

# Mechanisms of epigenetic memory

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**Although genetics has an essential role in defining the development, morphology, and physiology of an organism, epigenetic mechanisms have an essential role in modulating these properties by regulating gene expression. During development, epigenetic mechanisms establish stable gene expression patterns to ensure proper differentiation. Such mechanisms also allow organisms to adapt to environmental changes and previous experiences can impact the future responsiveness of an organism to a stimulus over long timescales and even over generations. Here, we discuss the concept of epigenetic memory, defined as the stable propagation of a change in gene expression or potential induced by developmental or environmental stimuli. We highlight three distinct paradigms of epigenetic memory that operate on different timescales.**

## Layers of memory

Epigenetic changes are 'mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in the DNA sequence', leading to the propagation of heritable changes in phenotype [1]. Epigenetic regulation can be either relatively stable (such as X inactivation, imprinting, silencing, or boundary activities) or dynamic [2–4]. Where epigenetic regulation is dynamic, it is often described as epigenetic memory: a heritable change in gene expression or behavior that is induced by a previous stimulus. The stimulus can be either developmental or environmental. Memory occurs by multiple mechanisms, but often requires chromatin-based changes, such as DNA methylation, histone modifications, or incorporation of variant histones [5]. DNA methylation can template its own inheritance through methylation of hemimethylated sites following DNA replication by maintenance DNA methylases [6]. However, most histone modifications are not heritable and the extent to which any can template their own inheritance is still somewhat contentious. In this review, we focus on epigenetic mechanisms that require chromatin changes, but we do not mean to suggest that it is clear that these changes are the source of epigenetic information and inheritance.

There are at least three types of epigenetic memory that utilize related mechanisms over different time scales: (i) cellular memory, mitotically heritable transcriptional states established during development in response to

developmental cues; (ii) transcriptional memory, mitotically heritable changes in the responsiveness of organisms to environmental stimuli in response to previous experiences; and (iii) transgenerational memory, meiotically heritable changes in the gene expression and physiology of organisms in response to experiences in the previous generations (Figure 1) [7–11].

## Cellular memory

Developmental signals induce changes in gene expression and chromatin structure [7]. Such changes define cell identity and potential for differentiation. They can be maintained through subsequent cell divisions, even in the absence of these signals. One of the best examples of this phenomenon is the developing *Drosophila* embryo, in which expression of homeotic genes is established by transient expression of the segmentation transcription factors. After these factors turn over, the expression patterns of many genes, including homeotic genes, are maintained through many cell divisions. This cellular memory requires the Trithorax and Polycomb group (PcG) proteins (Figure 1A) [12,13]. The Trithorax complex mediates methylation of histone H3 on lysine 4 (H3K4me) and is required to maintain genes in an active state [12,13]. The PcG proteins have two biochemically characterized complexes: Polycomb repressive complex 1 and 2 (PRC1 and PRC2). PRC2 methylates histone 3 lysine 27 (H3K27me) at genes targeted for silencing, whereas PRC1 binds H3K27me and induces spreading of structural changes in the chromatin [14,15]. This histone mark has been proposed to act as a repressive 'bookmark' during mitosis, where it is maintained through cell division and transmitted through DNA replication in the absence of the initial stimuli [16,17].

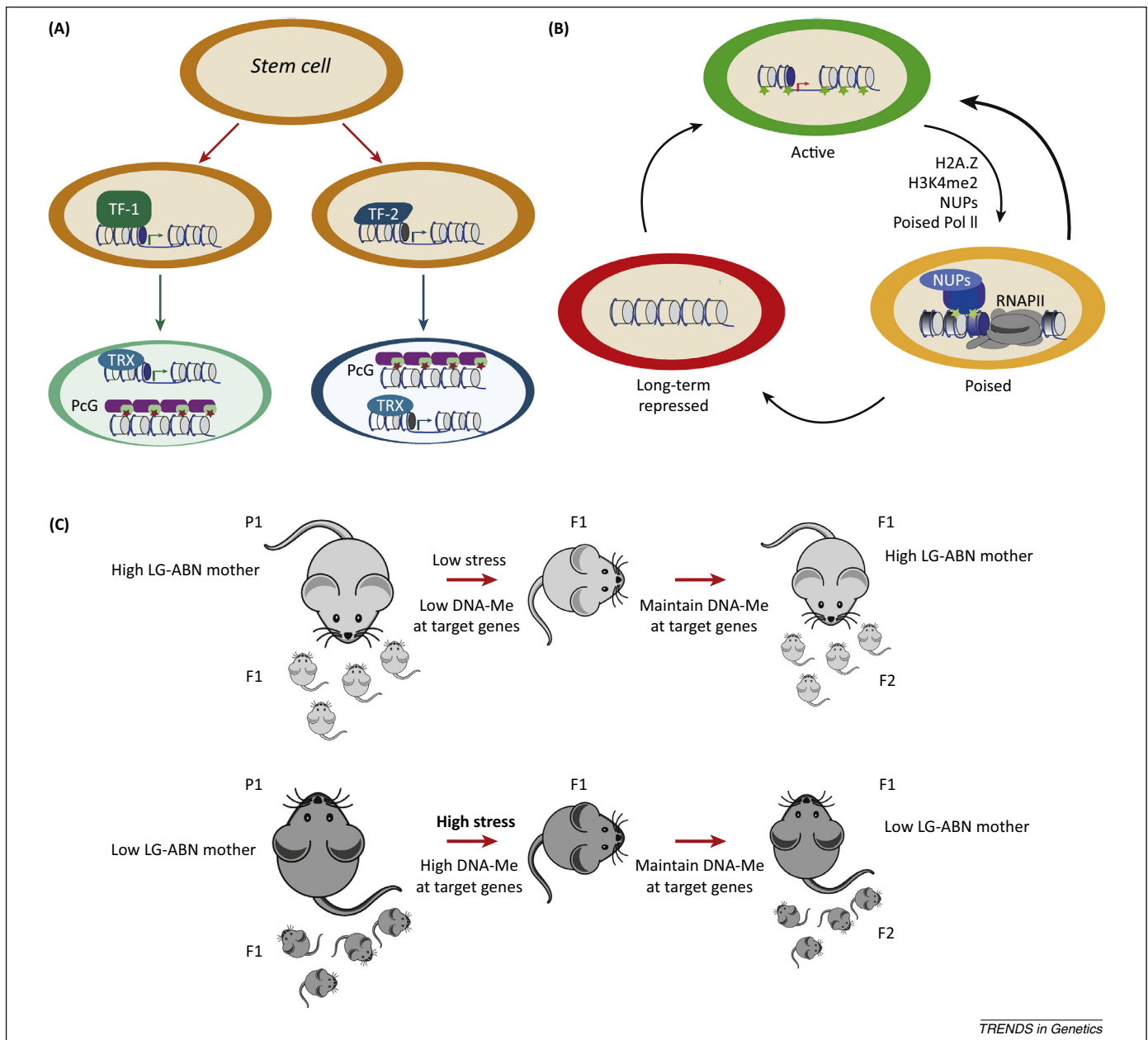
Bookmarking can also contribute to the maintenance and inheritance of active chromatin states. For instance, when cells enter mitosis, transcription is abruptly repressed and RNA polymerase II (RNAPII) is displaced during chromatin condensation [18,19]. The RNAPII transcription factor TFIID is largely removed from gene promoters by phosphorylation of histone H3 on threonine 3 (H3T3) during mitosis. However, TFIID is selectively retained in the promoters of certain active genes, bookmarking them for future expression in G2 [20,21]. The mechanism proposed for this phenomenon involves high levels of methylation of H3K4, which inhibits H3T3 phosphorylation. This allows TFIID and the phosphatase PP2 to be retained at these promoters through mitosis, counteracting chromatin compaction [22]. The role of histone modifications in bookmarking may be related to reader–protein binding complexes that contribute to epigenetic inheritance and the re-establishment of postmitotic transcription programs [17,23,24].

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**Figure 1.** Types of epigenetic memory. **(A)** Cellular memory: during early development, tissue-specific transcription factors establish different transcriptional programs. These programs are maintained through mitotic cell division later in development through the action of epigenetic regulators such as the Trithorax (TRX), which catalyzes methylation of histone H3, lysine 4 to promote sustained expression, and Polycomb, which catalyzes methylation of histone H3, lysine 27 to promote stable repression. **(B)** Transcriptional memory: environmental changes induce changes in gene expression. Following such an experience, some genes remain poised for faster reactivation for several generations. Upon gene activation, genes can experience a more robust secondary transcriptional response. Nuclear pore proteins (Nups) and specific histone marks at the nuclear pore (yeast) or nucleoplasm (higher eukaryotes) are required to establish and inherit this poised state. **(C)** Transgenerational memory: parental experiences can impact the behavior of the offspring. In this example, environmental stress reduces maternal licking and/or grooming, and arched-back nursing (LG-ABN), which reduces the stress tolerance of pups into adulthood. Low LG-ABN alters the expression of stress regulators, leading to greater stress sensitivity. This altered gene expression requires changes in DNA methylation and histone acetylation and is inherited in future generations (F1 and F2). Abbreviations: PcG, Trithorax and Polycomb group (PcG); RNAPII, RNA polymerase II; TF-1/2, transcription factor 1/2. Mouse image courtesy of Janet Barry ([www.clker.com/clipart-wardo-the-mouse.html](http://www.clker.com/clipart-wardo-the-mouse.html)).

Development can also be regulated by environmental conditions. For example, flowering in certain plant species requires previous exposure to cold, a phenomenon called ‘vernalization’. During this process, plants become competent to flower only after prolonged exposure to the cold winter, an epigenetic change that ensures that flowering occurs under favorable conditions in spring [25,26]. In *Arabidopsis thaliana*, flowering is controlled by the expression of the FLOWERING LOCUS C (*FLC*) gene, which encodes a transcription repressor that prevents flowering.

In the autumn, *FLC* expression is high, preventing flowering. Extended exposure to cold represses *FLC* transcription and the *FLC* mRNA gradually decreases during winter and stays low as the temperatures rise in the spring [27–29]. Extended cold induces the VERNALIZATION INSENSITIVE 3 (*VIN3*) gene, which interacts with the Polycomb homolog VERNALIZATION 2 (*VRN2*) to promote methylation of H3K27 at the *FLC* locus and reduce its expression [29,30]. Methylation of H3K9 and H3 deacetylation are also required for full repression of *FLC* [29]. This

process also involves the noncoding RNAs *COLDAIR* and *COOLAIR* [31–33]. These two noncoding RNAs have been proposed to bind and recruit PcG to FLC. Thus, environmental cues can impact developmental timing through a mechanism involving chromatin modification. The repression is mitotically stable through a large number of cell divisions in the absence of the inducing signals, creating a new epigenetic state [25,26]. This suggests that the mitotic epigenetic memory involves positive feedback loops where the repressive chromatin modifications recruit the chromatin-modifying complexes themselves to maintain FLC in a repressive state [25,26,34]. However, not all plants species exhibit the same vernalization behavior. For instance, some species flower during cold exposure because the chromatin changes are not mitotically maintained, suggesting this may be an adaptive response to climate change [25,26].

### Transcriptional memory

Cells and organisms must respond to changes in their environment to adapt and survive. In general, such responses involve changes in transcription. Work from several organisms suggests that these responses are quantitatively or qualitatively altered by previous experience through epigenetically heritable mechanisms. For example, previously expressed genes are frequently primed for reactivation, a phenomenon called ‘transcriptional memory’ (Figure 1B). This mechanism requires changes in chromatin structure and a physical interaction with nuclear pore proteins. Such a mechanism allows cells to mount a more rapid or robust transcriptional response to an environmental challenge that they have previously experienced [35,36].

The nuclear pore complex (NPC) is a large molecular portal that penetrates the nuclear envelope to facilitate nuclear–cytoplasmic trafficking. Nuclear pore proteins interact with particular parts of the genome in numerous species [37–39]. The targeting of such loci to the yeast NPC involves transcription factor binding to *cis*-acting DNA ‘zip codes’ and promotes both stronger transcription and epigenetic states, such as transcriptional memory and chromatin boundaries [35,38,40–47].

One well-established model for transcriptional memory at the NPC is the inducible inositol-1-phosphate synthase (*INO1*) gene in budding yeast. Upon activation, the *INO1* gene moves from the nucleoplasm to the nuclear periphery through interaction with the NPC [48]. After repression, *INO1* remains associated with the NPC for three to four future generations [35,44,45]. Thus, maintenance of recently repressed *INO1* at the NPC represents an epigenetic state. While at the nuclear periphery, recently repressed *INO1* is poised for transcriptional reactivation. The positioning of *INO1* at the NPC is mitotically inherited, although the molecular mechanism responsible for re-establishing it after cell division still is not fully understood. The yeast galactose-induced *GAL* genes are also maintained at the nuclear periphery after repression exhibiting a similar faster rate of transcriptional reactivation [35]. However, unlike *INO1* memory, *GAL* gene memory involves formation of an intragenic loop in association with the NPC-associated factor myosin-like protein 1 (Mlp1) [49].

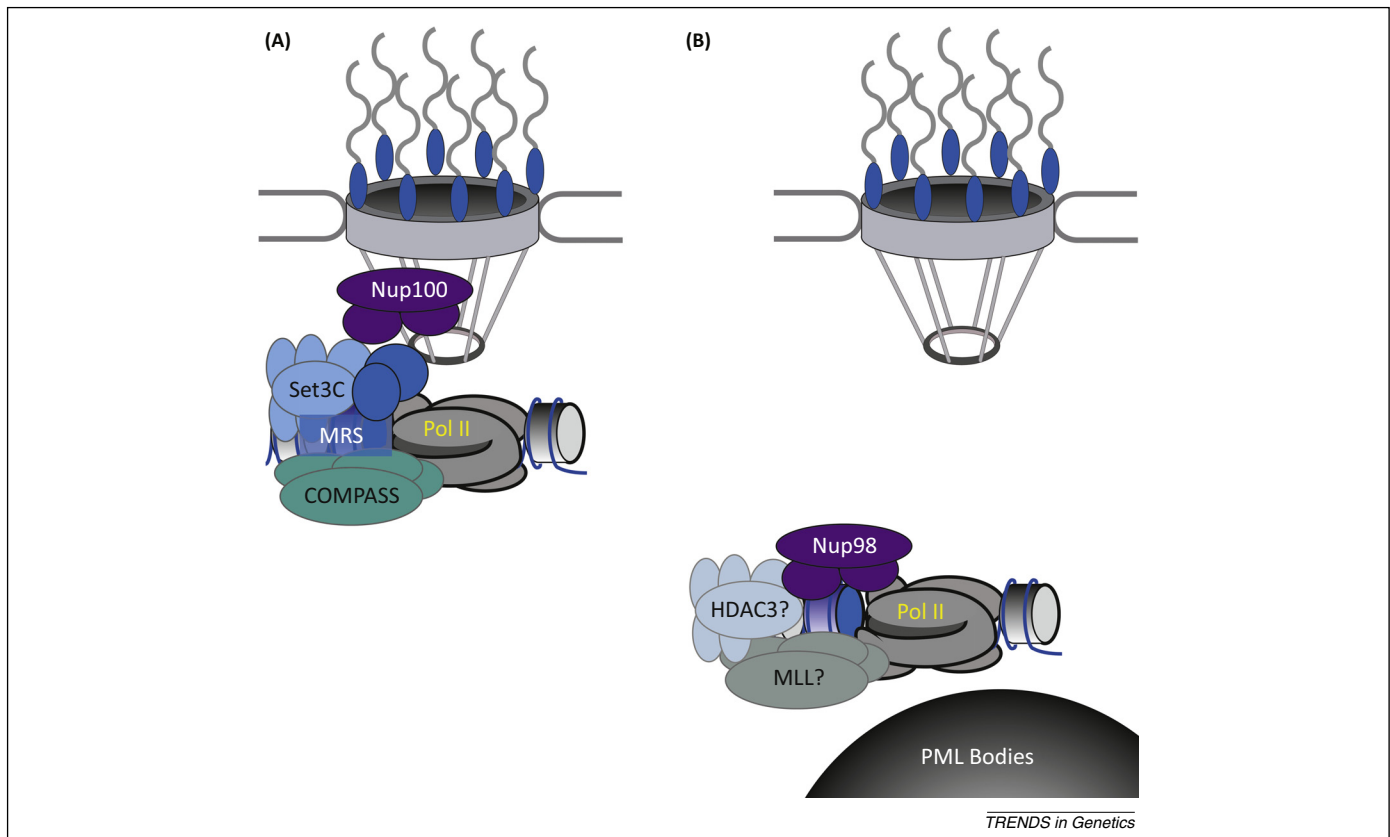
Two different mechanisms target *INO1* to the NPC, one when the gene is active and another when the gene is recently repressed. The targeting of active *INO1* to the NPC is controlled by two *cis*-acting DNA zip codes called ‘gene recruitment sequences’ (GRS) [44]. However, the maintenance of recently repressed *INO1* at the NPC is controlled by a different *cis*-acting DNA zip code called the ‘memory recruitment sequence’ (MRS) [45]. Mutation of the MRS sequence specifically disrupts the interaction of recently repressed *INO1* with the NPC and causes a strong defect in the rate of reactivation [45,46]. This mutation affects neither the initial activation rate of *INO1* nor its localization at the nuclear periphery when active, suggesting that two independent molecular mechanisms promote targeting of active *INO1* versus recently repressed *INO1* [45].

In addition to the MRS, *INO1* memory requires the interaction with components of the NPC and particular chromatin changes (Figure 2A) [35]. Mutations in several nuclear pore or NPC-associated proteins impact localization of *INO1* to the nuclear periphery [45]. Several of these proteins, including Nup100 are specifically required for localization of recently repressed *INO1* [45]. Based on ChIP experiments, Nup100 physically interacts with the *INO1* promoter only after repression and *nup100Δ* mutants exhibit slower *INO1* transcriptional reactivation rates [45].

The ultimate output of *INO1* memory is to allow binding of the pre-initiation complex and RNAPII to the promoter (Figure 2A) [45,46]. After repression, RNAPII remains bound to the *INO1* promoter in a poised, preinitiation form that is not phosphorylated on the carboxy terminal domain. Mutations that disrupt transcriptional memory (e.g., mutations in the MRS, *nup100Δ*) lead to loss of RNAPII from the recently repressed *INO1* promoter [45,46]. This suggests that *INO1* transcriptional memory primes *INO1* for reactivation by bypassing the rate-limiting step in transcriptional activation, recruitment of RNAPII.

Another type of epigenetic memory that leads to greater stress resistance after exposure to a previous stress is also connected to the NPC. Many yeast genes induced by oxidative stress are activated more rapidly in cells that have previously experienced salt stress [47]. This effect persists for up to four generations after the initial stress. The nuclear pore protein Nup42 is required for this faster induction and its loss leads to greater sensitivity to oxidative stress [47]. Interestingly, the promoters of genes that exhibit salt-induced memory are enriched for a DNA element similar to the *INO1* MRS [45,47]. Thus, various examples of transcriptional memory in yeast involve interactions with the nuclear pore complex and similar *cis*-acting elements.

The histone variant H2A.Z is highly enriched at gene promoters and plays conserved roles in transcriptional regulation [50]. In budding yeast, H2A.Z can have both a role in transcriptional gene activation or repression [51–53]. H2A.Z nucleosomes are often found in regions flanking a nucleosome-free region (NFR) near the transcription start site [51]. In fact, a NFR is sufficient in certain contexts to induce H2A.Z incorporation [54]. This suggests that H2A.Z affects nucleosome positioning and chromatin



**Figure 2.** Transcriptional memory is conserved between organisms. **(A)** Model for yeast inositol-1-phosphatase1 (*INO1*) transcriptional memory. Upon repression, *INO1* remains associated with the nuclear pore complex in the population of cells for three to four generations. This interaction requires a *cis*-acting DNA element called the memory recruitment sequence (MRS) and leads to an altered chromatin state involving the incorporation of H2A.Z, interaction with Nup100 and dimethylation of histone H3, lysine 4 (H3K4me2) by COMPASS. These changes, and effector complexes such as Set3C, are required to allow binding of poised, preinitiation RNA Polymerase II (RNAPII) to the promoter. **(B)** A conserved mechanism primes interferon gamma (IFN- $\gamma$ )-induced genes for faster or stronger reactivation in HeLa cells. After exposure to IFN- $\gamma$ , the nuclear pore protein Nup98 (homologous to yeast Nup100) binds to the promoters of genes with memory. This interaction occurs in the nucleoplasm, near PML bodies. Similar to the yeast *INO1* gene, genes that exhibit IFN- $\gamma$  memory maintain H3K4me2 and poised RNAPII on their promoters. These similarities suggest the possibility of recruiting similar chromatin effector complexes. Abbreviations: HDAC3, histone deacetylase 3; PML, promyelocytic leukemia; MLL, mixed lineage leukemia protein.

structure, perhaps explaining the discordant, gene-specific effects of H2A.Z on transcription [53].

H2A.Z is found in most inducible promoters, and facilitates faster induction [52,55]. For instance, oleate-responsive genes require H2A.Z for rapid and robust activation [52,56]. Hence, the incorporation of noncanonical histone variants, such as H2A.Z, can produce specialized chromatin domains that influence the rates of transcriptional induction.

H2A.Z is also required for *INO1* transcriptional memory; mutants lacking H2A.Z do not retain *INO1* at the nuclear periphery after repression, fail to recruit RNAPII, and show a defect in the rate of reactivation [35,45]. After repression of *INO1*, H2A.Z is incorporated into a particular nucleosome in the promoter [35,45]. Incorporation of H2A.Z into the recently repressed *INO1* promoter requires the MRS sequence and the Nup100 protein [45]. Furthermore, insertion of the MRS sequence at ectopic sites leads to incorporation of H2A.Z, suggesting that the MRS sequence is sufficient to promote incorporation of H2A.Z [35,45]. Thus, specific chromatin structural changes at the *INO1* promoter are required for *INO1* transcriptional memory.

Aspects of *INO1* transcriptional memory are evolutionarily conserved and also occur in human cells. The

interferon gamma (IFN- $\gamma$ )-induced class II major histocompatibility gene DR alpha (*HLA-DRA*) is more rapidly and robustly induced if cells have previously been exposed to IFN- $\gamma$  [36]. This response persists for at least four mitotic generations and is associated with dimethylation of H3K4 in the *HLA-DRA* promoter [36]. This behavior is widespread; of the approximately 650 genes that are induced by IFN- $\gamma$ , approximately 250 exhibit faster or stronger activation upon subsequent treatment with IFN- $\gamma$  [46]. The molecular mechanism of IFN- $\gamma$ -induced memory is similar to the molecular mechanism of transcriptional memory of the *INO1* gene in yeast [45,46]. *HLA-DRA* memory requires a physical interaction with the nuclear pore protein Nup98, which is homologous to yeast Nup100 [45,46]. As in yeast, a poised, pre-initiation form of RNAPII binds to promoters of genes that exhibit IFN- $\gamma$  memory (Figure 2B). However, unlike yeast *INO1*, *HLA-DRA* does not localize at the NPC, but instead interacts with Nup98 in the nucleoplasm [46,57,58] (Figure 2B).

Both *INO1* memory in yeast and IFN- $\gamma$ -induced memory in HeLa cells is associated with dimethylation of H3K4 in promoters [36,46]. In yeast, mutations that block ubiquitylation of histone H2B or methylation of H3 lysine 4 disrupt *INO1* transcriptional memory. Furthermore, the Set3C histone deacetylase complex, which recognizes



H3K4me<sub>2</sub>, is also required for *INO1* transcriptional memory, suggesting that it is an important reader of this mark (Figure 2).

### Transgenerational memory

Meiosis, gametogenesis, and embryogenesis are associated with global changes in chromatin structure and transcription [10]. Despite this, previous experiences can impart epigenetic changes in gene expression in subsequent generations. For example, in *Drosophila*, activating transcription factor 2 (dATF-2) binds to heterochromatin and is required for H3K9 methylation [59]. Upon heat or osmotic shock, stress-activated protein kinases (SAPKs) phosphorylate dATF-2 and the protein is released from heterochromatin. This leads to loss of H3K9me<sub>2</sub>, and increased transcription [59]. The change in localization of dATF-2 is transmitted to the next generation [60,61]. If the stress is applied over multiple generations, the effect persists over several additional generations before gradually returning to the original state [59]. This suggests that the transgenerational memory effect is adaptive, helping the organism to adjust to the environment, and that the new induced chromatin state is unstable [59]. Disruption of heterochromatin may improve tolerance to variable or challenging environmental conditions. The heterochromatin that is lost during stress might be re-established through reprogramming in germ cells or early embryogenesis [59]. dATF-2 phosphorylation and function is conserved in mammals and *Schizosaccharomyces pombe*, suggesting that epigenetic reprogramming by environmental stimuli is a conserved mechanism [59,62,63].

Transgenerational epigenetic memory also maintains proper germline development in *Caenorhabditis elegans*. During early embryogenesis, germline blastomere cells (P cells) contain high levels of H3K4me<sub>2</sub> [64]. P cells undergo asymmetric cell division into primordial cells and Z2/Z3 cells and the primordial cells lose the H3K4me<sub>2</sub> histone mark at specific target genes. This mark is also removed in the germline pole cells in *Drosophila*, suggesting a similar epigenetic phenomenon [64]. In *C. elegans*, the protein responsible for the erasure of the specific H3K4me<sub>2</sub> histone mark is the demethylase protein SPR-5, which belongs to the lysine demethylase 1 (LSD1/KDM1) family of demethylases [65,66]. Loss of SPR-5 results in germline mortality and a high level of H3K4me<sub>2</sub>, stably maintained across the germline in future generations [67,68]. The propagation of this mark results in the misregulation of gamete and meiosis-specific genes [67,68]. In addition, the absence of SPR-5 activity causes a transgenerational accumulation of H3K4me<sub>2</sub> that eventually saturates a second mechanism of chromatin remodeling in the Z2/Z3 cells, resulting in the increased retention of H3K4me<sub>2</sub> in the primordial cells, increasing future generations sterility [67,68]. This suggests that the resetting of H3K4me<sub>2</sub> is required to prevent inappropriate transgenerational epigenetic memory from being transmitted from one generation to the next and it is essential for germline maintenance [67,68].

Also, *Caenorhabditis elegans* individuals that are wild type descendants of ancestors that are mutant for the highly conserved COMPASS H3K4 methyltransferase

exhibit increased longevity up to three generations compared with descendants from wild type worms [69–71]. In addition, when genetically wild type males are crossed with COMPASS mutant hermaphrodites, they are longer lived for up to three generations compared with wild type; this longer lifespan is dependent on the H3K4me<sub>3</sub> demethylase retinoblastoma-binding protein related (RBR-2). This epigenetic memory appears to be specific to the epigenetic changes of the COMPASS complex; manipulation in other longevity-related pathways, such as insulin or mitochondrial signaling, and other effector complexes do not result in transgenerational inheritance of enhanced longevity [69,70]. These findings suggest that changes in chromatin structure and histone modifications such as methylation of H3K4 can impact the physiology and development of future generations [72].

Epigenetic phenomena also have important impacts on human morphology, physiology, and health. For example, in many organisms including humans, genomic imprinting, the exclusive expression of a single parental allele (maternal or paternal), can lead to phenotypic differences between genetically identical individuals [73]. Imprinted genes have parental allele-specific epigenetic modifications that are maintained following fertilization when the genome is reprogrammed. Therefore, mutations in imprinted genes lead to phenotypes if the mutant allele is expressed. For example, a mutation in a paternally expressed gene will lead to a phenotype in offspring who inherited it from their fathers, but not those who inherited it from their mothers. Such ‘epimutations’ lead to human diseases such as Prader–Willi syndrome or Angelman’s syndrome [11,74]. Thus, the parental origin of individual chromosomes must impart heritable epigenetic marks that survive meiosis, fertilization, embryogenesis, and development.

Environmental factors experienced in one generation can impact the behavior of unborn offspring in mammals (Figure 1C). For example, environmental stresses, such as high exposure to predators, reduce maternal care in female rats, as measured by licking and/or grooming, and arch-back nursing (LG-ABN; Figure 1C) [75]. Pups reared under conditions of low maternal protection and LG-ABN are more fearful and more sensitive to environmental stresses. These pups exhibit less LG-ABN with their offspring compared with normal pups, even in the absence of environmental stressors, and this behavior is passed on to future generations (Figure 1C) [75].

Pups reared under low LG-ABN conditions show reduced levels of glucocorticoid receptor (GR) in the hippocampus, which controls expression of approximately 300 genes and is responsible for dampening the stress response [76,77]. Low LG-ABN leads to a decrease in the binding of the transcriptional activator NGFI-A (nerve growth factor inducible protein A), an increase in DNA methylation and histone deacetylation, and reduced expression of the GR gene over the first week of life [76,78]. These epigenetic marks persist and dictate GR expression for the rest of the life of the animal [76,78]. However, the phenotypic and molecular effects of stress are reversible: inhibition of histone deacetylases leads to decreased DNA methylation, increased expression of GR, and reduced stress sensitivity

(Figure 1C) [76]. Thus, the environmental experiences of the maternal generation can result in epigenetic changes in behavior that require changes in chromatin structure. These changes can maintain the phenotype into adulthood and for subsequent generations [75].

Paternal behavior and environment can also impact the physiology of the offspring through epigenetic mechanisms [79]. Male mice consuming a low-protein diet father offspring with decreased hepatic levels of cholesterol esters and altered hepatic expression of lipid and/or cholesterol biosynthesis genes [80]. Likewise, blood glucose levels and pancreatic function in rats and mice are affected by paternal diet; high-calorie diets leads to  $\beta$  cell dysfunction in the female progeny [81,82]. Although the molecular mechanism by which paternal diet impacts future generations is not clear, DNA methylation and expression of several genes involved in lipid metabolism is impacted by paternal diet [80]. For example, an enhancer for the lipid regulator peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ) is more highly methylated in the livers of low-protein offspring. However, the mechanism is still unclear; global DNA methylation in sperm was not dramatically affected by paternal diet and the altered methylation of the PPAR $\alpha$  enhancer was not observed in sperm. Regardless, it is clear that paternal environmental factors can impact the physiology of offspring through epigenetic mechanisms.

### Concluding remarks

It is important to integrate the concept of epigenetic memory into our thinking about phenotypes that are subject to evolutionary selection [10]. Plastic responses to heterogeneous environmental conditions are one of the most common phenomena characterizing the living world [83]. Epigenetic variation and plasticity is an integral part of how organisms develop and interact with their environment [83]. The examples mentioned in this review demonstrate that epigenetic memory can modify phenotype to impact fitness. To understand biology and evolution, we must understand the role of epigenetic mechanisms in regulating behavior, physiology, and gene expression over varying timescales. How, and to what extent, epigenetic mechanisms impact evolutionary fitness remains a fascinating question. It is also important to consider that, depending on the context, memory may be both adaptive and harmful. For example, parental experience can either improve or diminish the health of offspring. Likewise, although transcriptional memory induced by IFN- $\gamma$  may improve the response of cells to potential infection, it might also contribute to pathological states of inflammation. Future work must illuminate both the molecular basis for epigenetic regulation of phenotype and the ways in which it can be either adaptive or pathological.

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