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Functions and application of circRNAs in vascular aging and aging-related vascular diseases

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Abstract

Circular RNAs (circRNAs), constituting a novel class of endogenous non-coding RNAs generated through the reverse splicing of mRNA precursors, possess the capacity to regulate gene transcription and translation. Recently, the pivotal role of circRNAs in controlling vascular aging, as well as the pathogenesis and progression of aging-related vascular diseases, has garnered substantial attention. Vascular aging plays a crucial role in the increased morbidity and mortality of the elderly. Endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) are crucial components of the intima and media layers of the vascular wall, respectively, and are closely involved in the mechanisms underlying vascular aging and aging-related vascular diseases. The review aims to provide a comprehensive exploration of the connection between circRNAs and vascular aging, as well as aging-related vascular diseases. Besides, circRNAs, as potential diagnostic markers or therapeutic targets for vascular aging and aging-related vascular diseases, will be discussed thoroughly, along with the challenges and limitations of their clinical application. Investigating the role and molecular mechanisms of circRNAs in vascular aging and aging-related vascular diseases will provide a novel insight into early diagnosis and therapy, and even effective prognosis assessment of these conditions.

Keywords circRNAs, Endothelial cells, Vascular smooth muscle cells, Vascular aging, Aging-related vascular diseases

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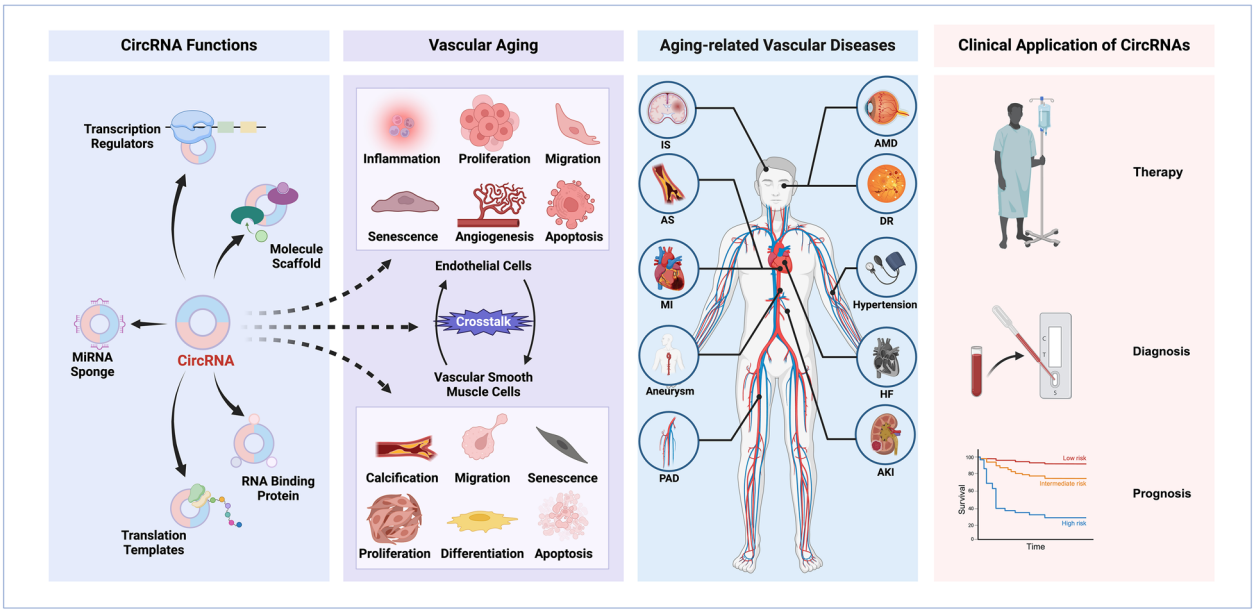
Graphical Abstract



Introduction

Increasing life expectancy and declining fertility rates have made aging a global healthcare concern. According to World Population Prospects 2022 issued by the United Nations [1], the population aged 60 and above, commonly referred to as the 'aging population', is projected to surpass 2 billion by 2050. Among this group, approximately 450 million individuals will be over 80. However, the demographic transition is accompanied by an increased prevalence of aging-related diseases [2]. Vascular aging refers to the progressive deterioration of normal vascular structure and function associated with advanced age [3]. Given that aging is an irreversible biological process and an independent risk factor for numerous chronic diseases, understanding the complexities of vascular aging will facilitate the prediction of prognosis and identification of potential therapeutic targets for aging-related diseases [4].

Non-coding RNAs (ncRNAs), which regulate gene expression, have garnered increasing attention, with circular RNAs (circRNAs) emerging as a noteworthy subtype. Characterized by their covalently closed circular structures, circRNAs have gained recognition as a novel class of RNA regulatory molecules due to their stability, conservation, endogenous nature, and abundance [5]. However, the extent of circRNAs' involvement in diseases relatively remains relatively unexplored.

The primary focus of this review is to provide an overview of the latest advancements in research on circRNAs in vascular aging and aging-related vascular diseases. It will provide background information on circRNAs and their regulatory roles in the pathophysiological process of endothelial cells (ECs) and vascular smooth muscle cells (VSMCs), including how circRNAs mediate the crosstalk between ECs and VSMCs. Moreover, we will summarize and discuss the roles and functions that circRNAs play in the pathogenesis and progression of aging-related vascular diseases. Finally, the potential application of circRNAs as diagnostic markers or therapeutic targets for the clinical practice of vascular aging and aging-related diseases will be discussed, as well as the potential future challenges in their clinical application.

Vascular aging

The renowned 17th-century physician Thomas Sydenham once said, "A man is as old as his arteries", implying a strong correlation between vascular aging and individual aging [6]. Vascular aging serves as a significant bridge between aging and aging-related diseases. It is vital to understand vascular aging and how it contributes to the progression of aging-related vascular diseases.

General characteristics

Vascular aging refers to the progressive degeneration of the vessel wall, which includes both structural and

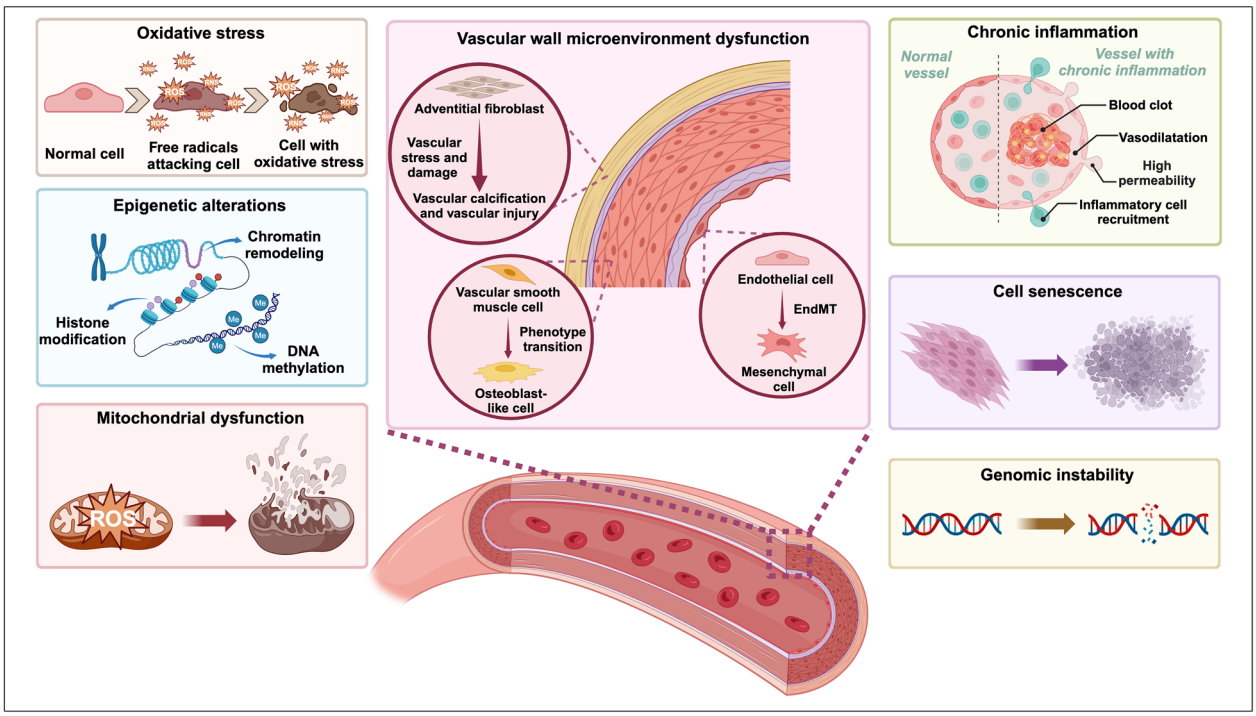


Fig. 1 Mechanisms of vascular aging. The pathology of vascular aging involving the intricate interplay of multiple factors, such as oxidative stress, mitochondrial dysfunction, cellular senescence, chronic inflammation, vascular wall microenvironment dysfunction, epigenetic alterations, and genomic instability, etc. These interrelated factors together lead to the development of vascular aging. (Created with BioRender.com). ROS, reactive oxygen species; RNS, reactive nitrogen species; EndMT, endothelial-mesenchymal transition

functional alterations [7]. It encompasses widespread alterations across the whole circulatory system, involving arteries, microvasculature, and veins. These changes together result in impaired blood flow regulation and cardiovascular dysfunction.

Arterial aging is one of the most significant aspects of vascular aging that cannot be ignored, as the structural and functional alterations in the arteries play a major role in the overall decline in aging-related vascular functions [8]. One of the main characteristics of vascular aging is thought to be arterial stiffness. Vascular aging is associated with increased rigidity of the arterial walls, influencing their capacity to finely regulate the blood flow dynamics [9, 10]. In the elderly, increased pulsatile energy is conveyed to the microvasculature of stiffened arteries, potentially inpairing organ function [11]. Furthermore, vascular calcification, defined by the deposition of ectopic calcium salts at the vascular sites, is regarded as an important phenotype of vascular aging [12]. Calcification is mainly divided into intimal and medial calcification. The former is commonly linked to atherosclerotic plaque, while the latter is considered a more diffuse arteriosclerotic process [13]. Both arterial stiffness and calcification are hallmarks of vascular aging, serving as key indicators of cardiovascular health risks [13].

The microvasculature is widely distributed throughout the body and serves a crucial function in regulating the local environment of various organs and tissues [14]. Aging leads to the gradual deterioration of microvascular function, resulting in tissue hypoxia, insufficient nutrient delivery, and waste accumulation [6]. These changes ultimately contribute to widespread negative effects on the function of multiple organs.

Venous aging can result from the same cellular and molecular aging mechanisms that affect arteries and microvasculature, potentially leading to a range of venous diseases, including varicose veins, chronic venous insufficiency, and deep vein thrombosis [15]. Although venous aging has not been extensively studied, it undoubtedly represents a significant and promising direction for vascular aging in the future.

General biochemical causes of vascular aging

The pathology of vascular aging is an intricate process involving the interplay of multiple factors, such as oxidative stress, mitochondrial dysfunction, cellular senescence, chronic inflammation, vascular wall microenvironment dysfunction, epigenetic alterations, and genomic instability, etc [6, 14, 16–19] (Fig. 1).

Oxidative stress, which leads to excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [20–23], aggravates ECs damage by upregulating free radical levels [24, 25], and plays a key role in accelerating vascular aging. Nitric oxide (NO) is a primary factor for maintaining vascular homeostasis in ECs. The ROS produced by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) increases with age [14]. The reaction of superoxide anion with NO that forms peroxynitrite reduces the bioavailability of NO, resulting in endothelial dysfunction and ultimately impacting the blood flow, vascular dilation, and the regulation of the internal environment [26, 27].

Mitochondrial dysfunction is directly correlated with vascular aging [28]. In aged ECs, dysfunctional mitochondria are one of the major contributors to increase ROS generation [14]. Mitochondrial-derived ROS contributes to pro-inflammatory phenotypic alterations via nuclear factor kappa-B (NF-κB) activation [29], and it activates the protein kinase B (Akt) signaling pathway and the NF-κB/NOX1 axis, thereby accelerating vascular aging [30, 31].

Cell senescence, a cell aging process initiated by responses to various endogenous and exogenous stressors, involves various unique phenotypic alterations in cells [32, 33]. Despite the proportion of senescent cells in the vascular system of the elderly is generally low, several mechanisms of cellular senescence have been demonstrated that may damage vascular function and promote the progression of age-related vascular diseases [6]. Apart from inducing cell-cycle arrest, a notable feature of cellular senescence is the production of proinflammatory cytokines, growth factors, and proteases, collectively known as the senescence-associated secretory phenotype (SASP), which contributes to chronic inflammation [17, 34–36]. In addition, via the paracrine processes, senescent cells may affect the phenotypes and functions of neighboring cells in the vascular system [6]. Through these mechanisms, senescent cells may lead to endothelial dysfunction, impaired barrier function, elevated inflammatory status, and pathological remodeling of senescent blood vessels [6].

Chronic inflammation prompts the release of cytokines, activating an inflammatory cascade, resulting in poor immune function and an inability to clear senescent cells and inflammatory factors, which create a vicious cycle of inflammation and senescence [36–38]. It is worth mentioning that there is an important interaction between oxidative stress and inflammation. Specifically, ROS functions as a signaling molecule that activates the inflammatory signaling pathway (e.g. the NF-κB signaling pathway) that promotes inflammation. Conversely, inflammatory mediators can trigger oxidative stress (e.g. the tumor necrosis factor (TNF) signaling induces ROS/RNS production) [14, 39].

Under a variety of healthy and pathological conditions, vascular wall cells interact with each other, enabling the vascular wall to function as a whole via cell crosstalk, known as the "vascular wall microenvironment" [40]. The stability of the vascular wall microenvironment is closely linked to the normal function of blood vessels. Age-associated changes in the vascular wall microenvironment may contribute to the intricate changes in the local tissue fluid and cellular environment, thereby initiating or exacerbating the development of vascular aging [6].

Simultaneously, epigenetic mechanisms such as DNA methylation and histone modification are key features of vascular aging and influence the sensitivity and activities of signaling pathways in cells and tissues by regulating genes expression [41–44], while genomic instability also accelerates the vascular aging process [45, 46]. These interrelated factors together lead to the development of vascular aging, highlighting the overall imbalance of the vascular system and the multifaceted interactions.

Cellular and tissue remodeling in vascular aging

Recent investigations have provided evidence supporting the involvement of molecular-mediated cell senescence in vascular aging [32, 47]. The vascular walls are structurally composed of the intima, media, and adventitia, which primarily consist of ECs, VSMCs, adventitial fibroblasts (AFs), and immune cells [19]. In the context of vascular aging, the functions of these cells undergo significant changes, leading to impaired vascular function.

ECs, as the barrier between the blood and vessel wall, are responsible for regulating key functions, including vascular contraction and relaxation, inhibition of intimal thickening, etc [48]. ECs become dysfunctional as aging progresses, making them one of the key drivers of vascular aging. Senescent ECs contribute to a decrease in the vascular density, thickening of the intima and media, increased collagen deposition, and a decline in elastin deposition, ultimately leading to diminished arterial elasticity and vessel lumen dilation. This not only exacerbates endothelial dysfunction, but also impairs angiogenesis and vascular tone [49].

VSMCs, primarily located in the medial of vessel wall, play a crucial role in providing essential structural support to the blood vessels, and maintaining vascular tone through coordinated contraction and relaxation, thereby influencing vascular function [50]. During aging, with the gradual accumulation of adverse factors such as mitochondrial dysfunction and oxidative stress, VSMCs transition into SASP [47]. This phenotypic transition leads to the overexpression of cytoskeletal proteins and integrins in VSMCs, which enhances vascular stiffness.

Additionally, by secreting matrix metalloproteinases (MMPs), VSMCs exacerbate collagen deposition and elastin degradation, further impairing vascular elasticity and function [47, 51]. Furthermore, under conditions of high calcium or phosphate, VSMCs could switch to osteogenic phenotype which promotes vascular calcification [47, 52, 53].

AFs are not only involved in maintaining vascular structure, but also serve essential immune and endocrine functions that regulate vascular remodeling [54, 55]. Aging-related alterations in AFs can impair their ability to maintain vascular integrity and regulate vascular remodeling. Liu et al. reported that sirtuin 6 (SIRT6) was down-regulated in the aorta of aged rats, which contributed to an aging phenotype in AFs, affecting their proliferation, collagen secretion, migration, and the expression of α-smooth muscle actin (α-SMA), thereby accelerating vascular aging [56].

In addition to ECs, VSMCs, and AFs, the role of immune cells in vascular aging has become increasingly significant. As aging progresses, the immune system gradually becomes dysregulated, leading to aging-related chronic low-grade inflammation, which promotes the process of vascular aging [57]. Senescent macrophages secrete pro-inflammatory cytokines and MMPs, promoting inflammatory responses and extracellular matrix (ECM) degradation, playing a key role in vascular aging and remodeling [58, 59]. Moreover, senescent T-cells and B-cells contribute to vascular aging by promoting inflammatory responses, enhancing antigen presentation, and secreting pro-inflammatory cytokines, thereby exacerbating the inflammatory environment within the blood vessels [60, 61].

Cells within the vessel wall do not work independently but communicate with each other to modulate the vascular functions, commonly constituting the vascular wall microenvironment. Exosomes (Exos) are capable of transmitting biological messages between adjacent cells and distant cells, such as stimulating the deposition of hydroxyapatite crystals, modulating the alteration of phenotype, and interfering with underlying signaling [19]. Recent studies have focused on exploring the communication between vascular wall cells, and have found that the communication plays an important role in modulating vascular aging [62–64]. Our previous studies have revealed that both Exos released from high phosphate-induced ECs and AFs enhance VSMC calcification by transmitting miR-21-5p and miR-670-3p, respectively [40, 62].

Therefore, the cells within the vascular wall microenvironment serve not only as physical structural barriers, but also as regulators of vascular function, highlighting the crucial role of the vascular wall microenvironment in the occurrence and development of vascular aging.

Consequences of vascular aging

Vascular aging stands as an independent risk factor for aging-related diseases [12], and the prevalence of aging-related vascular diseases has consistently risen each year [6]. Vascular aging plays a key role in a variety of aging-related macrovascular diseases, including atherosclerosis (AS) [65], aneurysm [66], peripheral arterial disease (PAD) [67], myocardial infarction (MI) [68, 69], and ischemic stroke (IS) [70]. Moreover, the multifaceted structural and functional microvasculature damage generated by vascular aging results in the occurrence of aging-related microvascular diseases, including acute kidney injury (AKI) [71, 72], age-related macular degeneration (AMD) [73], diabetic retinopathy (DR) [73], heart failure (HF) [69], and hypertension [74, 75]. Consequently, in-depth research into the potential molecular mechanisms of vascular aging will help advance the development of prevention and treatment strategies.

History and characteristics of circRNAs

Recently, a new generation of RNA-sequencing (RNA-seq) has successfully and comprehensively explored the characteristics of circRNAs, revealing their critical role in various biological processes [76], establishing circRNA as a rising star in the large family of ncRNAs. Next, we provide an overview of the history development and characteristics of circRNAs, highlighting their tremendous regulatory potential.

History development of circRNAs

To trace the discovery and research history of circRNAs in aging-related vascular diseases, a comprehensive review of the circRNA timeline would be helpful (Fig. 2A). CircRNAs were first identified as viroids in 1976 [77]. Their presence in eukaryotic cells was initially observed through electron microscopy in 1979 [78], and in 1986, circRNAs were identified within the hepatitis delta virus [79]. These findings suggest that circRNAs, as covalently closed single-stranded RNA molecules, are ubiquitous across various organisms, from viruses to mammals. However, the specific mechanism of circRNA formation remains unclear.

Only a few circRNAs were initially reported, likely due to their low expression levels, and were considered the by-products of alternative splicing errors or experimental mistakes [80, 81]. In 1991, researchers identified the first examples of human endogenously spliced circRNAs, transcribed from the deleted in the colorectal carcinomas (DCC) gene with ends joined in a scrambled order compared to the typical linear sequence [82]. Concurrently,

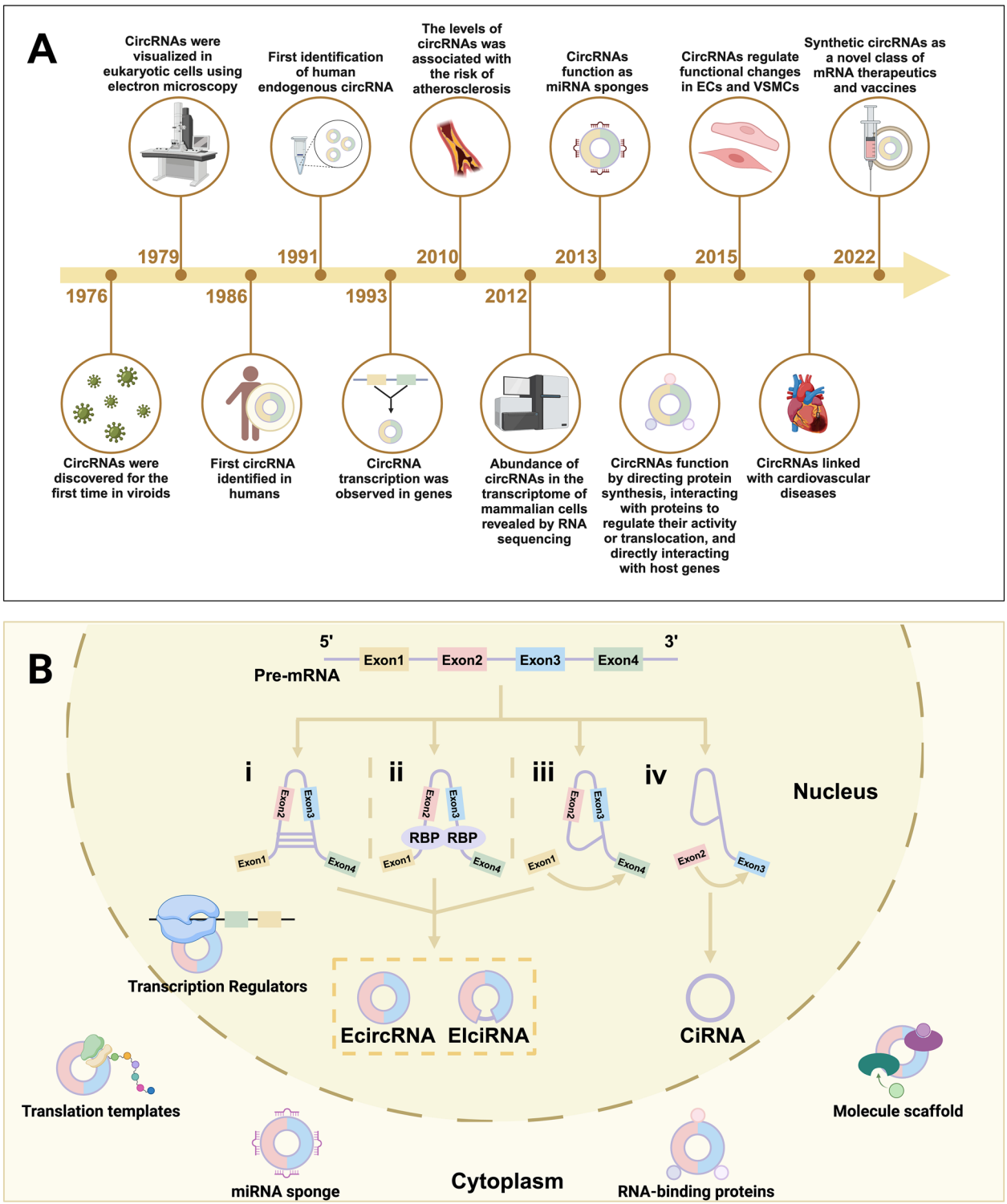


Fig. 2 History and characteristics of circRNAs. **A** Milestones in the discovery and study of circRNAs in vascular diseases. **B** Biogenesis and functions of circRNAs. Four different models of circRNA biogenesis have been presented: (i) intron-pairing-driven circularization promotes circRNAs biogenesis; (ii) RBP-driven circularization leads to the formation of circRNAs; (iii) exon-skipping generates ElcircRNAs and EcircRNAs; (iv) intron lariat-driven circularization forms CiRNAs. CircRNAs localized primarily in the nucleus can function as transcription regulators, while other circRNAs localized mainly in the cytoplasm act as translation templates and miRNA sponges, interact with RNA-binding proteins, as well as serve as molecule scaffolds. (Created with BioRender.com). CircRNAs, circular RNAs; MiRNA, microRNA; ECs, endothelial cells; VSMCs, vascular smooth muscle cells; RBP, RNA binding protein; EcircRNAs, exon circRNAs; ElciRNAs, exon–intron circRNAs; CiRNAs, circular intronic RNAs

in 1993, Capel et al. observed circRNA transcription in genes in mouse male germ cells, suggesting a potential role in normal cell function [83]. Despite these early discoveries, large-scale circRNA recognition was hindered by the elaborate traditional study methods and a lack of useful information.

In 2012, with the use of RNA-seq technology, Salzman et al. revealed the abundance of circRNAs in the transcriptome of mammalian cells through high-throughput sequencing [84]. This discovery propelled circRNAs into the spotlight, with their unique characteristics, such as the exceptional stability compared to linear mRNA transcripts, attributed to the resistance against exonucleolytic decay by exoribonucleases [85]. By 2013, reports confirmed the function of circRNAs as miRNA sponges, highlighting their specific regulatory ability [78, 86]. Further exploration unveiled various biological functions of circRNAs, including the direction of protein synthesis [87], interaction with proteins to regulate their activity or translocation [88, 89], and direct interaction with their host genes [90].

As the molecular functions and mechanisms of circRNAs continue to be explored, they have been found to possess diverse epigenetic regulatory functions in various organisms, actively participating in regulating physiological and pathological processes associated with human diseases [5, 91–95]. In 2010, it was found that the level of circRNAs was associated with the risk of AS, providing a new direction for future vascular diseases [96]. Additionally, ECs and VSMCs are crucial components of blood vessels, and circRNAs were found to regulate their functional changes in 2015 [93, 97]. As more circRNAs are discovered in vascular diseases, showing different expression patterns in various cells or under different physiological and pathological conditions, this suggests that these biomolecules have potential roles in the occurrence and development of different diseases, making them promising diagnostic and therapeutic tools for cardiovascular diseases (CVDs) [98, 99]. Since 2022, numerous studies have found that synthetic circRNAs can be engineered to explore their applications as a novel class of mRNA therapeutics and vaccines [92, 100, 101], which represent a potential clinical application in vascular diseases. Therefore, in this review, we specifically focus on the relationship between circRNAs and vascular aging and aging-related vascular diseases.

Characteristics of circRNAs

CircRNAs are characterized by the absence of 5′-caps and 3′-poly(A) tails. Unlike typical RNA splicing, circRNA formation involves back splicing of pre-mRNAs using RNA-polymerase II [76, 102]. In intron-pairing-driven circularization, two complementary introns are joined by direct base pairing, forming a circular structure with multiple introns and exons by intron removal. RNA-binding protein (RBP)-driven circularization involves RBPs acting as carriers to bind non-adjacent introns, which are then removed. Lariat-driven circularization, resulting from exon-skipping, produces exon circRNAs (EcircRNAs) and exon–intron circRNAs (EIciRNAs), while intron lariats give rise to circular intronic RNAs (ciRNAs) [5, 103, 104]. The majority of circRNAs originate from known protein-coding genes, exhibiting cell-specific and tissue-specific expression patterns, and their biogenesis is regulated by specific cis-acting elements and trans-acting factors [5].

Nuclear circRNAs enhance gene transcription, while cytoplasmic circRNAs function as microRNA (miRNA) sponges, interact with circRNA-binding proteins (cRBPs), serve as molecular scaffolds, or even translate into proteins [105] (Fig. 2B). For example, nuclear circRNAs have been shown to exert transcriptional and translational control, especially over their parent genes in the nucleus. The study has shown that circYap can directly bind its parent mRNA and its translation initiation proteins eukaryotic translation initiation factor 4G (eIF4G) and poly(A)-binding protein (PABP), and the overexpression of circYap disrupts the interaction between PABP on the 3′-tail with eIF4G on the 5′-cap of yes-associated protein (Yap) mRNA, thereby blocking translation [106]. The most extensively reported function of cytoplasmic circRNAs is as miRNA sponges, which bind miRNAs to decrease their availability and thereby up-regulate the expression of their target mRNAs [107–109]. The first identified miRNA sponge is CDR1as, which contains over 70 conserved target sites for miR-7, and circSry, which contains 16 binding sites for miR-138 [107]. Therefore, various functions of circRNAs have gradually been clarified [89, 110].

Numerous studies have demonstrated the regulatory functions of circRNAs in various cellular processes [111–113]. Through numerous mechanisms described above, circRNAs play a pivotal role in the regulation of signaling pathways involved in various CVDs, such as AS, MI and aneurysm, making them potential diagnostic and therapeutic targets [76, 114, 115]. Abnormal circRNA levels in response to pathological stimulation make them promising biomarkers for disease diagnosis and prognosis [91, 116], offering a novel approach to investigate cellular physiology and disease pathology.

The role of circRNAs in vascular aging

Vascular dysfunction is commonly associated with abnormal gene regulation and the impaired function of vascular wall cells [117]. This review focuses on ECs and VSMCs, since they are crucial components of blood

Table 1 Summary of circRNAs and the mechanisms involved in EC functions

CircRNAs	Mechanisms	Functions	References
circGNAQ	Increases PLK2 expression by sponging miR-146a-5p	Inhibits senescence	[121]
ciPVT1	Regulates the miR-24-3p/CDK4/pRb pathway	Delays senescence, promotes proliferation and increases angiogenic activity	[122]
circ_0005699	Regulates the miR-450b-5P/NFKB1 axis	Induces inflammation and apoptosis	[127]
circ-USP36	Elevates VCAM1 expression by sponging miR-98-5p	Accelerates apoptosis and inflammation but suppresses viability	[128]
	Sponges miR-637 to enhance WNT4 expression	Inhibits proliferation and migration	[134]
circRSF1	Regulates the miR-758/CCND2 axis	Improves viability, tube formation, and migration	[129]
	Modulates the miR-135b-5p/HDAC1 axis	Inhibits inflammation, apoptosis, and proliferation	[118]
circAFF1	Regulates the miR-516b/SAV1/YAP1 axis	Inhibits proliferation, tube formation, migration, and apoptosis	[131]
circ_0003204	Increases E-cadherin expression but reduces N-cadherin and vimentin expression	Inhibits proliferation and migration	[132]
	Increases HDAC9 expression by sponging miR-942-5p	Promotes apoptosis, oxidative stress, and inflammation	[119]
circ_0074673	Regulates the miR-1200/MEOX2 axis	Inhibits proliferation, migration, and angiogenesis	[136]
circGSE1	Regulates the miR-323-5p/NRP1 axis	Promotes proliferation, migration, and tube formation	[137]
circCOL1A2	Regulates the miR-29b/VEGF axis	Promotes proliferation, migration, and angiogenesis	[138]
circ_0086296	Forms the circ_0086296/miR-576-3p/IFIT1/STAT1 feedback loop	Promotes inflammation	[142]

CircRNAs, circular RNAs; ECs, endothelial cells; PLK2, polo-like kinase 2; CDK4, cyclin-dependent kinase 4; NFKB1, nuclear factor kappa B subunit 1; VCAM1, vascular cell adhesion molecule 1; WNT4, wingless type MMTV integration site family, member 4; CCND2, cyclin D2; HDAC1, class IIa histone deacetylase 1; SAV1, salvador homolog 1; YAP1, yes-associated protein 1; HDAC9, class IIa histone deacetylase 9; MEOX2, mesenchyme homeobox 2; NRP1, neuropilin 1; VEGF, vascular endothelial growth factor; IFIT1, interferon-induced protein with tetratricopeptide repeats 1; STAT1, signal transducer and activator of transcription 1

vessels and play a significant role in aging-induced vascular dysfunction. Recently, circRNAs have been linked to the pathophysiological processes leading to vascular aging, including function changes in ECs and VSMCs. However, our current understanding of their intricate biological functions remains limited. To demonstrate the potential role of circRNAs in the process of vascular aging, we will summarize how circRNAs influence the development of vascular aging by modulating the functions of ECs and VSMCs, as well as the crosstalk between them, as follows.

circRNAs and EC functions

EC Dysfunction is widely recognized as a key risk factor for vascular aging [17]. In contrast to the general vascular remodeling process, ECs exhibit senescent phenotype during the vascular aging process, characterized by cell cycle arrest, impaired metabolic function, DNA damage, and mitochondrial dysfunction, which collectively lead to a loss of endothelial function [49]. Meanwhile, various functions of ECs are significantly altered, including decreased proliferation and angiogenic ability, increased apoptosis, weakened migration capacity, and exacerbated inflammatory response. These alterations accelerate the normal vascular function and ultimately contribute to the progression of vascular aging. Existing studies have reported the involvement of circRNAs in regulating the physiological and pathological processes in ECs, including senescence, apoptosis, proliferation, migration, angiogenesis, and inflammation, suggesting their potential role in the occurrence and progression of vascular aging [24, 118, 119] (Table 1) (Fig. 3).

Senescence and apoptosis

Exploring cellular senescence and apoptosis, particularly within the context of vascular aging, reveals the intricate and multifaceted regulatory role of circRNAs in these biological processes. Cellular senescence, characterized by irreversible cell cycle arrest and stressor-induced metabolic changes, stands as a key feature of age-related EC dysfunction [49, 120]. Recent investigations have shown specific circRNAs, such as circGNAQ [121] and ciPVT1 [122], as crucial players in modulating EC senescence. Notably, circGNAQ enhances Polo-like kinase 2 (PLK2) expression by acting as a sponge for miR-146a-5p, suggesting a potential role in inhibiting EC senescence. Similarly, ciPVT1 has been shown to be increased in EC senescence and acts as a sponge for miR-24-3p, thereby enhancing cyclin-dependent kinase 4 (CDK4) expression and promoting Rb phosphorylation, thus reversing EC senescence.

Similar to senescence, EC apoptosis is linked to the progression of vascular aging. There is increasing evidence that EC apoptosis is an early event in

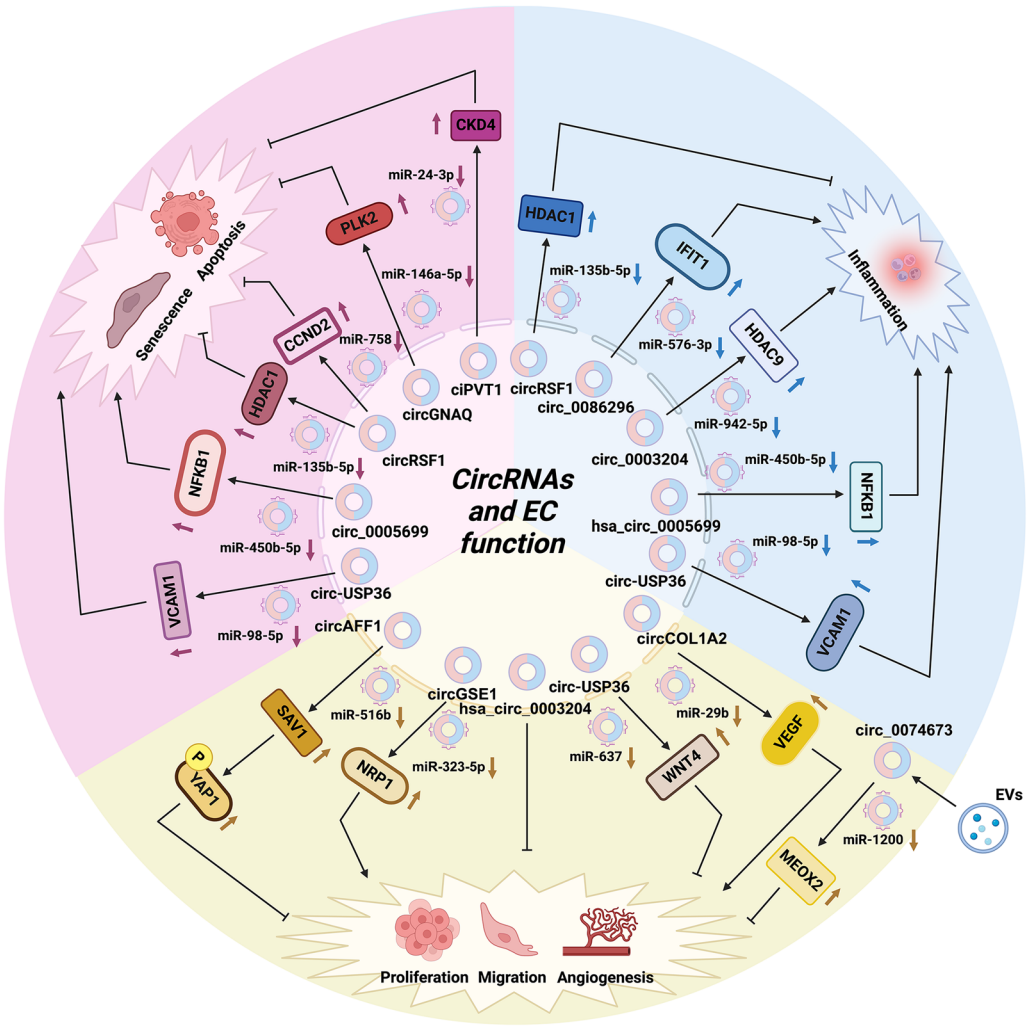


Fig. 3 Roles of circRNAs in the physiological and pathological processes of ECs. CircRNAs participate in the occurrence and progression of vascular diseases by regulating physiological and pathological processes in ECs, including proliferation, differentiation, apoptosis, migration, and inflammation. (Created with BioRender.com). Abbreviations: CircRNAs, circular RNAs; ECs, endothelial cells; VCAM1, vascular cell adhesion molecule 1; NFKB1, nuclear factor kappa B subunit 1; HDAC1, class IIa histone deacetylase 1; CCND2, cyclin D2; PLK2, polo-like kinase 2; CDK4, cyclin dependent kinase 4; IFIT1, interferon induced protein with tetratricopeptide repeats 1; HDAC9, class IIa histone deacetylase 9; VEGF, vascular endothelial growth factor; MEOX2, mesenchyme homeobox 2; WNT4, wingless type MMTV integration site family, member 4; NRP1, neuropilin 1; SAV1, salvador family WW domain-containing protein 1 gene; YAP1, yes-associated protein 1

the development of AS [123]. The close association between EC apoptosis and aging-related vascular diseases like AS further emphasizes the significance of circRNAs in modulating the functions of blood vessels [124, 125]. Oxidized low-density lipoprotein (ox-LDL) serves as a common inducer of AS in vitro [126]. Chen et al. identified a higher expression of circ_0005699 in patients with AS; however, silencing of circ_0005699 led to the up-regulation of miR-450b-5p, subsequently mitigating ox-LDL-induced apoptosis of human umbilical vein ECs (HUVECs) [127]. Peng et al. observed that the binding of miR-98-5p to vascular cell adhesion molecule 1 (VCAM1) inhibited LDL-induced HUVEC injury, while circ-USP36 overexpression can up-regulate VCAM1 expression by sponging miR-98-5p to promote HUVEC apoptosis [128]. Interestingly, under the same stimulation conditions, some RNA molecules can induce different effects. For example, Zhang et al. reported that circRSF1 exerted a suppressive effect on the pathogenesis of AS by modulating ox-LDL-induced vascular EC apoptosis, proliferation, and inflammation via sponging miR-135b-5p and targeting histone deacetylase 1 (HDAC1) [118]. Similarly, Wei et al. found

that circRSF1 in human aortic EC (HAECs) can act as a miR-758 sponge, regulating cyclin D2 (CCND2) expression to reverse HAEC apoptosis and improve migration and angiogenesis [129].

The above studies show the diverse pathways of circRNAs in modulating EC senescence and apoptosis, which demonstrate their ability to influence key factors, such as miRNAs and target genes, resulting in varying outcomes depending on the cellular contexts.

Proliferation, migration, and angiogenesis

The recognition of EC damage as a pivotal pathological feature in the development of AS highlights its intimate association with crucial functions governing EC integrity, including proliferation, migration, and angiogenesis [130, 131]. A body of research has revealed the intricate regulatory network formed by circRNAs in mediating various EC functions [131–133]. Wang et al. demonstrated that hypoxia-induced up-regulation of circAFF1 promoted the expression of salvador homolog 1 (SAV1) by sponging miR-516b, and then induced YAP1 phosphorylation, ultimately inhibited EC proliferation and angiogenesis [131]. Furthermore, the knockdown of hsa_circ_0003204 significantly reduces E-cadherin expression while enhancing the expression of N-cadherin and vimentin in ox-LDL-induced HUVECs, which consequently promotes EC proliferation and migration [132]. Beyond these previously mentioned findings, one study revealed that the overexpression of circ-USP36 in ox-LDL-induced ECs exacerbated endothelial injury by sponging miR-637 and enhancing wingless type MMTV integration site family member 4 (WNT4) expression, thereby inhibiting EC proliferation and migration [134]. Mesenchyme homeobox 2 (MEOX2) is considered to be an angiogenic phenotypic regulator of ECs [135]. Huang et al. demonstrated that the lower expression of exosomal circ_0074673 led to decreased MEOX2 expression, and promoted proliferation, migration, and angiogenesis in high glucose (HG)-induced HUVECs [136]. In light of the critical role played by increased neuropilin-1 (NRP1) in the angiogenesis of senescent ECs, Qiu et al. analyzed circGSE1 expression in aortic ECs from aged and young mice, and discovered that circGSE1 overexpression could regulate the miR-323-5p/NRP1 axis, and promote the regeneration of senescent blood vessels in vitro [137]. Zou et al. demonstrated that increasing levels of circCOL1A2 could promote proliferation, migration, angiogenesis, and permeability in HG-induced human retinal microvascular ECs (HG-RMECs) [138].

Overall, these insights underscore the key role of the intricate regulatory network of circRNAs in influencing EC proliferation, migration, and angiogenesis. By regulating the expression and functions of circRNAs, it is expected to protect vascular integrity and delay the development of vascular aging.

Inflammation

As individuals age, a concomitant increase in EC inflammation heightens the risk of vascular dysfunction and CVDs [49]. Low-grade inflammation, a hallmark of aging, serves as a fundamental driver for age-related injuries and diseases, with a well-established association between inflammation and AS [139–141]. Several studies have demonstrated that high expression levels of hsa_circ_0005699 and circ_0003204 in ox-LDL-induced ECs contribute to the promotion of inflammation [119, 127]. The former modulates the nuclear factor kappa B subunit 1 (NFKB1) expression and inflammatory cytokines, while the latter exacerbates ox-LDL-induced HUVEC injury through the regulation of the miR-942-5p/HDAC9 pathway [119, 127]. Conversely, the up-regulation of circRSF1 reduces ox-LDL-induced inflammation in HUVECs via the miR-135b-5p/HDAC1 signaling pathway [118]. Moreover, circ-USP36 up-regulation could increase ox-LDL-induced HUVEC inflammation by enhancing the expression of VCAM1 through sponging miR-98-5p [128]. Additionally, Zhang et al. proposed that circ_0086296 inhibition decreased the level of interferon-induced protein with tetratricopeptide repeats 1 (IFIT1) and subsequently reduced the production of proinflammatory cytokines in ox-LDL-treated HUVECs [142].

Remarkably, the implications of these findings extend to clinical relevance, as evidenced by large trials confirming the benefits of anti-inflammatory therapy for patients with high risk of MI [143, 144]. This insight opens a promising door for the development of anti-inflammatory therapies for CVDs. Collectively, these findings emphasize the crucial role of circRNAs in modulating EC inflammation during the aging process, providing a valuable foundation for developing targeted interventions that may mitigate the impact of inflammation on cardiovascular health. These discoveries not only deepen our understanding of the molecular mechanisms underlying aging-related vascular diseases, but also pave the way for innovative therapeutic strategies aimed at alleviating inflammation and improving cardiovascular outcomes in aged individuals.

In summary, ECs are integral components of the blood vessel wall, crucial for preserving the stability of vascular function and structure. CircRNAs manifest a multifaceted role and diverse mechanisms in regulating EC functions, involving critical processes such as proliferation, apoptosis, and angiogenesis. Currently, predominant research focuses on the mechanism of circRNAs with miRNA sponges, while studies on protein sponges, scaffolds, and upstream regulatory mechanisms in

Table 2 Summary of circRNAs and the mechanisms involved in VSMC functions

CircRNAs	Mechanisms	Functions	References
circACTA2	Regulates the NF-κB/NLRP3 axis	Inhibits inflammation	[173]
	Regulates the ILF3/CDK4 axis	Promotes senescence	[151]
circRNA-0077930	Regulates the circRNA0077930-miR622-Kras ceRNA network	Promotes senescence	[152]
circTEX14	Modulates the miR-6509-3p/THAP1 axis	Inhibits proliferation and migration, but enhances apoptosis	[154]
circ_0002168	Regulates the miR-545-3p/CKAP4 axis	Induces proliferation and suppresses apoptosis	[155]
circNRG-1	Regulates the miR-193b-5p/NRG-1 axis	Promotes apoptosis	[156]
circWDR77	Regulates the miR-124/FGF2 axis	Promotes proliferation and migration	[160]
circ_Lrp6	Suppresses miR-145	Hinders migration, proliferation, and differentiation	[161]
hsa_circ_0008896	Regulates CDC20B expression by sponging hsa-miR-633	Promotes proliferation and migration	[162]
circDiaph3	Suppresses miR-148a-5p to increase the level of Igf1r and activates the IGF-1 signaling pathway	Promotes differentiation, proliferation, and migration	[163]
circCHFR	Regulates the miR-370/FOXO1/Cyclin D1 axis	Promotes proliferation and migration	[164]
circHIPK3	Regulates the miR-106a-5p/MFN2 axis	Inhibits calcification and differentiation	[170]
	Regulates the FUS/SIRT1/PGC-1α/MFN2 signaling pathway	Inhibits calcification	[168]
hsa_circRNA_0008028	Sponges miR-182-5p to regulate TRIB3	Induces proliferation, calcification, and autophagy	[171]
CDR1as	Regulates the miR-7-5p/CNN3 and CAMK2D axis	Promotes proliferation and calcification	[172]
circMAP3K5	Regulates the miR-22-3p/TET2 axis	Promotes differentiation	[108]
circEsyt2	Regulates p53β splicing via binding to PCBP1	Enhances proliferation and migration, but inhibits apoptosis and differentiation	[174]
circZXDC	Regulates the miR-125a-3p/ABCC6 axis	Promotes phenotypic transition, proliferation, and migration	[175]

CircRNAs, circular RNAs; VSMCs, vascular smooth muscle cells; NF-κB, nuclear factor kappa-B; NLRP3, NOD-like receptor pyrin domain containing 3; ILF3, interleukin enhancer-binding factor 3; CDK4, cyclin-dependent kinase 4; Kras, kirsten rat sarcoma viral oncogene; THAP1, THAP domain-containing protein 1; CKAP4, cytoskeleton-associated protein 4; NRG-1, neuregulin-1; FGF2, fibroblast growth factor 2; CDC20B, cell division cycle 20B; IGF-1, insulin-like growth factor-1; FOXO1, forkhead box protein O1; MFN2, mitofusin2; FUS, fused in sarcoma; SIRT1, sirtuin 1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; TRIB3, tribbles pseudokinase 3; CNN3, calponin 3; CAMK2D, calcium/calmodulin dependent protein kinase II delta; TET2, tet methylcytosine dioxygenase 2; PCBP1, poly (C)-binding protein 1; ABCC6, ATP-binding cassette subfamily C member 6

modulating EC functions are still limited [142, 145, 146]. Hence, further exploration of the role of circRNAs in ECs can enhance our understanding of the complex processes that drive vascular aging.

CircRNAs and VSMC functions

Serving as the major component of the middle layer in arterial walls, VSMCs are essential for preserving normal vascular function. The differentiation, proliferation, and migration of VSMCs help repair vascular injury in general vascular remodeling. However, during vascular aging, VSMCs undergo abnormal proliferation and phenotypic switching, shifting from a contractile phenotype to a synthetic or osteogenic phenotype [147]. This phenotypic switching contributes to vascular stiffness and calcification, ultimately impairing vasomotor function. Additionally, VSMCs experience increased senescence and apoptosis, with reduced proliferation and migration, further accelerating vascular aging. In the context of vascular aging, circRNAs are closely linked to various aspects of VSMC senescence, apoptosis, proliferation, migration, calcification, and phenotypic switching [148] (Table 2) (Fig. 4).

Senescence and apoptosis

Studies have demonstrated that senescent VSMCs exhibit cellular senescence-related phenotypes, such as the SASP, which is linked to aging-related vascular diseases such as hypertension, AS, and diabetes [149, 150]. The up-regulation of circACTA2 in VSMCs competitively binds interleukin enhancer-binding factor 3 (ILF3) with CDK4 mRNA, leading to reduced stability and protein expression of CDK4 mRNA, and ultimately contributing to AngII-induced VSMC senescence [151]. On the other hand, circRNA-0077930 from HUVECs-Exos induced VSMC senescence by down-regulating the expression of miR-622 while up-regulating the expression of kirsten rat sarcoma viral oncogene (Kras), p21, p53, and p16. Exos without circRNA-0077930 are unable to promote VSMC senescence, indicating that circRNA-0077930 serves as

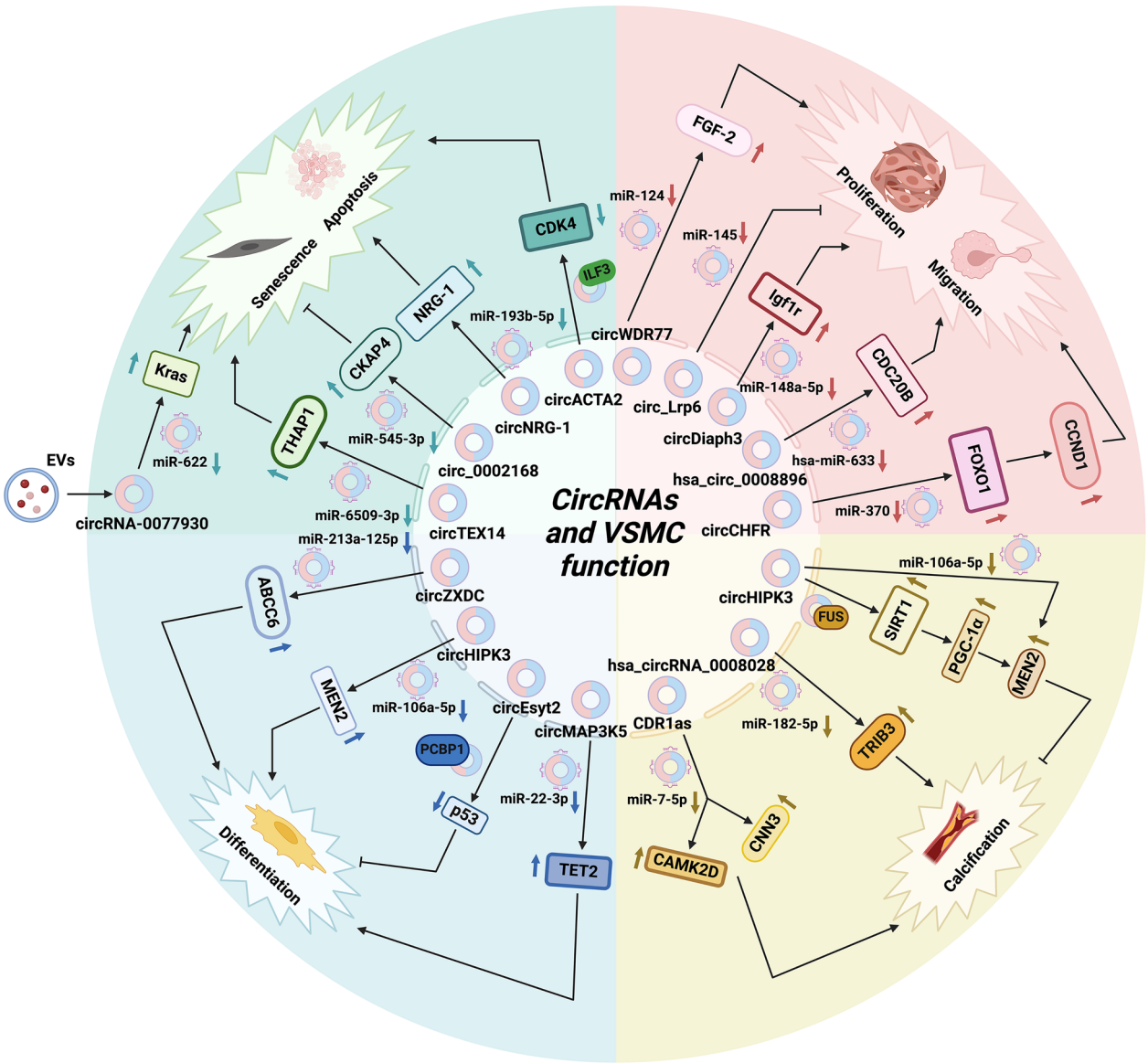


Fig. 4 Roles of circRNAs in the physiological and pathological processes of VSMCs. CircRNAs are closely linked to various aspects of VSMC senescence, apoptosis, proliferation, migration, calcification, and phenotypic switching, thereby playing a regulatory role in VSMC aging. (Created with BioRender.com). Abbreviations: CircRNAs, circular RNAs; VSMCs, vascular smooth muscle cells; Kras, kirsten rat sarcoma viral oncogene; THAP1, THAP domain-containing, apoptosis-associated protein 1; CKAP4, cytoskeleton-associated protein 4; NRG-1, neuregulin-1; CDK4, cyclin-dependent kinase 4; ILF3, interleukin enhancer-binding factor 3; FGF-2, fibroblast growth factor 2; CDC20B, cell division cycle 20B; FOXO1, forkhead box protein O1; CCND1, cyclin D1; FUS, fused in sarcoma; SIRT1, sirtuin 1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; MFN2, mitofusin2; TRIB3, tribbles pseudokinase 3; CAMK2D, calcium/calmodulin dependent protein kinase II delta; CNN3, calponin 3; TET2, tet methylcytosine dioxygenase 2; PCBP1, poly (C)-binding protein 1; ABCC6, ATP-binding cassette subfamily C member 6

an effective therapeutic target for VSMC senescence [152].

As a response to numerous pathological signals present in CVD conditions, such as pro-inflammatory cytokines, ox-LDL, high levels of NO, and mechanical damage, VSMC apoptosis has been identified as a crucial process in numerous CVDs [148, 153]. A study has reported a significant reduction in circTEX14 levels among patients with AS. circTEX14 enhances ox-LDL-induced VSMC apoptosis while suppressing proliferation and migration by targeting miR-6509-3p to increase the expression of THAP domain-containing, apoptosis-associated protein 1 (THAP1) [154]. Wei et al. identified circ_0002168 as a key player in the formation of abdominal aortic

aneurysm (AAA) and protected against VSMC apoptosis via the miR-545-3p/CKAP4 axis [155]. Furthermore, Sun et al. observed that increased circNRG-1 expression could counteract the apoptotic inhibition effect of AngII on mouse aortic smooth muscle cells (SMCs), suggesting its potential as a therapeutic target for renin–angiotensin–aldosterone system (RAAS)-mediated vascular remodeling in AS and hypertension [156].

Taken together, these studies demonstrate that the involvement of specific circRNAs in regulating the life cycle of VSMCs, and aberrant expression of circRNAs may result in vascular structural disorders and functional deterioration. These findings provide a valuable perspective on the dual roles of circRNAs in regulating VSMC senescence and apoptosis, which opens avenues for targeted interventions in vascular aging and aging-related vascular diseases.

Proliferation and migration

VSMC proliferation and migration are essential for preserving vascular homeostasis and closely associated with the development of AS and the progression of aging-related vascular diseases [157–159]. Numerous circRNAs have been identified as pivotal regulators of VSMC proliferation and migration, primarily serving as endogenous RNAs that compete with miRNAs [148, 160, 161]. For instance, circWDR77 facilitates VSMC proliferation and migration by modulating fibroblast growth factor 2 (FGF-2) expression through targeting miR-124, while circ_Lrp6 inhibits VSMC proliferation, migration, and differentiation via regulating miR-145 [160, 161]. Through competitive binding with hsa-miR-633, hsa_circ_0008896 enhances cell division cycle 20B (CDC20B) expression, promoting VSMC proliferation and migration and thereby contributing to the progression of AS [162]. Additionally, circDiaph3 serves as a competitive endogenous RNA (ceRNA) to suppress miR-148a-5p and activate the insulin-like growth factor-1 (IGF-1) signaling pathway, thereby enhancing VSMC proliferation and migration [163]. CircCHFR is significantly up-regulated in ox-LDL-induced VSMCs, and functions as a sponge for miR-370 to up-regulate the expression of the target gene forkhead box protein O1 (FOXO1), finally promoting VSMC proliferation and migration [164].

In conclusion, these findings highlight the role of circRNAs as important regulators of VSMC behavior. Under pathological conditions, circRNAs promote excessive VSMC proliferation and migration by interacting with miRNAs and target genes, contributing to abnormal vascular remodeling.

Calcification

The osteogenic differentiation of VSMCs serves as the pivotal cytological basis underlying vascular calcification, which represents a crucial phenotype associated with vascular aging [165, 166]. The biological process involves circRNAs as key regulators to control the balance of VSMC functions [167]. Recent studies have highlighted the regulatory role of circRNAs in AS by modulating VSMC calcification [168, 169]. For instance, circHIPK3 has been extensively studied for its regulatory effects on VSMC calcification [168, 170]. Firstly, Feng et al. reported significantly reduced circHIPK3 expression in both calcified VSMCs and the serum of AS patients. They demonstrated that circHIPK3 would attenuate VSMC calcification by activating the SIRT1/PGC-1α signaling pathway and promoting the expression of mitofusin 2 (MFN2) [168]. Secondly, Zhang et al. found that circHIPK3 overexpression indirectly up-regulated MFN2 expression via interacting with miR-106a-5p, and then inhibited VSMC calcification and the development of AS [170]. Moreover, circRNAs emerge as crucial players in the pathogenesis of diabetes-related vascular diseases. Hsa_circRNA_0008028, widely expressed in HG-induced VSMCs, functions as a sponge for miR-182-5p, facilitating tribbles pseudokinase 3 (TRIB3) up-regulation and subsequently promoting vascular calcification [171]. Additionally, under hypoxic conditions, it was found that the up-regulation of CDR1as facilitated the phenotypic transition of human pulmonary artery smooth muscle cells (HPASMCs) from a contractile to an osteogenic phenotype in patients with pulmonary hypertension [172]. This effect was mediated by CDR1as sponging miR-7-5p and up-regulating the expression of calcium/calmodulin-dependent kinase II-delta (CAMK2D) and calponin 3 (CNN3) [172].

In conclusion, these findings suggest that specific circRNAs play direct or indirect roles in the process of VSMC calcification by regulating the expression of genes associated with calcium ion regulation, including not only regulating calcium channel expression, but also influencing key proteins that impact the intracellular calcium ion concentration balance. Through the precise regulation of these pathways, circRNAs actively contribute to the homeostatic control of calcium ions in VSMCs, thereby influencing the occurrence and progression of calcification.

Differentiation

As universally acknowledged, VSMC differentiation in response to pathological and physiological stimuli during the process of vascular injury and repair, leads to abnormal vascular remodeling and arterial lumen narrowing, ultimately contributing to vascular aging.

Study has revealed that vascular injury-related intimal hyperplasia is associated with CVDs such as AS and hypertension-induced restenosis [173]. Previous study has demonstrated that the increased expression of circMAP3K5 induced by ten-eleven translocation-2 (TET2) could inhibit intimal hyperplasia and promote SMC differentiation, suggesting that circMAP3K5 may act as a critical regulator for SMC phenotypic transition [108]. Apart from the findings, we have already shared that the overexpression of circHIPK3 may also hinder osteogenic differentiation by raising the levels of smooth muscle 22 alpha (SM22α) and reducing the activity of alkaline phosphatase (ALP), runt-related transcription factor 2 (RUNX2), and osteoclastogenesis inhibitory factor (OPG). These findings provide further evidence that circHIPK3 reduces the osteogenic differentiation of VSMCs to enhance vascular calcification and hence promote the progression of AS [170]. Gong et al. revealed that circEsyt2 could inhibit VSMC differentiation and modulate VSMC phenotype switching and vascular remodeling in a mouse model of AS. The mechanism involved circEsyt2 binding to poly(C)-binding protein 1 (PCBP1) and modulating its nuclear translocation, which in turn regulated p53 alternative splicing and the production of p53β [174]. Additionally, it is noteworthy that circZXDC acts as a sponge for miR-213a-125p, causing a rise in ATP-binding cassette sub-family C member 3 (ABCC3) expression, which promotes VSMC transdifferentiation from a contractile to synthetic phenotype in individuals with moyamoya disease [175].

These findings suggest that circRNAs, as active regulators of VSMC fate, play a crucial role in guiding the differentiation and phenotypic changes of VSMCs during vascular injury and remodeling by modulating intracellular signaling pathways and influencing the activity of key transcription factors.

Taken together, the investigation of circRNAs in regulating VSMC dysfunction offers comprehensive insights into our understanding of vascular physiological and pathological processes. These studies unveil the diverse functions of circRNAs in almost all key physiological processes of VSMCs, encompassing the regulation of senescence, apoptosis, proliferation, migration, calcification, and differentiation, suggesting that circRNAs serve

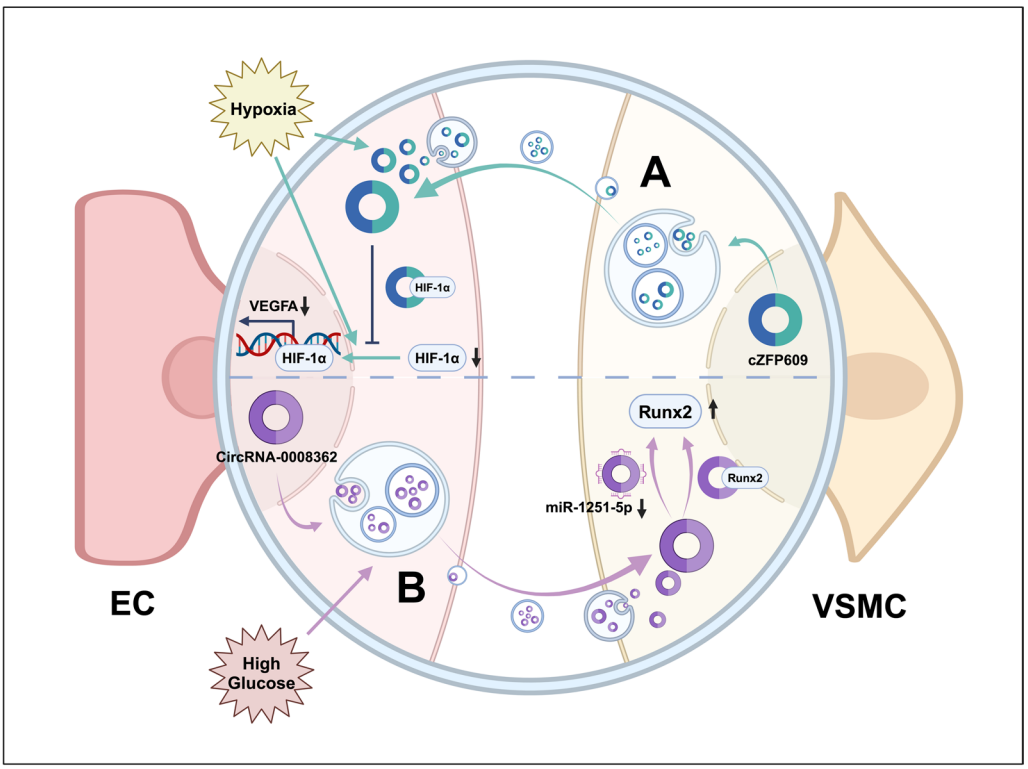


Fig. 5 CircRNAs in the crosstalk between ECs and VSMCs. **A** The cZFP609 derived from VSMCs could be transported to ECs via Exos to reduce endothelial angiogenic capacity, mechanically suppressing the expression of VEGFA and inhibiting the nuclear translocation of HIF1α in response to hypoxia. **B** The exosomal hsa_circ_0008362 secreted by high glucose-induced ECs promotes VSMC calcification by up-regulating Runx2 expression via miR-1251-5p sponging, as well as directly interacting with Runx2 protein to exacerbate VSMC calcification. (Created with BioRender.com). CircRNAs; circular RNAs; ECs, endothelial cells; VSMCs, vascular smooth muscle cells; Exos, exosome; VEGFA, vascular endothelial growth factor-A; ECs, endothelial cells; Runx2, Runt-related transcription factor 2

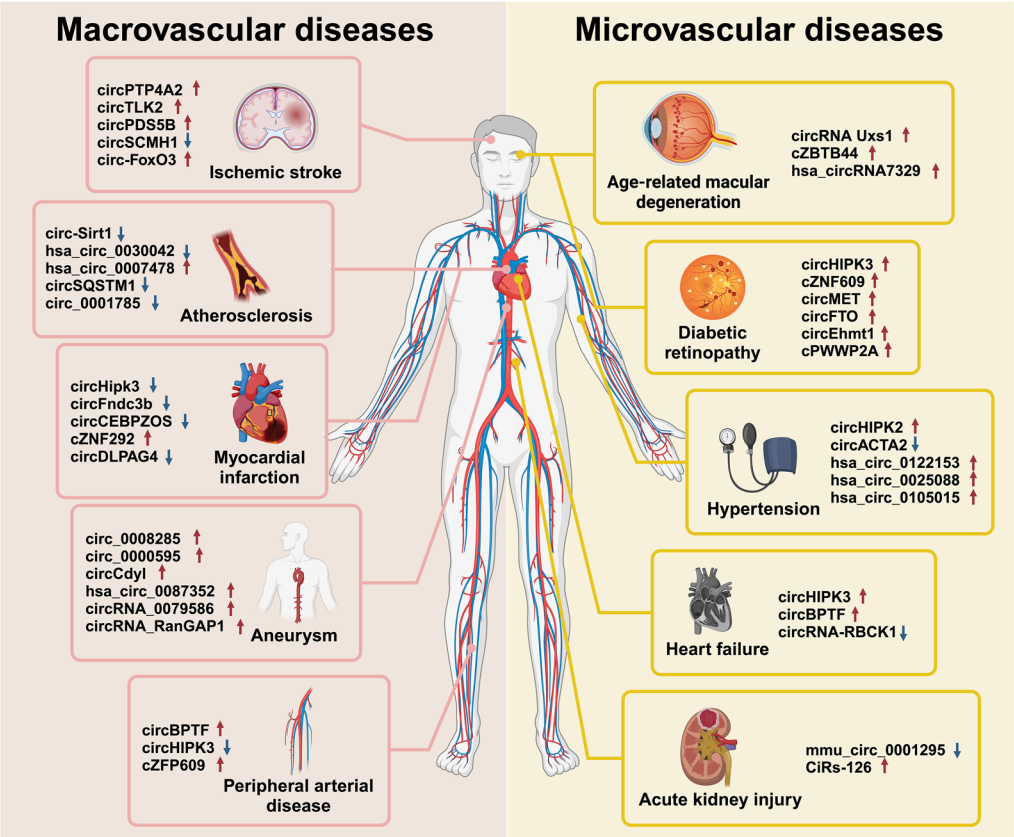


Fig. 6 Effects of up-regulated or down-regulated circRNA expression on aging-related vascular diseases (Created with BioRender.com). CircRNAs, circular RNAs

as key regulators in VSMCs function through an intricate and comprehensive regulatory network and multiple signaling pathways.

CircRNAs mediating ECs and VSMCs crosstalk

The intricate intercellular communication within the cardiovascular system relies heavily on extracellular vesicles (EVs) that encapsulate diverse molecules, including proteins, RNA, DNA, and lipids. Exosomes (Exos), as a kind of small EVs, serve as crucial vehicles for the stable enrichment of circRNAs and facilitate the exchange of biological information between cells and even organs [176, 177]. The physiological communication between ECs and VSMCs in the cardiovascular system plays a crucial role in systemic development and homeostasis regulation. Various pathological conditions, such as vascular wall remodeling, are closely associated with abnormal intercellular communication between these two cell types [178]. Recent studies have indicated that circRNAs could be found in Exos and act as mediators for information exchange between ECs and VSMCs, influencing the development of recipient cells [179, 180]. For instance, increased expression of cZFP609 has been observed in VSMCs-specific human Sirtuins 1 (SIRT1) transgenic mice and in the plasma of patients with AS or diabetic PAD of the lower extremities. The underlying mechanism involves the delivery of cZFP609 from VSMCs to ECs via Exos. Moreover, with SIRT1-dependent suppression of hypoxia-inducible factor 1-alpha (HIF1α) activation, cZFP609 reprograms ECs to reduce angiogenesis after IS [180] (Fig. 5A). In addition to materials secreted from VSMCs to ECs, ECs can also secrete materials to VSMCs. In the presence of hyperglycemia, hsa_circ_0008362 derived from ECs-Exos induces VSMC calcification via two pathways: on the one hand, hsa_circ_0008362 promotes VSMC calcification by sponging miR-1251-5p to upregulate Runx2 expression. On the other hand, hsa_circ_0008362 exacerbates VSMC calcification by directly interacting with Runx2 protein, respectively [181] (Fig. 5B).

Therefore, by exhibiting multidimensional and multifaceted characteristics, circRNAs emerge as crucial regulators of vascular aging, mediating the intricate interactions between ECs and VSMCs, and coordinating the transmission of information to either facilitate or hinder the process of vascular aging.

Table 3 Functions of circRNAs in aging-related macrovascular diseases

Diseases	CircRNAs	Regulatory mechanisms	Functions	Expression	References
AS	circ-Sirt1	Interacts with and sequesters NF-κB p65, promoting SIRT1 expression by binding to miR-132/212	Inhibits the inflammatory phenotypic switching of VSMCs and improves vascular inflammation and neointimal formation	Down-regulated	[184]
	circSQSTM1	Sponges miR-23b-3p to suppress Sirt1 expression in the cytoplasm, while promoting Sirt1 expression by regulating the eIF4A3/FOXO1 axis in the nucleus	Suppresses EC inflammation and oxidative stress, and promotes autophagy in ECs	Down-regulated	[187]
	circ_0001785	Regulates the miR-513a-5p/TGFBR3 axis	Promotes proliferation and inhibits apoptosis and migration in ECs	Down-regulated	[189]
	hsa_circ_0030042	Acts as eIF4A3 sponge	Inhibits EC autophagy and maintains plaque stability	Down-regulated	[145]
	hsa_circ_0007478	Promotes EFNA3 expression by sponging miR-765	Promotes the inflammatory responses and lipid metabolism of macrophages	Up-regulated	[191]
Aneurysm	circ_0008285	Regulates the miR-150-5p/BASP1 axis	Promotes VSMC apoptosis	Up-regulated	[193]
	circ_0000595	Increases ADAM10 expression by sponging miR-582-3p	Suppresses proliferation and promotes apoptosis in VSMCs	Up-regulated	[194]
	circCdyl	Prevents IRF4 from entering the nucleus and acts as a sponge for let-7c to promote C/EBP-δ expression in macrophages	Promotes M1 macrophage polarization and M1-type inflammation	Up-regulated	[195]
	hsa_circ_0087352	Sponges hsa-miR-149-5p to enhance IL-6 and TNF-α expression, expands the signal transduction of the ERK/NF-κB pathway, and then IκB phosphorylation promotes NF-κB p65 phosphorylation and nuclear translocation	Induces VSMC apoptosis	Up-regulated	[196]
	circRNA_0079586	Regulates the miR-183-5p/MPO signaling pathway	Up-regulates the expression of MPO to be involved in the pathogenesis of IA rupture	Up-regulated	[197]
	circRNA_RanGAP1	Regulates the miR-877-3p/MPO signaling pathway	Up-regulates the expression of MPO to involve in the pathogenesis of IA rupture	Up-regulated	[197]
PAD	circBPTF	Regulates LIN28B expression via targeting miR-384	Inhibits cell viability and promotes apoptosis, the release of proinflammatory cytokines, and oxidative stress in ECs	Up-regulated	[204]
	circ_HIPK3	Targets the miR-124 pathway	Inhibits EC death and apoptosis	Down-regulated	[205]
	cZFP609	Inhibits HIF1α activation in SIRT1-dependent manner	Inhibits endothelial angiogenic functions	Up-regulated	[180]
MI	circCEBPZOS	Regulates the miR-1178-3p/PDPK1 axis	Alleviates MI-induced left ventricular dysfunction while expanding the functional capillary network	Down-regulated	[208]
	circFndc3b	Interacts with the RBP Fused in Sarcoma to regulate VEGF expression and signaling	Enhances EC angiogenic activity while reducing apoptosis in CMs and ECs	Down-regulated	[209]
	circHipk3	Regulates the circHipk3-miR-133a- CTGF axis	Promotes coronary artery EC proliferation, migration, tube formation, and angiogenesis	Down-regulated	[210]
	circDLPAG4	Regulates HECTD1 expression by sponging miR-143	Enhances cell viability while Inhibiting migration and apoptosis in ECs	Down-regulated	[211]
	cZNF292		Increases globular angiogenesis and the proliferation of ECs	Up-regulated	[93]

Table 3 (continued)

Diseases	CircRNAs	Regulatory mechanisms	Functions	Expression	References
IS	circPTP4A2			Up-regulated	[216]
	circTLK2				
	circPDS5B	Recruits hnRNPL to stabilize Runx1/ZNF24 and subsequently inactivates VEGFA	Induces apoptosis, migration, and angiogenesis, and inhibits cell viability in ECs	Up-regulated	[146]
	circ-FoxO3	Sequesters mTOR and E2F1 to inhibit mTORC1 activity	Promotes EC autophagy and maintains blood–brain barrier integrity	Up-regulated	[218]
	circSCMH1	Binds to FTO and promotes its transfer to the nucleus, which decreases the m^6A methylation of Plpp3 mRNA	Enhances vascular repair	Down-regulated	[219]

CircRNAs, circular RNAs; AS, atherosclerosis; NF-κB, nuclear factor kappa-B; SIRT1, sirtuin 1; VSMCs, vascular smooth muscle cells; eIF4A3, eukaryotic initiation factor 4A-III; FOXO1, forkhead box protein O1; ECs, endothelial cells; TGFBR3, transforming growth factor beta receptor 3; EFNA3, ephrin A3; BASP1, brain acid-soluble protein 1; ADAM10, A disintegrin and metalloprotease 10; IRF4, interferon regulatory factor 4; C/EBP-δ, CCAAT/enhancer binding protein delta; IL-6, interleukin 6; TNF-α, tumor necrosis factor α; ERK, extracellular regulated protein kinases; IκB inhibitor of nuclear factor kappa-B; MPO, myeloperoxidase; IA, intracranial aneurysm; PAD, peripheral arterial disease; LIN28B, lin-28 homolog B; HIF1α, hypoxia-inducible factor 1 alpha; MI, myocardial infarction; PDPK1, phosphoinositide-dependent kinase-1; RBP, RNA binding protein; VEGF, vascular endothelial growth factor; CMs, cardiomyocytes; CTGF, connective tissue growth factor; HETCD1, HECT domain containing 1; IS, ischemic stroke; hnRNPL, human heterogeneous nuclear ribonucleoprotein L; Runx1, Runt-related transcription factor 1; ZNF24, zinc finger protein 24; VEGFA, vascular endothelial growth factor A; mTOR, mammalian target of rapamycin; E2F1, E2F transcription factor 1; mTORC1, mechanistic target of rapamycin complex 1; FTO, fat mass and obesity-associated protein; m^6A, N^6-methyladenosine; Plpp3, phospholipid phosphatase 3

circRNAs in aging-related vascular diseases

Aging involves the degradation of various organs within the body system, representing a natural biological phenomenon, as well as the accumulation of damage caused by stressors. Widely acknowledged as an irreversible biological process, aging stands out as a major risk factor for chronic diseases, especially CVDs associated with aging [141, 182]. While vascular aging contributes to the occurrence of aging-related macrovascular diseases, age-related changes in microvascular phenotype, function, and structure are equally pivotal to the occurrence of aging-related microvascular diseases [6]. As described above, circRNAs regulate the cellular physiological alterations and functions of ECs and VSMCs in the vascular wall, suggesting their potential role in the pathological process of various aging-related vascular diseases. Therefore, the primary purpose of this section is to summarize the role of circRNAs in the occurrence and progression of aging-related vascular diseases, including macro- and microvascular diseases (Fig. 6).

Macrovascular diseases

The relationship between the molecular levels of circRNAs and macrovascular diseases is widely explored, and circRNAs play a pivotal role in the pathogenesis of macrovascular diseases, with a particular focus on AS [183]. They exert influence on gene expression, engage with miRNAs, and actively participate in intricate signaling pathways, impacting crucial processes such as inflammation and plaque formation. A comprehensive understanding of the specific roles of circRNAs within these pathways holds great promise for advancing our comprehension of the molecular mechanisms underlying macrovascular diseases, paving the way for innovative therapeutic interventions. The subsequent discussion introduces and summarizes the crucial role of circRNAs in macrovascular diseases (Table 3).

Atherosclerosis

Aging significantly influences atherosclerotic CVDs, a prevalent vascular condition contributing to several age-related vascular diseases [18]. In recent years, various studies have delved into the potential mechanisms underlying circRNA-mediated AS [145, 184, 185], with a focus on the crucial role of VSMC phenotypic switching and neointima formation in AS. Kong et al. demonstrated that the overexpression of circ-Sirt1 effectively suppressed the inflammatory phenotypic switching of VSMCs both in vitro and in vivo, leading to improved injury-induced vascular inflammation and neointimal formation [184]. The mechanism involved circ-Sirt1 binding to miR-132/212 to prevent miR-132/212 from inhibiting SIRT1 expression, which resulted in the deacetylation and inactivation of nuclear NF-κB p65. Another study demonstrated that miR-132/212 were involved in vascular endothelial function and inflammation via targeting the inhibition of SIRT1 expression in ECs, contributing to impaired angiogenic responses during postnatal development in adult mice [186]. Another novel circRNA, named circSQSTM1, was screened in atorvastatin-stimulated ECs, which could reduce inflammation, inhibit oxidative stress and promote autophagy by up-regulating Sirt1 in ECs. The overexpression of circSQSTM1 in ECs attenuates AS progression in mice [187]. These studies underscore that circ-Sirt1 and circSQSTM1 exhibit protective effects against the inflammatory phenotype of VSMCs and ECs, shedding light on the mechanisms of circRNAs for AS [187, 188].

Tong et al. reported that Exos-derived circ_0001785 could mitigate EC injury, delaying AS through the miR-513a-5p/TGFBR3 ceRNA network mechanism, providing a potential Exos-based intervention strategy for AS [189]. Additionally, the dysregulation of autophagy might contribute to the development of AS [190]. Hsa_circ_0030042 is down-regulated in patients with coronary artery diseases (CADs), preventing ox-LDL-induced aberrant autophagy in HUVECs by sponging endogenous eukaryotic initiation factor 4A-III (eIF4A3). The overexpression of hsa_circ_0030042 ameliorates plaque stability in a high-fat-diet-fed AS mice model [145]. Meanwhile, ox-LDL-induced inflammation in macrophages is essential to the pathophysiology of AS. Ye et al. discovered that hsa_circ_0007478 was up-regulated and exhibited stable expression, along with decreased miR-765 expression and elevated ephrin A3 (EFNA3) expression in ox-LDL-stimulated macrophages, which regulated the macrophage inflammatory response to expedite AS development [191].

These studies underline the significant role of circRNAs in the occurrence and progression of AS through their regulation of ECs, VSMCs, and macrophages. By influencing these key vascular wall cells, circRNAs contribute to the development of AS and could serve as promising molecular biomarkers, offering potential avenues for targeted therapies.

Aneurysm

Aneurysm refers to a localized abnormal dilation of artery wall filled with blood due to weakness or injury in the vessel wall, primarily observed in critical arterial vessels such as the cerebral arteries and abdominal aorta [192]. Recent studies have demonstrated that circRNAs also hold significant potential in modulating aneurysms. For instance, circ_0008285 and circ_0000595 exhibit high expression levels in thoracic aortic aneurysm (TAA) and are involved in the pathogenesis and progression of TAA.

Circ_0008285 and circ_0000595 modulate the miR-150-5p/BASP1 and miR-582-3p/ADAM10 pathways, respectively, via the sponge mechanisms, ultimately promoting VSMC apoptosis and resulting in TAA formation [193, 194].

CircRNAs also serve as crucial regulatory factors of macrophages during AAA development. Song et al. demonstrated that circCdyl stimulated the inflammatory response and promoted classically activated M1 macrophage polarization to contribute to AAA formation. The mechanism involved circCdyl inhibiting interferon regulatory factor 4 (IRF4) nuclear translocation via acting as a sponge for let-7c, resulting in elevated CCAAT/enhancer binding protein delta (C/EBP-δ) expression [195]. Similarly, the up-regulation of hsa_circ_0087352 in human AAA samples enhances the inflammatory response in lipopolysaccharide (LPS)-stimulated macrophages by increasing the expression and secretion of interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α) through sponging with hsa-miR-149-5p in the cytoplasm [196]. Beyond the previously mentioned, circRNAs are essential for the pathogenesis and progression of intracranial aneurysm (IA). Myeloperoxidase (MPO) has been identified in previous studies as being connected to both aneurysm formation and ruptured IA following degenerative remodeling. Zhang et al. revealed that the mechanism underlying IA rupture involves two different signaling pathways of circRNA_0079586/miR-183-5p/MPO and circRNA_RanGAP1/miR-877-3p/MPO. Patients with ruptured IA have elevated expression of circRNA_0079586 and circRNA_RanGAP1, along with enhanced MPO expression [197].

Taken together, circRNAs play a key role in the development of aneurysms, not only affecting the activity and phenotypic transformation of VSMCs and macrophage function, but also regulating the development and rupture of aneurysms. The complex regulatory role of circRNAs underscores their potential as therapeutic targets for aneurysmal diseases.

Peripheral arterial disease

PAD development is primarily attributed to AS, thus always accompanied by CVDs and/or cerebrovascular diseases, leading to increased mortality [198]. Occlusion and diffuse diseases in distal vessels commonly result in multi-segmental impairment. As a prevalent vascular complication of diabetes, PAD has been associated with tissue defects in over half of patients with diabetic foot ulcer (DFU) [199]. With the rapid development of the circRNA field, circRNAs in the wound tissues or blood of DFU patients have been detected by RNA-seq or gene microarray analysis, revealing a potential correlation between the levels of circRNAs and DFU. Liao et al. analyzed microarray data from tissues with non-diabetes mellitus (DM) patients and that with DFU patients, identifying 8 differentially expressed circRNAs [200]. These results suggest that circRNAs may be involved in specific biological processes and signaling pathways related to the healing process of DFU.

DFU represents a common and severe complication of DM in the elderly, with EC dysfunction serving as the initial stage. Hyperglycemia exposure directly affects EC dysfunction by increasing inflammatory factors, oxidative stress, and apoptosis [201–203]. CircBPTF knockdown blocks cell apoptosis, the release of interleukin-1β (IL-1β), IL-6, TNF-α, and monocyte-chemoattractant protein-1 (MCP-1), and the production of ROS and malondialdehyde, via mediating the miR-384/LIN28B axis in HUVECs, which substantially ameliorates HG-induced HUVEC inflammatory damage and oxidative stress [204]. Shan et al. observed that circHIPK3 was significantly up-regulated in HG-ECs and acted as a sponge for endogenous miR-30a-3p to promote the expression of frizzled homolog 4 (FZD4), wingless-type MMTV integration site family member 2 (WNT2), and vascular endothelial growth factor C (VEGFC), ultimately leading to EC dysfunction and increased production of pro-inflammatory chemokines that interfere with wound healing [205]. Additionally, hyperglycemia may induce excessive VSMC proliferation and migration, leading to vascular occlusion, which is also a major cause of PAD. High levels of cZFP609 are associated with reduced ankle-brachial index in the plasma of diabetic patients with lower extremities PAD. The underlying mechanism involves the delivery of exosomal cZFP609 from VSMCs to ECs. With SIRT1-dependent suppression of HIF1α activation, cZFP609 reprograms ECs to reduce angiogenesis after ischemia in vitro, and knockdown of cZFP609 improves blood flow recovery after hindlimb ischemia [180]. This indicates that circRNAs have regulatory effects on well-known targets for alleviating endothelial dysfunction and inflammatory response. Understanding the roles of circRNAs in DFU holds promise for advancing therapeutic strategies in diabetic patients.

Myocardial infarction

MI is a prevalent CVD caused by myocardial ischemia and ischemia–reperfusion (I/R) injury, which results in apoptosis and necrosis of myocardial cells [206]. It tends to occur in patients with coronary stenosis and coronary spasm. A significant pathological event of MI is angiogenesis, which is associated with many circRNAs [207]. CircCEBPZOS in serum EVs is reduced in patients with adverse cardiac remodeling. In vivo experiments reveal that circCEBPZOS overexpression alleviates MI-induced left ventricular dysfunction while expanding

the functional capillary network. The process involves circCEBPZOS directly binding to miR-1178-3p to up-regulate phosphoinositol-dependent kinase 1 (PDPK1) expression, which reduces post-MI remodeling, promotes revascularization, and ultimately enhances heart function [208]. Similarly, another study demonstrated that the overexpression of circFndc3b exhibits cardio protective effects by reducing cardiomyocyte (CM) apoptosis, enhancing neovascularization, limiting infarct size, and preserving post-MI cardiac function and integrity, through the FUS/VEGF signaling mechanisms partly [209]. Furthermore, Si et al. found that circHipk3 played a critical role in coronary angiogenesis by promoting coronary artery EC proliferation, migration, tube formation, and increasing capillary density in the vicinity of infarction via the circhipK3/miR-133a/CTGF axis [210]. There are numerous other circRNAs linked to I/R damage. The I/R-induced decrease of HECT domain containing 1 (HECTD1) could be reversed by circDLGAP4 sponging miR-143, thereby increasing EC viability and reducing apoptosis and migration. This suggests that circDLGAP4 is an effective therapeutic target for I/R injury [211]. In HUVECs, hypoxia up-regulates the expression of cZNF292, cAFF1, and cDENND4C while down-regulating cTHSD1 expression. The inhibition of cZNF292 expression decreases globular angiogenesis and cell proliferation [93, 207]. Undoubtedly, a deeper comprehension of the connection between MI and circRNAs will lay the foundation for the development of circRNAs-based approaches to MI diagnosis and treatment.

Ischemic stroke

Maintaining optimal oxygenation and nutritional enrichment in cerebral tissue is crucial due to the high metabolic demands of the brain. However, the intrinsic regulation capacity of brain function declines, potentially leading to vascular dysfunction and subsequently increasing susceptibility with aging [212]. Recent studies have clarified the crucial role that circRNAs play in vascular endothelial damage linked to IS, highlighting the intricate interactions between inflammation, oxidative stress, and IS pathogenesis [213]. AS represents a significant pathogenic factor in IS [214]. Recent studies have reported a significant up-regulation of circRNAs in human brain microvascular ECs (hBMECs), associated with endothelial dysfunction, which play a crucial role in regulating various biological processes following IS and may contribute to the development of unstable atherosclerotic plaques [215]. Besides, the levels of plasma circPTP4A2 and circTLK2 are shown to be significantly higher in patients with severe stroke compared to those with mild stroke, indicating their close association with large artery atherosclerotic stroke [216, 217]. CircPDS5Bhas been discovered to promote the migration and angiogenesis of hBMECs exposed to glucose deprivation/reoxygenation in middle cerebral artery occlusion mice [146]. The blood–brain barrier (BBB), which consists of capillaries formed by hBMECs, as well as pericytes and astrocytes around the capillaries, plays a key role in maintaining central nervous system homeostasis [218]. CircRNAs have been found to protect BBB integrity by targeting miRNAs against IS. Yang et al. have demonstrated that circ-FoxO3 activates EC autophagy by inhibiting mechanistic target of rapamycin complex 1 (mTORC1) to clear cytotoxic aggregates, thereby alleviating BBB damage. These findings suggest a novel role for circRNAs in maintaining the integrity of the BBB and may be a prospective therapeutic strategy for the treatment of neurological diseases such as IS [218]. Additionally, Li et al. found that circSCMH1 facilitated vascular repair in the peri-infarct cortex following a photo-thrombotic stroke and mitigated ischemia-induced m^6A methylation. By binding with fat mass and obesity-associated protein and promoting its nuclear translocation through ubiquitination, circSCMH1 reduced the m^6A methylation of phospholipid phosphatase 3 (Plpp3) mRNA in ECs and inhibited Plpp3 degradation, ultimately improving motor functional behaviors [219]. These findings underscore the important role of circRNAs in the context of IS, providing insights into potential therapeutic targets for mitigating vascular damage and promoting recovery after stroke.

Microvascular diseases

In addition to acknowledging the critical role of vascular aging in the pathogenesis of aging-related macrovascular diseases, its significance in aging-related microvascular diseases is also increasingly recognized [6]. After summarizing circRNAs implicated in aging-related macrovascular diseases, the focus now shifts to discussing circRNAs that contribute to aging-related microvascular diseases (Table 4).

Acute kidney injury

AKI is a syndrome marked by the swift decline of renal function within hours to days, often triggered by sudden myocardial and cerebral infarction, especially in elderly individuals and those with pre-existing renal conditions [220]. Substantial evidence suggests a correlation between the dysregulated expression of circRNAs and AKI induced by various etiologies, which may contribute to disrupted intracellular signaling, increased oxidative stress, heightened apoptosis, exacerbated inflammation, and sepsis-induced tissue damage associated with AKI [220–222]. Renal I/R injury is a common cause of AKI [223]. Kölling et al. found that CiRs-126 was significantly

Table 4 Functions of circRNAs in aging-related microvascular diseases

Diseases	CircRNAs	Regulatory mechanisms	Functions	Expression	References
AKI	CiRs-126	Serves as part of a signaling cascade involving LRIG and miR-126-5p	The protective mechanism of AKI	Up-regulated	[224]
	mmu_circ_0001295		Alleviates microvascular dysfunction and reduces inflammatory factors	Down-regulated	[225]
AMD	cZBTB44	Acts as miR-578 sponge to increase VEGFA and VCAM1 expression	Enhances EC viability, proliferation, migration, and tube formation	Up-regulated	[228]
	circRNA Uxs1	Sponges miR-335-5p to increase PGF expression and activate the mTOR/p70 S6k pathway	Promotes EC tube formation, migration, and proliferation	Up-regulated	[229]
	hsa_circRNA7329	Regulates SCD through sponging hsa-miR-9	Promotes macrophage-mediated inflammation and pathological angiogenesis	Up-regulated	[230]
DR	circHIPK3	Sponges miR-30a-3p and inhibits miR-30a-3p activity to increase VEGFC, FZD4, and WNT2 expression	Inhibits EC viability, proliferation, migration, and tube formation	Up-regulated	[233]
	cZNF609	Sponges miR-615-5p and inhibits miR-615-5p activity to increase MEF2A expression	Inhibits migration and tube formation, but improves apoptosis in ECs	Up-regulated	[234]
	circMET	Enhances the interaction between IGF2BP2 and NRARP/ESM1	Induces EC pathological angiogenesis and tip cell specialization	Up-regulated	[236]
	circFTO	Up-regulates TXNIP by binding to miR-128-3p	Induces EC viability and angiogenesis	Up-regulated	[237]
	circEhmt1	Mediates the NFIA/NLRP3 signaling	Protects ECs against HG-induced injury	Up-regulated	[238]
	cPWWP2A	Sponges miR-579 to increase angiopoietin 1, occludin, and SIRT1 expression	Maintains vascular integrity	Up-regulated	[239]
HF	circHIPK3	Regulates the miR-29a/IGF-1 pathway	Decreases oxidative stress-induced CMVEC dysfunction	Up-regulated	[241]
		Regulates the miR-17-3p-ADCY6 axis	Improves Ca^{2+} concentration in the cytoplasm	Up-regulated	[281]
	circBPTF		Improves EC proliferation	Up-regulated	[243]
	circRNA-RBCK1	Binds miR-133a to up-regulate GTPCH1 expression	Improves diastolic dysfunction	Down-regulated	[244]
Hypertension	circHIPK2	Sponges miR-145-5p to up-regulate disintegrin and ADAM17 expression	Promotes VSMC phenotypic transition	Up-regulated	[246]
	circACTA2	Targets the circACTA2-NF-κB-NLRP3 axis	Inhibits VSMC inflammation	Down-regulated	[173]
	hsa_circ_0105015	Targets hsa-miR-637	Promotes EC dysfunction and vascular inflammation	Up-regulated	[248]
	hsa_circ_0122153	Regulates the RAAS-related hsa_circ_0122153/hsa-miR-483-3p axis	Increases the risk of EH	Up-regulated	[249]
	hsa_circ_0025088	Regulates the RAAS-related hsa_circ_0025088/hsa-miR-27a-3p axis	Increases the risk of EH	Up-regulated	[249]

CircRNAs, circular RNAs; AKI, acute kidney injury; LRIG, leucine-rich repeats and immunoglobulin-like domains protein; AMD, age-related macular degeneration; VEGFA, vascular endothelial growth factor A; VCAM1, vascular cell adhesion molecule 1; ECs, endothelial cells; PGF, placental growth factor; mTOR, mammalian target of rapamycin; SCD, stearoyl-CoA desaturase; DR, diabetic retinopathy; VEGFC, vascular endothelial growth factor C; FZD4, frizzled family receptor 4; WNT2, wingless type MMTV integration site family, member 2; MEF2A, myocyte specific enhancer factor 2A; IGF2BP2, insulin-like growth factor 2 mRNA binding protein 2; NRARP, notch regulated ankyrin repeat protein; ESM1, endothelial cell specific molecule 1; TXNIP, thioredoxin interacting protein; NFIA, nuclear factor IA; NLRP3 NLR family pyrin domain containing 3; HG, high glucose; SIRT1, sirtuin 1; HF, heart failure; IGF-1, insulin-like growth factor-1; CMVECs, cardiac microvascular endothelial cells; ADCY6, adenylate cyclase 6; GTPCH1, GTP cyclohydrolase 1; ADAM17, A disintegrin and metalloprotease 17; VSMCs, vascular smooth muscle cells; ILF3, interleukin enhancer binding factor 3; CDK4, cyclin dependent kinase 4; NF-κB, nuclear factor kappa-B; RAAS, renin–angiotensin–aldosterone system; EH, essential hypertension

elevated in hypoxic ECs in patients with AKI, highlighting its specificity as a potential biomarker for AKI. In addition, CiRs-126 was found to sponge with miR-126-5p, an important ncRNA that impacts endothelial homeostasis and hypoxia signaling. Besides, CiRs-126's linear counterpart, leucine-rich repeats and immunoglobulin-like domains protein 1 (LRIG1), is reported to be important in early cell protection and regeneration in ischemia AKI. Therefore, CiRs-126 might serve as part of a signaling cascade involving LRIG and miR-126 to against renal injury [224]. Sepsis is the leading underlying cause of AKI in severely ill patients, accounting for 40–50% of

AKI [225]. The current understanding focuses on inflammation, microcirculatory dysfunction, and metabolic reprogramming as key pathways in septic AKI [220]. Mesenchymal stem cell-derived Exos have been reported to alleviate microvascular dysfunction and decrease the expression of inflammatory factors in sepsis through the delivery of mmu_circ_0001295, thus inhibiting sepsis-induced AKI [225]. These studies emphasize the role of circRNAs in modifying AKI and demonstrate the feasibility of using circRNAs as novel therapeutic targets for kidney injury. More research into the mechanisms by which circRNAs regulate microcirculatory dysfunction in AKI may identify novel therapeutic targets and offer more effective strategies for the prevention and treatment of AKI.

Age-related macular degeneration

AMD is a degenerative disease that affects the macular area of the retina and severely damages vision in elderly people [73]. One of the main causes of vision loss in AMD is choroidal neovascularization (CNV) [226] and endothelial dysfunction plays a key part in the occurrence of CNV [227]. Recent studies have verified that circRNAs play significant regulatory roles in CNV. A significant increased level of cZBTB44 was observed by Zhou et al. in the CNV choroid. The knockdown of cZBTB44 reduced the activity, proliferation, migration, and tubular formation of ECs, which had an anti-angiogenic effect. Mechanistically, cZBTB44 sponged miR-578 and resulted in enhanced expression of vascular endothelial growth factor A (VEGFA) and VCAM1 [228]. Similarly, Wu et al. demonstrated that circRNA Uxs1 sponged miR-335-5p, activating the downstream mTOR-p70 S6K pathway and up-regulating placental growth factor (PGF) expression. The increased expression of circRNA Uxs1 promoted CNV by enhancing EC tube formation, migration, and proliferation [229]. These studies suggest that circRNAs play a key role in CNV by regulating endothelial angiogenesis function.

Macrophages are critical to maintaining inflammatory homeostasis in AMD [73]. Using bioinformatics analysis, Su et al. identified a regulatory axis of hsa_circRNA7329/hsa-miR-9/SCD. Specifically, hsa_circRNA7329 modulated stearoyl-CoA desaturase (SCD) by sponging hsa-miR-9. This promoted macrophage-mediated inflammation and pathological angiogenesis, contributing to AMD progression [230]. In addition, it has been reported that circRNAs may alter ECM expression in the pathogenesis of CNV. ECM maintains the shape of vascular tissue structure and regulates the proliferation and differentiation of vascular cells. Huang et al. identified 117 differently expressed circRNAs between control and laser-induced choroids. The most significant mechanism among these circRNAs-mediated regulatory pathways is the ECM-receptor interaction, indicating that circRNAs in CNV may target ECM to promote angiogenesis [226]. Therefore, circRNAs are expected to be promising therapeutic targets for AMD treatment and even other ocular diseases involving CNV.

Diabetic retinopathy

Diabetes, a prevalent chronic metabolic disorder, is characterized by elevated blood glucose levels, which can result in long-term microvascular complications [231]. Diabetic vascular complications are closely associated with vascular aging, and damage to vascular ECs is a precursor to retinal vascular dysfunction in DR [232]. Recent studies have underscored the crucial role of circRNAs in maintaining the metabolic homeostasis of ECs in the context of DR [138, 233–235]. It has been discovered that circHIPK3 is significantly up-regulated in the diabetic retina and retinal ECs [233]. By acting as a miR-30a-3p sponge and inhibiting its expression, circHIPK3 can modulate the vitality, proliferation, migration, and lumen formation of ECs in vitro, promoting EC proliferation as well as vascular dysfunction associated with DR [233]. Another study has highlighted the marked up-regulation of cZNF609 under conditions of hyperglycemia and hypoxic stress, both in vivo and in vitro. The knockdown of cZNF609 enhances EC migration and tube formation, protecting ECs from oxidative and hypoxic stress in vitro, meanwhile reducing retinal vascular loss and inhibiting pathological angiogenesis in vivo [234].

The specialization of endothelial tip cells is critical for angiogenesis, with NOTCH-regulated ankyrin repeat protein (NRARP) and endothelial cell-specific molecule-1 (ESM-1) serving as key regulators of both angiogenesis and tip cell behavior. Through its interaction with insulin-like growth factor 2 mRNA binding protein 2 (IGF2BP2), circMET can stabilize the expression of NRARP mRNA and ESM-1, hence regulating the endothelial sprouting and pathological angiogenesis. CircMET knockdown diminishes endothelial migration and sprouting in vitro, while also greatly decreases pathological angiogenesis and suppresses tip cell specialization in vivo [236]. The up-regulation of circFTO in HG-induced retinal vascular ECs leads to enhanced angiogenesis, but this effect is reversed by circFTO knockdown. Mechanistically, circFTO is thought to up-regulate thioredoxin interacting protein (TXNIP) by binding to miR-128-3p, ultimately promoting angiogenesis in DR [237].

The interplays and communication between different cells also play a pivotal role in both the steady state of DR and microvascular remodeling. Lin et al. discovered that the hypoxia-induced expression of circEhmt1 in ECs

facilitated secretion from adjacent cells, hence protecting ECs against HG-induced damage [238]. Similarly, Exos-derived cPWWP2A could be transferred from pericytes to ECs. By interacting with miR-579 to promote the expression of angiogenin 1, occludin, and SIRT1, cPWWP2A can maintain vascular integrity and alleviate DM-induced retinal vascular dysfunction [239].

By modulating key processes such as endothelial proliferation, migration, and angiogenesis, circRNAs significantly contribute to vascular dysfunction and pathological changes in DR. These findings highlight the potential of circRNAs as therapeutic targets for addressing microvascular complications in DR.

Heart failure

HF is a serious chronic disease with high global mortality and significant adverse health effects [240]. Microcirculation dysfunction is a major cause of HF. By connecting the circulation and CMs, cardiac microvascular ECs (CMVECs) are essential for regulating and maintaining cardiac function. CMVECs-related oxidative stress complications after myocardial ischemia are the main reason for cardiac dysfunction [241]. Recent studies have revealed the roles of Exos-drived circRNAs in maintaining CMVEC function. CircHIPK3 released from hypoxic-preconditioned CMs is transferred to CMVECs by Exos and mediates the expression of IGF-1 via targeting miR-29a in CMVECs, thereby alleviating CMVECs dysfunction caused by oxidative stress [241]. Interestingly, it has also been found that circHPIK3 impairs cardiac function in the long term by raising Ca^{2+} concentration via the circHPIK3-miR-17-3p-Adcy6 axis, which may be a therapeutic target for HF [242]. Furthermore, Madè et al. discovered that the level of circBPTF increased in ECs exposed to hypoxia, as well as in cardiac samples from patients with end-stage ischemic HF. Subsequent study demonstrated that circBPTF silencing resulted in EC cycle arrest [243]. HF with preserved ejection fraction (HFpEF) is associated with EC dysfunction. Li et al. found that statins up-regulate the expression of circRNA-RBCK1 via the AP-2α/circRNA-RBCK1 signaling pathway. The interaction between circRNA-RBCK1 and miR-133a enhances diastolic function, thereby preventing HFpEF [244]. Overall, these studies highlight the critical involvement of circRNAs in regulating EC function and maintaining cardiac microvascular integrity in HF, suggesting that circRNAs could serve as promising therapeutic targets for improving vascular and cardiac outcomes in HF patients.

Hypertension

Hypertension, a clinical syndrome characterized by elevated systemic arterial blood pressure, is considered a disease associated with vascular aging. The factors contributing to the vascular function deterioration accelerate with aging [245]. Investigating and modulating circRNAs in the development of hypertension are crucial. Study has elucidated the significance of phenotypic transition in primary hypertension-associated vascular remodeling in VSMCs [246]. Notably, circHIPK2 is found to be significantly up-regulated in VSMCs of hypertension patients and acts as a sponge for miR-145-5p, facilitating AngII-induced phenotypic alteration in VSMCs [246]. Inflammation is considered a key mechanism leading to the phenotypic transformation of VSMCs [247]. Via regulating the expression of α-actin in VSMCs, circACAT2 has an impact on the VSMC inflammation and neointimal hyperplasia. Yang et al. showed that circACTA2 interacted with p50 and suppressed the expression of the NF-κB p65 and p50 subunits. This not only prevented TNF-α-induced dimerization of p50/p65 and subsequent nuclear translocation, thereby inhibiting NLRP3 gene transcription activation, but also reduced inflammation by suppressing NLRP3 inflammasome activity [173].

EC dysfunction resulting from chronic inflammation is one of the pathogenic mechanisms for hypertension. He et al. discovered that vascular inflammation is accompanied by the up-regulation of hsa_circ_0105015. By sponging has-miR-637 to induce inflammation and EC dysfunction, hsa_circ_0105015 promotes hypertension progression [248]. Additionally, there is a strong correlation between the development of hypertension and the imbalance of the RAAS. A study has indicated that the hsa_circ_0122153/hsa-miR-483-3p and hsa_circ_0025088/hsa-miR-27a-3p axes have an effect in the development and progression of hypertension by regulating the RAAS [249].

These studies underscore the significant role of circRNAs in hypertension, particularly in regulating VSMC phenotype, EC function, inflammation, and affecting critical signaling pathways like the RAAS, pointing to circRNAs as potential targets for innovative therapeutic strategies in managing hypertension.

The clinical application of CircRNAs in aging-related vascular diseases

CircRNAs play a pivotal role in the pathogenesis and progression of various aging-related vascular diseases due to their strong stability and specific expression in cells and tissues [250]. Recent studies have established that circRNAs are emerging as potential diagnostic biomarkers for various diseases, as they are closed circular molecules resistant to RNA exonucleases or RNase R, ensuring the stability in blood and other body fluids. Besides, the characteristics of conservation across mammals, high sensitivity, and specificity make circRNAs potential new

therapeutic targets and markers for the diagnosis, therapies and prognosis of diseases [251–254].

CircRNA detection and investigation methods

To gain a deeper understanding of the clinical role of circRNAs in aging-related vascular diseases, it is crucial to employ appropriate detection and investigation methods.

Accurate and reliable circRNA detection methods lay the groundwork for researching how they function in aging-related vascular diseases. Several methods are available for detecting circRNAs, including RNA-seq, quantitative reverse transcription PCR (qRT-PCR), and microarrays [255]. High-throughput RNA-seq enables comprehensive analysis of circRNA expression profiles [85, 256], allowing researchers to identify circRNAs linked to aging-related vascular diseases and uncover potential biomarkers for early diagnosis and personalized treatment. qRT-PCR is commonly used to quantitatively measure the expression levels of specific circRNAs and to validate RNA-seq results [257]. By utilizing specific probes, microarrays can effectively identify circRNAs associated with aging-related vascular diseases, supporting biomarker discovery [258]. In addition, northern blotting and RNA in situ hybridization are employed to detect specific expression patterns of circRNAs [85]. These detection methods provide reliable tools for researchers to gain a deeper understanding of the dynamic changes of circRNAs under different physiological and pathological conditions.

In vitro and in vivo experiments are the two main approaches for studying the function of circRNAs. In the context of vascular aging, in vitro experiments use cell culture models to explore the effects of circRNAs on processes such as proliferation, migration, and apoptosis in ECs and VSMCs. Through transfection techniques, specific circRNAs can be overexpressed or suppressed, enabling researchers to observe their effects on cellular functions. RNA interference and clustered regularly interspaced short palindromic repeats (CRISPR)-Cas systems allow precise modulation of circRNA expression, enabling the exploration of circRNA function [259]. In vivo studies employ animal models, such as mice, to assess the long-term impacts of circRNAs on tissues like blood vessels. Gene knockdown or overexpression mouse models are commonly used to investigate the roles of circRNAs in different physiological and pathological conditions. Preclinical studies serve as a crucial bridge between basic research and clinical application, helping to validate the efficacy and safety of circRNAs as potential therapeutic targets. They also explore the combination of circRNAs with other therapeutic strategies, such as anti-inflammatory and antioxidant therapies, thereby expanding their potential in the management of aging-related vascular diseases [260].

These methods not only provide new insights for basic scientific research of circRNAs, but also offer valuable clinical guidance for the early diagnosis, treatment, and prognosis of aging-related vascular diseases. Despite advances in current detection and research techniques, the detection and investigation of circRNAs still face challenges, including issues of stability, specificity, and cost-effectiveness, as well as interspecies differences and the reproducibility of experimental results need further resolution [257]. Future research should continue to optimize existing technologies and develop more efficient and reliable circRNA detection and research methods to facilitate their clinical translation.

CircRNAs act as potential biomarkers for diagnosis

CircRNAs have been identified as prospective markers for improved specificity in the diagnosis of aging-related vascular diseases [261–263]. CircRNAs provide distinct advantages over other existing methodologies and biomarkers: in addition to possessing very stable and highly conserved features with a longer half-life in plasma, circRNAs are broadly distributed in blood, plasma, and EVs, thereby they can be easily detected via non-invasive methods. Currently, hundreds of cell-specific circRNAs in mammal cells and tissues have been found using RNA detection technologies, providing more candidates for the selection of disease biomarkers [240, 264].

The potential of circRNAs as biomarkers for clinical application in aging-related vascular diseases is well supported by the compelling evidence. Firstly, circRNAs contribute to the enhancement of diagnostic specificity for aging-related vascular diseases. For example, an analysis of serum samples from individuals with CAD identified 624 significantly up-regulated circRNAs and 171 significantly down-regulated circRNAs, with hsa_circ_0001879 and hsa_circ_0004104 emerging as promising candidates for CAD diagnosis [251]. Secondly, the severity of vascular diseases can be assessed by the expression levels of circRNAs. Hou et al. identified three differentially expressed circRNAs (hsa_circ_0016868, hsa_circ_0001364, hsa_circ_0006731) in the left main coronary artery with high levels of AS [253]. Moreover, as circRNAs are abundant in blood EVs, and their fraction is substantially higher in EVs than in cells, circRNAs in EVs may have significant implications for disease diagnosis [265]. Xiong et al. demonstrated that the overexpression of small EVs (sEVs)-derived circNPHP4 was linked with aggressive clinicopathologic features in patients with coronary atherosclerotic disease, as well as a strong capacity for risk prediction in coronary atherosclerotic disease [266]. Thus, monitoring the levels of specific circRNAs

not only serves as a diagnostic tool, but also predicts disease progression.

CircRNAs act as potential targets for therapy

CircRNAs mainly act as miRNA sponge that regulate the downstream target proteins. Therefore, blocking or mimicking a certain circRNAs/miRNAs/mRNAs axis may successfully alleviate disease progression [207]. Some RNA drugs such as antisense oligonucleotides and small interfering RNAs have successfully entered clinical research and have become promising therapeutic strategies for many diseases. They can reverse the regulation of downstream target genes by reducing the expression of circRNAs. In fact, most of the circRNAs discussed in Sects. "The role of CircRNAs in vascular aging" and "CircRNAs in aging-related vascular diseases" exhibit substantial potential as therapeutic targets for aging-related vascular diseases. However, their therapeutic values need to be further evaluated in clinical practice. In addition to engaging in downstream target gene regulation through miRNA sponge mechanisms, some circRNAs can contribute to diseases via RBP or small peptide translation mechanisms [267]. For example, circ_0002331 alleviated ox-LDL-induced HUVEC dysfunction by interacting with RBP ELAVL1, indicating a potential therapeutic target for AS [268].

It is well known that natural oligonucleotides are challenging to reach the target site intactly. Fortunately, EVs, especially Exos, have the advantages of low immunogenicity and long half-life, as well as the capacity to target tissues and cross biological barriers [269, 270]. Therefore, they exhibit significant promise as natural drug delivery carriers in treatment. EVs loaded with circ-ITCH can promote EC angiogenesis and accelerate wound healing in DFU [271]. circSHOC2 in Exos can inhibit neuronal apoptosis and alleviate neuronal injury, which might provide a potential therapeutic strategy for IS [272]. Innovatively, selecting candidates focused on a single disease from multiple circRNAs and downstream signal pathways is extremely difficult. This issue can be partially resolved with synthetic circRNAs. For example, the integration of several effective targets into a single synthetic circRNA shows much potential for the diagnosis and treatment of diseases [264].

All of these studies imply that circRNAs are involved in the treatment of aging-related vascular diseases, and mediating the circRNA-miRNA-mRNA regulatory axis may reverse the disease process. Therefore, precisely regulating circRNAs in vascular ECs and VSMCs could emerge as a novel approach for treating aging-related vascular diseases, laying the groundwork for developing novel targeted therapies and drugs, and bringing new hope for personalized and accurate treatment.

CircRNAs act as potential biomarkers for prognosis

Prognosis, a paramount concern in clinical investigations, appears intricately linked to the expression profiles of specific circRNAs in the onset and progression of diseases, as evidenced by recent studies [273]. By employing multifactorial logistic regression models and Cox proportional hazards regression models to scrutinize the role of inflammation-related circRNA polymorphisms in predicting IS recurrence, the findings highlight a notable association between the expression of circ-STAT3 and recovery at 90 days post-IS, suggesting circ-STAT3 as a novel biomarker for forecasting post-stroke functional outcomes [274]. Among patients with moderate to severe strokes, the plasma levels of circPTP4A2 and circTLK2 exceed those with mild strokes, and these alterations reliably predict the adverse clinical outcomes 90 days post-IS. These results reinforce the close correlation between the plasma levels of circPTP4A2 and circTLK2 with stroke severity, subtype, and prognosis [216]. In a cohort study involving 216 IA patients and 186 healthy volunteers, Huang et al. revealed that hsa_circ_0000690 exhibited diminished expression in the plasma of patients with IA (AUC ROC = 0.752) and was tightly correlated with the type of surgical procedure, underscoring its potential as a diagnostic marker for IA and its proficiency in predicting prognosis three months post-surgery [275]. Therefore, circRNAs emerge as promising biomarkers for prognosis, potentially enhancing clinical prognosis assessments and tailoring individualized treatment strategies.

Challenges and limitations of CircRNAs in clinical practice

CircRNAs possess the potential to serve as both therapeutic targets and biomarkers for diagnosis and prognosis, with a close correlation between their expression levels and pathological and clinical features (Fig. 7).

Despite these promising findings, the clinical application of circRNAs still faces many challenges and limitations. Currently, most circRNAs lack sensitivity and reliability as biomarkers. According to Schulte et al., although there is a significant abundance of circRNAs in cardiac tissue, circRNAs in plasma were difficult to detect and did not increase following myocardial damage [276]. Furthermore, research findings should take into account the impact of confounding factors such as sample size, age, gender, race, CVDs risk factors, drugs, and lifestyle. These problems have the potential to cause inaccurate and misleading results that have a negative effect on health [207]. Therefore, to drive the translation and application of research, reliable methods and standardized strategies are required. To further assess the advantages of circRNAs as diagnostic and prognostic biomarkers in comparison to other chemical entities and

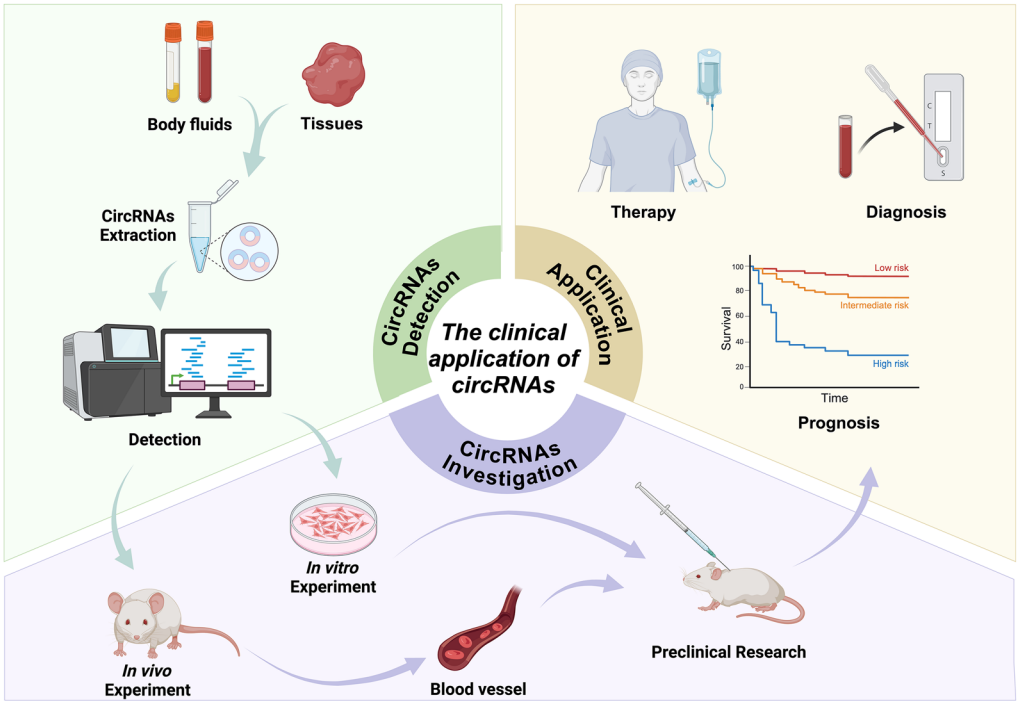


Fig. 7 The clinical application of circRNAs in aging-related vascular diseases. CircRNAs are extracted from samples such as tissues or body fluids, and subsequently identified and quantified using various detection techniques, including RNA sequencing, qRT-PCR, and microarrays, thereby laying the groundwork for understanding the role of circRNAs in vascular aging. In vitro studies use cell culture models to investigate the functional effects of circRNAs, while in vivo studies assess the long-term effects of circRNAs on tissues like blood vessels using animal models. Moreover, preclinical research serves as a crucial bridge between basic studies and clinical applications. By employing these detection and investigation methods, specific circRNAs can be identified and explored as potential biomarkers and/or therapeutic targets. (Created with BioRender.com). Abbreviations: CircRNAs, circular RNAs

already existing markers, larger clinical samples and AUC measurements are required.

Besides the challenges mentioned above, another major challenge before the therapeutic application of circRNAs is figuring out how to accurately deliver circRNAs to the target site. Fortunately, EV-delivered circRNAs have shown promising therapeutic potential. However, numerous challenges remain to be addressed before their application in actual clinical treatments. Firstly, Exos isolation and purification techniques are still in their infancy. Secondly, research is limited since the specific mechanisms of vascular aging are still unknown. Additionally, it is critical to precisely identify the particular pathological conditions and signaling axes that regulate different circRNAs in vascular aging, as well as consider the disruption of other metabolic products in EVs. Thus, further investigation into their specific mechanisms is required, along with more studies to accurately target specific circRNAs. Last but not least, circRNAs have a variety of cellular target sites and different regulatory mechanisms that could result in unfavorable side effects and off-target effects in other tissues or cells. Before applying circRNAs into clinical treatment, the safety and efficacy of circRNA-based therapeutics must be thoroughly assessed [207].

In conclusion, it will be the focus of future research to explore new candidate diagnostic biomarkers or therapeutic targets by elucidating the pathophysiological mechanisms of aging-related vascular diseases. The ongoing efforts in this area aim to unlock the full potential of circRNAs in clinical applications and improve our understanding of their role in the progression and management of diseases.

Conclusion and prospective

CircRNAs, as pivotal regulatory factors in vascular aging and aging-related vascular diseases, affect the function of vascular wall cells, particularly ECs and VSMCs. Despite being in its early stages, research on this subject is gaining momentum. As mentioned earlier, AFs are integral components of the blood vessel wall. However, there is a paucity of studies directly investigating the relationship between circRNAs and AF function, and this research gap could offer a new avenue for future exploration. In addition, although our review highlights the role of immune cells, such as macrophages, in vascular aging

and aging-related vascular diseases under the regulation of circRNAs, this area remains lacking extensive research. As the significance of immune cells in vascular aging becomes increasingly recognized, future studies should focus on how circRNAs regulate immune cell functions, particularly in the crosstalk between immune cells and vascular wall cells like ECs and VSMCs, and their potential contributions to vascular aging and aging-related vascular diseases. This research could deepen our understanding of the molecular mechanisms of vascular aging and pave the way for novel therapeutic strategies, especially in immune modulation and targeted treatments for aging-related vascular diseases.

An increasing number of studies have been dedicated to elucidating the potential molecular mechanisms by which circRNAs regulate vascular aging. Given their exonuclease resistance and relative stability, circRNAs may potentially serve as forefront biomarkers and therapeutic targets for aging-related diseases in the future. Thus, it is crucial to elucidate the physiological and pathogenic roles of circRNAs in aging. However, it should be noted that the functions of circRNAs are not isolated; they may regulate multiple intracellular processes, thereby affecting the overall function and stability of the cells. Furthermore, circRNAs may influence each other through different signaling pathways or different functions of the same pathway, thus interacting within the same cellular process.

Aging often leads to the occurrence of various diseases, but there is increasing evidence that cell senescence is a double-edged sword. Senescent cells could be beneficial under certain conditions. For example, cell senescence promotes acute wound healing [277]; nevertheless, in chronic wounds, it might result in chronic inflammation and delayed wound healing [278]. Furthermore, the safety issues raised by the removal of senescent cells deserve careful consideration. A study found that elimination of senescent pulmonary ECs exacerbated pulmonary hypertension in mice [279]. Consequently, the significance of aging in human disease warrants further studies to comprehensively understand the regulatory mechanisms of aging, which is necessary for the development of more targeted and effective treatments.

In this review, we deliberately focus on the role of circRNAs in a specific subset of aging-related vascular diseases. It is noteworthy, in fact, that circRNA regulation is implicated in numerous aging-related diseases. One prominent example is diabetic cardiomyopathy (DCM), which stands as the primary cause of morbidity and mortality among individuals with DM worldwide. The pathology of DCM is linked to myocardial fibrosis. Wang et al. demonstrated that silencing circHIPK3 resulted in a reduction of myocardial fibrosis and an improvement in cardiac function in the mice with DCM. The underlying mechanism involved circHIPK3 functioning as a ceRNA to inhibit the expression of miR-29b-3p but up-regulating the expression of Col3a1 and Col1a1, thereby promoting myocardial fibrosis in DCM [280]. However, the current body of evidence is insufficient to definitively establish whether circRNAs regulate the homeostasis of vascular wall cells like VSMCs or ECs to either promote or inhibit the development of DCM. This knowledge gap presents a fertile area for further exploration, offering a novel direction for investigating other diseases in the future.

In conclusion, vascular aging plays a pivotal role in aging-related vascular diseases, and circRNAs have emerged as a prominent research hotspot in the biomedical field. In the present review, we comprehensively explore the role of circRNAs in vascular aging along with aging-related vascular diseases, elucidating their regulatory impact on ECs, VSMCs, as well as various kinds of macro- and microvascular diseases. Additionally, we explore the potential of circRNAs as tools for clinical application, including diagnosis, therapies, and prognosis, in the context of aging-related vascular diseases. The challenges and limitations, as well as the possible future research directions of circRNAs in clinical practice, are also be discussed thoroughly. Therefore, this review will help enhance understanding of the interconnection among circRNAs, vascular aging, and aging-related vascular diseases, thereby facilitating the acceleration of development, optimization, and clinical application of diagnostic or therapeutic tools grounded in circRNA-related research. Subsequent research endeavors are imperative to identify additional circRNAs serving as potential biomarkers and therapeutic targets for vascular aging and aging-related vascular diseases.

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Author contributions
J.L and X.L conceived the idea and directed the writing. S.-Q. H and B.H wrote the manuscript, summarized the table, designed the figures and collected the related references. J.-J. Y, L.-Q. Y and C.L supervised the manuscript and modified the figures. F.X and F.-R. L polished language and corrected grammar errors. All authors approved the final manuscript.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Division DoEaSAP. World population prospects 2022. 2022.
2. Sun L, Wang L, Ye KX, Wang S, Zhang R, Juan Z, et al. Endothelial glycocalyx in aging and age-related diseases. Aging Dis. 2023;14:1606–17.
3. Wang Y, Wang J, Zheng XW, Du MF, Zhang X, Chu C, et al. Early-life cardiovascular risk factor trajectories and vascular aging in midlife: a 30-year prospective cohort study. Hypertension. 2023;80:1057–66.
4. Guo J, Huang X, Dou L, Yan M, Shen T, Tang W, et al. Aging and aging-related diseases: from molecular mechanisms to interventions and treatments. Signal Transduct Target Ther. 2022;7:391.
5. Kristensen LS, Andersen MS, Stagsted LVW, Ebbesen KK, Hansen TB, Kjems J. The biogenesis, biology and characterization of circular RNAs. Nat Rev Genet. 2019;20:675–91.
6. Ungvari Z, Tarantini S, Sorond F, Merkely B, Csiszar A. Mechanisms of vascular aging, a geroscience perspective: JACC focus seminar. J Am Coll Cardiol. 2020;75:931–41.
7. Zheng J, He J, Li H. FAM19A5 in vascular aging and osteoporosis: mechanisms and the "calcification paradox." Ageing Res Rev. 2024;99: 102361.
8. van der Linden J, Trap L, Scherer CV, Roks AJM, Danser AHJ, van der Pluijm I, et al. Model systems to study the mechanism of vascular aging. Int J Mol Sci. 2023;24:15379.
9. Oliveira AC, Cunha P, Vitorino PVO, Souza ALL, Deus GD, Feitosa A, et al. Vascular aging and arterial stiffness. Arq Bras Cardiol. 2022;119:604–15.
10. Castelli R, Gidaro A, Casu G, Merella P, Profili NI, Donadoni M, et al. Aging of the arterial system. Int J Mol Sci. 2023;24:6910.
11. Mistriotis P, Andreadis ST. Vascular aging: molecular mechanisms and potential treatments for vascular rejuvenation. Ageing Res Rev. 2017;37:94–116.
12. Du S, Ling H, Guo Z, Cao Q, Song C. Roles of exosomal miRNA in vascular aging. Pharmacol Res. 2021;165: 105278.
13. Sutton NR, Malhotra R, St Hilaire C, Aikawa E, Blumenthal RS, Gackenbach G, et al. Molecular mechanisms of vascular health: insights from vascular aging and calcification. Arterioscler Thromb Vasc Biol. 2023;43:15–29.
14. Ungvari Z, Tarantini S, Donato AJ, Galvan V, Csiszar A. Mechanisms of vascular aging. Circ Res. 2018;123:849–67.
15. Molnar AA, Nadasy GL, Dornyei G, Patai BB, Delfavero J, Fulop GA, et al. The aging venous system: from varicosities to vascular cognitive impairment. Geroscience. 2021;43:2761–84.
16. Ghebre YT, Yakubov E, Wong WT, Krishnamurthy P, Sayed N, Sikora AG, et al. Vascular aging: implications for cardiovascular disease and therapy. Transl Med (Sunnyvale). 2016;6:183.
17. Roth L, Dogan S, Tuna BG, Aranyi T, Benitez S, Borrell-Pages M, et al. Pharmacological modulation of vascular ageing: a review from VascAgeNet. Ageing Res Rev. 2023;92: 102122.
18. Ya J, Bayraktutan U. Vascular ageing: mechanisms, risk factors, and treatment strategies. Int J Mol Sci. 2023;24:11538.
19. Wu YY, Shan SK, Lin X, Xu F, Zhong JY, Wu F, et al. Cellular crosstalk in the vascular wall microenvironment: the role of exosomes in vascular calcification. Front Cardiovasc Med. 2022;9: 912358.
20. Harman D. Aging: a theory based on free radical and radiation chemistry. J Gerontol. 1956;11:298–300.
21. Xu Z, Elrashidy RA, Li B, Liu G. Oxidative stress: a putative link between lower urinary tract symptoms and aging and major chronic diseases. Front Med (Lausanne). 2022;9: 812967.
22. Li Y, Zhao T, Li J, Xia M, Li Y, Wang X, et al. Oxidative stress and 4-hydroxy-2-nonenal (4-HNE): implications in the pathogenesis and treatment of aging-related diseases. J Immunol Res. 2022;2022:2233906.
23. Francia P, delli Gatti C, Bachschmid M, Martin-Padura I, Savoia C, Migliaccio E, et al. Deletion of p66shc gene protects against age-related endothelial dysfunction. Circulation. 2004;110:2889–95.
24. Jia G, Aroor AR, Jia C, Sowers JR. Endothelial cell senescence in aging-related vascular dysfunction. Biochim Biophys Acta Mol Basis Dis. 2019;1865:1802–9.
25. El Assar M, Alvarez-Bustos A, Sosa P, Angulo J, Rodriguez-Manas L. Effect of physical activity/exercise on oxidative stress and inflammation in muscle and vascular aging. Int J Mol Sci. 2022;23:8713.
26. Incalza MA, D'Oria R, Natalicchio A, Perrini S, Laviola L, Giorgino F. Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases. Vascul Pharmacol. 2018;100:1–19.
27. Forstermann U, Xia N, Li H. Roles of vascular oxidative stress and nitric oxide in the pathogenesis of atherosclerosis. Circ Res. 2017;120:713–35.
28. Foote K, Reinhold J, Yu EPK, Figg NL, Finigan A, Murphy MP, et al. Restoring mitochondrial DNA copy number preserves mitochondrial function and delays vascular aging in mice. Aging Cell. 2018;17: e12773.
29. Ungvari Z, Orosz Z, Labinskyy N, Rivera A, Xiangmin Z, Smith K, et al. Increased mitochondrial H2O2 production promotes endothelial NF-kappaB activation in aged rat arteries. Am J Physiol Heart Circ Physiol. 2007;293:H37-47.
30. Erusalimsky JD. Vascular endothelial senescence: from mechanisms to pathophysiology. J Appl Physiol. 1985;2009(106):326–32.
31. Salazar G, Huang J, Feresin RG, Zhao Y, Griendling KK. Zinc regulates Nox1 expression through a NF-kappaB and mitochondrial ROS dependent mechanism to induce senescence of vascular smooth muscle cells. Free Radic Biol Med. 2017;108:225–35.
32. Bloom SI, Islam MT, Lesniewski LA, Donato AJ. Mechanisms and consequences of endothelial cell senescence. Nat Rev Cardiol. 2023;20:38–51.
33. Regnault V, Challande P, Pinet F, Li Z, Lacolley P. Cell senescence: basic mechanisms and the need for computational networks in vascular ageing. Cardiovasc Res. 2021;117:1841–58.
34. Kumari R, Jat P. Mechanisms of cellular senescence: cell cycle arrest and senescence associated secretory phenotype. Front Cell Dev Biol. 2021;9: 645593.
35. Mehdizadeh M, Aguilar M, Thorin E, Ferbeyre G, Nattel S. The role of cellular senescence in cardiac disease: basic biology and clinical relevance. Nat Rev Cardiol. 2022;19:250–64.
36. Li X, Li C, Zhang W, Wang Y, Qian P, Huang H. Inflammation and aging: signaling pathways and intervention therapies. Signal Transduct Target Ther. 2023;8:239.
37. Pezone A, Olivieri F, Napoli MV, Procopio A, Avvedimento EV, Gabrielli A. Inflammation and DNA damage: cause, effect or both. Nat Rev Rheumatol. 2023;19:200–11.
38. Sanchez-Cabo F, Fuster V, Silla-Castro JC, Gonzalez G, Lorenzo-Vivas E, Alvarez R, et al. Subclinical atherosclerosis and accelerated epigenetic age mediated by inflammation: a multi-omics study. Eur Heart J. 2023;44:2698–709.
39. Blaser H, Dostert C, Mak TW, Brenner D. TNF and ROS crosstalk in inflammation. Trends Cell Biol. 2016;26:249–61.
40. Zheng MH, Shan SK, Lin X, Xu F, Wu F, Guo B, et al. Vascular wall microenvironment: exosomes secreted by adventitial fibroblasts induced vascular calcification. J Nanobiotechnology. 2023;21:315.
41. Pal S, Tyler JK. Epigenetics and aging. Sci Adv. 2016;2: e1600584.
42. Duan R, Fu Q, Sun Y, Li Q. Epigenetic clock: a promising biomarker and practical tool in aging. Ageing Res Rev. 2022;81: 101743.

43. Li A, Koch Z, Ideker T. Epigenetic aging: biological age prediction and informing a mechanistic theory of aging. J Intern Med. 2022;292:733–44.
44. Lin Z, Ding Q, Li X, Feng Y, He H, Huang C, et al. Targeting epigenetic mechanisms in vascular aging. Front Cardiovasc Med. 2021;8: 806988.
45. Wu H, Roks AJ. Genomic instability and vascular aging: a focus on nucleotide excision repair. Trends Cardiovasc Med. 2014;24:61–8.
46. Niedernhofer LJ, Gurkar AU, Wang Y, Vijg J, Hoeijmakers JHJ, Robbins PD. Nuclear genomic instability and aging. Annu Rev Biochem. 2018;87:295–322.
47. Cao G, Xuan X, Hu J, Zhang R, Jin H, Dong H. How vascular smooth muscle cell phenotype switching contributes to vascular disease. Cell Commun Signal. 2022;20:180.
48. Xu Y, Kovacic JC. Endothelial to mesenchymal transition in health and disease. Annu Rev Physiol. 2023;85:245–67.
49. Hwang HJ, Kim N, Herman AB, Gorospe M, Lee JS. Factors and pathways modulating endothelial cell senescence in vascular aging. Int J Mol Sci. 2022;23:10135.
50. Shi J, Yang Y, Cheng A, Xu G, He F. Metabolism of vascular smooth muscle cells in vascular diseases. Am J Physiol Heart Circ Physiol. 2020;319:H613–31.
51. Wang G, Jacquet L, Karamariti E, Xu Q. Origin and differentiation of vascular smooth muscle cells. J Physiol. 2015;593:3013–30.
52. Shanahan CM, Crouthamel MH, Kapustin A, Giachelli CM. Arterial calcification in chronic kidney disease: key roles for calcium and phosphate. Circ Res. 2011;109:697–711.
53. Fang YP, Zhao Y, Huang JY, Yang X, Liu Y, Zhang XL. The functional role of cellular senescence during vascular calcification in chronic kidney disease. Front Endocrinol (Lausanne). 2024;15:1330942.
54. Haurani MJ, Pagano PJ. Adventitial fibroblast reactive oxygen species as autacrine and paracrine mediators of remodeling: bellwether for vascular disease? Cardiovasc Res. 2007;75:679–89.
55. Sartore S, Chiavegato A, Faggin E, Franch R, Puato M, Ausoni S, et al. Contribution of adventitial fibroblasts to neointima formation and vascular remodeling: from innocent bystander to active participant. Circ Res. 2001;89:1111–21.
56. Liu X, Jiang D, Huang W, Teng P, Zhang H, Wei C, et al. Sirtuin 6 attenuates angiotensin II-induced vascular adventitial aging in rat aortae by suppressing the NF-kappaB pathway. Hypertens Res. 2021;44:770–80.
57. Dong R, Ji Z, Wang M, Ma G. Role of macrophages in vascular calcification: from the perspective of homeostasis. Int Immunopharmacol. 2025;144: 113635.
58. Ding YN, Wang HY, Chen HZ, Liu DP. Targeting senescent cells for vascular aging and related diseases. J Mol Cell Cardiol. 2022;162:43–52.
59. Wu CM, Zheng L, Wang Q, Hu YW. The emerging role of cell senescence in atherosclerosis. Clin Chem Lab Med. 2020;59:27–38.
60. DeConne TM, Buckley DJ, Trott DW, Martens CR. The role of T cells in vascular aging, hypertension, and atherosclerosis. Am J Physiol Heart Circ Physiol. 2024;327:H1345–60.
61. Pattarabanjird T, Li C, McNamara C. B cells in atherosclerosis: mechanisms and potential clinical applications. JACC Basic Transl Sci. 2021;6:546–63.
62. Lin X, Shan SK, Xu F, Zhong JY, Wu F, Duan JY, et al. The crosstalk between endothelial cells and vascular smooth muscle cells aggravates high phosphorus-induced arterial calcification. Cell Death Dis. 2022;13:650.
63. Guo B, Shan SK, Xu F, Lin X, Li FX, Wang Y, et al. Protective role of small extracellular vesicles derived from HUVECs treated with AGEs in diabetic vascular calcification. J Nanobiotechnology. 2022;20:334.
64. Xu F, Zhong JY, Lin X, Shan SK, Guo B, Zheng MH, et al. Melatonin alleviates vascular calcification and ageing through exosomal miR-204/miR-211 cluster in a paracrine manner. J Pineal Res. 2020;68: e12631.
65. Tyrrell DJ, Goldstein DR. Ageing and atherosclerosis: vascular intrinsic and extrinsic factors and potential role of IL-6. Nat Rev Cardiol. 2021;18:58–68.
66. Fhayli W, Boete Q, Harki O, Briancon-Marjollet A, Jacob MP, Faury G. Rise and fall of elastic fibers from development to aging. consequences on arterial structure-function and therapeutical perspectives. Matrix Biol. 2019;84:41–56.
67. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. Circ Res. 2015;116:1509–26.
68. Zhang Q, Wang L, Wang S, Cheng H, Xu L, Pei G, et al. Signaling pathways and targeted therapy for myocardial infarction. Signal Transduct Target Ther. 2022;7:78.
69. Xie S, Xu SC, Deng W, Tang Q. Metabolic landscape in cardiac aging: insights into molecular biology and therapeutic implications. Signal Transduct Target Ther. 2023;8:114.
70. Koutsaliaris IK, Moschonas IC, Pechlivani LM, Tsouka AN, Tselepis AD. Inflammation, oxidative stress, vascular aging and atherosclerotic ischemic stroke. Curr Med Chem. 2022;29:5496–509.
71. Li Y, Lerman LO. Cellular senescence: a new player in kidney injury. Hypertension. 2020;76:1069–75.
72. Infante B, Franzin R, Madio D, Calvaruso M, Maiorano A, Sangregorio F, et al. Molecular mechanisms of AKI in the elderly: from animal models to therapeutic intervention. J Clin Med. 2020;9:2574.
73. Zhao B, Zhu L, Ye M, Lou X, Mou Q, Hu Y, et al. Oxidative stress and epigenetics in ocular vascular aging: an updated review. Mol Med. 2023;29:28.
74. Forte M, Stanzione R, Cotugno M, Bianchi F, Marchitti S, Rubattu S. Vascular ageing in hypertension: focus on mitochondria. Mech Ageing Dev. 2020;189: 111267.
75. Cheng J, Wu H, Xie C, He Y, Mou R, Zhang H, et al. Single-cell mapping of large and small arteries during hypertensive aging. J Gerontol A Biol Sci Med Sci. 2024;79:glad188.
76. Misir S, Wu N, Yang BB. Specific expression and functions of circular RNAs. Cell Death Differ. 2022;29:481–91.
77. Sanger HL, Klotz G, Riesner D, Gross HJ, Kleinschmidt AK. Viroids are single-stranded covalently closed circular RNA molecules existing as highly base-paired rod-like structures. Proc Natl Acad Sci USA. 1976;73:3852–6.
78. Hsu MT, Coca-Prados M. Electron microscopic evidence for the circular form of RNA in the cytoplasm of eukaryotic cells. Nature. 1979;280:339–40.
79. Kos A, Dijkema R, Arnberg AC, van der Meide PH, Schellekens H. The hepatitis delta (delta) virus possesses a circular RNA. Nature. 1986;323:558–60.
80. Cocquerelle C, Mascrez B, Hetuin D, Bailleul B. Mis-splicing yields circular RNA molecules. FASEB J. 1993;7:155–60.
81. Danan M, Schwartz S, Edelheit S, Sorek R. Transcriptome-wide discovery of circular RNAs in archaea. Nucleic Acids Res. 2012;40:3131–42.
82. Nigro JM, Cho KR, Fearon ER, Kern SE, Ruppert JM, Oliner JD, et al. Scrambled exons. Cell. 1991;64:607–13.
83. Capel B, Swain A, Nicolis S, Hacker A, Walter M, Koopman P, et al. Circular transcripts of the testis-determining gene sry in adult mouse testis. Cell. 1993;73:1019–30.
84. Salzman J, Gawad C, Wang PL, Lacayo N, Brown PO. Circular RNAs are the predominant transcript isoform from hundreds of human genes in diverse cell types. PLoS ONE. 2012;7: e30733.
85. Szabo L, Salzman J. Detecting circular RNAs: bioinformatic and experimental challenges. Nat Rev Genet. 2016;17:679–92.
86. Memczak S, Jens M, Elefsinioti A, Torti F, Krueger J, Rybak A, et al. Circular RNAs are a large class of animal RNAs with regulatory potency. Nature. 2013;495:333–8.
87. Wang Y, Wang Z. Efficient backsplicing produces translatable circular mRNAs. RNA. 2015;21:172–9.
88. Huang A, Zheng H, Wu Z, Chen M, Huang Y. Circular RNA-protein interactions: functions, mechanisms, and identification. Theranostics. 2020;10:3503–17.
89. Zhou WY, Cai ZR, Liu J, Wang DS, Ju HQ, Xu RH. Circular RNA: metabolism, functions and interactions with proteins. Mol Cancer. 2020;19:172.
90. Xu X, Zhang J, Tian Y, Gao Y, Dong X, Chen W, et al. CircRNA inhibits DNA damage repair by interacting with host gene. Mol Cancer. 2020;19:128.
91. Altesha MA, Ni T, Khan A, Liu K, Zheng X. Circular RNA in cardiovascular disease. J Cell Physiol. 2019;234:5588–600.
92. Liu X, Zhang Y, Zhou S, Dain L, Mei L, Zhu G. Circular RNA: an emerging frontier in RNA therapeutic targets, RNA therapeutics, and mRNA vaccines. J Control Release. 2022;348:84–94.
93. Boeckel JN, Jae N, Heumuller AW, Chen W, Boon RA, Stellos K, et al. Identification and characterization of hypoxia-regulated endothelial circular RNA. Circ Res. 2015;117:884–90.

94. Wang K, Long B, Liu F, Wang JX, Liu CY, Zhao B, et al. A circular RNA protects the heart from pathological hypertrophy and heart failure by targeting miR-223. Eur Heart J. 2016;37:2602–11.
95. Knupp D, Miura P. CircRNA accumulation: a new hallmark of aging? Mech Ageing Dev. 2018;173:71–9.
96. Burd CE, Jeck WR, Liu Y, Sanoff HK, Wang Z, Sharpless NE. Expression of linear and novel circular forms of an INK4/ARF-associated non-coding RNA correlates with atherosclerosis risk. PLoS Genet. 2010;6: e1001233.
97. Zheng C, Niu H, Li M, Zhang H, Yang Z, Tian L, et al. Cyclic RNA hsa-circ-000595 regulates apoptosis of aortic smooth muscle cells. Mol Med Rep. 2015;12:6656–62.
98. Bayoumi AS, Aonuma T, Teoh JP, Tang YL, Kim IM. Circular noncoding RNAs as potential therapies and circulating biomarkers for cardiovascular diseases. Acta Pharmacol Sin. 2018;39:1100–9.
99. He AT, Liu J, Li F, Yang BB. Targeting circular RNAs as a therapeutic approach: current strategies and challenges. Signal Transduct Target Ther. 2021;6:185.
100. Qu L, Yi Z, Shen Y, Lin L, Chen F, Xu Y, et al. Circular RNA vaccines against SARS-CoV-2 and emerging variants. Cell. 2022;185(1728–44): e16.
101. Niu D, Wu Y, Lian J. Circular RNA vaccine in disease prevention and treatment. Signal Transduct Target Ther. 2023;8:341.
102. Jae N, Dimmeler S. Noncoding RNAs in vascular diseases. Circ Res. 2020;126:1127–45.
103. Barrett SP, Wang PL, Salzman J. Circular RNA biogenesis can proceed through an exon-containing lariat precursor. Elife. 2015;4: e07540.
104. Saaoud F, Drummer IVC, Shao Y, Sun Y, Lu Y, Xu K, et al. Circular RNAs are a novel type of non-coding RNAs in ROS regulation, cardiovascular metabolic inflammations and cancers. Pharmacol Ther. 2021;220: 107715.
105. Pan YH, Wu WP, Xiong XD. Circular RNAs: promising biomarkers for age-related diseases. Aging Dis. 2020;11:1585–93.
106. Wu N, Yuan Z, Du KY, Fang L, Lyu J, Zhang C, et al. Translation of yes-associated protein (YAP) was antagonized by its circular RNA via suppressing the assembly of the translation initiation machinery. Cell Death Differ. 2019;26:2758–73.
107. Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, et al. Natural RNA circles function as efficient microRNA sponges. Nature. 2013;495:384–8.
108. Zeng Z, Xia L, Fan S, Zheng J, Qin J, Fan X, et al. Circular RNA circMAP3K5 acts as a microRNA-22-3p sponge to promote resolution of intimal hyperplasia Via TET2-mediated smooth muscle cell differentiation. Circulation. 2021;143:354–71.
109. Lavenniah A, Luu TDA, Li YP, Lim TB, Jiang J, Ackers-Johnson M, et al. Engineered circular RNA sponges act as miRNA inhibitors to attenuate pressure overload-induced cardiac hypertrophy. Mol Ther. 2020;28:1506–17.
110. Liu CX, Chen LL. Circular RNAs: characterization, cellular roles, and applications. Cell. 2022;185:2016–34.
111. Zong Y, Wang X, Cui B, Xiong X, Wu A, Lin C, et al. Decoding the regulatory roles of non-coding RNAs in cellular metabolism and disease. Mol Ther. 2023;31:1562–76.
112. Hu F, Peng Y, Fan X, Zhang X, Jin Z. Circular RNAs: implications of signaling pathways and bioinformatics in human cancer. Cancer Biol Med. 2023;20:104–28.
113. Zhang F, Jiang J, Qian H, Yan Y, Xu W. Exosomal circRNA: emerging insights into cancer progression and clinical application potential. J Hematol Oncol. 2023;16:67.
114. Yang L, Wilusz JE, Chen LL. Biogenesis and regulatory roles of circular RNAs. Annu Rev Cell Dev Biol. 2022;38:263–89.
115. Wang K, Gao XQ, Wang T, Zhou LY. The function and therapeutic potential of circular RNA in cardiovascular diseases. Cardiovasc Drugs Ther. 2023;37:181–98.
116. Han B, Chao J, Yao H. Circular RNA and its mechanisms in disease: from the bench to the clinic. Pharmacol Ther. 2018;187:31–44.
117. Ding Q, Shao C, Rose P, Zhu YZ. Epigenetics and vascular senescence-potential new therapeutic targets? Front Pharmacol. 2020;11: 535395.
118. Zhang X, Lu J, Zhang Q, Luo Q, Liu B. CircRNA RSF1 regulated ox-LDL induced vascular endothelial cells proliferation, apoptosis and inflammation through modulating miR-135b-5p/HDAC1 axis in atherosclerosis. Biol Res. 2021;54:11.
119. Wan H, You T, Luo W. circ_0003204 Regulates cell growth, oxidative stress, and inflammation in ox-LDL-induced vascular endothelial cells via regulating miR-942-5p/HDAC9 axis. Front Cardiovasc Med. 2021;8: 646832.
120. Muhleder S, Fernandez-Chacon M, Garcia-Gonzalez I, Benedito R. Endothelial sprouting, proliferation, or senescence: tipping the balance from physiology to pathology. Cell Mol Life Sci. 2021;78:1329–54.
121. Wu WP, Zhou MY, Liu DL, Min X, Shao T, Xu ZY, et al. circGNAQ, a circular RNA enriched in vascular endothelium, inhibits endothelial cell senescence and atherosclerosis progression. Mol Ther Nucleic Acids. 2021;26:374–87.
122. Min X, Cai MY, Shao T, Xu ZY, Liao Z, Liu DL, et al. A circular intronic RNA ciPVT1 delays endothelial cell senescence by regulating the miR-24-3p/CDK4/pRb axis. Aging Cell. 2022;21: e13529.
123. Bu LL, Yuan HH, Xie LL, Guo MH, Liao DF, Zheng XL. New dawn for atherosclerosis: vascular endothelial cell senescence and death. Int J Mol Sci. 2023;24:15160.
124. Duan H, Zhang Q, Liu J, Li R, Wang D, Peng W, et al. Suppression of apoptosis in vascular endothelial cell, the promising way for natural medicines to treat atherosclerosis. Pharmacol Res. 2021;168: 105599.
125. Shan R, Liu N, Yan Y, Liu B. Apoptosis, autophagy and atherosclerosis: relationships and the role of Hsp27. Pharmacol Res. 2021;166: 105169.
126. Cao Q, Guo Z, Du S, Ling H, Song C. Circular RNAs in the pathogenesis of atherosclerosis. Life Sci. 2020;255: 117837.
127. Chen T, Li L, Ye B, Chen W, Zheng G, Xie H, et al. Knockdown of hsa_circ_0005699 attenuates inflammation and apoptosis induced by ox-LDL in human umbilical vein endothelial cells through regulation of the miR-450b-5p/NFKB1 axis. Mol Med Rep. 2022;26:1.
128. Peng K, Jiang P, Du Y, Zeng D, Zhao J, Li M, et al. Oxidized low-density lipoprotein accelerates the injury of endothelial cells via circ-USP36/miR-98-5p/VCAM1 axis. IUBMB Life. 2021;73:177–87.
129. Wei Z, Ran H, Yang C. CircRSF1 contributes to endothelial cell growth, migration and tube formation under ox-LDL stress through regulating miR-758/CCND2 axis. Life Sci. 2020;259: 118241.
130. Qiu J, Wang G, Zheng Y, Hu J, Peng Q, Yin T. Coordination of Id1 and p53 activation by oxidized LDL regulates endothelial cell proliferation and migration. Ann Biomed Eng. 2011;39:2869–78.
131. Wang HG, Yan H, Wang C, Li MM, Lv XZ, Wu HD, et al. circAFF1 aggravates vascular endothelial cell dysfunction mediated by miR-516b/SAV1/YAP1 Axis. Front Physiol. 2020;11:899.
132. Liu H, Ma X, Mao Z, Shen M, Zhu J, Chen F. Circular RNA has_circ_0003204 inhibits oxLDL-induced vascular endothelial cell proliferation and angiogenesis. Cell Signal. 2020;70: 109595.
133. Li CY, Ma L, Yu B. Circular RNA hsa_circ_0003575 regulates oxLDL induced vascular endothelial cells proliferation and angiogenesis. Biomed Pharmacother. 2017;95:1514–9.
134. Huang JG, Tang X, Wang JJ, Liu J, Chen P, Sun Y. A circular RNA, circUSP36, accelerates endothelial cell dysfunction in atherosclerosis by adsorbing miR-637 to enhance WNT4 expression. Bioengineered. 2021;12:6759–70.
135. Dhahri W, Dussault S, Legare E, Rivard F, Desjarlais M, Mathieu R, et al. Reduced expression of microRNA-130a promotes endothelial cell senescence and age-dependent impairment of neovascularization. Aging (Albany NY). 2020;12:10180–93.
136. Huang Y, Liang B, Chen X. Exosomal circular RNA circ_0074673 regulates the proliferation, migration, and angiogenesis of human umbilical vein endothelial cells via the microRNA-1200/MEOX2 axis. Bioengineered. 2021;12:6782–92.
137. Qiu J, Chen R, Zhao L, Lian C, Liu Z, Zhu X, et al. Circular RNA circGSE1 promotes angiogenesis in ageing mice by targeting the miR-323-5p/NRP1 axis. Aging (Albany NY). 2022;14:3049–69.
138. Zou J, Liu KC, Wang WP, Xu Y. Circular RNA COL1A2 promotes angiogenesis via regulating miR-29b/VEGF axis in diabetic retinopathy. Life Sci. 2020;256: 117888.
139. Gulen MF, Samson N, Keller A, Schwabenland M, Liu C, Gluck S, et al. cGAS-STING drives ageing-related inflammation and neurodegeneration. Nature. 2023;620:374–80.
140. Zhao Y, Simon M, Seluanov A, Gorbunova V. DNA damage and repair in age-related inflammation. Nat Rev Immunol. 2023;23:75–89.

141. Barbu E, Popescu MR, Popescu AC, Balanescu SM. Inflammation as a precursor of atherothrombosis, diabetes and early vascular aging. Int J Mol Sci. 2022;23:963.
142. Zhang M, Zhu Y, Zhu J, Xie Y, Wu R, Zhong J, et al. circ_0086296 induced atherosclerotic lesions via the IFIT1/STAT1 feedback loop by sponging miR-576-3p. Cell Mol Biol Lett. 2022;27:80.
143. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017;377:1119–31.
144. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. N Engl J Med. 2019;381:2497–505.
145. Yu F, Zhang Y, Wang Z, Gong W, Zhang C. Hsa_circ_0030042 regulates abnormal autophagy and protects atherosclerotic plaque stability by targeting eIF4A3. Theranostics. 2021;11:5404–17.
146. Jiang Z, Jiang Y. Circular RNA CircPDS5B impairs angiogenesis following ischemic stroke through its interaction with hnRNPL to inactivate VEGF-A. Neurobiol Dis. 2023;181: 106080.
147. Xie M, Li X, Chen L, Zhang Y, Chen L, Hua H, et al. The crosstalks between vascular endothelial cells, vascular smooth muscle cells, and adventitial fibroblasts in vascular remodeling. Life Sci. 2025;361: 123319.
148. Wu M, Xun M, Chen Y. Circular RNAs: regulators of vascular smooth muscle cells in cardiovascular diseases. J Mol Med (Berl). 2022;100:519–35.
149. Csiszar A, Sosnowska D, Wang M, Lakatta EG, Sonntag WE, Ungvari Z. Age-associated proinflammatory secretory phenotype in vascular smooth muscle cells from the non-human primate *Macaca mulatta*: reversal by resveratrol treatment. J Gerontol A Biol Sci Med Sci. 2012;67:811–20.
150. Chi C, Li DJ, Jiang YJ, Tong J, Fu H, Wu YH, et al. Vascular smooth muscle cell senescence and age-related diseases: state of the art. Biochim Biophys Acta Mol Basis Dis. 2019;1865:1810–21.
151. Ma Y, Zheng B, Zhang XH, Nie ZY, Yu J, Zhang H, et al. circACTA2 mediates Ang II-induced VSMC senescence by modulation of the interaction of ILF3 with CDK4 mRNA. Aging (Albany NY). 2021;13:11610–28.
152. Wang S, Zhan J, Lin X, Wang Y, Wang Y, Liu Y. CircRNA-0077930 from hyperglycaemia-stimulated vascular endothelial cell exosomes regulates senescence in vascular smooth muscle cells. Cell Biochem Funct. 2020;38:1056–68.
153. Grootaert MOJ, Moulis M, Roth L, Martinet W, Vindis C, Bennett MR, et al. Vascular smooth muscle cell death, autophagy and senescence in atherosclerosis. Cardiovasc Res. 2018;114:622–34.
154. Kou L, Yang N, Dong B, Yang J, Song Y, Li Y, et al. Circular RNA testis-expressed 14 overexpression induces apoptosis and suppresses migration of ox-LDL-stimulated vascular smooth muscle cells via regulating the microRNA 6509–3p/thanatos-associated domain-containing apoptosis-associated protein 1 axis. Bioengineered. 2022;13:13150–61.
155. Wei J, Wang H, Zhao Q. Circular RNA suppression of vascular smooth muscle apoptosis through the miR-545-3p/CKAP4 axis during abdominal aortic aneurysm formation. Vasc Med. 2023;28:104–12.
156. Sun Y, Zhang S, Yue M, Li Y, Bi J, Liu H. Angiotensin II inhibits apoptosis of mouse aortic smooth muscle cells through regulating the circNRG-1/miR-193b-5p/NRG-1 axis. Cell Death Dis. 2019;10:362.
157. Newby AC, Zaltsman AB. Fibrous cap formation or destruction–the critical importance of vascular smooth muscle cell proliferation, migration and matrix formation. Cardiovasc Res. 1999;41:345–60.
158. Gallardo-Vara E, Ntokou A, Dave JM, Jovin DG, Saddouk FZ, Greif DM. Vascular pathobiology of pulmonary hypertension. J Heart Lung Transplant. 2023;42:544–52.
159. Jiang Y, Qian HY. Transcription factors: key regulatory targets of vascular smooth muscle cell in atherosclerosis. Mol Med. 2023;29:2.
160. Chen J, Cui L, Yuan J, Zhang Y, Sang H. Circular RNA WDR77 target FGF-2 to regulate vascular smooth muscle cells proliferation and migration by sponging miR-124. Biochem Biophys Res Commun. 2017;494:126–32.
161. Hall IF, Climent M, Quintavalle M, Farina FM, Schorn T, Zani S, et al. Circ_Lrp6, a circular RNA enriched in vascular smooth muscle cells, acts as a sponge regulating miRNA-145 function. Circ Res. 2019;124:498–510.
162. Hou X, Dai H, Zheng Y. Circular RNA hsa_circ_0008896 accelerates atherosclerosis by promoting the proliferation, migration and invasion of vascular smooth muscle cells via hsa-miR-633/CDC20B (cell division cycle 20B) axis. Bioengineered. 2022;13:5987–98.
163. Xu JY, Chang NB, Rong ZH, Li T, Xiao L, Yao QP, et al. circDiaph3 regulates rat vascular smooth muscle cell differentiation, proliferation, and migration. FASEB J. 2019;33:2659–68.
164. Yang L, Yang F, Zhao H, Wang M, Zhang Y. Circular RNA circCHFR facilitates the proliferation and migration of vascular smooth muscle via miR-370/FOXO1/Cyclin D1 pathway. Mol Ther Nucleic Acids. 2019;16:434–41.
165. Chin DD, Wang J, Mel de Fontenay M, Plotkin A, Magee GA, Chung EJ. Hydroxyapatite-binding micelles for the detection of vascular calcification in atherosclerosis. J Mater Chem B. 2019;7:6449–57.
166. Zhu L, Zhang N, Yan R, Yang W, Cong G, Yan N, et al. Hyperhomocysteinemia induces vascular calcification by activating the transcription factor RUNX2 via Kruppel-like factor 4 up-regulation in mice. J Biol Chem. 2019;294:19465–74.
167. Ryu J, Ahn Y, Kook H, Kim YK. The roles of non-coding RNAs in vascular calcification and opportunities as therapeutic targets. Pharmacol Ther. 2021;218: 107675.
168. Feng S, Qi Y, Xiao Z, Chen H, Liu S, Luo H, et al. CircHIPK3 relieves vascular calcification via mediating SIRT1/PGC-1α/MFN2 pathway by interacting with FUS. BMC Cardiovasc Disord. 2023;23:583.
169. Ryu J, Choe N, Kwon DH, Shin S, Lim YH, Yoon G, et al. Circular RNA circSmoc1-2 regulates vascular calcification by acting as a miR-874-3p sponge in vascular smooth muscle cells. Mol Ther Nucleic Acids. 2022;27:645–55.
170. Zhang WB, Qi YF, Xiao ZX, Chen H, Liu SH, Li ZZ, et al. CircHIPK3 regulates vascular smooth muscle cell calcification via the miR-106a-5p/MFN2 axis. J Cardiovasc Transl Res. 2022;15:1315–26.
171. Shi L, Li Y, Shi M, Li X, Li G, Cen J, et al. Hsa_circRNA_0008028 deficiency ameliorates high glucose-induced proliferation, calcification, and autophagy of vascular smooth muscle cells via miR-182-5p/TRIB3 axis. Oxid Med Cell Longev. 2022;2022:5142381.
172. Ma C, Gu R, Wang X, He S, Bai J, Zhang L, et al. circRNA CDR1as promotes pulmonary artery smooth muscle cell calcification by upregulating CAMK2D and CNN3 via sponging miR-7-5p. Mol Ther Nucleic Acids. 2020;22:530–41.
173. Bai Y, Zhang L, Zheng B, Zhang X, Zhang H, Zhao A, et al. circACTA2 inhibits NLRP3 inflammasome-mediated inflammation via interacting with NF-κB in vascular smooth muscle cells. Cell Mol Life Sci. 2023;80:229.
174. Gong X, Tian M, Cao N, Yang P, Xu Z, Zheng S, et al. Circular RNA circEsyt2 regulates vascular smooth muscle cell remodeling via splicing regulation. J Clin Invest. 2021;131: e147031.
175. Liu Y, Huang Y, Zhang X, Ma X, He X, Gan C, et al. CircZXDC promotes vascular smooth muscle cell transdifferentiation via regulating miRNA-125a-3p/ABCC6 in Moyamoya disease. Cells. 2022;11:3792.
176. Zou W, Lai M, Jiang Y, Mao L, Zhou W, Zhang S, et al. Exosome release delays senescence by disposing of obsolete biomolecules. Adv Sci (Weinh). 2023;10: e2204826.
177. Wang Y, Liu J, Ma J, Sun T, Zhou Q, Wang W, et al. Exosomal circRNAs: biogenesis, effect and application in human diseases. Mol Cancer. 2019;18:116.
178. Méndez-Barbero N, Gutiérrez-Muñoz C, Blanco-Colio LM. Cellular crosstalk between endothelial and smooth muscle cells in vascular wall remodeling. Int J Mol Sci. 2021;22:7284.
179. Yu H, Douglas HF, Wathieu D, Braun RA, Edomwande C, Lightell DJ Jr, et al. Diabetes is accompanied by secretion of pro-atherosclerotic exosomes from vascular smooth muscle cells. Cardiovasc Diabetol. 2023;22:112.
180. Dou YQ, Kong P, Li CL, Sun HX, Li WW, Yu Y, et al. Smooth muscle SIRT1 reprograms endothelial cells to suppress angiogenesis after ischemia. Theranostics. 2020;10:1197–212.
181. Lin X, He SQ, Shan SK, Xu F, Wu F, Li FX, et al. Endothelial cells derived extracellular vesicles promote diabetic arterial calcification via circ_0008362/miR-1251-5p/Runx2 axial. Cardiovasc Diabetol. 2024;23:369.
182. Ren J, Zhang Y. Targeting autophagy in aging and aging-related cardiovascular diseases. Trends Pharmacol Sci. 2018;39:1064–76.
183. Emanuelsson F, Benn M. LDL-cholesterol versus glucose in microvascular and macrovascular disease. Clin Chem. 2021;67:167–82.
184. Kong P, Yu Y, Wang L, Dou YQ, Zhang XH, Cui Y, et al. circ-Sirt1 controls NF-κB activation via sequence-specific interaction and enhancement of

SIRT1 expression by binding to miR-132/212 in vascular smooth muscle cells. Nucleic Acids Res. 2019;47:3580–93.
185. Xiong Y, Huang H, Chen F, Tang Y. CircDLGAP4 induces autophagy and improves endothelial cell dysfunction in atherosclerosis by targeting PTPN4 with miR-134-5p. Environ Toxicol. 2023;38:2952–66.
186. Kumarswamy R, Volkmann I, Beermann J, Napp LC, Jabs O, Bhayadia R, et al. Vascular importance of the miR-212/132 cluster. Eur Heart J. 2014;35:3224–31.
187. Chen Z, Wang R, Zhu Y, Huang Z, Yang X, Li Q, et al. A novel circular RNA, circSQSTM1, protects the endothelial function in atherosclerosis. Free Radic Biol Med. 2023;209:301–19.
188. Zhang L, Huang D, Wang Q, Shen D, Wang Y, Chen B, et al. MiR-132 inhibits expression of SIRT1 and induces pro-inflammatory processes of vascular endothelial inflammation through blockade of the SREBP-1c metabolic pathway. Cardiovasc Drugs Ther. 2014;28:303–11.
189. Tong X, Dang X, Liu D, Wang N, Li M, Han J, et al. Exosome-derived circ_0001785 delays atherogenesis through the ceRNA network mechanism of miR-513a-5p/TGFBR3. J Nanobiotechnology. 2023;21:362.
190. Kim KH, Lee MS. Autophagy–a key player in cellular and body metabolism. Nat Rev Endocrinol. 2014;10:322–37.
191. Ye B, Liang X, Zhao Y, Cai X, Wang Z, Lin S, et al. Hsa_circ_0007478 aggravates NLRP3 inflammasome activation and lipid metabolism imbalance in ox-LDL-stimulated macrophage via miR-765/EFNA3 axis. Chem Biol Interact. 2022;368: 110195.
192. Gao J, Cao H, Hu G, Wu Y, Xu Y, Cui H, et al. The mechanism and therapy of aortic aneurysms. Signal Transduct Target Ther. 2023;8:55.
193. Zhang L, Zhao Z, Quan X, Xie Z, Zhao J. Circ_0008285 silencing suppresses angiotensin II-induced vascular smooth muscle cell apoptosis in thoracic aortic aneurysm via miR-150-5p/BASP1 axis. Thorac Cancer. 2023;14:2158–67.
194. Wang H, Wang H, Liu K, Qin X. Circ_0000595 knockdown alleviates CoCl2-mediated effects in VSMCs by regulating the miR-582–3p/ADAM10 axis. Vascular. 2023;32:920.
195. Song H, Yang Y, Sun Y, Wei G, Zheng H, Chen Y, et al. Circular RNA Cdyl promotes abdominal aortic aneurysm formation by inducing M1 macrophage polarization and M1-type inflammation. Mol Ther. 2022;30:915–31.
196. Ma X, Xu J, Lu Q, Feng X, Liu J, Cui C, et al. Hsa_circ_0087352 promotes the inflammatory response of macrophages in abdominal aortic aneurysm by adsorbing hsa-miR-149-5p. Int Immunopharmacol. 2022;107: 108691.
197. Zhang Z, Sui R, Ge L, Xia D. CircRNA_0079586 and circRNA_RanGAP1 are involved in the pathogenesis of intracranial aneurysms rupture by regulating the expression of MPO. Sci Rep. 2021;11:19800.
198. Nordanstig J, Behrendt CA, Bradbury AW, de Borst GJ, Fowkes F, Golledge J, et al. Peripheral arterial disease (PAD)—a challenging manifestation of atherosclerosis. Prev Med. 2023;171: 107489.
199. Forsythe RO, Brownrigg J, Hinchliffe RJ. Peripheral arterial disease and revascularization of the diabetic foot. Diabetes Obes Metab. 2015;17:435–44.
200. Liao S, Lin X, Mo C. Integrated analysis of circRNA-miRNA-mRNA regulatory network identifies potential diagnostic biomarkers in diabetic foot ulcer. Noncoding RNA Res. 2020;5:116–24.
201. Dvorin EL, Wylie-Sears J, Kaushal S, Martin DP, Bischoff J. Quantitative evaluation of endothelial progenitors and cardiac valve endothelial cells: proliferation and differentiation on poly-glycolic acid/poly-4-hydroxybutyrate scaffold in response to vascular endothelial growth factor and transforming growth factor beta1. Tissue Eng. 2003;9:487–93.
202. Blakytny R, Jude EB. Altered molecular mechanisms of diabetic foot ulcers. Int J Low Extrem Wounds. 2009;8:95–104.
203. Falanga V. Wound healing and its impairment in the diabetic foot. Lancet. 2005;366:1736–43.
204. Zhang W, Sui Y. CircBPTF knockdown ameliorates high glucose-induced inflammatory injuries and oxidative stress by targeting the miR-384/LIN28B axis in human umbilical vein endothelial cells. Mol Cell Biochem. 2020;471:101–11.
205. Cao Y, Yuan G, Zhang Y, Lu R. High glucose-induced circHIPK3 downregulation mediates endothelial cell injury. Biochem Biophys Res Commun. 2018;507:362–8.
206. Marti-Pamies I, Thoonen R, Morley M, Graves L, Tamez J, Caplan A, et al. Brown adipose tissue and BMP3b decrease injury in cardiac ischemia-reperfusion. Circ Res. 2023;133:353–65.
207. Wen ZJ, Xin H, Wang YC, Liu HW, Gao YY, Zhang YF. Emerging roles of circRNAs in the pathological process of myocardial infarction. Mol Ther Nucleic Acids. 2021;26:828–48.
208. Yu L, Liang Y, Zhang M, Yang PC, Hinek A, Mao S. Extracellular vesicle-derived circCEBPZOS attenuates postmyocardial infarction remodeling by promoting angiogenesis via the miR-1178-3p/PDPK1 axis. Commun Biol. 2023;6:133.
209. Garikipati VNS, Verma SK, Cheng Z, Liang D, Truongcao MM, Cimini M, et al. Circular RNA CircFndc3b modulates cardiac repair after myocardial infarction via FUS/VEGF-A axis. Nat Commun. 2019;10:4317.
210. Si X, Zheng H, Wei G, Li M, Li W, Wang H, et al. circRNA Hipk3 induces cardiac regeneration after myocardial infarction in mice by binding to Notch1 and miR-133a. Mol Ther Nucleic Acids. 2020;21:636–55.
211. Chen L, Luo W, Zhang W, Chu H, Wang J, Dai X, et al. circDLPAG4/HECTD1 mediates ischaemia/reperfusion injury in endothelial cells via ER stress. RNA Biol. 2020;17:240–53.
212. Johansen MC, Chen J, Schneider ALC, Carlson J, Haight T, Lakshminarayan K, et al. Association between ischemic stroke subtype and stroke severity: the atherosclerosis risk in communities study. Neurology. 2023;101:e913–21.
213. Yang K, Zeng L, Ge A, Wang S, Zeng J, Yuan X, et al. A systematic review of the research progress of non-coding RNA in neuroinflammation and immune regulation in cerebral infarction/ischemia-reperfusion injury. Front Immunol. 2022;13: 930171.
214. Koton S, Pike JR, Johansen M, Knopman DS, Lakshminarayan K, Mosley T, et al. Association of ischemic stroke incidence, severity, and recurrence with dementia in the atherosclerosis risk in communities cohort study. JAMA Neurol. 2022;79:271–80.
215. Cheng L, Liu Z, Xia J. New insights into circRNA and its mechanisms in angiogenesis regulation in ischemic stroke: a biomarker and therapeutic target. Mol Biol Rep. 2023;50:829–40.
216. Wang X, Zhang S, Zhang Z, Zu J, Shi H, Yu L, et al. Increased plasma levels of circPTP4A2 and circTLK2 are associated with stroke injury. Ann Clin Transl Neurol. 2023;10:1481–92.
217. Wang XZ, Li S, Liu Y, Cui GY, Yan FL. Construction of circRNA-mediated immune-related ceRNA network and identification of circulating circRNAs as diagnostic biomarkers in acute ischemic stroke. J Inflamm Res. 2022;15:4087–104.
218. Yang Z, Huang C, Wen X, Liu W, Huang X, Li Y, et al. Circular RNA circFoxO3 attenuates blood-brain barrier damage by inducing autophagy during ischemia/reperfusion. Mol Ther. 2022;30:1275–87.
219. Li B, Xi W, Bai Y, Liu X, Zhang Y, Li L, et al. FTO-dependent m(6)A modification of Plpp3 in circSCMH1-regulated vascular repair and functional recovery following stroke. Nat Commun. 2023;14:489.
220. You T, Kuang F. CIRC_0008882 Stimulates PDE7A to suppress septic acute kidney injury progression by sponging MIR-155-5P. Shock. 2023;59:657–65.
221. Meng F, Chen Q, Gu S, Cui R, Ma Q, Cao R, et al. Inhibition of Circ-Snrk ameliorates apoptosis and inflammation in acute kidney injury by regulating the MAPK pathway. Ren Fail. 2022;44:672–81.
222. Ouyang X, He Z, Fang H, Zhang H, Yin Q, Hu L, et al. A protein encoded by circular ZNF609 RNA induces acute kidney injury by activating the AKT/mTOR-autophagy pathway. Mol Ther. 2023;31:1722–38.
223. Xiong M, Chen H, Fan Y, Jin M, Yang D, Chen Y, et al. Tubular Elabela-APJ axis attenuates ischemia-reperfusion induced acute kidney injury and the following AKI-CKD transition by protecting renal microcirculation. Theranostics. 2023;13:3387–401.
224. Kolling M, Seeger H, Haddad G, Kistler A, Nowak A, Faulhaber-Walter R, et al. The circular RNA ciRs-126 predicts survival in critically ill patients with acute kidney injury. Kidney Int Rep. 2018;3:1144–52.
225. Cao S, Huang Y, Dai Z, Liao Y, Zhang J, Wang L, et al. Circular RNA mmu_circ_0001295 from hypoxia pretreated adipose-derived mesenchymal stem cells (ADSCs) exosomes improves outcomes and inhibits sepsis-induced renal injury in a mouse model of sepsis. Bioengineered. 2022;13:6323–31.
226. Huang J, Chen M, Xu K, Zhou R, Zhang S, Zhao C. Microarray expression profile and functional analysis of circular RNAs in choroidal neovascularization. J Biomed Res. 2019;34:67–74.

227. Yu DY, Yu PK, Cringle SJ, Kang MH, Su EN. Functional and morphological characteristics of the retinal and choroidal vasculature. Prog Retin Eye Res. 2014;40:53–93.
228. Zhou RM, Shi LJ, Shan K, Sun YN, Wang SS, Zhang SJ, et al. Circular RNA-ZBTB44 regulates the development of choroidal neovascularization. Theranostics. 2020;10:3293–307.
229. Wu J, Chen J, Hu J, Yao M, Zhang M, Wan X, et al. CircRNA Uxs1/miR-335-5p/PGF axis regulates choroidal neovascularization via the mTOR/p70 S6k pathway. Transl Res. 2023;256:41–55.
230. Su Y, Yi Y, Li L, Chen C. circRNA-miRNA-mRNA network in age-related macular degeneration: from construction to identification. Exp Eye Res. 2021;203: 108427.
231. Lyssenko V, Vaag A. Genetics of diabetes-associated microvascular complications. Diabetologia. 2023;66:1601–13.
232. Yang J, Tan C, Wang Y, Zong T, Xie T, Yang Q, et al. The circRNA MKLN1 regulates autophagy in the development of diabetic retinopathy. Biochim Biophys Acta Mol Basis Dis. 2023;1869: 166839.
233. Shan K, Liu C, Liu BH, Chen X, Dong R, Liu X, et al. Circular noncoding RNA HIPK3 mediates retinal vascular dysfunction in diabetes mellitus. Circulation. 2017;136:1629–42.
234. Liu C, Yao MD, Li CP, Shan K, Yang H, Wang JJ, et al. Silencing of circular RNA-ZNF609 ameliorates vascular endothelial dysfunction. Theranostics. 2017;7:2863–77.
235. Ryu J, Kwon DH, Choe N, Shin S, Jeong G, Lim YH, et al. Characterization of circular RNAs in vascular smooth muscle cells with vascular calcification. Mol Ther Nucleic Acids. 2020;19:31–41.
236. Yao MD, Jiang Q, Ma Y, Zhu Y, Zhang QY, Shi ZH, et al. Targeting circular RNA-MET for anti-angiogenesis treatment via inhibiting endothelial tip cell specialization. Mol Ther. 2022;30:1252–64.
237. Guo J, Xiao F, Ren W, Zhu Y, Du Q, Li Q, et al. Circular ribonucleic acid circFTO promotes angiogenesis and impairs blood-retinal barrier via targeting the miR-128-3p/thioredoxin interacting protein axis in diabetic retinopathy. Front Mol Biosci. 2021;8: 685466.
238. Ye L, Guo H, Wang Y, Peng Y, Zhang Y, Li S, et al. Exosomal circEhmt1 released from hypoxia-pretreated pericytes regulates high glucose-induced microvascular dysfunction via the NFIA/NLRP3 pathway. Oxid Med Cell Longev. 2021;2021:8833098.
239. Liu C, Ge HM, Liu BH, Dong R, Shan K, Chen X, et al. Targeting pericyte-endothelial cell crosstalk by circular RNA-cPWWP2A inhibition aggravates diabetes-induced microvascular dysfunction. Proc Natl Acad Sci USA. 2019;116:7455–64.
240. Sun C, Ni M, Song B, Cao L. Circulating circular RNAs: novel biomarkers for heart failure. Front Pharmacol. 2020;11: 560537.
241. Wang Y, Zhao R, Liu W, Wang Z, Rong J, Long X, et al. Exosomal circHIPK3 released from hypoxia-pretreated cardiomyocytes regulates oxidative damage in cardiac microvascular endothelial cells via the miR-29a/IGF-1 pathway. Oxid Med Cell Longev. 2019;2019:7954657.
242. Luo W, Cheng D, Chen S, Wang L, Li Y, Ma X, et al. Genome-wide association analysis of meat quality traits in a porcine large white x Minzhu intercross population. Int J Biol Sci. 2012;8:580–95.
243. Made A, Bibi A, Garcia-Manteiga JM, Tascini AS, Piella SN, Tikhomirov R, et al. circRNA-miRNA-mRNA deregulated network in ischemic heart failure patients. Cells. 2023;12:2578.
244. Li B, Bai WW, Guo T, Tang ZY, Jing XJ, Shan TC, et al. Statins improve cardiac endothelial function to prevent heart failure with preserved ejection fraction through upregulating circRNA-RBCK1. Nat Commun. 2024;15:2953.
245. McCarthy CG, Wenceslau CF, Webb RC, Joe B. Novel contributors and mechanisms of cellular senescence in hypertension-associated premature vascular aging. Am J Hypertens. 2019;32:709–19.
246. Liu C, Li N, Li F, Deng W, Dai G, Tang Y, et al. CircHIPK2 facilitates phenotypic switching of vascular smooth muscle cells in hypertension. J Hum Hypertens. 2023;37:1021–7.
247. Xu H, Du S, Fang B, Li C, Jia X, Zheng S, et al. VSMC-specific EP4 deletion exacerbates angiotensin II-induced aortic dissection by increasing vascular inflammation and blood pressure. Proc Natl Acad Sci USA. 2019;116:8457–62.
248. He X, Bao X, Tao Z, Sun J, Zheng S, Zhong F, et al. The microarray identification circular RNA hsa_circ_0105015 up-regulated involving inflammation pathway in essential hypertension. J Clin Lab Anal. 2021;35: e23603.
249. He X, Tao Z, Zhang Z, He W, Xie Y, Zhang L. The potential role of RAAS-related hsa_circ_0122153 and hsa_circ_0025088 in essential hypertension. Clin Exp Hypertens. 2021;43:715–22.
250. Zhou M, Gao X, Zheng X, Luo J. Functions and clinical significance of circular RNAs in acute myeloid leukemia. Front Pharmacol. 2022;13:1010579.
251. Wang L, Shen C, Wang Y, Zou T, Zhu H, Lu X, et al. Identification of circular RNA Hsa_circ_0001879 and Hsa_circ_0004104 as novel biomarkers for coronary artery disease. Atherosclerosis. 2019;286:88–96.
252. Li JJ, Wang W, Wang XQ, He Y, Wang SS, Yan YX. A novel strategy of identifying circRNA biomarkers in cardiovascular disease by meta-analysis. J Cell Physiol. 2019;234:21601–12.
253. Hou C, Gu L, Guo Y, Zhou Y, Hua L, Chen J, et al. Association between circular RNA expression content and severity of coronary atherosclerosis in human coronary artery. J Clin Lab Anal. 2020;34: e23552.
254. Gorlach A, Holdenrieder S. Circular RNA maps paving the road to biomarker development? J Mol Med (Berl). 2017;95:1137–41.
255. Drula R, Braicu C, Neagoe IB. Current advances in circular RNA detection and investigation methods: are we running in circles? Wiley Interdiscip Rev RNA. 2024;15: e1850.
256. Dong J, Zeng Z, Huang Y, Chen C, Cheng Z, Zhu Q. Challenges and opportunities for circRNA identification and delivery. Crit Rev Biochem Mol Biol. 2023;58:19–35.
257. Mi Z, Zhongqiang C, Caiyun J, Yanan L, Jianhua W, Liang L. Circular RNA detection methods: a minireview. Talanta. 2022;238: 123066.
258. Shi Y, Shang J. Circular RNA expression profiling by microarray-a technical and practical perspective. Biomolecules. 2023;13:679.
259. Aquino-Jarquin G. CircRNA knockdown based on antisense strategies. Drug Discov Today. 2024;29: 104066.
260. Huang CK, Kafert-Kasting S, Thum T. Preclinical and clinical development of noncoding RNA therapeutics for cardiovascular disease. Circ Res. 2020;126:663–78.
261. Zhang Z, Huang Y, Guo A, Yang L. Research progress of circular RNA molecules in aging and age-related diseases. Ageing Res Rev. 2023;87: 101913.
262. Cheng C, Wang Y, Xue Q, Huang Y, Wang X, Liao F, et al. CircRnas in atherosclerosis, with special emphasis on the spongy effect of circRnas on miRnas. Cell Cycle. 2023;22:527–41.
263. Miao L, Yin RX, Zhang QH, Liao PJ, Wang Y, Nie RJ, et al. A novel circRNA-miRNA-mRNA network identifies circ-YOD1 as a biomarker for coronary artery disease. Sci Rep. 2019;9:18314.
264. Zhang W, He Y, Zhang Y. CircRNA in ocular neovascular diseases: fundamental mechanism and clinical potential. Pharmacol Res. 2023;197: 106946.
265. Li Y, Zhao J, Yu S, Wang Z, He X, Su Y, et al. Extracellular vesicles long RNA sequencing reveals abundant mRNA, circRNA, and lncRNA in human blood as potential biomarkers for cancer diagnosis. Clin Chem. 2019;65:798–808.
266. Xiong F, Mao R, Zhang L, Zhao R, Tan K, Liu C, et al. CircNPHP4 in monocyte-derived small extracellular vesicles controls heterogeneous adhesion in coronary heart atherosclerotic disease. Cell Death Dis. 2021;12:948.
267. Chen LL. The expanding regulatory mechanisms and cellular functions of circular RNAs. Nat Rev Mol Cell Biol. 2020;21:475–90.
268. Chen F, Yu X. Circ_0002331 interacts with ELAVL1 to improve ox-LDL-induced vascular endothelial cell dysfunction via regulating CCND2 mRNA stability. Cardiovasc Toxicol. 2024;24:625–36.
269. Wen C, Li B, Nie L, Mao L, Xia Y. Emerging roles of extracellular vesicle-delivered circular RNAs in atherosclerosis. Front Cell Dev Biol. 2022;10: 804247.
270. Xu H, Ni YQ, Liu YS. Mechanisms of action of MiRNAs and LncRNAs in extracellular vesicle in atherosclerosis. Front Cardiovasc Med. 2021;8: 733985.
271. Chen J, Li X, Liu H, Zhong D, Yin K, Li Y, et al. Bone marrow stromal cell-derived exosomal circular RNA improves diabetic foot ulcer wound healing by activating the nuclear factor erythroid 2-related factor 2 pathway and inhibiting ferroptosis. Diabet Med. 2023;40: e15031.
272. Chen W, Wang H, Zhu Z, Feng J, Chen L. Exosome-shuttled circSHOC2 from IPASs regulates neuronal autophagy and ameliorates ischemic brain injury via the miR-7670-3p/SIRT1 axis. Mol Ther Nucleic Acids. 2020;22:657–72.

273. Zaiou M. circRNAs signature as potential diagnostic and prognostic biomarker for diabetes mellitus and related cardiovascular complications. Cells. 2020;9:659.
274. Liu X, Wang Q, Zhao J, Chang H, Zhu R. Inflammation-related circRNA polymorphism and ischemic stroke prognosis. J Mol Neurosci. 2021;71:2126–33.
275. Huang Y, Cao H, Qi X, Guan C, Que S. Circular RNA hsa_circ_0000690 as a potential biomarker for diagnosis and prognosis of intracranial aneurysm: closely relating to the volume of hemorrhage. Brain Behav. 2023;13: e2929.
276. Schulte C, Barwari T, Joshi A, Theofilatos K, Zampetaki A, Barallobre-Barreiro J, et al. Comparative analysis of circulating noncoding RNAs versus protein biomarkers in the detection of myocardial injury. Circ Res. 2019;125:328–40.
277. Demaria M, Ohtani N, Youssef SA, Rodier F, Toussaint W, Mitchell JR, et al. An essential role for senescent cells in optimal wound healing through secretion of PDGF-AA. Dev Cell. 2014;31:722–33.
278. Samarawickrama PN, Zhang G, Zhu E, Dong X, Nisar A, Zhu H, et al. Clearance of senescent cells enhances skin wound healing in type 2 diabetic mice. Theranostics. 2024;14:5429–42.
279. Born E, Lipskaia L, Breau M, Houssaini A, Beaulieu D, Marcos E, et al. Eliminating senescent cells can promote pulmonary hypertension development and progression. Circulation. 2023;147:650–66.
280. Wang W, Zhang S, Xu L, Feng Y, Wu X, Zhang M, et al. Involvement of circHIPK3 in the pathogenesis of diabetic cardiomyopathy in mice. Diabetologia. 2021;64:681–92.
281. Deng Y, Wang J, Xie G, Zeng X, Li H. Circ-HIPK3 strengthens the effects of adrenaline in heart failure by MiR-17-3p-ADCY6 axis. Int J Biol Sci. 2019;15:2484–96.

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