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The interplay of epigenetic remodelling and transposon-mediated genomic instability in ageing and longevity

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Ageing and age-related diseases are the result of complex biological processes that progressively cause deterioration of cellular and tissue function. Among the key hallmarks of ageing are epigenetic alterations and genomic instability, both of which are closely interconnected and significantly contribute to the ageing process. The epigenome, encompassing both DNA and histone modifications, regulates gene expression and maintains genomic integrity throughout life. With age, these regulatory systems become dysregulated, leading to genome-wide changes in chromatin structure, histone modifications and the reactivation of transposable elements (TEs). TEs, typically silenced in heterochromatic regions, become active in aged cells, contributing to genomic instability, mutagenesis, inflammation and metabolic disruption. Despite their significant implications, the role of TEs in the ageing process remains underexplored, and the interplay between epigenomic remodelling and TE activity remains poorly understood. In this review, we explore the molecular mechanisms underlying epigenetic alterations and TE reactivation during ageing, the impact of these changes on genomic stability and the potential therapeutic interventions targeting this interplay. By deciphering the role of epigenetic modifications and TE derepression in the ageing process, we aim to highlight novel avenues for anti-ageing and pro-longevity strategies.

1. Introduction

Embedded within every cell is a vast network of complex processes that sustain proper functionality. As cells age, these processes falter, leading to a progressive loss of integrity, functional impairments and ultimately, cell death [1]. Ageing is a primary driver of disease, serving as the leading risk factor for chronic conditions such as cardiovascular disease, cancer, neurodegeneration and diabetes due to its pervasive impact on cellular and molecular systems [1–3]. Nearly all living organisms are impacted by ageing, a complex process that can be categorized into 12 distinct hallmarks [4]. Among the hallmarks of ageing, two key features that stand out are epigenetic alterations and genomic instability. Epigenetic alterations, including both DNA methylation (DNAme) and histone modifications, play a crucial role in regulating gene expression and maintaining genomic stability throughout life by orchestrating proper gene expression or repression in the epigenome. Over time, epigenetic alterations can lose their proper function which can disrupt gene expression and genomic stability, contributing to ageing and age-related diseases [1,4].

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Age-related genome instability manifests through DNA damage, accumulation of mutations and other key factors like activation of transposable elements (TEs).

TEs, often referred to as 'jumping genes', are mobile genetic elements capable of moving within the genome [5]. While tightly regulated in young, healthy cells, the ageing process disrupts the chromatin landscape, leading to its reactivation [6]. This reactivation can disrupt essential gene functions, compromise genomic stability and promote antiviral responses [6–8]. TEs constitute approximately 46% of the human genome, in contrast to the approximately 2–3% of the genome that encodes proteins [5]. TEs are classified into two major groups based on their mode of transposition: DNA-mediated transposons (Class II) and RNA-mediated transposons (Class I) [7]. DNA transposons move using a 'cut and paste' mechanism, excising themselves from one location and inserting into another location. In contrast, RNA transposons, also called retrotransposons, move via a 'copy and paste' mechanism [7], transcribing their genomic sequence into an mRNA intermediate, which is then reverse-transcribed into DNA and inserted at a new genomic site. RNA-mediated transposons are further classified into long terminal repeats (LTR) and non-long terminal repeats (non-LTR) [7]. This review heavily focuses on non-LTR elements as they are considerably more abundant and still remain active in humans. This retrotransposition process resembles viral replication and can drive immune responses when TE-derived fragments are detected within the cell [7]. Despite representing significant proportions of eukaryotic genomes (up to 85%; [7]), TEs were historically dismissed as 'junk DNA' due to their repetitive sequences, which were erroneously thought to lack functional importance [5]. More recently, they were rebranded as 'genome invaders' [5], and while their role in diseases has been observed, the underlying mechanisms are poorly understood. Moreover, emerging research suggests that their presence and activity may be required for some physiological processes (e.g. long-term memory consolidation, senescence maintenance, etc. [8]). To this day, it is unclear if TE activation is a mere by-product of the ageing process or if it may in itself drive aspects of ageing. The relationship is likely not mutually exclusive, as the answer is likely more complex, influenced by a combination of environmental, genetic and other factors.

In this review, we delve into the dynamic changes in the epigenome with ageing and relate them to mechanisms underlying TE regulation and reactivation. By exploring modern insights and emerging strategies, we illuminate the critical role of TEs in ageing and their potential as therapeutic targets.

2. Ageing leads to widespread changes in the epigenomic landscape

As highlighted above, the epigenome is loosely defined as the collection of DNA and histone modifications that modulate chromatin structure to regulate genomic architecture and transcription [9–11]. Normal 'healthy' function and levels of epigenetic modifications promote genomic stability, while age-related changes are thought to lead to genomic dysregulation to hallmarks of age and disease such as mutation [12] and cellular senescence [13]. In this section, we discuss age-associated widespread changes in chromatin structure, DNA and histone modifications, histone levels, histone variants and epigenetic-modifying enzymes (table 1).

2.1. Global chromatin structure changes associated with ageing

Chromatin is generally thought to exist in two compartments: (i) euchromatin, which has a loosely packed structure permissive to transcription, and (ii) heterochromatin, which is more compact and restrictive to transcription, where most repetitive sequences at TEs are found in young healthy cells [6,9]. Ageing disrupts chromatin homeostasis, leading to loss of heterochromatin, aberrant expansion of euchromatin and increased genomic exposure to mutational risks (figure 1) [9,55–59]. In addition to normal ageing, progeroid syndromes such as Werner syndrome (WS) or Hutchinson–Gilford progeria syndrome (HGPS) also lead to genomic instability and heterochromatin loss [35,60,61]. Thus, these observations highlight the connection between ageing and changes in chromatin organization, as the loss of heterochromatin is seen in both premature and normal ageing. Single-cell epigenome analyses reveal tissue-specific variability in chromatin accessibility changes, with excitatory neurons particularly prone to heterochromatin loss [62]. Contrastingly, emerging evidence suggests that excessive heterochromatin compaction in some contexts may suppress critical gene expression and contribute to cellular senescence [62].

Importantly, chromatin structure is maintained by endogenous and exogenous mechanisms that typically make modifications to the histones or DNA itself that signal condensation or uncoiling of the genome [11]. With age, the efficacy of chromatin maintenance mechanisms is altered in ways that cause changes in chromatin structure [6]. Recent studies suggest that there is variability in how different cells and tissues express epigenetic changes. Advances in chromatin profiling techniques have revealed both global and local changes in chromatin architecture during ageing. Global analyses, such as mass spectrometry, have demonstrated distinct organ-specific ageing profiles in chromatin composition [63]. In contrast, local chromatin remodelling events, identified through assays like ATAC-seq, have shown increased promoter accessibility in ageing liver tissue without corresponding increases in transcriptional output [64]. This indicates that when looking at chromatin structure changes, there is nuance and details between various tissues and cell types that a broad global approach may overlook (in contrast to a more detailed locus-specific approach).

2.2. DNA modifications change with ageing

DNA modifications, of which CpG DNAme is the best studied, play a crucial role in regulating gene expression and repression, which is essential for maintaining cellular function and genomic stability [65].

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Table 1. Different types of epigenetic modifications and reported changes with ageing/cell senescence. 5hmC, 5-hydroxymethylcytosine; 5mC, 5-methylcytosine; *C. elegans*, *Caenorhabditis elegans*; ChIP–chip, chromatin immunoprecipitation followed by microarray hybridization; ChIP–seq, chromatin immunoprecipitation followed by sequencing; *D. melanogaster*, *Drosophila melanogaster*; H3K9me, histone 3 Lys 9 monomethylation; H3K56ac, histone 3 Lys 56 acetylation; hMSC, human mesenchymal stem cells; *H. sapiens*, *Homo sapiens*; HP1, heterochromatin protein 1; HSCs, haematopoietic stem cells; LINEs, long interspersed nuclear elements; mHSC, murine haematopoietic cells; *M. musculus*, *Mus musculus*; MSCs, mesenchymal stem cells; *N. furzeri*, *Nothobranchius furzeri*; NSC, neural stem cell; *S. cerevisiae*, *Saccharomyces cerevisiae*; SILAC–MS, stable isotope labelling by amino acids in cell culture followed by mass spectrometry

epigenetic mark	functional role	ageing paradigm	change in epigenetic mark with ageing	change observed in tissue or cells	method of detection	species	references
5mC	transcriptional repression	cellular senescence	decrease	senescent SVts8 cells	gene expression, DNAme microarrays	*H. sapiens*	[14,15]
		organismal	increase	muscle	western blot	*N. furzeri*	[16]
		organismal	increase (LINEs), local decreases and rare local increases	sperm	pyrosequencing (LINEs) bead chip arrays	*H. sapiens*	[17]
5hmC	transcriptional repression (despite presence in transcriptionally active regions)	organismal	minor increase, dependent on tissue type	brain (cortex, cerebellum, hippocampus), heart, lung, liver, spleen, kidney and muscle	nano liquid chromatography tandem mass spectrometry (nLC-MS/MS)	*M. musculus*	[18]
		cellular senescence	increase	fibroblasts	dot blotting	*H. sapiens*	[18]
histone H1	core chromatin component	cellular senescence	decrease	fibroblasts	immunostaining	*H. sapiens*	[19]
histone H2A	core chromatin component	cellular (senescence)	decrease	fibroblasts	western blot	*H. sapiens*	[20]
		organismal (replicative lifespan)	decrease	yeast cells	western blot	*S. cerevisiae*	[21,22]
histone H2A.J	core chromatin component variant	cellular senescence	increase	epidermal cells	immunofluorescence microscopy	*H. sapiens*	[23,24]
		cellular senescence	increase	fibroblasts	western blot	*H. sapiens*	[24]
histone H2A.X	core chromatin component variant	cellular senescence	increase	fetal lung fibroblasts, epidermal fibroblasts	immunofluorescence staining	*H. sapiens*	[25]
histone H2A.Z	core chromatin component variant	organismal	increase	skeletal muscle	immunofluorescence staining	*M. musculus*	[26,27]
		organismal	increase	hippocampus	immunoprecipitation	*M. musculus*	[27]
histone H2B	core chromatin component	cellular (senescence)	decrease	fibroblasts	western blot	*H. sapiens*	[28]
H3	core chromatin component	cellular (senescence)	decrease	fibroblasts	western blot	*H. sapiens*	[28]
		organismal	local change in occupancy	heart, liver, cerebellum, olfactory bulb, primary NSC cultures	western blot	*M. musculus*	[29]
		organismal (replicative lifespan)	decrease	yeast cells	western blot	*S. cerevisiae*	[21,30]
H3.3	core chromatin component variant	organismal	increase	muscle	western blot, ChIP	*M. musculus*	[31,32]

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Table 1. (*Continued.*)

epigenetic mark	functional role	ageing paradigm	change in epigenetic mark with ageing	change observed in tissue or cells	method of detection	species	references
		organismal	increase increase decrease	liver, kidney, brain, heart hepatocytes (primary) hepatocarcinoma	quantitative mass spectrometry	*M. musculus* *H. sapiens* *H. sapiens*	[32]
H4	core chromatin component	cellular (senescence)	decrease	fibroblasts	western blot, SILAC–MS	*H. sapiens*	[28,33]
HP1	component of heterochromatin	organismal	remodelling	head, gut, fat cells	immunostaining ChIP–chip	*D. melanogaster*	[34]
HP1a	component of heterochromatin	organismal (HGPS and WS)	decrease	fibroblasts and MSCs	immunostaining, western blot	*H. sapiens*	[35]
HP1b	component of heterochromatin	cellular (senescence)	increase	fibroblasts	immunostaining, western blot	*H. sapiens*	[36]
macroH2A	component of heterochromatin	cellular (senescence)	increase, relocalization (21)	fibroblasts	immunostaining, western blot SA-β-Gal staining, fluorescence microscopy, immunoblotting	*H. sapiens*	[36,37]
		organismal	increase	lung, liver	immunostaining, western blot	*M. musculus*	[36]
		organismal	increase	liver	immunostaining, X-gal staining, western blot	*H. sapiens* *M. musculus*	[38]
HP1g	component of heterochromatin	organismal	decrease	brain	immunohistochemistry, western blot	*M.musculus*	[39]
		organismal (HGPS)	decrease	fibroblasts	immunostaining	*H. sapiens*	[40,41]
		organismal	decrease	fibroblasts	immunostaining	*H. sapiens*	[41]
H3K9me1	enriched in euchromatin along gene bodies, involved in transcriptional repression	cellular (senescence)	increase	fibroblasts	western blot, SILAC–MS	*H. sapiens*	[40]
H3K9me2	enriched along gene bodies, involved in transcriptional repression	organismal	decrease	whole male flies	western blot	*D. melanogaster*	[42]
		organismal	decrease	lung cell	flow cytometry, tissue histology	*M. musculus*	[43]
		cellular (senescence)	decrease	fibroblasts	western blot, SILAC–MS	*H. sapiens*	[33]
H3K9me3	enriched in heterochromatin regions, involved in transcriptional silencing	organismal	increase, remodelling	head	western blot ChIP–chip	*D. melanogaster*	[34]
		organismal	increase	muscle	western blot	*N. furzeri*	[16]

(*Continued.*)

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Table 1. (*Continued.*)

epigenetic mark	functional role	ageing paradigm	change in epigenetic mark with ageing	change observed in tissue or cells	method of detection	species	references
		organismal (HGPS and WS)	decrease	fibroblasts and MSCs	immunostaining, western blot, ChIP–seq	*H. sapiens*	[39,44]
		cellular (senescence)	decrease	fibroblasts	western blot, SILAC–MS	*H. sapiens*	[33]
H3K27me3	enriched in euchromatin along gene bodies, involved in transcriptional repression	organismal	increase	muscle	western blot, ChIP	*D. melanogaster*	[45]
		organismal	no change	HSC	ChIP–seq	*M. musculus*	[46]
		organismal (HGPS and WS)	decrease, remodelling	fibroblasts and MSCs	immunostaining, ChIP–seq	*H. sapiens*	[35]
		organismal	increase	muscle	western blot, confocal microscopy (CM)	*N. furzeri*	[16]
H4K20me2	DNA repair and genomic stability	cellular (senescence)	increase	fibroblasts	western blot, SILAC–MS	*H. sapiens*	[33]
H4K20me3	enriched in pericentric heterochromatin	organismal	increase	muscle	western blot	*N. furzeri*	[16]
		cellular (senescence)	increase	fibroblast	western blot	*H. sapiens*	[47]
H3K4me2	enriched in euchromatin along gene body, involved in transcriptional activation	organismal	global increase, remodelling	cortex	ChIP–seq	*M. mulatta*	[48]
		organismal	increase	brain	western blot	*M. musculus*	[49]
H3K4me3	enriched in euchromatin at promoters, involved in transcriptional activation	organismal	increase	HSC	ChIP–seq	*M. musculus*	[46]
		organismal (HGPS and WS)	no global change	fibroblasts and MSCs	ChIP–seq	*H. sapiens*	[35]
		organismal	decrease, remodelling	head	ChIP–chip	*D. melanogaster*	[34]
H3K36me3	enriched in euchromatin along gene body, involved in transcriptional elongation	organismal	no global change	somatic cells	ChIP, ChIP–seq	*C. elegans*	[50]
		organismal	decrease	mHSC NSC, hMSC	ChIP–seq	*M. musculus* *H. sapiens*	[51]
H3K9ac	DNA transcription elongation, connected to promoters	organismal	decrease	muscle	western blot, confocal microscopy (CM)	*N. furzeri*	[16]

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Table 1. (*Continued.*)

epigenetic mark	functional role	ageing paradigm	change in epigenetic mark with ageing	change observed in tissue or cells	method of detection	species	references
H3K56ac	DNA replication, DNA damage response and nucleosome assembly	organismal	no change	brain	western blot	*M. musculus*	[49]
H4K16ac	enriched in heterochromatin along gene body, regulation of telomere silencing and chromatin compaction (?)	organismal	decrease	muscle	western blot	*N. furzeri*	[16]
		organismal	no change	brain	western blot	*M. musculus*	[49]
		cellular (senescence)	decrease	fibroblast	western blot	*H. sapiens*	[52]
H4K12ac	enriched in euchromatin along gene body, involved in transcriptional elongation	organismal	decrease	head	western blot	*D. melanogaster*	[53]
		organismal	decrease upon contextual fear conditioning	hippocampus	western blot	*M. musculus*	[54]

'?' indicates that the functional role of the epigenetic mark is unclear.

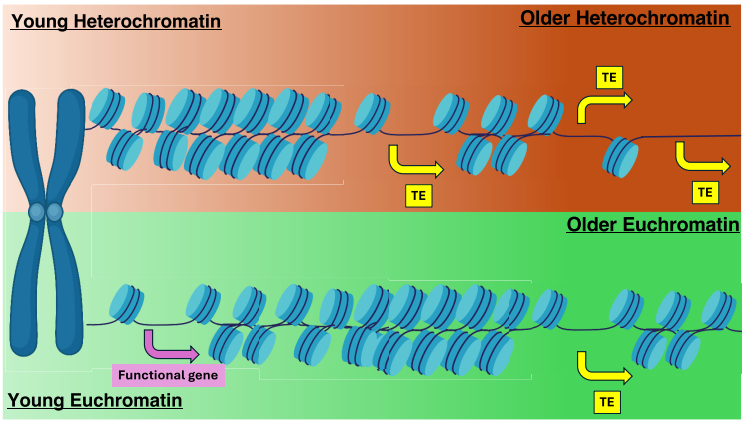


Figure 1. Schematic of transcription regulation in euchromatin/heterochromatin and overall changes with ageing. Top (brown), heterochromatin from young individuals is represented as tightly packed nucleosomes (blue discs), which effectively repress TE activity. In older individuals, heterochromatin becomes less compact, as shown by the loosening of nucleosome packing. This relaxation allows TEs to become transcriptionally active, indicated by yellow arrows emerging from TE regions. Bottom (green), euchromatin from young individuals is shown as a moderately open structure that permits functional gene transcription (purple arrow). In older individuals, the further relaxation of euchromatin facilitates additional TE activation, as represented by the yellow arrows. This increased TE activity disrupts the chromatin environment, potentially interfering with functional gene expression.

Ageing is associated with DNA hypomethylation (i.e. a reduction in overall DNAme levels), alongside localized hypermethylation, where specific gene regions become excessively methylated [62,66]. These epigenetic changes can disrupt the expression of genes involved in critical cellular processes like growth, differentiation and apoptosis, thereby contributing to the ageing process and increasing the risk of developing age-related diseases [55,56]. Understanding these methylation changes is essential for elucidating the mechanisms of ageing and developing strategies to maintain genomic integrity and function as organisms age. Research has demonstrated that global DNAme levels, measuring levels of 5-methylcytosine (5mC), show a significant negative correlation with age in certain tissues such as liver and muscle [56,67]. Age-dependent methylation patterns have demonstrated the ability to suppress transcription activity by recruiting proteins that promote gene repression or by preventing the binding of transcription factors to DNA, thereby silencing specific genes [56,67]. Through these mechanisms, DNAme contributes to the precise regulation of gene expression, ensuring that genes are expressed at appropriate levels and times.

A study using an ageing haematopoietic stem and progenitor cell (HSPC) model demonstrated a global loss of DNAme during ageing [68]. Through whole-genome bisulfite sequencing, Hong *et al.* revealed that both wild-type (WT) and *Tet2*-deficient (*Tet2KO*) HSPCs experienced reduced DNAme with age [68]. This reduction was particularly evident in H3K9me3-marked regions, which are known as differentially methylated regions. The study found distinct differences in DNAme between young and old HSPCs, with more pronounced changes occurring in heterochromatin compared to euchromatin. These findings suggest that DNAme deregulation within heterochromatin may disrupt the activity of epigenetic-modifying enzymes. Specifically, the study observed *Tet2*-mediated spatial relocalization of H3K9me3-positive regions, a topic that will be explored in greater detail in a subsequent section (table 1).

Intriguingly, the reproducible nature of DNAme changes with ageing has led to the development of high-performance 'ageing clocks', for both chronological and biological age [69,70]. Early models, like Horvath's clock, predicted chronological age across tissues, while second generations, such as PhenoAge and GrimAge, integrated health indicators and mortality risk factors for more accurate lifespan and healthspan predictions [69]. DunedinPACE, a third-generation clock, measures the pace of biological ageing (considering factors like obesity) along with the other measurements of first and second generation [71]. These clocks have shown promise in ageing research but face challenges, including tissue specificity, environmental variability and the need to establish causality between methylation changes and ageing [70]. The link between DNAme and ageing is well-established in humans, especially in whole blood samples [57,60] and to some extent in adipose and brain tissue [62,66]. A notable example is the CpG sites near the *ELOVL2* gene, which show consistent age-related methylation changes across various tissues, including blood, human mesenchymal stem cells, teeth and other tissues [72]. Interestingly, this age-methylation relationship has also been observed in mouse tissue [73] and the African turquoise killifish (*Nothobranchius furzeri*), a novel vertebrate ageing model [56].

2.3. Histone protein levels, histone variants substitution and histone modifications are remodelled with ageing

Histones are essential proteins that help organize and compact DNA within the nucleus by wrapping around a histone octamer, thereby allowing for the structural regulation of the transcriptional activity of the genome [74]. The histone octamer consists of H2A, H2B, H3 and H4, which are the sites for modification that can change the conformation of chromatin structure by tightening or unwinding the DNA from the histone octamer [9,11,74,75]. H1 is a linker histone that stabilizes chromatin by binding to DNA sites, anchoring nucleosomes and promoting the formation of higher-order chromatin structures [74].

Histone levels change with age in a manner that is both histone-selective and tissue-specific [76], indicating that certain systems may be more susceptible to alterations in the genomic landscape, such as the loss of heterochromatin. For example, a study using human diploid fibroblast cell lines found significant reductions in specific histones like H3 and H4 with age, while

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histones such as H1, H2A and H2B remained relatively stable [33]. This suggests that not all histones are equally affected by ageing. Similarly, research on mice demonstrated that ageing led to a global reduction of histones H1, H2A, H2B, H3 and H4 in the retinal pigment epithelium and choroid, but these reductions were not observed in the neural retina [77]. Interestingly, the phenomenon of histone loss with ageing is not restricted to actively dividing cells. In studies involving quiescent muscle stem cells from young and aged mice, researchers observed similar declines in histone levels, including H1, H2B, H3 and H4. This finding indicates that histone loss due to ageing occurs even in non-dividing cells, suggesting a broad impact of ageing on cellular regulation [78]. The changes in histone levels and modifications are also evident in immune cells [79]. Transcriptome analyses have shown that activated naive $CD4^+$ T cells from older individuals exhibit a globally lower expression of core histone genes compared to those from younger individuals [79]. The study also confirmed a significant reduction in core histones such as H2A, H2B, H3 and H4 in proliferating old T cells, whereas no differences were observed in unstimulated naive T cells from both young and old adults [79]. This suggests that the changes in histone levels in T cells are proliferation dependent. Consistently, a study by Yang *et al.* demonstrated that ageing is accompanied by global chromatin alterations in the liver, including increased heterochromatinization and transcriptional suppression, which are reversible upon liver regeneration [80]. Similarly, Bochkis *et al.* reported that aged murine liver exhibits increased chromatin accessibility at promoter regions without corresponding increases in transcriptional output, indicating tissue-specific chromatin remodelling during ageing [81]. Lastly, Chen *et al.* observed no global H3 differences in the liver and cerebellum in mice without extensive remodelling [29]. These findings highlight tissue specificity in histone loss with ageing [77].

Post-translational modifications of histone proteins, most particularly the acetylation and methylation of lysine residues, are critical in understanding the ageing process. These modifications have been extensively studied, revealing age-related changes in the levels of key histone marks such as H3K9me3, H4K20me3, H3K27me3 and H3K9ac [82]. These epigenetic marks are known to influence chromatin structure and gene expression. For example, the trimethylation of histone H3 on lysine 9 is commonly associated with heterochromatin and transcriptional repression, whereas acetylation at the same residue (H3K9ac) is linked to active chromatin and transcriptional activation [9,83,84]. Alterations in these modifications during ageing could lead to changes in gene expression patterns that contribute to the ageing phenotype.

In addition to age-related changes in histone levels, current evidence points to alterations in histone modifications as well. In a 2021 study using the *Caenorhabditis elegans* model, Li *et al.* employed ChIP–seq to examine how the histone modifications H3K9me3 and H3K27me3 change with age. They discovered that while H3K9me3 levels increased in the heterochromatic regions of chromosome arms, they decreased in the euchromatic central regions of autosomes as the worms aged. H3K27me3 levels, on the other hand, remained relatively stable. Notably, H3K9me3 exhibited significant gains and losses at specific genomic sites in older worms, with new heterochromatin forming in gene-rich regions that had been marked by high levels of other histone modifications in young worms. This finding suggests that H3K9me3 gains during ageing are shaped by the histone landscape established in youth rather than occurring randomly. The study also identified 578 regions that gained H3K9me3 with age, termed ageing-specific repressive regions (ASRRs). These ASRRs were enriched with H3K9me3 but not H3K27me3, differing from heterochromatic regions formed earlier in development, which were marked by both modifications (table 2).

2.4. Regulation of epigenetic-modifying enzymes in ageing and longevity

Epigenetic-modifying enzymes play crucial roles in the regulation of ageing and longevity by modulating chemical modifications on DNA and histones. These modifications influence gene expression without altering the underlying DNA sequence, thereby contributing to cellular function and organismal health. Dysregulation of these enzymes during the ageing process can lead to significant changes in cellular function, contributing to the development of age-related diseases such as cancer, cardiovascular diseases and neurodegenerative disorders [165].

In vertebrates, DNAme typically involves the addition of a methyl group to the C5 position of cytosine bases within CpG dinucleotides, a process mediated by DNA methyl transferases (DNMTs). Conversely, enzymatic demethylation is primarily facilitated by the ten-eleven translocation (TET) family of enzymes, which play a significant role in the dynamic regulation of DNAme states. The African turquoise killifish study referenced earlier identified multiple genomic copies of the de novo DNAme subfamily, alongside other key epigenetic regulators such as UHRF1 (a DNMT1 recruitment factor) and members of the TET family (TET1, TET2 and TET3) [56]. These enzymes exhibit a ubiquitous tissue distribution in adult fish, with age-related downregulation observed in specific tissues such as the liver and muscle. This downregulation correlates with a significant decrease in global DNAme levels in these tissues, suggesting that the regulation of DNMTs and TET enzymes plays a pivotal role in the ageing process.

The loss of heterochromatin in the aged epigenome may also allow TET enzymes to function more freely, in addition to the previously mentioned downregulation of these enzymes. In their 2023 study, Hong *et al.* identified a connection between disrupted DNAme at partially methylated domains and the spatial relocalization of H3K9me3-marked heterochromatin [68]. This relocalization, driven by TET2 in aged or DNAme-deficient HSPCs, leads to the upregulation of endogenous retroviruses (ERVs) and interferon-stimulated genes, which contribute to the functional decline of aged HSPCs. Aged WT HSPCs (18–24 months) exhibited reduced self-renewal and repopulation capacities compared to younger WT HSPCs (6–8 weeks), but TET2 depletion in *Tet2KO* HSPCs rescued this decline. In healthy young cells, functional DNAme machinery prevents TET2 from accessing H3K9me3-marked heterochromatin. Although the young group may have still been influenced by developmental signals due to its extremely young age, this study highlights the interplay between DNMTs and TETs in maintaining DNAme homeostasis in heterochromatin and euchromatin throughout life. Loss of either enzyme disrupts this balance, leading to abnormal transcription, genomic instability and the functional decline of aged HSPCs.

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Table 2. Impact of chromatin modifiers on ageing and longevity. 5-mC, 5-methylcytosine; Asf1, anti-silencing function 1; Bre1, brefeldin A-sensitive 1; *C. elegans*, *Caenorhabditis elegans*; Chd1, chromatin organization modifier, helicase and DNA-binding domains 1; COMPASS, complex proteins associated with SET1; *D. melanogaster*, *Drosophila melanogaster*; E(z), Enhancer of zeste; HNHA, N-hydroxy-7-(2-naphthylthio)heptanomide; *H. sapiens*, *Homo sapiens*; HIR, histone regulation; ISWI, imitation switch; JMJD-2, Jumonji domain protein 2; LET-418, lethal protein 418; *M. musculus*, *Mus musculus*; me1, monomethylation; me2, dimethylation; me3, trimethylation; NA, not applicable; NaBu, sodium butyrate; *N. furzeri*, *Nothobranchius furzeri*; NuRD, nucleosome remodelling and deacetylases; O-GlcNAc, O-N-acetylglucosamine; OGT-1, O-GlcNAc transferase 1; PCH, pericentromeric heterochromatin; PBA, 4-sodium phenylbutyrate; Rad6, radiation sensitive 6; *R. norvegicus*, *Ratus norvegicus*; *S. cerevisiae*, *Saccharomyces cerevisiae*; SAGA, SptAdaGcn5 acetyltransferase; SAHA, suberoylanilide hydroxamic acid; Sir2, silent information regulator 2; SIRT, sirtuin; TSA, trichostatin A; VAL, valproic acid; WDR5, WD-repeat 5.

chromatin modification activity	protein	target histone and/or residue	chemical inhibitor	chemical activator	wild-type effect on healthspan or lifespan	species	references
DNA methylation	DNMT1 (maintenance)	5mC CpG sites (preference for hemi-methylated DNA)	NA	NA	+	*M. musculus*	[85]
	DNMT3A (de novo)	5mC CpG sites	NA	NA	+	*M. musculus*	[86]
	DNMT3B (de novo)	5mC CpG sites	NA	NA	+	*M. musculus*	[86]
	DNMT family (studied genome-wide methylation)	CpG sites	NA	NA	+	*M. musculus* *M. mulatta* *H. sapiens*	[87]
	DAMT-1	6mA	NA	NA	?	*C. elegans*	[88]
DNA demethylation	TET 1	5mC	NA	NA	varies by context	*M. musculus*	[89–91]
	TET 2	5mC	NA	NA	+/= (?)	*H. sapiens (AML)*	[92,93]
	TET 3	5mC	NA	NA	+	*H. sapiens*	[94]
	TET 1, 2, 3	5mC	NA	NA	+	*H. sapiens*	[95]
histone acetyltransferase	Sas2	H4K16	NA	NA	–	*S. cerevisiae*	[96]
	Gcn5 (SAGA complex)	H3 H3K9 H3K14	NA	NA	–	*H. sapiens* *S. cerevisiae*	[97]
	Iki3 and Sas3	H3K9 H3K14 H3K18	spermidine	NA	–/=	*S. cerevisiae* *C. elegans* *D. melanogaster*	[98–100]
	CBP-1	H4K5 H3K56	NA	NA	+	*C. elegans*	[30,101]

(*Continued*.)

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Table 2. (*Continued.*)

chromatin modification activity	protein	target histone and/or residue	chemical inhibitor	chemical activator	wild-type effect on healthspan or lifespan	species	references
	P300/CBP	H3K27	NA	NA	– (?)	*H. sapiens*	[102,103]
	RTT109	H3K56	NA	NA	+	*S. cerevisiae*	[96]
	Hat1	H4K5 H4K12	NA	NA	+	*M. musculus*	[104]
histone deacetylase (class I and IIa/b)	HDAC class I and II	global effect	mocetinostat HNHA SAHA NaBu TSA	NA	–	*M. musculus* *R. norvegicus* *H. sapiens*	[105–108]
	HDAC2, HDAC4, HDAC7, HDAC 8	?	PBA VAL TSA	NA	–	*R. norvegicus*	[109]
	HDAC class I and IIb	?	MPT0E014 MS-275	NA	–	*M. musculus*	[110]
	HDAC1, HDAC2	?	mocetinostat	NA	–	*R. norvegicus*	[111]
	Rpd3	H3K9 H3K27 H4ac H4K5 H4K12 H4K20	NA	NA	–	*D. melanogaster*	[112–114]
histone deacetylase (class III)	Sir2 (yeast), SIR2.1 (worm) and Sir2 (fly)	H3K9 H3K14 H3K56 H4K16	nicotinamide	NA	+ (?) – (?)	*S. cerevisiae* *C. elegans (?)* *D. melanogaster (?)*	[96,103,115–118]
	SIRT 1	H1K26 H3K9 H3K14 H3K56 H4K16	nicotinamide	spermidine	+	*M. musculus* *H. sapiens*	[119–124]

(*Continued.*)

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Table 2. (*Continued.*)

chromatin modification activity	protein	target histone and/or residue	chemical inhibitor	chemical activator	wild-type effect on healthspan or lifespan	species	references
		p53					
	SIRT 2 (rat), SIRT 2.3 (mouse)	H4K16 p53 alpha tubulin	NA	NA	– = –	*R. norvegicus* *M. musculus* *H. sapiens*	[125–127]
histone deacetylase (class III) *continued*	SIRT 6	H3K9^ H3K14* H3K18^ H3K27 H3K36* H3K56* H3K79* ^main targets *not preferred	nicotinamide	NA	+	*M. musculus*	[128–130]
histone lys methyltransferase	Set2	H3K36	NA	NA	+ or –	*M. musculus* *S. cerevisiae*	[131,132]
	MET-1	H3K36(me3)	NA	NA	+	*C. elegans*	[50]
	SET-5	H4K5 H4K8 H4K12	NA	NA	+?	*C. elegans*	[127]
	SET-26 (SET-9 paralogue only expressed in germline)	H3K4me3	NA	NA	+	*C. elegans*	[133]
	SET-1	H3K4(me2/3)	NA	NA	+	*C. elegans* *S. cerevisiae*	[134,135]
	SET-2, WDR-5, ASH 2 (COMPASS complex)	H3K4(me2/3)	NA	NA	+	*C. elegans*	[134,136]
	E(z) (fly) and MES2 (worm) (polycomb complex)	H3K27	NA	NA	– + or –	*C. elegans* *D. melanogaster*	[137,138]
histone lys demethylase	Rph1	H3K36(me3)	NA	NA	–	*S. cerevisiae*	[139]
	LSD-1 (T08D10.2 gene)	H3K4(me1/2)	NA	NA	+	*M. musculus*	[140,141]

(*Continued.*)

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Table 2. (*Continued.*)

chromatin modification activity	protein	target histone and/or residue	chemical inhibitor	chemical activator	wild-type effect on healthspan or lifespan	species	references
	RBR2 (worm) and KDM5/Lid (fly)	H3K4(me3)	NA	NA	+ + (male) = (female)	*C. elegans* *D. melanogaster*	[136,142,143]
	JMJD-2 (worm) and KDM4a (fly)	H3K9(me2/3) H3K36(me2/3) H3K56(me3)	NA	NA	+	*D. melanogaster*	[144,145]
	UTX-1	H3K27	NA	NA	+ (in both overexpression and loss of function)	*C. elegans*	[138]
histone OGlcNAc regulation	OGT-1	H4K5 H4K8 H5K16	NA	NA	+	*C. elegans*	[146,147]
	OGT-A	?	NA	NA	+ (regenerative properties in overexpression and loss of function)	*C. elegans*	[148]
histone monoubiquitinyl transferase	Rad6 and Bre1 (H2B monoubiquitylation complex)	H2BK123	NA	NA	–	*S. cerevisiae*	[149]
nucleosome remodellers	Isw2 (ISWI complex)	H3K6me2 in PCH	NA	NA	–	*C. elegans* *S. cerevisiae*	[150]
	SWI/SNF complex	NA	NA	NA	+	*S. cerevisiae*	[151]
	Chd1	NA	NA	NA	–	*S. cerevisiae*	[150]
	LET-418 (worm) and dMi2 (fly) (NurD complex)	NA	NA	NA	–	*C. elegans* *D. melanogaster*	[152,153]
histone chaperone	LIN-53	H3K4	NA	NA	+	*C. elegans*	[154]
	SIN-3	H3K4	NA	NA	+	*C. elegans*	[154]
	RBBP4/7	H3 H4	NA	NA	+	*M. musculus* (embryonic cells)	[155]
	Asf1/UNC-85 (worm)	NA	NA	NA	–	*C. elegans*	[135,156]
	HIR/Asf1/Rtt106	NA	NA	NA	–	*S. cerevisiae*	[135]
histone expression	HINFP	global	NA	NA	+	*H. sapiens*	[77]
	Npat	global	NA	NA	?	*H. sapiens*	[77]

(*Continued.*)

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Table 2. (*Continued.*)

chromatin modification activity	protein	target histone and/or residue	chemical inhibitor	chemical activator	wild-type effect on healthspan or lifespan	species	references
	Casp8ap2	global	NA	NA	?	*H. sapiens*	[77]
	H3 and H4	NA	NA	NA	+	*S. cerevisiae*	[135]
ubiquitin ligase	?	?	NA	NA	–?	*N. fuerzeri* *M. musculus*	[157]
	RLE-1	DAF-16	NA	NA	–	*C. elegans*	[158]
	VHL-1	HIF-1	NA	NA	–	*C. elegans*	[159]
sumoylation	SMO-1	DAF-16, SKN-1	NA	NA	+	*C. elegans*	[160]
	SMO-1	CAR-1	NA	NA	–	*C. elegans*	[161]
phosphorylation	PKM2	H3T6 H3T11 H3T45	NA	NA	?	*M. musculus* *H. sapiens*	[162]
	VprBP	H2AT120p	NA	NA	?	*M. musculus*	[163]
	CDK9	pS187-H1.4	NA	NA	?	*H. sapiens*	[164]

'?' indicates that the parameter is unknown or unconfirmed. *Effect the protein or complex has on lifespan in physiological conditions based on experimental knockdown, mutation or overexpression results ('–' indicates that the protein or complex normally restricts health or lifespan, '+' indicates that it normally promotes healthspan or lifespan and '=' indicates that no clear impact on lifespan was reported).

Importantly, histone levels and modifications play a key role in genomic stability, which is also controlled by epigenetic-modifying enzymes. A 2021 study by Kim *et al.* using naive T cells from older individuals and miR-181ab1-deficient mice linked the significant age-related decrease in miR-181a expression to the epigenetic enzyme SIRT1 [79]. This decline contributes to impaired T-cell function and greater vulnerability to viral infections, such as influenza and SARS-CoV-2. In ageing individuals, reduced levels of miR-181a result in heightened replication stress within T cells due to lower histone expression and delayed progression through the S-phase of the cell cycle. This decrease in histone expression is regulated by SIRT1, an epigenetic enzyme that suppresses histone gene transcription by binding to their promoters and reducing histone acetylation [79,166]. Inhibiting SIRT1 has demonstrated the potential to reverse the age-related changes as seen in a study that observed the amelioration of senescence of mesenchymal stem cells [167]. By inhibiting SIRT1, histone production can be increased, cell cycle progression normalized and inflammatory responses in T cells reduced, ultimately enhancing the immune system's ability to combat viral infections [79].

2.5. Epigenetic therapeutics and interventions

The most common therapies that exist to alter the epigenome revolve around the methylation status of histone proteins and their DNA. After hypermethylating DNA, for example, it becomes inaccessible to DNA polymerases, and the subsequent conversion into its gene products is decreased. As mentioned above, drugs such as 5-azacytidine [168] and decitabine [169] are DNMT inhibitors. Decitabine has proven to be limitedly efficacious in reducing the expression of tumours in cancer patients [169]. However, certain concerns remain about its potential to reprogram the entire genome [169]. This could cause protective TEs to be underexpressed and accelerate epigenomic degeneration. Enhancing the specificity of these drugs is essential to maintain their viability as potential therapeutics.

Similarly, histone deacetylase inhibitor (HDAI) prevents useful genes from being too tightly wound up. They maintain the expression of genes that contribute to the stability of an organism and its genome. Besides vorinostat [170], other drugs such as romidepsin [171] have been effective in promoting genes responsible for apoptosis and cell cycle maintenance. Romidepsin has proven effective against rare types of cancer [171] and does not suffer as many of the same unwanted side effects as some DNM inhibitors. Although senescent cells are typically resistant to apoptosis, romidepsin shows promise as a treatment for aged individuals and those experiencing age-related diseases.

Beyond targeting enzymes like DNM or histone deacetylases, proteins involved in genomic regulation are also a point of interest. By binding a target protein, small-molecule inhibitors (SMI) like JQ1 [172] stop the protein from performing its intended function. JQ1 inhibits bromodomain (BRD) [173], which is involved in the progression of tumours arising from gastric cancer [172]. These drugs are especially promising due to their ability to selectively bind proteins. While more research must be completed to find a drug that can accomplish this, creating an SMI for transposase proteins could prevent the erratic translocation associated with damaging TEs. This strategy provides the added advantage of decreasing the potential for cross-reactions due to SMIs being highly selective in their inhibition.

CRISPR technology is widely used in many areas of research. Its applications are countless, but its limitations can be especially detrimental in genome-wide editing. However, CRISPR GUARD [174] and CRISPR–dCas9 [175] are similar systems that diminish the ability of the Cas9 nuclease to introduce unwanted splice sites by instead utilizing guide RNAs. These safer CRISPR techniques have great potential for changing the way genomic editing is completed. Fusing target sequences to epigenetic modifiers such as DNMs, histone acetyltransferases or DNA methylases can allow therapies to modify genomic structure rather than its products. This can provide safer intervention, especially given that the target is not the genome but rather the enzymes that regulate its accessibility. Additionally, these technologies can reverse adverse changes observed in the epigenome, such as age-related TE overactivation.

While TEs do not use RNA intermediaries when translocating within a genome, their gene products still follow the canonical DNA to mRNA to protein pathway. RNA interference (RNAi) therapies [176] are promising interventions that can alter the expression of genes by repressing their products. While RNAi sequences have been used by certain organisms for millennia as a defence mechanism to repress TE activity [176], increasing their expression to target the products of harmful genes could be implemented in lieu of DNA or drug-based treatments. RNAi methods are also relatively simple to deliver in organisms, as they do not need to integrate themselves into DNA sequences.

3. Transposable elements are ubiquitous across species and can have both negative and positive influences

TEs are found in nearly all researched eukaryotic models to date [177], and they are a major contributor to genome size across a diverse range of species, albeit at different proportions. Generally, however, there appears to be a positive correlation between a species' genome size and number of TEs [178]. TEs occupy approximately 45% of human genome [5], 59% of zebrafish genome [179] and as high as 90% of genome in lungfish [180]. It is currently unknown whether a higher proportion of TEs in the host genome necessarily leads to more frequent transposition events.

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3.1. Silencing of transposable elements

Unsurprisingly, given TEs' potential ability to disrupt cellular homeostasis, species have evolved mechanisms to suppress the expression of TEs. The three mechanisms that are most widely understood are the P-element induced wimpy/argonaute (PIWI/AGO) system, Krüppel-associated box domain-containing zinc-finger protein (KRAB-ZFPs) system and the human silencing hub (HUSH) complex [181,182]. Furthermore, ongoing efforts are trying to characterize additional TE regulators in healthy somatic tissues. For example, Bravo *et al.* identified *IL16* and *STARD5* as regulators of long interspersed element 1 (LINE-1) expression, a class I TE. The study also found that genetic variants associated with overexpression of LINE-1 RNA levels were linked to ageing traits, suggesting a role for TEs in ageing processes [183]. Additionally, the GWAS approach identified both known and novel candidate genes involved in the regulation of TEs activity. Among these, MPHOSPH8, a component of the HUSH, is known to suppress LINE-1 activity by repressing its transcription. PABPC1 (Poly(A)-binding protein 1) plays a crucial role in stabilizing mRNA transcripts, including LINE-1 RNA molecules, which are essential for successful retrotransposition. Additionally, RHOT1 and XPR1, genes involved in mitochondrial dynamics and phosphate transport, respectively, were also implicated in TE regulation, though their precise roles remain unclear [184]. Expanding this regulatory landscape, a recent *Nature Genetics* study found that LINE-1 transcription itself regulates gene expression over long genomic distances, potentially acting as an enhancer, further underscoring the complexity of TE influence on genome function [185]. While multiple mechanisms suppress TE activity across different cell types, the PIWI and AGO systems are particularly notable for their roles in maintaining genomic integrity, especially in the germline.

Current research shows that while the PIWI system is only active in germline cells and the AGO system exists in somatic and germline cells [181], presumably due to the importance of germline cell genome integrity [186], both exert their TE repressive function through similar mechanisms. The system functions both intranuclearly and extranuclearly. Within the nucleus, the PIWI/AGO system recognizes nascent TE transcripts through base complementarity between the transcript and piRNA/miRNA, respectively, and methylates both cytosine bases and the histones, silencing TEs at the source [186]. Some examples of repressive heterochromatin structure include H3K9me3 and H4K20me [186,187]. Outside of the nucleus, the PIWI/AGO system targets and cleaves the mature transcript [182,186]. Intriguingly, we previously observed that, as African turquoise killifish individuals aged, there was a decline in the expression of PIWI proteins, which was associated with an increase in transposon expression in their ovarian tissue [188]. The findings suggest that the age-related decrease in PIWI protein levels may lead to increased transposon activity, potentially contributing to genomic instability and affecting reproductive health during ageing.

KRAF-ZFPs appear to have evolved from the last common ancestor of coelacanths and tetrapods and expanded their functions extensively in mammals [189]. In fact, KRAB-ZFPs are the largest class of transcriptional factors in humans [189], functioning both as transcriptional repressors and activators [190]. KRAF-ZFPs are also a major component of the TE silencing machinery, as approximately 2/3 of human KRAF-ZFPs bind to TEs [189]. It has been demonstrated that knockouts of KRAF-ZFPs lead to a significant upregulation of TEs in mice [191]. It also appears that clusters of KRAF-ZFPs are indeed evolutionarily related, and individual clusters suppress a specific type of transposons [192]. It is generally understood that KRAF-ZFPs suppress TE expression through the interaction between the zinc-finger motif and the DNA, which leads to the subsequent deposition of H3K9me3 [189].

The HUSH complex is one of the less-understood TE silencing mechanisms, and ongoing research is being conducted to fully elucidate the role of the HUSH complex. The complex was discovered during the study of position-effect variegation, a phenomenon where identical genes at different genomic positions have different expression profiles, presumably due to epigenetic regulation [193]. In 2015, the Lehner lab uncovered complexes of proteins that perform such epigenetic regulation through deposition of H3K9me3 and coined the machinery HUSH complex [194]. HUSH complex is conserved from fish to humans [194], hinting at its importance. Unsurprisingly, recent literature has proposed that the HUSH complex is a major epigenetic silencer of LINE-1s [195,196], which performs the majority of retrotransposition events in humans [197]. While the mechanism of HUSH-complex-mediated LINE-1 repression is not completely understood, the Lehner lab has proposed that the HUSH complex recognizes retrotransposons through its characteristics of having no introns and can suppress a broad range of intronless TEs through the deposition of H3K9me3 [195].

3.2. Ageing-related loss of transposable elements silencing

Recent literature has linked aberrant expression and transposition of TEs with various forms of diseases, including genetic diseases [198], malignant blood cell carcinogenesis [199] and neurodegenerative diseases (figure 2) [200]. While unregulated TE transposition may be harmful, it has also been proposed that TEs' ability to disrupt genome stability may be a major driver of evolution. It has been speculated that bursts of TE transposition may, in fact lead to novel gene functions and lead to higher fitness for the environment [81,84]. Furthermore, some TEs have been 'domesticated' by their host and serve critical functions. TEs were found to affect phenotypes in *Drosophila* [201]. A well-known case is the 'domestication' of RAG1 and RAG2 with its pivotal function in reorganizing the V(D)J region of T cells within the human adaptive immune system [202].

There is extensive evidence that de-repression of TEs is associated with organismal ageing. This phenomenon has been observed through multiple species, both *in vivo* and *in vitro* [203–207]. Interestingly, while the mechanisms are different, all three discussed TE repression systems exert their effects using silencing epigenetic signature, namely through the deposition of H3K9me3. Indeed, heterochromatin loss is a hallmark of ageing [208,209] and may be a major contributor to the aberrant upregulation of TEs. In a preprint, Mrabti *et al.* demonstrated that loss of H3K9me3 caused an accelerated phenotype in mice *in vivo* and is associated with a significant upregulation of TEs [210]. On the other hand, Xiao *et al.* demonstrated that hypermethylation of regions associated with H3K9me3 is a hallmark of centenarians and presumably of healthy ageing

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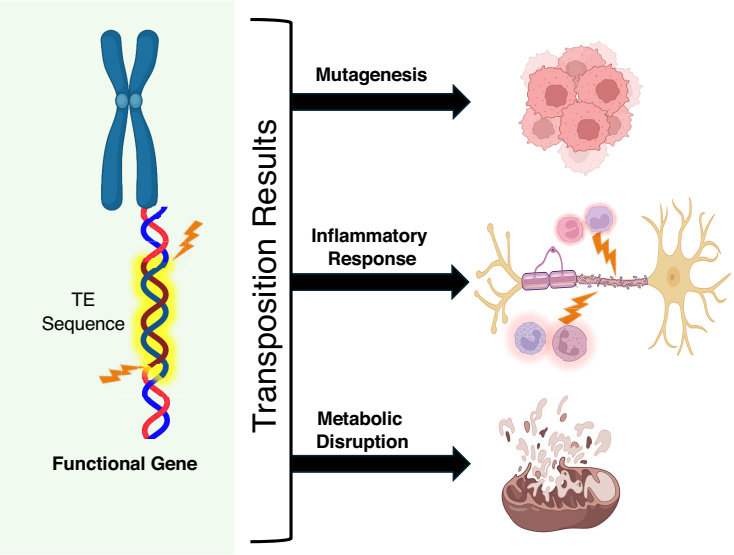


Figure 2. Schematic of how the TE dysregulation pathway can lead to diseases and ageing hallmarks. TE reactivation contributes to genomic instability, immune dysregulation and metabolic dysfunction, which are often associated with ageing and age-related diseases.

[211]. Taken together, there is mounting evidence that H3K9me3 and expression profile of TEs are significant determinants of healthy ageing. However, the underlying mechanism for age-related loss of heterochromatin remains poorly understood. Recent literature points out that methyl donor depletion may be a factor in the gradual loss of heterochromatin. Kang *et al.* demonstrated in muscle cells that depletion of methyl donor S-adenosylmethionine leads to a loss of heterochromatin. However, it is clear that more research is required to fully understand the relationship between ageing, heterochromatin and TEs.

Several *in vivo* models are available to study TE activity, and aged mice provide a relevant biological context for these investigations. Studies in aged mice have shown that certain RTEs become overactivated, contributing to inflammation and promoting senescence [212]—both associated with age-related genomic instability. For example, LINE-1 derepression leads to accumulation of LINE-1 cDNA in the cytoplasm, which activates cGAS (cytosolic DNA sensing pathway), which in turn triggers type I interferon response and proinflammatory cytokines promoting chronic inflammatory signalling and senescence-associated secretory phenotype [200,203,212]. These studies have also shown the identification of specific RTE and TE machinery like LINE-1 reverse transcriptase [212] and LINE-1 endonucleases that can be therapeutically targeted in the future. Using mice as a model has allowed researchers to note conserved TEs that become overactivated and cause histone modifications, oxidative stress and deleterious mutations [212,213].

Invertebrates such as *Drosophila*, *C. elegans* and *Hydra* [214–216] have also been used to understand TE regulation and the impact of its deregulation. In *C. elegans*, for example, it was found that reducing Tc1, Tc3 and Tc14 TE families by RNAi-mediated knockdown elongates their lifespan [215]. These organisms offer the advantage of having highly morphable genomes, leading to TE selection with ease. In *Hydra*, pathways for TE repression have been discovered [214]. The PIWI–piRNA pathway is actively expressed in somatic epithelial stem cells, where it represses TEs through ping-pong biogenesis and direct cleavage of TE RNAs. This suggests that somatic TE repression is an ancestral function of the PIWI–piRNA pathway, likely contributing to *Hydra*'s genomic stability and regenerative capacity. In fact, due to the abundance of data that exists for these regenerating nematodes, *Hydra* were found to have ancestral TE repression [214]. This suggests TE repression could be an evolutionary artefact that helps other organisms ward off the somatic mutations that often accompany ageing.

Other studies have evaluated TE activity in pluripotent stem cells and early embryonic development. Importantly, TEs are highly active during the early stages of development [217], enabling researchers to elucidate their potential physiological roles. This transient TE activation is crucial for processes like genome reprogramming and cell differentiation but also introduces opportunities for duplication events and transcriptional errors, some of which may parallel TE derepression observed in ageing organisms. *In vitro*, pluripotent stem cells provide a controlled system to study TE dynamics, particularly in relation to epigenetic regulation. Histone modifications can be more easily profiled in these systems, as histone deacetylases and DNMTs remain abundant in the pluripotent state [218]. While *in vitro* methods offer precise experimental control and cost-effectiveness, they do not fully recapitulate the complexity of *in vivo* developmental dynamics seen in model organisms (table 3).

3.3. Current models to study transposable elements function and mobility

Cell cultures are commonly used to study TEs due to their clonality and tractability. Advantages of using *in vitro* cell culture to study TEs include the ability to rapidly and precisely modify experimental conditions. Specifically, senescent fibroblasts, which model proliferative arrest commonly associated with ageing, are excellent tools to observe the function and regulation of TEs *in vitro*. Senescence can be induced through chemical agents (e.g. doxorubicin, etoposide, bleomycin) [226–228], and from here, the response of TEs can be monitored. TE activation has been observed in senescent cells, suggesting some might have an immune response [226].

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Table 3. Repetitive and TE genomic content in model organisms used in ageing research.

organism	percentage of TE and repetitive region in genome	references
Saccharomyces cerevisiae	3.1%	[219]
Caenorhabditis elegans	12–16%	[220]
Drosophila melanogaster	3.86%	[221]
Danio rerio (zebrafish)	53%	[179]
Nothobranchius furzeri (African turquoise killifish)	45%	[222]
Xenopus tropicalis (western clawed frog)	34.5%	[223]
Mus musculus	41.86%	[224]
Rattus norvegicus	41.76%	[224]
Heterocephalus glaber (naked mole-rat)	38.16%	[224]
Macaca mulatta (rhesus macaque)	49.33%	[225]
human	45%	[5]

To quantify TE activity [229], luciferase [230] and green fluorescent protein (GFP) reporter systems are employed. Doing so allows researchers to observe TE activity and identify which TEs are most greatly contributing to harmful DNA damage. This method allows researchers to study multiple polymorphisms of TEs at once [229], leading to precise identification of problematic TEs in real time. Correlating the activity of TEs with the location of DNA damage can provide further insight into target TEs and vulnerable components of the genome. Additionally, modifying these TEs through silencing or activation and monitoring them using the aforementioned systems can provide clues into their function as parasitic members of the aged genome.

TEs can also be studied computationally [231]. Tools such as RepBase [232] and Dfam [233] provide repositories of known TE sequences, allowing researchers to identify their evolution and compare them across species. Computational tools can be used to predict insertion sites [231] of TEs, which provide targets for future studies. Additionally, several bioinformatics pipelines have been developed to analyse TE expression and genomic integration. SalmonTE is a fast and lightweight tool designed for quantifying TE expression from RNA-seq data, leveraging the efficiency of pseudo-alignment methods [234]. HOMER provides motif enrichment analysis, allowing researchers to investigate regulatory elements associated with TE activity [235]. TE transcripts and TE peaks are widely used to differentiate TE-derived RNA from gene expression in bulk and single-cell transcriptomics data [236]. These tools help parse the contribution of TEs to overall transcriptional landscapes, identify differential TE activity across conditions and facilitate the discovery of TE regulatory mechanisms in ageing and disease. Their combined use allows for an integrated approach to studying TE dynamics across various biological contexts.

4. Age-related remodelling of the epigenome and age-related transposable elements derepression: two faces of the same coin?

Chromatin-modifying enzymes, integral to the regulation of chromatin structure, represent a primary mechanism through which TEs are repressed in healthy cells [237]. However, the progressive dysfunction of these enzymes with age facilitates TE reactivation, leading to widespread epigenomic remodelling. The reactivation of TEs during ageing exemplifies the intricate interplay between chromatin dynamics and genomic stability. This relationship between TEs and chromatin alterations underscores their synergistic role in ageing and age-associated diseases.

4.1. Chromatin-modifying enzymes are a major class of transposable element regulators

Chromatin-modifying enzymes, such as histone methyltransferases, histone acetyltransferases and DNA methyltransferases, are pivotal regulators of TE silencing. These enzymes deposit repressive epigenetic marks like H3K9me3 and DNAme, confining TEs to heterochromatic regions where transcriptional activity is suppressed [238]. For example, enzymes like SETDB1 and SUV39H1 catalyse the trimethylation of H3K9, creating a heterochromatic environment that restricts TE expression (figure 3) [239,240]. Decreased expression of these enzymes in ageing tissues disrupts this delicate balance, allowing TEs to escape silencing [10]. SETDB1 was found to repress TE activity. Loss of SETDB1 and consequently H3K9me3 led to increased TE transcription, premature ageing and necroptosis via RIPK3 and ZBP1 activation [241]. Furthermore, in neural precursor cells, SETDB1 showed restricted chromatin accessibility on a selective subset of SINEs by contributing to chromatin loop reorganization [242]. Overexpression of heterochromatin regulators such as Su(var)3-9 and Dicer-2 also reduced TE expression and extended the lifespan of *Drosophila melanogaster* [239]. In addition, a recent study has demonstrated that the reduction of SUV39H1 exhibits significant reductions in H3K9me3 levels and upregulation of TE activity and mobility [210]. The age-associated decline in these enzymes also compromises genomic stability by permitting aberrant transcriptional activity, genomic rearrangements and the propagation of inflammatory signals.

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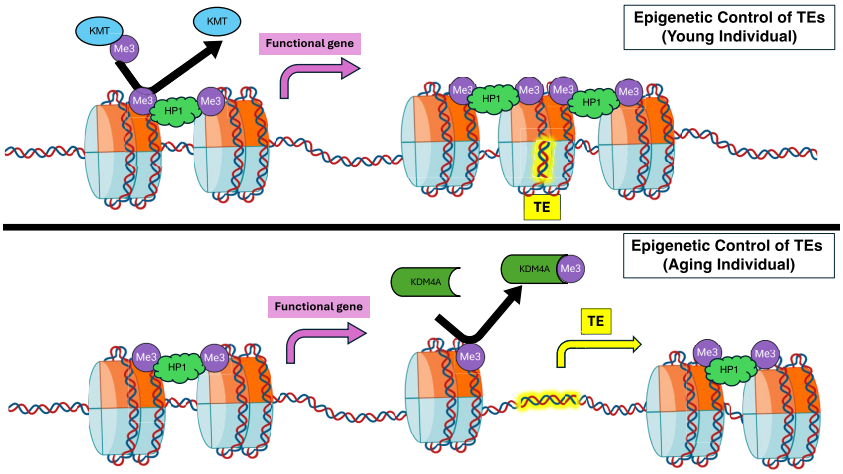


Figure 3. Schematic of TE regulation by epigenetic context in young cells and during ageing. Top, representing young individuals, lysine methyltransferases (KMTs) deposit trimethylation marks (H3K9Me3) on histones, facilitating the recruitment of heterochromatin protein 1 (HP1). This results in the formation of tightly packed chromatin, which effectively silences TEs while permitting transcription of nearby functional genes. The compact chromatin structure prevents TE reactivation and ensures genomic stability. Bottom, depicting ageing individuals, histone demethylases (e.g. KDM4A) actively remove H3K9Me3 marks. The loss of trimethylation disrupts HP1 recruitment, leading to chromatin relaxation. This relaxed chromatin environment permits TE reactivation, indicated by yellow transcription signals. TE reactivation can interfere with nearby gene expression, potentially disrupting functional gene activity.

4.2. Transposable elements activity can lead to epigenome remodelling

The activation of TEs further exacerbates the ageing epigenome by directly inducing chromatin remodelling. TE-derived transcripts and proteins can interfere with chromatin architecture by disrupting the recruitment of chromatin-modifying complexes or competing for binding sites with endogenous factors. For instance, the reverse transcription of retrotransposons generates double-stranded RNA intermediates that elicit an innate immune response through pathways like cGAS-STING [243]. Recent research indicates that the cGAS-STING pathway acts as a modifier of genomic instability syndromes, highlighting its role in the cellular response to TE activation [244]. Moreover, TE integration events during retrotransposition can introduce mutations, disrupt coding sequences and alter regulatory regions, compounding genomic instability [245]. Ferraj *et al.* demonstrated that TEs make up 39% of structural variants and account for 75% of altered bases in diverse bread mice. By refining the variant call set, they revealed TE heterogeneity in mouse embryonic stem cells and identified multiple TE classes that impact chromatin accessibility [246]. In addition, the longevity-associated protein SIRT6 plays a crucial role in repressing LINE1 retrotransposons by mono-ADP ribosylating the nuclear corepressor protein KAP1, facilitating the formation of transcriptionally repressive heterochromatin. During ageing or in response to DNA damage, SIRT6 is depleted from LINE-1 loci, leading to their activation and subsequent genomic instability [247]. The interplay between TE activation and chromatin remodelling thus forms a self-reinforcing cycle, where age-induced TE activity drives epigenomic alterations that further enhance TE mobilization.

4.3. Age-related changes in transposable element activity and chromatin structure can amplify each other

The accumulation of TE insertions over time increases the mutational burden and disrupts regulatory networks, impairing cellular homeostasis [248]. In neurodegenerative diseases such as Alzheimer's and Parkinson's, elevated TE activity has been linked to neuronal loss and inflammation, highlighting the pathogenic potential of TEs in age-related disorders [249]. Additionally, the activation of ERVs, a subclass of retrotransposons, contributes to the proinflammatory environment observed in aged tissues by mimicking viral infections [250]. These inflammatory signals perpetuate tissue damage and exacerbate age-related pathologies.

4.4. Implications for ageing and diseases

Understanding the bidirectional relationship between chromatin changes and TE activation offers valuable insights into the molecular underpinnings of ageing and its associated diseases. Targeting chromatin-modifying enzymes or restoring heterochromatic integrity could provide therapeutic strategies to mitigate TE-driven genomic instability and inflammation (figure 4). Emerging approaches such as CRISPR-based gene editing, SMIs of chromatin modifiers and epigenetic rejuvenation strategies hold promise in reversing age-related chromatin changes and silencing TEs. By dissecting the complex interplay between the ageing epigenome and TEs, future research may uncover novel avenues for promoting healthy ageing and preventing age-related diseases.

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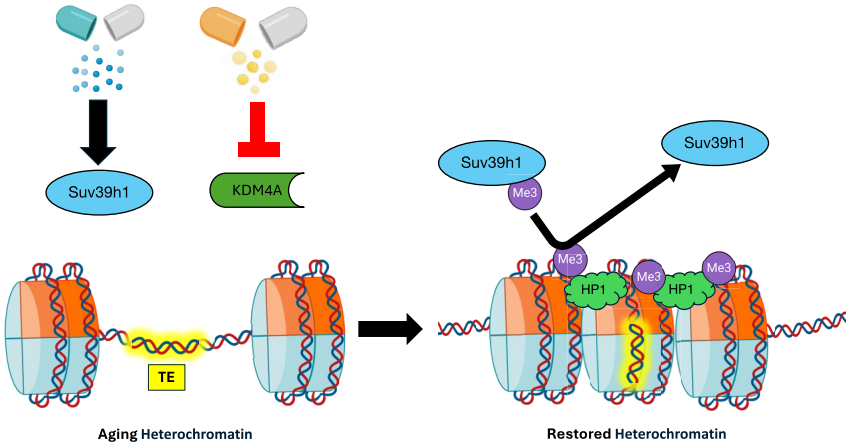


Figure 4. TE regulation as a therapeutic target for ageing through chromatin remodelling. Left: pharmacological approaches, such as activating *Suv39h1* (blue capsule) or inhibiting KDM4A activity (yellow capsule and inhibition symbol), can be potential interventions to counteract ageing heterochromatin. This loss of heterochromatin compaction allows TE reactivation. Right: restored heterochromatin with enhanced H3K9Me3 deposition by Suv39h1, leading to the recruitment of HP1. This restoration re-establishes chromatin compaction, effectively silencing TEs and maintaining genomic stability.

4.5. Current approaches to modulate epigenetic changes in ageing, and how they can apply to transposable element control (modification of chromatin enzymes, CRISPR-activation/CRISPR-inactivation arrays, etc.)

DNA hypomethylation is commonly associated with age-related degeneration of the epigenome. DNMs have long been understood to be associated with gene silencing, which increases with age [9]. Drugs such as 5-azacytidine inhibit DNMs [168]. Currently, this approach has been cautiously validated in aged humans with reports of treatment-resistant cancers such as acute myeloid leukaemia (AML) responding to these hypomethylating therapeutic agents [168]. Altering the target of DNMs can hypermethylate TEs [251], with recent evidence pointing to this as a potential target of such drugs, potentially silencing them or preventing their activation altogether.

Another chromatin-modifying approach involves TET enzymes, which demethylate DNA and can lead to increased gene expression [173]. While elevated TET activity has been linked to somatic anomalies [252], recent efforts have explored whether targeting TETs could modulate TE expression. Inhibiting TET activity could maintain TE silencing and prevent their mobilization during ageing, though further research is needed to establish its therapeutic potential in TE control. In contrast to methylation, histone acetylation forms loosely wound DNA and leads to the expression of genes. Promoting acetylation can be advantageous when trying to reverse age-related degeneration. Certain drugs, such as vorinostat, have proven to be highly effective against cutaneous T-cell lymphoma [170] due to their function as HDAI. Using these drugs as a reactionary measure to TE-mediated gene silencing can help those genes to be expressed. As a defence mechanism, HDAI shows promise as a therapeutic target in reversing epigenetic damage caused by overactivated TEs.

CRISPR technology is also currently used to modify TEs and their function. CRISPR-activation (CRISPR-a) allows target TEs to be 'turned on' whereas CRISPR-inactivation (CRISPR-i) inhibits their expression. While this technology is widely considered to be in its preliminary stages, it shows promising results [253,254]. Creating an ideal balance of activation and inactivation offers researchers the opportunity to further elucidate the role TEs play in age-related degeneration and selectively silence problematic sequences while promoting the expression of helpful ones. Another novel application of this method is utilizing CRISPR-associated TEs (CAST) to integrate programmable TEs directly into the genome [254]. Currently, this is being used to insert precise sequences that allow for enhanced specificity in genome-wide editing. Using RNA–DNA hybridization methods, the ability to insert TEs at will has allowed researchers [254] to identify new ways to target TE-mediated instability within an ageing epigenome. The CAST system has the potential to be used in complement with CRISPR-a and CRISPR-i to enhance the epigenome and prevent rogue TEs from silencing important genes while allowing other TEs to activate and preserve genetic composure.

5. Concluding remarks

Ageing represents a complex interplay of biological processes that progressively impair cellular and organismal function. Central to this phenomenon are the intertwined hallmarks of epigenetic alterations and genomic instability, which together underpin many of the cellular and molecular changes associated with ageing. The reactivation of TEs, long considered 'genomic parasites,' exemplifies the intricate relationship between these hallmarks. TEs, typically silenced within heterochromatin, become active during ageing due to the progressive loss of chromatin integrity and dysregulation of chromatin-modifying enzymes. This reactivation leads to widespread genomic instability, inflammation and epigenomic remodelling, amplifying the ageing process and contributing to age-related diseases.

TEs act as both drivers and amplifiers of epigenomic dysregulation during ageing. Age-associated declines in the function of chromatin-modifying enzymes, such as histone methyltransferases and DNA methyltransferases, weaken the repression of

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TEs, allowing their expression and mobilization. This activity, in turn, disrupts chromatin architecture, interferes with gene regulation and induces immune responses through TE-derived RNA and DNA intermediates. These changes create a feedback loop where epigenomic instability further promotes TE activation, compounding the molecular damage associated with ageing. This vicious cycle underscores the critical need to understand the reciprocal relationship between TE dynamics and the ageing epigenome.

Targeting the interplay between TEs and epigenetic alterations offers a promising avenue for therapeutic intervention in ageing and age-related diseases. Advances in technologies such as CRISPR-based genome editing, SMIs of chromatin-modifying enzymes and RNAi provide tools to selectively modulate TE activity and restore epigenomic stability. Additionally, understanding lifestyle factors and their impact on TE regulation presents opportunities for non-invasive interventions to promote healthy ageing. By integrating these strategies, future research can unravel the complexities of TE–epigenome interactions and develop novel approaches to mitigate the detrimental effects of ageing, thereby enhancing healthspan and delaying the onset of age-related disorders.

A significant knowledge gap remains in determining whether TE activation is a primary causal driver of ageing or merely a biomarker of broader epigenetic instability. While correlative evidence strongly links TE activation to age-related decline, definitive functional studies are required to establish causality. Additionally, current tools for studying TEs lack the resolution to track individual transposition events with precision *in vivo*. The development of advanced single-cell and spatial transcriptomics, coupled with long-read sequencing technologies, will be crucial for dissecting TE regulation at the cellular level. Furthermore, expanding computational models to integrate TE activity with chromatin state dynamics will provide deeper insights into their interplay. Addressing these gaps will help unravel the precise role of TEs in ageing and open new avenues for targeted interventions that restore genomic integrity and promote longevity.

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Data accessibility. This article has no additional data.

Declaration of AI use. We have not used AI-assisted technologies in creating this article.

Authors' contributions. A.J.J.L.: conceptualization, writing—original draft; E.T.: writing—original draft, writing—review and editing; R.B.: writing—original draft; A.G.: writing—original draft; A.X.: writing—original draft; B.A.B.: conceptualization, funding acquisition, supervision, writing—review and editing.

All authors gave final approval for publication and agreed to be held accountable for the work performed therein.

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