Mutation Research 788 (2016) 25–31

Contents lists available at ScienceDirect

Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis

journal homepage: www.elsevier.com/locate/molmut
Community address: www.elsevier.com/locate/mutres

Review

Reprint of "DNA, the central molecule of aging"☆

Peter Lenart[a], Lumir Krejci[a,b,c,*]

[a] Department of Biology, Masaryk University, Brno, Czech Republic
[b] International Clinical Research Center, Center for Biomolecular and Cellular Engineering, St. Anne's University Hospital Brno, Brno, Czech Republic
[c] National Centre for Biomolecular Research, Masaryk University, Brno, Czech Republic

ARTICLE INFO

Article history:
Received 17 December 2015
Received in revised form 16 January 2016
Accepted 30 January 2016
Available online 28 April 2016

Keywords:
DNA
Aging
Chromatin structure
Telomeres
DNA damage
DNA repair
Mutagenesis

ABSTRACT

Understanding the molecular mechanism of aging could have enormous medical implications. Despite a century of research, however, there is no universally accepted theory regarding the molecular basis of aging. On the other hand, there is plentiful evidence suggesting that DNA constitutes the central molecule in this process. Here, we review the roles of chromatin structure, DNA damage, and shortening of telomeres in aging and propose a hypothesis for how their interplay leads to aging phenotypes.

Contents

1. Introduction

Aging is a complex biological process resulting in the decline of almost all physiological functions, which in turn leads to a time-dependent increase in mortality. Many theories have tried to explain the aging process, but none is universally accepted [1,2]. Although many biomolecules could play a role in aging, DNA seems to be the most relevant. This is supported by several arguments. First, syndromes of accelerated aging are often associated with defects in DNA repair genes [3,4]. Second, changes of chromatin structure, shortening of telomeres and accumulation of DNA damage are all associated with aging and life span [5–9]. These chromosomal changes do not act in isolation but are rather tightly interconnected. Changes of chromatin structure can accelerate shortening of telomeres [10] alter susceptibility to DNA damage [11] and modify transcription [12] thus influencing almost all cellular functions. *Vice versa*, DNA damage can lead to changes of chromatin structure [13] and accelerate telomere shortening [14]. Here we review how these three types of chromosomal changes and their interplay influence the aging process.

DOI of original article: http://dx.doi.org/10.1016/j.mrfmmm.2016.01.007.
☆ This article is a reprint of a previously published article. For citation purposes, please use the original publication details "*Mutation Research* 786 (2016) 1–7".
* Corresponding author at: Department of Biology, Faculty of Medicine, Masaryk University, Kamenice 5/A7, Brno 62500, Czech Republic. Fax: +420-549-492-556.
E-mail address: lkrejci@chemi.muni.cz (L. Krejci).

http://dx.doi.org/10.1016/j.mrfmmm.2016.04.002
0027-5107/

1.1. Chromatin structure

Chromatin is a nucleoprotein complex that can be understood as a dynamic, three-dimensional, higher-order structural state of a chromosome. The basic unit of chromatin is a nucleosome consisting of four pairs of core histones (H2A, H2B, H3, H4) around which 147 bases of DNA are wrapped [15]. Higher-order chromatin structure is also formed by linker H1 histone and other non-histone proteins. There exists two basic types of chromatin: highly condensed heterochromatin or loosly condensed euchromatin, characterized by typically transcriptional inactivity and resistance to DNA damage or transcriptional activity and susceptibility to DNA damage, respectively [11].

Therefore, it is not surprising that several studies have shown depletion of core histones to be associated with aging. In yeast, histone concentration decreases with age and seems to be directly related to aging, since their overexpression leads to a 65 % increase in replicative life span [8]. The possible mechanism might be changes in transcription, as loss of nucleosome in yeast was reported to cause globally increased gene expression [16]. In addition, decreases in H3 and H4 histone levels also have been observed in human senescent fibroblasts, where their concentrations were reported as reduced by half compared to levels in young cells [5,17]. Although synthesis of new histones diminishes with age, it is notable that their expression actually increases [18]. Even as cells are trying to stabilize histone levels, therefore, this might be counteracted by an increased rate of mRNA degradation or increasingly ineffective translation. It would therefore be interesting to test whether overexpression of histones would extend the life span of human cells.

Chromatin structure can be altered not only by changes in the number of histones but also by their post-translational modifications. More than 60 modification sites have been identified on histones, which, together with the 8 basic types of modifications, means the number of specific modifications (type and position) is immense. Histone modifications are known to play important roles in regulation of many cellular processes such as replication, transcription, and DNA repair [19], and so it is not surprising that types and amounts of modifications change with age. For instance, acetylation of lysine 16 on histone 4 (H4K16ac) increases with age in yeast [5,20]. Other examples include increases in H3K9ac and reductions in H3K56ac [5]. Acetylation in general removes positive charge from lysine and could be expected to weaken the binding of DNA to histone and, in turn, make chromatin structure looser. Indeed, H4K16ac has been implicated in determining chromatin structure and influencing the interaction between non-histone proteins and chromatin [21,22]. In addition, the dynamic status of the modification plays an important role, as Sir2, the main deacetylase regulating this modification, is also known to extend life span in several invertebrates such as *Saccharomyces cerevisiae* [23], *Caenorhabditis elegans* [24], and *Drosophila melanogaster* [25]. It is not clear, however, if SIRT1, the human Sir2 orthologue [26,27], can extend life span in mammals, since overexpressing SIRT1 in all mouse tissues was shown to have no life-extending effects despite its having a positive effect on several pathologies associated with aging [28]. Surprisingly, another study overexpressing SIRT1 in mouse brains reported 11 % elongation of life span [29]. It can therefore be speculated that SIRT1 is beneficial to life span only in certain tissues or only at low concentrations.

Strong evidence for a connection of histone acetylation with chromatin maintenance and aging can be seen in the effect of the polyamine known as spermidine on life span and aging. In general, polyamines are associated with cell growth [30], their depletion inhibits apoptosis [31], and they are also implicated in carcinogenesis inasmuch as their concentrations are elevated in cancer cells [32]. In addition, it has been shown that yeast as well as mammalian cells synthesize less polyamines with age. Eisenberg et al. have shown that spermidine supplementation extends life span in yeast, nematodes, flies, mice, and also human cells and that this effect is accompanied by hypoacetylation of H3K9, H3K14 and H3K18. Accordingly, inactivation of acetyltransferases responsible for acetylation of these lysines also extended the life span of yeast and decreased the effect of spermidine treatment [33].

Histones modification by methylation of their lysine or arginine residues plays also important role. In contrast to the histone acetylation, methylation can be associated with either active or repressed transcription, depending on the affected residue [34]. While trimethylation of lysine 4 on histone 3 is associated with active transcription [35], trimethlyation of lysine 27 on the same histone is associated with repressed transcription [34]. Both of these modifications are linked to aging. In human senescent fibroblasts H3K4me3 is enriched and occupies new parts of genome [36]. Spreading of H3K4me3 during aging has bean also observed in mouse hematopoietic stem cells [37]. The most direct evidence of role of H3K4me3 in aging comes from *C. elegans*, where overexpression of RBR-2, the H3K4me3 demethylase, increase life span, while its knockdown has opposite effect. Furthermore knockdown or mutation of genes encoding H3K4 methyltransferases increases life span [38]. In contrast to H3K4me3 mark, H3K27me3 decreases during aging and knockdown of UTX-1, H3K27me3 demethylase extends life span of *C. elegans* [39]. However, role of H3K27me3 in aging is not as clear, as experiments in *D. melanogaster* have shown that mutation in H3K27-specific methyltransferase E(Z) increases life span of flies and reduce amount of H3K27me3 [40].

Other histone modifications are less characterized, but may nevertheless influence aging. For example low levels of ubiquitination of H2B were found to be necessary for yeast cells to attain normal life span possibly trough regulating Sir2 recruitment [41].

DNA methylation is also relevant in determining chromatin structure [42,43] and regulating gene expression [44]. Changes in methylation are typical for cancer cells, but similar changes have been observed also in senescent cells [45–47]. Aging cells exhibit global hypomethylation and local hypermethylation. While hypomethylation is typical for noncoding parts of the genome, sequences near the promotors of several genes regulating the cell cycle are often hypermethylated [48]. Several authors have been able recently to use methylation patterns to successfully predict the age of several different tissues, mostly by analyzing methylation of different CpG sites as an aging clock [49–51]. Furthermore, the methylation patterns of genomic DNA were also shown to predict mortality regardless of current health status, life style, and known genetic predispositions [52], thus suggesting a direct relationship between DNA methylation and aging. A causal role of DNA methylation in aging is also suggested by the ability of methionine restriction – a well-known dietary intervention – to prolong the life span of various model organisms [53–56] and human fibroblast [57]. It is expected that this is due to methionine's serving as a substrate for methyl-transferases and thus affecting the methylation state [58].

1.2. Telomeres shortening

Telomeres are nucleoprotein complexes protecting coding sequences from replicative shortening of chromosomes. Telomeric DNA consists of a G-rich repetitive sequence (TTAGGG in mammals) bound by numerous proteins forming a shelterin complex which also blocks these ends from being recognized as DNA double-strand breaks (DSBs) [59]. Telomeres progressively shorten after each cell division, limiting the number of divisions of somatic cells. They can be extended by a special enzyme termed telomerase, which in humans is active mostly in embryonic stem cells [60]. Telomeres and telomerase have long been implicated in the aging process,