Aging and Disease
www.aginganddisease.org
Early access date: January 9, 2026
http://dx.doi.org/10.14336/AD.2025.0882

Review

Alternative Polyadenylation in Aging and Aging-Related Diseases

Mengqi Chen[1#], Xiangyu Zhu[2#], Lejia Hang[2], Zijie Yan[3], Li Xu[4], Fang Liu[5], Qiong Zhang[1*], Jingjing Huang[1*]

[1]Department of Geriatrics, The Fourth Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China. [2]Nanjing Medical University, Nanjing, Jiangsu, China. [3]Kangda College of Nanjing Medical University, Lianyungang, Jiangsu, China. [4]Chronic Disease Management Department, Community Health Service Center, Nanjing, Jiangsu, China. [5]Department of Imaging, Shandong Medical College, Jinan, Shandong, China.

[Received July 15, 2025; Revised December 24, 2025; Accepted December 25, 2025]

ABSTRACT: Aging is a major risk factor for a wide range of chronic diseases. Elucidating the molecular mechanisms underlying aging-associated disorders is essential for developing effective preventive and therapeutic strategies. Recent research has unveiled the regulatory roles of non-coding genomic regions. Among these, alternative polyadenylation (APA), a conserved co-transcriptional mechanism, has emerged as a key modulator of gene expression, with an established involvement in various age-related pathologies. APA alters the length of the mRNA 3' untranslated region (3′ UTR), thereby affecting mRNA stability, localization, translational efficiency, and ultimately protein expression. Notably, approximately 70% of human genes undergo APA-mediated regulation, underscoring its extensive influence on cellular function. This review summarizes the advances in exploring the role of APA in aging-related diseases, including musculoskeletal disorders, neurodegenerative diseases, cardiovascular and respiratory diseases. These findings can verify the potential of APA as a novel regulatory player in aging biology and a mechanistic contributor to the pathogenesis of age-associated diseases, highlighting its promise as a therapeutic target.

Keywords: Alternative polyadenylation, aging, 3' untranslated region, gene expression regulation

INTRODUCTION

Aging refers to a progressive functional decline starting from adulthood in organisms. It occurs at the organismal, organ/tissue, and cellular levels, each of which reflects the cumulative effects of time on biological systems. At the molecular level, aging is defined by several hallmark features, such as genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, interrupted intercellular communication, chronic inflammation, dysbiosis, extracellular matrix changes, and psychosocial isolation. This process culminates in molecular damage accumulation, cellular dysfunction, and systemic homeostasis imbalance, ultimately eroding biological complexity and heightening susceptibility to age-related pathologies [1]. At the organismal level, aging is closely associated with an increased susceptibility to a wide spectrum of diseases, including musculoskeletal disorders; neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD); cardiovascular conditions, such as atherosclerosis (AS), heart failure (HF), and pulmonary hypertension (PH); and respiratory diseases, such as chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis. Additional aging-related conditions include systemic sclerosis, diabetic nephropathy, and osteoarthritis. Emerging evidence suggests that aging phenotypes and age-related pathologies arise from the

***Correspondence should be addressed to:** Dr. Jingjing Huang, The Fourth Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210031, China. Email: Jingjinghuang@njmu.edu.cn. Ms. Qiong Zhang, The Fourth Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210031, China. Email: 1067020228@qq.com. # These authors contribute equally to this work.

intricate interplay between external environmental factors and internal genetic regulatory mechanisms [2].

Among the key hallmarks driving the process of aging, epigenetic alterations have been identified as critical contributors, whereas the loss of genetic information has recently been proposed as a potentially reversible phenotype of aging [3]. In parallel, increasing evidence highlights the pivotal role of post-transcription in the initiation and progression of age-related diseases via regulating alternative isoform usage, RNA stability, localization, and translational efficiency [4-6]. Post-transcriptional regulation is mediated by a range of molecular processes, including RNA modifications such as N6-methyladenosine (m6A) methylation and RNA editing [7]. Additionally, non-coding regulatory elements, particularly within the 5′ and 3′ untranslated regions (UTRs) of mRNAs, play essential roles by serving as binding platforms for RNA-binding proteins (RBPs) and microRNAs (miRNAs) [8]. Features intrinsic to coding regions, such as codon usage bias, also contribute to the regulation of transcript fate and protein output [9].

Role and function of apa in gene regulation

In eukaryotic cells, messenger RNA (mRNA) maturation requires the cleavage at specific polyadenylation sites (PAS), followed by the addition of a poly(A) tail at the 3' end, a process tightly regulated by co-transcriptional factors, and essential for mRNA stability, export, and translation. Traditionally, the 3' UTR of mRNA is regarded as a non-coding segment with limited biological relevance. However, recent advances in co-transcriptional biology have fundamentally overturned this view. It is now well established that approximately 70% of human protein-coding genes contain multiple PAS, enabling the selective use of APA to generate transcript isoforms with variable 3' UTR lengths and distinct poly(A) tail structures [10-12].

APA is generally classified into three types based on the location of PAS. The first type, representing the predominant form of APA, is 3′ UTR-APA. It is characterized by cleavage within the 3' UTR that modulates transcript length and meanwhile preserves the original coding capacity. As the second type, alternative terminal exon APA involves the selection of an alternative terminal exon containing the PAS. This results in mRNA isoforms with divergent 3′UTR sequences and, when the alternative exon encodes protein sequence, distinct C-terminal protein domains due to altered coding sequences [13, 14]. The third type is coding region APA (CR-APA) that occurs within protein-coding exons or introns. Intronic APA and internal exon APA, both exhibiting a much lower prevalence, are defined by cleavage events proximal to the annotated stop codon, frequently generating truncated isoforms through premature transcriptional termination (Fig. 1) [15-17]. APA is regulated by a combination of cis-acting sequence elements and trans-acting RNA processing factors [18]. Key cis-elements include canonical PAS motifs, such as AAUAAA (commonly found in distal PAS [dPAS]) and its proximal PAS (pPAS) variants which are typically located 10–30 nucleotides upstream the cleavage site. Additional conserved motifs, including UGUA elements upstream and U-/GU-rich sequences downstream of the PAS, are essential for recruiting multi-protein complexes involved in APA-mediated regulation, namely CPSF, CstF, CFIm, and CFIIm [10, 11, 18].

The core cleavage and polyadenylation machineries comprise CPSF, CstF, CFIm, and CFIIm. CPSF (CPSF160, CPSF100, CPSF73, CPSF30, WDR33, FIP1) recognizes the AAUAAA signal, with CPSF73 functioning as the endonuclease and FIP1 recruiting poly(A) polymerase [19]. CstF (CSTF50, CSTF64/64τ, CSTF77) binds to downstream GU-rich elements through CSTF64/64τ to promote processing [20]. CFIm (CFIm25 with CFIm68/59) recognizes UGUA motifs and promotes distal PAS usage, while its depletion leads to widespread 3′UTR shortening [21, 22]. CFIIm couples with cleavage to transcription termination and favors proximal PAS [23]. Together, these complexes accurately orchestrate PAS selection and determine 3′UTR length dynamics in aging-related contexts.

Beyond cis-elements and transacting-factors, RNA polymerase II (Pol II) also plays a pivotal role in the regulation of APA through its transcriptional elongation kinetics. The elongation rate of Pol II influences the events in co-transcriptional RNA processing, including splicing and 3′ end formation. Pol II termination factors, including RBBP6, XRN2, the PAF1 complex, SCAF4/8, and SSU72, constitute a multifunctional protein system that mediates transcriptional termination and extensively interfaces with RBPs. These interactions, encompassing core splicing factors and cleavage and polyadenylation (CPA) components, allow to recognize RNA sequence motifs and coordinate the precise timing and location of pre-mRNA cleavage and polyadenylation [11, 18, 24].

Two principal models have been proposed to explain the mechanistic basis of APA-mediated regulation. In the “first come, first served” model, pPAS generally exhibit a lower functional potency relative to distal downstream counterparts [25]. The relative activity of PAS during transcription primarily determines APA outcomes. A stronger pPAS promotes the cleavage at upstream sites, yielding mRNA isoforms with shorter 3′ UTRs, whereas dominant dPAS usage results in longer 3′ UTRs. PAS strength is decided by both cis-acting sequences and trans-acting regulatory factors [26]. In contrast, the sequential polyadenylation model posits that CPA events

can occur co-transcriptionally. Under this model, the transcripts initially cleaved at dPAS may remain in the nucleus and undergo additional processing at upstream pPAS, producing shorter isoforms from longer precursors. This delayed cleavage provides a greater regulatory plasticity, as APA site selection is influenced not only by transcriptional kinetics and PAS accessibility, but also the events in co-transcriptional processing [27, 28].

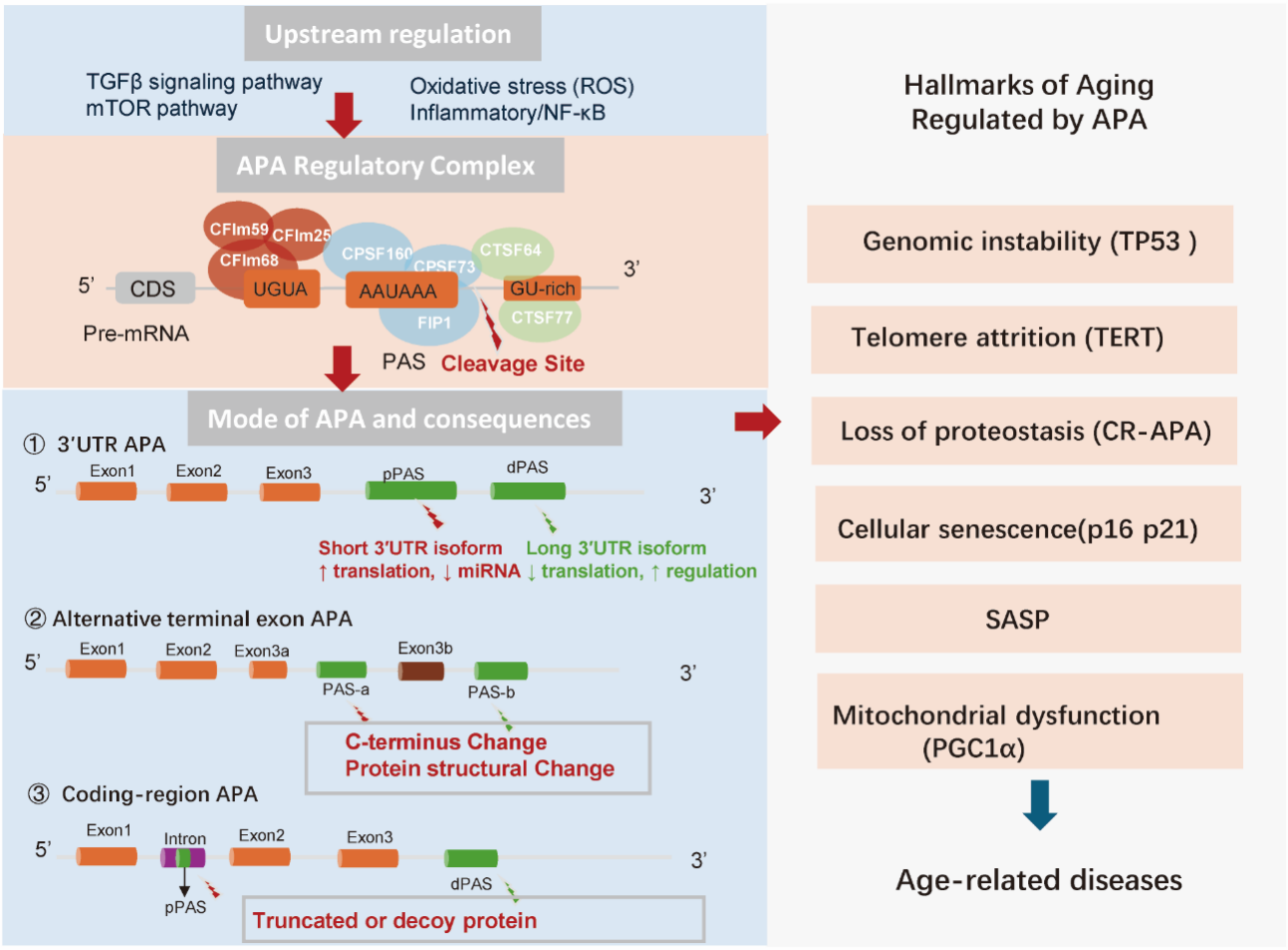

FIGURE 1. Co-transcriptional Alternative Polyadenylation (APA) links post-transcriptional gene regulation to aging hallmarks. This schematic illustrates how APA regulates transcript diversity and impacts aging hallmarks through a multi-layered mechanism. Upstream regulatory pathways (TGF β , mTOR, oxidative stress, inflammatory signaling) influence APA by modulating trans-acting factors (CPSF, CstF, CFIm) and RNA polymerase II elongation kinetics, thereby determining proximal versus distal polyadenylation site (PAS) usage. APA occurs co-transcriptionally on pre-mRNA and results in distinct APA modes: (i) 3'UTR APA alters UTR length without changing the coding sequence, affecting miRNA binding, mRNA stability, and translation efficiency; (ii) alternative terminal exon (ALE) APA generates isoforms with different protein C-termini and cellular localization; and (iii) coding-region APA (CR-APA, including intronic APA) produces truncated protein isoforms with modified or lost function. These APA-mediated changes in mRNA stability, translation, and protein isoforms converge on multiple hallmarks of aging, including genomic instability, telomere attrition, proteostasis loss, cellular senescence/SASP, and mitochondrial dysfunction, ultimately contributing to age-related diseases.

The selective usage of alternative PAS is tightly regulated by a complex network of APA-associated factors, till the generation of transcript isoforms with variable 3′ UTR lengths. This molecular diversity enables a single gene to produce multiple mRNA isoforms, thereby fine-tuning gene expression through transcript heterogeneity and expanding the functional repertoire of the genome. Transcripts with longer 3′ UTRs typically harbor multiple cis-regulatory elements that serve as binding platforms for microRNAs (miRNAs) and RNA-binding proteins (RBPs). These elements may disappear in short 3′ UTR isoforms, leading to divergent co-transcriptional fates [15]. Moreover, miRNAs regulate gene expression by binding to target sites within the 3′ UTR, thereby modulating mRNA stability and translation. Similarly, RBPs interact with cis-elements in the 3′ UTR to influence transcript localization, stability, or translational efficiency. Notably, miRNAs and RBPs may

act synergistically or antagonistically at overlapping or adjacent binding sites, adding further a complexity to APA-mediated gene regulation [24].

Dysregulation of APA can reprogram the output of intracellular signaling pathways and alter the cellular responsiveness to environmental cues. In addition to modulating protein abundance, APA has emerged as a key determinant for mRNA subcellular localization and the spatial dynamics of protein synthesis. Increasing evidence also implies APA as a critical co-transcriptional mechanism regulating age-related genes and contributing to the pathogenesis of aging and aging-associated diseases (Fig. 2) [11, 24].

Beyond tandem 3′UTR APA, coding-region APA, especially intronic polyadenylation (IPA) and internal-exon PAS usage, is implicated in age-associated pathology through modulating open-reading frames or reducing full-length output and. IPA preferentially truncates very long transcripts with low U1 small nuclear RNA to PAS ratio [29]. An example is IPA in *platelet-derived growth factor receptor alpha (PDGFR α)*, which produces a decoy receptor inhibiting PDGF signaling and modulating fibrotic activation in muscle progenitor cells. Dysregulation of this IPA contributes directly to fibrosis in aging, highlighting its mechanistical significance [30].

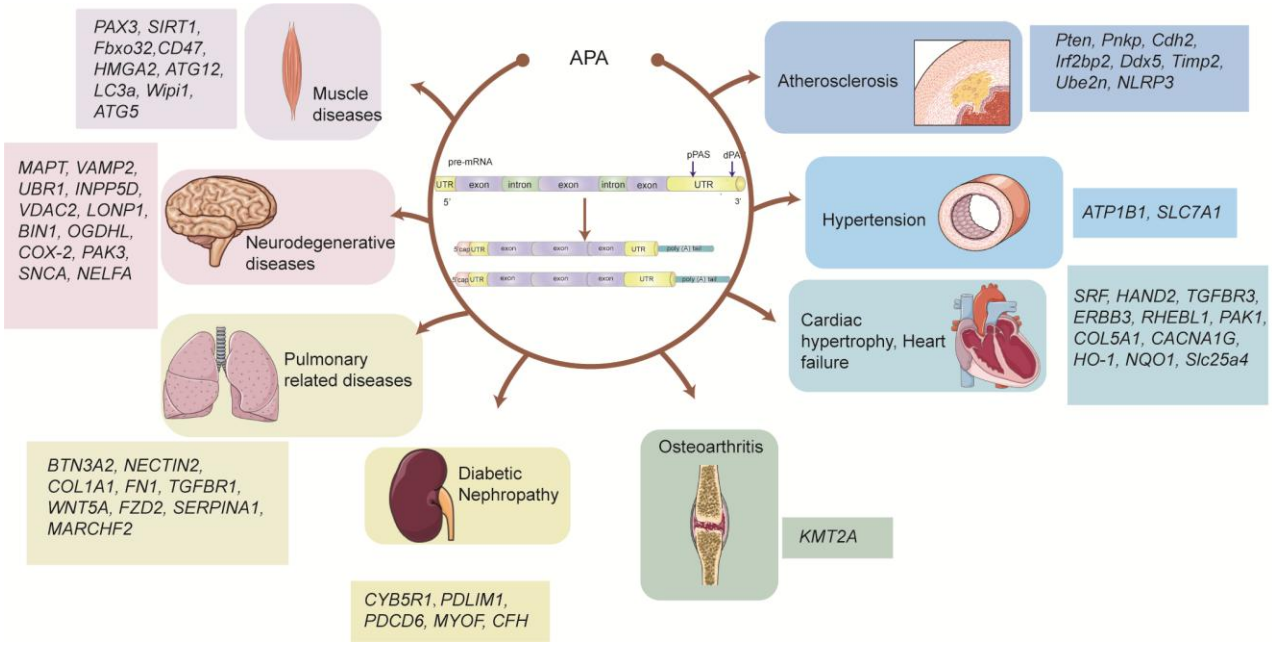

Figure 2. An overview of APA and aging-related diseases. Schematic overview of the role of APA dysregulation across various age-related conditions. Gene symbols within the diagram represent examples of genes whose expression or isoform balance is modulated by APA in the context of specific diseases. (Fig. 2 includes modified templates from Servier Medical Art (http://smart.servier.com), licensed under a Creative Commons Attribution 4.0 Unported License.)

APA and aging-related diseases

APA and muscle-related disorders

Sarcopenia is an aging-associated syndrome characterized by the progressive loss of skeletal muscle mass and strength, which significantly increases the risk of disability, morbidity, and mortality in older adults [31]. The pathogenesis of sarcopenia is multifactorial, involving mechanisms such as myofiber atrophy, impaired muscle regeneration, degeneration of neuromuscular junctions, cellular senescence, chronic low-grade inflammation, insulin resistance, adipose tissue dysfunction, and hormonal imbalances [32]. Among them, the dysfunction of muscle stem cells (MuSCs) plays a central role in age-related muscle deterioration and regeneration. Importantly, APA has emerged as a key co-transcriptional mechanism regulating stem cell fate and function [33].

CD47, a transmembrane protein involved in cell-cell communication, is closely associated with myogenic processes. In senescent MuSCs, elevated levels of U1 small nuclear RNA (U1 snRNA) promote the usage of dPAS within the *CD47* transcript. It has been demonstrated that the length of the 3′UTR directly influences CD47 protein localization: isoforms with shorter 3′UTRs produce CD47 proteins that are retained in the endoplasmic reticulum, whereas those with longer 3′UTRs bind to the RNA-stabilizing complex HuR, facilitating the trafficking to the cell membrane.

Consistent with this mechanism, aged MuSCs exhibit a significantly increased expression of U1 snRNA and a corresponding elevation in surface CD47 levels [16]. Furthermore, the inhibition on U1 snRNA activity via a targeted antisense morpholino (U1 AMO) can reduce the abundance of the long *CD47* mRNA isoform and decreases the content of membrane-localized CD47 protein. Thus, U1 snRNA-mediated APA shifts promote CD47 surface expression, which disrupts paracrine signaling, inhibits functional MuSC proliferation, and ultimately impairs muscle regeneration [34].. The activation of MuSCs is also regulated by the transcription factor Pax3. Specifically, miR-206 targets the binding sites located in the long 3′UTR isoforms of *Pax3* transcripts to repress translation. U1 snRNA influences APA site selection within *Pax3* mRNA, tilting the balance between long and short isoforms. This APA-dependent regulation of *Pax3* is critical for the transition of MuSCs from quiescence to an active, regenerative state [35, 36].

Another contributor to age-related muscle wasting is the reduced expression of poly(A)-binding protein nuclear 1 (PABPN1), a multifunctional RNA-binding protein that regulates poly(A) tail length, APA at both 3′UTRs and intragenic sites, and nuclear export of mRNA transcripts [37]. In addition, PABPN1 influences the expression of genes involved in the ubiquitin-proteasome system, autophagy, and mitochondrial function. PABPN1 is particularly enriched in human skeletal muscle, where its expression declines significantly with age. This reduction associates with myofiber atrophy and the diminishment of regenerative capacity. In the context of cellular aging, PABPN1 modulates translational efficiency through APA. When PABPN1 levels fall below a critical threshold, muscle atrophy and functional deterioration are triggered [38, 39]. Notably, reduced PABPN1 levels are a pathological feature of oculopharyngeal muscular dystrophy (OPMD). Clinically, OPMD is characterized by progressive ptosis and dysphagia, with later involving the proximal lower limb muscles, particularly the quadriceps [40]. The pattern of muscle degeneration in OPMD has been widely regarded as a prototypical manifestation of accelerated muscle aging [41]. One key downstream target of this pathway is silent information regulator 1 (SIRT1), a nicotinamide adenine dinucleotide (NAD+)-dependent deacetylase known to play a central role in muscle aging [32]. SIRT1 levels elevate to enhance deacetylation activity and thus disrupt proteostasis. Under conditions of PABPN1 deficiency, APA-mediated regulation of *SIRT1* is altered, resulting in increased pPAS usage and the production of shorter, more stable *SIRT1* transcripts. This, in turn, increases SIRT1 protein levels and enzymatic activity, which impairs the autophagic flux in skeletal muscle [42]. Additionally, a reduction in PABPN1 expression shifts APA towards pPAS usage in other transcripts, including those encoding Atrogin-1, a key E3 ubiquitin ligase involved in muscle atrophy. This shift upregulates Atrogin-1 expression but downregulates proteasome-related genes, collectively exacerbating muscle wasting [37]. Furthermore, in the absence of sufficient PABPN1, APA disruption of autophagy-related genes, such as *autophagy-related 5* (*Atg5*), *autophagy-related 12* (*Atg12*), *microtubule-associated protein 1 light chain 3 Alpha* (*LC3a*), and *WD repeat domain, phosphoinositide interacting 1*(*Wipi1*), leads to nuclear retention of their dPAS isoforms and a loose ribosome association. As a result, autophagic pathways are disrupted, and muscle aging is accelerated [43]. Thus, the maintenance of proper PABPN1 and SIRT1 expression levels is essential for preserving muscle homeostasis. Notably, RNA-sequencing analyses combined with computational tools, such as APA-shift, have confirmed that a reduced PABPN1 expression correlates with the global changes in APA site selection, overproduction of shorter mRNA isoforms, diminishment of translational efficiency, and impairment of muscle function [44].

Aging also impairs the regenerative capacity of various tissues and organs, including tendons, rendering them more vulnerable to injury. The incidence of tendon injuries and tendinopathy increases significantly with age-related tendon degeneration [45-47]. Degenerative rotator cuff tendon lesions are widely considered age-dependent and intrinsically degenerative, with their pathogenesis closely linked to the aging of tendon-derived stem cells (TSCs) [48]. TSCs play essential roles in maintaining tendon homeostasis, mediating pathological remodeling, and promoting post injury repair and regeneration [49]. Importantly, protective autophagy has been identified as a key mechanism that shields human TSCs (hTSCs) from oxidative stress-induced cellular damage.

High mobility group AT-hook 2 (HMGA2), a multifunctional chromatin-associated protein, is involved in regulating stem cell self-renewal, differentiation, and tumorigenesis. Its expression is post-transcriptionally suppressed by let-7 miRNA [50]. Overexpression of *HMGA2* enhances autophagy and preserves hTSC stemness and differentiation potential under hydrogen peroxide (H_2O_2)-induced oxidative stress. Under such a condition, the expression of *NUDT21*（CFIm25） is upregulated, promoting dPAS selection in HMGA2 transcripts via APA. This leads to 3′UTR extension, enhancement on let-7 miRNA binding, and subsequent repression of HMGA2 translation, ultimately weakening TSC stemness and pluripotency [51].

In summary, the dysregulation of APA emerges as a common mechanism in aging-associated diseases such as sarcopenia, OPMD, and tendon degeneration. Key regulators, including U1 snRNA, PABPN1, and CFIm25,

influence tissue homeostasis. For instance, CFIm25 downregulation and PABPN1 deficiency promote a shift toward proximal poly(A) site usage, contributing to fibrotic and atrophic phenotypes. Future therapeutic approaches may include the development of small molecules or antisense oligonucleotides that modulate APA site selection, or gene-editing tools that correct aberrant APA regulators (e.g., *PABPN1, NUDT21*) to restore normal gene expression profiles in aging muscle tissues.

APA and cardiovascular diseases

Aging-related cardiovascular diseases (CVDs) arise from a complex interplay of structural, functional, cellular, and molecular processes, including cardiac remodeling, progressive vascular stiffening, accumulation of senescent cells, dysregulation of neurohumoral pathways, and shows a bidirectional relationship with frailty in older adults. Age-related myocyte apoptosis and arterial stiffening are closely linked to both morphological and functional deterioration of the cardiovascular system, with arteriosclerosis worsening progressively over time. In response, compensatory mechanisms such as myocardial hypertrophy and interstitial fibrosis may develop, ultimately disrupting cardiac output. The functional integrity of the arterial system and the overall cardiac performance are highly interdependent [52]. Emerging evidence indicates that APA plays a role in these age-associated pathological processes.

Atherosclerosis, a progressive cardiovascular disease characterized by endothelial dysfunction, serves as an early pathological hallmark and impairs microvascular perfusion. Aging is a primary driver of endothelial dysfunction [53]. In elderly individuals, the development of atherosclerosis is closely associated with dysregulated signaling in vascular endothelial cells [54], involving angiotensin II (Ang II) [55]. Ang II, a key effector of the renin-angiotensin system, promotes endothelial cell senescence, enhances cell migration, and induces angiogenesis by upregulating vascular endothelial growth factor (VEGF) [56]. Recent findings in high-throughput sequencing, including Iso-Seq, have revealed that Ang II stimulation shifts APA towards pPAS usage through the modulation of 3′ end processing factors, resulting in widespread shortening of 3′UTRs. This process alters the expression of critical genes, such as *phosphatase and tensin homolog deleted on chromosome 10* (*PTEN*), a pivotal tumor suppressor that constrains cell survival and proliferation through its negative regulation of the PI3K/Akt/mTOR signaling axis, and *Cadherin-2* (*Cdh2*), activates senescence-associated signaling pathways, and engages the *tumor protein p53* (*p53*), mitogen-activated protein kinase (MAPK), and mechanistic target of rapamycin (mTOR) pathways, thereby accelerating vascular endothelial cell senescence [57]. Although *CDH2* has been demonstrated to significantly promote angiogenesis and enhance the cellular sensitivity to an exherin antagonist, the mechanistic modulation on *CDH2* by APA remains to be fully elucidated [58]. Beyond Ang II signaling, APA influences multiple aspects of atherosclerotic progression through various regulatory mechanisms. As a transcriptional co-regulator, interferon regulatory factor 2-binding protein 2 (IRF2BP2) suppresses inflammatory responses in macrophages and atherosclerotic plaque formation in murine models. A genomic deletion of *IRF2BP2* correlates with a heightened susceptibility to coronary artery disease in human populations [59]. DEAD-box protein-5 (DDX-5) demonstrates inhibitory effects on SMC proliferation, migration, and post-injury vascular remodeling, positioning it as a promising target for atherosclerosis interventions [60]. Additionally, comparative analyses reveal the inhibitor of metalloproteinase (TIMP)-2 exerts a more pronounced protective effect than TIMP-1 during atherosclerotic disease progression [61]. Moreover, studies have shown that activation of the mechanistic target of rapamycin complex 1 (mTORC1) signaling pathway induces 3′UTR shortening in multiple genes, including *IRF2BP2*, *DDX5*, *TIMP-2*, and *ubiquitin-conjugating enzyme E2 N* (*UBE2N*). These shorter isoforms exhibit enhanced translational efficiency, further exacerbating atherosclerotic progression [55, 62]. Inflammatory pathways are particularly susceptible to APA-mediated regulation. In macrophages, the accumulation of the NLRP3 inflammasome is another hallmark of age-associated vascular inflammation and has been strongly implicated in atherosclerosis [63]. The RNA-binding protein tristetraprolin (TTP) serves as a negative post-transcriptional regulator of NLRP3 by binding to AU-rich elements in the long 3′UTR isoforms of *NLRP3* mRNA, thereby suppressing its translation. However, APA-mediated generation of shorter *NLRP3* transcripts lacking TTP and miR-223 binding sites leads to elevated NLRP3 expression. TTP deficiency enhances inflammasome activation, thereby promoting inflammasome activation and accelerating atherosclerosis [64]. In addition, the gene *Flt1*, which encodes vascular endothelial growth factor receptor 1 (VEGFR1), has also been linked to atherosclerosis. Flt1 produces both a membrane-bound receptor and a soluble isoform (sFlt1), the latter of which reduces the angiogenic activity of VEGF-A and exhibits anti-atherosclerotic effects when overexpressed [65]. Notably, a polyadenylation signal located in intron 13 of Flt1 regulates both splicing and

APA, thereby controlling the expression of sFlt1 [66]. Hypertension, a major risk factor for heart failure, atrial fibrillation, valvular heart disease, atherosclerosis, aortic

syndromes, and ischemic cardiovascular events, is independently associated with arterial stiffness and advancing age [67]. Several hypertension-related genes harbor polymorphisms within their 3′UTRs that influence APA and, consequently, gene expression. One such gene is *ATP1B1*, which encodes the β1 subunit of sodium-potassium ATPase, is critical for maintaining cellular ionic gradients [68]. *ATP1B1* expression elevates in hypertension pathogenesis in rat models [69]. A polymorphic terminal repeat sequence (TRS) in the 3′ UTR of *ATP1B1* promotes pPAS usage via APA, leading to the generation of shorter 3′ UTR isoforms. This action results in increased ATP1B1 protein expression, enhanced sodium–potassium ATPase activity, and augmented sodium reabsorption culminating in elevated blood pressure [70]. Another gene affected by APA is *SLC7A1*, which encodes a high-affinity cationic amino acid transporter 1. A functional single nucleotide polymorphism (SNP) in its 3′ UTR regulates APA dynamics [71]. The minor T allele, in contrast to the common C allele, favors the use of dPASs, resulting in longer 3′ UTR isoforms and lower *SLC7A1* expression. In hypertensive patients, a high prevalence of the T allele correlates with endothelial dysfunction and a greater disease severity [72].

Pulmonary hypertension (PH) is a progressive and life-threatening disease, hemodynamically defined by an elevated mean pulmonary arterial pressure (mPAP > 20 mmHg) [73]. Histologically, it is characterized by extensive vascular remodeling and often culminates in right ventricular failure. Both hypoxia-induced and idiopathic forms of PH are associated with smooth muscle cell senescence and endothelial dysfunction, which play mechanistic roles in disease progression [74, 75]. In pulmonary arterial smooth muscle cells (PASMCs), hyaluronan synthase 2 (HAS2) acts in the dysregulation of hyaluronic acid (HA). Deletion of *NUDT21* leads to shortening of the *HAS2* 3′ UTR, and consequent increased *HAS2* mRNA stability and protein expression. Excessive HA accumulation impairs PASMC energy metabolism by disrupting mitochondrial oxidative phosphorylation and then induces a shift toward glycolysis. This metabolic reprogramming produces a pro-remodeling phenotype characterized by increases in cell proliferation, migration, resistance to apoptosis, and pulmonary vasoconstriction [76].

Aging-related cardiac remodeling encompasses structural reorganization, dysregulation of calcium homeostasis, and low ATP production, forming the pathological foundation of heart failure [77]. Central mechanisms include myocardial fibrosis, oxidative stress, aberrant activation of intracellular signaling pathways, spontaneous calcium release, and dysfunction of cardiac ryanodine receptor 2 (RyR2), all of which culminate in intracellular calcium overload [78-80]. APA contributes to the pathogenesis of cardiac hypertrophy, fibrosis, and heart failure. During the early stages of left ventricular hypertrophy, APA shifts mRNA 3′ UTR usage toward pPAS, resulting in shorter transcript isoforms. This alteration is most prominent within the first 48 hours following hypertrophy onset [81]. Gene set enrichment analysis (GSEA) has revealed that APA-regulated genes in this context are enriched in pathways related to RNA metabolism, mRNA splicing, protein ubiquitination, phosphorylation, and intracellular signaling—processes that are mechanistically central to maladaptive ventricular remodeling [81, 82]. The RNA-binding protein RBM10, a known regulator of apoptosis and inflammation, is highly expressed in cardiac tissue and interacts with the nuclear poly(A) polymerase Star-PAP (TUT1) to modulate 3′ end processing of select cardiac mRNAs. It facilitates the assembly of the Star-PAP complex at specific 3′ UTR regions, thereby enhancing the expression of anti-hypertrophic genes, including *HAND2, TGFBR3*, *ERBB3*, *RHEBL1*, *COL5A1*, *CACNA1G*, *and HO-1* [83]. Notably, *RBM10* expression is downregulated during cardiac hypertrophy and heart failure, while its ectopic overexpression reverses hypertrophic remodeling. In addition, NQO1 is a cellular defense protein processed through alternative RNA modification. NQO1 downregulation is associated with the loss of dPAS specific transcript, resulting in inherent reduction in Star-PAP level during CH. Expression of NQO1 by the dPAS-encoded transcript rescues hypertrophy induced by NQO1 downregulation. The interruption into dPAS selection by Star-PAP decreases NQO1 expression, further contributing to hypertrophic progression [84]. Other APA-regulating trans-acting factors also undertake key roles in cardiac dysfunction. For instance, RNA binding fox-1 homolog 2 (RBFOX2) regulates *solute carrier family 25 member 4* (*Slc25a4*) during APA by binding to the conserved motifs near the dPAS and promoting pPAS selection. *RBFOX2* depletion shifts polyadenylation to the dPAS, elongating the 3' UTR and reducing adenine nucleotide translocator 1 (ANT1) protein expression. *RBFOX2* manipulates APA to impair myocardial contractility [85]. Likewise, *SCN5A*, the gene encoding the voltage-gated sodium channel NaV1.5, undergoes APA to produce shorter transcript isoforms. The expression of N-terminal fragment of NaV1.5 (NaV1.5-NT) increases basal oxygen consumption, ATP generation, and mitochondrial ROS levels, and reduces the availability of NADH. A lower SCN5A expression correlates with a higher mortality in heart failure patients and a lower ejection fraction. Notably, these shorter SCN5A isoforms are significantly downregulated in heart failure [86, 87].

Cardiac fibrosis is a key pathological event that drives the progression of heart failure. In patients with heart failure, pro-fibrotic genes often exhibit shortened 3' UTRs which enhance their translational efficiency and promote myofibroblast differentiation. Notably, the expression of CSTF64 is significantly upregulated in the left ventricular tissue of heart failure patients, and APA-mediated 3' UTR shortening in genes, such as *collagen type I alpha 1 chain* (*COL1A1*) and *fibronectin 1* (*FN1*), leads to excessive collagen deposition. Furthermore, APA shortens the 3' UTRs of *TGFβR1* in cardiac fibroblasts, thereby amplifying fibroblast activation and fibrotic remodeling [88, 89].

Myocardial infarction (MI), a leading cause of heart failure, is associated with high morbidity and mortality worldwide. As an apoptosis and caspase activation inhibitor, AVEN protects by suppressing macrophage apoptosis [90]. AVEN interacts with anti-apoptotic BCL-2 family proteins, attenuating ischemia–reperfusion injury and improving post-infarction cardiac function [91]. Following MI, *AVEN* transcripts undergo 3' UTR lengthening, which introduces novel miRNA binding sites, thereby reducing AVEN expression, enhancing cardiomyocyte apoptosis, and worsening cardiac function. Following MI, the upregulation of APA-regulatory proteins, including PABPN1, NUDT21, CPSF6, and SRSF3, may contribute to this 3' UTR elongation. Importantly, AVEN overexpression has been shown to significantly reduce cardiomyocyte apoptosis and alleviate cardiac injury in preclinical models [92].

Calcific aortic valve disease (CAVD), increasingly prevailing among aging populations, is driven in part by senescence of aortic valve interstitial cells (VICs), a central player in pathological calcification [93]. The antioxidant enzyme catalase (CAT) undergoes APA-dependent 3' UTR shortening upon stimulation with basic fibroblast growth factor (bFGF). This modification increases CAT protein levels and reduces oxidative stress-mediated calcium deposition, thereby exerting protective effects against valve calcification [94].

A process recurring across diverse cardiovascular pathologies is the dysregulation of core 3' end processing factors, particularly the downregulation of CFIm25. This perturbation promotes widespread 3' UTR shortening, which in turn enhances the translation of pro-fibrotic and pro-remodeling genes. In fibrotic remodeling associated with APA dysregulation, this mechanism functionally links conditions such as cardiac hypertrophy, heart failure, and pulmonary hypertension. Emerging APA-targeted therapeutic strategies offer new avenues for modulating gene isoforms with distinct biological functions. Technologies, such as genome editing, RNA editing, and antisense oligonucleotides (ASOs), provide the potential to correct dysregulated APA and restore the expression of essential transcripts in the heart. Modified ASOs can modulate polyadenylation without degrading target mRNA. However, challenges such as off-target effects and delivery efficiency remain before therapeutic translation.

APA and neurodegenerative diseases

Neurodegenerative diseases (NDDs) constitute a heterogeneous group of disorders characterized by the progressive loss of neuronal structure and function, ultimately resulting in cognitive decline, psychiatric symptoms, motor deficits, and the gradual deterioration of essential physiological processes. Alzheimer's disease (AD) and Parkinson's disease (PD) are the most prevalent forms of NDDs. At the molecular level, these conditions share several pathological features, including protein aggregation, metabolic dysfunction, proteostasis disturbance, neuroinflammation, synaptic abnormalities, and neurotoxicity. Notably, APA elicits neurodegeneration by modulating the stability and translational efficiency of disease-relevant mRNAs, thereby affecting neuronal excitability and network function.

In AD, hallmark pathological changes include extracellular deposition of β-amyloid (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) formed by hyperphosphorylated tau protein [95]. APA influences the expression, degradation, and mitochondrial localization of proteins involved in these processes. APA-mediated changes primarily affect genes involved in tau pathology. For example, the *microtubule-associated protein tau (MAPT)* gene, encoding the tau protein, contains multiple APA sites within its 3′ UTR. Transcript length variation in *MAPT* is associated with AD risk. In AD, a low TAR DNA-binding protein 43 (TDP-43) expression leads to the accumulation of shorter *MAPT* isoforms that lack TDP-43 binding motifs, resulting in excessive tau protein production and NFT formation [96-98]. *Bridging integrator 1 (BIN1)*, another AD susceptibility gene, exhibits 3′ UTR elongation in the temporal and frontal cortices of AD patients. This APA-mediated elongation may increase BIN1 protein levels and participates in tau pathology and potentially exacerbate AD progression [99, 100]. Beyond tau-related pathways, APA also regulates genes involved in protein homeostasis and synaptic function. Additional APA-modulated genes implicated in AD are represented by *UBR1*, a ubiquitin ligase involved in protein degradation, and *vesicle associated membrane protein 2* (*VAMP2*) that regulates synaptic vesicle fusion and neurotransmitter release. Both genes exhibit shortened 3′ UTRs under pathological conditions, likely altering protein expression and undermining synaptic functions [101, 102]. Furthermore, APA regulates genes

central to inflammatory responses, oxidative stress, and energy metabolism, thereby significantly influencing these critical processes in AD. For example, *cyclooxygenase-2 (COX-2)* and *oxoglutarate dehydrogenase-like (OGDHL)* exhibit 3′ UTR elongation in AD, which may contribute to neuroinflammation and mitochondrial dysfunction [101, 103, 104]. Powered by integrative bioinformatics and machine learning, recent studies have uncovered novel APA signatures associated with AD. *PAK3*, a gene involved in dendritic morphogenesis and cytoskeletal remodeling, experiences 3′ UTR elongation; whereas *INPP5D*, which regulates myeloid cell proliferation and survival, displays 3′ UTR shortening in AD brain tissue [105]. RNA-sequencing data from the Mount Sinai Brain Bank (MSBB) and Mayo Clinic cohorts further support these findings. In AD patients, *voltage-dependent anion channel 2 (VDAC2)* in the para hippocampal gyrus preferentially utilizes proximal PAS, resulting in 3′ UTR shortening, a modification that may exacerbate mitochondrial dysfunction and bioenergetic failure [106]. Global APA profiling reveals tissue-specific patterns, but the predominance of correlative data necessitates caution; future work should integrate causal models to validate therapeutic targets for precision medicine applications.

Parkinson's disease (PD) is another age-associated neurodegenerative disorder, with its prevalence increasing markedly in older adults. The disease features the progressive degeneration of dopaminergic neurons in the substantia nigra, depletion of striatal dopamine, and pathological accumulation of α-synuclein aggregates (Lewy bodies), clinically manifesting as bradykinesia, resting tremors, and muscle rigidity. In PD brains, an increased production of long 3′ UTR isoforms of the *SNCA* gene, which encodes α-synuclein, has been observed. Moreover, intracellular dopamine facilitates dPAS usage, further amplifying α-synuclein accumulation. The excess α-synuclein dislocates from synaptic terminals to mitochondria, exacerbating mitochondrial dysfunction and leading to PD occurrence [107].

This mitochondrial impairment is further reinforced by APA-mediated changes in other genes. For example, *LONP1*, which encodes a mitochondrial matrix protease responsible for degrading oxidatively damaged or misfolded proteins, exhibits APA-mediated 3′ UTR shortening in PD. This alteration impairs mRNA translation and reduces LONP1 protein stability, leading to the accumulation of *PTEN-induced putative kinase 1 (PINK1)*, a key regulator of mitochondrial quality control, thereby activating neurodegenerative cascades [108]. Furthermore, *NELFA*, a component of the negative elongation factor (NELF) complex involved in RNA Pol II transcriptional pausing, shows 3′ UTR elongation in PD brain tissue, potentially altering transcript stability or translational dynamics [101, 109].

While AD and PD diseases exhibit distinct molecular etiologies, APA plays similar pathological roles in both conditions by dysregulating RNA-binding proteins (e.g., TDP-43), amplifying the expression of key pathological proteins, and compromising mitochondrial integrity. Taken together, APA profiling has emerged as a powerful tool for identifying novel disease risk factors and elucidating mechanisms underlying genetic susceptibility. The integration of APA signatures with predictive modeling may ease the discovery of pathogenic variants and refine our understanding of previously unexplained risk loci in neurodegenerative diseases.

APA and respiratory system-related diseases

Chronic obstructive pulmonary disease (COPD) is a progressive, age-associated respiratory disorder characterized by immune-metabolic dysregulation and cellular senescence [110]. Alpha-1 antitrypsin (A1AT), encoded by the *SERPINA1* gene, functions as a neutrophil elastase inhibitor and a mitigator of pulmonary inflammation [111]. In COPD, APA-mediated regulation of *SERPINA1* is disrupted, with a shift toward dPAS usage within the 3′ UTR. This shift results in longer 3′ UTR isoforms, a reduction in A1AT protein expression, and an exacerbation of lung inflammation due to protease–antiprotease imbalance [112].

APA dysregulation of *membrane associated ring-CH-type finger 2* (*MARCHF2*), along with other genes such as *butyrophilin subfamily 3 member A2* (*BTN3A2*) and *nectin cell adhesion molecule 2* (*NECTIN2*), is implicated in COPD pathogenesis. *MARCHF2,* a member of the membrane-associated RING-CH (MARCH) family of E3 ubiquitin ligases, regulates intracellular trafficking and the secretion of A1AT [113, 114]. Specifically, MARCHF2 shows reduced proximal PAS usage under pathological conditions, resulting in 3′ UTR elongation. These longer transcripts are more susceptible to miRNA-mediated degradation, ultimately impairing gene expression and contributing to the progressive decline of lung function [115].

BTN3A2 is a member of the immunoglobulin superfamily [116]. The risk allele (A), which is correlated with reduced lung function, allows 3′ UTR shortening and consequent downregulation of gene expression [115]. *NECTIN2*, a membrane-bound glycoprotein predominantly localized to epithelial cell-cell junctions. The rs3729640 variant, an *NECTIN2* APA quantitative trait locus, enhances lung function by reducing distal polyadenylation usage, shortening the 3' UTR and elevating NECTIN2 expression [115]. These regulatory

dynamics may cause airway remodeling and immune dysfunction in COPD.

Pulmonary fibrosis is a progressive, aging-associated interstitial lung disease characterized by fibroblast proliferation, excessive extracellular matrix (ECM) deposition, chronic inflammation, and irreversible tissue remodeling, ultimately the decline of respiratory capacity. Clinically, it presents with persistent dry cough and progressive exertional dyspnea [117, 118]. Given the limited efficacy of current therapeutic strategies, elucidating novel molecular mechanisms such as APA may offer potential targets for interventions.

During disease progression, components of the cleavage factor Im (CFIm) complex, particularly CFIm25, are significantly downregulated in fibrotic lung tissues, implying the engagement of APA dysregulation in fibrogenesis. CFIm25 enhances the usage of dPAS containing stop codons and reduces pPAS usage. RNA sequencing in lung fibroblasts reveals that CFIm25 downregulation leads to shortening of key genes involved in fibrosis (e.g., *TGFBR1, frizzled class receptor 2* [*FZD2*]*, collagen type I alpha 1 chain* [*COL1A1*]), and increases their protein translation[119, 120]. Interestingly, mice with CFIm25 deletion in Col1a1-expressing cells show acceleration of bleomycin-induced lung fibrosis, suggesting a close implication of CFIm25-mediated APA in fibroblasts during fibrosis. Loss of CFIm25 function leads to global 3′ UTR shortening, resulting in the elimination of AU-rich elements and microRNA binding sites, increases in mRNA stability and translation efficiency, and ultimately the acceleration of disease progression [121].

Transforming growth factor β1 (TGF-β1), a central profibrotic cytokine, has also been shown to regulate APA in the context of pulmonary fibrosis [122]. Under TGF-β1 stimulation, miR-203 is upregulated and directly targets the 3′ UTR of *NUDT21*, leading to its downregulation and promoting 3′ UTR shortening in lung fibroblasts. Subsequently, the expression of fibrosis-associated mediators and ECM proteins activates pathological signaling cascades. Additionally, TGF-β1 modulates APA-mediated regulation in multiple fibrosis-related genes, including *fibroblast growth factor 14* (*FGF14*), *RPTOR independent companion of MTOR complex 2* (*RICTOR*), *tropomodulin 2* (*TMOD2*), and *uncoupling protein 5* (*UCP5*), further evoking fibrogenic signaling and protein expression [123, 124].

APA and other diseases

Systemic sclerosis (SSc) is a chronic autoimmune disease primarily characterized by progressive fibrosis of the skin and internal organs. Increasing evidence implicates cellular senescence as an important contributor to the pathogenesis and progression of SSc [125]. TGF-β1, a central mediator of fibrosis, upregulates the expression of microRNAs miR-181a and miR-181b, which directly bind to the 3′ UTR of *NUDT21*, leading to its downregulation. This suppression of *NUDT21* promotes APA-mediated 3′ UTR shortening of downstream transcripts, thereby enhancing their translational efficiency. As a result, fibrosis-related genes, such as *COL1A1* and *SPARC*, are upregulated to exacerbate dermal fibrosis [123, 126]. Given the pivotal role of TGF-β1 in a wide range of fibrotic disorders, the TGF-β1/miR-181/NUDT21 axis may represent a conserved fibrogenic mechanism across multiple organ systems, including the heart, liver, and kidneys, and could serve as a potential therapeutic target for systemic fibrosis.

Hutchinson-Gilford progeria syndrome (HGPS) is a rare, fatal, autosomal dominant disorder characterized by the acceleration of aging. It is most commonly caused by a de novo mutation that leads to the aberrant splicing of exon 11 in the *LMNA* gene, resulting in the exclusion of this exon [127]. The *LMNA* gene gives rise to three major protein isoforms: lamin A, progerin, and lamin C. Lamin C expresses through APA mechanisms that preclude the concurrent production of lamin A and progerin isoforms through splicing pathways, and has been associated with longevity due to its role in suppressing cellular energy metabolism. In contrast, progerin, an aberrant splice variant of lamin A, accelerates aging by increasing the mitochondrial activity and the overall metabolic rate. In HGPS, progerin is overexpressed to enhance mitochondrial function and oxidative metabolism, thereby accelerating the aging phenotype [128].

Diabetic nephropathy (DN), a leading cause of end-stage renal disease (ESRD) globally, is closely linked to the accelerated senescence of glomerular podocytes and mesangial cells. Oxidative stress and chronic inflammation are key drivers of glomerular cell aging in DN [129, 130]. In renal glomeruli from DN patients, elevated expression of APA regulatory factors, such as CFIm25, CFIm68, SNRNP70, and PABPC1, promotes the preferential usage of distal polyadenylation sites (PAS), resulting in mRNA transcripts with extended 3′ UTRs [131-133]. These elongated 3′ UTRs enhance translation efficiency and promote disease progression [134].

Osteoarthritis (OA), a common age-related degenerative joint disease, is a major contributor to chronic pain and disability in the elderly. The accumulation of senescent cells in articular cartilage is strongly implicated in OA pathogenesis [135]. In the *OSMR* gene, the decreased utilization of intronic polyadenylation sites leads to the loss of its tumor-suppressive isoforms, thereby amplifying oncostatin M

signaling and subsequently promoting joint inflammation and cartilage degradation. Additionally, *KMT2A*, a gene encoding lysine methyltransferase 2A, is downregulated in OA tissues and correlates with reduced cartilage thickness [136]. In OA, *KMT2A* exhibits a proximal PAS usage markedly reduced, which alters its post-transcriptional processing dynamics. Transcriptome analysis across multiple cell lines shows that AC10 cells express both long and short *KMT2A* isoforms. Notably, the shortening of the *KMT2A* 3′ UTR decreases mRNA stability, further exacerbating OA pathogenesis [137]. While osteoarthritis does not exhibit global APA dysregulation, targeting specific polyadenylation events—such as intronic site usage in OSMR to modulate oncostatin M signaling—holds promise for precision therapies aimed at restoring cartilage homeostasis.

Conclusions and future directions

This review provides a comprehensive overview of the role of APA in aging and aging-related diseases, including those affecting the musculoskeletal, nervous, cardiovascular, and respiratory systems. APA, as a crucial co-transcriptional mechanism, is involved in precursor mRNA processing. As a key regulator in gene expression, it is significantly implicated in the onset and progression of age-associated pathologies. Rather than being regulated by a single determinant, PAS selection is orchestrated by a complex of transcriptional and co-transcriptional regulators, suggesting its importance in fine-tuning gene expression dynamics. Through a systematic exploration for APA regulatory networks in aging tissues, this research uncovers its critical mechanistic links to age-related disease pathogenesis (Table 1-3).

Table 1. 3'UTR-APA mRNAs with shortened mRNAs under pathological conditions.

Disease	Cells or tissue	Target genes	Molecular effect	Refs
Muscular aging	Mouse tibialis anterior, C2C12 immortalized mouse myoblasts	Fbxo32	PABPN1 downregulation causes a consistent decline in distal PAS utilization, upregulates Atrogin-1, reduces proteasome activity via APA, causing muscle wasting.	[37]
	Mouse tibialis anterior	SIRT1	PABPN1 downregulation alters SIRT1 APA, increases SIRT1 protein, exacerbating muscle atrophy and aging.	[42]
	Extensor digitorum longus (EDL) muscles, C2C12 immortalized muscle cell	ATG12, LC3a, Wipi1, ATG5	Reduced usage of the distal PAS of ATG genes shortens the 3' UTR, impedes autophagosome formation, and is associated with muscle aging.	[43]
Atherosclerosis	Primary rat aortic endothelial cells	Pten, Pnkp, Cdh2	A global 3'UTR shortening upon Ang II, stimulation, accelerates endothelial cell senescence.	[57]
	Mouse embryonic fibroblasts	Irf2bp2, Ddx5, Timp2, Ube2n	mTORC1 activation shortens 3'UTRs, boosts translation, and promotes atherosclerosis.	[55, 62]
	THP-1 cells, human macrophages	NLRP3	APA-induced short 3'UTR isoforms and loss of TTP activity act as drivers of NLRP3 expression, directly contributing to inflammasome hyperactivity and atherosclerosis.	[64]
Hypertension	Human kidney tissue, human lymphocytes	ATP1B1	TRS APA-mediated isoform switching in ATP1B1, increasing Na^+/K^+-ATPase activity via translational upregulation, thereby mechanistically connecting 3'UTR variation to hypertension susceptibility.	[70]
Pulmonary hypertension	Human pulmonary artery smooth muscle cells (PASMCs)	HAS2	NUDT21 loss shortens HAS2 3'UTR, raises HAS2/HA, promotes PASMC dysfunction and pulmonary contraction.	[76]
Cardiac hypertrophy	Mouse cardiomyocytes	SRF	3'UTR shortening in cardiac hypertrophy modulates RNA splicing machinery and amplifies pro-hypertrophic signaling.	[81]
	Rat cardiomyocytes, HEK293 cells	HAND2, TGFBR3, ERBB3, RHEBL1, COL5A1,	RBM10 binds to cardiac pre-mRNA, recruits Star-PAP to anti-hypertrophic genes.	[83]

		CACNA1G, HO-1		
	Rat cardiomyocytes, HEK293 cells	NQO1, PTBP2, PAK1	Downregulation of Star-PAP-Mediated dPAS selection leads to specific loss of the distal-specific mRNA isoform and promotes cardiac hypertrophy.	[84]
Cardiac fibrosis	Human cardiac fibroblasts	COL1A, FN1, TGFBR1	CSTF64 upregulation shortens COL1A/FN1 3'UTR, promotes fibrosis; TGFβR1 3'UTR shortens in fibroblasts.	[88, 89]
Calcific aortic valve disease	Porcine aortic valve interstitial cells	CAT	bFGF shortens CAT 3'UTR, boosts CAT protein, reduces oxidative calcium deposition.	[94]
Alzheimer's disease	Rat forebrain tissue, human medial prefrontal cortex and cerebellum	MAPT	In AD, significantly reduced levels of TDP-43 impair its binding to two UG-repeat motifs within the 3'UTR of tau mRNA, thereby increasing mRNA stability and ultimately upregulating tau expression.	[96-98]
	Human prefrontal cortex brain tissue	VAMP2	APA-mediated 3'UTR shortening of VAMP2 disrupts posttranscriptional regulation, reducing its protein levels and impairing synaptic vesicle fusion/neurotransmitter release, thereby exacerbating synaptic dysfunction and cognitive decline in AD.	[101, 102]
	Human hippocampus	UBR1	APA-mediated 3'UTR shortening of UBR1 evades miRNA repression, enhancing mRNA stability/translation and impairing UPS-mediated protein degradation, thereby exacerbating pathological protein aggregation in AD.	[101]
	Human prefrontal cortex	INPP5D	INPP5D undergoes APA-mediated 3'UTR shortening, which may disrupt its post-transcriptional regulatory network, thereby altering microglial function and amplifying neuroinflammatory responses, ultimately contributing to AD pathogenesis.	[105]
	Human brain tissues (prefrontal cortex, superior temporal gyrus, parahippocampal gyrus, inferior frontal gyrus, temporal cortex, and cerebellum)	VDAC2	VDAC2 utilizes a proximal PAS, resulting in shortened 3'UTRs that exacerbate mitochondrial dysfunction in AD.	[106]
Parkinson's disease	Human midbrain dopaminergic neurons	LONP1	APA-mediated 3'UTR shortening of LONP1 disrupts its mRNA translational regulation, leading to impaired mitochondrial protein homeostasis. This dysfunction activates PINK1/Parkin-dependent mitophagy, ultimately driving dopaminergic neurodegeneration in PD.	[101, 108]
Chronic obstructive pulmonary disease	Human lung tissue (LTRC)	BTN3A2	The A allele of rs72841536 induces APA-mediated 3'UTR shortening in BTN3A2, reducing mRNA stability and downregulating its expression, which compromises pulmonary immune homeostasis and exacerbates COPD progression.	[115]
Pulmonary fibrosis	Human lung tissue (IIAM), human lung fibroblasts, mouse lung fibroblasts	COL1A1, FN1, TGFBR1, WNT5A, FZD2	In pulmonary fibrosis, COL1A1, FN1, TGFBR1, WNT5A, and FZD2 are regulated by CFIm25 via APA-mediated 3'UTR shortening, evading miRNA repression to elevate protein levels. This activates TGF-β/Wnt pathways, triggering ECM deposition and myofibroblast differentiation.	[121, 124]
Systemic sclerosis	Human skin	COL1A1, TGFBR1, SPARC	In SSc, downregulation of NUDT21 triggers 3'UTR shortening of COL1A1, TGFBR1, and SPARC through the TGFβ/miR-181 axis, enabling escape from miRNA-mediated regulation. This results in	[123, 126]

			excessive protein expression, driving dermal fibrosis.	
	Human kidney	HECW2	HECW2, involved in the ubiquitin-proteasome pathway, exhibits a shortened 3'UTR when NUDT21 is knocked down.	[105, 141]
Hutchinson-Gilford progeria syndrome	Antagonistic adipose tissue, Mouse embryonic fibroblasts	LMNA	LMNA gives rise to lamin C through APA, causing a decline in mitochondria, reduced metabolism, and extended longevity in adipose tissue.	[128]

This review pivots its focus on aging-related diseases, and details how APA dysregulation drives pathological mechanisms across these conditions. These mechanisms may be translated into the design of therapeutic interventions and strategies against aging.

Advances in genomic technologies, such as single-cell RNA sequencing, long-read sequencing, and spatial transcriptomics, have substantially expanded our ability to investigate APA-mediated regulation with unprecedented resolution. By mapping age-associated APA alterations, researchers can identify specific signatures as candidate biomarkers for disease diagnosis, staging, and prognosis, as well as potential therapeutic targets for age-related disorders. However, each technology presents distinct limitations that must be addressed for reliable APA profiling.

Single-cell RNA sequencing enables cellular-resolution APA analysis, but also presents shallow sequencing depth and high transcript dropout rates, leading to inadequate 3' UTR coverage and noisy isoform quantification [138]. Long-read sequencing platforms provide full-length transcript information, but exhibit higher error rates and reduced quantitative accuracy compared to short-read methods, potentially missing low-abundance APA-mediated regulation. A more effective strategy often involves a synergistic approach that leverages the complementary strengths of the long-read sequencing for structural resolution, as well as the short-read data for quantitative power [139].

Table 2. 3'UTR-APA mRNAs with lengthened mRNA under pathological condition.

Disease	Cells or tissue	Target genes	Molecular effect	Refs
Muscular aging	Mouse muscle stem cells	PAX3	A low Pax3 protein level decreases the activity of MuSCs, affecting muscle regeneration and maintenance.	[36] [35]
	Mouse muscle stem cells	CD47	In senescent MuSCs, U1 snRNA upregulation drives pathogenic CD47 splicing via APA, triggering THBS1-mediated Gi/cAMP signaling that suppresses functional MuSC proliferation, ultimately impairing muscle regeneration and promoting sarcopenia.	[34]
Rotator cuff tendon lesions	Human tendon stem cells	HMGA2	Overexpression of NUDT21 promotes the generation of long HMGA2 3'UTR, inhibits HMGA2 expression and impairs the stemness of hTSCs.	[51]
Hypertension	Human peripheral blood cells	SLC7A1	SLC7A1 bearing a long 3'UTR contributes to a lower level of SLC7A1, resulting in endothelial dysfunction and hypertension.	[72]
Heart failure	Rat cardiomyocytes, HEK293 cells	Slc25a4	Loss of ANT1 function leads to mitochondrial dysfunction, resulting in heart failure.	[85]
Myocardial infarction	Human left ventricular tissue, Mouse cardiomyocyte, HEK293 cells	AVEN	Reduced AVEN expression promotes apoptosis and worsens cardiac function.	[92]
Alzheimer's disease	Human frozen prefrontal cortex brain tissue	BIN1	BIN1 3'UTR elongation increases BIN1 protein and worsens tau pathology.	[100]

	Human hippocampus	OGDHL	The extended 3'UTR of OGDHL may lead to reduced mRNA stability or translational efficiency via miRNA-mediated targeting, contributing to mitochondrial dysfunction in AD.	[101]
	Human neocortical brain tissue	COX-2	COX-2 3'UTR elongation promotes inflammation in AD.	[103]
	Human prefrontal cortex	PAK3	In AD, elongation of the PAK3 3'UTR may alter mRNA regulatory elements, potentially disrupting protein expression and thereby contributing to synaptic pathology.	[105]
Parkinson's disease	Human brain tissue, primary rat cortical neurons	SNCA	SNCA generates a long 3'UTR transcript (aSynL) via APA, which is upregulated and drives α-synuclein accumulation in mitochondria, leading to mitochondrial dysfunction in PD.	[107]
	Human midbrain dopaminergic neurons	NELFA	In PD, the prolonged 3'UTR of NELFA, potentially mediated by miR-133b downregulation, may disrupt post-transcriptional regulation, contributing to pathological neuronal dysfunction.	[101, 109]
Chronic obstructive pulmonary disease	Human lung tissue, HepG2 and A549 cell lines	SERPINA1	Increased SERPINA1 distal polyadenylation prolongs 3'UTRs, suppressing A1AT translation, reducing antiprotease activity, and exacerbating lung inflammation via protease imbalance in COPD.	[112]
	Human lung tissue (LTRC)	MARCHF2, NECTIN2	Increased usage of the dPAS affects lung function and may be related to the pathological mechanisms of COPD.	[115]
Diabetic nephropathy	Human glomeruli	CYB5R1, PDLIM1, PDCD6, MYOF, CFH	Increased protein expression level promotes the progression of diabetic nephropathy.	[134]
Osteoarthritis	Human knee joint chondrocytes	KMT2A	Reduced use of a pPAS in the 3'UTR regulates mRNA stability, influencing osteoarthritis progression.	[137]

Furthermore, emerging therapeutic modalities offer promising directions for translation, including genome editing techniques to correct pathogenic variants, small-molecule inhibitors targeting APA-regulated signaling pathways, RNA-based therapeutics (e.g., antisense oligonucleotides), cell-based therapies, and epigenetic modulation. Notably, APA occurs co-transcriptionally, but does not directly alter the DNA sequence, thereby reducing genotoxic risks compared to genomic interventions. Moreover, the interventions targeting core APA factors, such as CFIm25, can efficiently modulate APA-mediated regulation at the RNA level, avoiding direct DNA modification and offering a safer therapeutic alternative to gene editing techniques. Importantly, recent studies suggest that therapeutic redirection of PAS choice is feasible at multiple levels. At the cis-element level, antisense oligonucleotides or CRISPR-based editing can block proximal or intronic PAS, enforcing distal PAS usage and restoring full-length isoforms. At the trans-factor level, CFIm or PCF11 expression can be modulated to globally shift PAS usage toward distal or proximal sites, respectively; meanwhile, enhancing U1 snRNP "telescripting" activity can safeguard long transcripts, such as those encoding DNA repair factors, from premature cleavage. However, CFIm25 depletion can alter 3' UTR length in hundreds of genes, thereby disrupting normal physiological functions, underscoring the complexity of its regulation. At the level of transcriptional kinetics and environmental signaling, strategies to increase RNA polymerase II processivity, or to attenuate inflammatory and metabolic cues, may stabilize APA profiles associated with aging.

Table 3. Other APA-mediated regulation under pathological condition.

Disease	Cells or tissue	Target genes	Molecular effect	Refs
Cardiac hypertrophy	Mouse cardiomyocytes，HL-1 cells	GSK3B	APA in GSK3 β generates a longer mRNA variant that overrides repressive elements in upstream exons, enhancing translational efficiency, which may contribute to pathological cardiac hypertrophy in HL-1 cells.	[81]
Heart failure	Rat cardiomyocytes	Tpm1	RBFOX2 controls expression of shorter isoforms of essential contractile gene Tpm1 via splicing APA.	[85]
	Human heart tissue, mouse cardiomyocytes, rat cardiomyocytes	SCN5A	An APA signal downstream of the first SCN5A coding exon. The short transcript isoform NaV1.5-NT is downregulated in HF, which reduces mitochondrial respiration.	[86]
Atherosclerosis	Human umbilical vein endothelial cells, uterine microvascular endothelial cells, human microvascular endothelial cells, primary trophoblasts	Flt1	sFlt1 arises by one of two principal mechanisms: intronic polyadenylation or alternate splicing. Additionally, sFlt1 reduces the angiogenic activity of VEGF-A and exhibits anti-atherosclerotic effects when overexpressed.	[66]
Parkinson's disease	Human midbrain dopaminergic neurons	CHURC1	CHURC1 encodes a transcriptional activator involved in neuronal development, and its association with neurodegeneration is uncertain.	[101, 108]
Chronic obstructive pulmonary disease	Human lung tissue (LTRC)	SH3D21	Genetic colocalization links SH3D21's APA-QTL variants to lung function, where altered 3'UTR length may modulate COPD pathobiology via disrupted RNA stability or translational regulation.	[115]
Osteoarthritis	Human knee joint chondrocytes	OSMR	OSMR intronic polyadenylation decline activates oncostatin-M signaling to promote osteoarthritis inflammation.	[137]

The therapeutic consequences of such interventions are twofold. On the one hand, restoring distal PAS usage or suppressing aberrant intronic PAS may normalize protein dosage, preserve full-length isoforms, and counteract degenerative phenotypes in aging tissues. Additionally, APA occurs in various diseases, including metabolic disorders and neurodegenerative conditions, suggesting its potential to be designed into a multi-target therapeutic strategy. On the other hand, altering APA may inadvertently disrupt co-transcriptional regulatory networks, leading to widespread transcriptomic shifts, unintended changes in mRNA stability, translation, subcellular localization, and possible activation of nonsense-mediated decay. The complexity and dose-dependent effects of APA-mediated regulation may also introduce off-target risks, necessitating precise control to avoid unpredictable side effects in the context of aging and diseases. Moreover, APA also governs the spatiality of protein expression, such as membrane targeting via long 3' UTRs; therefore, interventions could influence cell-cell communication and tissue homeostasis in ways unpredictable. These potential benefits and risks herald gene-specific approaches, coupled with systemic monitoring, to harness APA modulation as a therapeutic strategy in aging-related diseases.

Nonetheless, several key challenges remain. APA may play a critical role in non-coding RNAs (e.g., long non-coding RNAs) and circular RNAs during aging, but these roles have not been fully explored. For example, the lncRNA Nuclear paraspeckle assembly transcript 1(NEAT1) generates two isoforms—NEAT1V1 (which retains a poly(A) tail) and NEAT1V2 (lacking a poly(A) tail)—via APA; NEAT1V1 overexpression disrupts paraspeckle assembly, a critical step in neurodegenerative diseases [119, 140]. The molecular determinants underpinning 3' UTR shortening in specific transcripts are not fully understood, and whether this phenomenon arises from enhanced pPAS usage or is driven by repression of dPAS remains to be clarified. Moreover, APA-mediated regulation on individual genes often involves multiple cis-and trans-acting elements, and the coordination among these factors in determining PAS choice remains largely unexplored. It is also unclear whether APA alterations are merely passive consequences of disease progression, or active contributors to pathogenesis.

Importantly, most current APA research relies heavily on animal models, which though informative, do not fully recapitulate human physiology. The validation in human tissues and disease-relevant cellular models is therefore essential to establish the clinical relevance of APA in aging and related human diseases. Future studies should

not only map APA regulatory networks, but also systematically test molecular interventions that redirect PAS choice, evaluate their efficacy and safety in relevant models, and integrate APA-targeted therapies into the broader framework of transcriptomic medicine and precision therapeutics.

Author contributions

Mengqi Chen and Xiangyu Zhu contribute equally to this work. Mengqi Chen and Xiangyu Zhu drafted this review and designed the figures. Lejia Hang and Zijie Yan contributed to literature search. Li Xu and Fang Liu edited the manuscript. Jingjing Huang and Qiong Zhang provided the design and revision of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

This work was supported by funds from the Jiangsu Province Cadre Health Research Project BJ24043 (JH), Jiangsu Provincial Geriatric Health Scientific Research Project LKM2024023 (JH), Nanjing Medical Science and technique Development Foundation YKK 24237 (JH), 2025 Key Projects of Jiangsu Geriatrics Society JGS2025ZD004 (JH), Shandong Provincial Medical and Health Science and Technology Project 202403011034 (FL) and College Students Innovation and Entrepreneurship Training Program of Kangda College of Nanjing Medical University 202313980018Y (ZY). Figures 2 includes modified templates from Servier Medical Art (http:// www.servier.com), licensed under a Creative Commons Attribution 4.0 Unported License.

Conflicts of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article

References

[1] Kroemer G, Maier AB, Cuervo AM, Gladyshev VN, Ferrucci L, Gorbunova V, et al. (2025). From geroscience to precision geromedicine: Understanding and managing aging. Cell, 188:2043-2062.

[2] Dragoumani K, Kletsas D, Chrousos GP, Vlachakis D, Balatsos NAA (2025). Molecular and Environmental Modulators of Aging: Interplay Between Inflammation, Epigenetics, and RNA Stability. Genes (Basel), 16.

[3] Yang JH, Hayano M, Griffin PT, Amorim JA, Bonkowski MS, Apostolides JK, et al. (2023). Loss of epigenetic information as a cause of mammalian aging. Cell, 186:305-326 e327.

[4] Das S, Vera M, Gandin V, Singer RH, Tutucci E (2021). Intracellular mRNA transport and localized translation. Nat Rev Mol Cell Biol, 22:483-504.

[5] Medioni C, Besse F (2018). The Secret Life of RNA: Lessons from Emerging Methodologies. Methods Mol Biol, 1649:1-28.

[6] Ule J, Blencowe BJ (2019). Alternative Splicing Regulatory Networks: Functions, Mechanisms, and Evolution. Mol Cell, 76:329-345.

[7] Roundtree IA, Evans ME, Pan T, He C (2017). Dynamic RNA Modifications in Gene Expression Regulation. Cell, 169:1187-1200.

[8] La Rocca G, Olejniczak SH, Gonzalez AJ, Briskin D, Vidigal JA, Spraggon L, et al. (2015). In vivo, Argonaute-bound microRNAs exist predominantly in a reservoir of low molecular weight complexes not associated with mRNA. Proc Natl Acad Sci U S A, 112:767-772.

[9] Mayr C (2019). What Are 3' UTRs Doing? Cold Spring Harb Perspect Biol, 11.

[10] Dharmalingam P, Mahalingam R, Yalamanchili HK, Weng T, Karmouty-Quintana H, Guha A, R AT (2022). Emerging roles of alternative cleavage and polyadenylation (APA) in human disease. J Cell Physiol, 237:149-160.

[11] Turner RE, Pattison AD, Beilharz TH (2018). Alternative polyadenylation in the regulation and dysregulation of gene expression. Semin Cell Dev Biol, 75:61-69.

[12] Derti A, Garrett-Engele P, Macisaac KD, Stevens RC, Sriram S, Chen R, et al. (2012). A quantitative atlas of polyadenylation in five mammals. Genome Res, 22:1173-1183.

[13] Tian B, Pan Z, Lee JY (2007). Widespread mRNA polyadenylation events in introns indicate dynamic interplay between polyadenylation and splicing. Genome Res, 17:156-165.

[14] Lan YL, Zhang J (2021). Modulation of untranslated region alternative polyadenylation in glioma tumorigenesis. Biomed Pharmacother, 137:111416.

[15] Mayr C, Bartel DP (2009). Widespread shortening of 3'UTRs by alternative cleavage and polyadenylation activates oncogenes in cancer cells. Cell, 138:673-684.

[16] Berkovits BD, Mayr C (2015). Alternative 3' UTRs act as scaffolds to regulate membrane protein localization. Nature, 522:363-367.

[17] Hoffman Y, Bublik DR, Ugalde AP, Elkon R, Biniashvili T, Agami R, et al. (2016). 3'UTR Shortening Potentiates MicroRNA-Based Repression of Pro-differentiation Genes in Proliferating Human Cells. PLoS Genet, 12:e1005879.

[18] Tian B, Manley JL (2017). Alternative polyadenylation of mRNA precursors. Nat Rev Mol Cell Biol, 18:18-30.

[19] Yuan F, Hankey W, Wagner EJ, Li W, Wang Q (2021). Alternative polyadenylation of mRNA and its role in cancer. Genes Dis, 8:61-72.

[20] Tian B, Graber JH (2012). Signals for pre-mRNA cleavage and polyadenylation. Wiley Interdiscip Rev RNA, 3:385-396.

[21] Masamha CP, Xia Z, Yang J, Albrecht TR, Li M, Shyu AB, et al. (2014). CFIm25 links alternative polyadenylation to glioblastoma tumour suppression. Nature, 510:412-416.

[22] Zhu Y, Wang X, Forouzmand E, Jeong J, Qiao F, Sowd GA, et al. (2018). Molecular Mechanisms for CFIm-Mediated Regulation of mRNA Alternative Polyadenylation. Mol Cell, 69:62-74 e64.

[23] Grzechnik P, Mischo HE (2025). Fateful Decisions of Where to Cut the Line: Pathology Associated with Aberrant 3' End Processing and Transcription Termination. J Mol Biol, 437:168802.

[24] Mitschka S, Mayr C (2022). Context-specific regulation and function of mRNA alternative polyadenylation. Nat Rev Mol Cell Biol, 23:779-796.

[25] Gruber AJ, Zavolan M (2019). Alternative cleavage and polyadenylation in health and disease. Nat Rev Genet, 20:599-614.

[26] Nanavaty V, Abrash EW, Hong C, Park S, Fink EE, Li Z, et al. (2020). DNA Methylation Regulates Alternative Polyadenylation via CTCF and the Cohesin Complex. Mol Cell, 78:752-764 e756.

[27] Hao Y, Cai T, Liu C, Zhang X, Fu XD (2023). Sequential Polyadenylation to Enable Alternative mRNA 3' End Formation. Mol Cells, 46:57-64.

[28] Tang P, Yang Y, Li G, Huang L, Wen M, Ruan W, et al. (2022). Alternative polyadenylation by sequential activation of distal and proximal PolyA sites. Nat Struct Mol Biol, 29:21-31.

[29] Krajewska M, Dries R, Grassetti AV, Dust S, Gao Y, Huang H, et al. (2019). CDK12 loss in cancer cells affects DNA damage response genes through premature cleavage and polyadenylation. Nat Commun, 10:1757.

[30] Mueller AA, van Velthoven CT, Fukumoto KD, Cheung TH, Rando TA (2016). Intronic polyadenylation of PDGFRalpha in resident stem cells attenuates muscle fibrosis. Nature, 540:276-279.

[31] Sayer AA, Cruz-Jentoft A (2022). Sarcopenia definition, diagnosis and treatment: consensus is growing. Age Ageing, 51.

[32] Wang T, Zhou D, Hong Z (2025). Sarcopenia and cachexia: molecular mechanisms and therapeutic interventions. MedComm (2020), 6:e70030.

[33] Cosgrove BD, Gilbert PM, Porpiglia E, Mourkioti F, Lee SP, Corbel SY, et al. (2014). Rejuvenation of the muscle stem cell population restores strength to injured aged muscles. Nat Med, 20:255-264.

[34] Porpiglia E, Mai T, Kraft P, Holbrook CA, de Morree A, Gonzalez VD, et al. (2022). Elevated CD47 is a hallmark of dysfunctional aged muscle stem cells that can be targeted to augment regeneration. Cell Stem Cell, 29:1653-1668 e1658.

[35] Boutet SC, Cheung TH, Quach NL, Liu L, Prescott SL, Edalati A, et al. (2012). Alternative polyadenylation mediates microRNA regulation of muscle stem cell function. Cell Stem Cell, 10:327-336.

[36] de Morree A, Klein JDD, Gan Q, Farup J, Urtasun A, Kanugovi A, et al. (2019). Alternative polyadenylation of Pax3 controls muscle stem cell fate and muscle function. Science, 366:734-738.

[37] Riaz M, Raz Y, van Putten M, Paniagua-Soriano G, Krom YD, Florea BI, Raz V (2016). PABPN1-Dependent mRNA Processing Induces Muscle Wasting. PLoS Genet, 12:e1006031.

[38] Mei H, Boom J, El Abdellaoui S, Abdelmohsen K, Munk R, Martindale JL, et al. (2022). Alternative Polyadenylation Utilization Results in Ribosome Assembly and mRNA Translation Deficiencies in a Model for Muscle Aging. J Gerontol A Biol Sci Med Sci, 77:1130-1140.

[39] Anvar SY, Raz Y, Verway N, van der Sluijs B, Venema A, Goeman JJ, et al. (2013). A decline in PABPN1 induces progressive muscle weakness in oculopharyngeal muscle dystrophy and in muscle aging. Aging (Albany NY), 5:412-426.

[40] Fischmann A, Hafner P, Fasler S, Gloor M, Bieri O, Studler U, Fischer D (2012). Quantitative MRI can detect subclinical disease progression in muscular dystrophy. J Neurol, 259:1648-1654.

[41] Raz Y, Raz V (2014). Oculopharyngeal muscular dystrophy as a paradigm for muscle aging. Front Aging Neurosci, 6:317.

[42] Olie CS, Riaz M, Konietzny R, Charles PD, Pinto-Fernandez A, Kielbasa SM, et al. (2019). Deacetylation Inhibition Reverses PABPN1-Dependent Muscle Wasting. iScience, 12:318-332.

[43] Raz V, Dickson G, t Hoen PAC (2017). Dysfunctional transcripts are formed by alternative polyadenylation in OPMD. Oncotarget, 8:73516-73528.

[44] Shademan M, Mei H, van Engelen B, Ariyurek Y, Kloet S, Raz V (2024). PABPN1 loss-of-function causes APA-shift in oculopharyngeal muscular dystrophy. HGG Adv, 5:100269.

[45] Zhou B, Zhou Y, Tang K (2014). An overview of structure, mechanical properties, and treatment for age-related tendinopathy. J Nutr Health Aging, 18:441-448.

[46] Teunis T, Lubberts B, Reilly BT, Ring D (2014). A systematic review and pooled analysis of the prevalence of rotator cuff disease with increasing age. J Shoulder Elbow Surg, 23:1913-1921.

[47] Albers IS, Zwerver J, Diercks RL, Dekker JH, Van den Akker-Scheek I (2016). Incidence and prevalence of lower extremity tendinopathy in a Dutch general practice population: a cross sectional study. BMC Musculoskelet Disord, 17:16.

[48] Dang A, Davies M (2018). Rotator Cuff Disease: Treatment Options and Considerations. Sports Med Arthrosc Rev, 26:129-133.

[49] Cai Z, Zhang Y, Liu S, Liu X (2022). Celecoxib, Beyond Anti-inflammation, Alleviates Tendon-Derived Stem Cell Senescence in Degenerative Rotator Cuff Tendinopathy. Am J Sports Med, 50:2488-2496.

[50] Lee YS, Dutta A (2007). The tumor suppressor microRNA let-7 represses the HMGA2 oncogene. Genes Dev, 21:1025-1030.

[51] Sun Y, Chen H, Ye H, Liang W, Lam KK, Cheng B, et al. (2020). Nudt21-mediated alternative polyadenylation of HMGA2 3'-UTR impairs stemness of human tendon stem cell. Aging (Albany NY), 12:18436-18452.

[52] Greco S, Gaetano C, Martelli F (2019). Long Noncoding Competing Endogenous RNA Networks in Age-Associated Cardiovascular Diseases. Int J Mol Sci, 20.
[53] Ungvari Z, Tarantini S, Kiss T, Wren JD, Giles CB, Griffin CT, et al. (2018). Endothelial dysfunction and angiogenesis impairment in the ageing vasculature. Nat Rev Cardiol, 15:555-565.
[54] Wu CM, Zheng L, Wang Q, Hu YW (2020). The emerging role of cell senescence in atherosclerosis. Clin Chem Lab Med, 59:27-38.
[55] Cao J, Kuyumcu-Martinez MN (2023). Alternative polyadenylation regulation in cardiac development and cardiovascular disease. Cardiovasc Res, 119:1324-1335.
[56] Shan H, Bai X, Chen X (2008). Angiotensin II induces endothelial cell senescence via the activation of mitogen-activated protein kinases. Cell Biochem Funct, 26:459-466.
[57] Wen H, Chen W, Chen Y, Wei G, Ni T (2023). Integrative analysis of Iso-Seq and RNA-seq reveals dynamic changes of alternative promoter, alternative splicing and alternative polyadenylation during Angiotensin II-induced senescence in rat primary aortic endothelial cells. Front Genet, 14:1064624.
[58] Zhuo H, Zhao Y, Cheng X, Xu M, Wang L, Lin L, et al. (2019). Tumor endothelial cell-derived cadherin-2 promotes angiogenesis and has prognostic significance for lung adenocarcinoma. Mol Cancer, 18:34.
[59] Chen HH, Keyhanian K, Zhou X, Vilmundarson RO, Almontashiri NA, Cruz SA, et al. (2015). IRF2BP2 Reduces Macrophage Inflammation and Susceptibility to Atherosclerosis. Circ Res, 117:671-683.
[60] Fan Y, Chen Y, Zhang J, Yang F, Hu Y, Zhang L, et al. (2019). Protective Role of RNA Helicase DEAD-Box Protein 5 in Smooth Muscle Cell Proliferation and Vascular Remodeling. Circ Res, 124:e84-e100.
[61] Di Gregoli K, George SJ, Jackson CL, Newby AC, Johnson JL (2016). Differential effects of tissue inhibitor of metalloproteinase (TIMP)-1 and TIMP-2 on atherosclerosis and monocyte/macrophage invasion. Cardiovasc Res, 109:318-330.
[62] Chang JW, Zhang W, Yeh HS, de Jong EP, Jun S, Kim KH, et al. (2015). mRNA 3′ -UTR shortening is a molecular signature of mTORC1 activation. Nature Communications, 6.
[63] Duewell P, Kono H, Rayner KJ, Sirois CM, Vladimer G, Bauernfeind FG, et al. (2010). NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature, 464:1357-1361.
[64] Haneklaus M, O'Neil JD, Clark AR, Masters SL, O'Neill LAJ (2017). The RNA-binding protein Tristetraprolin (TTP) is a critical negative regulator of the NLRP3 inflammasome. J Biol Chem, 292:6869-6881.
[65] Zhao Q, Egashira K, Hiasa K, Ishibashi M, Inoue S, Ohtani K, et al. (2004). Essential role of vascular endothelial growth factor and Flt-1 signals in neointimal formation after periadventitial injury. Arterioscler Thromb Vasc Biol, 24:2284-2289.
[66] Thomas CP, Raikwar NS, Kelley EA, Liu KZ (2010). Alternate processing of Flt1 transcripts is directed by conserved cis-elements within an intronic region of FLT1 that reciprocally regulates splicing and polyadenylation. Nucleic Acids Res, 38:5130-5140.
[67] Sun Z (2015). Aging, arterial stiffness, and hypertension. Hypertension, 65:252-256.
[68] Clausen T (1998). Clinical and therapeutic significance of the Na+,K+ pump*. Clin Sci (Lond), 95:3-17.
[69] Ferrandi M, Tripodi G, Salardi S, Florio M, Modica R, Barassi P, et al. (1996). Renal Na,K-ATPase in genetic hypertension. Hypertension, 28:1018-1025.
[70] Prasad MK, Bhalla K, Pan ZH, O'Connell JR, Weder AB, Chakravarti A, et al. (2013). A polymorphic 3'UTR element in ATP1B1 regulates alternative polyadenylation and is associated with blood pressure. PLoS One, 8:e76290.
[71] Yang Z, Venardos K, Jones E, Morris BJ, Chin-Dusting J, Kaye DM (2007). Identification of a novel polymorphism in the 3'UTR of the L-arginine transporter gene SLC7A1: contribution to hypertension and endothelial dysfunction. Circulation, 115:1269-1274.
[72] Yang Z, Kaye DM (2009). Mechanistic insights into the link between a polymorphism of the 3'UTR of the SLC7A1 gene and hypertension. Hum Mutat, 30:328-333.
[73] Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. (2022). 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J, 43:3618-3731.
[74] Culley MK, Chan SY (2022). Endothelial Senescence: A New Age in Pulmonary Hypertension. Circ Res, 130:928-941.
[75] Houssaini A, Breau M, Kebe K, Abid S, Marcos E, Lipskaia L, et al. (2018). mTOR pathway activation drives lung cell senescence and emphysema. JCI Insight, 3.
[76] Tseng V, Collum SD, Allawzi A, Crotty K, Yeligar S, Trammell A, et al. (2022). 3'UTR shortening of HAS2 promotes hyaluronan hyper-synthesis and bioenergetic dysfunction in pulmonary hypertension. Matrix Biol, 111:53-75.
[77] Pan Y, Xu L, Yang X, Chen M, Gao Y (2022). The common characteristics and mutual effects of heart failure and atrial fibrillation: initiation, progression, and outcome of the two aging-related heart diseases. Heart Fail Rev, 27:837-847.
[78] Fan D, Feng H, Song M, Tan P (2025). Gene expression profiles, potential targets and treatments of cardiac remodeling. Mol Cell Biochem, 480:1555-1567.
[79] Signore S, Sorrentino A, Borghetti G, Cannata A, Meo M, Zhou Y, et al. (2015). Late Na(+) current and protracted electrical recovery are critical determinants of the aging myopathy. Nat Commun, 6:8803.
[80] Wehrens XH, Lehnart SE, Reiken S, Vest JA, Wronska A, Marks AR (2006). Ryanodine receptor/calcium release channel PKA phosphorylation: a critical mediator of heart failure progression. Proc Natl Acad Sci U S A, 103:511-518.
[81] Soetanto R, Hynes CJ, Patel HR, Humphreys DT, Evers M, Duan G, et al. (2016). Role of miRNAs and alternative mRNA 3'-end cleavage and polyadenylation

of their mRNA targets in cardiomyocyte hypertrophy. Biochim Biophys Acta, 1859:744-756.

[82] Gruber AR, Martin G, Keller W, Zavolan M (2014). Means to an end: mechanisms of alternative polyadenylation of messenger RNA precursors. Wiley Interdiscip Rev RNA, 5:183-196.

[83] Mohan N, Kumar V, Kandala DT, Kartha CC, Laishram RS (2018). A Splicing-Independent Function of RBM10 Controls Specific 3' UTR Processing to Regulate Cardiac Hypertrophy. Cell Rep, 24:3539-3553.

[84] Sudheesh AP, Mohan N, Francis N, Laishram RS, Anderson RA (2019). Star-PAP controlled alternative polyadenylation coupled poly(A) tail length regulates protein expression in hypertrophic heart. Nucleic Acids Res, 47:10771-10787.

[85] Cao J, Verma SK, Jaworski E, Mohan S, Nagasawa CK, Rayavara K, et al. (2021). RBFOX2 is critical for maintaining alternative polyadenylation patterns and mitochondrial health in rat myoblasts. Cell Rep, 37:109910.

[86] Witmer NH, McLendon JM, Stein CS, Yoon JY, Berezhnaya E, Elrod JW, et al. (2024). Upstream alternative polyadenylation in SCN5A produces a short transcript isoform encoding a mitochondria-localized NaV1.5 N-terminal fragment that influences cardiomyocyte respiration. bioRxiv.

[87] Zhang X, Yoon JY, Morley M, McLendon JM, Mapuskar KA, Gutmann R, et al. (2018). A common variant alters SCN5A-miR-24 interaction and associates with heart failure mortality. J Clin Invest, 128:1154-1163.

[88] Gibb AA, Lazaropoulos MP, Elrod JW (2020). Myofibroblasts and Fibrosis: Mitochondrial and Metabolic Control of Cellular Differentiation. Circ Res, 127:427-447.

[89] Neupane R, Youker K, Yalamanchili HK, Cieslik KA, Karmouty-Quintana H, Guha A, Thandavarayan RA (2022). Cleavage stimulating factor 64 depletion mitigates cardiac fibrosis through alternative polyadenylation. Biochem Biophys Res Commun, 597:109-114.

[90] Huan W, Yandong L, Chao W, Sili Z, Jun B, Mingfang L, et al. (2021). YKL-40 Aggravates Early-Stage Atherosclerosis by Inhibiting Macrophage Apoptosis in an Aven-dependent Way. Front Cell Dev Biol, 9:752773.

[91] Zhang L, Jia X (2019). Down-regulation of miR-30b-5p protects cardiomyocytes against hypoxia-induced injury by targeting Aven. Cell Mol Biol Lett, 24:61.

[92] Yu P, Song S, Zhang X, Cui S, Wei G, Huang Z, et al. (2023). Downregulation of apoptotic repressor AVEN exacerbates cardiac injury after myocardial infarction. Proc Natl Acad Sci U S A, 120:e2302482120.

[93] Liu Z, Wang K, Jiang C, Chen Y, Liu F, Xie M, et al. (2024). Morusin Alleviates Aortic Valve Calcification by Inhibiting Valve Interstitial Cell Senescence Through Ccnd1/Trim25/Nrf2 Axis. Adv Sci (Weinh), 11:e2307319.

[94] Zhang J, Wu J, Gao Y, Fan X, Liu X, Zhang G, et al. (2024). Inhibition of valve mesenchymal stromal cell calcium deposition by bFGF through alternative polyadenylation regulation of the CAT gene. BMC Cardiovasc Disord, 24:128.

[95] LaForce GR, Philippidou P, Schaffer AE (2023). mRNA isoform balance in neuronal development and disease. Wiley Interdiscip Rev RNA, 14:e1762.

[96] Flores CC, Pasetto NA, Wang H, Dimitrov AG, Davis JF, Jiang Z, et al. (2024). Sleep and diurnal alternative polyadenylation sites associated with human APA-linked brain disorders. NPJ Biol Timing Sleep, 1:11.

[97] Gu J, Wu F, Xu W, Shi J, Hu W, Jin N, et al. (2017). TDP-43 suppresses tau expression via promoting its mRNA instability. Nucleic Acids Res, 45:6177-6193.

[98] Gu J, Chu D, Jin N, Chen F, Liu F (2019). Cyclic AMP-Dependent Protein Kinase Phosphorylates TDP-43 and Modulates Its Function in Tau mRNA Processing. J Alzheimers Dis, 70:1093-1102.

[99] Tan MS, Yu JT, Tan L (2013). Bridging integrator 1 (BIN1): form, function, and Alzheimer's disease. Trends Mol Med, 19:594-603.

[100] Chapuis J, Hansmannel F, Gistelinck M, Mounier A, Van Cauwenberghe C, Kolen KV, et al. (2013). Increased expression of BIN1 mediates Alzheimer genetic risk by modulating tau pathology. Mol Psychiatry, 18:1225-1234.

[101] Patel R, Brophy C, Hickling M, Neve J, Furger A (2019). Alternative cleavage and polyadenylation of genes associated with protein turnover and mitochondrial function are deregulated in Parkinson's, Alzheimer's and ALS disease. BMC Med Genomics, 12:60.

[102] Vallortigara J, Whitfield D, Quelch W, Alghamdi A, Howlett D, Hortobagyi T, et al. (2016). Decreased Levels of VAMP2 and Monomeric Alpha-Synuclein Correlate with Duration of Dementia. J Alzheimers Dis, 50:101-110.

[103] Lukiw WJ, Bazan NG (1997). Cyclooxygenase 2 RNA message abundance, stability, and hypervariability in sporadic Alzheimer neocortex. J Neurosci Res, 50:937-945.

[104] Dickson JR, Kruse C, Montagna DR, Finsen B, Wolfe MS (2013). Alternative polyadenylation and miR-34 family members regulate tau expression. J Neurochem, 127:739-749.

[105] Jonnakuti VS, Wagner EJ, Maletic-Savatic M, Liu Z, Yalamanchili HK (2023). PolyAMiner-Bulk: A Machine Learning Based Bioinformatics Algorithm to Infer and Decode Alternative Polyadenylation Dynamics from bulk RNA-seq data. bioRxiv.

[106] Chen C, Zhang Z, Liu Y, Hong W, Karahan H, Wang J, et al. (2025). Comprehensive characterization of the transcriptional landscape in Alzheimer's disease (AD) brains. Sci Adv, 11:eadn1927.

[107] Rhinn H, Qiang L, Yamashita T, Rhee D, Zolin A, Vanti W, Abeliovich A (2012). Alternative alpha-synuclein transcript usage as a convergent mechanism in Parkinson's disease pathology. Nat Commun, 3:1084.

[108] Jin SM, Youle RJ (2013). The accumulation of misfolded proteins in the mitochondrial matrix is sensed by PINK1 to induce PARK2/Parkin-mediated mitophagy of polarized mitochondria. Autophagy, 9:1750-1757.

[109] Kim J, Inoue K, Ishii J, Vanti WB, Voronov SV, Murchison E, et al. (2007). A MicroRNA feedback circuit in midbrain dopamine neurons. Science, 317:1220-1224.
[110] Roth-Walter F, Adcock IM, Benito-Villalvilla C, Bianchini R, Bjermer L, Caramori G, et al. (2024). Metabolic pathways in immune senescence and inflammaging: Novel therapeutic strategy for chronic inflammatory lung diseases. An EAACI position paper from the Task Force for Immunopharmacology. Allergy, 79:1089-1122.
[111] Brebner JA, Stockley RA (2013). Recent advances in alpha-1-antitrypsin deficiency-related lung disease. Expert Rev Respir Med, 7:213-229; quiz 230.
[112] Lackey L, Coria A, Ghosh AJ, Grayeski P, Hatfield A, Shankar V, et al. (2021). Alternative poly-adenylation modulates alpha1-antitrypsin expression in chronic obstructive pulmonary disease. PLoS Genet, 17:e1009912.
[113] McElvaney NG (2015). Diagnosing alpha1-antitrypsin deficiency: how to improve the current algorithm. Eur Respir Rev, 24:52-57.
[114] Thorvaldsdottir H, Robinson JT, Mesirov JP (2013). Integrative Genomics Viewer (IGV): high-performance genomics data visualization and exploration. Brief Bioinform, 14:178-192.
[115] Saferali A, Kim W, Xu Z, Chase RP, Cho MH, Laederach A, et al. (2024). Colocalization analysis of 3' UTR alternative polyadenylation quantitative trait loci reveals novel mechanisms underlying associations with lung function. Hum Mol Genet, 33:1164-1175.
[116] Lamontagne M, Berube JC, Obeidat M, Cho MH, Hobbs BD, Sakornsakolpat P, et al. (2018). Leveraging lung tissue transcriptome to uncover candidate causal genes in COPD genetic associations. Hum Mol Genet, 27:1819-1829.
[117] Phan THG, Paliogiannis P, Nasrallah GK, Giordo R, Eid AH, Fois AG, et al. (2021). Emerging cellular and molecular determinants of idiopathic pulmonary fibrosis. Cell Mol Life Sci, 78:2031-2057.
[118] Lin Y, Xu Z (2020). Fibroblast Senescence in Idiopathic Pulmonary Fibrosis. Front Cell Dev Biol, 8:593283.
[119] Briata P, Gherzi R (2020). Long Non-Coding RNA-Ribonucleoprotein Networks in the Post-Transcriptional Control of Gene Expression. Noncoding RNA, 6.
[120] Deng N, Sanchez CG, Lasky JA, Zhu D (2013). Detecting splicing variants in idiopathic pulmonary fibrosis from non-differentially expressed genes. PLoS One, 8:e68352.
[121] Weng T, Ko J, Masamha CP, Xia Z, Xiang Y, Chen NY, et al. (2019). Cleavage factor 25 deregulation contributes to pulmonary fibrosis through alternative polyadenylation. J Clin Invest, 129:1984-1999.
[122] Ko J, Mills T, Huang J, Chen NY, Mertens TCJ, Collum SD, et al. (2019). Transforming growth factor beta1 alters the 3'-UTR of mRNA to promote lung fibrosis. J Biol Chem, 294:15781-15794.
[123] Weng T, Huang J, Wagner EJ, Ko J, Wu M, Wareing NE, et al. (2020). Downregulation of CFIm25 amplifies dermal fibrosis through alternative polyadenylation. J Exp Med, 217.
[124] Zhou Z, Qu J, He L, Zhu Y, Yang SZ, Zhang F, et al. (2020). Stiff matrix instigates type I collagen biogenesis by mammalian cleavage factor I complex-mediated alternative polyadenylation. JCI Insight, 5.
[125] Tsou PS, Shi B, Varga J (2022). Role of cellular senescence in the pathogenesis of systemic sclerosis. Curr Opin Rheumatol, 34:343-350.
[126] Mills TW, Wu M, Alonso J, Puente H, Charles J, Chen Z, et al. (2024). Unraveling the role of MiR-181 in skin fibrosis pathogenesis by targeting NUDT21. FASEB J, 38:e70022.
[127] Duggan M, Torkzaban B, Ahooyi TM, Khalili K, Gordon J (2020). Age-related neurodegenerative diseases. J Cell Physiol, 235:3131-3141.
[128] Lopez-Mejia IC, de Toledo M, Chavey C, Lapasset L, Cavelier P, Lopez-Herrera C, et al. (2014). Antagonistic functions of LMNA isoforms in energy expenditure and lifespan. EMBO Rep, 15:529-539.
[129] Sun D, Wei S, Wang D, Zeng M, Mo Y, Li H, et al. (2023). Integrative analysis of potential diagnostic markers and therapeutic targets for glomerulus-associated diabetic nephropathy based on cellular senescence. Front Immunol, 14:1328757.
[130] Venkatachalam G, Surana U, Clement MV (2017). Replication stress-induced endogenous DNA damage drives cellular senescence induced by a sub-lethal oxidative stress. Nucleic Acids Res, 45:10564-10582.
[131] Berg MG, Singh LN, Younis I, Liu Q, Pinto AM, Kaida D, et al. (2012). U1 snRNP determines mRNA length and regulates isoform expression. Cell, 150:53-64.
[132] Li W, You B, Hoque M, Zheng D, Luo W, Ji Z, et al. (2015). Systematic profiling of poly(A)+ transcripts modulated by core 3' end processing and splicing factors reveals regulatory rules of alternative cleavage and polyadenylation. PLoS Genet, 11:e1005166.
[133] Martin G, Gruber AR, Keller W, Zavolan M (2012). Genome-wide analysis of pre-mRNA 3' end processing reveals a decisive role of human cleavage factor I in the regulation of 3' UTR length. Cell Rep, 1:753-763.
[134] Zhao T, Zhan D, Qu S, Jiang S, Gan W, Qin W, et al. (2023). Transcriptomics-proteomics Integration reveals alternative polyadenylation driving inflammation-related protein translation in patients with diabetic nephropathy. J Transl Med, 21:86.
[135] Borghesan M, Hoogaars WMH, Varela-Eirin M, Talma N, Demaria M (2020). A Senescence-Centric View of Aging: Implications for Longevity and Disease. Trends Cell Biol, 30:777-791.
[136] Castano-Betancourt MC, Evans DS, Ramos YF, Boer CG, Metrustry S, Liu Y, et al. (2016). Novel Genetic Variants for Cartilage Thickness and Hip Osteoarthritis. PLoS Genet, 12:e1006260.
[137] Winstanley-Zarach P, Rot G, Kuba S, Smagul A, Peffers MJ, Tew SR (2023). Analysis of RNA Polyadenylation in Healthy and Osteoarthritic Human Articular Cartilage. Int J Mol Sci, 24.

[138] Zhang Y, Huang Z, Lu W, Liu Z (2025). Alternative cleavage and polyadenylation: key regulatory mechanisms in health and disease. RNA Biol, 22:1-33.
[139] Wang JR, Holt J, McMillan L, Jones CD (2018). FMLRC: Hybrid long read error correction using an FM-index. BMC Bioinformatics, 19:50.
[140] Xu SM, Curry-Hyde A, Sytnyk V, Janitz M (2022). RNA polyadenylation patterns in the human transcriptome. Gene, 816:146133.
[141] Stern EP, Guerra SG, Chinque H, Acquaah V, Gonzalez-Serna D, Ponticos M, et al. (2020). Analysis of Anti-RNA Polymerase III Antibody-positive Systemic Sclerosis and Altered GPATCH2L and CTNND2 Expression in Scleroderma Renal Crisis. J Rheumatol, 47:1668-1677.