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Review

Histone methylation and aging: Lessons learned from model systems ☆

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ABSTRACT

Aging induces myriad cellular and, ultimately, physiological changes that cause a decline in an organism's functional capabilities. Although the aging process and the pathways that regulate it have been extensively studied, only in the last decade have we begun to appreciate that dynamic histone methylation may contribute to this process. In this review, we discuss recent work implicating histone methylation in aging. Loss of certain histone methyltransferases and demethylases changes lifespan in invertebrates, and alterations in histone methylation in aged organisms regulate lifespan and aging phenotypes, including oxidative stress-induced hormesis in yeast, insulin signaling in *Caenorhabiditis elegans* and mammals, and the senescence-associated secretory phenotype in mammals. In all cases where histone methylation has been shown to impact aging and aging phenotypes, it does so by regulating transcription, suggesting that this is a major mechanism of its action in this context. Histone methylation additionally regulates or is regulated by other cellular pathways that contribute to or combat aging. Given the numerous processes that regulate aging and histone methylation, and are in turn regulated by them, the role of histone methylation in aging is almost certainly underappreciated. This article is part of a Special Issue entitled: Methylation Multifaceted Modification—Looking at Transcription and Beyond.

1. The aging process

1.1. Physiological changes associated with aging

Aging is associated with a number of detrimental physiological effects that impact the health and overall function of an organism. Among humans and other mammals, these include a decline in immune function, increasing susceptibility to diseases, chronic inflammation, reduction of muscle mass (sarcopenia), increased incidence of cancer, and the onset of age-related degenerative disorders such as Alzheimer's and Huntington's diseases [1]. Although these phenotypes are manifest at a systemic or organismal level, they are ultimately caused by changes in cellular functions, and, indeed, molecular pathways that contribute to, or help slow, aging have been identified. Many processes, including autophagy, mitochondrial (oxidative phosphorylation) efficiency, and proteosome function, decline with age, while incidence of DNA damage increases; these have been implicated in various aging phenotypes [2–5]. A decrease in mitochondrial efficiency causes increased production of reactive oxygen species (ROS), which can damage macromolecules, including DNA, and also function as second messengers, thus ectopically activating signaling; both processes are thought to contribute to aging pathologies [6–8]. In addition to a potential increase in damaged molecules in aged cells due to accumulation of ROS, there is also lowered turnover of damaged or insoluble proteins by the proteosome and proteins and other macromolecules by autophagy [5,9]. The accumulation of protein aggregates that results from decreases in proteosome function and autophagy contributes to the pathophysiology of Alzheimer's and Huntington's diseases [9,10]. Increased ROS and damaged macromolecules are significant sources of cellular stress, and it is well known that activating stress response pathways can promote longevity and slow the progression of aging [11].

Improperly repaired DNA damage causes mutations, and the accumulation of mutations within one cell's genome can eventually lead to cancer; old cells are, of course, subject to more cumulative DNA damage and mutations than young ones. Cancer, during which cells undergo dysregulated cell divisions and disrupt the organism's physiology, is sufficiently detrimental that a process termed cellular senescence is thought to have evolved to counter it [12]. During cellular senescence, tumor suppressor genes are activated to irreversibly halt progression of the cell cycle [13]. As an organism ages, the number of senescent cells increases. Indeed, a general decline in stem cell function has been reported with age, which is thought to contribute to tissue degeneration [14–16]. This decline in function results from both reduced numbers of stem cells in older animals, possibly as the result of cellular senescence, and a reduction in their multilineage differentiation capacity [17–22]. The complex age-associated phenotypes are thus the result of alterations to cellular processes that occur during and/or as a result of the aging process.

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1.2. Model organisms and the study of longevity

Some physiological and many cellular aspects of aging are conserved among eukaryotes, and, indeed, much insight into the molecular mechanisms of aging has come from work done in various eukaryotic models, such as the budding yeast *Saccharomyces cerevisiae*, the nematode worm *Caenorhabditis elegans*, the fruit fly *Drosophila melanogaster*, and the house mouse *Mus musculus*, as well as mammalian tissue culture and progeria disorders, which cause premature aging, in humans. Like mammals, yeast are subject to the phenomenon of replicative senescence, in which individual cells are only able to undergo a limited number of mitoses [23]. Similarly, age-induced sarcopenia occurs in *C. elegans* and *Drosophila* [24,25], which may indicate that stem cell exhaustion contributes to aging in *Drosophila* as well. Although other physiological aspects of aging, including decreased immune function, chronic inflammation, and increased incidence of cancer, have not been shown to occur in invertebrate models, the molecular pathways and dysfunctions associated with aging are remarkably conserved. The age-associated decline in autophagy was first observed in yeast and only later found in *C. elegans*, *Drosophila*, and mice [2]. Activation of stress response pathways increases lifespan in yeast, *C. elegans*, and *Drosophila*, as well as delays cellular senescence in mammalian cell culture [26]. Similarly, restricting caloric intake (caloric or dietary restriction), increases lifespan from yeast to humans, was first described in rodents, and has been extensively studied in *C. elegans* [27]. In *C. elegans*, repression of the insulin and insulin-like signaling (IIS) pathway was shown to promote longevity [28], and correlative studies have subsequently suggested that this mechanism may be conserved in mice and humans [29]. Thus, model organisms, particularly invertebrate models, have been the source of much of our knowledge regarding the molecular pathways that drive aging physiology.

1.3. Chromatin and aging

Another more recently discovered molecular phenotype associated with aging is a dysregulation of transcription, as manifested by changes in gene expression. This phenomenon has been observed in many organisms, though it is not clear whether this dysregulation causes pathophysiologies associated with aging or is itself the result of the aging process [30–35]. Along with alterations in the transcriptome, in many organisms, chromatin structure changes with age [36], and, indeed, some of these changes have been shown to cause age-associated phenotypes in yeast [37]. In general, chromatin is thought to take on a more euchromatic and transcriptionally active ("open") conformation as an organism ages [38]. In particular, an increase in histone acetylation, mediated by decreased Sirtuin levels, contributes to this phenotype in some organisms [37,39,40], though global decreases in histone levels have also been observed [37,41,42]. Another indication that chromatin state impacts the aging process comes from the field of induced pluripotent stem cells (iPS cells). During the induction of pluripotency, terminally differentiated cells from adults are made to take on characteristics of embryonic stem cells [43]; in essence, to become younger. This reversion to a younger state is accompanied by, and depends on, altered chromatin structure [44]. Thus, changes to chromatin structure are likely to contribute to aging phenotypes.

In this review, we discuss the role of histone methylation in the aging process across eukaryotes. Although increased histone acetylation has been shown to cause age-associated phenotypes [37,39,40], to date, there are only a few studies showing a causal relationship between altered histone methylation and longevity or age-associated pathologies (with the notable exception of cellular senescence in mammals). Additional work has revealed changes in global methylation or methylation patterns in old versus young organisms, which suggests the possibility that misregulation of histone methylation may cause aging pathologies. We also discuss the roles of histone methylation in cellular pathways known to cause age-related phenotypes. Taken together, these data suggest many mechanisms by which changes in histone methylation may contribute to aging pathologies.

2. Global changes in histone methylation patterns in aged organisms and progeria models

Several studies in mammalian systems and *Drosophila* have identified age-associated changes in histone methylation states. These findings are summarized in Table 1. In human cells cultured from patients with Hutchinson–Gilford progeria syndrome (HGPS), a genetic condition that causes premature aging, there is an upregulation of trimethylated lysine 20 on histone H4 (H4K20me3), and a downregulation of both trimethylated lysine 9 on histone H3 (H3K9me3) and trimethylated lysine 27 on histone H3 (H3K27me3). Along with the decrease in H3K9me3, reduced association of the heterochromatin compaction protein HP1α with pericentrosomal DNA was observed [45]. The loss of H3K27me3 in HGPS was recently shown to be largely from gene poor regions [46], which is consistent with the loss of peripheral heterochromatin seen in cells from HGPS patients and invertebrate models of this disorder [47,48]. Thus, accelerated aging in HGPS is associated with a reduction in heterochromatin, though it should be noted that H4K20me3, which increases in cells derived from HGPS patients, also marks heterochromatin. Interestingly, HP1-associated heterochromatin has been shown to be required to slow aging phenotypes in *Drosophila* [49]. While H3K9me3 levels are increased in aging flies [50], a reduction in dimethylated H3K9 (H3K9me2), to which HP1 can also bind [51,52], is seen [49]. This reduction in H3K9me2 is correlated with a loss of HP1 from chromatin, and, indeed, reducing HP1 levels causes loss of muscle integrity and derepression of age-associated recombination of rDNA genes in *Drosophila* [49]. However, it should be noted that the increase in H3K9me3 levels were observed in the heads of female flies, the reduction in H3K9me2 is seen in the whole bodies of mixed male and female flies [49,50]; thus, it is possible that these differing results are due to cell type- or gender-specific alterations in methylation. Taken together, these data support the model of increasingly open chromatin with age.

Histone methylation has also been assessed in brain tissue from SAMP8 mice, a strain of mice bred under selection for accelerated aging that are subject to premature neurodegeneration [53,54]. In this system, both H3K27me3 and mono- and dimethylated lysine 79 on histone H3 (H3K79me1/2) increase, while monomethylated H4K20 (H4K20me1) and trimethylated lysine 36 of histone H3 (H3K36me3) decrease [55]. Thus, in SAMP8 mice, there is an increase in histone modifications associated with heterochromatin and a decrease in marks indicative of active transcription, which is different from the loss of heterochromatin associated with HGPS. The differences between HGPS and SAMP8 could be caused by 1) different mechanisms by which the modifications assessed accelerate aging, 2) different changes in histone methylation in different tissues, or 3) biological differences in

Table 1
Age-associated changes in histone methylation. The results from studies that have analyzed changes in global levels of histone methylation are summarized. HGPS, Hutchinson–Guilford progeria syndrome; this indicates tissues derived from human patients.

System	Tissue	Modification	Change	Reference
Mammals	rat kidney and liver	H4K20me3	increase	[56]
	mouse brain	H4K20me1	decrease	[55]
	mouse brain	H3K27me3	increase	[55]
	mouse brain	H3K36me3	decrease	[55]
	mouse brain	H3K79me1/2	increase	[55]
	macaque brain	H3K4me2	increase	[57]
HGPS	fibroblasts	H4K20me3	increase	[45]
	fibroblasts	H3K9me3	decrease	[45]
	fibroblasts	H3K27me3	decrease	[45,46]
Drosophila	whole animal	H3K4me3	decrease	[50]
	whole animal	H3K9me3	increase	[50]
	whole animal	H3K36me3	decrease	[50]
	whole animal	H3K9me2	decrease	[49]

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