Commentary
DOI 10.1007/s12038-011-9013-5

Tone up your chromatin and stay young

1. Chromatin commands

There are several observations that are difficult to explain using classical Mendelian inheritance. These include position effect variegation, transvection, telomere position effect and imprinting. These phenomena are now known to be based on changes in chromatin structure and epigenetic modifications that can be transmitted to daughter cells. It is, therefore, possible that abnormal chromatin packaging can lead to abnormal cellular processes that ultimately disturb the cell's sustenance. For example, de-repression of telomeric heterochromatin can lead to cellular senescence (Kennedy *et al.* 1997; Moazed 2001). This indicates that during aging the ability to compensate for cellular damage fails to meet the need for repair or replenishment of the maintenance factors (Steinkraus *et al.* 2008). Non-dividing cells maintain their pool to repair internal damage by optimizing the supply of chromatin components. Actively dividing cells need massive synthesis of such components. Eukaryotic cells cannot undergo cell division indefinitely and, therefore, have an inherent lifespan, called the replicative lifespan. After a certain number of replications, the mother cell accumulates aging-related damage, which ultimately causes it to cease further divisions. In multicellular organisms, each tissue has a characteristic replicative capacity (Cavalier-Smith 1978). Much of the information about aging has come from the yeast *Saccharomyces cerevisiae* (Steinkraus *et al.* 2008). Several key factors affecting aging are conserved from yeast to worms to mammals (Kaeberlein *et al.* 1999; Wood *et al.* 2004; Kenyon 2010). These include calorie restriction, radical oxygen species (ROS)-dependent signal transduction, sirtuin-mediated anti-aging functions and the target of rapamycin (TOR) pathway.

Budding yeasts try to prevent the passing of cellular components with aging-related damage such as damaged proteins, or extra-chromosomal DNA fragments, to the daughter cells during cell division (Kaeberlein *et al.* 1999). As a cell undergoes many divisions, it becomes increasingly difficult for the cell to prevent passage of this load to the daughter cells. So the accumulation of damaged components can itself act as a trigger for replicative senescence (Steinkraus *et al.* 2008). Consequently, factors that reduce this load assume the role of safeguarding against the aging process. Many of the factors that prevent aging can alter gene expression via chromatin modifications. Therefore, chromatin modifiers such as Sir2, the Polycomb group (PcG) of proteins (Jacobs *et al.* 1999), histone deacetylases and histone chaperones (Chen *et al.* 2008; Dang *et al.* 2009) are being related to aging processes. Can key structural components of chromatin such as the histone proteins be directly involved in replicative aging? A recent report demonstrates a direct connection between the levels of histones and the lifespan of budding yeast (Feser *et al.* 2010). It was shown that aging cells have low histone protein levels, resulting in loose packaging of the genome and hence inappropriate gene regulation.

2. Sir2 links chromatin silencing with aging

Sirtuins are a class of NAD^+-dependent histone deacetylases that are conserved from yeast to mammals (Brachmann *et al.* 1995; Landry *et al.* 2000; Blander and Guarente 2004). In yeast, Sir2 helps to maintain the compact state of telomeric heterochromatin, the rDNA genes and the MAT (mating type) locus (Steinkraus *et al.* 2008). Deletion of Sir2 causes de-repression of reporter genes inserted at these loci. Owing to the repeat nature of the rDNA, it can undergo homologous recombination if it is not repressed

Keywords. Aging; chromatin; epigenetics; histones

and can form extra-chromosomal circles, which are toxic for the cell (Sinclair and Guarente 1997). Interestingly, in *Drosophila* also Sir2 is required for silencing a tandem array of mini-white reporter genes along with physical interaction with the PcG member E(Z) (Furuyama *et al.* 2004). In yeast, sub-telomeric elements are repressed by Sir2 and de-repression of these loci shortens the lifespan (Dang *et al.* 2009). In flies too, Sir2 is required for heterochromatic silencing (Rosenberg and Parkhurst 2002). Conversely, Sir2 over-expression increases the lifespan in yeast, worms and flies (Wood *et al.* 2004). Changes taking place inside the nucleus during aging are safeguarded against aging-related damages by Sirtuins, which have attracted a lot of attention in aging research as the key players for lifespan extension. This finding has proved crucial in envisaging the link between chromatin packaging and lifespan extension. As Sir2 is a histone deacetylase, researchers have started probing the factors responsible for establishing the balance between deacetylation and acetylation at key silenced locations in the genome. Recently it was reported that progressive loss of Sir2 at sub-telomeric loci is accompanied by an increase in H4K16 acetylation levels during aging (Dang *et al.* 2009). Interestingly, this study also pointed out that changes in chromatin structure are due to depletion of histones at sub-telomeric locations. This pathway is distinct from the extra-chromosomal rDNA circle formation. In a nutshell, Sir2 links modification in chromatin structure to aging.

3. Polycomb-mediated chromatin repression and aging

The Polycomb group of proteins sets the epigenetic stage to bring about regulated gene expression during development and to act as cellular memory modules that maintain this differential expression throughout the lifespan (Cernilogar and Orlando 2005; Bantignies and Cavalli 2006; Ringrose and Paro 2007). Apart from modulating the expression of homeotic genes, PcG proteins control cell proliferation and cell senescence (Jacobs *et al.* 1999; Guney and Sedivy 2006; Guo *et al.* 2007).

Cell senescence and apoptosis are protective mechanisms designed to check uncontrolled proliferation. Tumour suppressor pathways play a crucial role in cell senescence and hence prevent tumour formation. The propensity of tumour formation increases with age, and PcG expression levels are noticeably de-regulated during tumourogenesis (Gil *et al.* 2005; Gil and Peters 2006). One of the key loci involved in regulating cell proliferation, *INKA4b-ARF-INKA4a,* is repressed by Bmi1, a member of the polycomb complex, by methylation on lysine 27 of H3 (Jacobs *et al.* 1999). Mammalian embryonic fibroblasts null for *Bmi1* show early senescence and up-regulation of *INKA4b-ARF-INKA4a* locus gene products $p15^{INK4b}$, $p19^{ARF}$ and $p16^{INK4a}$. Ectopic over-expression of the Bmi1 protein in mammalian fibroblasts increases their replicative lifespan. Repression by PcG requires deacetylase complexes and, consequently, tri-methylation of H3K27 (Muller *et al.* 2002). In *Drosophila,* PcG-mediated silencing requires its association with deacetylase Rpd3/HDAC1 (Tie *et al.* 2001). It was also shown that Sir2 associates with PcG complex containing E(Z) methyltransferase (Furuyama *et al.* 2004). Sir2 mutations enhance *Polycomb* mutant phenotypes, and Sir2 and *Polycomb* mutants both show defective replicative capacities and longevity. Both PcG and Sir2 complexes catalyse removal of acetylation marks and establishment of repressive chromatin by nucleosomal assembly factors. Metazoans maintain a fine balance between cell proliferation and replicative aging by bringing together chromatin factors that silence key loci by regulating higher-order chromatin structures.

4. Histone chaperones and histone acetyl-transferases in aging

In the backdrop of chromatin modulators, the mechanism of genome packaging is becoming important in order to understand aging. Assembly and disassembly of histones onto chromatin is required for enhancing the accessibility of DNA, which is carried out by histone chaperones. During replication, histone assembly is mediated by CAF-1 and Asf1, and during transcription the FACT complex carries out the histone assembly (Ransom *et al.* 2009; Das *et al.* 2010). Histone synthesis peaks in the S phase of the cell cycle, when DNA is replicated (Osley 1991). DNA replication is coupled with its immediate packaging into chromatin. H3K56 is crucial for replicative as well as DNA-repair-coupled chromatin assembly (Chen *et al.* 2008). A prerequisite for incorporation of fresh histones is the acetylation of lysine56 in H3

(Fillingham and Greenblatt 2008). Subsequently, chromatin-modelling factors orchestrate the functionality of chromatin, depending on the level of compaction required for cellular processes. This replication-dependent histone assembly is brought about by histone chaperone Asf1 along with CAF-1 (Tyler *et al.* 1999). Asf1 also positively regulates histone gene expression during the S phase, and negatively regulates histone gene expression in the absence of replication (Mousson *et al.* 2007). During the non-replicative phase, Asf1 takes care of the free histones by either sequestering them or by targeting them for Rad53-dependent degradation (Gunjan and Verreault 2003). Asf1 helps histone acetyltransferases (HATs) such as Sas2 in the acetylation of H4K16 and Rtt109 for acetylation of H3K56 (Dang *et al.* 2009). The recent study by Feser *et al.* (2010) showed that Asf1-mediated H3K56 acteylation is critical for lifespan extension and that deletion of Asf1 leads to reduction in the replicative lifespan, which is equivalent to that of Rtt109 mutant, a HAT. Deletion of Sas2, a HAT for H4K16, increases lifespan relative to that of the wild type. It was shown that during aging the level of H4K16 increases while that of H3K56 decreases; also during aging, there is a concomitant loss of histones at sub-telomeric loci (Dang *et al.* 2009). Hir proteins (histone information regulator) repress histone genes in a replication-independent manner (Spector *et al.* 1997). Hir mutants show increased lifespan compared with wild-type cells and accumulate histones, most of which are chromatinized (Feser *et al.* 2010). Feser *et al.* (2010) also observed that during aging the histone transcript level increases in wild-type yeast, while cells having mutated Rtt109 and Asf1 have low levels of histone mRNA. Interestingly, the Rtt109 mutant is defective in chromatinization of histones; instead, it accumulates a high level of free histones. The short-lived Asf1 mutant, when supplied with extra histones H2A/H2B, shows an increase in lifespan by 65%, while, as expected, H3/H4 over-expression has no effect in the absence of its chaperone. Over-expression of histone extending the lifespan of Asf1 mutant is an interesting observation in support of the notion that chromatinization of histones is an important factor in aging.

5. Histone supply rejuvenates chromatin

Studies linking aging and chromatin structure suggest that aging is a naturally occurring process involving inherent loss of higher-order chromatinization. Mutants that result in increased histone levels generally extend the lifespan (Steinkraus *et al.* 2008). Deletion of the HAT Sas2 results in concomitant increase in histone levels and increased transcriptional silencing (Dang *et al.* 2009). During aging, telomeric silencing is abrogated and genes near the telomeres are de-repressed. Loss of silencing positively correlates with the aging process, which essentially implies a loss of compactness of the chromatin. To directly test the histone levels and lifespan extension, Feser *et al.* (2010) expressed histones ectopically in wild-type yeast and obtained lifespan extension by over-expression of H3/H4 but not by over-expression of H2A/H2B, presumably because the H3/H4 heterodimer formation precedes the nucleosomal assembly on DNA. By providing extra histones to the cell, histone-depleted regions get replenished and restore their appropriate chormatin structure. This study also showed that old cells accumulate higher levels of histone mRNAs and reasoned that it may be an anticipatory mechanism to restore proper histone protein levels. The transcriptional regulation of histone genes is very tightly regulated. Upon receiving signals that a cell is losing histones from the chromatin, histone gene transcription might be up-regulated. Providing extra histones rejuvenates the aging chromatin and buffers the assembly and disassembly process. This essentially protects not only the silenced chromatin but also those euchromatic regions, which operate chromatin-structure-dependent gene regulation.

6. How do metazoans interpret high histone levels?

This new insight in aging makes it exciting to study the effect of elevated histone levels in metazoans. Recently it has been shown that late passage of human fibroblasts leads to compromised Asf1 function, which in turn triggers reduced histone synthesis due to mis-regulation of histone mRNAs (O'Sullivan *et al.* 2010). This finding corroborates with the study in yeast that implicates replicative senescence directly to the loss of histones (Feser *et al.* 2010). As in yeast where deletion of Rtt109 reduces replicative lifespan,

in humans there is increase in H3K56 acetylation by Rtt109 in multiple types of cancers, a situation that can be compared with enhanced replicative lifespan (Das *et al.* 2009). The latter may, however, lead to reduced lifespan of the organism. Although aging is accompanied by loss of histones in human fibroblasts, it remains to be seen whether extra histones extend the lifespan of cells having different replicative capacities. The brain is an almost non-dividing tissue with long chronological lifespan. The mechanism of chronological aging that operates in brain should be replication independent. On the other hand, in dividing cell, such as germ cells, the capacity to carry out meiotic divisions is also not indefinite. Age-related meiotic segregation errors in oocytes are related to the depletion of cohesin, a chromosome-condensing protein. Reduced cohesin levels during reproductive aging compromise centromere functions, leading to segregation defects (Chiang *et al.* 2010; Lister *et al.* 2010). What triggers decreased association of cohesin to centromeres is still not known. However, during mitosis in *Schizosaccharomyces pombe*, at H3K9 methylated loci, cohesin interacts with Swi6 during heterochromatin formation to terminate transcription and prevent accumulation of aberrant transcripts (Gullerova and Proudfoot 2008). It is yet to be seen whether cohesin depletion can be linked with de-repressed centromeric chromatin, which results in chromosomal instabilities during aging. Correlating histone levels with chromatin compaction in meiotically dividing cells may provide a better understanding of reproductive

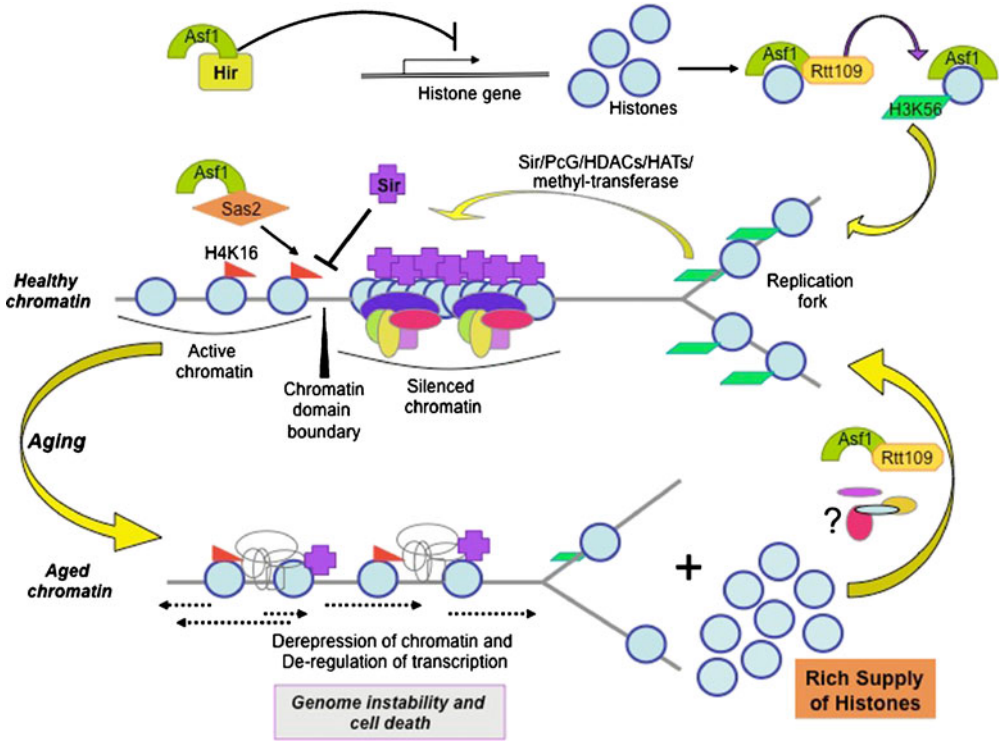

Figure 1. Loss of chromatin compaction is the hallmark of the aging process**.** Different classes of proteins such as histone chaperones, acetylases and chromatin assembly/disassembly factors play crucial roles at various levels in the establishment and maintenance of 'healthy' chromatin. The loss of histones impedes the functioning of these factors and leads to aging. Hir proteins regulate the pool of histones, which are available for incorporation in to chromatin. Rtt109 transfers the acetyl group at lysine 56 of H3 with the help of histone chaperone Asf1. This H3K56 acetylation is a crucial mark for incorporation of histones at the replication fork. Asf1 works at multiple levels in the assembly/disassembly of nucleosomes. After nucleosome positioning, chromatin factors such as Sir, PcG proteins, HDACs, HATs and histone methyl-transferases come into play to establish the epigenetic marks, depending upon the functional state of the locus. Replicative senescence is accompanied by loss of histones from chromatin during each cell cycle. Thus, during the aging process chromatin erosion and loosening takes place by inefficient maintenance of chromatin structure, probably caused by accumulation of damage and apparent shortage of structural components. This results in global change of the chromatin state, leading to pleiotropic alteration in the expression profile that may cause cellular aging. The supply of elevated levels of histones overcomes such effects and maintains 'healthy chromatin'.

aging. While accounting for different levels of regulation operating to bring about chromatin compaction, it is still to be seen how 200 different cell-type-specific epigenetic landscapes in humans employ increased histone levels to counter aging.

7. Chromatin structure and insulators: Do chromatin insulators age?

The linking of aging to de-repression of silent chromatin in the case of PcG and Sir2 mutants introduces a plethora of chromatin factors into the repression process and to age-related destabilization of chromatin. Not far behind are the structural maintenance of chromosomes (SMC) proteins such as cohesin and condensins, mutants of which have been shown to de-repress the mating-type locus in yeast (Bhalla *et al.* 2002) and *Fab7*-PRE in *Drosophila* (Lupo *et al.* 2001). Condensin also regulates heterochromatin to repress RNAPII transcription. These proteins maintain the overall chromosome architecture during various stages of the cell cycle (Wood *et al.* 2010). Aging may also accompany reduction in levels of SMC proteins. Taking a clue from the findings that aging accompanies de-repression of transcription and silenced chromatin, it may not be too far-fetched to say that chromatin insulators or boundary elements weaken during the aging process. This proposition, however, is comparatively less explored. The CTCF-mediated DNA loop structures are maintained by cohesion, which in turn reinforces the inter-phase nuclear architecture (Wood *et al.* 2010). Loss of cohesin results in destabilization of this loop structure. Chromatin domain boundary elements bring about changes in the local chromatin structure not only to regulate gene expression but also to demarcate chromosomal domains within the nucleus. Loss of Sir2 changes peripheral localization of telomeres, suggesting that Sir2 also tags telomeres for their proper nuclear localization (Taddei *et al.* 2009). Similarly, centromeric and peri-centromeric chromatins are also tightly packed and may perform more than just the single function of sequestering the pool of free nuclear proteins. Unpublished results from our lab show that disturbances in chromatin structure of peri-centromeric heterochromatin adversely affect viability in *Drosophila.* Therefore, implicating loss of silencing at peri-centromere with its dis-localization within the nucleus and de-repression of nearby silenced genes seems a plausible cause of aging. Insulators or chromatin domain boundaries restrict the silent and active chromatin domains. A 'healthy' chromatin structure that requires well-positioned nucleosomes at boundary elements may be sensitive to histone dosage. Here, it is tempting to implicate disturbances in the structure of chromatin domain boundaries and nuclear organization in the aging process. The finding that surplus histone supply ensures repression of silenced chromatin and replenishes histones for tight chromatin packaging implicates many other mechanisms of aging, which essentially disturb the global nuclear chromatin structure

8. Conclusion

Chromatin-mediated mechanisms of aging seem to emerge with the unifying theme of efficient chromatin packaging (figure 1). Tight packaging of silent chromatin plays an important role in maintaining genome integrity. With advancing age, this compaction loosens up, which leads to de-regulation of crucial loci for cell survival. As a result, many genes, which are meant to be downregulated, start transcribing and result in accumulation of damaged components, ultimately leading to erosion of chromatin, which results in loss of genome integrity and thus aging.

Acknowledgements

NKM acknowledges CSIR for financial support. RKM acknowledges research grants from HFSP, CEFIPPRA and DBT, Government of India.

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ePublication: 14 March 2011