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Review

Chromatin structure as a mediator of aging

Jason Feser [a], Jessica Tyler [b,*]

[a] Molecular Biology Program, University of Colorado School of Medicine, Aurora, CO, USA
[b] Department of Biochemistry and Molecular Biology, UT MD Anderson Cancer Center, Houston, TX, USA

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ABSTRACT

The aging process is characterized by gradual changes to an organism's macromolecules, which negatively impacts biological processes. The complex macromolecular structure of chromatin regulates all nuclear processes requiring access to the DNA sequence. As such, maintenance of chromatin structure is an integral component to deter premature aging. In this review, we describe current research that links aging to chromatin structure. Histone modifications influence chromatin compaction and gene expression and undergo many changes during aging. Histone protein levels also decline during aging, dramatically affecting chromatin structure. Excitingly, lifespan can be extended by manipulations that reverse the age-dependent changes to chromatin structure, indicating the pivotal role chromatin structure plays during aging.

1. Introduction

The basic repeating unit of chromatin, the nucleosome, consists of just under 150 bp of DNA wrapped around an octamer of histone proteins including two molecules of each core histone – H2A, H2B, H3, and H4 [1]. The addition of linker histones and non-histone proteins enables the folding of arrays of nucleosomes into 30 nm fibers and higher order chromatin structures. Packaging of our DNA into chromatin regulates all the genomic processes that occur within the cell. The reason for this is that the degree of chromatin compaction determines accessibility to the underlying DNA sequences. Tightly structured chromatin, or heterochromatin, minimizes genomic instability and misregulated gene expression, whereas more open chromatin, known as euchromatin, facilitates increased gene expression and genomic instability.

Aging is the prime risk factor for many human diseases such as cancer, heart disease, and diabetes. As such, elucidating the alterations to macromolecules that promote aging will be critical to develop treatments to delay or minimize age-related diseases and potentially extend lifespan. Aging is accompanied by changes in the transcriptional profile of cells and increased genomic instability [2,3]. The reasons for these age-related changes remain unclear but given that chromatin structure regulates genomic integrity and gene expression, potential changes to the chromatin structure during aging are likely to play an important role. Indeed, it has been previously suggested that changes to chromatin structure may partially explain the age-related changes to biological functions in cells and the increased incidence of disease states with age [4,5].

Chromatin structure is modified by the cell in a variety of ways to facilitate or limit access to the DNA. The most profound alteration to chromatin structure consists of the removal of histones from DNA and the opposite process of re-deposition of histones onto the DNA to re-establish chromatin. Another way to alter chromatin structure is via the addition or removal of post-translational modifications (PTMs) on specific amino acid residues on the histones. Histone PTMs exist in complex patterns including phosphorylation, acetylation, methylation and ubiquitination. PTMs on histones and DNA methylation of cytosines (collectively referred to as epigenetic marks) influence the ability of proteins to bind to the chromatin [6] which subsequently regulates the degree of compaction of the chromatin structure and the activities of the genome. For example, normal patterns of epigenetic marks are required for growth, development and the prevention of human disease. Growing evidence indicates that the patterns of epigenetic marks are altered during aging and human disease states including cancer [7]. In contrast to the genetic changes to the DNA sequence,

Abbreviations: PTMs, post-translational modifications; rDNA, ribosomal DNA; H4 K16ac, histone 4 lysine 16 acetylation; Sir, silencing information regulator; HDAC, histone deacetylase; HAT, histone acetyltransferase; SAS, something about silencing; H3 K56ac, histone 3 lysine 56 acetylation; Asf1, anti-silencing function 1; Rtt109, repressor of Ty 1 transposition; WT, wild type; ChIP, chromatin immunoprecipitation; Hir, histone information regulator; RLS, replicative lifespan; ERCs, extrachromosomal rDNA circles; HGPS, hutchinson-gilford progeria syndrome; NURD, nucleosome remodeling deacetylase; CLS, chronological lifespan; SAHFs, senescent-associated heterochromatin foci

* Corresponding author. Address: Unit 1000, 1515 Holcombe Blvd, Houston, TX 77030, USA. Fax: +1 713 834 6266.
E-mail address: jtyler@mdanderson.org (J. Tyler).

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epigenetic changes are reversible and therefore represent a promising therapeutic target for the treatment of human disease and hold equally promising potential for delaying the aging process.

Long-term maintenance of chromatin structure is required to promote normal biological functions during the aging process. Individuals with Hutchinson-Gilford progeria syndrome (HGPS), exhibit early aging characteristics such as hair-loss, decreased joint mobility, and heart disease that represent at least a subset of age-related problems [8]. Noteworthy, HGPS is accompanied by disrupted chromatin structure and nuclear organization. Moreover, the accelerated changes to the chromatin structure that occur in HGPS partially mirror the changes that occur normally in aged humans, suggesting a causal link between altered chromatin structure and aging.

In this review we will discuss the changes to chromatin structure that occur with age in multiple organisms and discuss recent publications that further demonstrate how chromatin structure impacts aging. Aging is accompanied by gross changes in DNA methylation, but this will not be discussed further here as this subject has been covered comprehensively in recent reviews [9,10]. Rather, we will summarize the changes to histone PTMs, and changes in the abundance of histone proteins, histone variants and non-histone chromatin proteins during aging. These and future studies will enable the field to answer many of the remaining questions, such as what are all the age-related changes to chromatin? Which of the age related changes to chromatin cause aging? Which of the age related changes to chromatin function to delay premature aging? Which age related chromatin changes are simply a consequence rather than a cause of aging? We will also summarize very recent reports showing manipulations to chromatin structure can reverse age related changes and delay the aging process, demonstrating that the changes to the chromatin structure during aging are indeed a cause of aging.

2. Chromatin modulation and aging in yeast

The budding yeast *Saccharomyces cerevisiae* has become a leading model organism for the study of aging as a consequence of the ease of its genetic manipulation, short cell division cycles, accuracy of lifespan determination and conservation of aging mechanisms across eukaryotes. One measurement of aging in budding yeast is the replicative lifespan (RLS), which is the number of times mother cells can divide to form daughter cells, modeling the finite mitotic divisions that occurs in metazoan cells. One of the first hints that chromatin structure changes during aging came from the realization that replicative aging in yeast is accompanied by the loss of transcriptional silencing which is thought to reflect a decrease in the degree of chromatin compaction [11].

Budding yeast maintain silencing in three main regions of the genome: the telomere proximal regions, the mating-type loci, and the ribosomal DNA (rDNA). Silencing of mating-type loci prevents sterility from occurring, which happens when gene products for both mating types are simultaneously expressed, preventing the cell from responding to mating pheromone. Aged yeast experience increased sterility due to the loss of silencing of the mating-type loci and subsequent expression of both mating-types [11]. Regions that contain repetitive DNA sequences such as the rDNA and telomere proximal DNA are silenced, which helps to prevent recombination, genomic instability and the formation of extra ribosomal chromosomal circles (ERCs). Silencing of reporter genes inserted near telomeres is lost upon replicative aging [12]. This occurs concomitantly with the movement of silencing proteins, including the NAD-dependent histone deacetylase (HDAC) Silencing information regulator 2 (Sir2), away from telomeric regions to the rDNA [13]. Failure to silence the rDNA results in higher levels of recombination and the formation of ERCs. Noteworthy, ERCs accumulate with age and can limit the RLS of yeast [14].

Sir2 mediated silencing of chromatin influences the RLS. Deletion of *SIR2* reduces the RLS, while introducing an extra genomic copy of *SIR2* extends the RLS, indicating that Sir2 is a limiting factor during aging [15]. Although the exact nature of the changes to the chromatin structure during aging were not clear, the increased genomic instability, the accumulation of ERCs, the loss of silencing with age and the ability of the Sir2 HDAC to influence yeast RLS were highly suggestive of a more relaxed chromatin structure during aging, at least at the silent regions of the genome.

2.1. Sir2 and telomeric histone acetylation

Recently, Sir2's function as a HDAC has been shown to directly affect aging in budding yeast. Sir2 is the primary HDAC for acetylated lysine 16 of histone 4 (H4 K16ac) [16]. Old yeast cells were found to have decreased amounts of Sir2 protein compared to young cells and this is the likely reason for increased global levels of H4 K16ac in old cells [17] (Table 1; Fig. 1). H4 K16ac is a unique epigenetic mark in that it inhibits the formation of the 30 nm chromatin fiber and impedes the ability of chromatin to form cross-fiber interactions [18]. As such, increased levels of H4 K16ac in old cells presumably lead to a more open chromatin structure. Examination of H4 K16ac levels on the chromatin of old cells demonstrated increased levels of H4 K16ac at the X core and X elements within the telomeric regions examined [17]. The increased level of H4 K16ac with age also correlated with decreased silencing of reporter genes inserted near these telomere proximal

Table 1
Comparison of histone variants and modifications that change with age. Compilation of known changes to the abundance of histone modifications and histone variants that change from young to old organisms (in vivo) or cells (in vitro).

Modification	Change with age	Organism	Citation
Global histone acetylation	Decrease	Human (in vitro)	[50]
Bulk H4 ac	Decrease	Rat (in vivo)	[65]
H3 K9me	Increase	Human (in vitro)	[53]
H3 K9me2	Decrease	Human (in vitro)	[53]
H3 K9me3	Decrease	Human (in vivo)	[45]
		(in vitro)	[53]
	Increase	Mouse (in vivo)	[66]
	Increase	Fly (in vivo)	[71]
H3 K9ac	Decrease	Rat (in vivo)	[67]
	Increase	Human (in vitro)	[53]
H3 S10ph	Increase,	Rat (in vivo)	[67]
	Decrease	Human (in vitro)	[53]
H3 K14ac	Increase	Mouse (in vivo)	[68]
H3 K27me3	Decrease	Human (in vitro),	[69]
		Mouse (in vitro)	
H4 K8ac	Increase	Mouse (in vivo)	[68]
H4 K12ac	Increase	Mouse (in vivo)	[68]
H3 K56ac	Decrease	Yeast (in vivo),	[17]
		Human (in vitro)	[53]
H4 K16ac	Increase	Yeast (in vivo),	[17]
		Human (in vitro)	[53]
H4 K20me	Increase	Human (in vitro)	[53]
H4 K20me2	Increase	Human (in vitro)	[53]
H4 K20me3	Increase	Rat (in vivo)	[51]
	Decrease	Human (in vitro)	[53]
H3.1	Decrease	Human (in vitro)	[59]
		Rat (in vivo)	[70]
H3.2	Decrease	Rat (in vivo)	[70]
H3.3	Increase	Human (in vitro)	[59]
		Rat (in vivo)	[70]
H2A.1	Decrease	Human (in vitro)	[59]
		Rat (in vivo)	[70]
H2A.2	Increase	Human (in vitro)	[59]
		Rat (in vivo)	[70]