From cell to disease: Regulatory networks and mechanisms of super-enhancers in aging (Review)

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Abstract. Aging is accompanied by a gradual loss of cellular function and systemic weakening of the homeostasis of multiple tissues, leading to a variety of age-related diseases and eventual mortality. Super-enhancers are a distinct class of cis-regulatory elements with strong transcriptional activation properties; they are bound by a large number of key transcription factors and cofactors, and possess distinct characteristic modification marks of enhancers. The past decade has seen an exponential growth in the field of super-enhancer research, partly because of the strong transcriptional activity of super-enhancers. Super-enhancers are notably activated in response to aging or aging-related factors, and serve a pivotal role in aging and aging-related diseases by modulating key biological processes, including cell proliferation, differentiation and senescence. In the present review, the changes in super-enhancers under aging-related stimuli are initially discussed. The mechanistic contributions of super-enhancers to cellular senescence from the perspective of DNA damage and mitochondrial dysfunction, two hallmarks of aging, are then systematically summarized. Furthermore, the pathogenic involvement of super-enhancer dysregulation in specific age-related disorders, including atherosclerosis and type II diabetes, is explored, highlighting the potential of super-enhancers as therapeutic targets. Finally, the current challenges and prospects of super-enhancers within the context of aging biology are discussed, aiming to provide novel theoretical guidance for the treatment of age-associated diseases.

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1. Introduction

Aging is the result of a series of pathological, physiological and psychological processes, and refers to the biological processes in the last stage of individual growth and development. Epigenetic disorders, cellular gene instability, chromosomal telomere shortening (1), mitochondrial damage (2), DNA methylation changes (3), chromatin remodeling abnormalities and non-coding RNA dysfunction (4) all lead to aging. Notably, aging is the greatest risk factor for the majority of chronic metabolic diseases, including diabetes, atherosclerosis, hypertension, Alzheimer's disease and osteoporosis. The course of these diseases is long, and while some may show slow recovery, others may experience sudden worsening without prior recovery. For some of these diseases, such as hypertension and early-stage osteoporosis, there may be no obvious symptoms or signs in the early stage, making clinical manifestations difficult to detect. After the disease progresses, symptoms may become diverse. At present, although improving aging-related diseases such as Hutchinson-Gilford progeria syndrome, age-related metabolic dysfunction and type II diabetes has been achieved by delaying aging in specific parts of the body through a variety of methods, such as the activation of autophagy by rapamycin to promote the dissolution and clearance of premature aging proteins (5), intermittent treatment with the combination of aging scavengers dasatinib and quercetin (6), treatment with antisense oligonucleotides to inhibit DNA damage signal transduction (7) and metformin therapy (8,9), further research is still required.

Super-enhancers are a class of DNA cis-regulatory elements with transcriptional activation properties (10). They are mainly concentrated in variable regions of the genome and these regions are closely related to various disease lineages; therefore, they serve an important role in disease

diagnosis and treatment (11,12). When compared with ordinary enhancers, super-enhancers have a wider range of regional spans, a larger number of binding tissue factors and stronger sensitivity to interference (13). Under the influence of aging and aging-related factors, super-enhancers exhibit altered H3K27 acetylation levels and/or disrupted enhancer-promoter looping, which changes the transcription of their target genes (including MDM2, ANG and RNASE4 in senescent cells). Such dysregulation subsequently affects downstream gene networks and contributes to the pathogenesis of certain diseases and the aging process (14-16). Numerous studies have confirmed that super-enhancers can regulate cell senescence by regulating cell-cycle arrest, cell-cycle genes and DNA damage to cells, such as the cell cycle/cell senescence-related gene p16, which is considered a key marker of aging (14,16-18). Moreover, super-enhancers regulate cell senescence by regulating the expression of certain cytokines, such as IL-6, IL-8 and CCL2 (14,18,19), as well as by regulating mitochondrial function (20). Therefore, a comprehensive understanding of the relationship between super-enhancers and aging will assist in further understanding the mechanisms underlying the occurrence and development of age-related diseases.

In the present review, a systematic comprehensive analysis of the super-enhancers covering various age-related diseases has been conducted [such as atherosclerosis, type II diabetes (T2D), Alzheimer's disease, osteoporosis and hypertension], thereby addressing the key gap in the field of 'super-enhancers-aging-disease' axis that has not been fully explored. Additionally, the present review proposes that super-enhancers mainly drive cellular senescence through two core pathways: DNA damage and mitochondrial dysfunction, and link this mechanism to specific diseases (such as atherosclerosis, Alzheimer's disease and osteoporosis). The current review also performed in-depth multi-cell type analyses of atherosclerosis (endothelial cells, smooth muscle cells and macrophages), Alzheimer's disease (microglia, neurofibrillary tangles and amyloid plaques) and osteoporosis (osteoblasts and osteoclasts), to emphasize those nodes that have received less research or have not been studied yet. Finally, the current limitations and future development directions are discussed, aiming to provide research ideas and frameworks for the future study of super-enhancers in the prevention and treatment of aging and age-related diseases.

2. Changes of super-enhancers under aging or aging-related factors

Super-enhancers are a class of large genome domains, which have enriched enhancer activity, and are the main centers for regulating cell fate, pluripotency and disease occurrence. Super-enhancers are mainly concentrated in variable regions of the genome, which are large clusters of transcriptional enhancers with high concentrations of key transcription factors, cofactors and epigenetic modification marks. When compared with ordinary enhancers, super-enhancers have stronger activation characteristics (21). Super-enhancers identified by highly enriched chromatin immunoprecipitation sequencing (ChIP-seq) signals typically exceed 10 kb, whereas ordinary enhancers have a regional span of 200-300 bp; therefore, super-enhancers can provide a broader intensity range for specific enhancer markers, such as H3K27ac and H3K4me1 (22-24). In addition, the number of tissue factors to which super-enhancers bind and their sensitivity to interference differ from those of ordinary enhancers. Super-enhancers are largely composed of enhancer-associated RNA polymerase II and its associated cofactors and chromatin regulators, which contribute to the high levels of transcription of related genes (22). Super-enhancers control cell identity and coordinate cellular gene expression patterns in multiple types of cells and tissues during cell differentiation (22,25,26) and in multiple diseases, including various types of cancer (27,28), atherosclerosis (29) and autoimmune diseases (30-32).

Notably, super-enhancers are susceptible to local microenvironments. During senescence or under aging-related stress, super-enhancers exhibit distinct mechanisms of pathway enrichment. In the Wnt/β-catenin pathway, they mediate gene gating by tethering active MYC alleles to nuclear pores through β-catenin-AHCTF1 bridging (33). In the MAPK pathway, a super-enhancer-associated gene TTC8 promotes PHOX2B nuclear translocation to activate MAPK signaling (34), and in the TLR pathway, BRD4-bound super-enhancers drive SASP gene expression, linking to TLR-related inflammatory responses (18). For example, during cell differentiation and proliferation, super-enhancers are enriched in Wnt, TLR signaling pathways (35,36); during apoptosis, super-enhancers are enriched in MAPK signaling pathways; and during cellular inflammation, super-enhancers are enriched in MAPK, Wnt/β-catenin signaling pathways (37,38). The super-enhancer-regulated genes and the corresponding changes in age-related diseases are shown in Table I. This table indicates that there is a disorder of super-enhancers in a number of diseases related to aging, including atherosclerosis (39,40), myocardial infarction (41), heart failure (42,43), cardiac hypertrophy (44), coronary artery disease (45), abdominal aortic aneurysm (46), calcific aortic valve disease (47) and dilated cardiomyopathy (48) in cardiovascular diseases, hypertension (49,50) and type II diabetes (51) in metabolic diseases, osteoporosis (26) in metabolic bone diseases, Alzheimer's disease (52) in neurodegenerative diseases and multiple myeloma (53) in hematological malignancies. For example, in atherosclerosis, super-enhancers upregulate the expression of COX2/ICAM-1 to maintain the stability of endothelial cells (39,40); in osteoporosis, the BRD4/H3K27ac super-enhancer upregulates ZBTB16 to promote bone formation (26); in Alzheimer's disease, the H3K27ac super-enhancer upregulates the expression of BIN1, thereby increasing the risk of disease (52). In summary, super-enhancers regulate the progression of diseases by modulating the expression of adjacent genes. Therefore, an in-depth exploration of the expression patterns of super-enhancers in different diseases and pathological processes can provide effective targets for drug development and precise treatment of aging-related diseases.

3. Super-enhancers regulate cellular senescence

Cellular senescence is the termination of the permanent cell cycle, which affects the proliferation and differentiation of neighboring cells through synergistic interactions with the

Table I. Changes of super-enhancers and their regulatory genes in aging-related diseases.

Aging-related disease	Super-enhancer related genes/sequences	Genes regulated by super-enhancers	Biological effects on target genes	(Refs.)
Atherosclerosis	H3K27ac, H3K4me1	COX2, FOXL1, DLL4, CLDN5 and ICAM-1 increased	Modifies endothelial function to protect against atherosclerosis	(39,40)
Myocardial infarction	H3K27ac, H3K4me3, H3K9ac	CXCL2 and CXCL3 increased	Inflammatory chemokines are increased, exacerbating myocardial damage	(41)
Heart failure	BRD4, WISPER	SERTAD4 increased; COL3A1, FN1 and TGFB2 reduced	Cardiac fibroblast activation is increased and myofibroblast-associated α-smooth muscle actin is downregulated	(42,43)
Cardiac hypertrophy	IRX, HOX	NPPA and NPPB increased	Promotes hypertrophy of the ventricular myocardium	(44)
Coronary artery disease	ZMIZ1, DIP2B, CBFA2T3	CAMK2G and MAPK1 increased	Increases abnormal Ca^{2+} processing and apoptosis	(45)
Abdominal aortic aneurysm	ERG intronic SNP (rs2836411)	ERG reduced	Increases inflammatory response to abdominal aortic aneurysms	(46)
Calcific aortic valve disease	LINC01013	CCN2 increased	Increases aortic valve fibrosis	(47)
Dilated cardiomyopathy	SMYD1	PPARGC1, CASQ2 and SLC27A3 reduced	Regulates cardiometabolism in heart failure	(48)
Hypertension	MED1, PRDM6	AKR1B7 and SOX6 increased	Renin-producing cells are upregulated	(49,50)
Type II diabetes	THADA, ADCY5, WFS1, TCF7L2	KCNJ11, PPARG, ABCC8 and TCF7L2 increased	Apoptosis of pancreatic β cells is negatively regulated	(51)
Osteoporosis	BRD4, H3K27ac	ZBTB16 increased	Promotes mesenchymal cell osteogenesis	(26)
Alzheimer's disease	H3K27ac	BIN1 upregulated	Increases the risk of Alzheimer's disease	(52)
Multiple myeloma	NSD2, FGFR3	HJURP increased	Promotes multiple myeloma disease progression	(53)

immune system, and regulates the occurrence and development of organ senescence (54,55). Cellular senescence is affected by various endogenous and exogenous factors, including telomere shortening, DNA damage, genomic instability, epigenetic disorders and mitochondrial dysfunction (56-59). Notably, several studies have determined that super-enhancers can influence cellular senescence by regulating the transcription of cellular senescence-related genes (14,60). Based on this, in the present review, a unified mechanism is proposed: Upstream damage signals (including DNA damage and mitochondrial dysfunction) reconfigure the activity of super-enhancers, thereby initiating or inhibiting the transcriptional programs of specific aging-related genes, driving cells into an aging state, and the continuous accumulation of senescent cells further promotes the deterioration of tissue function and the occurrence of various age-related diseases. The present review aimed to elaborate on the regulatory mechanisms of super-enhancers in DNA damage-induced aging, aging related to mitochondrial dysfunction and the process of aging transforming into disease within this framework.

Super-enhancer-regulated DNA damage. DNA carries the genetic information necessary for the synthesis of RNA and proteins, and is a biological macro-molecule essential for the development of organisms. DNA damage refers to the abnormal changes in the structure of DNA molecules that occur spontaneously or under the influence of physical, chemical or biological factors during replication, including base mismatches and breaks. Nucleic acids are unstable and susceptible to both endogenous (genomic instability, epigenetic modification, oxidative stress and telomere shortening) and exogenous interference (such as ultraviolet radiation, ionizing radiation and alkylating agents); therefore, DNA damage is a constant threat. Sustained DNA damage triggers a signaling cascade that promotes cellular senescence in order to prevent replication of the damaged genome (61). Notably, super-enhancers serve a key role in this process by interacting with DNA damage repair pathways. Therefore, it is necessary to elucidate the underlying mechanisms and to identify potential targets for the protection against DNA damage. As shown in Fig. 1, the present study explored the molecular mechanisms

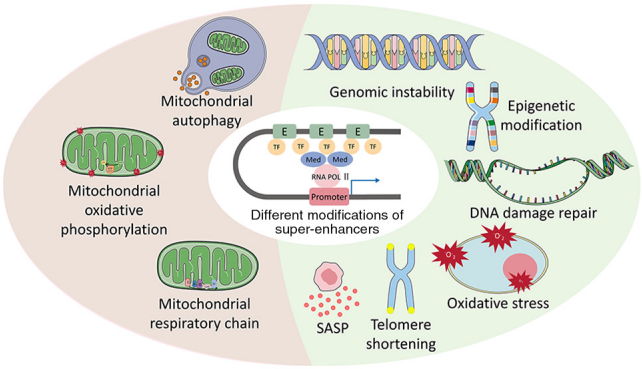

Figure 1. Super-enhancers exert different modifying functions in the regulation of cellular senescence. Cellular senescence is affected by a variety of factors, including DNA damage (genomic instability, DNA damage repair, epigenetic modification, oxidative stress, telomere shortening and SASP) and mitochondrial dysfunction (mitochondrial respiratory chain function, mitochondrial oxidative phosphorylation and mitochondrial autophagy). Super-enhancers regulate cellular senescence by modulating these aforementioned factors. E, enhancer; Med, mediator complex; RNA POL II, RNA polymerase II; SASP, senescence-associated secretory phenotype; TF, transcription factor.

by which super-enhancers regulate cellular senescence through genomic instability, epigenetic modifications, DNA damage repair, oxidative stress, telomere shortening and the senescence-associated secretory phenotype (SASP) in the DNA damage pathway.

Super-enhancers and genomic instability. Notably, the genome is unstable and any abnormal changes, such as base substitutions, deletions or insertions and copy number variations, lead to DNA damage, disrupt cell proliferation and reproduction, and hinder cell function. Studies have suggested that super-enhancers can cause DNA damage by regulating the translocation of chromosomes and the mutation of genes within the genome. For example, Meng *et al* (62) reported that super-enhancers can act on cytidine deaminase-related genes, such as IL4R, IL21R and NSMCE1, causing them to undergo translocation and leading to DNA damage. Glodzik *et al* (63) revealed that mutations in super-enhancers promote the expression of genes, such as ESR1 and ZNF217, which in turn induce DNA damage (63). In addition, super-enhancers induce activation-induced cytidine deaminase (AID) through recruitment activation, leading to partial mutation of antibody genes and chromosomal translocations (64). Abnormal enrichment of AID in the super-enhancer region may exacerbate DNA damage through antisense transcription (65).

Super-enhancers and epigenetic modifications. Epigenetic modifications include DNA methylation, histone modifications and chromatin remodeling, which are mostly unstable during the life cycle of somatic cells and are associated with DNA damage and aging (66-68). Previous studies have shown that super-enhancers regulate gene expression through changes in histone modifications, resulting in DNA damage. For example, the Aire factor in H3K27ac-related super-enhancers interacts with topoisomerase 1 to promote DNA damage (69). H3K27ac-related super-enhancers also alter epigenetic modifications by increasing the expression of the PDZK1IP1 gene (38). In addition, Zhang *et al* (70) demonstrated that deletion of H3K27ac-related super-enhancers can lead to mutations in BRCA1, resulting in DNA damage. In addition to histone modifications that can cause DNA damage, chromatin remodeling can also cause DNA damage. The SWI/SNF complex is a chromatin remodeling factor associated with super-enhancer activity, and aging-related mutations in SWI/SNF subunits, such as SMARCE1, disrupt super-enhancer-driven gene expression, and exacerbate DNA damage accumulation and cell senescence (71). By integrating histone modification and chromatin remodeling, super-enhancers display a dual function in DNA damage response: On the one hand, they drive the expression of repair genes to maintain genome stability, and on the other hand, they may cause genomic instability due to overactive transcription or abnormal recruitment of injury-related enzymes, thereby increasing cell senescence.

Super-enhancers and DNA damage repair. The interaction with DNA damage repair is also an important aspect of the regulation of DNA damage by super-enhancers. Super-enhancers have been confirmed to modulate genomic stability in senescent cells by the transcriptional regulation of DNA repair genes or recruitment of repair complexes. However, aberrant over-activation of these repair sites may accelerate replication stress, paradoxically accelerating aging (72). Studies have shown that super-enhancers drive the expression of the DNA repair gene HNRNPF by recruiting transcriptional coactivators such as BRD4, MED1 and P300. HNRNPF further regulates the expression of epigenetic modification enzymes such as PRMT1, thereby synergistically regulating the process of ribosome biogenesis and DNA repair (73). In addition, super-enhancers maintain the open state of chromatin by enriching active histone markers such as H3K27ac and H3K4me1, and promote the rapid recruitment of repair proteins such as 53BP1 and BRCA1 to the damage site. Notably, RCAN1.4 gene expression is dependent on the interaction of enhancers and promoters within topologically associating domains, and disruption of this structure can markedly impair the efficiency of DNA damage repair (74,75). Notably, super-enhancers can also promote recruitment of DNA damage repair factors by binding enhancer RNA (eRNA) produced by transcription to chromatin remodeling complexes. For example, the AT-hook domain of BRG1 can bind eRNA and mediate the enrichment of coactivators such as MLL3/4 and Med1 in the enhancer region, thereby regulating DNA damage response (76). However, studies have thus far mainly focused on the regulatory effects of super-enhancers on repair genes, and it is unclear whether repair pathway-related proteins regulate the activity of super-enhancers through epigenetic modification or chromatin remodeling feedback.

Super-enhancers and oxidative stress, telomere shortening and the SASP. In addition to the aforementioned genomic instability and epigenetic modifications, DNA damage is also affected by a range of other molecular factors such as oxidative stress, telomere shortening and the SASP. The essence of oxidative stress is that free radicals have negative effects on the body and can directly or indirectly oxidize or damage DNA, proteins and lipids; induce gene mutations, protein degeneration and lipid peroxidation; and cause physiological or pathological reactions in cells and tissues (77). Studies have shown that genes such as MUTYH, γH2AX and RNaseH2 are involved in oxidative stress-mediated DNA damage

responses, and also promote physiological and pathological changes such as colorectal carcinogenesis, disease progression in chronic myeloid leukemia and the pathogenesis of systemic autoimmune diseases (78-80). In the absence of telomerase, DNA polymerase cannot fully replicate linear DNA, resulting in the gradual shortening of telomeres during karyolysis (81). When telomeres reach a critical length, DNA damage response proteins mistakenly recognize the telomeres and activate DNA damage signals (1,56). Studies have shown that genes such as 53BP1, ATM, γH2AX and TRF2 can cause non-homologous end joining-mediated end-to-end fusion of short telomeres (82-86), which leads to DNA damage. In addition, senescent cells are special intervention targets for a variety of aging-related diseases as they secrete a complex set of pro-inflammatory cytokines, known as the SASP, which on one hand maintains and diffuses senescence, and on the other serves a role in promoting proliferation (87). Super-enhancers drive formation of the SASP by activating transcription programs of pro-inflammatory factors and matrix-remodeling proteins. For example, in DNA damage-induced aging models, super-enhancers recruit transcriptional regulators, such as Zscan4 and TAK1, forming a positive feedback loop that notably enhances the broad-spectrum expression of SASP and promotes the development of aging (88). Notably, to the best of our knowledge, little research has been conducted on whether super-enhancers can mediate DNA damage by regulating the genes involved in oxidative stress and telomere shortening, and the specific mechanisms involved have not yet been elucidated and require further exploration.

Super-enhancers regulate mitochondrial dysfunction. Mitochondria are dynamic organelles that produce and transport ATP for energy, and participate in cell differentiation, information transmission, fate determination and other processes (89,90). Mitochondria can malfunction when stimulated by age-related factors, including mitochondrial morphological changes, decreased mitochondrial content, impaired mitochondrial membrane potential (59), reduced electron transport chain complex activity (91), increased mitochondrial outer membrane permeability (92), mitochondrial respiratory chain abnormalities and increased levels of reactive oxygen species (ROS) (93). Mitochondria therefore serve an important role in aging and age-related diseases (59). Recently, several studies have confirmed that super-enhancers are involved in the regulation of mitochondrial function (94-96). Therefore, the present review not only aimed to elucidate the mechanisms by which super-enhancers regulate cellular senescence through the DNA damage pathway, but also to systematically summarize the key role of super-enhancers in regulating mitochondrial functions from the perspectives of mitochondrial respiratory chain function, oxidative phosphorylation (OXPHOS) and mitochondrial autophagy (Fig. 1).

Super-enhancers and mitochondrial respiratory chain. The mitochondrial respiratory chain, also known as the mitochondrial electron transport chain, contains a variety of enzyme complexes involved in important biological processes, such as inflammation, thermogenesis, hypoxia tolerance and glycolipid metabolism (97). When there is an insufficient oxygen supply to the cell, a chronic lack of nutrients or mutations in mitochondrial DNA, the mitochondrial respiratory chain is damaged, which leads to mitochondrial dysfunction, causes adverse reactions such as cell aging and eventually leads to aging and age-related diseases of the body. Super-enhancers can affect the mitochondrial respiratory chain by altering the degree of mitochondrial oxidative stress and lipid metabolism. For example, BET) inhibitors can block the action of BRD4-related super-enhancers, and thus reduce the expression of peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α). The reduced level of PGC-1α hinders mitochondrial respiration and its antioxidant stress ability, and it eventually damages the mitochondrial respiratory chain, resulting in the decline or loss of mitochondrial respiratory function (98). Simultaneously, the inhibition of BRD4-related super-enhancers reduces the level of mitochondrial lipid metabolism and destroys complex proteins in the mitochondrial respiratory chain, resulting in excessive accumulation of lipid peroxides and ultimately leading to ferroptosis (99). Through epigenetic regulatory mechanisms, super-enhancers upregulate NADPH oxidase genes, inhibit the expression of antioxidant oxidase genes and increase the levels of mitochondrial ROS, resulting in mitochondrial electron transport chain dysfunction (100). Cytoplasmic and organelle ion signaling also affects mitochondrial respiratory chain function by influencing the formation of respiratory chain complexes (101,102). In addition, it has been shown that communication between mitochondria and other organelles, or between themselves, can impact the uptake and release of ion signals and further affect the mitochondrial respiratory chain (103). However, the effects of super-enhancers on the signal transduction of the aforementioned ion signal transduction and inter-organelle communication in the mitochondria have not been clearly explained.

Super-enhancers and mitochondrial OXPHOS. The process by which mitochondria supply energy to cells depends on OXPHOS. ROS are almost entirely produced during this process and regulate and maintain the normal physiological functions of the body;. however, when the mitochondria are damaged, ROS levels markedly increase, preventing them from functioning normally, thus promoting cell senescence (104,105). It has been demonstrated that super-enhancers are involved in mitochondrial OXPHOS and ROS production, thereby affecting mitochondrial function. For example, histone deactelyase inhibitors can block the H3K27ac super-enhancer action of the c-Myc gene, resulting in abnormal mitochondrial OXPHOS, mitochondrial dysfunction and reduced cell viability (106). By contrast, MLX-related super-enhancers can regulate the SLC7A11 gene to promote the uptake of amino acids by cells, thus causing the production of antioxidants, and maintaining the redox-reduction balance in cells. However, in the case of MLX knockout, the super-enhancer loses its regulatory function in maintaining redox balance, leading to the elevation of intracellular ROS and metabolic disorders, thereby affecting the OXPHOS of mitochondria (107). Notably, substances such as glucose, fatty acids and amino acids produced by glycolysis have key roles in mitochondrial OXPHOS (108). Super-enhancers can change the energy metabolism balance of mitochondria by driving the high expression of genes related to glucose metabolism, lipid metabolism and amino acid metabolism. For example,

super-enhancers drive metabolic reprogramming of cells by activating transcription of key glycolytic enzyme genes (such as HK2 and LDHA), which manifests as increased aerobic glycolysis and decreased mitochondrial OXPHOS (96). Super-enhancers increase the uptake of amino acids such as glutamine by upregulating the expression of amino acid transporter alanine-serine-cysteine transporter 2 and glucose transporter 1, thereby promoting the mitochondrial tricarboxylic acid cycle to produce ATP. However, this metabolic reprogramming may exacerbate mitochondrial metabolic stress (96).

Super-enhancers and mitochondrial autophagy. A decline in mitochondrial autophagy is also an important cause of cellular senescence, in addition to mitochondrial respiratory chain damage and abnormal OXPHOS. Mitochondrial autophagy regulates the number of mitochondria required to meet the energy needs of cells; functionally defective mitochondria are selectively degraded as much as possible which prevents the accumulation of functionally defective mitochondria in the body, which has an important role in maintaining the normal function and shape of cells (109). Decreased or defective mitochondrial autophagy can lead to mitochondrial dysfunction and, if left unchecked, cellular senescence (110). Studies have shown that autophagy in organelles is associated with the regulation of super-enhancers. For example, curcumin promotes the expression of H3K4me1- and H3K27ac-related super-enhancers to promote lysosomal autophagy, thereby reducing the production of ROS, inhibiting the expression of BRD4 and effectively improving inflammation in the body (111,112). In addition, under hypoxia, the circular RNA calmodulin 4 and PURB proteins promote Beclin1 expression through the regulation of H3K27ac-related super-enhancers, thereby regulating endoplasmic reticulum autophagy (113). These findings suggest that super-enhancers are closely related to autophagy in lysosomes, the endoplasmic reticulum and other organelles. However, it is still unclear whether super-enhancers can also regulate mitochondrial autophagy, and this process requires further study.

4. Role of super-enhancers in aging-related diseases

Aging is a key driving factor for the occurrence and development of various age-related diseases such as atherosclerosis, Alzheimer's disease, osteoporosis, diabetes, coronary heart disease, hypertension and cerebral infarction. After elaborating on the dynamic changes and regulatory roles of super-enhancers in aging and age-related phenotypes, the present review will subsequently focus on the specific functions and molecular mechanisms of super-enhancers involved in atherosclerosis, Alzheimer's disease, osteoporosis and T2D.

Super-enhancers in atherosclerosis. Atherosclerosis is a chronic cardiovascular disease associated with aging and a common cause of death in older adults. According to the 2023 World Heart Report released by the World Heart Federation, 20.5 million individuals died from cardiovascular diseases worldwide in 2021, accounting for one-third of total global deaths, whereas in 1990 and 2019, the number of deaths from cardiovascular diseases was 12.1 million and 18.6 million, respectively, indicating that the number of deaths from cardiovascular diseases worldwide is increasing (114,115). Atherosclerosis refers to the formation of plaques by lipid deposition on the arterial wall of medium and large arteries, resulting in reduced blood flow or blocked blood outflow (116), which is characterized by the migration and infiltration of macrophages, proliferation of smooth muscle cells, endothelial damage and accumulation of intracellular and extracellular lipids. Although various factors contribute to the development of atherosclerosis, such as chronic inflammation (117), lipid metabolism and accumulation (118), epigenetics (119), immune disorders (120), hypertension, diabetes, smoking, mental health and environmental pollution, aging has been confirmed to be a markedly independent factor when all other factors are controlled. Thus, the present review aimed to explore the effects of super-enhancers on atherosclerosis in terms of the effects of aging and related factors on endothelial cells, smooth muscle cells and macrophages.

Endothelial cells, which cover the inner surface of blood vessels and are composed of a layer of flat cells, complete the metabolic exchange of plasma and interstitial fluid, regulate blood flow in blood vessels, and synthesize and secrete various bioactive substances to control blood pressure, vasoconstriction and relaxation. Endothelial injury is an initial stage of atherosclerosis. After endothelial injury, the integrity and permeability of the vascular intima change (121), and the apoptosis and shedding of endothelial cells promote the adhesion and aggregation of platelets (122). In addition, dysfunctional endothelial cells secrete various growth factors, such as VEGF-A and PDGF (123,124), as well as vasoactive substances, including endothelin-1 and angiotensin II (125,126), in order to stimulate smooth muscle cell proliferation and vascular wall contraction, exacerbating the progression of atherosclerosis. Previous studies have reported that super-enhancers are involved in endothelial cell proliferation, vascular development and formation, regulation of vascular homeostasis and other functions. Mushimiyimana *et al* (127) revealed that the endothelial cell-specific super-enhancer SE12313 modulates the ADAMTS18 gene to affect endothelial cell proliferation, leading to reduced or shortened endothelial sprouts and decreased cell proliferation. Kalna *et al* (40) demonstrated that H3K27ac super-enhancers can regulate the expression of ERG and endothelial genes, such as DLL4, CLDN5 and NRARP, to affect the development and generation of blood vessels (Fig. 2A). Endothelial cells not only influence the development of atherosclerosis through growth and proliferation, but also produce nitric oxide (NO), which serves an important role in regulating vascular tone and inhibiting platelet aggregation and leukocyte adhesion. Lubos *et al* (128) demonstrated that oxidative stress caused by endothelium-derived NO and ROS has a key role in vascular endothelial dysfunction and atherosclerotic thrombosis. Whether super-enhancers can affect the process of atherosclerosis by regulating the ability of endothelial cells to produce NO remains unclear, and further research on the relationship between super-enhancers and endothelial cells to produce NO is required in the future.

Vascular smooth muscle cells are the main components of vascular wall tissue and are essential for the maintenance of vascular tension; changes in their structure and function affect the basic function of blood vessels. During atherogenesis, vascular smooth muscle cells proliferate and

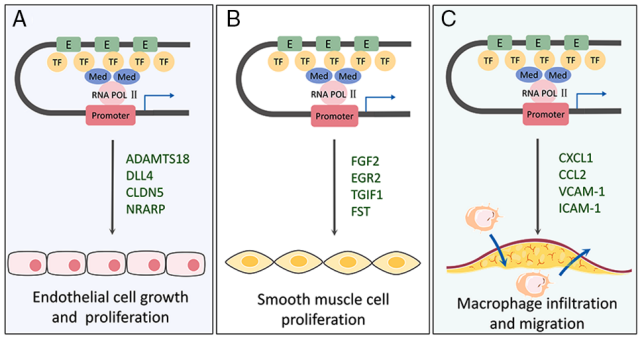

Figure 2. Function of super-enhancers in atherosclerosis. (A) Super-enhancers modified by SE12313, H3K27ac and other modifications can affect endothelial cell growth and proliferation by regulating the expression of genes such as ADAMTS18, DLL4, CLDN5 and NRARP, which in turn promotes the development of atherosclerosis. (B) Super-enhancers can be modified by H3K27ac and BRD4 to regulate angiotensin II-induced expression of genes such as FGF2, EGR2, TGIF1 and FST to control smooth muscle cell proliferation, which in turn promotes the development of atherosclerosis. (C) By driving the expression of CXCL1, CCL2 and other chemokines, and upregulating integrins VCAM-1 and ICAM-1, super-enhancers promote the migration of monocytes into plaques and differentiation into macrophages, thus promoting the formation of atherosclerotic plaques. E, enhancer; Med, mediator complex; RNA POL II, RNA polymerase II; TF, transcription factor.

migrate abnormally, secreting a variety of biologically active molecules, including extracellular matrix components such as collagens, elastin and proteoglycans, as well as cytokines such as MCP-1 and IL-1β, to form a fibrous cap that promotes vessel calcification, subsequently leading to plaque rupture, triggering apoptosis and exacerbating the disease process (129,130). Currently, there are few studies on the controlling role of super-enhancers in vascular smooth muscle cells. Some studies have suggested that super-enhancers can influence the proliferation function of vascular smooth muscle cells. For example, Das *et al* (39) reported that when H3K27ac- and BRD4-specific super-enhancers were missing, the expression of angiotensin II-induced FGF2, ERG2, TGIF1 and FST was notably reduced, which affected the proliferative and the protective functions of vascular smooth muscle cells (Fig. 2B). However, it is notable that although super-enhancers have been shown to serve a key role in vascular smooth muscle cell proliferation for the development of atherosclerosis, their other functions in the development of this disease have not been clearly elucidated. This provides a new research direction: To explore in depth how super-enhancers contribute to the development of atherosclerosis by influencing other behaviors and functions of vascular smooth muscle cells. Future studies should focus on how super-enhancers promote or inhibit the migration of vascular smooth muscle cells in the vessel wall, the formation of tough and structurally complex fibrous caps, and the promotion of vascular calcification.

Macrophages are immune cells with a strong phagocytic function and antigen-presenting ability that can secrete a large number of cytokines and chemokines. In the early stages of atherosclerosis, monocytes are recruited to the subendothelium to differentiate into macrophages, which further migrate and infiltrate as the disease progresses, and polarize into different subtypes according to the altered microenvironment (131). Studies have shown that super-enhancers recruit monocytes for targeted migration by directly regulating the expression of CXCL1, CCL2 and other chemokines (132,133). In addition, super-enhancers markedly enhance the interaction between macrophages and activated endothelial cells by upregulating adhesion molecules, such asVCAM-1 and ICAM-1, and promote the retention and differentiation of inflammatory cells in plaques (134) (Fig. 2C). In plaques, macrophages absorb lipid deposition particles and transform them into foam cells, thereby inducing an inflammatory response (135). Super-enhancers drive the transformation of macrophages into foam cells by regulating gene networks of glycolysis and lipid metabolism. Specifically, Wang *et al* (134) showed that super-enhancers activate the SREBP1/2 transcription factor, drive the expression of lipid synthesis genes, and promote the accumulation of intracellular lipid droplets and the formation of foam cells. In addition to regulating the migration and transformation of macrophages, super-enhancers can affect the pathological process of atherosclerosis by mediating the polarization of macrophages. Specifically, super-enhancers have been shown to notably increase the inflammatory response of plaques by driving the expression of pro-inflammatory genes and regulating the polarization of macrophages towards M1 type (111,136,137). Macrophages are also found in a number of other organs and tissues; for example, adipose tissue-associated macrophages, microglia, liver Kupffer cells, alveolar macrophages and renal macrophages (138-140). Recent evidence indicates that adipose tissue-derived exosomes can promote atherosclerosis progression by delivering bioactive molecules to vascular cells (141), and that super-enhancers regulate macrophage polarization and inflammation in atherosclerosis (136). However, the specific molecular mechanism of how super-enhancers regulate adipose tissue macrophages to affect atherosclerosis progression through exosome-mediated remote signaling still needs to be further explored.

Super-enhancers in Alzheimer's disease. Alzheimer's disease is a progressive neurodegenerative disease and is one of the most common causes of dementia in elderly individuals worldwide. Characteristic pathological changes include cerebral cortex atrophy, continuous proliferation of microglia, reduction in the number of memory neurons, formation of age plaques, β-amyloid deposition and neurofibrillary tangles (142). According to the United Nations Department of Economic and Social Affairs, the global proportion of individuals aged ≥65 years increased from ~7% in 2000 and is projected to reach 12% by 2030. Furthermore, according to the Centers for Disease Control and Prevention, the incidence of Alzheimer's disease approximately doubles every 5 years after 65 years of age. A total of 50% of individuals aged ≥ 85 years in the United States have Alzheimer's disease (143-145). Therefore, aging is considered the greatest risk factor for Alzheimer's disease (146-148). The present review discusses the influence of super-enhancers on Alzheimer's disease resulting from aging and its related factors on the continuous proliferation of microglia, and the formation of neurofibrillary tangles and amyloid plaques.

Microglia, which reside in the central nervous system, are mononuclear macrophages that are widely distributed throughout the brain and spinal cord, and are important for maintaining nervous system homeostasis. Microglia, the

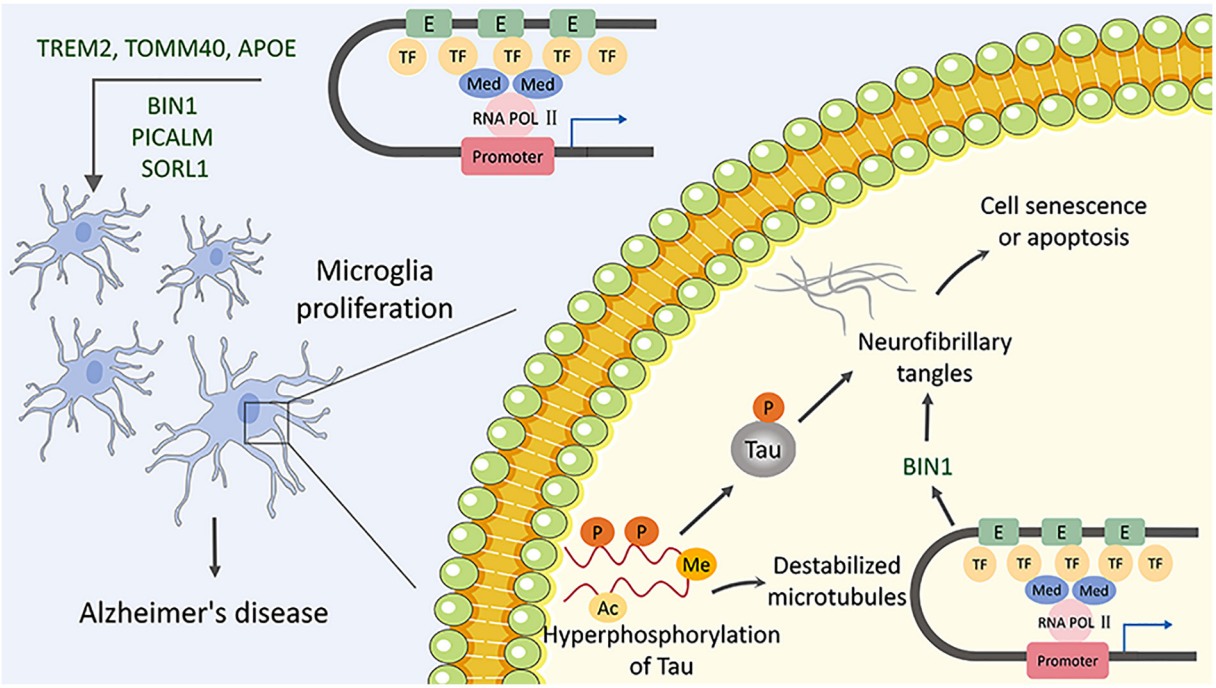

Figure 3. Function of super-enhancers in Alzheimer's disease. Super-enhancers, characterized by high levels of H3K27ac, can regulate TREM2, TOMM40 and APOE genes to activate microglia, and can also regulate BIN1, PICALM and SORL1 genes to promote the proliferation of microglia, which increases the risk of Alzheimer's disease. Tau proteins stabilize microtubules by phosphorylation but lose their biological activity in the presence of intracellular hyperphosphorylation and aggregate to form neurofibrillary tangles. Super-enhancers in microglia can affect the formation of neurofibrillary tangles by regulating the expression of the BIN1 gene, which leads to cellular senescence and apoptosis, and promotes the development of Alzheimer's disease. E, enhancer; Med, mediator complex; RNA POL II, RNA polymerase II; TF, transcription factor.

main regulators of neuroinflammation, are more sensitive to inflammation during aging, and their continuous proliferation is considered a hallmark of Alzheimer's disease (149,150). During aging, persistent inflammation and overexposure to oxidative environments results in microglia being continuously activated, leading to neurodegeneration, neuroinflammation and neurotoxicity (151,152). Previous studies have reported that microglial super-enhancers serve an important role in the risk of developing Alzheimer's disease. For example, Nott *et al* (153) revealed that H3K27ac super-enhancers can regulate genes, such as BIN1, PICALM and SORL1, to promote microglial proliferation, thereby increasing the risk of Alzheimer's disease. Jansen *et al* (154) demonstrated that H3K27ac super-enhancers can regulate TREM2, TOMM40, APOE and other genes to activate microglia, leading to neurodegeneration (Fig. 3). In Alzheimer's disease, microglia undergo sustained proliferation, abnormally phagocytose synapses and mediate synaptic loss. Lipid signaling in neuron-glia interactions is a key factor in this process, which involves relevant receptors or lipids such as TREM2, GM1 ganglioside and ApoE (155). Therefore, whether super-enhancers can modulate lipid signaling between neurons and glial cells, and thus the process of phagocytosis of synapses by the microglia, needs to be investigated in depth in the future.

Two pathological markers of Alzheimer's disease are the formation of neurofibrillary tangles and amyloid plaques (148,156). Neurofibrillary tangle formation is caused by the accumulation of tau proteins via hyperphosphorylation in cells. Tau protein is a soluble microcore-related protein that mainly stabilizes microtubules by phosphorylation. However, it loses its biological activity and becomes an insoluble protein under hyperphosphorylation, subsequently aggregating to form neurofibrillary tangles (157). Tau protein phosphorylation can promote the aging of brain cells, causing memory decline and neuropathological changes in Alzheimer's disease (158). Studies on neurofibrillary tangles have mainly focused on the relationship between the tau protein and BIN1. Chapuis *et al* (159) demonstrated that a genetic change caused by a 3-bp insertion in the 5' regulatory region of the BIN1 gene (~28 kb upstream of BIN1) can cause upregulation of BIN1 *in vivo*, which can increase the risk of Alzheimer's disease by interfering with tau biology. Furthermore, Nott *et al* (153) found that super-enhancers in microglia can regulate the level of the genetically determined BIN1 gene, increase the expression of the BIN1 gene and thus increase the risk of Alzheimer's disease, as well as the neuroinflammatory response and the activity of specific cell signaling pathways that promote the formation of neurofibrillary tangles (Fig. 3). Super-enhancers may reduce the neuroinflammatory response by modulating the activity of glial cells or inhibiting the release of inflammatory factors, thereby decreasing the extent of neurofibrillary tangles and reducing the risk of Alzheimer's disease (160-162). Specific cell signaling pathways also serve key roles in the formation of neurofibrillary tangles. Super-enhancers may reduce the formation of neurofibrillary tangles by modulating the activity of signaling pathways, such as the Wnt or nerve growth factor signaling pathways, in order to affect the function and structure of neurons (15,163,164). Research into the

mechanisms by which these super-enhancers regulate the formation of neurofibrillary tangles is required.

The accumulation of amyloid plaques is also a hallmark of Alzheimer's disease. In a degenerative disease state, β-secretase and γ-secretase break down amyloid precursor protein (APP), causing β-amyloid protein (Aβ) to produce Aβ40 and Aβ42 insoluble oligomers, which deposit amyloid plaques outside the cell and ultimately lead to neuronal death (165). Similar to tau phosphorylation, increased β-amyloid deposition promotes the aging of brain cells via mechanisms such as oxidative stress, DNA damage and activation of the p16/p21 senescence pathways, which in turn serves a key role in Alzheimer's disease (166,167). Thus far, research on amyloid plaques has mainly focused on APP gene mutations that lead to the development of Alzheimer's disease. Tanzi *et al* (168) reported that mutations in the APP, PSEN1 and PSEN2 genes alter the sequence of the APP exon encoding β-amyloid, demonstrating that mutations in these genes can affect chromosomal genetics. Although studies have determined that mutations in APP affect amyloid plaque formation, there is no evidence of a relationship between super-enhancers and APP or amyloid plaques (169-171). Furthermore, the aggregation and clearance of β-amyloid and transport of proteins within neurons also affect amyloid plaque formation (172,173). Notably, super-enhancers may affect the aggregation and clearance process of β-amyloid; they may reduce β-amyloid deposition by promoting β-amyloid degradation, for example by activating autophagy and proteasome pathways within cells, thereby reducing the formation of amyloid plaques (174,175). Abnormal intra-neuronal transport may also lead to abnormal aggregation of β-amyloid within neurons, thereby promoting amyloid plaque formation. Super-enhancers may regulate protein transport within neurons by affecting intracellular molecular mechanisms, thereby reducing the aggregation of β-amyloid within neurons and lowering the formation of amyloid plaques (15,176,177). An in-depth study of the aforementioned mechanisms of super-enhancers in regulating the formation of amyloid plaques will further promote the understanding of Alzheimer's disease and provide novel options for its treatment.

Super-enhancers in osteoporosis. Osteoporosis is a bone disease closely related to aging, characterized by bone mass loss, bone structure damage and increased bone brittleness, ultimately leading to a notable increase in the risk of fractures (178). As global population aging increases, osteoporosis has become one of the important causes of disability and death among the elderly. Under normal physiological conditions, the bones maintain skeletal homeostasis through the dynamic balance between bone formation by osteoblasts and bone resorption by osteoclasts (179). However, during the aging process, changes in hormone levels, such as estrogen and androgens, oxidative stress responses, chronic inflammation, dysregulation of epigenetic regulation and decreased differentiation ability of mesenchymal stem cells, all disrupt this bone homeostasis (180-183). In recent years, more evidence has shown that super-enhancers serve a key role in determining the fate of bone formation by osteoblasts and bone resorption by osteoclasts (22,26,184). Therefore, clarifying the regulatory network of super-enhancers in osteoporosis is expected to provide new targets for the treatment of osteoporosis, an aging-related disease.

In the process of bone formation by osteoblasts, super-enhancers directly affect the function of osteoblasts by regulating key transcription factors and signaling pathways involved in osteoblast differentiation. Yu *et al* (26) revealed that, during osteoblast differentiation, osteoblast-related genes such as ZBTB16, RUNX2 and SP7 are enriched around a large number of H3K27ac super-enhancers. Among them, the enhanced activity of super-enhancers targeting ZBTB16 was shown to markedly upregulate the expression of the ZBTB16 gene, promote osteoblast differentiation and increase the formation of mineralized nodules (26). Additionally, BRD4, as a key cofactor of super-enhancers, collaboratively drives the transcription of genes such as Runx2 and Osterix (also known as SP7) with H3K27ac super-enhancers during osteoblast bone formation, and the use of BRD4 inhibitors can notably inhibit osteoblast differentiation (185,186). However, there is a lack of dynamic mapping analysis at the single-cell level in aging bone tissue regarding how super-enhancers integrate upstream signals from estrogen deficiency or oxidative stress.

In terms of osteoclastic bone resorption, super-enhancers also affect the occurrence and development of osteoporosis by regulating osteoclast differentiation and function. Bae *et al* (22) discovered that, during the osteoclast differentiation induced by RANKL, multiple genes related to osteoclasts, such as NFATC1, C-FOS, ACP5 and CTSK, form new super-enhancers around them. The establishment of these super-enhancers depends on BRD4 and p300. Notably, RANKL shows a marked dose-dependent effect on super-enhancers in osteoclasts: Low concentrations of RANKL only activate ordinary enhancers, whereas high concentrations of RANKL or the formation of a chronic inflammatory microenvironment can induce the formation of super-enhancers, leading to excessive activation of osteoclasts (22). However, the distribution of osteoclast super-enhancers in aged bone tissue within the body and their interaction with osteoblast super-enhancers still require further investigation. Osteoclast-secreted exosomes are emerging as critical mediators of intercellular communication in the bone microenvironment, capable of delivering bioactive cargoes such as proteins and miRNAs to regulate the function of recipient cells (187). Additionally, whether super-enhancers can remotely inhibit osteoblast function by regulating exosomes secreted by osteoclasts remains unexplored.

Although super-enhancers have shown notable regulatory potential in osteoporosis, current research still faces a number of unanswered questions and knowledge gaps. On one hand, super-enhancers exhibit opposite regulatory characteristics in different environments. For example, ZBTB16-related super-enhancers can promote osteoblastic bone formation, while super-enhancers related to the NF-κB signaling pathway promote osteoclastic bone resorption and inhibit osteoblastic bone formation (185). On the other hand, the heterogeneity of super-enhancers in different types of bone cells, such as osteoblasts, osteocytes and osteoprogenitor cells, has not yet been systematically mapped. In osteoporosis, bone marrow mesenchymal stem cells exhibit an imbalanced differentiation pattern, with increased adipogenic differentiation at the expense of osteogenic differentiation, leading to bone marrow

adiposity accumulation and reduced bone formation (15,188). Future research on super-enhancers in osteoporosis should focus on developing *in vivo* super-enhancer tracing techniques, clarifying the heterogeneity of super-enhancers in different bone cell types and assessing the role of metabolic reprogramming, such as glycolytic reprogramming, regulated by super-enhancers in the determination of osteogenic and adipogenic differentiation.

Super-enhancers in T2D. T2D is a chronic metabolic disease characterized by insulin resistance and impairment of islet β-cell function, which accounts for 90-95% of all diabetes cases. Insulin resistance is a key feature of T2D; over time, the pancreas may produce less insulin in response to the body's needs, leading to hyperglycemia. The pathogenesis of T2D is complex, involving the interaction between multiple organs and systems. The main mechanisms include epigenetic regulation, insulin resistance and functional defects of islet β cells (189).

As a key element of epigenetic regulation, super-enhancers notably affect the progression of T2D by regulating the function of islet β cells, and insulin synthesis and secretion. Suzuki *et al* (190) showed that a T2D risk variant (rs231361) located in the KCNQ1 locus disrupts the interaction between the super-enhancer and the INS gene, ultimately triggering insulin secretion dysfunction. Notably, their single-cell chromatin accessibility analysis further revealed that the super-enhancers of T2D risk genes are enriched in islet β cells and can affect their transcriptional regulatory networks (189,190). Recent studies have suggested that the understanding of the pathogenesis of T2D needs to break through the traditional single-organ perspective and turn to multi-organ interaction network analysis at the level of systems biology. Super-enhancers may serve a role in the interaction between intestinal, fat, liver, muscle and islet β cells through dynamic regulation of metabolic organ core functions and cross-tissue signal transduction, thus driving the pathological process of T2D (191-194).

In addition, some clinical studies have revealed that non-coding single nucleotide polymorphisms (SNPs) serve an important role in T2D. Sun *et al* (51) demonstrated through 3D genomics analysis that T2D SNPs re mostly enriched in space-adjacent super-enhancers, and participate in chromatin interaction to regulate and affect transcription factor binding. Such SNP-super-enhancer interaction modules are markedly enriched in the Wnt signaling pathway, which may provide novel insights into the pathogenesis of T2D (51). Future studies may combine single-cell epigenomics and gene-editing techniques to further elucidate the dynamic regulatory mechanisms of super-enhancers in multi-organ interactions.

5. Concluding remarks and future perspectives

As a class of cis-regulatory elements with strong transcriptional activation properties, super-enhancers have stronger regulatory functions than enhancers and serve key roles in cell type-specific development, differentiation and the development of various diseases. Since their discovery, super-enhancers have received increasing attention from researchers and they are considered a new target and a new strategy for the treatment of disease. In addition, in a variety of diseases, such as atherosclerosis (29), Alzheimer's disease (149) and autoimmune diseases (30), super-enhancers have been shown to regulate the expression of genes and control cell differentiation, aging, death and other processes. Genetic and SNP analyses also support the contribution of super-enhancers to human aging and associated diseases. These findings have prompted researchers to investigate the role of super-enhancers in age-related diseases.

The present review systematically elaborates that in an aging microenvironment, the expression intensity of super-enhancers undergoes notable changes, and they drive the occurrence of cellular senescence through multiple pathways, thereby promoting the development of various aging-related diseases. As shown in Fig. 4, in the aging microenvironment, the expression of aging-related super-enhancers is upregulated, and induces the occurrence and development of cellular senescence through DNA damage pathways and mitochondrial dysfunction pathways. Among them, the DNA damage pathway includes genomic instability, abnormal epigenetic modifications, DNA damage repair, oxidative stress and telomere shortening; and the mitochondrial dysfunction pathway involves changes in mitochondrial respiratory chain function, OXPHOS and mitochondrial autophagy. The cellular senescence caused by the abnormal expression of super-enhancers can further promote the occurrence and progression of various aging-related diseases, such as atherosclerosis, Alzheimer's disease, osteoporosis and T2D. Specifically, cellular senescence affects the proliferation of endothelial cells and smooth muscle cells, as well as the migration and infiltration of macrophages, promoting atherosclerosis; it affects the proliferation of microglia and the formation of neurofibrillary tangles, promoting Alzheimer's disease; it regulates the bone formation process of osteoblasts and the bone resorption process of osteoclasts, promoting osteoporosis; and it damages the function of pancreatic β cells and insulin secretion, promoting the occurrence of T2D (Fig. 4). These findings reveal the core role of aging-related super-enhancers in connecting aging molecular mechanisms and the development of various pathological processes, providing evidence for the mechanistic research and exploration of therapeutic strategies for aging-related diseases.

Cellular senescence is affected by various endogenous and exogenous factors, partly depending on the action of super-enhancers, particularly DNA damage, telomere shortening and mitochondrial dysfunction. With the development of ChIP-seq and its combination with other omics-related studies, the potential role and mechanism of super-enhancers in cell aging and aging-related diseases has gradually been revealed (195-197). Current research on cell senescence has mainly focused on the effects of super-enhancers on DNA damage, organelle stress and oncogene activation (198-200). Therefore, the role of super-enhancers in other factors that influence cell aging, such as macrophage autophagy, protein homeostasis, nuclear integrity and nutritional dysregulation, should be further explored in subsequent studies. Concurrently, current research on age-related diseases has focused on the influence of super-enhancers on causative factors or genetics. For example, studies on atherosclerosis have mainly focused on the regulation of super-enhancers in

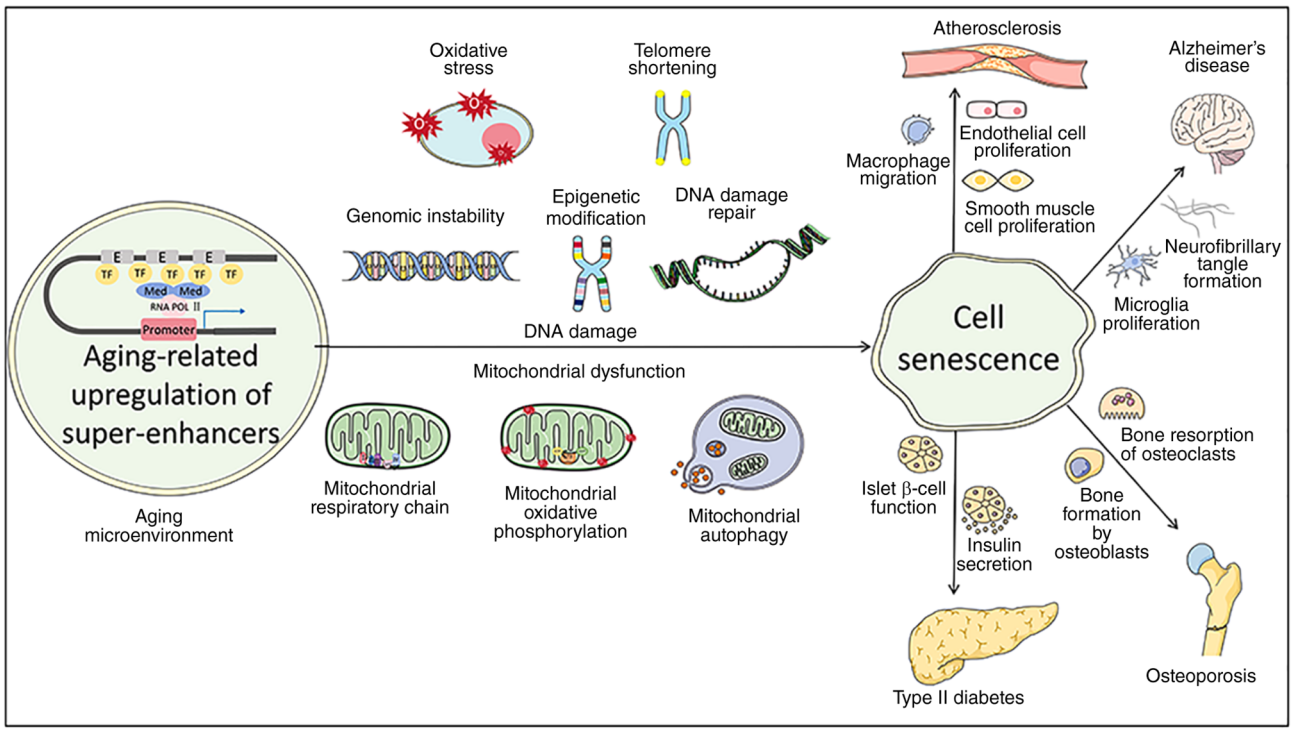

Figure 4. Aging-related super-enhancers drive cellular senescence through DNA damage and mitochondrial dysfunction, thereby promoting various aging-related diseases. In the aging microenvironment, the upregulated aging-related super-enhancers induce cellular senescence through two major pathways: DNA damage pathway (genomic instability, epigenetic modification, DNA damage repair, oxidative stress and telomere shortening) and the mitochondrial dysfunction pathway (changes in the respiratory chain, oxidative phosphorylation and mitochondrial autophagy). Cellular senescence further promotes atherosclerosis (endothelial cell proliferation, smooth muscle cell proliferation, and macrophage migration and infiltration), Alzheimer's disease (microglial cell proliferation and formation of neurofibrillary tangles), osteoporosis (osteoblast bone formation and osteoclast bone resorption) and type II diabetes (islet β-cell dysfunction and impaired insulin secretion). E, enhancer; Med, mediator complex; RNA POL II, RNA polymerase II; TF, transcription factor.

the accumulation of endothelial cells, proliferation of smooth muscle cells, and the migration and infiltration of macrophages. Research on Alzheimer's disease has focused on the super-enhancer regulation of microglial proliferation, neurofibrillary tangle formation and amyloid plaque formation. Therefore, the role of super-enhancers in the pathogenesis of age-related diseases, such as dysplasia of phagocyte exocytosis, low-density lipoprotein accumulation, cholesterol metabolism imbalance in atherosclerosis, synaptic dysfunction, neurotransmitter imbalance and neuroinflammation in Alzheimer's disease, should be further explored in subsequent studies.

Although super-enhancers have received increasing attention in regulating cellular senescence and related diseases, current research still faces a series of contradictory findings, methodological limitations and key knowledge gaps. Firstly, the functions of super-enhancers in aging show obvious duality. On one hand, super-enhancers can activate protective transcription programs to delay aging, for example, the transcription factor FOXP1 activates SESN3 through the super-enhancer mechanism, thereby delaying endothelial cellular senescence and inhibiting the progression of atherosclerosis (201); on the other hand, super-enhancers can drive pathological aging-related secretory phenotypes and promote the occurrence of related diseases. Additionally, the functions of regulatory factors also show contradiction. For example, the histone acetyltransferase p300 can induce the generation of new super-enhancers to drive cellular senescence during aging. However, in pathologically altered cellular states, such as in certain cancer cells where p300 function is disrupted or bypassed, or when hijacked by oncogenic transcriptional programs, p300 can conversely promote proliferation, facilitate senescence evasion and drive disease progression (16,202,203). Secondly, some methodological limitations also affect in-depth research on super-enhancers. Most current evidence comes from immortalized *in vitro* cell models, while *in vivo* studies using aging tissues or cells face significant hurdles. These include the challenge of detecting senescent cells with conventional markers that often perform poorly in native tissues, the extremely low abundance of senescent cells within tissue and their pronounced biological heterogeneity (14). The *in vitro* culture of senescent cells may not fully reflect the dynamic functions of senescent cells in the complex microenvironment *in vivo*. In terms of detection techniques, the enhancer identification methods such as ChIP-seq and CUT&Tag are highly dependent on the quality of antibodies and the setting of signal thresholds, and the identification results from different laboratories and instruments may have notable differences, making direct comparison difficult (133). Finally, it is not yet clear how super-enhancers integrate upstream signals from DNA damage response and mitochondrial dysfunction. Whether the super-enhancers identified from mouse cells have common regulatory patterns in human cells of different aging-related diseases (such as atherosclerosis and Alzheimer's disease) has also

Table II. The mechanism of action of super-enhancer regulators and their clinical trial stages.

First author, year	Drug name(s)	Target	Mechanism	Clinical trial stage	(Refs.)
Huang *et al*, 2019	THZ1	CDK7	Inhibits CDK7 and blocks transcription driven by super-enhancers	Preclinical, Phase I	(205)
Chen *et al*, 2022	CCS1477	CBP/p300	Inhibits the bromine domain of CBP/p300 and downregulates the activity of the super-enhancers	Phase I, Phase II	(206)
Li *et al*, 2022	JQ1, OTX015 and IBET-762	BET	Inhibits the BET protein and disrupts the binding of super-enhancers to the transcriptional complex	Phase I, Phase II	(111)
Skorupan *et al*, 2022	Minnelide	Super-enhancer complex	Inhibits heat shock factors and affects the function of super-enhancers	Phase II	(207)
Li *et al*, 2023	LSD1 inhibitors (such as GSK2879552) in combination with BET inhibitors	LSD1 + BET	Synergistic inhibition of transcription driven by super-enhancers	Preclinical, Phase I	(208)
Zheng *et al*, 2022	BRD4 inhibitors in combination with RET inhibitors (such as selpercatinib)	BRD4 + RET	Blocks the function of super-enhancers and the RET kinase signal	Preclinical, Phase I	(209)

CBP, CREB-binding protein; LSD1, lysine-specific histone demethylase 1.

not been clarified (204). The research on the mechanisms of super-enhancers in these aspects is largely lacking and further exploration is needed in the future.

By considering the differential expression of super-enhancers in aging-related diseases and their roles in regulating the occurrence and development of diseases, there is an urgent need to precisely control the levels of super-enhancers. Currently, the known super-enhancer modulators include the CDK7 inhibitor THZ1 (205), CREB-binding protein/p300 inhibitor (206), Minnelide (207), lysine-specific histone demethylase 1 inhibitor, BET inhibitor combination therapy (208), BRD4 inhibitor and RET inhibitor combination therapy (209). The super-enhancer regulators and their clinical trial stages are all listed in Table II. Although the discovery of these super-enhancer modulators makes it possible for them to serve as key targets for the treatment of age-related diseases, several questions remain unanswered before these modulators can be applied. First, there are a number of downstream target genes in the region where the super-enhancer modulator acts, and whether the regulator acts on these downstream target genes should be considered. Second, the issue of the dosage of super-enhancer modulators is should be considered to ensure that the regulator has a chance to work in the body without causing toxicity. Third, although combination therapy has an additive effect on super-enhancers, the potential accumulation of side effects should be considered in a clinical setting.

Furthermore, with the rapid development of science and technology, intelligent healthcare devices based on the Internet of Things have improved the early detection rate of age-related diseases by tracking the health data of the elderly in real time, bringing innovative changes (210). At the same time, super-enhancers are becoming a new hotspot in aging research because of their central role in gene expression regulation, and their potential to become biomarkers for disease diagnosis and treatment. Interventions such as small molecule inhibitors and gene editing techniques targeting the regulatory mechanism of super-enhancers may provide innovative strategies for delaying the aging process (211). Although super-enhancers as possible candidates for biomarkers show great potential in the intervention of aging-related diseases, there are still a number of challenges to achieving this goal. In the future, with the continuous development of gene sequencing technology, gene editing technology and epigenetic regulation technology, the dynamic regulatory mechanism of super-enhancers, as well as the development of cross-disease common targets and innovative intervention technologies, can be focused on so as to find more effective and safe treatment methods.

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Availability of data and materials

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Authors' contributions

XW reviewed the literature, synthesized the data, constructed tables and charts, and drafted and wrote the initial version of the paper. WD established a literature database, organizing the references, and made critical revisions to important academic content. ST was responsible for project management, created visual content, and participated in the writing and editing of the paper. HT designed the review framework, formulated the literature search strategy, verified the data, and made critical revisions to the initial draft. KY provided institutional resources, software access rights, and administrative support, and assisted in the review and editing of the paper. XZ was responsible for the overall research design, revised the paper, sorted out the feedback and ultimately approved the final version. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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