Published in final edited form as:
Exp Cell Res. 2008 June 10; 314(9): 1909–1917. doi:10.1016/j.yexcr.2008.02.023.

Aging by epigenetics - a consequence of chromatin damage?

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Abstract

Chromatin structure is not fixed. Instead, chromatin is dynamic and is subject to extensive developmental and age-associated remodeling. In some cases, this remodeling appears to counter the aging and age-associated diseases, such as cancer, and extend organismal lifespan. However, stochastic non-deterministic changes in chromatin structure might, over time, also contribute to the break down of nuclear, cell and tissue function, and consequently aging and age-associated diseases.

Introduction

As reviewed in this volume and elsewhere, organismal longevity and aging may be influenced by many complex interacting factors [1]. These include accumulation of nuclear and mitochondrial genome mutations; shortened and dysfunctional chromosome telomeres; oxidative damage of DNA and other macromolecules; systemic hormonal factors, such as insulin/IGF signaling; and senescence, apoptosis and altered differentiation in self-renewing tissues that depend on stem cells. In many cases, these factors are, or are likely to be, overlapping and/or interacting. In this chapter, we discuss another possible determinant of aging, “epigenetics”.

Strictly speaking, “epigenetics” refers to chromatin and DNA modifications that are heritable through cell division, but do not involve changes in the underlying DNA sequence [2]. However, since the aging process is not restricted to proliferating tissues and may, in fact, be influenced by irreversible proliferation arrest, we will use the term more loosely to refer to effects mediated by chromatin structure and DNA methylation, but not DNA sequence.

The dynamic and stochastic properties of chromatin

The basic repeating unit of chromatin structure is the nucleosome, comprised of about 146bp of DNA wrapped around an octamer of histones [3]. Chromatin can be broadly divided into two types, heterochromatin and euchromatin [4]. Euchromatin is decondensed during interphase, relatively transcriptionally active and replicates early in S-phase. Conversely, heterochromatin remains condensed during interphase, is more transcriptionally silent and is late replicating. Heterochromatin is itself further subdivided into two types, constitutive and facultative heterochromatin. Constitutive heterochromatin, for example at repetitive

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pericentromeric and telomeric DNA, is heterochromatic in all cells of an organism and has typically been considered to be essentially fixed and irreversible through the lifetime of the organism, although this may not be entirely true, as discussed below. In contrast, facultative heterochromatin is usually made as part of regulated cell differentiation processes or other changes in cell phenotype. For example, a single X chromosome is silenced by heterochromatinization in female mammal cells [5], for sex chromosome dosage compensation. Whether chromatin forms euchromatin or heterochromatin is dictated by modifications of the histones and DNA [6]. For example, acetylation of the N-terminal tails of histones promotes formation of euchromatin. Conversely, DNA methylation is characteristic of heterochromatin.

Despite this seemingly clear distinction between heterochromatin and euchromatin, it is increasingly being appreciated that chromatin is a highly dynamic and stochastic entity. The phenomenon of position effect variegation (PEV) first indicated the dynamic and stochastic properties of chromatin [7]. PEV was originally described in flies as a mottled red and white eye phenotype [8]. Due to a chromosomal inversion and change in position of the *white* gene relative to centromeric heterochromatin, the gene can be silenced by heterochromatin in a subset of cells that give pigment to the eye. The ability of genes subject to PEV to switch between active and inactive states reflects the dynamic nature of chromatin structure. This dynamic nature has been confirmed by more recent cell and molecular studies. First, essential processes, such as gene transcription, DNA replication and repair, all involve disruption and reassembly of chromatin structure [9,10]. Second, Fluorescence recovery after photobleaching (FRAP) studies have shown that most chromatin-bound proteins are not statically bound, but exhibit relatively high "off" and "on" rates, even in supposedly "closed" heterochromatin [11,12]. Third, remarkably and paradoxically, formation of heterochromatin actually depends on a degree of transcription, which contributes to heterochromatinization through the RNAi pathway [4]. Consistent with this, recent genome-wide analyses have shown that virtually all DNA nucleotides of the human genome are, to some degree, transcribed into RNA [13–15]. Indeed, telomeric heterochromatin was recently shown to be transcribed [16,17]. These observations indicate that even heterochromatin is not a static, closed entity. Fourth, heterochromatin can "spread" along chromatin, through cooperative interactions between the enzymes and binding proteins responsible for its formation [18]. The random occurrence of *white* expression in cells of the fly eye reflects the stochastic nature of heterochromatin's establishment and maintenance. The stochastic nature of chromatin structure and function is reaffirmed by many studies that have demonstrated a stochastic component to the control of gene expression [19].

In sum, an analysis of chromatin structure and its underlying biochemistry indicates that chromatin has dynamic as well as stochastic properties. Chromatin is not fixed, but is continuously remodeled and can redistribute and "breathe", sometimes in a not completely deterministic fashion. As discussed below, in some cases this dynamic property appears to counter the aging process and extend organismal lifespan. However, the stochastic, unpredictable component of chromatin structure might, over time, also contribute to the break down of nuclear, cell and tissue function, and consequently aging and age-associated diseases.

Aging is associated with epigenetic changes, from yeast to humans

The enzymes that add and remove acetyl groups, the histone acetyltransferases (HATs) and histone deacetylases (HDACs) respectively, determine the steady-state level of histone acetylation [10]. In *S. cerevisiae*, inactivation of the histone deacetylase, Sir2, shortens replicative lifespan [20–22]. Conversely, activation of Sir2 extends lifespan. The anti-aging effects of Sir2 in yeast are, at least in part, due to translocation of a Sir2-containing protein complex from telomeres to ribosomal DNA (rDNA) repeats [23]. These repeats are prone to

recombination to form extrachromosomal rDNA circles (ERCs), which curtail yeast lifespan. At the rDNA repeats, Sir2-mediated histone deacetylation, and consequent heterochromatinization by the Sir2-associated proteins (Sir3 and Sir4), prevents recombination and formation of ERCs, thereby extending lifespan [21,22]. In sum, yeast aging is associated with nuclear redistribution of a histone modifying enzyme, Sir2, and its partner heterochromatin-binding proteins. This epigenetic redistribution counteracts organismal aging.

Orthologs of Sir2 have anti-aging functions in many other species, including nematodes and flies, although the mechanisms do not appear to involve ERCs in these organisms [21,22]. Significantly, a decreased level of expression of the closest mammalian ortholog of Sir2, SirT1, correlates with apparent premature aging of mice with increased activity of p53 family members [24]. Moreover, in aging wild type mice, SirT1 protein level decreases with age in mitotic tissues [25]. Thus, the ability of Sir2-like proteins to regulate aging appears to be conserved through evolution. However, SirT1 has many non-chromatin substrates [22], so whether any effect on mammalian aging is epigenetically determined remains to be established.

In mammals, there is an age-associated decline in total genomic DNA methylation [26–28]. This occurs mostly at repetitive DNA sequences, and so probably occurs predominantly in domains of constitutive heterochromatin. Since DNA methylation promotes formation of transcriptionally silent heterochromatin [6], this change will facilitate deheterochromatinization of these regions.

However, although genome-wide levels of methylation decrease with age in mammals, at specific sites there is a tendency for DNA methylation to increase [29–37]. This occurs at CpG islands, some of which are in the promoter regions of genes. CpG islands are CG rich sequences that are typically unmethylated, but can become methylated. In addition, the total abundance of histone H4 methylated on lysine 20 (H4K20Me) has also been reported to increase with age in rat liver and kidney [38]. Like DNA methylation, H4K20Me is linked to transcriptional repression [6], supporting the notion that heterochromatin accumulates with tissue aging, at least at some sites.

Histone chaperones are histone binding proteins that mediate assembly of histones into nucleosomes [39]. Consequently, they are key determinants of chromatin structure and function. Significantly, at least one of these, the histone chaperone HIRA, has been shown to increase in expression or undergo some level of regulation in aging baboon skin [40,41]. Although the HIRA histone chaperone may have some functions linked to transcription activation [42–48], this chaperone is known to have an evolutionarily conserved role in heterochromatin formation [49–56].

Together, these observations suggest that mammalian aging is also associated with remodeling of chromatin structure. In particular, analysis of DNA methylation patterns suggests that mammalian aging is associated with an overall decrease in heterochromatin, but an increase at specific sites in the genome. Conceivably, there is a "redistribution" of transcription-silencing heterochromatin from repetitive DNA, that is normally packaged into constitutive heterochromatin, to regions of the genome that are normally transcribed [57–59].

Cellular senescence is associated with redistribution of heterochromatin

Cellular senescence is characterized by an irreversible proliferation arrest [60]. Cellular senescence can be initiated by various triggers, including an excessive number of cell divisions, in part due to shortened chromosome telomeres (so-called replicative senescence). Because of senescence, most primary human cells have a finite proliferative lifespan, and evidence has been presented that senescence contributes to tissue aging *in vivo*, in part by limiting the self-

renewal of tissues [61–63]. Specifically, senescent cells and/or molecular markers of the senescent phenotype have been reported to increase in some aging tissues [40,41,64–69], and are linked to some age-associated tissue pathologies, such as osteoarthritis, atherosclerosis and liver cirrhosis [70–72]. Moreover, manipulation of the cell signals that initiate senescence, such as telomere length and expression of the proliferation inhibitor p16INK4a [66–68,70,73–80], can modulate some aspects of organismal aging [70–72]. In addition to a likely role in tissue aging, cellular senescence is also a well-established tumor suppression process, by virtue of its ability to arrest proliferation and neoplastic progression of cells harboring oncogenic lesions [81–87].

Many senescent cells, whether triggered by excessive rounds of cell proliferation or activated oncogenes, show dramatic changes in chromatin structure. First, many senescent cells form specialized domains of facultative heterochromatin, called Senescence-Associated Heterochromatin Foci (SAHF) [88]. SAHF are visibly more condensed than interphase chromatin and contain histone modifications and associated proteins characteristic of heterochromatin. These SAHF have been proposed to silence expression of proliferation-promoting genes, and thus contribute to senescence-associated proliferation arrest. Accumulating evidence indicates that SAHF, or similar chromatin changes, are relevant to organismal aging. First, similar changes in chromatin structure have been described in the skin of aging baboons [41]. Second, the histone chaperone HIRA plays a key role in formation of SAHF [89–92]. As noted previously, based on immunostaining assays, this chaperone is upregulated in the dermal fibroblasts of aging baboons [40].

Remarkably, although SAHF appear to result from the condensation of almost entire chromosomes, DNA sequences that are typically contained in constitutive heterochromatin, such as pericentromeres and telomeres, actually appear to be excluded from the bulk of the condensed chromosome [57,90,91,93]. This suggests that these normally constitutively heterochromatic regions are perhaps deheterochromatinized in senescent cells. Consistent with this idea at least for telomeres, Maria Blasco and coworkers have shown that the shortened telomeres in mice lacking telomerase have reduced heterochromatin compared to telomeres from normal cells [94]. In sum, like tissue aging, cellular senescence appears to be accompanied by a redistribution of heterochromatin from constitutive heterochromatin to other normally-euchromatic sites, specifically to specialized domains of facultative heterochromatin, called SAHF.

Progeria cells exhibit accelerated changes in chromatin

Hutchinson-Gilford Progeria Syndrome (HGPS) is a rare syndrome that is characterized by rapid onset of some debilitating phenotypes that are typically indicative of aging [95]. These include severe growth retardation, loss of subcutaneous fat, alopecia, reduced bone density and poor muscle development. The average age of death in HGPS is 12–15 years, usually by myocardial infarction or stroke. However, HGPS patients do not accelerate all aspects of aging. For example, cancer incidence is rare and immune dysfunction is not typically reported. Therefore, whether HGPS is really a mechanistically accelerated aging syndrome or whether it merely phenocopies some aspects of aging through unrelated mechanisms has been debated [96].

Recent studies have demonstrated similarities between the epigenetic defects of HGPS cells and cells from very old normal individuals, supporting the notion that, at this molecular level, HGPS may represent accelerated aging. HGPS is caused by a splicing defect in exon 11 of the Lamin A gene (LMNA), removing 50 amino acids from the carboxy-terminus of the encoded protein. HGPS cells show numerous phenotypes, including dramatic defects in nuclear envelope structure, DNA damage and repair defects, changes in gene expression and a reduced

rate of proliferation [95]. Fibroblasts from HGPS cells also exhibit epigenetic defects, including decreased abundance of heterochromatic markers, such as histone H3 lysine 9 methylation (H3K9Me) and HP1 proteins [97–99]. These changes are exacerbated by prolonged passage in culture. Interestingly, after passage in culture, cells from aging normal individuals (>80 years) show similar changes in heterochromatin structure as HGPS individuals [98]. In sum, studies of HGPS cells are consistent with the idea that changes in chromatin structure - specifically loss of heterochromatin - may contribute to the aging phenotype. Whether or not HGPS cells also show increased heterochromatinization at other sites has not been reported.

The consequences of age-associated epigenetic changes

Not surprisingly, the consequence of these age-associated epigenetic changes is best understood in yeast. As discussed above, in this organism redistribution of Sir2 and heterochromatic proteins counteracts the aging process [21,22]. The consequence of the various modes of age-associated epigenetic regulation in mammals remains somewhat speculative. However, aging is accompanied by various altered phenotypes that might be linked to age-associated epigenetic changes. Studies going back to the 1960's by Richard Doll and coworkers indicated that aging is associated with cell aneuploidy [41]. Since proper chromosome segregation is dependent upon constitutive pericentromeric heterochromatin structure and function [100,101], decreased DNA methylation and deheterochromatinization of repetitive pericentromeric sequences might contribute to faulty chromosome segregation and age-associated aneuploidy. Recent studies in yeast showed that aneuploidy confers various altered cell phenotypes, including a proliferative impairment, which might contribute to decreased tissue renewal capacity with age [102]. Aneuploidy may also promote cancer [103], a disease for which age is the biggest risk factor.

Aging is also associated with changes in patterns of gene expression. Importantly, linking back to the previous discussion of PEV, some of these changes appear to have a stochastic component. For example, aging is associated with increased variability in gene expression in cardiomyocytes [104]. Aging hematopoietic stem cells also exhibit changes in gene expression. These changes are consistent with a bias towards myeloid differentiation, and so appear to parallel the "lymphoid to myeloid shift" that accompanies aging of the immune system, and contributes to declining adaptive immunity [105,106]. Whether these age-associated changes in gene expression are due to epigenetic alterations or genetic alterations (i.e. accumulated DNA damage) is not clear, but it is feasible that epigenetics accounts for at least part of the change. Underscoring this possibility, age-associated divergence of DNA methylation and histone acetylation profiles has been found in pairs of monozygous twins that are genetically identical [107] (but see also ref [108]). Remarkably, in the twin study, those genes that were differentially modified were also differentially expressed, suggesting that age-associated epigenetic divergence drives age-associated divergence of gene expression profiles. This age-associated divergence of genetically identical individuals is again consistent with a stochastic component to the change.

Age-associated methylation of CpG islands may have profound functional consequences. Methylation of CpG islands is a well-described mode of silencing of some tumor suppressor genes, such as INK4a and VHL [109]. Remarkably, age-associated CpG methylation of some tumor suppressor genes has been reported in histologically normal tissue, and appears to precede the development of neoplastic changes in tissue organization [32–34,36,37]. This suggests that tissue-wide, age-associated CpG methylation may be an early causative event in development of neoplasms. If one consequence of this CpG methylation is to silence tumor suppressor genes, a process that seems disadvantageous to the organism, it is possible that it is linked to other beneficial changes in chromatin structure, but reflects a stochastic, non-determined mis-targeting of that process. For example, since SAHF contribute to the

senescence phenotype, they might primarily contribute to senescence-mediated tumor suppression [81–87]. However, stochastic “errors” in the SAHF assembly process might erroneously contribute to methylation of CpG islands of some tumor suppressor genes, accounting for the age-associated silencing of these genes that has been reported. Even if these age-associated stochastic epigenetic errors occur only rarely, like rare genetic mutations, they might confer the first selective advantage on the road to cancer.

Summary, outstanding questions and therapeutic implications

From the preceding discussion, it is apparent that chromatin structure does change with aging, in organisms as diverse as yeast and mammals. However, with the exception of Sir2 in yeast, the extent to which this impacts the aging process has not yet been defined. Although it is early days for this field, we propose that some age-associated epigenetic alterations in mammals, such as formation of SAHF, might extend lifespan by suppressing age-associated diseases, such as cancer. However, as encapsulated within the hypothesis of "antagonistic pleiotropy" [110,111], SAHF and other events that drive senescence might ultimately promote aging by decreasing the long term renewal capacity of tissues. In addition, we suggest that a stochastic and presumably unregulated component of the age-associated change in chromatin structure, which appears inherent given the underlying biochemistry of chromatin, may lead to gradual deterioration in cell and tissue function with age. By analogy to age-associated genetic alterations (DNA damage) that are thought to contribute to aging, these accumulated epigenetic changes can be considered "chromatin damage".

In sum, the effects of chromatin on aging are likely to be complex and bidirectional. To test and define the impact of specific epigenetic determinants on aging will be a challenging task. Arguably, a pre-requisite to properly understanding the contribution of epigenetics to aging is to better understand the specific cell, tissue and system-wide malfunctions that are responsible for specific aging phenotypes, such as osteoporosis, sarcopenia, declining immune function, alopecia, cancer and many others. Then, it will be feasible to dissect out the contribution to each phenotype of each candidate epigenetic determinant, such as global hypomethylation, CpG island hypermethylation and SAHF.

While these studies are ongoing, we can already consider applying the knowledge gained. For example, we may be able to use age-associated epigenetic alterations as a means of early detection and risk stratification for age-associated diseases. There is already considerable interest in the development of high-throughput methods for early detection of cancer, based on detection of tumor suppressor gene CpG hypermethylation in very small numbers of tumor cells found in blood or other accessible body fluids [112]. However, if CpG hypermethylation is a frequent age-associated, tissue-wide, pre-neoplastic event, it might be possible to extend this technology to cancer risk assessment, based upon age-associated hypermethylation in pre-neoplastic tissue. Likewise, it might also be possible to use age-associated epigenetic changes in cardiac or immune cells for risk assessment or early detection of cardiovascular disease or declining immune function [104–106].

An ultimate goal of aging research is to delay or alleviate some of the most debilitating age-associated diseases, thereby prolonging healthy lifespan. For aspects of aging driven by epigenetics this may be an achievable goal, because in principle, epigenetic alterations are more readily reversible than are genetic alterations. Not only might epigenetic alterations be used in cancer risk assessment and early detection, but reversal of these epigenetic changes might also be a cancer chemoprevention strategy [113]. Chemopreventative strategies may also counter age-associated diseases other than cancer. Remarkably, addition of a SirT1 activator, resveratrol, to the diet of mice fed a high fat diet prolongs the healthy lifespan of those mice [114,115], apparently mimicking the well-established contribution of dietary caloric restriction

to longevity [116]. Although there are questions as to whether resveratrol extends lifespan through SirT1 and whether SirT1 acts through chromatin [117,118], these studies demonstrate the potential of chemopreventative strategies to combat aging.

Acknowledgements

PDA is supported by the NIH (RO1 GM062281, P01 AG031862 and R01 CA129334-01) and is a scholar of the Leukemia and Lymphoma Society. JMS is supported by the NIH (R01 GM041690 and R01 AG016694), and a Senior Scholar Award from the Ellison Medical Foundation. PDA thanks members of the Adams lab as well as Shelley Berger, Ronen Marmorstein and Brad Johnson for discussions.

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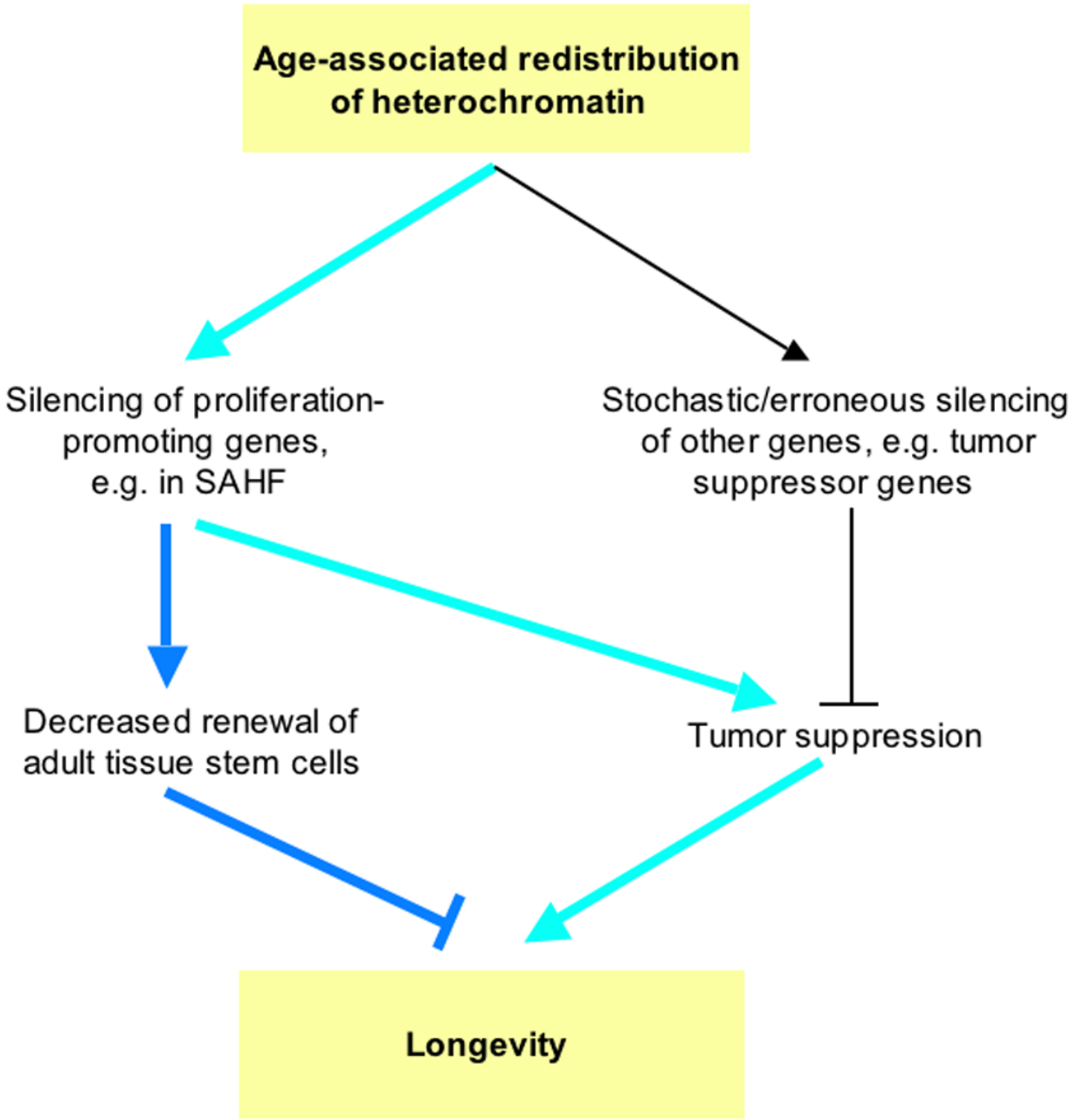

Figure 1. A model depicting the proposed impact of heterochromatin on longevity of mammals

Considerable evidence, discussed in the text, supports the idea that heterochromatin redistributes in cells during cellular and organismal aging. The primary purpose of this redistribution might be to extend longevity by promoting tumor suppression (green arrows). According to the idea of antagonistic pleiotropy, this will also lead to decreased renewal of adult tissue stem cells and renewable tissues, and consequently tissue aging (blue arrows). Stochastic errors in the redistribution of heterochromatin (e.g. excessive spreading of heterochromatin along chromosomes) might lead to erroneous silencing of other genes, e.g. tumor suppressor genes. In this case, redistributed heterochromatin will tend to decrease

longevity (thin black lines). Actual organismal longevity will ultimately be determined by the balance between these competing processes.