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Common features of chromatin in aging and cancer - Cause or Coincidence?

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Abstract

Age is a major risk factor for cancer. Alterations in DNA methylation, histone modifications, chromatin structure and epigenetic regulatory mechanisms are prominent hallmarks of both the aging process and of cancer. Intriguingly – or possibly coincidentally - several chromatin features are common between aging and cancer. Here we ask whether, and if so how, aging-associated chromatin modifications contribute to tumor susceptibility and tumorigenesis.

At the intersection of aging, cancer and chromatin

The functional properties of genomes are shaped by the secondary features of chromatin [1, 2]. The hard-wired hereditary information contained in the primary genome sequence is modified by DNA methylation, histone modifications, higher order chromatin structure, non-coding RNAs and epigenetic regulatory mechanisms [1, 2]. These chromatin features determine and modulate gene expression programs and perform critical regulatory roles in numerous biological processes, particularly in response to environmental factors such as nutrition and chemical pollutants [3, 4].

Changes in chromatin features have been closely linked to cancer susceptibility and tumor growth [5, 6]. Many cancer cells and tissues exhibit global and/or local changes in histone modifications and chromatin structure. Chromatin alterations likely contribute substantially to tumorigenesis and numerous examples in which chromatin changes drive tumorigenesis have been described [5, 6]. Changes in chromatin features, brought about by environmental insult and intrinsic events, may influence multiple steps of tumorigenesis by stimulating cell proliferation, promoting genomic instability and facilitating cellular transformation [7].

Chromatin changes and epigenetic alterations are also one of the prominent hallmarks of aging cells and organisms [8]. The progressive loss of physical function over time, which characterizes the aging process, is often accompanied by epigenetic modifications. Exposure to environmental toxins and endogenous stress has been linked to aging, possibly *via* interference with chromatin regulatory mechanisms [9]. It has also been speculated that

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epigenetic alterations contribute to the age-related changes in biological functions as well as to the observed increased genomic instability in aging organisms and cells [7, 10].

Since advanced age is a primary risk factor for cancer, and because epigenetic alterations are hallmarks of both aging and cancer, an obvious question is whether aging-associated chromatin changes actively contribute to cancer susceptibility and growth and whether these changes are the basis for the strong age-dependence of cancer – or whether they are mere coincidental changes with no functional links [11]. In this review, we highlight several epigenetic features which are prominently affected both in mammalian aging and cancer, and we discuss their potential and mechanisms to drive age-related tumorigenesis.

DNA Methylation

DNA methylation is one of the major genome regulatory mechanisms. Addition of a methyl group to the 5-carbon on cytosine (5mC) in cytosine-phosphate–guanine (CpGs) dinucleotides has been implicated in regulating gene expression by gene silencing and epigenetic memory in diverse biological processes [12]. Three DNA methyltransferases (DNMTs) mediate this modification: DNMT3a and DNMT3b function as *de novo* methyltransferases and DNMT1 acts as a maintenance methyltransferase [6, 8]. Changes in DNA methylation patterns have been documented in aging and in cancer (Table 1). Both processes are characterized by loss of methylation (DNA hypo-methylation) from CpGs located in repeat regions of the genome and concomitant increases in DNA methylation (DNA hyper-methylation) in CpGs located in the promoter regions of the genes known as CpG islands (CGIs) (Fig. 1; Table 1) [5, 9, 13, 14]. The same phenomena of DNA hypo-methylation and focal hyper-methylation is observed in senescence a state when cells cease to divide and which has been suggested to represent cellular aging and implicated as both a tumor protective and promoting mechanism [15].

Loss of cytosine methylation from the repeat regions of the genome, such as in LINEs (long interspersed nucleotide elements) and SINEs (short interspersed nucleotide elements), which comprise ~50% of the genome, significantly contributes to a global decrease in DNA methylation observed during aging [16–21]. Hypo-methylation of these repeat regions is associated with the decline of organ functions during aging [17, 18]. Global DNA hypo-methylation of repeat-rich regions is also observed in numerous cancers [13, 19]. LINE-1 hypo-methylation is correlated with increased risk of developing cancer and poor survival of cancer patients as seen, for example, in head and neck squamous cell carcinoma, myeloma and bladder cancer [13, 22–26]. DNA hypo-methylation of repeat elements has also been proposed to contribute to cellular transformation by promoting chromosomal rearrangements and elevating mutation rates [13, 27–29]. Apart from hypo-methylation of repeat elements, loss of methylation from genic regions also causes aberrant gene expression and promotes tumorigenesis [13, 30].

Global DNA hypo-methylation associated with aging and senescence is, intriguingly, accompanied by local DNA hyper-methylation at CGIs[15, 20, 21]. CGI hyper-methylation in promoter regions generally aids in gene silencing by recruitment of enzymatic machinery to establish silent chromatin by proteins such as methyl-CpG binding domain (MBD) or may

block binding of chromatin modifiers and transcription factors to methylated DNA [12, 31, 32]. CGIs methylation patterns are altered in a predictable fashion during aging and analysis of the methylation status of 353 defined CGIs is sufficient to accurately determine tissue age [33]. Hyper-methylation also appears to be relevant to cancer, since CGIs which are normally unmethylated are frequently hyper-methylated in cancer [5, 14]. Since CGI methylation has been observed in several tumor suppressor genes, it has been suggested that aberrant CGI methylation is a major contributor to neoplastic transformation via the stabilization of transcriptional repression, thereby leading to loss of function of tumor suppressor genes [11, 14]. CpG hyper-methylation of promoters also affects the expression of various non-coding RNAs that may have a role in malignant transformation [5, 34].

The phenomenon of CGI promoter hyper-methylation in aged tissues and cancer cells may suggest that methylation of CGIs pre-disposes aged cells to neoplastic transformation [11, 20]. For instance, similar patterns of CGI methylation of the estrogen receptor (ER) gene occur during aging in normal colon tissue and in colon cancer cells [35] and exogenous expression of ER suppresses colon cancer cell growth *in vitro*, suggesting that aging-associated repression of ER expression facilitates tumorigenesis [35]. In addition, promoters of genes which are targets of the repressive polycomb group of chromatin proteins are methylated during aging [36] as is the case for numerous cancers, where chromatin modifications by polycomb group proteins overlap with DNA hyper-methylated genes [37, 38]. Interestingly, some of these genes are involved in stem cell differentiation suggesting that age-dependent methylation of polycomb target genes may predispose the aging genome to neoplastic transformation by stabilizing stem cell-like features [36]. The link between aging, cancer and DNA hyper-methylation is also supported by the intriguing fact that genes whose mutations are associated with aggressive premature aging phenotypes, such as *WRN* in Werner Syndrome and *LMNA*, the causative agent of Hutchinson Gilford Progeria Syndrome, are frequently silenced by DNA methylation in a wide variety of cancers [39, 40]. Of note in this context is the fact, that some of these pre-mature aging disorders are characterized by increased tumor susceptibility [41].

The mechanisms underlying the opposing fate of DNA methylation, i.e DNA hypo-methylation of repeated sequences, and at the same time hyper-methylation of CGIs, observed during aging and cancer are not known [11, 13]. The DNA methylating activity of both maintenance methytransferase DNMT1 and de novo methyltransferases DNMT3a and DNMT3b are altered during aging and neoplastic transformation [42, 43]. Whereas the activities of DNMT1 and DNMT3a decrease, DNMT3b activity increases in cells approaching senescence [42, 43], suggesting that global DNA hypo-methylation during aging cells is due to reduced DNMT1 activity. DNMT1 has also been reported to be mislocalized in senescent cells possibly triggering hypo-methylation at specific genomic sites, particularly in lamin-associated domains [15]. CGI hyper-methylation during aging is assumed to be due to de novo activity of DNMT3b. In contrast to aging cells, which show reduced DNMT1 activity, several tumors show DNMT 1 over-expression and its activity has been linked to CGIs hyper-methylation [44], although DNMT1 over-expression is not always associated with CGI hyper-methylation [45]. DNMT3b and DNMT3a are also frequently over-expressed in tumors with DNMT3b generally at higher levels than DNMT3a

[46]. It thus appears that, although aged cells and cancer cells share several common features of DNA methylation, no common mis-regulation of the DNA methylation machinery is apparent, suggesting that other, yet unknown, factors determine the methylation patterns of aging and cancer cells.

Histone modifications

Core histones throughout the genome are modified at numerous amino acid residues by a diverse set of chemical modifications, most prominently acetylation, methylation, ubiquitylation, SUMOylation and phosphorylation [47]. The addition or removal of these modifications creates binding sites for chromatin proteins and often alters the degree of compaction of chromatin [47, 48]. Aberrant patterns of histone modifications are hallmarks of both aging [8] and cancer [49] (Table 1).

Studies in yeasts and in senescent cells suggest that aging is accompanied by a reduction of the global histone levels thus affecting chromatin structure. H3, H4, H2A and H2B levels are decreased in replicatively old yeast budding cells [50, 51] and in senescent human fibroblasts generated either through replicative senescence or oncogene-induced senescence [52, 53]. General loss of core histones is thought to lead to nucleosome depletion and accompanying genome-wide increase in gene expression, elevated levels of DNA damage, retrotransposition, large-scale chromosome rearrangement, and translocation during yeast aging [50, 54].

One of the most prominently altered histone modification is H4K16 acetylation, which is reduced during the aging process [52] as well as in various types of tumors [55]. H4K16 acetylation has been implicated in higher-order chromatin organization [56, 57] and plays an important role in the DNA damage response, allowing for the possibility that aging-associated decrease in H4K16ac promotes genomic instability [58–60]. Although multiple, partially redundant, histone acetyltransferases promote acetylation of H4K16, Sirt1 appears to be the major modifying enzyme [61, 62]. Sirt1 is the focus of much attention in the aging field due to reports that its invertebrate homolog, Sir2, promotes longevity in yeast, worms and flies [63–65]. However, although over-expression of Sirt1 improves various aspects of health during aging and promotes survival in a mouse model of genomic instability, Sirt1 does not appear to increase longevity in mammals [66, 67]. Beyond its role in aging, Sirt1 also seems to play a role in cancer [68]. Its expression is up-regulated in a wide range of cancer types including leukemia, breast, prostate, lung, colon and gastric cancers [68, 69]. The reasons why Sirt1 may promote longevity in lower organisms, but promotes tumor growth in higher organisms are unknown.

Trimethylation of histone H4 on lysine 20 is also affected both in aging and cancer. H4K20me3 is highly enriched at pericentric heterochromatin, telomeres, imprinted genome regions and repetitive elements, suggesting that this modification is involved in transcriptional silencing [70, 71]. Levels of H4K20me3 are decreased in many cancers, including liver, breast, bladder and lung [72–74]. Loss of H4K20me3 in cancer may be due to reduced expression of the H4K20-specific methyltransferase Suv4–20h as observed in hepatocarcinoma in a rat model and in breast cancer cells [73, 74]. Interestingly, Suv4-20h

has been implicated in maintenance of genome stability [75] and Suv4-20h double knock-out mice present with chromosomal aberrations due to less efficient DNA double-strand break repair [76]. H4K20me3 levels are also reduced in late-passage cycling human diploid fibroblasts (HDFs) [52]. Furthermore, exogenous expression of telomerase does not restore H4K20me3 levels, suggesting that replicative senescence and DNA damage responses are not responsible for elevation of trimethyl-H4K20 in HDFs [52]. In contrast, up-regulation of H4K20me3 has been observed in the premature aging disorder Hutchinson Gilford Progeria Syndrome [77] and in livers and kidneys of old rats [78]. Of note, in contrast to senescent fibroblasts derived by extensive passaging [52], H4K20me3 levels were found to be elevated in ras-induced senescent cells [79], suggesting differences in the senescence states depending on how senescence is induced [15].

Other aging-associated histone modifications include H3K9 acetylation, and trimethylation of H3K4, H3K9 and H3K27, and changes in these modifications have been observed in cancers, although their levels vary depending on tumor-type (Table 1). For example, breast cancer cells show low H3K9ac [80], whereas lung cancer cells show high H3K9ac levels [81]. Similarly, an increase in H3K9ac, the substrate for the histone deacetylase Sirt6 [82], which increases longevity in mammals, occurs in aged cycling human fibroblasts *in vitro* [52]. Mice deficient in SIRT6 exhibit accelerated aging [83], whereas transgenic mice overexpressing SIRT6 have a longer lifespan than control animals [84]. These findings are interesting in the light of the fact that much evidence points to a role of SIRT6 as a tumor suppressor, particularly via its role in DNA repair and genomic stability. Mouse embryonic fibroblasts from SIRT-6 deficient mice exhibit chromosomal aberrations including fragmented chromosomes and detached centromeres [83]. Along with H3K9ac levels, SIRT6 levels vary depending on the tumor type. SIRT6 is downregulated in several human cancers such as pancreatic cancer, colorectal cancer, and HCC [68], but up-regulated in prostate cancer [85]. It has been suggested that SIRT6 exerts its longevity function by reducing harmful levels of H3K9ac [86].

Aged cells are also characterized by increased levels of H3K4me3, a mark of active chromatin, and a decrease of H3K9me3, a mark of repressed chromatin [52]. In contrast H3K9me3 levels are elevated in oncogene-induced senescent cells and the mark accumulates in compacted heterochromatin foci [87, 88]. H3K9me3 has been associated with both positive and negative patient prognosis in several cancers depending on tumor type such as acute myeloid leukemia [89], salivary adenoid cystic carcinoma [90] and gastric adenocarcinoma [91]. Trimethylation of H3K4 also seems to play a role in cancer since the gene encoding one of the enzymes catalyzing the methylation of H3K4, the mixed lineage leukemia (MLL) protein lysine methyltransferase, is commonly translocated in leukemias leading to aberrant expression of developmental and hematopoietic genes [92]. A role of H3K4me3 in aging is supported by the fact that the deficiency in a member of the Ash-2 complex, which trimethylates H3K4, prolongs lifespan of *Caenorhabditis elegans* and conveys trans-generational longevity [93]. Based on observations in mouse cells, H3K4me3 also appears to be inter-dependent with the repressive mark H3K27me3, which is catalyzed by polycomb-group proteins, during development and cell differentiation [94–96]. Genome-wide distribution patterns of these two histones modifications differ in senescent

cells compared to proliferating cells [97] and they exhibit bivalent regions enriched in H3K27me3 and H3K4me3 at lamin-associated domains and H3K27me3-depleted regions respectively referred to “mesas” and “canyons” between lamin-associated domains corresponding to genes and enhancers[97]. These “mesas” overlap with DNA hypomethylation regions observed in senescent [15] and cancer cells [98]. Loss of H3K27me3 and H3K4me3 “mesas” has also been reported in the premature aging disease Hutchinson-Gilford Progeria Syndrome [77, 97] and in senescent cells [99]. H3K27me3 is a target of EZH2, a methyltransferase and component of the polycomb repressive complex 2 (PRC2), whose expression is decreased in senescent cells [99]. Conversely, overexpression of EZH2 and H3K27me3 has been associated with poor survival in gastric, breast, prostate cancers and cutaneous melanoma [100, 101]. A reduction in H3K27me3 in pediatric high-grade gliomas harboring two mutations, K27M and G34R/V, in histone H3.3 has also been reported and this reduction of H3K27me3 has been associated with DNA hypo-methylation [102]. Indeed, in cancer cells, H3K27 seems to target loci for *de novo* DNA methylation [103]. However, the relationship between H3K27me3, DNA methylation and cancer is not clear since silencing of genes marked by trimethyl-H3K27 in the absence of DNA methylation has also been reported [104].

Most of the human studies on histone post-translational modifications in cancer and aged cells are correlative and it is unknown whether these modifications are causative or represent merely a consequence of these processes. In addition to the obvious local effects, changes in histone modification patterns may have on individual tumor-promoting or repressive genes, one of the most likely scenarios for how aging-associated chromatin modifications might contribute to tumorigenesis is by inducing changes to higher order chromatin structure which in turn may make chromatin susceptible to damage [105]. Since one of the major hallmarks of aging is the accumulation of DNA damage, it is possible that changes in higher order chromatin structure affect the DNA damage response in aged cells. In support, DNA-damage induced reorganization of chromatin due to redistribution of chromatin modifiers such as SIRT1 upon DNA damage has been reported. The resulting chromatin reorganization led to changes in gene expression patterns similar to those observed during aging [67].

Long non-coding RNAs

Non-coding RNAs have emerged as important regulatory molecules modulating gene expression [106, 107]. Using tiling arrays and deep sequencing to study gene expression at a genome-wide scale, it has become clear that the human genome is pervasively transcribed and transcription is not limited to protein coding regions [108–110]. In addition to different types of small non-coding RNAs [106], which function via interaction with RNA-binding proteins or mRNA, the human genome expresses a high number of non-coding transcripts larger than 200bp, known as long non-coding RNAs (lncRNAs), which play regulatory roles in various biological processes [107]. LncRNAs can affect the expression of genes in *cis* or *trans* via association with other RNAs [111, 112] or proteins such as transcription factors, RNA binding proteins or chromatin modifying enzymes [107].

Numerous lncRNAs have been linked to cancer [113], many of which associate with chromatin or chromatin-modifying enzymes (Table I). HOTAIR, which is transcribed from the HOX gene cluster, is over-expressed in a subset of breast cancers and its expression promotes metastasis and is correlated with poor prognosis [114]. HOTAIR binds to the repressive Polycomb complex 2 (PRC2) and the histone demethylase LSD1 complex to modulate target gene expression [114, 115]. Another lncRNA generated from the HOX gene cluster, HOTTIP, is over-expressed in hepato-cellular carcinoma where its expression is associated with poor patient survival [116]. Interestingly, HOTTIP acts by inducing gene expression by interacting with adaptor protein WDR5 of the MLL complex implicated in leukemia [117]. CTBP1-AS is an androgen responsive lncRNA, which is over-expressed in prostate cancer, where it exerts tumor suppressive effects by inhibiting the expression of its antisense gene CTBP1, a co-repressor for androgen receptor [118]. CTBP1-AS binds to the HDAC–mSin3A complex to decrease histone H3 acetylation and H3K4 methylation levels at the *CTBP1* promoter [118]. The lncRNA ANRASSF1 is over-expressed in breast and prostate cells and it inhibits the tumor-suppressor gene RASSF1A [119] by forming an RNA/DNA hybrid that recruits the silencing complex PRC2 to the *RASSF1A* gene promoter [119]. The deletion of XIST, the prototypical lncRNA which mediates X chromosome inactivation and female dosage compensation by interacting with PRC2 [120], in the blood compartment of mice, results in genome instability and female-specific fully penetrant lethal blood cancer [121], suggesting a tumor protective role for XIST. It is generally not clear whether the observed changes in lncRNAs and the associated changes in gene expression are the drivers or consequence of cancer.

Early observations also point to the relevance of lncRNAs in aged cells and tissues. It has been noticed that young and senescent cells show differential expression of several lncRNAs [122]. The expression of some lncRNAs such as *MALAT1*, *XIST* and *MIAT* is lower in cells undergoing senescence and knockdown of MALAT1 and MIAT in early passage fibroblast induces senescence [122]. One lncRNA, *SAL-RNA1*, prevents senescence and its knockdown promotes phenotypic traits of senescence, including enlarged cell size and positive β-galactosidase staining, possibly via modulating p53 levels [122]. Further studies are required to probe whether lncRNAs play any direct functional roles in senescence and aging.

A possible model for the action of lncRNA in aging-associated tumorigenesis emerges from the analysis of the regulatory mechanisms of the *INK4A-ARF-INK4B* tumor suppressor gene cluster, which is deleted in several cancer types [123]. Expression of the protein coding genes $p15^{INK4b}$, $p16^{INK4a}$ and ARF from this locus is increased during aging and the locus has been linked to aging-related diseases by genome-wide association studies (GWAS) [123, 124]. This locus also encodes the antisense lncRNA ANRIL, which negatively regulates the expression of protein coding genes from the *INK4A-ARF-INK4B* locus [125–127]. GWAS have identified ANRIL as a risk locus for cancer and other age-related diseases [128]. The levels of ANRIL are reduced in cells undergoing senescence [126] and ANRIL silences $p15^{INK4b}$ by heterochromatin formation [127]. ANRIL binds to polycomb repressive components CBX7 and SUZ12 and epigenetically represses the expression of $p16^{INK4a}$ and $p15^{INK4b}$, respectively, by promoting H3K27 methylation [125, 126]. The fact that ANRIL

is over-expressed in prostate cancer and leukemia and participates in epigenetic silencing of tumor suppressors suggests that it may be involved in cancer progression [126, 127].

A prominent feature of the aging process is the appearance of DNA damage [105]. Several lncRNAs are altered upon DNA damage, such as lncRNAp21 and PANDA [129]. Interestingly, lncRNA ANRIL is induced upon DNA damage, and elevated levels of ANRIL suppress the expression of tumor suppressors $p15^{INK4b}$, $p16^{INK4a}$ and ARF upon DNA damage [130]. Another such DNA damage-inducible lncRNA is JADE, which upon DNA damage induces the expression of its neighboring gene Jade1, which acts as a cofactor in histone acetylation complex HBO1 (human acetylase binding to ORC1) [131]. Interestingly, lncRNA JADE is over-expressed in breast cancer, and its knockdown significantly reduces breast tumor growth *in vivo* [131]. Albeit preliminary, these observations suggest that lncRNAs function and expression is altered due to DNA damage during aging and contribute to subsequent tumor formation.

Models of chromatin-based aging-related cancer formation

How might aging-related changes in chromatin contribute to tumor formation? Several models can be envisioned (Fig. 2). First, chromatin properties may directly interfere with regulation of individual, or groups of, genes involved in tumor suppression or promotion. While aging-associated changes to chromatin likely occur at a global scale, alterations of chromatin properties at particular sites as part of such global alterations of chromatin structures during aging may affect expression of key genes such as tumor suppressors or oncogenes. Similarly, lncRNAs may act in this model by affecting, either directly or indirectly, the expression of tumor suppressors or genes involved in cell proliferation or apoptosis (Fig. 2). Alternatively aging-associated changes in chromatin properties may increase susceptibility to oncogenic transformation by triggering aberrant differentiation of tissue stem cells or somatic cells allowing them to assume properties of cancer initiating cells (Fig. 2) [132]. Such global changes may not necessarily be sufficient to cause cancer, but they may set the stage for tumor formation by predisposing and facilitating transformation [133]. This notion is supported by reports of similarities in chromatin properties of tumor initiating cells and stem cells [134]. A further scenario, not mutually exclusive with others, relies on the fact that chromatin properties affect a cell's response to DNA damage and aging-associated changes in chromatin features may thus impair DNA repair processes and in this way increase the frequency of mutations and elevate genomic instability, heightening the probability of oncogenic transformation [105, 135]. NITR [136–141].

Concluding remarks

Aging and tumorigenesis are two highly complex processes. It is not surprising to find alterations in chromatin properties in both, and even the occurrence of similar changes in both processes is expected. The question then arises whether common changes to chromatin features are merely coincidental or whether aging-associated chromatin features contribute to tumorigenesis. The jury is clearly still out. To understand the interplay of chromatin, aging and cancer it will be critical to extend the current studies beyond their correlative

nature and specifically test the functional and causal role of aging-associated chromatin features in promoting tumor phenotype and delineating their mechanisms. A major challenge in these studies is the scarcity of experimental model systems. It is difficult to relate human cell culture systems to *in vivo* behavior. Similarly, animal models are only of limited relevance since both the aging and the tumorigenesis process in humans differs significantly from that in animal models. It will be important to develop suitable, well controlled experimental systems to directly test the impact of aging on cancer formation. This is a significant challenge. One interesting, albeit similarly imperfect, option is the study of naturally occurring human pre-mature aging disorders. Intriguingly, while some aging syndromes, such as Blooms Syndrome and Werner Syndrome, are associated with elevated tumor susceptibility, others, such as Cockayne Syndrome and Hutchinson Gilford Progeria Syndrome, are characterized by premature aging but no tumor formation. The similarities and differences between these diseases may provide insights into the link between aging and cancer.

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Highlights

- Chromatin features are altered in aging and in cancer
- Several changes to chromatin are common between aging and cancer
- Several mechanisms by which aging-associated changes in chromatin may contribute to tumorigenesis can be envisioned

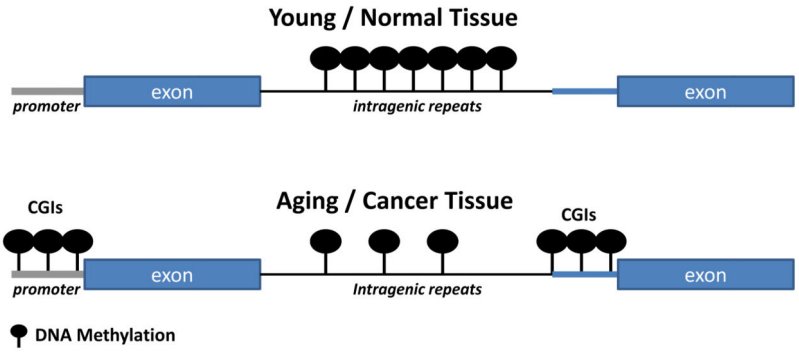

Figure 1. Changes in DNA methylation during aging and cancer

CpGs located in the promoter regions of the genes known as CpG islands (CGIs) show increased propensity for methylation during aging and cancer. CpGs located in the repeat regions of the genome in contrast generally show loss of methylation with age and in cancer.

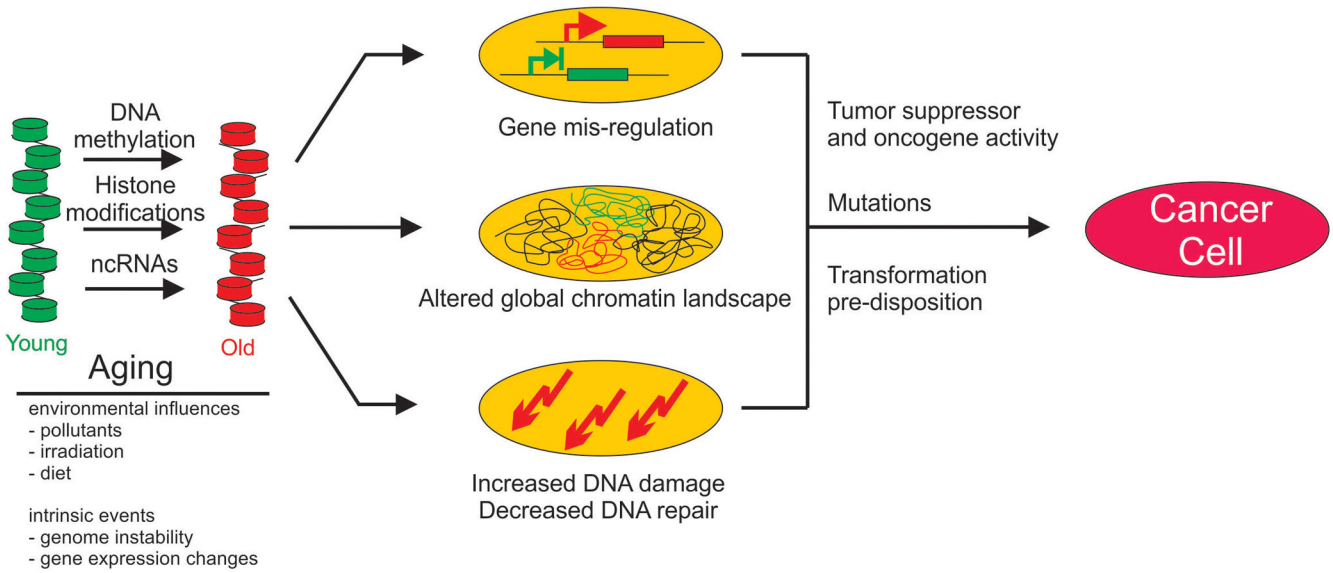

Figure 2. Chromatin-based mechanism of aging-associated tumorigeneis

Aging is accompanied by global and local changes in DNA methylation, histone modifications and ncRNA expression brought about by intrinsic and environmental factors. Aging-associated changes in chromatin may promote tumorigenesis by silencing tumor suppressors or activating oncogenes (top), altering the global chromatin landscape and chromatin organization (b), and leading to increased DNA damage (c).

Table 1

Chromatin features in aging and cancer

	Aging	Cancer
DNA Methylation		
DNA hypo-methylation	↑LINE and SINE regions [16–21]	↑LINE and SINE regions[13,19,24–26]
DNA hyper-methylation	↑CGIs [20–21, 33, 35]	↑ CGIs [5,14,34–36]
Histones modifications		
H4K16ac	↓ *in vitro* in aged cycling human fibroblasts[52]	↓various cancers[55]
H4K20me3	↓ *in vitro* in aged cycling human fibroblasts[52] ↑ *in vivo* in livers and kidneys of old rats[78] ↑ Hutchinson-Gilford Progeria cells[77]	↓various cancers[55, 74] ↓ rats model[73]
H3K9ac	↑ *in vitro* in aged cycling human fibroblasts[52]	↑ lung cancer[81] ↓ breast cancer[80]
H3K4me3	↑ *in vitro* in aged cycling human fibroblasts[52]	↓ breast cancer[141] ↑ glioblastoma[136], renal cell carcinomas[137]
H3K9me3	↓ *in vitro* in aged cycling human fibroblasts[52]	↑ humans[91] ↓ pancreatic carcinomas[138]
H3K27me3	↓ Hutchinson-Gilford Progeria cells[77] ↓ senescent cells[99]	↑ esophageal squamous cell carcinoma[139] ↓ pediatric high-grade gliomas[102]
LncRNA		
HOTAIR	ND	↑ breast[114]
HOTTIP	ND	↑ liver, leukemia [116, 117]
CTBP1-AS	ND	↑ prostate[118]
ANRASSF1	ND	↑ breast, prostate[119]
XIST	↓ senescence[122]	ND
MALAT1	↓ senescence[122]	↑ various cancers[140]
SAL-RNA1	↓ senescence[122]	ND
ANRIL	↓ senescence[126]	↑ prostate, leukemia [126–127]

ND: not determined; Red: reduction of indicated feature; Green: increase of indicated feature