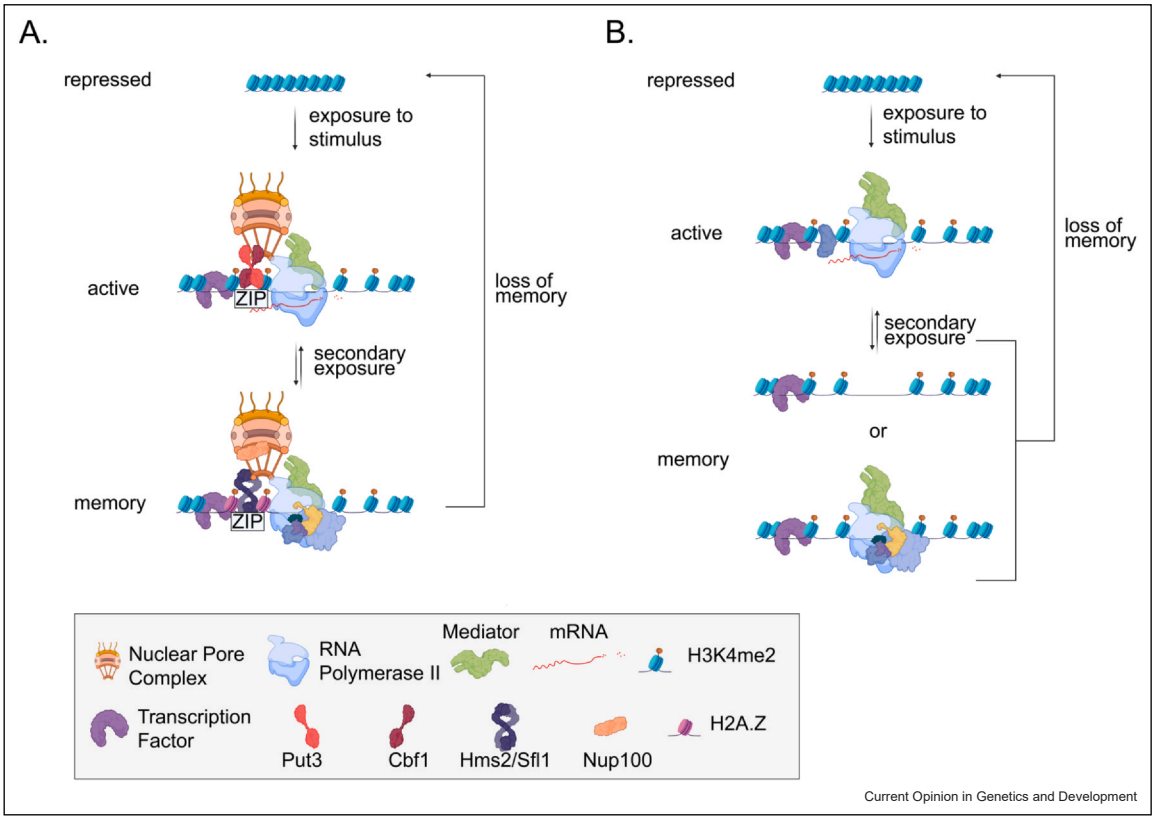
Epigenetic transcriptional memory

A potential exception to the previous statement is the phenomenon of epigenetic transcriptional memory, which has been observed in yeast [55,67], flies [68], plants [69,70], and mammals [6,11]. Certain inducible genes remain poised for rapid reactivation for several generations after removal of the inducing stimulus [11,62,67,68,71,72], and mitotic inheritance of this type of transcriptional memory requires histone modifications. Memory consists of 1) activation of inducible genes, 2) upon removal of the stimulus, a poised state (i.e. transcriptional memory) is established at certain genes, 3) memory is inherited through mitosis, and 4) upon a second exposure to the inducing stimulus, these genes are activated more rapidly or more strongly than in naive cells (Figure 2). This process is akin to priming or acclimation in plants in response to various stresses such as drought, heat, salt, irradiation, and pathogens [73–76]. In several cases, memory requires a physical interaction with the nuclear pore complex (NPC), which has been shown to play a part in regulating gene expression [11,77,78].

A well-characterized model for memory is a set of yeast genes induced by starvation for the essential sugar inositol. When yeast cells are starved for inositol, target genes such as *Inositol requiring 1* (*INO1)* and *choline requiring 1* are activated and rapidly targeted to the nuclear periphery through a physical interaction with the NPC [67]. The interaction with the NPC requires binding of the TFs Cbf1 and Put3 does *cis*-acting DNA zip codes upstream of the promoter [79,80]. Resupplementation of inositol leads to rapid repression of these genes, but they remain poised at the nuclear periphery for approximately four generations [62,71]. Retention at the nuclear periphery after repression involves a distinct molecular mechanism from that utilized during active transcription (i.e. different nuclear pore proteins, different TFs, and different molecular requirements, see Figure 2a). During memory, the nucleosomes over the promoters and 5'-ends of these genes are both unacetylated and possess dimethylated histone H3 lysine 4 (H3K4me2). This combination of low acetylation and H3K4me2 appears to be unique to memory [55]. In the case of the *INO1* promoter, memory also leads to incorporation of H2A.Z into upstream nucleosomes (Figure 2a). Finally, the promoters of such poised genes are associated with a pre-initiation form of RNAPII [11,14,55,71]. Upon a second exposure to inositol starvation, these genes exhibit faster reactivation, leading to a fitness advantage over naive cells [14].

Similar phenomena have been observed in flies responding to hormonal signals [77], in mammalian cells responding to cytokine signaling and wounds [81], in worms responding to starvation during larval development [82], and in plants responding to environmental stressors, including drought and temperature changes [70,74,76]. In some cases, the molecular players are similar. For example, in flies and human cells, the nuclear pore protein Nup98 has been implicated in memory, and a homologous protein (Nup100) is essential for memory in yeast. In these organisms, Nup98 does not localize exclusively at the NPC, so this may not reflect interaction with the NPC [84]. In flies, Nup98 is not only involved in gene activation [83,84], but it is also required for enhancer–promoter looping and epigenetic transcriptional memory at genes induced by the hormone ecdysone [68]. Likewise, H3K4 methylation is associated with both interferon gamma (IFN-γ) memory in

Figure 2



Epigenetic transcriptional memory in yeast and mammalian cells. **(a)** Yeast *INO1* memory. Upon primary exposure to a stimulus, the Ino2/4 activators recruit HAT complexes to acetylate histones and thus increase DNA accessibility to TFs and the transcriptional machinery. This leads to binding of Put3 and Cfb1 to DNA zip codes (ZIP) and interaction with the NPC. Upon repression, transcriptional memory is established. The Sfl1/Hms2 TF binds to the MRS DNA zip code, leading to interaction with the NPC. This interaction stimulates RNAPII-independent H3K4 dimethylation, H2A.Z incorporation, and binding of poised RNAPII [14,55,71]. If the cells are starved for inositol again, *INO1* is more rapidly induced. Eventually, memory is lost and the gene relocalizes to the nucleoplasm and the chromatin returns to a repressed state. **(b)** Transcriptional memory in mammals. Following removal of an inducing stimulus, the activated gene is repressed, epigenetic transcriptional memory is established through binding of specific TFs. Memory is associated with maintenance of accessible chromatin and/or through read–write systems to promote H3K4 methylation. Memory can require interaction with nuclear pore proteins, recruitment of a form of mediator with Cdk8, and poised RNAPII. Once memory is lost, chromatin returns to a repressed hypoacetylated state [62]. *INO1; Inositol requiring 1*.

human cells [11,85] and heat shock memory in plants [86,87]. Thus, evolutionarily distant organisms utilize mechanistically similar, mitotically heritable mechanisms to integrate previous environmental stimuli into future responses.

Molecular mechanisms of epigenetic transcriptional memory

Memory is associated with H3K4me2, but not H3K4me3. This is due to the recruitment of an alternative form of the H4K4 methyltransferase Set1/COMPASS lacking the Spp1 subunit during memory (Figure 1d) [55]. H3K4me2 has a critical role in epigenetic transcriptional memory. This mark is associated with memory in yeast, humans, and plants. Inactivation of Nup100 in yeast, which causes loss of interaction with the NPC and consequently H3K4 methylation, or Nup98 in human cells leads to loss of both H3K4me2 and poised RNAPII [11,14,55,71]. Likewise, mutation of H3K4 to alanine or arginine, inactivation of either the writer of H3K4 methylation (Set1/COMPASS) or the putative reader of H3K4me2 (the SET3C complex), leads to loss of both H3K4 methylation and RNAPII [55]. Furthermore, conditional genetic experiments demonstrate that H3K4me2 is essential for recruitment of RNAPII during memory [14]. A similar relationship between H3K4 methylation and RNAPII was also seen in mouse embryonic stem cells, where depletion of a core COMPASS subunit resulted in depletion of H3K4 methylation and a loss of paused RNAPII [11,55,71], which negatively impacted gene expression [88]. However, this is not always true; inactivation of the sole

H3K4 methyltransferase (Set1/COMPASS) in yeast does not strongly affect RNAPII activity and has no apparent effect on RNAPII association with active *INO1* [55].

The relationship between H3K4 methylation and the NPC is complex. Loss of Sfl1, the TF that mediates interaction with the NPC, or the NPC protein Nup100 (Figure 2a), leads to loss of H3K4me2 during memory [11,14,55]. However, loss of H3K4 methylation results in loss of both H2A.Z and Sfl1, the TF that mediates interaction with the NPC [14]. This suggests that H3K4 methylation and the interaction with the NPC represent a positive-feedback loop — interaction with the NPC promotes H3K4 methylation and incorporation of H2A.Z, which promotes binding of the TF that mediates interaction with the NPC.

Could H3K4me2 be the source of inherited information during memory? In certain cases, H3K4 methylation can be inherited. H3K4 methylation can persist through mitosis in yeast [89] and is required to perpetuate transcription through multiple cell divisions from a transplanted nucleus in frogs [90] and the transgenerational effects from a high-fat diet in worms [3]. However, when an active gene that lacks memory is repressed, H3K4 methylation is quickly lost [55]. This suggests that the stability and heritability of H3K4 methylation are context-dependent.

The H3K4me2 associated with epigenetic transcriptional memory is the product of a pathway that is mechanistically distinct from H3K4 methylation associated with active transcription. H3K4 methylation associated with transcription is dependent on RNA polymerase II (RNAPII); Set1/COMPASS is recruited to active RNAPII via the Paf1 complex [14], which binds to the phosphorylated carboxy-terminal domain of RNAPII. This type of H3K4 methylation does not require nuclear pore proteins or reader complex SET3C. However, H3K4me2 associated with *INO1* memory requires not only Set1/COMPASS and the Paf1 complex, but also Nup100 and SET3C. In fact, one subunit of the Paf1 complex (Leo1) is required for H3K4me2 during memory but does not impact H3K4 methylation at active genes [14]. Finally, H3K4 dimethylation during memory does not require RNAPII, which suggests that memory utilizes an RNAPII-independent, Nup100-dependent mechanism to recruit Spp1$^-$ Set1/COMPASS. And unlike the H3K4 methylation associated with active transcription, H3K4me2 associated with memory is mitotically heritable.

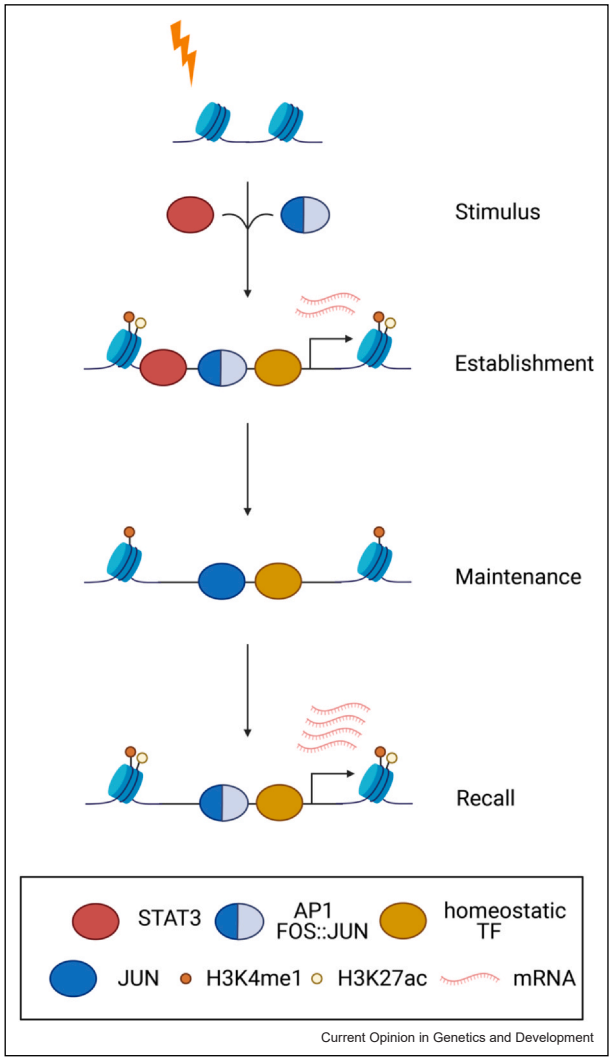
Can the H3K4me2 mark itself be inherited? *INO1* memory requires a specific *cis*-acting DNA element DNA zip code called the Memory Recruitment Sequence (MRS) that recruits the TFs Sfl1 and Hms2 to mediate interaction with the NPC via Nup100 [62,71]. Conditional inactivation of Sfl1 disrupts most aspects of transcriptional memory (i.e. localization to the nuclear periphery and RNAPII recruitment). However, after memory has been established, inactivation of Sfl1 has no effect on H3K4me2, which persists and is reintroduced for up to 4 generations after loss of Sfl1 [14]. Thus, once established, H3K4me2 does not require interaction with the NPC to be inherited. This mechanism of inheritance does require the putative reader protein SET3C [55], suggesting that the recognition of H3K4me2 may function as part of a read–write mechanism of chromatin replication where Spp1$^-$ Set1/COMPASS is recruited by SET3C following DNA replication to maintain H3K4 dimethylation.

Mammalian cells exhibit transcriptional memory in response to cytokine signaling. Upon viral, bacterial, or parasitic infection, the cytokine interferon gamma (IFN-γ) is produced. When cells (i.e. macrophages and fibroblasts) previously exposed to IFN-γ are restimulated, they exhibit transcriptional memory, resulting in faster and stronger expression of certain target genes [12]. Furthermore, this transcriptional memory can be inherited over multiple generations [11,13], confers more antiviral protection to the cells, and results in increased histone H3.3 and H3K36me3 marks on primed genes, which were associated with faster recruitment of RNAPII, TFs, and chromatin factors (Figure 2b) [12,13]. Some primed genes in yeast and human cells interact with both nucleoporins and poised RNAPII and exhibit H3K4me2 [11,62,85]; however, poised RNAPII was not seen in mouse fibroblasts nor at all genes that exhibit memory in HeLa cells (Figure 2b) [12,13].

Genes with strong IFN-γ-induced transcriptional memory are often located within clusters and their memory is constrained by Cohesin, which mediates DNA looping, sister chromatid cohesion, and homologous recombination [13]. These genes were also found to have enhanced chromatin accessibility at target gene promoters in primed cells that correlated with faster targeting of TFs STAT1 and Interferon Regulatory Factor 1 at several guanylate-binding protein gene promoters in primed HeLa cells [91]. In fact, Signal Transducer and Activator of Transcription 1 (STAT1) is required for establishment but not maintenance of IFN-γ-induced transcriptional memory in human cells [91] (Figure 3).

Another example of transcriptional epigenetic memory in mammals is the inflammatory response. During the first experience of wound repair or inflammation stimulated by an acute stimulus called imiquimod, epidermal stem cells (EpdSCs) develop an epigenetic memory to promote future wound healing via faster gene reactivation upon subsequent exposures. In forming memory in these cells, lncRNAs are transcribed to interact with

Figure 3



Inflammation memory. Upon wound repair or inflammation caused by an acute stimulus (lightning bolt), EpdSCs mount a transcriptional response mediated by stress-response-associated TFs FOS (light blue) and JUN (navy) and stimulus-specific TFs such as STAT3 (red). These three factors are essential in establishing memory following inflammation, but STAT3 functions upstream of FOS–JUN. During inflammation, chromatin changes, including H3K4me1 (orange circles) and H3K27ac (light-yellow circles), are associated with regions that will exhibit memory. Once the inflammation has resolved, memory domains retain some of the H3K27ac but more of the H3K4me1; furthermore, these regions retain JUN as well as other homeostatic TFs (yellow), which are sufficient for their maintenance. Upon subsequent exposure to similar stimuli, FOS is quickly re-recruited to the memory domains in a STAT3-independent manner. FBJ; Murine Osteosarcoma viral oncogene homolog.

Mediator and recruit histone remodelers similar to inflammatory TFs, which are required to make chromatin regions near inflammation-induced genes accessible for transcription [15]. The accessibility and inflammation-associated histone modifications (mainly H3K4me1, but in some instances H3K27ac) remain at these regions or 'memory domains' long after the inflammation and increased transcription levels have subsided [10]. In the case of EpdSCs, a cell-type and stimulus-specific TF, STAT3, and stress-response Activator Protein 1 (a protein complex comprising FBJ Murine Osteosarcoma viral oncogene homolog (FOS) and JUN proteins) are required for inflammation-induced memory. STAT3 is required for allowing FOS–JUN to access, bind, and establish memory domains. While STAT3 and FOS are reduced after inflammation subsides, JUN — alongside Activating Transcription Factor 3 and p63— remains bound to memory domains to keep chromatin accessible and primed [10]. Upon subsequent exposures, FOS can be quickly recruited to JUN-bound memory domains for rapid reactivation and enhanced expression of inflammation-associated genes in a STAT3-independent fashion [10]. Thus, similar to other forms of transcriptional memory, inflammation memory involves an interplay between TFs and histone modifications to regulate transcription in *cis*.

Concluding remarks

Cells utilize epigenetic transcriptional regulation to both stabilize transcriptional states and to remember recent experiences. During development, differentiation is achieved by establishment and maintenance of very stable transcriptional programs through a combination of mechanisms involving DNA methylation, lncRNA-mediated regulation, and histone modifications. These epigenetic mechanisms also mediate transcriptional changes over intermediate timescales. Here, we have focused on epigenetic transcriptional memory, which has been observed in diverse eukaryotic organisms in response to diverse stimuli. Various models of transcriptional memory are beginning to reveal new insights into how TFs, histone modifications, and chromosome folding can impact future transcription and how this state can be inherited. Depending on the organism and stimuli, distinct mechanisms are used to mediate memory. Thus, while it is unlikely that all forms of epigenetic transcriptional memory utilize the same mechanism, nonetheless, this diversity strongly supports the idea that remembering previous experiences provides a strong fitness advantage.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to recognize our colleagues cited for their contributions to the field, colleagues that could not be cited due to space limitations, the editors of this edition for their patience, and members of the Brickner laboratory for helpful discussions and comments on this paper. Thank you to Calvin Brickner for the translation of *ju-nana*. T.G. also thanks her friends and family for their unwavering support and encouragement. Illustrations were generated using BioRender. T.G. was supported by National Institute of General Medical Sciences (NIGMS) Grant T32 (GM008061-35). T.G. and J.B. were supported by NIGMS Grant R35 (to J.B.).

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. Waddington CH: **The epigenotype. 1942**. *Int J Epidemiol* 2012, **41**:10-13.

2. Berger SL, Kouzarides T, Shiekhattar R, Shilatifard A: **An operational definition of epigenetics**. *Genes Dev* 2009, **23**:781.

3. Wan QL, *et al*.: **Histone H3K4me3 modification is a transgenerational epigenetic signal for lipid metabolism in Caenorhabditis elegans**. *Nat Commun* 2022, **13**:1-14.

4. Lin XH, *et al*.: **Maternal high-fat-diet exposure is associated with elevated blood pressure and sustained increased leptin levels through epigenetic memory in offspring**. *Sci Rep* 2021, **11**:1-13.

5. Hata M, *et al*.: **Past history of obesity triggers persistent epigenetic changes in innate immunity and exacerbates neuroinflammation**. *Science* 2023, **379**:45-62.

6. •• Takahashi Y, *et al*.: **Transgenerational inheritance of acquired epigenetic signatures at CpG islands in mice**. *Cell* 2023, **186**:715-731 e19.
This study showed that integration of CpG-free DNA into targeted CGIs can induce *de novo* DNA methylation and silencing that can be inherited across generations.

7. Eickelberg V, Lüersen K, Staats S, Rimbach G: **Phenotyping of Drosophila melanogaster—a nutritional perspective**. *Biomolecules* 2022, **12**:221.

8. Riggs A.D., Porter T.N.: **Overview of epigenetic mechanisms**. *Epigenetic Mechanisms of Gene Regulation*; 1996.

9. Li B, *et al*.: **Differential regulation of mRNA stability modulates transcriptional memory and facilitates environmental adaptation**. *Nat Commun* 2023, **14**:1-17.

10. •• Larsen SB, *et al*.: **Establishment, maintenance, and recall of inflammatory memory**. *Cell Stem Cell* 2021, **28**:1758-1774 e8.
This paper investigated inflammatory memory and the temporal dynamics of histone modifications and involved TFs at memory domains after injury and saw that recruitment of factors comprising a stress-response TF to these memory domains is dependent on stimulus-specific TF STAT3 for establishing memory but not for maintenance of memory.

11. Light WH, *et al*.: **A conserved role for human Nup98 in altering chromatin structure and promoting epigenetic transcriptional memory**. *PLoS Biol* 2013, **11**:e1001524.

12. Kamada R, *et al*.: **Interferon stimulation creates chromatin marks and establishes transcriptional memory**. *Proc Natl Acad Sci USA* 2018, **115**:E9162-E9171.

13. Siwek W, Tehrani SSH, Mata JF, Jansen LET: **Activation of clustered IFNγ target genes drives cohesin-controlled transcriptional memory**. *Mol Cell* 2020, **80**:396-409 e6.

14. •• Sump B, Brickner DG, D'urso A, Kim SH, Brickner JH: **Mitotically heritable, RNA polymerase II-independent H3K4 dimethylation stimulates INO1 transcriptional memory**. *Elife* 2022, **11**:77646.
This paper investigated memory in yeast and found that epigenetic memory involving H3K4me2 requires an RNAPII-independent form of the histone mark, interaction with the nuclear pore, SET3C, and the Paf1 complex for stable inheritance.

15. Naik S, Fuchs E: **Inflammatory memory and tissue adaptation in sickness and in health**. *Nature* 2022, **607**:249.

16. Tang Y, Gao XD, Wang Y, Yuan BF, Feng YQ: **Widespread existence of cytosine methylation in yeast DNA measured by gas chromatography/mass spectrometry**. *Anal Chem* 2012, **84**:7249.

17. Greer EL, *et al*.: **DNA methylation on N6-adenine in C. elegans**. *Cell* 2015, **161**:868.

18. Schmitz RJ, Lewis ZA, Goll MG: **DNA methylation: shared and divergent features across eukaryotes**. *Trends Genet* 2019, **35**:818.

19. Petryk N, Bultmann S, Bartke T, Defossez PA: **Staying true to yourself: mechanisms of DNA methylation maintenance in mammals**. *Nucleic Acids Res* 2021, **49**:3020-3032.

20. Hervouet E, Vallette FM, Cartron PF: **Dnmt3/transcription factor interactions as crucial players in targeted DNA methylation**. *Epigenetics* 2009, **4**:487-499.

21. Weinberg DN, *et al*.: **Two competing mechanisms of DNMT3A recruitment regulate the dynamics of de novo DNA methylation at PRC1-targeted CpG islands**. *Nat Genet* 2021, **53**:794-800.

22. He L, *et al*.: **DNA methylation-free Arabidopsis reveals crucial roles of DNA methylation in regulating gene expression and development**. *Nat Commun* 2022, **13**:1-16.

23. Chang W, *et al*.: **Dynamic changes in whole genome DNA methylation, chromatin and gene expression during mouse lens differentiation**. *Epigenetics Chromatin* 2023, **16**:1-30.

24. Kaluscha S, *et al*.: **Evidence that direct inhibition of transcription factor binding is the prevailing mode of gene and repeat repression by DNA methylation**. *Nat Genet* 2022, **54**:1895-1906.

25. Lee S, *et al*.: **DDM1-mediated gene body DNA methylation is associated with inducible activation of defense-related genes in Arabidopsis**. *Genome Biol* 2023, **24**:1-30.

26. Jones MJ, Goodman SJ, Kobor MS: **DNA methylation and healthy human aging**. *Aging Cell* 2015, **14**:924-932.

27. Sriraman A, Debnath TK, Xhemalce B, Miller KM: **Making it or breaking it: DNA methylation and genome integrity**. *Essays Biochem* 2020, **64**:687-703.

28. Xu P, Chen H, Hu J, Cai W: **Potential evidence for transgenerational epigenetic memory in Arabidopsis thaliana following spaceflight**. *Commun Biol* 2021, **4**:1-14.

29. Wang Q, *et al*.: **Maize dna methylation in response to drought stress is involved in target gene expression and alternative splicing**. *Int J Mol Sci* 2021, **22**:8285.

30. Arora H, *et al*.: **DNA methylation dynamics in response to abiotic and pathogen stress in plants**. *Plant Cell Rep* 2022, **41**:1931-1944.

31. Ortega-Recalde O, Hore TA: **DNA methylation in the vertebrate germline: balancing memory and erasure**. *Essays Biochem* 2019, **63**:649-661.

32. Kaikkonen MU, Lam MTY, Glass CK: **Editor's choice: non-coding RNAs as regulators of gene expression and epigenetics**. *Cardiovasc Res* 2011, **90**:430.

33. Clark MB, *et al*.: **Genome-wide analysis of long noncoding RNA stability**. *Genome Res* 2012, **22**:885.

34. Xu J, Xu J, Liu X, Jiang J: **The role of lncRNA-mediated ceRNA regulatory networks in pancreatic cancer**. *Cell Death Discov* 2022, **8**:1-11.

35. Yang M, *et al*.: **lncRNAfunc: a knowledgebase of lncRNA function in human cancer**. *Nucleic Acids Res* 2022, **50**:D1295-D1306.

36. Liu Z, *et al*.: **Machine learning-based integration develops an immune-derived lncRNA signature for improving outcomes in colorectal cancer**. *Nat Commun* 2022, **13**:1-14.

37. Khodayi M, Khalaj-Kondori M, Feizi MAH, Bonyadi MJ, Talebi M: **Plasma lncRNA profiling identified BC200 and NEAT1 lncRNAs**

as potential blood-based biomarkers for late-onset Alzheimer's disease. *EXCLI J* 2022, **21**:772.

38. Chen X, *et al*.: **Level of LncRNA GAS5 and hippocampal volume are associated with the progression of Alzheimer's disease**. *Clin Inter Aging* 2022, **17**:745-753.

39. Yang P, Lin G, Wang M, Chen X, Huang J: **Long non-coding RNA ANRIL interacts with microRNA-34a and microRNA-125a, and they all correlate with disease risk and severity of Parkinson's disease**. *J Clin Lab Anal* 2022, **36**:e24037.

40. Akbari M, *et al*.: **Expression of BDNF-associated lncRNAs in Parkinson's disease**. *Metab Brain Dis* 2022, **37**:901-909.

41. Rey F, *et al*.: **Identification of a novel pathway in sporadic Amyotrophic Lateral Sclerosis mediated by the long non-coding RNA ZEB1-AS1**. *Neurobiol Dis* 2023, **178**:106030.

42. Yu Y, *et al*.: **The expression discrepancy and characteristics of long non-coding RNAs in peripheral blood leukocytes from amyotrophic lateral sclerosis patients**. *Mol Neurobiol* 2022, **59**:3678-3689.

43. Irwin AB, Bahabry R, Lubin FD: **A putative role for lncRNAs in epigenetic regulation of memory**. *Neurochem Int* 2021, **150**:105184.

44. Mattick JS, *et al*.: **Long non-coding RNAs: definitions, functions, challenges and recommendations**. *Nat Rev Mol Cell Biol* 2023, **24**:430-447.

45. Zhu C, Wang X, Wang Y, Wang K: **Functions and underlying mechanisms of lncRNA HOTAIR in cancer chemotherapy resistance**. *Cell Death Discov* 2022, **8**:1-10.

46. Arunkumar G, Baek S, Sturgill D, Bui M, Dalal Y: **Oncogenic lncRNAs alter epigenetic memory at a fragile chromosomal site in human cancer cells**. *Sci Adv* 2022, **8**:eabl5621.

47. Motosugi N, *et al*.: **De-erosion of X chromosome dosage compensation by the editing of XIST regulatory regions restores the differentiation potential in hPSCs**. *Cell Rep Methods* 2022, **2**:100352.

48. Barbour H, Daou S, Hendzel M, Affar EB: **Polycomb group-mediated histone H2A monoubiquitination in epigenome regulation and nuclear processes**. *Nat Commun* 2020, **11**:1-16.

49. Wang Q, *et al*.: **LncRNA TINCR impairs the efficacy of immunotherapy against breast cancer by recruiting DNMT1 and downregulating MiR-199a-5p via the STAT1–TINCR-USP20-PD-L1 axis**. *Cell Death Dis* 2023, **14**:1-12.

50. Fanucchi S, *et al*.: **Immune genes are primed for robust transcription by proximal long noncoding RNAs located in nuclear compartments**. *Nat Genet* 2019, **51**:138-150.

51. Bannister AJ, Kouzarides T: **Regulation of chromatin by histone modifications**. *Cell Res* 2011, **21**:381-395.

52. Martin BJE, *et al*.: **Transcription shapes genome-wide histone acetylation patterns**. *Nat Commun* 2021, **12**:1-9.

53. Kouzarides T: **Chromatin modifications and their function**. *Cell* 2007, **128**:693-705.

54. Kang Y, Kim YW, Kang J, Kim AR: **Histone H3K4me1 and H3K27ac play roles in nucleosome eviction and eRNA transcription, respectively, at enhancers**. *FASEB J* 2021, **35**:e21781.

55. D'Urso A, *et al*.: **Set1/COMPASS and Mediator are repurposed to promote epigenetic transcriptional memory**. *Elife* 2016, **5**:e16691.

56. Bernstein BE, *et al*.: **Methylation of histone H3 Lys 4 in coding regions of active genes**. *Proc Natl Acad Sci USA* 2002, **99**:8695-8700.

57. Harris HL, *et al*.: **Chromatin alternates between A and B compartments at kilobase scale for subgenic organization**. *Nat Commun* 2023, **14**:1-17.

58. Rao SSP, *et al*.: **A 3D map of the human genome at kilobase resolution reveals principles of chromatin looping**. *Cell* 2014, **159**:1665-1680.

59. Reverón-Gómez N, *et al*.: **Accurate recycling of parental histones reproduces the histone modification landscape during DNA replication**. *Mol Cell* 2018, **72**:239-249 e5.

60. • Zofall M, Sandhu R, Holla S, Wheeler D, Grewal SIS: **Histone deacetylation primes self-propagation of heterochromatin domains to promote epigenetic inheritance**. *Nat Struct Mol Biol* 2022, **29**:898-909.
This paper shows that Clr3 deacetylase activity and chromatin association is a determinant for heterochromatin inheritance and propagation.

61. Ragunathan K, Jih G, Moazed K: **Epigenetic inheritance uncoupled from sequence-specific recruitment**. *Science (1979)* 2015, **348**:1258699.

62. Sump B, Brickner J: **Establishment and inheritance of epigenetic transcriptional memory**. *Front Mol Biosci* 2022, **9**:977653.

63. Kaneshiro KR, Egelhofer TA, Rechtsteiner A, Cockrum C, Strome S: **Sperm-inherited H3K27me3 epialleles are transmitted transgenerationally in cis**. *Proc Natl Acad Sci USA* 2022, **119**:e2209471119.

64. Shen Q, Lin Y, Li Y, Wang G: **Dynamics of H3K27me3 modification on plant adaptation to environmental cues**. *Plants* 2021, **10**:1165.

65. • Liu C, *et al*.: **Histone H1 facilitates restoration of H3K27me3 during DNA replication by chromatin compaction**. *Nat Commun* 2023, **14**:1-17.
This paper shows that linker histone H1 promotes propagation of H3K27me3 marks via chromatin compaction.

66. Eeftens JM, Kapoor M, Michieletto D, Brangwynne CP: **Polycomb condensates can promote epigenetic marks but are not required for sustained chromatin compaction**. *Nat Commun* 2021, **12**:1-12.

67. Brickner DG, *et al*.: **H2A.Z-mediated localization of genes at the nuclear periphery confers epigenetic memory of previous transcriptional state**. *PLoS Biol* 2007, **5**:704-716.

68. Pascual-Garcia P, *et al*.: **Metazoan nuclear pores provide a scaffold for poised genes and mediate induced enhancer-promoter contacts**. *Mol Cell* 2017, **66**:63-76 e6.

69. Ding Y, Fromm M, Avramova Z: **Multiple exposures to drought 'train' transcriptional responses in Arabidopsis**. *Nat Commun* 2012, **3**:1-9.

70. Crawford T, *et al*.: **The Mediator kinase module enhances polymerase activity to regulate transcriptional memory after heat stress in Arabidopsis**. *EMBO J* 2024, **43**:437-461, https://doi.org/10.1038/S44318-023-00024-X

71. Light WH, Brickner DG, Brand VR, Brickner JH: **Interaction of a DNA zip code with the nuclear pore complex promotes H2A.Z incorporation and INO1 transcriptional memory**. *Mol Cell* 2010, **40**:112.

72. Maxwell CS, *et al*.: **Pol II docking and pausing at growth and stress genes in C. elegans**. *Cell Rep* 2014, **6**:455.

73. Kappel L, Kosa N, Gruber S: **The multilateral efficacy of chitosan and trichoderma on sugar beet**. *J Fungi* 2022, **8**:137.

74. Gallusci P, *et al*.: **Deep inside the epigenetic memories of stressed plants**. *Trends Plant Sci* 2023, **28**:142-153, https://doi.org/10.1016/j.tplants.2022.09.004

75. Mazhar MW, *et al*.: **Seed nano-priming with Zinc Oxide nanoparticles in rice mitigates drought and enhances agronomic profile**. *PLoS One* 2022, **17**:e0264967.

76. Zioutopoulou A, Patitaki E, Xu T, Kaiserli E: **The epigenetic mechanisms underlying thermomorphogenesis and heat stress responses in Arabidopsis**. *Plants* 2021, **10**:2439.

77. Pascual-Garcia P, Little SC, Capelson M: **Nup98-dependent transcriptional memory is established independently of transcription**. *Elife* 2022, **11**:e63404.

78. • Kumar S, *et al*.: **Nuclear pore complexes mediate subtelomeric gene silencing by regulating PCNA levels on chromatin**. *J Cell Biol* 2023, **222**:e202207060.

This paper shows how the NPC plays a role in establishing heterochromatin via modulating PCNA levels through interaction with PCNA loader Ctf18-RFC.

79. Brickner DG, *et al.*: **Transcription factor binding to a DNA Zip code controls interchromosomal clustering at the nuclear periphery**. *Dev Cell* 2012, **22**:1234.

80. Randise-Hinchliff C, *et al.*: **Strategies to regulate transcription factor–mediated gene positioning and interchromosomal clustering at the nuclear periphery**. *J Cell Biol* 2016, **212**:633-646.

81. Levra Levron C, *et al.*: **Tissue memory relies on stem cell priming in distal undamaged areas**. *Nat Cell Biol* 2023, **25**:740-753.

82. Ow MC, Nichitean AM, Hall SE: **Somatic aging pathways regulate reproductive plasticity in Caenorhabditis elegans**. *Elife* 2021, **10**:e61459.

83. Capelson M, *et al.*: **Chromatin-bound nuclear pore components regulate gene expression in higher eukaryotes**. *Cell* 2010, **140**:372-383.

84. Kalverda B, Pickersgill H, Shloma VV, Fornerod M: **Nucleoporins directly stimulate expression of developmental and cell-cycle genes inside the nucleoplasm**. *Cell* 2010, **140**:360-371.

85. Gialitakis M, Arampatzi P, Makatounakis T, Papamatheakis J: **Gamma interferon-dependent transcriptional memory via relocalization of a gene locus to PML nuclear bodies**. *Mol Cell Biol* 2010, **30**:2046.

86. He S, *et al.*: **H3K4me2, H4K5ac and DNA methylation function in short- and long-term heat stress responses through affecting the expression of the stress-related genes in G. hirsutum**. *Environ Exp Bot* 2022, **194**:104699.

87. Kappel C, *et al.*: **Genomic and epigenomic determinants of heat stress-induced transcriptional memory in Arabidopsis**. *Genome Biol* 2023, **24**:1-23.

88. Hu S, *et al.*: **H3K4me2/3 modulate the stability of RNA polymerase II pausing**. *Cell Res* 2023, **33**:403-406.

89. Serra-Cardona A, Duan S, Yu C, Zhang Z: **H3K4me3 recognition by the COMPASS complex facilitates the restoration of this histone mark following DNA replication**. *Sci Adv* 2022, **8**:6246.

90. Ng RK, Gurdon JB: **Epigenetic memory of an active gene state depends on histone H3.3 incorporation into chromatin in the absence of transcription**. *Nat Cell Biol* 2008, **10**:102-109.

91. •• Tehrani SS, *et al.*: **STAT1 is required to establish but not maintain interferon-γ-induced transcriptional memory**. *EMBO J* 2023, **42**:e112259.

In this study, STAT1 was found to be required to establish, but not inherit, IFN-γ-induced memory, which relies on a pathway independent of gene transcription.