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REVIEW

Epigenetic regulation in cell senescence

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Abstract Cell senescence, which is an irreversible state of cell proliferative arrest, has emerged as a potentially important contributor to tissue dysfunction and organismal ageing. Cell senescence is triggered by a variety of senescence stressors, which affect gene expression and multiple signalling pathways that give rise to various senescence phenotypes. Epigenetic mechanisms, as critical regulators of chromosomal architecture and gene expression, have added an extra dimension to the molecular mechanisms of cell senescence. Cell senescence is accompanied by changes in DNA methylation, histone-associated epigenetic processes, chromatin remodelling and ncRNA expression. Those senescence-associated epigenetic alterations interact with the senescence regulatory programme networks and lead to various cell senescence phenotypes. This review provides a comprehensive overview of epigenetic changes and their effects on cell senescence. The differences in epigenetic alterations among different types of senescence are also discussed. Furthermore, we summarise the interactions among different epigenetic mechanisms during cell senescence and analyse the possibility of using epigenetic signatures as biomarkers and therapeutic targets for the treatment of senescence-associated diseases.

Keywords Senescence · DNA methylation · Histone modification · Chromatin remodelling complex · ncRNA

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Introduction

Cell senescence has been widely reported to occur during organismal ageing and ageing-related diseases [1, 2]. Cell senescence has been recognised as a hallmark of ageing and an important contributor to ageing-related diseases [3]. Senescent cells have been shown to accumulate over time and lead to tissue dysfunction [4]. Cell senescence can be triggered by a variety of senescence stressors, such as replicative stress, oxidative stress and DNA instability, which affect gene expression and multiple signalling pathways that give rise to various senescence phenotypes. However, the mechanisms underlying the response of senescent cells to senescence stress have not been well characterised. Epigenetic mechanisms that gradually alter chromatin structure and gene expression in response to the environmental stress and DNA damage signals gradually without a corresponding alteration in the genome may add an extra dimension to the molecular mechanisms of cell senescence [5]. Senescence-associated epigenetic alterations have been widely reported in cell senescence. Epigenetic mechanisms play a significant role in the initiation and progression of cell senescence. Hence, appreciating how epigenetic mechanisms contribute to cell senescence is fundamental to our understanding of cell senescence. However, the involvement of epigenetic mechanisms in cell senescence has not been systematically reviewed yet. Here, we summarise the epigenetic changes in senescent cells, highlight the epigenetic mechanisms of cell senescence and discuss potential epigenetic therapies for cell senescence.

Epigenetic regulation of senescent cells

Cell senescence is an evolving process generally established and maintained by the p53-p21 pathway and/or the $p16^{INK4a}$ pathway, which may lead to an irreversible cell cycle arrest.

Mounting evidences suggest that cellular senescence is a dynamic process driven by epigenetic changes. These epigenetic changes include changes in DNA methylation, histone-associated epigenetic processes, ATP-dependent chromatin remodelling complexes and the expression of non-coding RNAs (ncRNAs) (Fig. 1). Replicative senescence, stress-induced premature senescence (SIPS) and embryonic senescence, which are induced by different induction factors (Table 1), harbour considerable variations in gene expression profiles and phenotypes, as well as epigenetic patterns. The epigenetic mechanisms of these different types of cell senescence are widely investigated.

DNA methylation

DNA methylation is a critical epigenetic mechanism that is functionally involved in many biological processes [9]. DNA methylation of promoter CpG dinucleotide is a marker of transcriptional silencing [9]. Replicative senescence is characterised by global DNA hypomethylation and focal hypermethylation (Table 2). The senescence-associated DNA hypomethylation is attributed to DNA methyltransferase 1 (DNMT1) mislocalization, decreased activity or expression [13, 14]. The senescence-associated focal hypermethylation may be induced by senescence-associated heterochromatin foci (SAHF), which may recruit DNMTs to focal sites through heterochromatin protein 1 (HP1) [15, 16]. Senescence-associated DNA methylation alterations are good predictors of cell passage numbers and cumulative population doublings [17]. Moreover, changes in mitochondrial DNA (mtDNA) methylation have also been shown in replicative senescent cells. An analysis of the cytosine in the mtDNA non-coding region revealed that 76% is hypomethylated and 24% is hypermethylated in senescent cells [18]. The hypomethylation of mtDNA may be associated with the downregulation of mitochondrial specific DNMT (mtDNMT1), which is mediated by p53 [19]. The hypomethylation of mtDNA non-coding region may give rise to upregulated mitochondria-derived ncRNAs and thus effects on the expression of mitochondrial genes and the function of mitochondria.

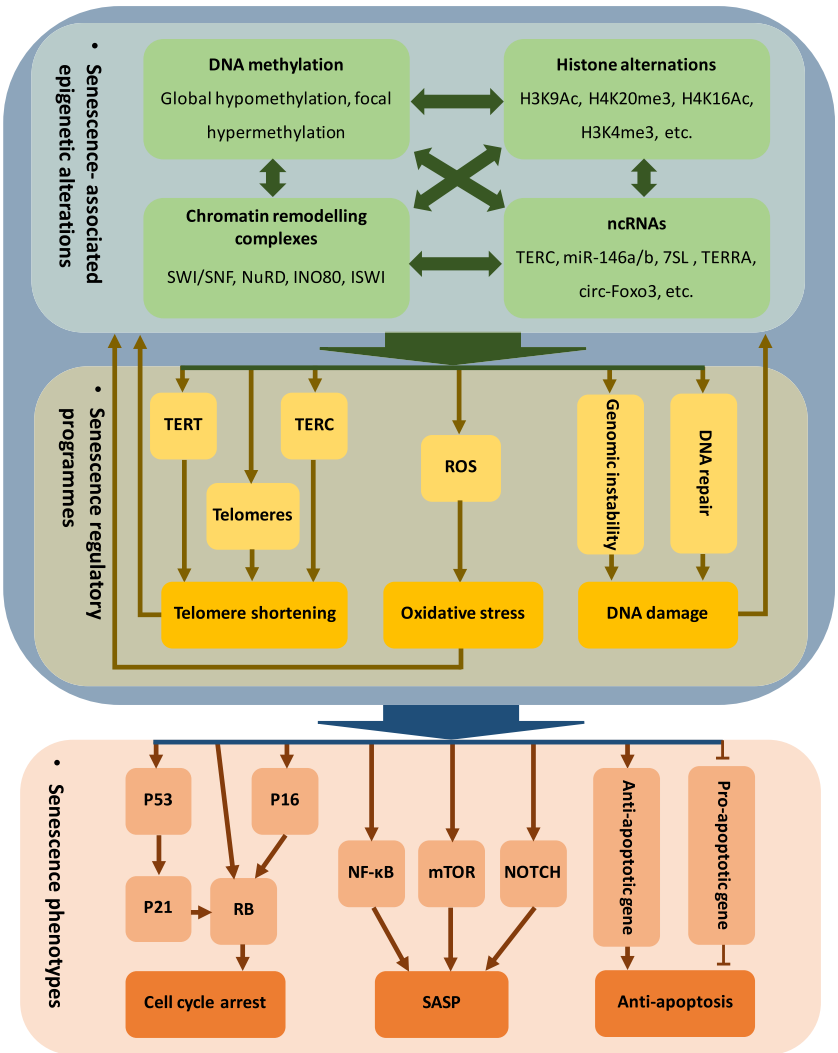

Fig. 1 Epigenetic mechanisms of cell senescence. Cell senescence is accompanied by alterations in DNA methylation, histone-associated epigenetic processes, chromatin remodelling and ncRNA expression. Different epigenetic modifications interact with each other and comprise a complicated network. The combination of these epigenetic modifications affects senescence regulatory programmes by regulating the chromatin structure and the transcription, translation and post-translational modifications of a variety of genes. The interaction between epigenetic mechanisms and other senescence regulatory programmes leads to various senescence phenotypes, such as cell cycle arrest and SASP. Abbreviation: SASP: senescence-associated secretory phenotype

Table 1 Traits of cell senescence classified by their induction factors

Types	Induction factors	Regulatory programmes	Senescence establish pathway	Effects
Replicative senescence	Replication stress	Telomere dysfunction, DNA damage, and epigenetic stress	The p53-p21 pathway and/or the $p16^{INK4a}$ pathway [6]	Tissue dysfunction
SIPS	Oncogene activation, ROS, radiation, and chemotherapeutics	Oxidative stress, DNA damage, and epigenetic stress	The p53-p21 pathway and/or the $p16^{INK4a}$ pathway [7]	Tissue dysfunction
Embryonic senescence	Physiological signals	Physiological signals and epigenetic regulation	The TGFβ/SMAD-$p21^{Cip1}$ pathway and the FOXO/PI3K-$p21^{Cip1}$ pathway [8]	Embryonic patterning and organogenesis

SIPS stress-induced premature senescence, *ROS* reactive oxygen species

Regarding SIPS, no significant global DNA methylation changes are observed in doxorubicin-induced senescence, ionising irradiation-induced senescence, Ras-induced senescence (RIS) and non-permissive temperature-induced senescence [20–22]. There are two main reasons why the DNA methylation profile maintains stability in some types of SIPS. First, there are not enough rounds of cell division to accumulate DNA methylation errors for premature senescent cells, which are rapidly induced to a senescent state. Second, some DNA methylation modifiers, which are markedly decreased in replicative senescent cells, are only slightly reduced in premature senescent cells [21]. However, when there are enough rounds of cell division, senescence-associated DNA methylation can also occur in SIPS. Global DNA hypomethylation, DNMT1 downregulation and hypermethylation of the apoptosis pathways have been detected in high-dose radiation-induced cell senescence [23]. The diversity of senescence-associated DNA methylation changes in different types of cell senescence eventually leads to distinct gene expression patterns and phenotypes.

Senescence-associated DNA methylation alterations are engaged in the regulation of telomere dysfunction and DNA damage and eventually lead to cell senescence. Hypermethylation of the telomerase reverse transcriptase (TERT) promoter during senescence reportedly induces diminished TERT expression and decreased telomerase activity [24]. However, there is no linear relationship between hypermethylation and TERT expression. Hypermethylation of the TERT promoter simultaneously prevents the binding of both transcriptional activators and transcriptional repressors. DNA hypomethylation induced by the DNA demethylating agent 5-aza-2′-deoxycytidine (DAC) has also been shown to be able to trigger senescence by reducing TERT expression via decreased binding of c-myc to the TERT promoter [25]. Moreover, DNA hypomethylation has been reported to upregulate the expression of $p16^{INK4a}$ and $p21^{Cip1}$ and may affect the wrapping of DNA ends and expose the hypomethylated DNA to DNA damage stress [26, 27].

Taken together, senescence-associated DNA methylation alterations accumulated during cell senescence interact with telomere dysfunction and DNA damage and thus lead to cell cycle arrest. However, the epigenetic pattern in embryonic senescence remains unknown. Therefore, further investigations are required to explore the epigenetic pattern in embryonic senescence and determine the differences among the epigenetic mechanisms underlying replicative senescence, SIPS and embryonic senescence.

Histone-associated epigenetic processes

Histone-associated epigenetic processes include histone modifications, histone variation and histone depletion. Those processes regulate nearly all DNA-templated processes, such as replication, transcription and repair. Replicative senescence cells harbour various histone-associated epigenetic changes

Table 2 The alteration of DNA modulators in replicative senescence and their effects on senescence phenotypes

Epigenetic modulator	Epigenetic function	Alteration	Phenotype	Mechanism
DNMT1	Maintaining DNA methylation during cell division	↓	Cell cycle arrest	Upregulating $p16^{INK4a}$ and $p21^{Cip1}$ via promoter hypomethylation [10]
DNMT3	Catalysing DNA methylation de novo	↑	Telomere shortening	Downregulating TERT expression and telomerase activity via hypermethylation [11]
TET	Converting methyl-cytosine to hydroxyl-methyl-cytosine and promoting demethylation	↓	Proliferation suppression	Blocking the cells at G1 phase via the recruitment of PRC2 [12]

DNMT DNA methyltransferase, *TET* ten-eleven translocation, *PRC2* polycomb repressive complex 2, *TERT* telomerase reverse transcriptase

(Table 3). Histone depletion is triggered in response to telomere shortening [42]. Telomere shortening leads to decreased telomere binding sites of repressor activator protein 1 (Rap1), which relocates to histone genes and represses their expression [43]. Histone depletion gives rise to an open chromatin configuration, which increases the RNA polymerase II elongation rates and leads to pre-mRNA splicing defects in senescence [44]. Histone variations, such as phosphorylated H2AX (γ H2AX), H3.3 and macroH2A.1.1, are also detected in replicative cell senescence [41, 45]. In addition, replicative cell senescence is characterised by global decreases in H4K16Ac, H3K4me3, H3K9me3 and H3K27me3 and global increases in H3K9Ac and H4K20me3 [46–48]. These histone modification changes are relevant even after substantial passaging in culture. Histone modification changes have also been detected in SIPS. However, the histone marker alteration pattern in different types of SIPS appears to vary according to their induction factors. For example, neither H3K27me3 nor H3K9me3 undergoes large-scale changes during oncogene-induced senescence [49]. The heterogeneity of histone modifications between cells induced by different senescence mechanisms may give rise to diverse gene expression pattern and senescence phenotype in those cells.

The role of senescence-associated histone alterations in the senescence regulatory programmes has been extensively investigated. On the one hand, histone modifications and histone variations are increasingly recognised as significant regulators of telomere shortening. Histone γ-H2AX has been reported as a sensitive marker of telomere shortening, which colocalizes with double-strand breaks (DSB) repair factors [40]. Telomeres are enriched for the H3K9me3, H4K20me3, H3K79me2 and H3K9Ac markers [11, 50]. These histone modifications of the telomere region and TERT play significant roles in the transcription and activity of telomeres [33, 50, 51]. On the other hand, the establishment and maintenance of senescence growth arrest are tightly regulated by senescence-associated histone alterations. The role of the histone methyltransferases complex, polycomb repressive complex (PRC), in repressing the

Table 3 The alteration of histone-associated epigenetic processes in replicative senescence and their effects on senescence phenotypes

Epigenetic modulator	Alteration	Phenotype	Mechanism
Histone deacetylases, class I			
HDAC 1/2	↑	Cell cycle arrest	Promoting $p16^{INK4a}$ upregulation and pRB dephosphorylation by deacetylating H3K9Ac [28]
HDAC2	↑	Telomere shortening	Coordinating with the SWI/ SNF complex to inhibit expression of TERT [29]
Histone deacetylases, class II			
HDAC4	↓	Cell cycle arrest	Increasing endogenous SIRT1 expression by enhancing its sumoylation modification levels [30]
Histone deacetylases, class III			
Sirt1	↓	Cell cycle arrest; SASP	Upregulating $p21^{Cip1}$ by inhibiting the expression of MCP-1; hyperacetylating of the promoters of IL-8 and IL-6 [31, 32]
Sirt6	↓	Telomere dysfunction	Inducing telomere dysfunction-induced foci via upregulated H3K9Ac level [33]
Histone methyltransferases			
G9a	↓	Proliferation suppression	Inducing DNA damage response and inhibiting cell proliferation [34]
PRC2-EZH	↓	Cell cycle arrest	Increasing the expression of $p14^{ARF}$, $p15^{INK4b}$, and $p16^{INK4a}$ by repressing their H3K27me3 marker [35]
MLL1	↑	SASP	Depositing H3K4me3 at TSSs of SASP genes [36]
Histone demethyltransferases			
JMJD3	↑	Cell cycle arrest; SASP	Increasing the expression of $p14^{ARF}$, $p15^{INK4b}$, $p16^{INK4a}$, and SASP genes by repressing their H3K27me3 marker [37]
KDM6-UTX	↑	Proliferation suppression	Altering gene expression programs during cell fate changes by removing the H3K27me3 mark [38]
Histone variations			
H3.3cs1	↑	Cell cycle arrest	Silencing RB/E2F target genes [39]
γ-H2AX	↑	Telomere shortening	Colocalizing with DSB repair factors [40]
macroH2A.1.1	↑	SASP	Transcriptionally activating SASP genes [41]

HDAC histone deacetylase, *Sirt1* sirtuin 1, *PRC2* polycomb repressive complex 2, *EZH* enhancer of zeste homologue 2, *MLL1* myeloid/lymphoid or mixed-lineage leukaemia 1, *JMJD3* Jumonji domain 3, *KDM6* lysine demethylase 6, *UTX* tetratricopeptide repeat, X chromosome, *TERT* telomerase reverse transcriptase, *MCP-1* monocyte chemoattractant protein-1, *SASP* senescence-associated secretory phenotype, *TSS* transcriptional start sites, *RB* retinoblastoma

INK4/ARF locus has been thoroughly investigated. PRCs bind directly to the INK4/ARF locus and induce H3K27 trimethylation, which leads to repression of its transcription [52]. In addition, cell senescence can be prevented via inhibition of histone acetyltransferases (HATs) and can be induced by inhibiting histone deacetylases (HDACs) [31, 53, 54]. The NAD^+-dependent Sirtuins (SIRTs), especially SIRT1, are famous for their effects in ageing and senescence. Different Sirtuins have shared deacylation activity but harbour multiple differences in subcellular localization, regulation and substrate selectivity [55]. Accordingly, their roles in senescence and their epigenetic mechanisms vary among different Sirtuins. Nuclear Sirtuins (SIRT1, SIRT6 and SIRT7) may catalyse modifications of histone or non-histone proteins, such as transcription factors, and impact on senescence by regulating gene transcription and genome instability. SIRT6 depletion has been shown to give rise to the formation of telomere dysfunction-induced foci during cell senescence [33]. Reduction of SIRT1 leads to cell senescence by upregulating p53 acetylation and p21Cip1 expression [31, 56]. In contrast, extranuclear Sirtuins (SIRT2, SIRT3, SIRT4, SIRT5) may target enzymes involved in metabolism and antioxidative process and indirectly defend against senescence. For instance, SIRT3 has been reported to inhibit senescence phenotypes by deacetylating forkhead box protein O1 (FOXO1) and elevating the expression of its target genes, catalase and manganese superoxide dismutase (MnSOD) [57].

Those senescence-associated histone alterations interact with the senescence regulatory programmes giving rise to various senescence phenotypes, especially the senescence-associated secretory phenotype (SASP). The histone variant macroH2A.1.1 may upregulate the activity of the poly-ADP-ribose polymerase (PARP) 1 enzyme and induces SASP through the PARP-1/NF-κB signalling cascade [58]. In turn, secreted SASP factors upregulate the expression of macroH2A1 and form a positive feedback loop that further supports SASP gene expression [41]. Histone modifiers have also been reported to play an essential role in SASP. For example, methyltransferase MLL1 deposits H3K4me3 at transcriptional start sites (TSSs) of SASP genes and increases their expression by interacting with γH2A.X in oncogene-induced senescence [36].

Some histone modifications in senescence and ageing may be different and even contradictory. Ageing organisms show increased H4K16Ac, H4K20me3 or H3K4me3, along with decreased H3K9me and H3K27me3, which are quite different from cell senescence [59]. There are two main reasons for the difference of histone modification between cell senescence and ageing. First, ageing, which is characterised with the age-dependent accumulation of physiological and functional damage to cells, tissues and organs, is much complicated than senescence. Multiple potential sources for ageing-associated damage, such as gene mutagenesis, reactive oxygen species (ROS) and environmental insults, may have an impact on the epigenetic profile of ageing and make it different from cell senescence [60]. Second, although ageing organisms may create an environment that facilitates the initiation and progression of cell senescence, ageing organisms do not always show high cell senescence level [31]. Some epigenetic changes of the aged people may even play a protective function against senescence and contribute to their long life [61].

Altogether, histone-associated epigenetic processes directly respond to various induction factors, which lead to changes in chromatin structure and the gene expression profile that ultimately result in cell senescence. However, very few studies have focused on how these different senescence-associated histone alterations are induced by different factors. Therefore, further investigations are needed to explore the underlying mechanisms of the various senescence-associated histone alterations.

Chromatin remodelling complexes

Chromatin remodelling complexes use the power generated by ATP hydrolysis to alter DNA-histone contacts and thus impact chromatin status [62]. In eukaryotes, the four classes of chromatin remodelling complex families are as follows: switching defective/sucrose non-fermenting (SWI/SNF), nucleosome remodelling and deacetylation (NuRD)/chromodomain, helicase, DNA binding (Mi-2/CHD), inositol requiring 80 (INO80) and imitation switch (ISWI) [63]. These different subfamilies catalyse a diverse range of structural transformations, such as sliding histone octamers across DNA, removing histone octamers from DNA and changing the composition of the nucleosomes [64], and play an important role in the senescence process (Table 4).

The most researched and best understood ATP-dependent chromatin remodelling complex in cell senescence is the SWI/SNF complex. The SWI/SNF subunits BRM and BRG1 are involved in the regulation of cell cycle progression by modulating the transcription of cell cycle regulators, including RB, p53 and E2F [70, 71]. And the interaction between BRG1 and pRB may facilitate the formation of SAHF [72]. The SWI/SNF subunits BRD7 and BAF180 are required for both p53-dependent and independent regulation of $p21^{Cip1}$ [73, 74]. Moreover, the SWI/SNF subunit ARID1B can induce DNA damage and reactive oxygen species (ROS), which eventually leads to increased transcription of $p16^{INK4a}$, $p21^{Cip1}$ and p53 and results in cell senescence [65, 75].

The NuRD/Mi-2/CHD complex, as a prominent regulator of the establishment of heterochromatin, is critical for cell viability and proliferation. NuRD can be recruited to telomeres, which results in remodelling of telomeric chromatin and promotes homology-directed DNA repair at telomeres and thus prevents the onset of senescence [66]. Knockdown of CDK2AP1, a member of the NuRD complex, induces remarkable DNA damage and increases p53 and $p21^{Cip1}$

Table 4 The effects of chromatin remodelling complexes on senescence and their alteration in replicative senescence

Epigenetic modulator	Effects	Alteration
The SWI/SNF complex	Upregulating the transcription of $p16^{INK4a}$, $p21^{Cip1}$, and p53 [65]	Unknown
The NuRD/Mi-2/CHD complex	Promoting homology-directed DNA repair at telomeres; inhibiting DNA damage and the expression of p53 and $p21^{Cip1}$ [66, 67]	Unknown
The INO80 complex	Promoting homology-directed DNA repair at telomeres and inhibiting G2/M-G1 transition arrest by downregulating $p21^{Cip1}$ [41, 68]	Unknown
ISWI	Facilitating the recruitment of ATM and mediator of DNA damage checkpoint 1 (MDC1) [69]	Unknown

expression levels, which leads to cell senescence via G1-S phase transition arrest [67].

The INO80 complex plays important roles in telomere replication, dysfunctional telomere repair and the maintenance of genome stability. Ino80 deletion inhibits homology-directed DNA repair at telomeres by blocking the generation of single-strand DNA [68]. The INO80 complex helps ensure the normal progression of the cell cycle process, and it can be recruited to the $p21^{Cip1}$ promoter and negatively regulates its expression. Ino80 deletion induces G2/M-G1 phase transition arrest by increasing $p21^{Cip1}$ expression [76].

Taken together, the changes in chromatin remodelling enzymes may give rise to the DNA damage, genome stability, oxidative stress and telomere dysfunction that play an important role in cell senescence. However, the specific alteration pattern of these chromatin remodelling enzymes during cell senescence in vivo remains unknown. Further studies are needed to elucidate the substantial changes in chromatin remodelling enzymes in cell senescence and explore mechanisms underlying these changes.

ncRNAs

ncRNAs are non-protein-coding RNA transcripts, and the DNA sequence transcribing ncRNAs accounts for greater than 80% of the whole genome [77]. These transcripts have been regarded as transcription noise and junk RNA for many years but are now recognised to be essential regulators of gene expression and abundant cellular activities [78]. Numerous ncRNAs are differentially expressed during cell senescence (Table 5). Genome-wide RNA screening has identified a number of downregulated and upregulated ncRNAs in senescent cells compared with normal cells [84, 85]. Senescence has been reported to be an endogenous trigger for the expression changes in these ncRNAs and serves as their underlying signalling pathway [86]. Specifically, p53 promotes the expression of a wide range of senescence-associated ncRNAs by binding to their enhancer regions [87].

Senescence-associated ncRNAs play an important role in cell senescence by impacting on senescence regulatory programmes. Some ncRNAs are important for telomere integrity and genome stability. In particular, the ncRNA telomerase RNA component (TERC) is an integral part of the telomerase ribonucleoprotein (RNP) complex. TERC may function as the template for telomeric repeats and can facilitate the assembly of the telomerase complex [82]. In contrast, telomeric repeat-containing RNA (TERRA) can compete against TERT to bind telomeres and thus suppresses telomere elongation [83]. The senescence-associated ncRNAs that affect the senescence regulatory programmes eventually lead to various senescence phenotypes. First, many ncRNAs are involved in the regulation of cell proliferation and cell cycle arrest. Some ncRNAs play a role in inhibiting the transcript of the INK4/ARF locus. For example, the expression of the antisense lncRNA ANRIL is downregulated during cell senescence, which leads to increased $P14^{ARF}$, $P15^{INK4b}$, $P16^{INK4a}$ and Bcl-2 (a regulator of proliferation) [79]. Alternatively, some ncRNAs may promote the expression of the INK4/ARF locus. For instance, a very long intergenic ncRNA (VAD) and MIR31HG are strongly induced during senescence, which leads to increased $P14^{ARF}$, $P15^{INK4b}$ and $P16^{INK4a}$ [88, 89]. Second, some ncRNAs can modulate the expression of SASP genes. For instance, miR-146a/b inhibits the production of IL-1 receptor-associated kinase 1 (IRAK1). Suppression of miR-146a/b induces SASP via the upregulation of IRAK1 activity and the consequent activation of the NF-κB signalling cascade [81]. Moreover, cytoplasmic ncRNAs can regulate the translation of senescence- or proliferation-associated proteins or directly interact with them to modulate their activity. For example, circ-Foxo3 can interact with the anti-senescence protein ID-1, anti-stress proteins FAK and HIF1α and the transcription factor E2F1 in the cytoplasm. These interactions suppress the activity of these proteins and lead to increased cellular senescence [80].

In summary, cell senescence triggers changes in the expression of numerous ncRNAs. These senescence-associated ncRNAs affect cell senescence in turn and form a complicated network. These ncRNAs are required for the maintenance of

Table 5 The alteration of ncRNAs in replicative senescence and their effects on senescence phenotypes

Epigenetic modulator	Alteration	Phenotype	Mechanism
ANRIL	↓	Cell cycle arrest	Increasing the expression of $P14^{ARF}$, $P15^{INK4b}$, $P16^{INK4a}$, and Bcl-2 [79]
circ-Foxo3	↑	Cell cycle arrest	Suppressing the activity of ID-1, FAK and HIF1a, and E2F1 in the cytoplasm [80]
miR-146a/b	↓	SASP	Upregulating IRAK1 activity and the consequent activated NF-κB signalling cascade [81]
TERC	↓	Telomere shortening	Inhibiting the assembly of the telomerase complex [82]
TERRA	↑	Telomere shortening	Competing against TERT to bind telomeres [83]

TERT telomerase reverse transcriptase, *TERRA* telomeric repeats-containing RNA, *MCP-1* monocyte chemoattractant protein-1, *SASP* senescence-associated secretory phenotype, *IRAK1* IL-1 receptor-associated kinase 1, *ID-1* DNA binding protein inhibitor 1, *FAK* focal adhesion kinase, *HIF1a* hypoxia-inducible factor 1-alpha

senescence features and regulate almost all senescence phenotypes. Further studies are expected to explore the role of these senescence-associated ncRNAs in ageing-related diseases and the potential to use them as senescence biomarkers.

Interactions among different epigenetic mechanisms

The senescence epigenome is attributed to integrative cooperativity and multiple interlocking feedback mechanisms among various epigenetic modifiers, ATP-dependent chromatin remodelling complexes and ncRNAs. The combination of different epigenetic modifications establishes and maintains the specific senescence epigenetic landscapes.

In normal cells, the maintenance of DNA methylation and the establishment of H3K9 methylation are interdependent [90]. However, DNA methylation profiles reveal consistent senescence-associated hypomethylation in regions associated with H3K9me3 [91]. This finding suggests that senescence-associated hypomethylation is a passive process rather than an active process. This notion is supported by the mislocalization, decreased activity or expression of DNMT1 in senescent cells [13, 14]. Decreased DNMT1 results in the unsuccessful maintenance of DNA methylation patterns during cell division, which ultimately results in DNA hypomethylation. Senescence-associated hypermethylation typically associated with euchromatic histone markers, including H3K27me3, H3K4me3 and H3K4me1 [91], which may be induced by senescence stress. In contrast, de novo DNA methylation usually occurs around heterochromatic histone markers in normal cells [90]. Further studies are needed to clarify the mechanisms underlying the entirely different interactions between DNA methylation and histone modification in normal cells and senescent cells.

In addition to the interaction with DNA methylation, histone modifications are crucial for the activity of chromatin remodelling complexes. The ATPase activity of chromatin remodelling complexes is under the control of histone determinants [92]. Acetylated core histones can interact with the bromodomain of the central ATPase of SWI/SNF CRCs, which affects their activities [93]. In turn, chromatin remodelling complexes modify the balance between euchromatin and heterochromatin and act as important regulators of DNA methylation and histone modifications. For example, SWI/SNF CRCs facilitate the eviction of PRC2, which result in enhanced expression of the polycomb-targeted INK4/ARF locus [94]. The CTCF-CHD8 complex affects DNA methylation at CTCF binding sites [92]. Moreover, chromatin remodelling complexes may recruit a DNA modifier while inhibiting a histone modifier and vice versa. For example, BRG1 impedes the binding of DNMT1, P53, RB and retinoblastoma-like protein 2 RB2/P130 and recruits HDAC at the NANOG promoter [95].

ncRNAs are involved in the differential recruitment of epigenetic modifiers to specific loci and play an important role in the regulation of chromatin architecture. Both DNA methyltransferases and DNA demethyltransferases are under the regulation of ncRNAs during cell senescence. For example, MiR-29 can regulate DNMT3A, DNMT3B and the ten-eleven translocation (TET) family, which leads to senescence-associated DNA methylation alterations [96]. For histone modifications, ncRNAs have an impact on various histone modifiers by regulating their expression levels or affecting their interactions with their target genes. For instance, ANRIL has been shown to mediate PRC recruitment and repression of $p16^{INK4a}$ [97]. The activities of some histone variants may also be influenced by ncRNAs. For instance, the antisense very long intergenic ncRNA (vlincRNA) VAD inhibits the incorporation of the repressive histone variant H2A.Z at the promoters of INK4A genes, which gives rise to their increased expression [88]. Moreover, ncRNAs have an impact on chromatin remodelling complexes during cell senescence. For example, ncRNA MIR31HG is required for

PcG-mediated repression of the INK4A locus [89]. Altogether, these findings suggest that ncRNA may function as the scaffold of DNA methylation, histone modifications and chromatin remodelling and play a critical role in the senescence epigenome.

Taken together, different epigenetic modifications interact with each other, which result in specific senescence epigenetic landscapes and special senescence gene expression profiles. Senescence-associated histone modification alterations appear to be the most direct epigenetic response to senescence stress. Histone alterations induced by senescence stress facilitate senescence-associated changes in DNA methylation, chromatin remodelling complex activities and ncRNA expression [98]. These subsequent epigenetic alterations interact with each other and affect histone modifications in turn. Various senescence-associated epigenetic alterations and cell senescence interact with each other and comprise a complicated network to regulate various senescence phenotypes [99]. In many cases, there is only correlative evidence for the roles of epigenetic changes in cell senescence. Therefore, more functional evaluations of those senescence-associated epigenetic alterations using epigenetic perturbation experiments are looked forward. With the advent of gene-editing tools [100, 101], it is now possible to adjust histone modifications precisely and test their roles in cell senescence specifically. In addition, some epigenetic changes occurring during the onset of senescence have been shown to be neither responsible for induction nor prevention of senescence [102]. Those epigenetic changes are consequences of senescence other than causes but may function as markers of cellular senescence and even help in maintaining the senescent state [102].

Epigenetic therapy targeting cell senescence

As stated above, epigenetic mechanisms play an essential role in the initiation and development of cell senescence. Senescence-associated epigenetic alterations are attractive targets for the treatment of cell senescence. Epigenetic therapies targeting cell senescence may inhibit the accumulation of senescent cells and provide a new method to treat ageing-related diseases. Several inhibitors of DNA methylation or histone deacetylation are approved for the treatment of some haematological malignancies by the US FDA and have been used in the clinic for several years [103]. Interventions targeting histone methylation and ncRNAs are also widely used in clinical trials.

Recently, attempts have been made to use epigenetic drugs for the treatment of cell senescence. For example, the treatment of a DNMT inhibitor, RG108, has been shown to increase the expression of anti-senescence genes, downregulate the expression of $p21^{Cip1}$ and p53 and lead to significantly decreased SA-β-gal positive cells [14]. However, some DNMT inhibitors, such as 5-aza-2′-deoxycytidine (decitabine), have been shown to induce increased expression of $p16^{INK4a}$ and p53 and lead to a high number of DNA double-strand breaks [104]. Therefore, efforts to change specific DNA methylation patterns in the target senescent cells and select suitable epigenetic drugs are required for using DNMT inhibitors.

Targeting histone modification enzymes is more complex than targeting DNMTs because of their multiple subclasses and different cellular localizations. Nonetheless, drugs targeting histone modification enzymes could still be extremely powerful tools. The most studied and recognised epigenetic drug targeting cell senescence is resveratrol, an activator of SIRT1. The effect of resveratrol on cell senescence and proliferative dysfunction is mainly associated with the activation of SIRT1 and the AMPK-FOXO3 cascade [105].

Regarding ncRNAs, antisense ncRNAs or ncRNA mimics may facilitate the inhibition of senescence phenotypes [97]. Because ncRNAs may act as the scaffold of other epigenetic modifications and affect various phenotypes, epigenetic therapies targeting ncRNAs may simultaneously modulate multiple senescence-associated pathways, and the same is true for epigenetic drugs targeting DNA methylation or histone modifications. This characteristic of the action of epigenetic drugs allows for the simultaneous correction of the expression of abundant senescence-associated genes and the activity of multiple signalling pathways, which may lead to a better therapeutic effect [106]. However, due to the lack of specificity, side effects arising from inappropriate changes in some epigenetic modifications should also be considered. In addition, drugs inhibiting the senescence programme may promote tumour development. It is recommended to specifically administer epigenetic drugs to senescent cells by targeting cells with senescence biomarkers, such as $p16^{INK4a}$ [107].

Conclusions

Cell senescence is accompanied by changes in DNA methylation, histone-associated epigenetic processes, chromatin remodelling and ncRNA expression. Different epigenetic modifications interact with each other and regulate chromatin structure and gene expression and facilitate telomere dysfunction, DNA damage and oxidative stress, which result in cell senescence. The establishment of epigenetic mechanisms and cell senescence promote mutually and comprise a complicated network to regulate various senescence phenotypes. Epigenetic therapies targeting cell senescence may facilitate the inhibition of senescence phenotypes and lead to the reactivation of normal cellular activity. Those epigenetic therapies may modulate multiple senescence-associated pathways simultaneously and lead to a better therapeutic effect.

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