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WormBook

Chromatin and epigenetics in aging biology

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This book chapter will focus on modifications to chromatin itself, how chromatin modifications are regulated, and how these modifications are deciphered by the cell to impact aging. In this chapter, we will review how chromatin modifications change with age, examine how chromatin-modifying enzymes have been shown to regulate aging and healthspan, discuss how some of these epigenetic changes are triggered and how they can regulate the lifespan of the individual and its naïve descendants, and speculate on future directions for the field.

Keywords: aging; chromatin; epigenetics; histone modifications; WormBook

Introduction

Seminal discoveries in *Caenorhabditis elegans* have revealed that aging, defined as a decline in function accompanied by an increase in mortality rate, is not simply a consequence of wear and tear but is regulated by genetic pathways (Johnson and Wood 1982; Friedman and Johnson 1988a; Kenyon *et al.* 1993; Morris *et al.* 1996; Kimura *et al.* 1997; Vellai *et al.* 2003). These initial discoveries have since been bolstered by findings in a variety of other species (Partridge and Fowler 1992; Brown-Borg *et al.* 1996; Sun and Tower 1999; Clancy *et al.* 2001; Tatar *et al.* 2001; Bluher *et al.* 2003; Holzenberger *et al.* 2003; Taguchi *et al.* 2007). Because organisms are complex, altered function of many genes will cause an organism to die prematurely; however, for these genes to be considered *bona fide* regulators of aging, their functional manipulation in some context must delay aging or prolong healthspan (Kenyon 2010; Mack *et al.* 2018; Son *et al.* 2019). The paradigm shift in defining aging as a regulated process, rather than organisms simply becoming sick, is what has allowed longevity regulation to be distinguished from aging as a simple consequence of increased entropy with time. In addition to genetic pathways that have been deciphered to regulate aging, simple manipulations of the environment [such as dietary restriction (DR)] can also extend lifespan (Masoro 2005).

Work of the past ~15 years, including several substantial discoveries in *C. elegans*, has demonstrated that aging is regulated by not only genetics and environment but also epigenetics. While many definitions of epigenetics exist, for the purposes of this review, we refer to epigenetics as changes in gene expression that occur without alterations in the DNA sequence. Gene expression itself is regulated transcriptionally, posttranscriptionally—including RNA splicing, RNA stability, and by modifications to RNAs—and at the level of translation. Similarly, aging has been demonstrated to be regulated at each of these levels as well. Epigenetics exists at the interface between genetics and the environment, allowing cells or organisms to sense its environmental conditions and alter how the cell responds without permanently altering the DNA code. Epigenetic mechanisms can include post-translational modifications to the histone tails, DNA methylation, noncoding RNAs, and others.

In this chapter, we will review how chromatin modifications change with age in *C. elegans*, examine how chromatin-modifying enzymes have been shown to regulate *C. elegans* aging and healthspan, discuss how some of these epigenetic changes are triggered and how they can regulate the lifespan of the individual and its naïve descendants, and speculate on future directions for the field. While there is an extensive body of literature on chromatin organization in *C. elegans*, in this chapter, we will confine most of the discussion to chromatin modifications that have been demonstrated to alter lifespan and healthspan, although we will attempt to integrate these studies on *C. elegans* aging with the broader roles of these chromatin modifications in regulating animal physiology. However, for a comprehensive and thorough consideration of chromatin modifications in *C. elegans*, the reader is referred to related WormBook chapters on Nematode chromosomes (Carlton *et al.* 2022) and heterochromatin (Ahringer and Gasser 2018). In addition, for reviews on the involvement of chromatin in aging in mammals and other organisms, please consult (Booth and Brunet 2016; Lee *et al.* 2020; Zhao *et al.* 2023).

Chromatin changes that accompany aging

Chromatin refers to the DNA/protein complex that packages the DNA genome. DNA is wrapped around histone proteins, and the assembled nucleosomes are packaged into higher-order chromatin fibers to facilitate its compaction and ensure that the appropriate regions of DNA are accessible for transcription and other DNA transactions. Nucleosomes, the core particles of chromatin, are

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octamers consisting of 2 H2A-H2B dimers and 1 H3-H4 tetramer. Canonical histones (H2A, H2B, H3, and H4) are synthesized and deposited concurrent with DNA replication, whereas histone variants, which contain slight sequence variations from their canonical counterparts, can be incorporated into nucleosomes independently of DNA replication. Nucleosomes with canonical histones or histone variants can have differential epigenetic impact (Henikoff and Smith 2015). Posttranslational modifications to the histone tails can occur at any point and help to regulate the chromatin structure and impact gene expression.

Chromatin regulates gene expression

Chromatin can be divided into 2 broad classes: euchromatin and heterochromatin. These 2 classes are mainly distinguished by their composition, posttranslational modifications on histones, and their association with transcription (Allis and Jenuwein 2016). These histone posttranslational modifications include the addition of chemical moieties to the histone tails that are thought to contribute to the control of gene expression by altering chromatin compaction or signaling to other protein complexes (Strahl and Allis 2000; Tan *et al.* 2011). Some of the most well-studied histone modifications include histone acetylation and methylation, both of which occur on lysine residues while histone methylation also occurs on arginines and histidines (Strahl and Allis 2000; Fischle *et al.* 2008; Tan *et al.* 2011). Histone acetylation can be deposited on many different lysine residues and is typically correlated with euchromatin, more open transcriptionally accessible chromatin (Shahbazian and Grunstein 2007). Histone methylation can be associated with euchromatin or the more transcriptionally quiescent heterochromatin depending on which specific amino acid is methylated (Greer and Shi 2012). Thus, for instance, euchromatin is open and accessible for transcription and is enriched for methylation on histone H3 lysines 4, 36, and 79 (H3K4me, H3K36me, H3K79me) and acetylation of histone tails. Heterochromatin regions, on the other hand, tend to be closed and quiescent for transcription and are enriched for methylation of histone H3 lysines 9 and 27 (H3K9me and H3K27me) and methylation of histone H4 on lysine 20 (H4K20me). However, these correlations are not absolute; H3K4me2 and H3K4me3 for instance can be associated with transcriptional repression (Bernstein *et al.* 2006; Shi *et al.* 2006). Furthermore, the causal roles of histone modifications in transcriptional regulation remain intensely studied (Morgan and Shilatifard 2020).

In the *C. elegans* genome, chromatin composition varies between chromosomes (Bessler *et al.* 2010; Garrigues *et al.* 2015; Meyer 2022) between gene-poor chromosome ends and gene-rich centers of chromosomes (McMurchy *et al.* 2017; Ahringer and Gasser 2018), between promoter regions and gene bodies (Evans *et al.* 2016; Carelli *et al.* 2017), in different cells and tissues of the organism (Evans *et al.* 2016; Methot *et al.* 2021; de la Cruz-Ruiz *et al.* 2023), throughout the organism's developmental trajectory and lifespan (Janes *et al.* 2018), and between generations of animals (Lee *et al.* 2019). The effects of chromatin modifications are pervasive and impact all of genome biology from gene expression, genome stability, genome organization, and architecture, to genome evolution. Thus, because of their universal impact, in many cases, it is difficult to deconvolve mechanisms that cause changes to chromatin from the durable consequence of chromatin changes. For instance, the repressive mark H3K27 is the most abundant mark in the *C. elegans* genome (Evans *et al.* 2016), yet its abundance not only represses transcription but also "functions" to organize chromatin into open and close regions (Cabianca *et al.* 2019), which in turn would also indirectly influence transcription factor binding, replication, nuclear physiology, and several other aspects of cellular function. Similarly, H3K4me3 can reflect gene expression and also modulate origins of replication during cell division (Ho *et al.* 2014; Pourkarimi *et al.* 2016; Serra-Cardona *et al.* 2022). It is also worth noting that none of these chromatin modifications function in isolation, and there can be extensive crosstalk between different chromatin modifications. In addition, these chromatin modifications are in almost all cases, reversible.

Because the adult *C. elegans* soma is composed entirely of differentiated cells and lacks tissue-resident stem cells, one might predict that the major mechanisms by which the animal ages would be through those that trigger cellular aging, such as dysregulated transcription, genomic instability, and perturbation to the differentiated states of its cells, leading to the inevitable loss of cellular and tissue homeostasis. Therefore, chromatin states in cells would be expected to have a major impact on the healthspan and lifespan of the animal. Indeed, single-cell RNA-seq experiments (scRNA-seq) on *C. elegans* conducted during aging indicate that aging is associated with cell-type-specific gene expression changes (Roux *et al.* 2023; Gao *et al.* 2024). RNA-seq from aging animals has also shown a loss of transcriptional integrity and increased transcriptional noise during aging (Rangaraju *et al.* 2015). In addition, a large body of data show that intertissue interactions also influence the rates of organismal aging, and signals from 1 tissue can coordinate aging-related changes in other tissues and throughout the whole organism (Apfeld and Kenyon 1998; Hsin and Kenyon 1999; Miller *et al.* 2020). Moreover, the history of environmental exposures such as early-life stress, or changes in developmental trajectory as occurs upon passage through a dauer stage, can result in programmed, durable changes in gene expression and affect adult phenotype and longevity (Klass 1977; Ow *et al.* 2018; Oleson *et al.* 2021; Jiang *et al.* 2024). Thus, identifying the roles of chromatin in aging in *C. elegans*, and other multicellular organisms, is particularly challenging especially when chromatin changes are likely to cause tissue-specific effects (Delaney *et al.* 2022; Padeken *et al.* 2022), but the majority of assays to evaluate chromatin are still only feasible in bulk samples from populations of *C. elegans* (although see Methot *et al.* 2021). Notwithstanding these difficulties, *C. elegans* has contributed enormously to our understanding of how chromatin alterations affect and are affected by aging.

Alterations in histones during aging

While replicative aging in budding yeast is accompanied by substantial histone loss and overexpression of histone genes can extend lifespan (Dang *et al.* 2009; Feser *et al.* 2010), the data are more complex in *C. elegans*. Younger adults contain both postmitotic somatic cells and rapidly proliferating and differentiating germ cells, whereas older adults contain mainly postmitotic somatic cells, as the germline begins to degenerate around day 5 of adulthood (Garigan *et al.* 2002), although some endoreplication of the DNA continues in the intestine and the germline (Golden *et al.* 2007). RNAi knockdown of *his-3*, which encodes histone H2A, results in compensatory upregulation of the other core histones, including H2B, H3, and H4, and a mild lifespan extension (Matilainen *et al.* 2017). Additionally, overexpression of H4 also mildly increases lifespan (Sural *et al.* 2020). In the temperature-sensitive germlineless *glp-1* mutant, H3 levels in somatic cells are decreased in day 12 older adults relative to day 2 young adults (Ni *et al.* 2012). However, the genome-wide distribution of H3 appears well correlated between young (day 2) and old (day 12) germlineless mutants (Pu *et al.* 2015, 2018; Li *et al.* 2021), suggesting no

major changes in nucleosome occupancy during aging in somatic cells. It is possible that more dramatic changes in nucleosome occupancy or positioning would become more apparent if probed at a more advanced age or in specific tissues. Alternatively, changes in the free histone pool might also contribute to lifespan changes in *C. elegans*.

Consistent with the observation that core histone occupancy remains stable with aging in the germlineless *glp-1* mutant, genome-wide profiling of open chromatin regions, using assay for transposase-accessible chromatin with sequencing (ATAC-seq), along an aging time course (days 2, 6, 9, and 13) reveals largely stable open chromatin promoter regions through aging (Janes *et al.* 2018). It is important to keep in mind that this investigation was done using whole worms, and more subtle cell- or tissue-specific changes in chromatin accessibility would likely be masked. Furthermore, gene transcription can experience drastic alteration without detectable changes in ATAC-seq signal (Methot *et al.* 2021). Nevertheless, ~13% of the promoter regions do show age-dependent changes in chromatin accessibility. Further analysis of whether and how these changes in promoter accessibility might impact age-dependent gene expression and aging phenotypes will provide valuable insights.

In addition to core histones, the H3.3 variant, encoded by *his-71* and *his-72*, shows increased expression with aging (Piazzesi *et al.* 2016). Interestingly, while the loss of *his-71* or *his-72* does not substantially impact the lifespan of otherwise wild-type worms, their loss shortens the lifespan of multiple long-lived mutants; including mutants of the insulin receptor *daf-2*, the mitochondrial respiratory chain complex I member *nuo-6*, and the notch receptor *glp-1*, which inhibits germ cell proliferation (Piazzesi *et al.* 2016), suggesting H3.3 is required for the lifespan extension in several different genetic contexts that promote longevity.

Alterations in histone modifications during aging

To avoid the effect of a changing germline size and content with age, a series of studies have examined how several major histone methylations change with aging in somatic cells using the germlineless *glp-1* mutant (Maures *et al.* 2011; Ni *et al.* 2012; Pu *et al.* 2015, 2018; Li *et al.* 2021), including H3K4me3 and H3K36me3 that are typically associated with active gene expression and H3K27me3 and H3K9me3 that are typically associated with repressed gene expression. The age-dependent profiles of histone acetylation have not yet been reported, although both histone acetyltransferases (HATs) and deacetylases have been implicated in modulating lifespan in *C. elegans* (Emerson and Lee 2023).

H3K4me3 usually, but not always, marks promoters of actively expressed genes (Bernstein *et al.* 2002, 2006; Santos-Rosa *et al.* 2002; Shi *et al.* 2006; Howe *et al.* 2017; Wang, Fan, *et al.* 2023). Using chromatin-immunoprecipitation coupled with sequencing (ChIP-seq) to profile the genome-wide patterns of H3K4me3 at young (day 2) and old (day 12) in *glp-1* germlineless mutant, it was found that the H3K4me3 occurring on the chromatin at the 5′ end of genes is generally established by larval stage 3 and remains stable over the time points assayed (Pu *et al.* 2018). However, ~30% of H3K4me3 modifications, predominantly occurring in chromatin in the gene body of some genes, become detectable in adult worms and show significant changes with age (Pu *et al.* 2018). Genes whose gene body H3K4me3 changes with age generally display correlative changes in RNA expression, including genes implicated in aging biology, raising the possibility that changes in H3K4me3 could modulate aging itself. How the specificity of H3K4me3 changes is defined and what regulates the age-dependent H3K4me3 changes remain to be determined. Nevertheless, the dynamic changes of H3K4me3 with aging are consistent with the findings that H3K4me3-modifying enzymes and binding proteins have been shown to regulate longevity (see below) (Greer *et al.* 2010; Wang *et al.* 2018).

H3K36me3 usually, but not always, marks the gene body of actively expressed genes, with higher enrichment at the 3′ end of genes (Wagner and Carpenter 2012). ChIP-seq profiling of H3K36me3 at young (day 2) and old (day 12) *glp-1* germlineless mutants shows that genome-wide pattern of H3K36me3 remains stable from larval stage 3 through aging (Pu *et al.* 2015). Interestingly, the genes that are actively expressed, but are nevertheless marked by low or undetectable levels of H3K36me3, tend to show significantly more dramatic mRNA expression changes with aging (Pu *et al.* 2015). This anticorrelation between H3K36me3 marking and mRNA expression change with aging is independent of the mRNA expression levels of the genes. A similar anticorrelation is also observed in *Drosophila* (Pu *et al.* 2015), suggesting a conserved regulatory mechanism whereby genes with lower H3K36me3 deposition display greater age-dependent dynamic RNA expression changes. Interestingly, loss of MET-1, the major putative enzyme that deposits H3K36me3 in somatic cells in *C. elegans*, leads to global decrease of H3K36me3, greater significant RNA expression changes, and reduced lifespan (Pu *et al.* 2015). The finding suggested a role of H3K36me3 in maintaining gene expression stability through aging. In addition to MET-1, which is responsible for the vast majority of H3K36me3, MES-4 is a conserved histone methyltransferase that is essential for H3K36me1 and me2 modifications (Kreher *et al.* 2018; Cabianca *et al.* 2019; Cockrum and Strome 2022) but has not been tested for lifespan effects. In multiple species, aging is associated with deregulated cryptic transcription of a subset of genes, which also display lower H3K36me3 (Sen *et al.* 2015; McCauley *et al.* 2021). It is possible that deregulated cryptic transcription with age can contribute to age-dependent RNA expression changes and contribute to aging.

H3K27me3 usually marks repressed or silenced genes (Wiles and Selker 2017), but some genes can be marked by both H3K27me3 and H3K4me3 and they are poised to be quickly turned on or turned off (Bernstein *et al.* 2006). ChIP-seq profiling of H3K27me3 at young (day 2) and old (day 12) *glp-1* germlineless mutant worms shows that genome-wide pattern of H3K27me3 remains stable, and only ~1% of the H3K27me3-modified chromatin regions show significant changes (Li *et al.* 2021). However, another group found that by western blotting, there was an age-dependent decline in H3K27me3 in *glp-1* mutant worms (Maures *et al.* 2011), which became particularly apparent by day 14. It is possible that this mark becomes dramatically reduced in animals of advanced age or that different culturing conditions or different methodologies with different sensitivities could reveal more or less dramatic changes in histone methylation with aging. Interestingly, H3K27me3 deposition at specific heat-induced promoters becomes substantially increased midway through reproduction in wild-type worms (Labbadia and Morimoto 2015), which greatly dampened the heat shock response in postreproductive adults. Importantly, this change was not detected in the genome-wide profiling of H3K27me3 in the *glp-1* germlineless mutant, reinforcing the notion that histone modifications can be highly dynamic and cell-type specific.

H3K9me2 and H3K9me3 are generally associated with constitutive heterochromatin, particularly in regions of the genome that are highly repetitive (Zeller *et al.* 2016; Padeken *et al.* 2019). Loss of heterochromatin and consequent deregulated gene

silencing has been proposed to be a contributor to aging (Villeponteau 1997; Tsurumi and Li 2012). On the other hand, replicative senescence results in the accumulation of local regions of heterochromatin (Narita *et al.* 2003), indicating different regions of the genome can lose or gain heterochromatin. Age-dependent profiling of H3K9me2 has not yet been reported, but ChIP-seq profiling of H3K9me3 at young (day 2) and old (day 12) *glp-1* germline-less mutant worms shows that global levels of H3K9me3 somewhat decrease with aging, but different regions of the genome can lose or gain H3K9me3 marking with aging (Li *et al.* 2021). Interestingly, ~500 regions of the genome show significant gain in H3K9me3, and the H3K9me3 marking in these regions appears to be aging specific, meaning those regions are devoid of H3K9me3 at the younger time point (Li *et al.* 2021). Intriguingly, unlike the canonical H3K9me3 pattern that concentrates at chromosomal arms that tend to be gene poor and heterochromatic, these regions that gain aging-dependent de novo H3K9me3 are in gene-rich regions of the genome. The emergence of these H3K9me3-modified histones in aged worms does not appear to correlate with mRNA expression changes; thus, their functional significance remains to be determined. Additional analysis reveals that these regions significantly correlate with regions highly enriched for H3K9me2 and H3K36me2 in juvenile worms at the L3 stage (Li *et al.* 2021). This is particularly intriguing, as the overlapping H3K9me2 regions have been linked to longevity in other contexts (Lee *et al.* 2019) (see below). Importantly, recent studies indicate that H3K9me2 in particular has an essential role in maintaining appropriate silencing of tissue-specific genes and by doing so helps maintain tissue integrity in multicellular organisms, even in the absence of detectable changes in chromatin compaction (Methot *et al.* 2021; Padeken *et al.* 2022). Further investigation of how the profile of H3K9me2 changes with aging and how the putative methyltransferase MET-2, which deposits H3K9me2, and SET-25, which deposits H3K9me3, affect lifespan and healthspan during aging will be critical.

Together, these studies have revealed that several major histone modifications are dynamic during aging and raise the possibility that changes in histone modifications and chromatin landscape could contribute to the regulation of aging. However, these earlier studies profiling of H3K4me3, H3K36me3, H3K27me3, and H3K9me3 in young vs old adults were all done using whole worms, which significantly limit interpretation as many chromatin changes would be expected to be cell-type specific. Going forward, cell-type-specific analyses will be key to further delineate how the chromatin landscape in different cells/tissues changes in aging and whether they play a causative role in aging biology. It will be important in future studies to perform directed chromatin changes, using nuclease null Cas9 fused to specific chromatin-modifying enzymes (Nakamura *et al.* 2021; Policarpi *et al.* 2021), to determine whether changes in chromatin modifications at specific loci per se are sufficient to regulate longevity.

Altering chromatin states modifies lifespan

While gene expression and chromatin states display dynamic changes with age, this is no guarantee that enzymes that regulate gene expression on a global level, such as chromatin-modifying enzymes, regulate aging itself. This has been addressed by experiments directly manipulating chromatin-modifying enzymes and assessing their effects on organismal aging (Fig. 1). The results of such experiments suggest that chromatin modifications themselves could be important in regulating aging.

Role of histone acetylation-regulating enzymes in regulating lifespan

The earliest investigation of chromatin-modifying enzymes in regulating lifespan in *C. elegans* is probably the histone and protein deacetylase *sir-2.1* (Imai *et al.* 2000; Tissenbaum and Guarente 2001), which is part of a larger sirtuin family of enzymes that had initially been shown to regulate lifespan in yeast (Kennedy *et al.* 1995; Kaeberlein *et al.* 1999), and is described in more detail later in this chapter. It was demonstrated that overexpression of *sir-2.1* led to a 15–50% increase in lifespan in *C. elegans* (Tissenbaum and Guarente 2001). Sirtuins have also been shown to regulate lifespan in *Drosophila* (Rogina and Helfand 2004) and SIRT6 deletion in mice causes an aging-like phenotype (Mostoslavsky *et al.* 2006) while overexpression in male mice leads to a subtle increase in lifespan (Kanfi *et al.* 2012). However, a number of groups have had difficulty reproducing these results in yeast, worms, and flies where they proposed that these discrepancies were dependent on genetic backgrounds and controls (Kaeberlein *et al.* 2004; Burnett *et al.* 2011), and mixed findings remain as to whether *Sir2* can indeed regulate lifespan in *C. elegans* and *Drosophila* (Rizki *et al.* 2011; Viswanathan and Guarente 2011; Whitaker *et al.* 2013). Since epigenetic-regulating enzymes are inherently responsive to the environment, different laboratories could very readily have different culturing conditions that could contribute to the dependency or lack thereof of chromatin-regulating enzymes on controlling longevity. In addition, given the presence of multiple Sir2 homologs, potential roles for SIRT6 and its homologs in modulating lifespan remain a distinct possibility (Chiang *et al.* 2012; Jedrusik-Bode 2014; Tasselli *et al.* 2017).

More recently, the HAT CBP-1 has been shown to be required for lifespan extension by DR, mutation in the insulin receptor gene *daf-2(e1370)* (Zhang *et al.* 2009), and temperature-induced hormetic lifespan extension (Zhou *et al.* 2019). Similarly, the MYS-1/TRR-1 acetyltransferase complex is required for lifespan extension induced by intermittent fasting; the complex is recruited to the promoter of DAF-16 where it enhances histone acetylation and expression of DAF-16 (Agger *et al.* 2007). Interestingly, this regulation appears conserved in mammalian cells (Ikeda *et al.* 2017). Overexpression of PCAF-1 is also sufficient to extend lifespan in wild-type *C. elegans* and broad elevation of histone acetylation appears to mediate the longevity of the COMPASS complex mutants (see below) (Silva-García *et al.* 2023). In contrast, mutation of another HAT, *hat-1*, can extend *C. elegans* lifespan (Müthel *et al.* 2019). Reduction of the putative histone deacetylases HDA-2 or HDA-3 by RNAi has been shown to modestly extend lifespan, whereas constitutive knockout of *hda-2* (Edwards *et al.* 2014) or *hda-3* (Edwards *et al.* 2014; Kawamura and Maruyama 2020) surprisingly has shortened lifespans, suggesting that partial, but not complete, inhibition of HDACs could be beneficial for longevity. Müthel *et al.* (2019) also demonstrated that mutation in *sin-3*, a component of a HDAC, results in shortened lifespan. These histone acetylation-regulating enzymes appear to be essential in multiple species as in *Drosophila*, heterozygous loss of Rpd3, the HDAC1 homolog, leads to an extended lifespan (Rogina *et al.* 2002), but homozygous loss of Rpd3 is lethal (Mannervik and Levine 1999). Histone acetylation on various residues is generally associated with euchromatin and active gene expression (Rice and Allis 2001). It remains to be determined whether HATs and deacetylases are regulating lifespan through direct manipulation of chromatin and, if so, whether this is because of regulation of specific target gene expression (Ikeda *et al.* 2017; Müthel *et al.* 2019) or more global changes in chromatin accessibility.

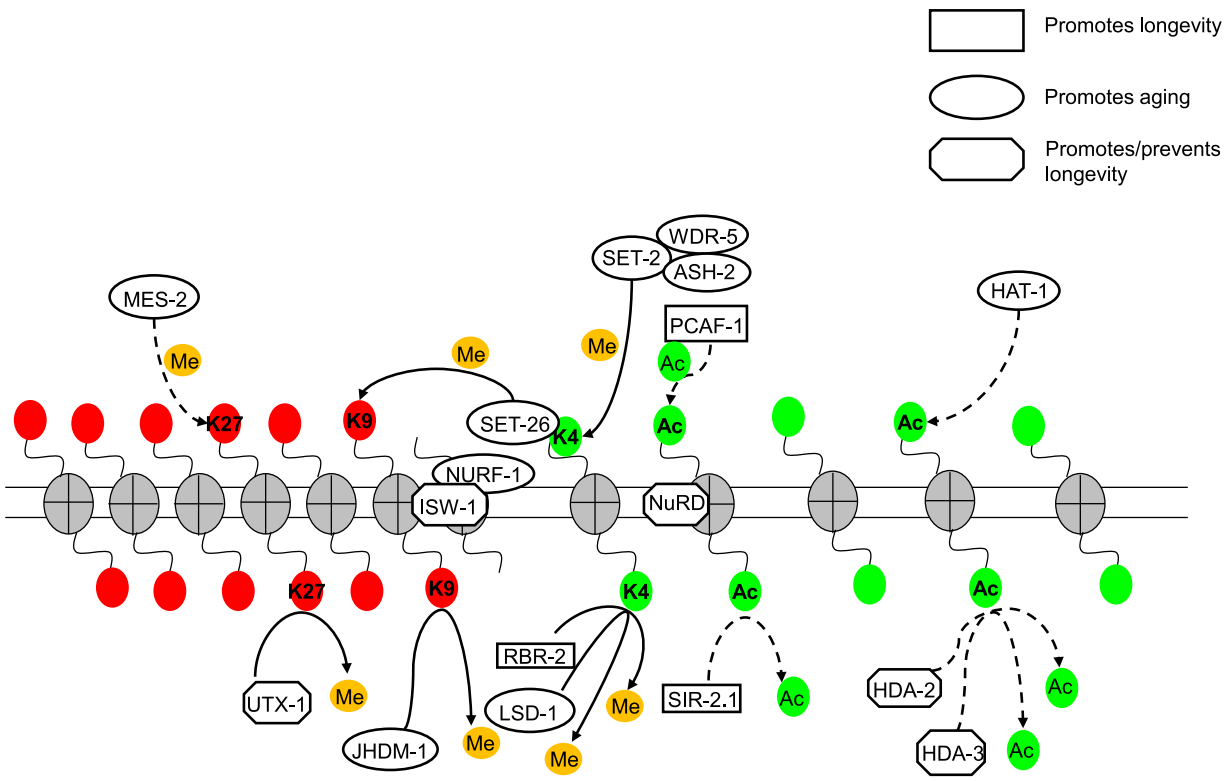

Fig. 1. Summary of the chromatin factors shown to regulate lifespan. Many chromatin-modifying enzymes and chromatin-binding proteins have been shown to regulate longevity in *C. elegans*. Those demonstrated to extend lifespan when mutated or overexpressed are highlighted. Proteins shown in circles have been shown to promote aging while proteins shown in boxes have been shown to promote longevity. Proteins shown in hexagons have conflicting results where proteins have been shown to promote or prevent longevity by different groups. Solid lines indicate that a direct biochemical activity has been demonstrated while doted lines indicate a putative activity based on homology or changes in chromatin modifications after altered gene activities. Modifications that are correlated with increased chromatin accessibility are shown in green on the right side of the figure while modifications that are correlated with repressed chromatin are shown in red on the left side of the figure. Information about tissue specificity or genomic location is not included in this figure. K, lysine; Ac, acetyl; Me, methyl.

Role of histone methylation enzymes in regulating lifespan

The next chromatin-modifying enzymes to be extensively examined for their role in regulating longevity were histone methyltransferases and demethylases (Greer *et al.* 2010; Maures *et al.* 2011). Directed RNAi screens in *C. elegans* revealed that ablation of the histone H3 lysine 4 (H3K4) trimethyltransferase complex, consisting of *ash-2*, *wdr-5.1*, and the methyltransferase *set-2*, had the most dramatic effect on extending longevity (Greer *et al.* 2010). It was found that this complex functioned in the *C. elegans* germline to regulate organismal longevity (Greer *et al.* 2010). The lifespan-extending effects of *ash-2*, *wdr-5.1*, and *set-2* were independently validated by several groups (Jin *et al.* 2011; Wang *et al.* 2018; Silva-García *et al.* 2023), but recently another group has found that loss of the H3K4 trimethyltransferase *set-2* decreased, rather than increased, lifespan in their hands (Caron *et al.* 2022). Because of the germline dependency of the H3K4 trimethyltransferase complex for regulating lifespan, it was found that the use of the pyrimidine analog chemical 5-fluorodeoxyuridine (FUdR), a drug that inhibits DNA synthesis and also RNA formation and is frequently used in *C. elegans* longevity experiments due to the fact that it inhibits reproduction and therefore eliminates the potential confusion of the *C. elegans* whose lifespan is being examined with their progeny (Mitchell *et al.* 1979), completely eliminated the lifespan-extended effects of manipulation of this complex (Greer *et al.* 2010). Subsequent work demonstrated that ablation of the H3K4me3 methyltransferase complex promotes enrichment of monounsaturated fatty acids to regulate lifespan (Han *et al.* 2017).

Consistent with the role of H3K4me3 in regulating lifespan, knockdown of *rbr-2*, the H3K4me3 demethylase in *C. elegans* (Christensen *et al.* 2007), leads to a decrease in lifespan while overexpression of RBR-2 extends lifespan (Greer *et al.* 2010). In *Drosophila*, the opposite result was observed, where inactivation of the RBR-2 homolog, Lid, leads to an extension of male but not female lifespan (Li *et al.* 2010). Findings with *rbr-2* have also not been consistent across different labs. An initial genome-wide RNAi screen found that *rbr-2* knockdown increased rather than decreased overall lifespan (Lee *et al.* 2003), and this was further validated (Ni *et al.* 2012; Alvares *et al.* 2013). Part of these opposing results can be explained by the use of the drug FUdR, which was employed in Lee *et al.* (2003) and Ni *et al.* (2012). In the manuscript that found that depletion of *rbr-2* leads to a shortening of *C. elegans* lifespan, they also found that FUdR addition caused deletion of *rbr-2* to extend rather than shorten lifespan (Greer *et al.* 2010). These opposing results depending on the usage of FUdR further highlight the importance of the germline and reproduction for these longevity-regulating phenotypes. It is unclear from the methods as to whether Alvares *et al.* (2013) used FUdR but they do discuss using worms that had been starved for varying periods of time before initiating their lifespan assays that also could have dramatic effects on the epigenetic state of the wild-type worms and also the importance of deletion of *rbr-2*. Interestingly, treatment of *C. elegans* with lithium that causes a reduced expression

of the H3K4me1/me2 demethylase LSD-1 as well as knockdown of *lsd-1* itself both caused a lifespan extension (McColl *et al.* 2008), suggesting that H3K4 itself is a particularly important residue for regulating lifespan.

Intriguingly, the loss of *wdr-5.1* has complex effects on lifespan regulation that may depend on the ancestors of the worm in question; Lee *et al.* reported that mutants are not longer lived than wild-type siblings of the same generation, but over generations, the wild-type descendants from heterozygote *wdr-5+/−* become shorter lived, while *−/−* siblings become longer lived (see additional discussion on Transgenerational Effect on Lifespan below). These observations could have several explanations including the gradual accumulation of epigenetic changes over generations in a *wdr-5.1* mutant background, the compensatory changes to chromatin that likely occur upon loss of certain key epigenetic marks, and/or the differences in the locus modified. Indeed, consistent with the latter possibility and a cross-regulation between H3K4me3 and H3K9me2, loss of *met-2*, which encodes the methyltransferase that account for a majority of H3K9me2 in *C. elegans* (Towbin *et al.* 2012), shortens the lifespan of *wdr-5* mutant and abrogates lifespan extension even in late generation *wdr-5* mutant (Lee *et al.* 2019). Furthermore, loss of the H3K9 demethylase JHDM-1 results in longer lifespan (Lee *et al.* 2019; Huang *et al.* 2022), indicating that H3K9me likely plays a key role in modulating aging (see below for more details on transgenerational inheritance of lifespan changes). Another possible connection between H3K4me and H3K9me in lifespan was revealed through a series of studies on SET-26. Initial RNAi screens found that knockdown of *set-9/set-26* (Greer *et al.* 2010), 2 homologous paralogs that would therefore both be knocked down by RNAi against either one, increased lifespan in a manner that is partially dependent on *daf-16*, the *C. elegans* homolog of the Forkhead box O (FOXO) transcription factor (Ni *et al.* 2012). Subsequent studies suggested the SET domain of SET-26 to have H3K9 trimethyltransferase activity in vitro (Greer *et al.* 2014). In a follow-up study, SET-26 was found to bind H3K4me3, via its PHD domain, in vitro. ChIP-seq studies revealed that the majority of the SET-26 binding in day 1 adult worms coincide with H3K4me3 but only a small fraction coincide with H3K9me3 (Wang *et al.* 2018). A lack of colocalization with a modification does not imply that SET-26 does not modify that mark, as enzymatic activity is transient, but this finding could suggest that SET-26's predominant function is as a methyl-binding protein rather than a methyltransferase in vivo. SET-26 was also suggested to prevent the spread of the H3K4me modification (Greer *et al.* 2014; Wang *et al.* 2018). SET-26 was shown to function in the soma to regulate lifespan (Wang *et al.* 2018), while the SET-2 H3K4 trimethyltransferase complex has been shown to function in the germline to regulate lifespan (see above) (Greer *et al.* 2010). These findings highlight how additional work is required to determine whether an enzyme or putative enzyme that is supposed to function by modulating 1 particular histone modification is really regulating downstream function by affecting that modification, some other histone modification, or potentially some nonhistone protein that shares a lysine within a similar motif. It is worth reiterating that none of these chromatin modifications function in isolation and there is extensive crosstalk between different chromatin modifications for their regulation of gene expression and subsequently longevity. The importance of histone modification crosstalk is further highlighted by the finding that *set-26* ablation-induced lifespan extension is partially dependent on the histone deacetylase HDA-1 (Emerson *et al.* 2024).

Three independent groups identified consistent consequences of ablating *utx-1*, which encodes a H3K27 demethylase in *C. elegans*, to lead to extended longevity (Jin *et al.* 2011; Maures *et al.* 2011; Ni *et al.* 2012). Unlike the H3K4me3-regulating complex that was shown to function in the worm's germline to regulate aging (Greer *et al.* 2010), the germline was found to be dispensable for the lifespan-extending effects of *utx-1* depletion (Maures *et al.* 2011). It was found that H3K27me3 itself decreases in the soma of *C. elegans* as they age (Maures *et al.* 2011) and therefore depletion of *utx-1*, the H3K27me3 demethylase, could potentially regulate lifespan by maintaining a more elevated, and hence more youthful, level of H3K27me3. These lifespan-regulating phenotypes were found to be dependent on the insulin signaling pathway (Jin *et al.* 2011; Maures *et al.* 2011). Interestingly, an independent group found that both depletion and overexpression of UTX-1 caused an extension in *C. elegans* lifespan (Guillermo *et al.* 2021). Additionally, it was found that decreasing expression of MES-2, the putative H3K27me3 trimethylase also causes an extension of lifespan in sterile *C. elegans* (Ni *et al.* 2012). Similarly heterozygous mutation of *Enhancer of zeste (E(z))*, the H3K27 trimethyltransferase in *Drosophila*, leads to an extension in lifespan (Siebold *et al.* 2010). These findings highlight the context-dependent nature of chromatin-regulating enzymes; chromatin factors often act in different specific complexes and can have differential or even opposing functions in different cellular, temporal, and genomic contexts.

Role of chromatin remodelers in regulating lifespan

Chromatin remodelers are enzymes that use ATP hydrolysis to insert, evict, or move histones and can have a big impact on chromatin organization. The SWI/SNF family of chromatin remodelers has been shown to act as cofactors of the prolongevity transcription factor DAF-16 on specific transcriptional targets and are required for the extended lifespan of the *daf-2* insulin-like signaling mutant (Riedel *et al.* 2013; Bansal *et al.* 2014). The ISW1 family of chromatin remodelers has more context-dependent effects on longevity: components of ISW1 have been demonstrated to be required for the extended lifespan of the *daf-2* insulin-like signaling mutant and mitochondrial electron transport chain (ETC) mutant and RNAi worms (Curran *et al.* 2009; Matilainen *et al.* 2017). However, the *isw-1(n3294)* loss-of-function mutation and *isw-1* RNAi have also been shown to extend lifespan in wild-type worms (Müthel *et al.* 2019), indicating ISW1 can limit lifespan. Loss or reduced function of *nurf-1*, a component of the NURF complex and a subclass of ISW1, results in lifespan extension in several studies (Large *et al.* 2016; Matilainen *et al.* 2017; Müthel *et al.* 2019), supporting its normal role in limiting lifespan. Thus, the ISW1 family appears to have variable effects on lifespan depending on context and experimental conditions. The CHD family of chromatin remodelers similarly has complex effects on lifespan: several components of the nucleosome remodeling and deacetylase (NuRD) complex appear to limit lifespan as their loss-of-function mutations lead to longer lifespan (De Vaux *et al.* 2013; Müthel *et al.* 2019), although these results are not confirmed by all research groups (Golden *et al.* 2022). In additional studies, NuRD subunits have been shown to be required for the full extended longevity of the *daf-2* insulin-like signaling mutant (De Vaux *et al.* 2013) and worms with depletion of specific ETC subunits (Shao *et al.* 2020; Zhu *et al.* 2020). Considering that chromatin remodelers are indispensable for almost all processes that involve the DNA, it is not surprising that different subunits/complexes have context-dependent effects on longevity.

Summarizing, it is clear that both chromatin modifications change with age, and manipulating chromatin-modifying enzymes can have favorable or detrimental effects on lifespan of *C. elegans*. However, it still remains to be determined whether these chromatin-modifying enzymes are altering organismal lifespan through changes of specific histone modifications at specific genomic loci or whether these enzymes are functioning through chemical modifications of nonhistone proteins and the changes in chromatin modifications are simply bystander changes. Identification of which tissue-specific chromatin-modifying enzymes function in and where chromatin modifications change with age and then performing directed chromatin manipulations will help to reveal whether these enzymes function through direct manipulation of chromatin accessibility at specific genomic loci. In addition, chromatin modifications do not function in isolation, and there is extensive crosstalk between different chromatin modifications; it will be important in future studies to determine which, if any, of the chromatin modification changes are critical for changes in gene expression and subsequently longevity.

Mechanisms through which the chromatin state is altered during aging

What are the proximate triggers for the epigenetic changes that alter lifespan? Because alterations in chromatin are necessary events accompanying normal transcription, the complex changes in histones and chromatin proteins that occur during aging can be conceived as the integration of all transcriptional events across the course of the organism's lifespan. However, normal transcription alone cannot explain the persistent alterations in chromatin seen in aged animals since almost all epigenetic changes to chromatin are reversible, and there is no *a priori* reason for their persistence at genomic regions. In addition, in mammalian cells, chromatin changes can precede or occur independent of transcriptional events [for examples, see Petesch and Lis 2008; Stewart-Morgan *et al.* 2019; Kiani *et al.* 2022]. Thus, the proximate triggers that alter the epigenetic landscape of organisms during aging are not completely understood. In this regard, it is worth restating the difficulty in disentangling the effects of any specific chromatin change from downstream chromatin alterations that can occur due to the complex interactions and feedback loops that govern the epigenetic landscape of cells at any given time.

C. elegans has been a paradigmatic model for understanding the molecular and signaling mechanisms that modulate aging, and a number of genetic and environmental manipulations regulate longevity (Kenyon 2010). Several of the universal hallmarks of aging (López-Otín *et al.* 2013, 2023) are also applicable to *C. elegans*, and some of these "hallmarks" can act as proximate triggers for the observed alterations in chromatin seen during aging. In this section, we will discuss what is known regarding how environmental, metabolic, and genetic factors that modulate aging rates in *C. elegans* also drive the lasting epigenetic changes seen with age. Thus, we first discuss the effects of known longevity manipulations such as DR, insulin signaling, reactive oxygen species, metabolites, environmental stressors, DNA damage, nuclear integrity, and intercellular communication on chromatin modifications that occur during *C. elegans* aging. It is important to note that some processes that have been identified to cause premature death are not yet considered *bona fide* regulators of aging here, given the requirement that regulators of aging be both necessary as well as sufficient to alter lifespan. However, we mention them here due to their exciting roles in the maintenance of transcriptional integrity and cellular aging in other species. Finally, we examine what is known regarding epigenetic changes that accompany transgenerational alterations in lifespan, suggestive of developmental programming of lifespan.

Nutrient-sensing pathways and chromatin states

Nutrient-sensing pathways are highly conserved and have profound effects on the lifespan of all metazoa. *C. elegans*, like other organisms, senses and responds to nutrient scarcity through the activity of intracellular nutrient sensors, such as signaling through insulins and insulin-like growth factors (IGFs), modulation of the mammalian target of rapamycin (MTOR/LET-363), AMP-activated protein kinases (AMPK/AAK-2), and changes in NAD:NADH balance through enzymes such as the histone deacetylase *sir-2.1* and the *sir-2.4* (the mammalian SIRT 6/7 homolog). DR, the reduction in available food without starvation, which has been shown to extend lifespan in all species, reshuffles nutrients to allow an organism to respond to the altered food availability. DR favors catabolic reactions, increases the activation of adaptive cellular stress responses such as autophagy, antioxidant defense, and DNA repair, and suppresses or holds in check anabolic pathways such as protein synthesis and DNA replication. Changes in nutrient balance can also trigger more efficient mitigation of damage, as seen with the role of SIRT6 in the efficiency of DNA damage repair that contributes to the extended lifespan of long-lived rodent species (Mostoslavsky *et al.* 2006; Kanfi *et al.* 2012; Tian *et al.* 2019). As epigenetics exists at the interface between the environment and the genome, these nutrient-sensing pathways typically partially implement their responses through epigenetic alterations.

Insulin signaling pathway

The best characterized and most robust longevity-regulating genetic pathway is the insulin/IGF signaling (IIS) pathway, where reduced levels or activities of the insulin receptor, *daf-2*, or its immediate downstream signaling components, including the phosphoinositide 3-kinase, *age-1*, can lead to 2-fold to up to 10-fold extension in *C. elegans* lifespan (Friedman and Johnson 1988b; Kenyon *et al.* 1993; Morris *et al.* 1996; Kimura *et al.* 1997; Ayyadevara *et al.* 2008). These lifespan-extending genetic mutations were subsequently found to require the action of the downstream transcription factor FOXO/*daf-16*, such that the inactivation of *daf-16* suppresses the lifespan extension associated with disrupted insulin receptor signaling (Lin *et al.* 1997; Ogg *et al.* 1997). The IIS pathway remains the most robust genetic pathway that can extend lifespan in worms, and its effect has been demonstrated to be conserved across diverse species (Clancy *et al.* 2001; Tatar *et al.* 2001; Bluher *et al.* 2003; Holzenberger *et al.* 2003; Giannakou *et al.* 2004; Hwangbo *et al.* 2004; Taguchi *et al.* 2007). Given the importance of the local chromatin context in regulating gene transcription, it is not surprising that several chromatin factors have been implicated in cooperating with FOXO/DAF-16 and are required for the extended longevity of IIS mutants. Presumably changes in the chromatin architecture would facilitate binding of DAF-16 to its target binding sites to allow transcription of DAF-16-dependent transcripts. The SWI/SNF remodeler complex acts as a cofactor of DAF-16 on specific transcriptional targets and is required for the extended lifespan of *daf-2* mutants (Riedel *et al.* 2013; Bansal *et al.* 2014). As described above, RNAi of *isw-1*, a subunit of the ISW1 chromatin remodeler complex, is also required for the extended lifespan of the IIS mutants (Curran *et al.* 2009). Another study showed that while H3.3 deficiency does not decrease lifespan in *C. elegans* wild-type animals, H3.3 is essential for the pronounced transcriptional changes that cause lifespan extension of *C. elegans* in *daf-2*, insulin/IGF-1 signaling pathway mutants. These studies

suggest that the epigenetic alterations could be initiated by insulin signaling pathways when these pathways are experimentally altered to modulate lifespan, but the same pathways may not be active or may not have the same effect during normal aging. Given that DAF-16 is activated in response to numerous developmental, metabolic, and environmental challenges, these studies imply large-scale and possibly constant chromatin remodeling accompanies almost all stress responses in *C. elegans* (Riedel *et al.* 2013).

AMP-activated protein kinase (AMPK) and epigenetic changes

AMPK is considered a master metabolic regulator that senses changes in the intracellular AMP/ATP ratio (Cheung *et al.* 2000; Kahn *et al.* 2005). Some methods of DR increase the AMP:ATP ratio and require AMPK/*aak-2* to extend lifespan (Greer *et al.* 2007; Greer and Brunet 2009). AMPK has been shown to phosphorylate many targets, which could mediate these lifespan-regulating phenotypes, including the transcription factors DAF-16/FOXO and the CREB-regulated transcriptional coactivator (CRTC-1) as well as the mTORC1 inhibitor TSC2 and Raptor one of the components of mTOR complex 1 (Inoki *et al.* 2003; Greer *et al.* 2007; Gwinn *et al.* 2008; Mair *et al.* 2011). Not only can AMPK phosphorylate and regulate other energy-sensing pathways and critical longevity-regulating transcription factors, but AMPK can also directly phosphorylate histone H2B at serine 36 (Bungard *et al.* 2010), suggesting that this enzyme can directly modulate chromatin to affect chromatin state and transcription. During periods of acute starvation in *C. elegans* larvae, AMPK activation plays a critical role in blocking the activity of the COMPASS H3K4 trimethyltransferase complex and activating small RNA pathways in the primordial germline cells that are fated to develop into the *C. elegans* germline, sperm and oocytes, to ensure that activating chromatin marks and transcription are paused until the nutrient/energy contingencies are satisfied (Demoinet *et al.* 2017). Without AMPK, metabolism is disrupted, and the germline precursor cells overproliferate and lose their reproductive capacity, resulting in a consumption of lipid stores as well as misregulation of metabolic enzymes and reduced survival (Demoinet *et al.* 2017; Kadekar and Roy 2019). AMPK has also been reported to trigger a novel mechanism that involves the topoisomerase II/condensin II axis acting upstream of heterochromatin assembly (Belew *et al.* 2021).

Metabolic changes that trigger epigenetic changes

Since the discovery that the key tricarboxylic acid (TCA) cycle metabolite, acetyl-coenzyme A (CoA), is the substrate used by HAT enzymes to modify histone tails in eukaryotic cells, several studies have shown that chromatin states and chromatin modifiers can be modulated by changes in metabolites such as $NADH^{+}$/NAD, S-adenosylmethionine (SAM), and mitochondrial acetyl-CoA and alpha-ketoglutarate, providing a direct link between consumable nutrients, respiration, mitochondrial activity, and epigenetic changes (Lee and Workman 2007; Shahbazian and Grunstein 2007). Parallel mechanisms by which metabolism modulates chromatin changes have also been identified in *C. elegans* (Gao *et al.* 2015; Yeo and Brunet 2016) and influence lifespan (Greer *et al.* 2007, 2009; Greer and Brunet 2009; Greer *et al.* 2010, 2016; Han and Brunet 2015; Yeo and Brunet 2016; Han *et al.* 2017; Matilainen *et al.* 2017; Papsdorf and Brunet 2019; Booth *et al.* 2022; Hamsanathan *et al.* 2022; Papsdorf *et al.* 2023).

Early genetic screens to identify modulators of longevity (Hansen *et al.* 2005), and subsequently, other studies (Dang *et al.* 2009; Greer *et al.* 2010; Han and Brunet 2012; Han *et al.* 2017), including those that identified the longevity-promoting mechanism of action of metformin (Cabreiro *et al.* 2013) identified a role for the worm SAM synthases in aging. SAM is the methyl donor for almost all methyltransferases, including for H3K4me2/3, and transcriptional responses, particularly in response to some stressors, fail in *C. elegans* with low SAM (Ding *et al.* 2015, 2018). Consequently, S-adenosyl methionine synthetase (SAMS-1) is required for the effects of DR on lifespan, through its role in permitting an increase in histone methylation during the induction of autophagy genes through the activities of the transcription factors HLH-30/TFEB and PHA-4/FOXA (Lim *et al.* 2023). Likewise, the different SAMS enzymes contributed differentially to H3K4me3 at chaperone genes required to maintain proteostasis upon heat shock (Godbole *et al.* 2023; Lim *et al.* 2023) (also see below).

Several studies have shown that mitochondrial activity modulates lifespan, through mitochondrial reactive oxygen species (ROS) (Schulz *et al.* 2007; Schmeisser, Schmeisser, *et al.* 2013; Weimer *et al.* 2014) or metabolites (Chin *et al.* 2014; Zhu *et al.* 2020; Lin *et al.* 2022). A notable study showed that the levels of developmental ROS in larvae, associated with their respiration, determined the variation in their adult lifespans as adults, through modulation of the MLL/SET-2 enzymes (Bazopoulou *et al.* 2019). Specifically, increased oxidative stress during early larval stages, increased ROS, and reduced H3K4me3 levels throughout the lifespan of the exposed animals and, as observed in previous experiments, mimicked the lifespan extension seen upon downregulating the ASH-1, SET-2, and WRD-5.1 (Bazopoulou *et al.* 2019). Another study showed that the lifespan extension observed upon mitochondrial stress in *C. elegans* occurred through acetyl-CoA-mediated chromatin remodeling by the NuRD histone deacetylase complex (Zhu *et al.* 2020). Upon mitochondrial stress, the impaired tricarboxylic acid cycle caused a decrease in citrate levels, which subsequently decreased the production of acetyl-CoA and induced the nuclear accumulation of the NuRD and a homeodomain-containing transcription factor DVE-1, enabling decreased histone acetylation and chromatin reorganization. As seen with developmental ROS, this metabolic stress response was imposed during early life and, through epigenetic effects, had long-lasting effects on transcriptional regulation for lifespan extension (Zhu *et al.* 2020). Supplementation of alpha-ketoglutarate has been shown to increase lifespan in *C. elegans* (Chin *et al.* 2014; Lin *et al.* 2022). This occurs through the inhibition of ATP synthase and TOR (Chin *et al.* 2014) or through the activity of the TCA cycle enzyme, isocitrate dehydrogenase alpha-1, which, when overexpressed, increases the NADPH/NADP(+) ratio, and elevates the tolerance to oxidative stress. The latter 2 studies have not shown an association with chromatin changes, although studies from mammalian cells suggest this could be a possibility.

Similarly, alterations in lipid metabolism can trigger chromatin changes. Studies linking the downregulation of COMPASS H3K4 trimethylation complex (*ash-1*, *set-2*, and *wdr-5.1*) to lifespan extension showed that the effects on lifespan occurred through alterations in lipid metabolism (Han and Brunet 2015; Han *et al.* 2017). Specifically, the deficiency in H3K4me3 methyltransferase, which extends lifespan, promoted an increase in monounsaturated fatty acids, by modulating intestinal delta-9 fatty acid desaturases (Han and Brunet 2015; Han *et al.* 2017). Lipid profiles themselves change with age, likely due to several changes in physiology, but more importantly due to the change in reproductive status (Papsdorf and Brunet 2019). While these studies support the possibility that changes in lipid metabolism could be a critical switch between somatic maintenance and reproduction, they also offer the attractive possibility that lipid metabolism might be provisioning some of the carbon sources for histone modifications such as acetylation (Hamsanathan *et al.* 2022).

Sirtuins and energy status trigger epigenetic changes

The role of sirtuins in aging has been of particular interest since the early studies on lifespan extension by calorie restriction in the yeast *Saccharomyces cerevisiae* implicated the NAD+-dependent histone deacetylase, Sir2 (discussed in more detail above). In mammals, sirtuins play a particularly pivotal role in integrating the energy status of the cell with its epigenome (Korotkov *et al.* 2021). Thus, SIRT6 deletion in mice causes an aging-like phenotype (Mostoslavsky *et al.* 2006), while overexpression in male mice leads to a subtle increase in lifespan (Kanfi *et al.* 2012). In addition, SIRT6 modulates the efficiency of DNA damage repair that contributes to the extended lifespan of long-lived rodent species (Mostoslavsky *et al.* 2006; Kanfi *et al.* 2012; Tian *et al.* 2019). In *C. elegans*, changes in NAD:NADH balance signaled through enzymes *sir-2.1* and *sir-2.4* (the mammalian SIRT 6/7 homolog) have been shown to alter lifespan, most likely through interaction with other metabolic or cellular pathways and molecules (Tissenbaum and Guarente 2001; Rizki *et al.* 2011; Viswanathan and Guarente 2011; Schmeisser, Mansfeld, *et al.* 2013).

Stress and epigenetic changes

While extreme stress exposure is detrimental, exposure to nonlethal environmental stressors such as heat or oxidative conditions promotes pronounced increases in lifespan through a phenomenon termed hormesis. Hormesis is the adaptive response of an organism to low levels of stress that inures the animal to subsequent lethal stress exposure (Mattson 2008). In many cases, the longevity-extending effects of hormesis occur through the prolonged activation of genes and pathways that protect the animal from the initial insult, such as maintaining proteostasis, enhanced autophagy, increased levels of oxidative stress response genes, and molecular chaperones. This involves the upregulation or altered expression of genes or signaling pathways for the duration of the organism lifespan and occurs through epigenetic changes to chromatin, which result in large-scale transcriptional remodeling (Schulz *et al.* 2007; Shore and Ruvkun 2013; Taki *et al.* 2014; Qian *et al.* 2015; Kishimoto *et al.* 2017; Kumsta *et al.* 2017, 2019; Matai *et al.* 2019; Das *et al.* 2021; Oleson *et al.* 2021; Yerevanian *et al.* 2022; Liberman *et al.* 2023; Schiavi *et al.* 2023; Xu *et al.* 2023).

Mitochondrial unfolded protein response (mtUPR)

A well-studied way of prolonging lifespan in *C. elegans* is mild disruption of the ETC, either due to constitutive point mutations or RNAi knockdown of ETC subunits (Feng *et al.* 2001; Dillin *et al.* 2002; Lee *et al.* 2003; Yang and Hekimi 2010). These perturbations activate the proteostasis machinery and mitochondrial unfolded protein response (mtUPR), which culminate in the coordinated transcriptional induction of mitochondrial chaperons and other genes (Haynes *et al.* 2007, 2010; Kirstein-Miles and Morimoto 2010; Labbadia *et al.* 2017; Williams *et al.* 2020), in an attempt to restore homeostasis. Interestingly, and as described above, mild ETC disruptions need to occur during larval stages L3/L4 in order to induce lifespan extension (Dillin *et al.* 2002; Rea *et al.* 2007). Mild ETC disruption during adulthood, while reducing respiration and other mitochondrial functions, can no longer affect lifespan. Thus, it is particularly fascinating that ETC disruptions and mtUPR engage chromatin factors to promote lifespan, suggesting metabolic alterations early in development trigger chromatin changes that lead to lifelong longevity benefits (Merkwirth *et al.* 2016; Tian, Merkwirth, and Dillin 2016). Indeed, DVE-1-binding sites are one of the few promoter regions that show altered chromatin accessibility during aging (Janes *et al.* 2018).

A number of chromatin factors have been found to mediate mtUPR and longevity in response to mitochondrial perturbations. *jmjd-3.1* and *jmjd-1.2* are 2 demethylases that contribute to lifespan increase upon mild mitochondrial ETC disruption (Merkwirth *et al.* 2016; Tian, Merkwirth, and Dillin 2016). *jmjd-3.1*/JMJD3 can remove H3K27me2/3 (Agger *et al.* 2007), while *jmjd-1.2*/PHF8 has broader range of activities, including H3K9me1/2, H3K27me2, and H4K20me1 (Feng *et al.* 2010; Fortschegger *et al.* 2010; Kleine-Kohlbrecher *et al.* 2010; Liu *et al.* 2010; Qi *et al.* 2010). Since these factors act to remove repressive marks, they likely share stimulatory activities on gene expression. Transcriptomic analysis revealed that overexpression of JMJD-1.2 and JMJD-3.1 recapitulates gene expression changes that resemble those induced by ETC disruptions (Merkwirth *et al.* 2016; Tian, Merkwirth, and Dillin 2016). These 2 demethylases are likely core mediators of a transcriptional response to mild ETC disruption and mtUPR activation. Excitingly, mammalian homologs of these factors also positively regulate mtUPR, indicating functional conservation (Merkwirth *et al.* 2016; Tian, Merkwirth, and Dillin 2016).

In another study, the nuclear protein LIN-65 (Mutlu *et al.* 2018; Delaney *et al.* 2019), which resembles activating transcription factor 7-interacting protein, and the MET-2 putative H3K9 methyltransferase were shown to be critical for mtUPR induction in response to mitochondrial ETC disruptions (Tian, Garcia, *et al.* 2016). Here, mitochondrial ETC disruption results in the nuclear translocation of LIN-65, which requires MET-2; LIN-65 is also essential for MET-2 stability and H3K9me/me2 activity (Delaney *et al.* 2019). Using microscopy, the MET-2 and LIN-65 coregulation leads to more condensed DNA in the intestinal cells, interpreted to represent more condensed chromatin. Furthermore, the MET-2 and LIN-65 coregulation helps recruit DVE-1, a key transcription factor for mtUPR, to the nucleus to facilitate transcriptional responses. Even more interestingly, DVE-1 appears localized to nuclear puncta excluded from H3K9me/me2 staining (Tian, Garcia, *et al.* 2016). In a follow-up study, DVE-1 was found to form a complex with the NuRD chromatin remodeling complex. The NuRD complex contains the ATP-dependent remodeler LET-418 and the histone deacetylase HDA-1 (Zhu *et al.* 2020). *C. elegans* with mild ETC disruption shows lower levels of citrate and acetyl-coA, which is speculated to limit chromatin histone acetylation. The NuRD complex likely either acts in parallel to LIN-65 and MET-2 or acts cooperatively to help regulate chromatin compaction upon mitochondrial stress. Further detailed analysis will be necessary to provide genome-wide resolved patterns of DVE-1 location and H3K9me/me2 and histone acetylation markings in response to mild ETC disruption.

Yet another study revealed that RNAi knockdown of *cco-1*, a subunit of mitochondrial respiratory chain complex IV, and inhibition of mitochondrial translation altered the histone balance by increasing the expression of the core histone H3 and H2A.Z levels, similar to that of *his-3* (encoding H2A) knockdown (see earlier section; Matilainen *et al.* 2017). Both mitochondrial and histone stressors also mildly upregulate the different classes of chromatin remodelers and are thought to induce chromatin remodeling (Matilainen *et al.* 2017). RNA-seq analysis indicates that the 2 treatments share induction of cytosolic chaperones mediated by the chromatin remodeler ISW-1. Together, these studies suggest interesting coordination and regulation between mitochondrial activities and nuclear chromatin regulation, which likely reflects part of the complex endosymbiotic interaction between the mitochondria and the nucleus.

Heat shock response or cytoplasmic UPR

Several regimens of transient exposure to heat also provide long-lasting benefits to lifespan (Kumsta *et al.* 2017, 2019; Zhou *et al.* 2019). Exposure to mild heat activates a unique transcriptional program mimicking the pathogen defense response, showing an enhanced expression of innate immune and detoxification genes that persist long after the heat exposure has been terminated (Zhou *et al.* 2019). As described above, this occurs through the activity of the HAT CBP-1 and the chromatin remodeling SWI/SNF complex. Increased activity of heat shock factor 1 (HSF-1), the key transcription factor that induces cytosolic chaperones upon heat shock, promotes longevity that is mediated by elevated levels of histone H4 (Sural *et al.* 2020). Fascinatingly, H4 elevation also leads to greater compaction of mitochondrial DNA and lower mitochondrial activity, which is thought to contribute to longer longevity. In other studies, it was shown that exposure to heat stress and activation of the heat shock transcription factor, HSF-1, prompted HSF-1 to physically interact with MET-2, the putative H3K9 methyltransferase, and increase H3K9me2 marks at HSF1 target genes following the upregulation of these genes. The H3K9me2 marks at these HSF-1 target genes persisted in progeny that had been stressed in utero. The consequence of this apparently counterintuitive mechanism was that it switched the stress-response strategy of organisms that underwent stress exposure in utero from an HSF-1-dependent mechanism that upregulated chaperones to one that utilized decreased insulin signaling and DAF-16 (Das *et al.* 2021). These studies again highlight that sequelae of epigenetic changes can be triggered by a single environmental exposure to stress. Transient heat stress exposure that extends the lifespan of *C. elegans* also relies on transcription factors and other chromatin modifiers, such as the endoribonuclease ENDU-2 (Xu *et al.* 2023). ENDU-2 interacted with H3 and several chromatin modifiers, SWI/SNF complex: SWSN-1, SWSN-4, and ISW-1, and 3 subunits of RNA polymerase II (RPB-2, RPB-5, and RPB-7), and displayed a dynamic localization on chromatin in response to heat stress, while at the same time, modulated the sequence and intensity of expression of stress-responsive genes.

Models of accelerated aging and epigenetic changes

In humans, maintenance of nuclear architecture through the functions of the nuclear lamins and lamin-associated proteins plays a critical role in modulating lifespan, as is evident from the premature aging syndrome, Hutchinson–Gilford progeria syndrome (HGPS). HGPS patients harbor mutations in the lamin A (LMNA) gene, which results in the aberrant splicing of lamin A. Because the nuclear lamins can bind interphase chromatin, chromosomes during mitosis, and even specific DNA sequences, and play a profound role in organizing chromatin, the *LMNA* mutation causes profound changes to nuclear architecture, triggers heterochromatin loss, and altered chromatin organization, aberrant gene expression, and genomic instability (Liu *et al.* 2000; Snyder *et al.* 2016; Gonzalo *et al.* 2017). In *C. elegans* embryos and in differentiated tissues, heterochromatin is also anchored to the nuclear lamina by the inner membrane-bound chromodomain protein CEC-4, which binds H3K9me1-, me2-, and me3-modified histones (Gonzalez-Sandoval *et al.* 2015; Cabianca *et al.* 2019). In differentiated cells, the absence of heterochromatin leads to aberrant H3K27Ac deposition (Cabianca *et al.* 2019) by misregulating CBP/p300, thus antagonizing the anchoring of tissue-specific genes. Major changes in nuclear architecture and shape have also been shown to occur across several *C. elegans* cell types during aging and are also associated with a loss of peripheral heterochromatin (Haithcock *et al.* 2005; Gonzalez-Aguilera *et al.* 2014; Cohen-Fix and Askjaer 2017). These changes include the appearance of invaginations and distortions to the nuclear lamina and nuclear fragmentation, alterations in the integral inner nuclear membrane protein EMR-1, and nuclear pore complex components NPP-1 and appear to affect different cell types differently, with neuronal nuclei appearing to be spared. The aging-related changes in nuclear architecture were found to be stochastic and progressive, resembling changes that occur in HGPS patients during accelerated aging. These studies suggest that changes in the composition or structure of the nuclear lamina and associated architectural proteins can act as causal triggers to alter chromatin modifications during aging. In support of this possibility, decreasing the expression of lamin and lamin-associated LEM domain proteins shortened lifespan (Haithcock *et al.* 2005; Bank *et al.* 2012). Abnormal nuclear morphology can be alleviated in *daf-2* mutants, or upon altering components of the insulin/IGF-1-like signaling pathway (Haithcock *et al.* 2005; Bank *et al.* 2012; Perez-Jimenez *et al.* 2014). However, as with normal aging, the correlation between nuclear morphology and lifespan can be uncoupled in longevity-promoting mutations, such as *daf-2*, by altering their growth temperature (Perez-Jimenez *et al.* 2014). Together, these data fit with the growing appreciation that the normal epigenetic changes that accompany aging in several model systems differ from those that occur with longevity interventions imposed through mutations, small molecules, or even physiological regimen (Moqri *et al.* 2023).

DNA damage and epigenetic changes

Another hallmark of aging that could lead to aging-related alterations in epigenetic marks is an increase in DNA damage. This has been demonstrated in yeast and mammalian cells where chromatin-modifying proteins are recruited to sites of DNA breaks, leading to the erosion of epigenetic information over time (Pollina *et al.* 2023; Yang *et al.* 2023), and the activity of SIRT6 in long-lived rodent species was responsible for more efficient DNA repair and thereby guarded their longer lifespans (Tian *et al.* 2019). Parallel processes likely exist in *C. elegans*. A recent study showed that persistent nuclear DNA damage that occurs in DNA repair-deficient *C. elegans* lacking an evolutionarily conserved nuclease complex called ERCC1-XPF (Excision Repair Cross-Complementing), that plays important roles in DNA repair and genomic stability, also shortens lifespan (Marchal *et al.* 2021). Similarly, disrupting CDC-48-dependent DNA replication in *C. elegans* increased the numbers of stalled replication forks and R-loops in developing *C. elegans* embryos and, perhaps not surprisingly, decreased lifespan (Franz *et al.* 2016). In the case of ERCC1-XPF, the authors went on to show that *xpf-1* mutants also displayed a marked increase in histone hyperacetylation through the activity of a HAT MYS-1, which was triggered by increased mitochondrial β-oxidation occurs as a consequence of DNA damage, and the associated increase in acetyl-CoA (Hamsanathan *et al.* 2022). H4K16 hyperacetylation in turn led to the expression of several innate immune response genes and alterations in lipid content, both of which could plausibly result in the observed effects on lifespan; however, decreasing H4K16ac levels by knocking down MYS-1 shortened the already shortened lifespan of *xpf-1* mutants, suggesting, again, that the effects of epigenetic changes on lifespan were not linear (Hamsanathan *et al.* 2022).

While DNA damage can be a proximal driver of epigenetic changes, the converse has also been observed, and the loss of MET-2, which abolishes H3K9me2 marks in *C. elegans*, in turn results in the increased expression of repetitive elements and transposable elements (TEs) and an accumulation of DNA damage due to R loop formation (Zeller *et al.* 2016). While increases in R-loop formation per se have yet to be directly linked to increasing aging rates in *C. elegans*, animals lacking the H3K9me1/2 writer, MET-2, or the H3K9me1/2 or me3 reader, CEC-1, have short lifespans and incur a loss of germline cells and somatic cell damage (Lee *et al.* 2019; Hou *et al.* 2023). As mentioned above, examination of whether overexpression of these enzymes would, in turn, cause an extension of organismal lifespan would go a long way toward establishing these enzymes and pathways as bona fide mechanisms that regulate aging. However, consistent with the loss of silencing of TEs that occurs in MET-2 mutants, a driver of aging, an exciting recent study showed that DNA N^6-adenine methylation at TEs gradually increases during *C. elegans* aging, elevating the expression of TEs and their mobilization and contributing to the genomic instability and shortening of lifespan (Sturm *et al.* 2023). Downregulation of TEs extended *C. elegans* lifespan, suggesting that epigenetic changes that decrease the mobility of TEs or transcription of simple repeats could also be expected to protect lifespan extension.

Altered intercellular communication and epigenetic changes

The multicellular nature of *C. elegans* has allowed more nuanced questions regarding how intertissue signaling triggers epigenetic changes and affects organismal lifespan. In this regard, the nervous system has emerged as an important node in the control of chromatin across the animal. The nervous system, by virtue of its dedicated role in sensing environmental changes, plays an important role in controlling organismal stress responses, metabolism, and fecundity, integrating these physiological functions with behavior (Drachman 1997; Wolkow 2002; Mair 2013; van Oosten-Hawle and Morimoto 2014; Prahlad 2020). One mechanism that has been reported is through sensory neuron and serotonergic modulation of the histone chaperone FACT (FAcilitates Chromatin Transcription) that alters histone dynamics and initiates stress-induced transcriptional activation through HSF1 (Das *et al.* 2020). Another recent study showed that the activity of CREB-regulated transcriptional coactivators, CRTC-1, in the nervous system tunes histone acetylation and methylation to link energetics to longevity and promote healthy aging (Silva-García *et al.* 2023). Thus, these studies together suggest that day-to-day encounters with the environment, likely continuously, impose changes to chromatin organization that eventually impact the organism's lifespan.

Developmental programming of aging and epigenetic changes

As in all organisms, in *C. elegans*, the memory of transcriptional activity of germline genes, such as spermatogenesis genes, is erased or reset in gametes as they pass through the germline. However, exciting studies have shown that some chromatin modifications and histone variant patterns assembled in the germline are retained in mature gametes, and despite extensive chromatin remodeling events at fertilization, these marks can persist in early embryo (Arico *et al.* 2011; Kerr *et al.* 2014; Carpenter *et al.* 2023), to influence the rates of aging in adults (Greer *et al.* 2011; Benayoun and Brunet 2012; Rankin 2015; Woodhouse *et al.* 2018; Lee *et al.* 2019; Emerson *et al.* 2020; Das *et al.* 2021; Zhang *et al.* 2021; Wan *et al.* 2022; Rodriguez and Katz 2023; Wang, Meyer, and Schumacher 2023). Thus, epigenetic marks can be transmitted through the maternal or paternal genome and involve methylation of H3K4, H3K9, and H3K27, H4 acetylation, and other modifications (Greer *et al.* 2010, 2011, 2016; Maures *et al.* 2011; Guillermo *et al.* 2021). Thus, as described above, the LSD1 H3K4me2 demethylase SPR-5 and MET-2 cooperate to maintain the epigenetic status of germ cells in *C. elegans*, and the transgenerational longevity of *wdr-5* mutants corresponds with a global enrichment of the repressive H3K9me2 mark over several generations (Greer *et al.* 2014; Kerr *et al.* 2014; Lee *et al.* 2019). Transcriptional memory is also transmitted through the activity of machinery that enforces X chromosome silencing and dosage compensation and these pathways also regulate aging rates (Hartman and Ishii 2007; Rechtsteiner *et al.* 2010; Gaydos *et al.* 2012; Chew *et al.* 2013; Webster *et al.* 2013; Tower 2015; Farina *et al.* 2017; Anderson *et al.* 2019; Dixon 2019; Cockrum and Strome 2022). These studies, therefore, raise the question of whether aging rates are programmed at development. While this may be too simplistic hypothesis, especially given environmental influences on lifespan, the observation that regulatory elements mapped by defining regions of chromatin accessibility are shared between development and aging suggests that there may be specific genomic loci, set aside during development, that remain more influential in driving aging-related changes during adulthood (Janes *et al.* 2018). Indeed, the establishment of heterochromatin domains characterized by dimethylated histone H3K9 occurs very early during *C. elegans* embryogenesis through the nuclear accumulation of MET-2, and the nuclear proteins, LIN-65 and ARLE-14, the *C. elegans* ortholog of ARL14EP, adenosine 5′-diphosphate-ribosylation factor-like 14 effector protein (Mutlu *et al.* 2018). These domains of heterochromatin are established at TEs, satellite repeats, and tissue-specific genes, and in the latter case, restrict the binding of transcription factors to lineage-specific promoters and enhancer elements (Padeken *et al.* 2019; Padeken *et al.* 2021). Thus, it is conceivable that these epigenetic marks not only specify cell fate during development (Zeller *et al.* 2016; Methot *et al.* 2021; Padeken *et al.* 2022) but also maintain tissue integrity during aging.

Perhaps the best rationale for the developmental programming of aging comes from studies on chromatin changes that accompany the developmental programming of dauer, a larval stage in which *C. elegans* typically exists in the wild (Frézal and Félix 2015). Passage through the dauer state typically prolongs *C. elegans* lifespan (Burnell *et al.* 2005; Cypser *et al.* 2006; Gonzalez-Aguilera *et al.* 2014). Exciting studies have shown that chromatin changes that occur to maintain the dauer state can persist into adulthood to modify behavior and physiology and gene expression through networks of small RNA pathways (Hall *et al.* 2013; Sims *et al.* 2016; Ow *et al.* 2018, 2021). Similarly, the small RNAs and microRNAs responsible for developmental timing in *C. elegans* also regulate lifespan in the adults (Boehm and Slack 2005; de Lencastre *et al.* 2010; Inukai *et al.* 2018; Matai *et al.* 2023; Matai and Slack 2023). The first example of this involved some aspect of developmental timekeeping, where *lin-4* and its target, *lin-14*, were shown not only to control the timing of larval molts during but also reduce the activity of *lin-4* shortened lifespan and accelerated tissue aging, whereas overexpressing *lin-4* or reducing the activity of *lin-14* extended lifespan (Boehm and Slack 2005).

Transgenerational effects on lifespan through chromatin

Another exciting indication for developmental inheritance of lifespan and chromatin states comes from studies that demonstrate

that some nongenetic information can be transmitted from ancestors to their descendants (Rothi and Greer 2023). In *C. elegans*, mutation of the H3K4me3 complex (*set-2* and *wdr-5.1*) can extend lifespan in the worms with the mutation (Greer *et al.* 2010) and also in their genetically wild-type descendants for up to 3 generations (Greer *et al.* 2011). Similarly, knockdown of *ash-2* can induce a lifespan extension in the descendants who have never been exposed to RNAi (Greer *et al.* 2011). This transgenerational lifespan extension is associated with heritable changes in gene expression, but interestingly, these transgenerational lifespan extensions were not associated with inherited global decreases in H3K4me3 itself (Greer *et al.* 2011). The lack of heritable global changes in H3K4me3 could reflect that the inherited changes in H3K4me3 are occurring at specific loci rather than the whole chromatin architecture or that other epigenetic molecules are altered and transmitted to regulate the transgenerational lifespan. Persistent mutation of an H3K4me1/me2 demethylase, *spr-5*, also induces progressive transgenerational phenotypes, including a transgenerational fertility decline (Katz *et al.* 2009) as well as a transgenerational increase in H3K4me2 and lifespan extension (Greer *et al.* 2014, 2016). Another group identified that persistent depletion of *wdr-5* leads to extended transgenerational longevity (Lee *et al.* 2019). They found that persistent knockout of *wdr-5* led to an increase in the heterochromatin mark H3K9me2 and that this transgenerational lifespan extension was dependent on *met-2*, the putative H3K9me3 methyltransferase. Interestingly persistent depletion of the predicted H3K9 demethylase, *jhdm-1*, which led to increased H3K9me2 in specific regions, also caused a transgenerational increase in lifespan independently of *wdr-5* (Lee *et al.* 2019). These findings suggest that progressive accumulation of H3K9me2 over the generations could prolong lifespan independently of changes in H3K4me3 (Lee *et al.* 2019). Interestingly, the genomic regions that Lee *et al.* uncovered to be associated with higher levels of H3K9me2 in the long-lived strains show significant overlap with the genomic regions observed to gain H3K9me3 in aged *glp-1* mutant worms (see above) (Li *et al.* 2021). One hypothesis is that a gradual switch from H3K9me2 to H3K9me3 with age in those specific genomic regions could be proaging.

Interestingly transgenerational lifespan can not only be extended by genetic mutations but also by ancestral starvation (Rechavi *et al.* 2014; Liberman *et al.* 2023). Ancestral starvation can lead to altered heritable small RNAs (Rechavi *et al.* 2014) as well as an altered transmission of premethylated ribosomal RNAs, which prepare the next generation for lower food availability by altering which transcripts are translated (Liberman *et al.* 2023). It will be interesting to determine the precise mechanisms by which nongenetic information is transmitted across generations, what specific nongenetic heritable cues are regulating transgenerational lifespan, and how these epigenetic molecules can influence the lifespan of naïve descendants.

Continued studies to elucidate how chromatin regulation responds to various stressors and metabolic fluctuations will be key to further understanding how chromatin and epigenetic regulation interface with longevity.

How does altered chromatin state impact lifespan?

Aging *C. elegans* displays a decrease in function across several tissues, such as decreased mobility, decreases in sensory ability, memory, and learning, decreased stress resilience, a decrease in fecundity, increased colonization by bacteria, etc. This is accompanied by several of the cellular and molecular hallmarks of aging, such as proteostasis disruption, decreased transcriptional response to changing environments, increases in oxidative damage, and a decrease in the regenerative capacity of germline stem cells and neurons, etc. Thus, one can conceive of several ways in which alterations in chromatin exacerbate or mitigate aging-associated cellular and physiological dysfunction by preventing or promoting different gene expression programs that alter proteostasis, genomic stability, or metabolic flexibility. Several such examples have been described in *C. elegans*.

One of the prominent features of aging is the systemic dysregulation in the proteome. This dysregulation is manifested both as discordant transcription and translation, as well as the dysfunction of the protein quality control mechanisms that act to prevent the accumulation of aberrant protein species. During aging, *C. elegans* has been shown to display systemic alterations in transcription, which has been called "transcriptional noise or drift," resulting in opposing changes in the expression of genes within functional groups, arguably causing a disruption in mRNA stoichiometry and coexpression patterns in aging tissues and has been described in aging *C. elegans* (Rangaraju *et al.* 2015). Similarly, like in mammals where H3K9me2/3-induced gene repression is required for differentiation and the maintenance of tissue identity (Methot *et al.* 2021), studies in *C. elegans* show that MET-2 in maintaining transcriptional repression to license proper development (Methot *et al.* 2021) and tissue identity, and loss of MET-2 triggers a loss of silencing, increased histone acetylation (Delaney *et al.* 2022). scRNA-seq data from aging animals also show a marked dysregulation of cell-type-specific transcriptional signatures with aging (Wang *et al.* 2022; Roux *et al.* 2023). Because chromatin state is so essential for maintaining appropriate accessibility of genes for transcription, it is likely that a disorganization of chromatin that occurs with age could be the root cause of this transcriptional drift and dysregulation, either throughout the organism or specific cell types disrupting cellular and tissue homeostasis (Müthel *et al.* 2019). Remarkably, increasing transcriptional fidelity, either through systemic interventions that downregulate transcription (Rangaraju *et al.* 2015) or by modulating the activity of tissue-specific epigenetic factors such LIN-53 (RBBP4/7) protected aging-dependent decline and/or prolonged lifespan.

A recent study also showed that aging in *C. elegans* and other invertebrate species was accompanied by a global increase in RNA polymerase II-mediated elongation rates and restraining RNAP II elongation rates prolonged lifespan (Debès *et al.* 2023). These experiments support the hypothesis that increased rates of protein biogenesis accelerate aging and that epigenetic changes that result in a decrease in the rates of protein biogenesis or mRNA synthesis likely allow cellular quality control mechanisms to function optimally and prevent aging-related disruptions to proteostasis.

Epigenetic changes that enhance the expression of protein quality control machinery have also been shown to prolong lifespan. During aging, there is a marked decrease in the expression of stress-responsive gene expression, accounting in part, for the increased vulnerability of animals to environmental stressors during aging. As described above, the repression of stress gene expression, through HSF1, was shown to occur due to an increase in H3K27me3 marks at stress gene loci, due to reduced expression of the H3K27 demethylase *jmjd-3.1* with aging (Labbadia and Morimoto 2015). Reversal of the increased H3K27 levels restored stress-responsive gene expression and decreased stress-induced frailty. Another examples, where epigenetic changes protect animals from stressors while also promoting metabolic flexibility, are studies showing that IIS and DR converge on a common chromatin modifier, ZFP-1/AF10, which in turn acts as a rheostat to

tune the amplitude and duration of target gene expression during low IIS or DR, thereby determining lifespan extension through these 2 pathways (Singh *et al.* 2016).

Conclusion

In conclusion, there is much to be explored regarding the role of epigenetic changes in driving *C. elegans* aging. While specific histone modifications change as organisms age and histone-modifying enzymes can regulate aging itself, it still remains to be seen whether direct manipulation of histone modifications at specific loci directly regulates lifespan. Functional experiments, such as using a nuclease null Cas9 fused with specific chromatin-modifying enzymes to direct chromatin modifications at critical loci (Pulecio *et al.* 2017), will be essential for determining whether chromatin modifications at critical loci are truly the cause of altered longevity or whether the chromatin-modifying enzyme, through functions of modulating nonhistone proteins, can regulate lifespan. Additionally, as chromatin modifications do not function in isolation, it will be important to determine which specific chromatin modifications are regulating lifespan and which ones are indirect consequences of the bona fide regulators. The downstream mechanisms by which these chromatin-modifying enzymes function to regulate lifespan, as well as how environmental changes are directly affecting chromatin-modifying enzyme function, will be exciting mysteries for the field to tackle in the coming years.

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Conflicts of interest

The author(s) declare no conflict of interest.

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