Aging Research

ISSN 2957-8701 (print); 2957-9295 (online)
https://doi.org/10.26599/AGR.2025.9340072

Review

The impact of 3D chromatin remodeling on cellular senescence and aging

Weicong Chen[§], Qiang Zhan[§], Feng Xiao, Zhenyu Ju (✉), Zhiyang Chen (✉)

Key Laboratory of Regenerative Medicine of Ministry of Education, Institute of Aging and Regenerative Medicine, Department of Developmental & Regenerative Medicine, College of Life Science and Technology, Jinan University, Guangzhou 510632, China
[§]These authors contributed equally to this work.

Received: 5 October 2025 | **Revised:** 9 February 2026 | **Accepted:** 15 March 2026

ABSTRACT

Cellular senescence is a stress-induced and stable cellular state that contributes to organismal aging and a broad spectrum of age-related diseases. Among the multifaceted senescence-associated alterations, progressive reorganization of higher-order chromatin structure has emerged as a pivotal regulatory layer. The three-dimensional (3D) architecture of chromatin, including lamin-associated domains (LADs), A/B compartments, topologically associating domains (TADs), and chromatin loops, undergoes profound and dynamic remodeling during cellular senescence and in aging contexts. Accumulating evidence suggests that such architectural changes are closely associated with key senescence-related phenotypes, including genomic instability, transcriptional dysregulation, stem cell functional decline, and chronic inflammatory signaling. Enabled by technologies such as Hi-C and Chromatin Interaction Analysis by Paired-End Tag sequencing (ChIA-PET), recent studies have begun to map tissue- and context-dependent patterns of 3D genome remodeling and connect them to age-associated pathologies, ranging from Alzheimer's disease (AD) and hematopoietic dysfunction to cancer. This review synthesizes advances in understanding how multiscale chromatin reconfiguration influences gene regulation and cellular identity in senescence, and summarizes representative disease settings and implicated structural layers. We further discuss major technical challenges, including limited resolution of cellular heterogeneity, constraints of fixed-cell assays for capturing chromatin dynamics, and difficulties in robust multi-omics integration, and propose future directions for leveraging single-cell and spatiotemporal 3D genomics to dissect mechanisms linking senescence to organismal aging and to inform therapeutic development.

KEYWORDS

senescence, aging, three-dimensional (3D) architecture of chromatin

1 Introduction

Aging is an irreversible and systemic process characterized by a gradual decline in cellular functions, loss of tissue homeostasis, and deterioration of overall physiological capacity over time. With advancing age, aging has been established as a primary risk factor for a broad spectrum of chronic non-communicable diseases, including Alzheimer's disease (AD), Parkinson's disease, cardiovascular disease, metabolic syndrome, and cancer [1]. Against the backdrop of a rapidly aging global population, unraveling the mechanisms of aging and its intrinsic connections with disease holds profound social and biomedical implications [2].

It should be noted that "cellular senescence" and "organismal aging" are two related but non-interchangeable biological concepts [3]. Organismal aging refers to the progressive, time-dependent decline in overall functional capacity of multicellular organisms, involving multiple organ systems, disruption of tissue homeostasis, and the cumulative risk of age-associated diseases; in contrast, cellular senescence is a stable and usually irreversible cellular state induced by specific stresses, characterized by permanent cell-cycle arrest, metabolic and epigenetic remodeling, and pronounced alterations in the secretory phenotype [4]. Current studies indicate that cellular senescence represents one of the key cellular foundations of organismal aging and many age-related diseases; however, the two are not equivalent in terms of their underlying mechanisms, temporal scales, or biological levels. Cellular senescence can be triggered by a variety of endogenous or exogenous stimuli, and its major forms include replicative senescence driven by telomere shortening or

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✉ Address correspondence to Zhenyu Ju, zhenyuju2016@jnu.edu.cn; Zhiyang Chen, zhiyangchen@jnu.edu.cn

Cite this article as Chen, W. C., et al. *Aging Research*, **2025**, 3: 9340072.

replication stress, oncogene-induced senescence (OIS) caused by aberrant oncogenic signaling, and therapy-induced senescence elicited by radiotherapy, chemotherapy, or other cytotoxic insults [5, 6]. Despite differences in their initiating stimuli, these senescent cells typically share a set of common molecular and phenotypic hallmarks, including activation of the $p16^{Ink4a}$/$p21^{Cip1/Waf1}$ pathways, increased SA-β-gal activity, persistent activation of the DNA damage response, remodeling of chromatin organization and three-dimensional genome architecture, and the establishment of the senescence-associated secretory phenotype (SASP) [7–10]. The accumulation of senescent cells within tissues and the chronic release of their SASP are thought to play critical roles in shaping inflammatory microenvironments, driving tissue functional decline, and promoting the development of multiple age-related diseases. Meanwhile, extensive animal studies have demonstrated that targeted elimination of senescent cells can markedly improve the function of multiple tissues and extend health span. For example, clearance of $p16^{Ink4a}$-positive senescent cells has been shown to delay the onset of aging-associated pathologies [11]. Pharmacological senolytics, such as dasatinib plus quercetin (D+Q) and fisetin, have been shown in multiple aged mouse models to reduce the burden of senescent cells and improve a range of outcomes, including physical performance and organ function [12]. In addition, inhibitors targeting the BCL-2 pro-survival pathways, as well as peptide-based strategies such as FOXO4-DRI, have demonstrated the potential to restore tissue function in aged mice [13]. Some early clinical explorations, for example, D+Q in patients with diabetic kidney disease, have also reported reductions in senescence-associated markers accompanied by functional improvements, with an acceptable safety profile [14].

Based on a clear understanding of the relationship between cellular senescence and organismal aging and their potential for intervention, current aging research has further identified several core hallmarks at the systemic level, including genomic instability, telomere attrition, loss of proteostasis, mitochondrial dysfunction, accumulation of senescent cells, and stem cell functional decline [15]. Among these, epigenetic regulation emerges as a critical mediator that bridges environmental cues and dynamic gene expression changes. Mechanisms such as DNA methylation, histone modifications, chromatin remodeling, and the activity of non-coding RNAs not only influence cellular identity and functionality but also significantly dictate the pace and phenotype of aging [16, 17]. The advent of tools like the "epigenetic clock" has revealed that aging is not merely a cumulative effect of time but a manifestation of progressive dysregulation in epigenetic networks, including alterations in DNA methylation patterns, deacetylase/sirtuin enzymatic activities, and chromatin remodeling complexes [18, 19].

Traditional epigenetic studies have predominantly focused on linear genome modifications, often overlooking the significance of the 3D organization of chromatin within the nucleus. Recent progress in 3D genome sequencing approaches, exemplified by Hi-C, has provided critical insights into the dynamic organization of chromatin architecture, encompassing chromosome territories (CTs), A/B compartments, topologically associating domains (TADs), and chromatin loops [20–23]. These structures are not static, rather, they undergo dynamic reorganization in response to cell type, developmental stage, and external stimuli, thereby finely regulating gene expression networks and cell fate decisions.

CTs represent the fundamental units of nuclear organization, where individual chromosomes occupy distinct spatial regions, ensuring functional compartmentalization. During aging, disruptions in the spatial organization of CTs can perturb gene expression and contribute to age-associated phenotypes [20]. A/B compartments further stratify chromatin into transcriptionally active (A) and inactive (B) regions, corresponding to open euchromatin and compacted heterochromatin states, respectively. Aging often leads to a blurring of A/B compartment boundaries, skewing gene expression patterns and compromising cellular functionality.

TADs defined by boundary proteins such as CCCTC-binding factor (CTCF) and cohesin, are self-interacting chromatin units that provide a structural framework to regulate diverse chromatin interactions. Maintenance of TAD boundaries is critical for gene expression stability. However, disruptions of higher-order chromatin structures during aging, ranging from TAD boundary weakening to loop disintegration, disturb the spatial coordination of regulatory elements, hereby driving transcriptional dysregulation and pathological gene activation, including the activation of oncogenes.

The 3D genome serves as a pivotal regulator in fundamental processes such as stem cell differentiation, embryonic development, and chromatin homeostasis. Evidence indicates that chromatin decompaction, blurred A/B compartment boundaries, and TAD/loop remodeling during aging are closely linked to cellular dysfunction and disease phenotypes. This review aims to systematically consolidate current knowledge on the aging-related remodeling of chromatin architecture, focusing on the dynamic changes in CTs, compartments, TADs, and loops. Additionally, it explores the implications of these structural alterations in aging-associated diseases, providing a foundation for future anti-aging strategies targeting the 3D genome.

2 Nuclear and chromatin reorganization as the structural and dynamic basis of cellular senescence

2.1 Nuclear lamina degradation and heterochromatin disruption: key structural basis of cellular senescence

Cellular senescence involves significant remodeling of nuclear architecture, prominently marked by nuclear lamina degradation and heterochromatin destabilization [24]. Nuclear lamina proteins (e.g., Lamin B1) anchor lamina-associated domains (LADs), ensuring heterochromatin stability and peripheral localization [25]. During cellular senescence, reduced Lamin B1 leads to LAD detachment, chromatin relaxation, aberrant activation of repetitive sequences, genomic instability, and innate immune pathway activation [26].

Multiple regulatory layers contribute to nuclear lamina integrity and heterochromatin stability during cellular senescence [24, 25]. Members of the sirtuin family have been implicated in maintaining heterochromatin organization and

genome stability under stress conditions [27]. In particular, SIRT3 has been shown to stabilize heterochromatin and counteract senescence-associated chromatin relaxation in human mesenchymal stem cells, where SIRT3 depletion leads to decreased levels of the repressive mark H3K9me3, increased chromatin accessibility, and accelerated senescence phenotypes; re-introduction of SIRT3 restores heterochromatin compaction and alleviates senescence markers [28]. Additionally, the miRNA-processing factor DGCR8 regulates heterochromatin independently of miRNA pathways by stabilizing KAP1 and HP1γ, its loss leads to LAD detachment, chromatin decompaction, and osteoarthritis-like phenotypes [29]. Post-transcriptional regulation of nuclear lamina components also contributes to senescence-associated chromatin reorganization. Reduction of lamin B receptor levels mediated by miR-340-5p disrupts heterochromatin organization and promotes cellular senescence [30]. Nuclear lamina damage also reprograms chromatin positioning and 3D topology. Detached heterochromatin migrates inward, disrupting active-silent compartments and TADs [31]. Furthermore, damage to telomeric and centromeric heterochromatin exacerbates genomic instability and cellular senescence phenotypes [32]. These changes are tightly linked to pathological states, progerin accumulation in Hutchinson-Gilford progeria syndrome disrupts LAD anchoring and heterochromatin integrity [33], while prelamin A accumulation in chronic kidney disease causes nuclear deformation [34].

Importantly, nuclear lamina deterioration and the resulting destabilization of heterochromatin during cellular senescence retain plasticity. Overexpression of SIRT3, ZKSCAN3, or Lamin B1 restores LAD structures, H3K9me3 levels, and delays cellular senescence [30, 35]. Moreover, inhibition of Cdc42 or CK2 boosts nuclear lamina integrity, offering potential for both anti-aging and anti-cancer therapies [36, 37]. In conclusion, nuclear lamina degradation and heterochromatin disruption are fundamental to cellular senescence, presenting actionable targets for therapeutic intervention.

2.2 Dynamic reprogramming of 3D chromatin architecture in cellular senescence

2.2.1 A/B compartment remodeling

A/B compartments reflect the macro-level partition of chromatin: A compartments consist of transcriptionally active genes and open chromatin, while B compartments contain compact heterochromatin and silent genomic regions [21]. During aging and cellular senescence, A/B compartment organization undergoes significant reprogramming, which varies depending on the aging model [38, 39]. In OIS B–B interactions are strengthened while A–B interactions are reduced, leading to spatial isolation and the formation of senescence-associated heterochromatin foci (SAHF) structures [23, 39]. DNMT1 was identified as a key regulator in OIS-specific chromatin folding, as *DNMT1* knockdown blocks SAHF formation and shifts compartmental reorganization toward RS [39]. In contrast, replicative senescence (RS) exhibits enhanced inter-compartment (A–B) interactions and reduced compartmental segregation, without the formation of SAHF, as revealed by genome-wide Hi-C analyses [39, 40].

2.2.2 TAD deconstruction

TADs are crucial 3D chromatin units maintained by CTCF and cohesin, ensuring enhancer–promoter specificity [22]. During cellular senescence and aging-related contexts, TAD boundaries lose insulation, intra-domain interactions decline, and inter-domain interactions increase, disrupting chromatin modularity and causing mis-regulated gene expression [41, 42]. For instance, in aged B cells, TAD boundary weakening impairs the proper expression of key developmental genes like *Ebf1* and *Pax5* [43]. These findings emphasize the significance of TAD instability as a key epigenetic mechanism of aging and a potential target for intervention.

2.2.3 Chromatin loop reprogramming

Chromatin loops, which are formed by CTCF and cohesin, mediate precise long-range gene regulation by connecting enhancers with their target promoters [23]. During aging and cellular senescence, these loops undergo widespread collapse and reorganization, resulting in the destabilization of transcriptional programs [44, 45]. For instance, in OIS models, regulatory loops associated with developmental genes are diminished, whereas those linked to senescence-associated secretory phenotype (SASP) genes, such as interleukin-1 beta (*Il-1β*) and interleukin-8 (*IL-8*), are reinforced, thereby promoting inflammatory pathway activation [40, 46]. During cellular senescence, cohesin, a key factor mediating chromatin loop formation, undergoes redistribution, resulting in rewiring of enhancer–promoter interactions [46]. In contrast, during cellular aging, altered activity of transcription factors such as YY1 and AP-1 contributes to progressive disruption of super-enhancer-associated chromatin loops and age-associated transcriptional reprogramming [47, 48]. Notably, loop dynamics are intricately linked to higher-order chromatin architecture. For example, CTCF depletion not only disrupts chromatin loops but also alters TAD boundaries and A/B compartmentalization, collectively exacerbating 3D genome disorganization [49]. These structural alterations not only reflect but also actively contribute to age-related transcriptional dysregulation and the onset of aging-associated diseases. In summary, the remodeling of chromatin loops represents a central mechanism underlying 3D genomic dysfunction in aging, functionally connecting transcriptional imbalance with cellular senescence and pathology, thereby highlighting its potential as a target for therapeutic strategies.

Collectively, these studies indicate that although cellular senescence and organismal aging share convergent features of 3D genome remodeling, including compartment blurring, TAD destabilization, and loop reprogramming (Fig. 1), the underlying drivers and structural outcomes are highly context-dependent, varying across senescence modalities and aging tissues.

3 Alterations in higher-order chromatin architecture in aging-related diseases

3.1 Dynamic changes in the 3D genome in neurodegenerative disorders

The 3D genome in the nervous system exhibits dynamic

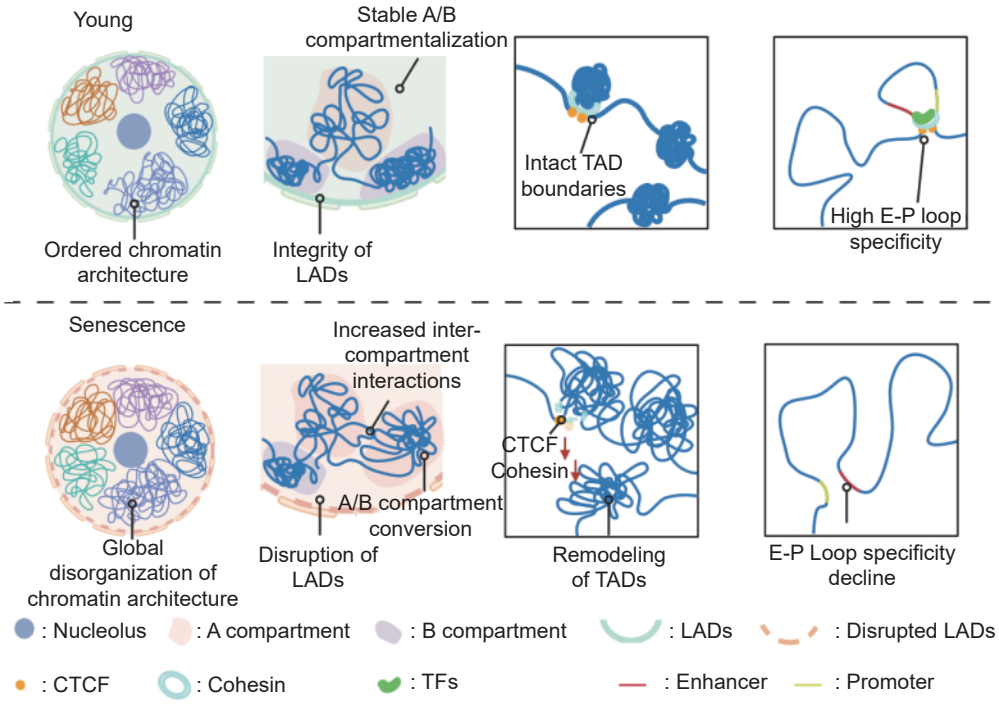


Figure 1 Multiscale chromatin remodeling during cellular senescence. Schematic comparison of multiscale chromatin organization in "Young" versus "Senescence" nuclei. Top: young cells; bottom: senescent cells. From left to right the panels illustrate global nuclear compartmentalization, A/B compartments, TADs and contacts between regulatory elements. The young nucleus depicts canonical lamina-associated heterochromatin and ordered compartmentalization around the nucleolus; chromatin exhibits regular layered folding, intact A/B compartments, preserved TADs and chromatin loops, and short-range enhancer–promoter interactions that maintain steady-state gene expression. By contrast, the senescent nucleus shows relocalization/detachment of lamina-associated domains (LADs), disruption of chromatin domains and A/B compartment switching; reduced expression or altered function of architectural proteins such as CTCF and cohesin leads to loss or remodeling of TADs and long-range chromatin interactions, while enhancer–promoter contact frequency and specificity decline, resulting in reprogramming of gene expression profiles.

reorganization under physiological conditions, yet becomes destabilized in aging and neurodegeneration. During normal states, neural activity induces chromatin remodeling, including enhancer–promoter interactions and TAD reorganization. For example, under physiological and behaviorally relevant conditions, neuronal activity can rapidly remodel the 3D genome, most prominently manifested as a rapid strengthening and reorganization of enhancer–promoter interactions. Immediate early genes such as *Fos* and *Arc* are activated within ~20 min after stimulation through de novo short-range loops, whereas secondary response genes such as *Bdnf* are regulated within 1–6 hours through the combined action of pre-existing and newly formed loops. These enhanced interactions are tightly associated with increased H3K27ac levels and are accompanied by changes in A/B compartment assignment and long-range interaction frequencies, as well as the formation of "gene loops" connecting transcription start sites (TSSs) and transcription termination sites (TTSs) to support high-throughput transcription [50, 51]. In cerebellar granule neurons, sensory experience further reshapes enhancer–promoter interactions and alters their association with the active A compartment; deletion of the cohesin core subunit *Rad21* disrupts these interactions and activity-dependent transcription, and significantly impairs the acquisition of delayed tactile startle learning, indicating a causal role of such structural remodeling in motor learning [52]. Overall, these multilevel changes exhibit an immediate-to-delayed temporal stratification: during the encoding phase, increased enhancer accessibility serves as a "priming" event, followed by spatial reorganization of chromatin fragments and de novo long-range interactions during memory consolidation and retrieval, enabling pre-primed enhancers to engage their cognate promoters and drive subsequent transcriptional responses [53].

In pathological aging, the stability of 3D genome organization becomes progressively compromised. In AD brain tissue, widespread reorganization of A/B chromatin compartments has been observed, accompanied by alterations in histone acetylation landscapes, particularly at H3K27ac-marked regulatory regions, which correlate with tau pathology and disease severity [54]. In addition, AD–associated risk variants, including loci near *BIN1* and *PICALM*, are enriched within distal regulatory elements and have been linked to altered enhancer–promoter interactions and dysregulated neuronal gene expression, suggesting a potential contribution of chromatin looping perturbations to genetic susceptibility [55].

Beyond neurons, microglia, the resident immune cells of the central nervous system, play critical roles in both development and the progression of neurodegenerative disorders, including AD, Parkinson's disease, and multiple sclerosis. During aging, microglia undergo extensive epigenetic reprogramming, characterized by changes in enhancer activity and higher-order chromatin organization that reshape immune-related gene loci, such as *APOE*, and promote a neurotoxic transcriptional state [56].

Accumulating DNA damage and defects in DNA repair, which are hallmarks of aging and neurodegeneration, further

contribute to 3D genome instability. Neuronal DNA double-strand breaks (DSBs) have been shown to disrupt chromatin architecture, compromise genome integrity, and perturb synaptic gene networks, thereby potentially accelerating neurodegenerative progression [57]. Consistent with this view, activity-dependent chromatin loops—essential for neuronal plasticity and stimulus-responsive gene regulation—can lose robustness in aging-related contexts, which may contribute to cognitive decline [51].

Current evidence suggests that 3D genome instability in neurodegeneration may arise from multiple converging processes. Accumulated DNA damage, declining CTCF/cohesin function, and nuclear lamina deterioration could weaken chromatin boundaries and anchoring. Meanwhile, activity-dependent chromatin loops in neurons may lose plasticity, and microglia may undergo compartment and enhancer reprogramming toward neurotoxic states. Together, these alterations may disrupt the epigenetic balance between neuronal and immune cells, offering a potential spatial-genomic framework for understanding disorders such as AD.

From a translational perspective, epigenetic modulators targeting chromatin acetylation, enhancer activity and inflammation-associated transcription have been explored in neurodegenerative disease contexts. Broad-spectrum histone deacetylase (HDAC) inhibitors, including valproate, have reached randomized clinical testing in AD, providing proof-of-concept that acetylation-dependent regulatory pathways are druggable, albeit with limited efficacy and tolerability [58]. More selective approaches, such as HDAC6 inhibitors and BET bromodomain inhibitors, have shown the ability to modulate proteostasis- and inflammation-linked transcriptional programs in experimental models [59–61]. Although these interventions have not yet been directly evaluated using 3D genome readouts, they highlight the clinical relevance of chromatin regulatory mechanisms implicated in neurodegeneration.

3.2 Remodeling of higher-order chromatin architecture: spatial regulatory basis of hematopoietic system aging

The aging of hematopoietic stem cells (HSCs) is accompanied by multi-layered remodeling of 3D chromatin architecture, including state transitions in A/B compartments, reduced insulation of TADs, chromatin loop disruptions, and heterochromatin relaxation. These alterations are associated with impaired enhancer–promoter coupling and destabilize transcriptional regulatory networks, correlating with lineage bias, particularly myeloid skewing, and impaired immune functions [43, 62].

Inflammatory signaling plays a significant role in driving chromatin architectural changes in HSCs. For instance, inflammation induces TAD relaxation and expansion of active compartments, upregulating myeloid-specific genes such as *Cebpa*. This process is coupled with the loss of heterochromatin marks, such as H3K9me3 and Heterochromatin Protein 1α, leading to transposon activation and aberrant immune responses [63]. Additionally, mutations in clonal hematopoiesis-related genes, such as *TET2* and *DNMT3A*, alter chromatin accessibility and potentially impact higher-order chromatin organization, thereby contributing to pre-leukemic conditions in elderly populations [64, 65].

Beyond aging, abnormal remodeling of 3D chromatin architecture is closely associated with hematologic malignancies. For example, in T-cell acute lymphoblastic leukemia (T-ALL), chromatin loop reorganization drives aberrant activation of *HOXA13*, a key mechanism underlying spatial reprogramming in malignancies [66]. During B cell aging, the 3D genome undergoes pronounced remodeling, including rearrangement of enhancer–promoter interactions, TAD boundary disruption or fusion, A/B compartment switching, and loop restructuring, which may reduce BCR diversity and impair antigen recognition. In B cell malignancies, these 3D genome alterations are tumor-specific; in multiple myeloma plasma cells, they manifest as CNV breakpoints overlapping TAD boundaries, increased TAD number with smaller average size, ~20% genome-wide A/B compartment switching, and promoter–enhancer loop reorganization. These observations suggest that age-associated 3D genome fragility may facilitate structural variations invading regulatory boundaries, thereby promoting malignant transformation of B cells or plasma cells [43, 67, 68]. In summary, the abnormal remodeling of higher-order chromatin structure in HSC aging and related diseases disrupts gene regulatory programs and hematopoietic lineage stability. Unraveling the molecular mechanisms underlying this 3D genome reorganization will provide new insights into the aging of the hematopoietic system and structural bases for targeted therapeutic interventions.

Chromatin regulatory abnormalities in the aging hematopoietic system have already been successfully exploited therapeutically. DNA methyltransferase inhibitors and histone deacetylase inhibitors constitute standard-of-care or approved treatments in myelodysplastic syndromes and hematological malignancies, demonstrating that epigenetic reprogramming can yield tangible clinical benefit [69–72]. In addition, selective *EZH2* inhibitors and emerging BET or *CDK9* inhibitors target enhancer- and Polycomb-dependent transcriptional programs that are frequently reinforced during clonal expansion and disease progression [73–75]. These advances underscore the direct clinical relevance of chromatin remodeling pathways implicated in hematopoietic aging.

3.3 Mechanisms of chromatin architectural variations driving cancer: 3D genome reprogramming in the context of aging

Emerging evidence indicates that certain cells can escape OIS and re-enter the cell cycle, a process closely linked to 3D chromatin remodeling. In particular, alterations in chromatin loops can rewire enhancer–promoter interactions to reactivate proliferation-associated genes, thereby promoting malignant progression. This suggests that 3D genome remodeling may serve as a mechanistic bridge between cellular senescence escape and tumor initiation, highlighting a potential aging-associated risk for cancer development [76–79].

The reprogramming of A/B compartments is one of the most prevalent alterations in the 3D genome of cancers. Inflammatory microenvironmental stimuli can relocate chromatin from transcriptionally repressive B compartments to transcriptionally active A compartments, associated with aberrant activation of oncogenes such as *CHI3L2* [80]. This

process is often accompanied by alterations in epigenetic modifications, such as the removal of the H3K27me3 mark and the remodeling of epigenetic landscapes at specific genomic integration or structural rearrangement sites, resulting in the reprogramming of tumor-associated transcriptional networks [78, 79, 81, 82].

Further, the disruption of TAD structures exacerbates spatial disorganization of genomic regulation. Under tumorigenic conditions, the weakening or rearrangement of TAD boundaries compromises enhancer–promoter insulation, leading to the formation of "neo-TADs." Structural variants (SVs), such as chromosomal deletions and inversions, are key drivers of TAD instability. For example, in pancreatic cancer and multiple myeloma, chromosomal alterations disrupt original TAD boundaries, enabling oncogenes such as *MYC* and *EGFR* to interact with non-native enhancers, driving rapid tumor cell proliferation [79, 81].

Aberrant chromatin loop remodeling is another critical mechanism promoting cancer. Enhancer hijacking is a hallmark of such loop disruptions. When chromatin anchor factors such as CTCF or STAG2 are mutated or depleted, non-target genes like *IRF9* and *SOX9* gain aberrant enhancer-mediated activation, initiating immune evasion or metastasis-associated transcriptional programs [83, 84]. Additionally, imbalances in transcriptional condensate phase separation intensify transcriptional loop strength, amplifying proto-oncogene expression [85].

Inflammatory responses and epigenetic imbalances cooperatively contribute to the accumulation of 3D genome variations, synergizing with progressive chromatin remodeling in pre-cancerous states. For instance, telomere dysfunction exacerbates TAD boundary deterioration and chromosomal abnormalities while interacting with inflammatory signaling pathways to accelerate tumor initiation. These structural reprogramming events not only elucidate the origin of cancers but also provide critical insights for cancer risk assessment, early detection, and the development of targeted therapeutic strategies [82].

In cancer, widespread reorganization of higher-order chromatin structure provides multiple actionable therapeutic entry points. Beyond conventional DNA methyltransferase and histone deacetylase inhibitors, drugs targeting enhancer-driven transcription, including BET bromodomain and CDK7/9 inhibitors, have shown activity in tumors exhibiting transcriptional addiction [86–89]. Selective inhibitors of chromatin modifiers such as EZH2 or DOT1L further illustrate how spatially reinforced regulatory programs can betherapeutically disrupted in genetically defined contexts [73, 90]. Together, these strategies highlight how aberrant chromatin architecture and enhancer wiring can be translated into clinically actionable vulnerabilities.

3.4 Alterations in higher-order chromatin architecture in aging-related diseases

Beyond the nervous system, hematopoietic system, and cancer, abnormal remodeling of 3D chromatin architecture also plays a critical role in numerous aging-related diseases. These changes disrupt the spatial regulatory networks of key genes, accelerating tissue functional decline and pathological progression.

In skeletal muscle aging and sarcopenia, satellite cells exhibit significant remodeling of higher-order chromatin structure, including redistribution of A/B compartments, weakened insulation of TAD boundaries, and loss of enhancer–promoter loops. Such changes impair critical transcriptional regulatory networks that govern muscle stem cell regeneration, leading to compromised muscle repair and the onset of age-related sarcopenia [38].

In COPD and lung aging, disease-associated alterations in distal enhancer–promoter interactions have been linked to persistent transcriptional dysregulation of inflammation-related genes, providing a spatial regulatory context for airway epithelial dysfunction in COPD [91]. Large-scale A/B compartment reorganization may also occur in aging lung tissue, potentially contributing to altered transcriptional programs, although direct evidence in human COPD samples remains limited. These findings highlight the epigenetic mechanisms underlying lung aging and COPD progression.

In osteoarthritis, chondrocytes experience significant 3D genome remodeling. Hi-C analysis reveals altered enhancer–promoter interactions at disease-related loci, promoting the activation of matrix degradation pathways and inflammatory mediators, which are central to cartilage degeneration and joint inflammation [92].

In metabolic diseases, the disorganized chromatin architecture of pancreatic islet β cells is closely linked to type 2 diabetes (T2D). In the context of metabolic disease, disruption of long-range enhancer–promoter interactions in pancreatic islet β cells affects the coordinated regulation of genes involved in insulin secretion and β-cell identity, offering a structural framework for understanding dysregulated glucose homeostasis in T2D [93].

Collectively, organs such as skeletal muscles, lungs, cartilage, and pancreatic islets all exhibit systemic remodeling of their 3D genome during aging and related diseases Table 1. These changes disrupt spatial regulatory chromatin networks, triggering pathological gene expression programs and offering critical insights into the molecular mechanisms underlying multi-organ system aging.

In other aging-associated disorders, including chronic inflammatory and metabolic diseases, epigenetic and senescence-modulating strategies are being actively explored. Senolytic and senomorphic interventions, as well as JAK inhibition and NAD^+-boosting approaches, have entered early-stage clinical studies and have been shown to attenuate inflammation and tissue dysfunction [14, 94–97]. Although these strategies have not been explicitly linked to higher-order chromatin architecture, they likely intersect with enhancer-driven inflammatory transcriptional programs characteristic of aged tissues. Such observations support the translational relevance of chromatin remodeling in a broader spectrum of age-related diseases.

4 Advancing 3D genomics: progress, challenges, and prospects

We systematically reviewed the dynamic remodeling of higher-order chromatin architecture during aging and its underlying mechanisms. Cellular senescence is accompanied by marked changes across multiple layers of chromatin organization, including the detachment and relaxation of peripheral

Table 1 Higher-order chromatin architecture changes in aging and age-associated diseases

Disease/System	Major cell type	Key 3D genome alterations	Research level	Structural level keywords	References
Alzheimer's disease	Neurons	Large-scale A/B compartment switching, H3K27ac abnormalities, AD-risk SNPs (BIN1, PICALM) disrupt enhancer–promoter loops, affecting neuronal gene expression	Human brain tissue	Compartment switching; loop abnormalities	[54, 55]
Microglial aging/neurodegenerative diseases	Microglia	Compartment reprogramming and enhancer repositioning at loci such as APOE, driving a neurotoxic transcriptional state	Mouse/human samples	Compartment switching; enhancer repositioning	[56]
Age-related cognitive decline	Neurons	Accumulation of DNA damage and reduced plasticity of activity-dependent chromatin loops, perturbing synaptic gene networks	Mouse/human samples	Loop abnormalities; TAD weakening	[57, 98]
HSC aging	Hematopoietic stem cells	A/B compartment switching, reduced TAD insulation, chromatin loop remodeling, heterochromatin relaxation, associated with lineage bias (myeloid skewing)	Mouse/human samples	Compartment switching; TAD weakening; loop remodeling	[43, 62]
HSC aging+inflammation	Hematopoietic stem cells	Inflammation induces TAD relaxation and expansion of active compartments, upregulating myeloid-specific genes such as *Cebpa*, accompanied by H3K9me3/HP1α loss	Mouse models	TAD weakening; active compartment expansion	[63]
HSC aging+clonal hematopoiesis	Hematopoietic stem cells	TET2/DNMT3A mutations associated with altered chromatin accessibility and higher-order chromatin organization, increasing pre-leukemic risk	Human/mouse models	Chromatin accessibility; higher-order chromatin disorganization	[64, 65]
B cell aging	B cells	Enhancer–promoter rewiring, TAD boundary disruption/fusion, A/B compartment switching, associated with impaired immune function	Human/mouse samples	Compartment switching; TAD boundary disruption; loop remodeling	[43, 67]
Multiple myeloma	Plasma cells	CNV breakpoints enriched at TAD boundaries, increased TAD number with smaller size, widespread A/B compartment switching, and loop reorganization	Human samples	TAD boundary disruption; compartment switching; loop remodeling	[43, 68]
Pancreatic cancer/multiple myeloma	Tumor cells	Structural variants disrupt original TAD boundaries, enabling oncogenes such as MYC and EGFR to interact with non-native enhancers	Human/mouse models	TAD boundary disruption; enhancer hijacking	[79, 81]
Melanoma/breast cancer	Tumor cells	STAG2/CTCF dysfunction triggers chromatin loop remodeling, activating non-target genes such as *IRF9* and *SOX9*	Human/cell lines	Loop remodeling; enhancer hijacking	[83, 84]
Prostate cancer	Tumor cells	Imbalances in transcriptional condensate phase separation enhance loop strength, amplifying proto-oncogene expression	Human/cell lines	Loop strengthening; phase separation	[85]
Skeletal muscle aging/sarcopenia	Muscle satellite cells	Redistribution of A/B compartments, weakened TAD insulation, loss of enhancer–promoter loops, impairing stem cell regenerative capacity	Mouse/human samples	Compartment switching; TAD weakening; loop loss	[38]
Chronic obstructive pulmonary disease (COPD)/lung aging	Lung epithelial cells	Distal enhancer–promoter loop dysregulation associated with persistent inflammation; potential A/B compartment reorganization in aging lung tissue	Human samples	Enhancer–promoter loop abnormalities; compartment switching (putative)	[91]
Osteoarthritis (OA)	Chondrocytes	Disease-associated loci show altered enhancer–promoter interactions, promoting activation of matrix degradation and inflammatory pathways	Human samples	Enhancer–promoter rewiring	[92]
Type 2 diabetes (T2D)	Pancreatic β cells	Disruption of long-range enhancer–promoter interactions, impairing coordinated regulation of insulin secretion genes	Human samples	Enhancer–promoter loop abnormalities	[93]

heterochromatin due to nuclear lamina disassembly, reconfiguration of A/B compartments, weakened insulation of TADs boundaries, and the disruption or aberrant formation of chromatin loops. Similar patterns of 3D genome reorganization are also observed in primary cells undergoing chronological aging *in vivo* [38, 43, 56]. These alterations in 3D genome architecture are not merely markers of aging but may act as active contribute of hallmark aging phenotypes, including dysregulated gene expression, increased genomic instability, stem cell exhaustion, and chronic inflammation.

Studies have shown that aging-associated 3D genome remodeling exhibits significant heterogeneity across different tissues and cell types. For instance, the reorganization of A/B compartments exhibits opposite directions in OIS versus replicative senescence (RS), suggesting that different aging triggers may lead to distinct epigenetic endpoints. Similarly, widespread compartment switching and TAD boundary collapse have been implicated in the progression of AD, while the remodeling of the 3D genome in hematopoietic stem cells (HSCs) disrupts regulatory networks, enhances myeloid differentiation bias (e.g., upregulation of *Cebpa* expression), and diminishes lymphoid differentiation and immune

function during aging. In cancer, structural variations (SVs) contribute to oncogene activation through enhancer hijacking, further accelerating tumor progression. These findings underscore the critical role of 3D genome remodeling in both aging and the pathogenesis of aging-related diseases.

In recent years, advances in 3D genome technologies have provided valuable tools for understanding the dynamic chromatin changes underlying aging and disease. Since the first high-resolution 3D genome map was generated in 2014 [23], studies have revealed the hierarchical roles of chromatin loops, TADs, and A/B compartments in gene regulation, significantly advancing our understanding of genomic regulatory networks. However, several important challenges remain in this field. One major limitation is that most current studies rely on bulk-sequencing data, which can reveal overall patterns but fail to resolve cellular heterogeneity and subpopulation-specific regulatory mechanisms in complex tissues. Another obstacle is that most existing datasets do not capture the temporal dynamics of chromatin architecture, thereby limiting our ability to establish causal links between structural remodeling and functional outcomes. A further challenge lies in data integration: although early attempts have combined 3D genome information with transcriptomics, epigenomics, or metabolomics, true multi-omics integration at single-cell resolution remains in its infancy and requires significant methodological advances.

At the methodological level, many of the above challenges arise from intrinsic limitations of current chromatin conformation capture technologies. Hi-C–based approaches suffer from high background noise and strong distance-dependent interaction biases, complicating robust detection of chromatin loops and subtle TAD boundary changes, particularly in heterogeneous aging tissues [98]. Loop calling and domain identification are highly sensitive to sequencing depth, normalization strategies, and computational pipelines, often leading to inconsistent results across studies [98–100]. Bulk Hi-C further masks rare or transient cell subpopulations, which may disproportionately contribute to aging phenotypes or disease initiation [99, 101]. Moreover, most 3D genome assays rely on fixed cells, resulting in loss of spatial continuity and precluding direct observation of real-time chromatin dynamics during senescence or aging progression [102]. Together, these technical constraints limit causal inference between chromatin architecture and functional outcomes, underscoring the need for single-cell, spatially resolved, and dynamic 3D genomics approaches in future aging research.

To address these challenges, future advances in 3D genome research must prioritize single-cell resolution and spatiotemporal dynamics. Techniques such as single-cell Hi-C and single-cell methylation sequencing could help uncover the 3D chromatin features of distinct cell subpopulations in complex tissues [99–101], elucidating cell-type-specific regulatory mechanisms, while dynamic imaging technologies could provide real-time insights into the role of chromatin folding states in response to stimuli or cell fate transitions [102]. Additionally, establishing robust multi-omics integration frameworks by combining single-cell 3D genome data with transcriptomic, epigenomic, and proteomic information may further elucidate the multi-layered impacts of higher-order chromatin structure on functional regulatory networks [98]. These advances are expected to shed light on the role of 3D genome architecture in aging and disease mechanisms, facilitating the identification of biomarkers and therapeutic targets for precision intervention.

Looking forward, the integration of single-cell technologies with dynamic 3D genome mapping may enable the construction of systematic spatiotemporal models of chromatin evolution during aging. This approach could not only help delineate causal relationships between chromatin remodeling and aging or disease phenotypes but also advance 3D genomics from theoretical studies to clinical applications, offering novel strategies for aging intervention, cancer therapy, and the prevention of complex diseases.

Author contributions

Z.J., and Z.C. contributed to the concept generation. W.C., Q.Z., and F.X. completed the literature searching and manuscript writing. W.C. contributed to figure preparation. All authors read and approved the final manuscript.

Funding

This work was supported by the National Key R&D Program of China (Nos. 2021YFA1100103 and 2024YFA0918701), the National Natural Science Foundation of China (Nos. 82230047, 82030039, and 32341004), the innovation team project of universities in Guangdong province (No. 2023KCXTD004).

Conflict of interests

The authors declare no competing interests.

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