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Review Article

Recent advances of miR-23 in human diseases and growth development

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ABSTRACT

MicroRNA (miRNA) is broadly manifested in eukaryotes and serves as a critical function in biological development and disease occurrence. With the rapid advancement of experimental research tools, researchers have discovered functional correlations among different miRNA isoforms and clusters within the same miRNA family. As a highly conserved member in the miR-23-27-24 cluster, miR-23 exhibits different isoforms and participates in various essential development. Although the miR-23-27-24 cluster has overlapping target sites, their differential expression can demonstrate independent biological functions. Furthermore, the untapped effects of miR-23 on organisms, whether as a functional cluster or a single regulator, has not been systematically elucidated yet. In this review article, we analyze the genomic location of miR-23 and its sequence variances among its isoforms or family members while summarizing its regulatory functions in metabolic diseases, immune responses, cardiovascular diseases, cancer, organ development as well as nervous system function. This review highlights the significant role of miR-23 as a biomarker for disease diagnosis and a key regulatory factor in pathogenesis, which can help us comprehend the diverse functions of miRNAs and provide a theoretical reference for the functional differences among miRNA isoforms.

1. Introduction

MicroRNAs (miRNAs), known as one kinds of non-coding RNAs, are essential for controlling post-transcriptional gene expression. There is a difference in miRNA length between animals and plants, with animals having a length range from 19 to 25 nucleotides in length. In the canonical miRNA biogenesis pathway of animals, miRNAs are initially transcribed from miRNA genes into primary miRNAs (pri-miRNAs) through RNA polymerase II. Subsequently, the nuclear RNase III Drosha-DGCR8 processes pri-miRNAs into precursor miRNAs (pre-miRNAs), which are approximately 70–90 base-long [1]. Soon afterwards, Exportin-5 transports pre-miRNAs from the nucleus to the cytoplasm, where they undergo Dicer-mediated cleavage to form mature miRNAs. These two complementary short fragments are designated as miRNA-5p and miRNA-3p. Within the regulatory mechanism of miRNAs, the mature miRNA associates with Argonaute proteins to form an RNA-induced silencing complex (RISC), which then interacts with target mRNAs in a complementary manner, leading to translational inhibition or degradation of mRNAs [2]. Interestingly, an alternative pathway for miRNA biogenesis exists, in which certain debranched introns, known as mirtrons, mimic the structural characteristics of pre-miRNAs and enter the miRNA processing pathway independently of Drosha-mediated cleavage [3]. Increasing evidence demonstrated that both the miRNA-5p and miRNA-3p strands of a mature miRNA can exert regulatory functions. Examples include miR-23–5p and miR-23–3p [4,5], as well as miR-184–5p and miR-184–3p [6,7]. Consequently, the regulatory function of miRNA is largely determined by the base sequence. It engages in the post-transcriptional regulation of genes within organisms through sequence binding to downstream targets. Furthermore, miRNA can also bind to circular RNA or long non-coding RNA to be involved in

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more regulatory pathways [8], affecting the growth, development and basic metabolism of organisms.

miR-23 is highly conserved across species and belongs to the miR-23-27-24 cluster but exists in different isoforms. In the human genome, this cluster is composed of the miR-23a cluster (miR-23a–27a–24–2) and the miR-23b cluster (miR-23b–27b–24–1). As shown in Fig. 1, the chromosomal locations of miR-23a and miR-23b are differ across species. The has-mir-23a/b are located in chromosomes 19 and 9 of the human genome, respectively, whereas mmu-mir-23a/b are found on chromosomes 8 and 13 in the mouse genome, respectively. Despite differences in their chromosomal locations and pre-miRNA sequences, their mature sequences exhibit significant conservation (Fig. 1A–D). Sometimes, miR-23, miR-27, and miR-24 can share a common target site [9], but their biological functions are distinct due to variations in expression regulation. Notably, despite only differing by one nucleotide outside the seed sequence region, miR-23a and miR-23b can still display dissimilar functional roles when sharing identical target predictions. Besides, miR-23 was further subdivided into miR-23–3p and miR-23–5p. By analyzing the mature sequence of miR-23 from different species, including fish, reptiles, and mammals, we found differences in conservation between miR-23–3p and miR-23–5p. The results displayed that miR-23–3p has higher conservation among species, while miR-23–5p undergoes more nucleotide shifting. Additionally, sequence alignment revealed that miR-23b-5p is more conserved than miR-23a-5p, whereas miR-23b-3p is less conserved than miR-23a-3p (Fig. 1E–H). Recently studies have analyzed genetic variants in miRNA genes, indicating that mutations may affect the substantial biosynthesis of miRNAs, leading to alterations in miRNA expression levels, 5p/3p miRNA balance, miRNA processing accuracy, and miRNA target recognition specificity [10]. The nucleotide shifting in miRNA genes can bring new functions or silence their functions, resulting in both loss-of-function mutations and gain-of-function mutations. The conservation analysis of miR-23 isoforms suggests that base mutations in the bases of miR-23a-5p and miR-23b-5p in higher animals may lead to broader involvement of their functions in regulating various diseases. Because mutations in the miRNA sequence bases may alter its secondary structure, expression levels, and target recognition [11]. To date, some studies have shown that abnormal expression levels of miR-23 enable it to serve as a potential biomarker for the diagnosis and progression of diseases such as metabolic and immune disorders [12,13]. Here, we review the current knowledge on miR-23 participates in the regulation of metabolism, immunity, cardiovascular disease, cancer, organ growth and development, and the nervous system through functional clusters or single regulatory factors.

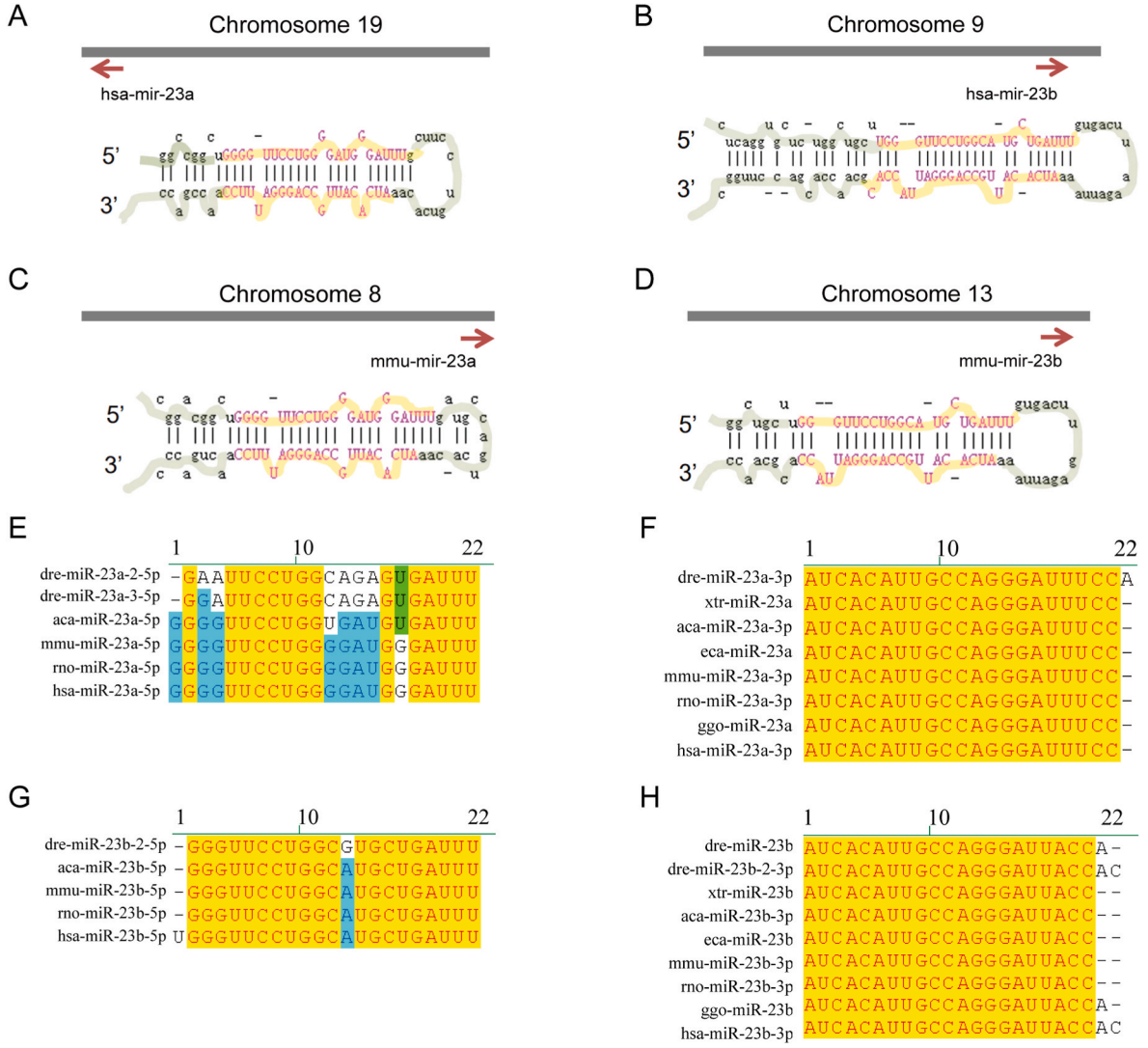

Fig. 1. Conservative analysis of miR-23 mature sequence. (A–D) The genome location of mir-23 in *Mus musculus*. (E–H) The miR-23a/b sequences alignment analysis of *Danio rerio*, *Xenopus tropicalis*, *Anolis carolinensis*, *Equus caballus*, *Mus musculus*, *Rattus norvegicus*, *Gorilla*, *Homo sapiens* were performed in Vector NTI software. The sequences data were obtained in NCBI and miRbase (https://mirbase.org/hairpin/MI0000079).

2. A regulatory biomarker and therapeutic target in metabolic diseases

miR-23 plays a regulatory role in metabolic diseases through its interaction with different target genes. Firstly, miR-23 can serve as a biomarker for the diagnosis of diabetes. By measuring the abnormal expression level of miR-23 in plasma, liver, and adipose tissue of patients, the development stage of diabetes can be assessed. For instance, as presented in Table 1, up-regulated expression of miR-23 has been witnessed in the plasma of patients with type 1 diabetes (T1DM) and type 2 diabetes mellitus (T2DM). Additionally, miR-23–3p is implicated in the occurrence and development of diabetes as a regulatory hub [14,15]. In diabetic complications, the expression level of miR-23–3p was observed to be decreased in the serum of Type 2 diabetic nephropathy (T2DN) patients (totally 112 cases), with levels being lower than both the control group and the simple diabetes group. Furthermore, this decrease was more significant with increasing severity of the disease [12,16]. Secondly, miR-23 not only impacts the proliferation of liver cells but also influences lipid metabolism in the liver. The functional studies in mice of different ages have identified the miR-23 functional cluster as a regulator of liver fibrosis. The liver is a crucial metabolic organ, direct injection of exogenous miR-23-27-24 cluster-specific inhibitor (named antagomirs) into neonatal mice promoted bile duct differentiation and reduced hepatocyte proliferation. Antagomirs can inhibit fibrosis development in newborn Alb/TGF-β1 transgenic mice, while injection in old mice restored the existing fibrosis [17]. Following the occurrence of liver fibrosis and the activation of hepatic stellate cells, the up-regulated expression of miR-23a-5p targets *phosphatase and tensin homolog* (PTEN) for degradation, thereby activating the PI3K/Akt/mTOR/Snail pathway, providing a new target for improving fibrosis [18]. Currently, the miR-23-27-24 cluster has also been identified as an emerging target in non-alcoholic fatty liver disease pathogenesis. Among them, miR-23a-3p can be mediated by isoglycyrrhizinate, and its expression is heightened in alcoholic liver disease. *In vivo* and *in vitro* experiments have indicated that it can combine with *peroxisome proliferator activated receptor-gamma coactivator 1-alpha* (PGC -1α) to advance lipid metabolism and lessen alcoholic liver injury [9,19].

In the depth study of fat metabolism, it has been discovered that miR-23–3p or functional clusters may play a significant role in the metabolism and energy balance of adipocytes. Using high-through sequencing technology, a micro-expression profile analysis of different cell lines revealed that the miR-23-27-24 cluster can be used as a biomarker to distinguish bone marrow mesenchymal stem cells from different sources of fat deposition [20]. Furthermore, overexpression of miR-23a-3p in Hep1-6 cells of db/db mice can up-regulate the expression of *sterol regulatory element binding protein-1* (SREBP-1) and *fatty acid synthase* (FAS), leading to an accumulation of triglycerides in hepatocytes. This also drives the proliferation of lipid-associated macrophages in obese adipose tissue and prevents diet-induced obesity metabolic dysfunction [21,22]. Additionally, patients who suffer from acute myocardial infarction often undergo systemic metabolic dysfunction. The expression levels of members within the miR-23-27-24 cluster are significantly increased in myocardial cells exhibiting this pathological manifestation. This cluster participate in endoplasmic reticulum stress within adipocytes and improve their endocrine function through protease targeting *ER degradation enhancing alpha-mannosidase like protein 3* (EDEM3) [23]. In terms of other metabolic regulation, it has been observed that miR-23 can readjust the biological ability of Chinese hamster ovary (CHO) cells. Proteomics analysis indicates that it can enhance oxidative metabolism and mitochondrial activity through multiple targets, thereby altering the balance of mammalian production cells and increasing productivity [24]. Furthermore, upregulation of miR-23–3p has been associated with metabolic syndrome in postmenopausal women. There exists a marked positive correlation among miR-23–3p, body composition, and indicators regarding metabolic disorders. Therefore, it could potentially serve as an accurate marker for identifying metabolic syndrome and its associated risk factors [25]. The aforementioned research has demonstrated that miR-23 is directly involved in the regulation of the development procedure of many metabolic diseases, such as liver fibrosis, obesity, and diabetes, and commonly, the expression level of miR-23 is unusually up-regulated. More regulatory studies have focused on miR-23–3p, while miR-23–5p has only been specifically studied in liver fibrosis (Table 1).

Table 1
The expression pattern of miR-23 as a biomarker in metabolic diseases.

Name	Disease	Position	Target gene	Expression pattern	Ref.
miR-23a-3p	Type 1 diabetes	Plasma	unverified	up	[14]
miR-23a	Type 2 diabetes mellitus	Plasma	unverified	up	[12]
miR-23a-3p	type 2 diabetic nephropathy	serum	unverified	down	[16]
miR-23b	Newborn	liver	*Smad4*	knockout	[17]
miR-23a-5p	Hepatic fibrosis	liver	*PTEN*	up	[18]
miR-23a-3p	Alcoholic liver disease	liver	*PGC-1α*	up	[19]
miR-23a	Adipose-derived stem cells	markers	unverified	up	[20]
miR-23a-3p	Hepatic lipid accumulation	liver	*Srebp-1c* *Fas*	up	[21]
miR-23-27-24	Obese	adipose macrophage	*Eif4ebp2*	down	[22]
miR-23-27-24	Acute myocardial infarction	adipose	unverified	up	[23]
miR-23	Re-programming cellular metabolism	CHO cell	unverified	down	[24]
miR-23a-3p	Metabolic syndrome	plasma	unverified	down	[25]

3. Immune response

3.1. Versatile regulator of immune cell function and polarization

A range of studies have indicated that the functions of immune cells are directly regulated by miR-23 (Fig. 2). The miR-23-27-24 cluster regulates multiple dimensions of T cell biology and is an essential regulatory factor in T cell differentiation and function, playing a key role in controlling type II immunity [26]. Follicular helper T cells are crucial for the generation of protective humoral immunity, and the miR-23-27-24 cluster coordinates the control of follicular helper T cells by targeting essential gene networks, thereby promoting humoral immunity [27]. Pioglitazone modulates macrophage polarization by targeting *interferon regulatory factor 1* (IRF1) and *Pknox1* through miR-23, transforming inflammatory M1 type macrophages into anti-inflammatory M2 type macrophages, significantly reducing renal macrophage infiltration, thus decreasing calcium oxalate crystal formation and renal inflammatory damage [28]. Furthermore, long non-coding RNA (lncRNA) *metastasis-associated lung adenocarcinoma transcript-1* (Malat1) associated with metabolism in macrophages competitively adsorbs miR-23–3p to regulate autophagy processes by releasing *lysosomal-associated membrane protein 1* (LAMP1) expression [29]. Langerhans cells (LCs), active skin-resident macrophages responsible for capturing and processing

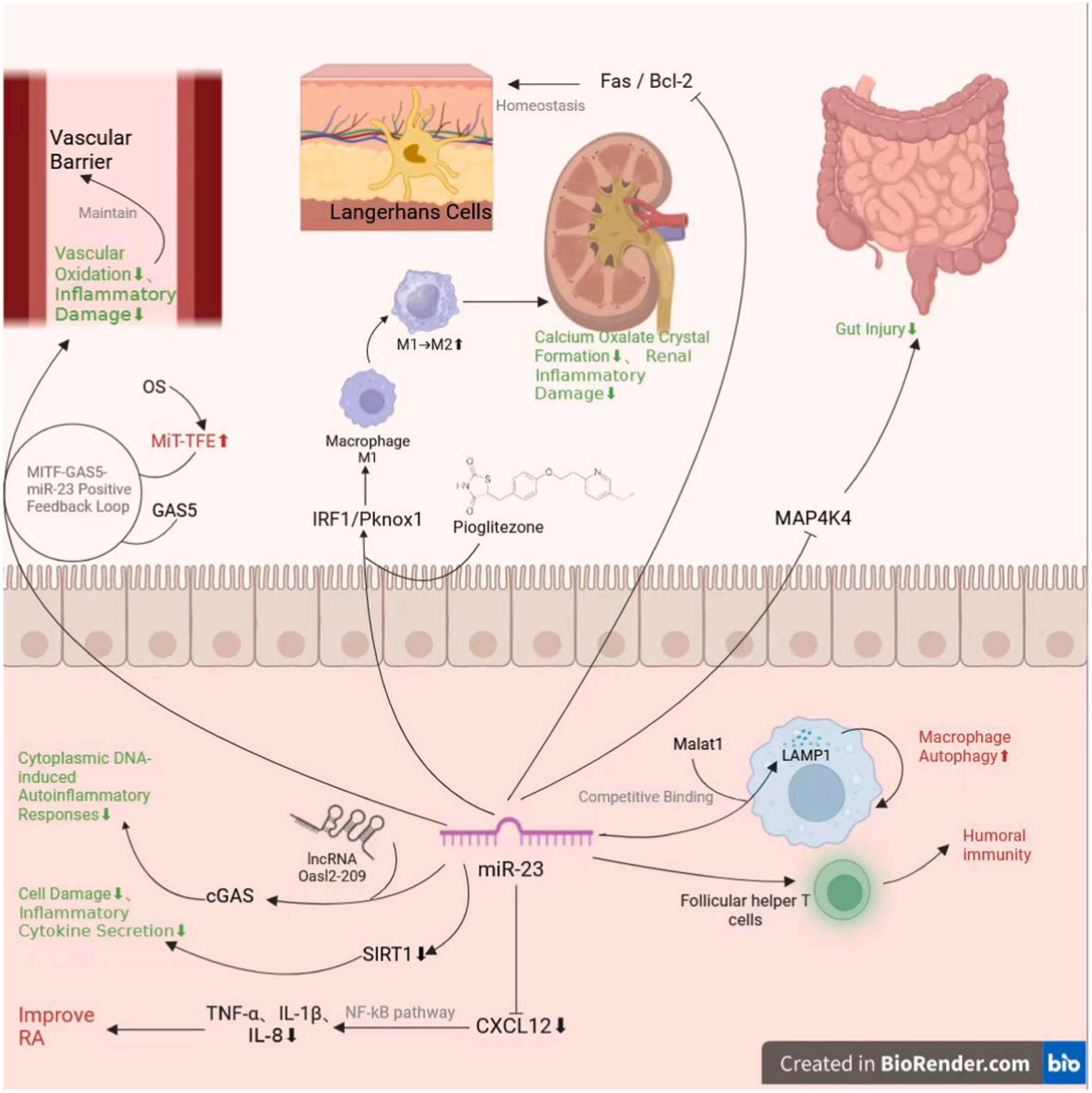

Fig. 2. The diagram depicts the complex functions and interactions of miR-23 in immunity. By affecting specialized immune cells such as Langerhans cells, T cells and Macrophage cells through various signaling mechanisms, miR-23 representing its contributions to the maintenance of the intestinal barrier, vascular barrier and Renal inflammatory. LncRNA *Malat1* and *Oasl2-209* displayed a competitive binding to miR-23 thereby involved in regulating immune processes. The overall color scheme of red and green highlights their different functional aspects. Bio-render was used to construct this networks (https://www.biorender.com/library).

antigens, are regulated by miR-23a through targeted regulation of phagocytosis and endocytosis molecules; specifically targeting *Fas* and the Bcl-2 family's pro-apoptotic molecules to promote homeostasis in bone marrow-derived LCs [30].

3.2. Biomarker and regulator in inflammatory and autoimmune disorders

Apart from directly regulating immune cells, miR-23 has also been established as a biomarker as well as a regulatory factor for inflammatory and autoimmune disorders, such as Rheumatoid arthritis (RA). Clinical researches have revealed that the expression levels of miR-23a were de-regulated in RA patient samples compared to healthy synovial tissue and serum samples, while miR-23–3p in serum was significantly upregulated by anti-TNFα/DMARDs combination therapy. Further investigation has demonstrated that miR-23 targets *C-X-C motif ligand 12* (CXCL12) to modulate the NF-κB signaling pathway, leading to decreased *TNF-α*, *IL-1β*, and *IL-8* expression levels which inhibit inflammation and enhance RA. Overexpression of *CXCL12* activates the NF-κB signaling pathway to promote inflammation [13,31]. Additionally, the overexpression of miR-23a/b via angomirs in mice results in an elevated susceptibility to herpes simplex virus type 1 (HSV-1) infection. The interaction between miR-23a/b and lncRNA *Oasl2-209* immediately controls the expression of *Cyclic GMP-AMP synthase* (cGAS), thereby suppressing cytoplasmic DNA-induced autoinflammatory responses and evoking innate immunity against infection [32]. Furthermore, miR-23 was found to be upregulated following phytosomal curcumin (PC) treatment and is involved in regulating PI3K/AKT1/NF-κB signaling pathways to enhance the immune modulation potential ability of Human dental pulp stem cells (hDPSCs) [33].

3.3. miR-23 regulates inflammatory reactions and anti-inflammatory roles in tissues injury

In other inflammatory reactions, miR-23 exerts regulatory effects

through various signaling pathways. Cardiac inflammation is a sophisticated biological and pathophysiological response that can result in heart damage and heart failure. Specific downregulation of miR-23 is observed in serum samples from patients with virus negative inflammatory dilated cardiomyopathy (152 patients with heart failure clinically) [34]. In a sepsis mouse model of systemic inflammatory disease induced by pathogen invasion, it was confirmed through chip PCR that the positive feedback loop, called MITF-GAS5-miR-23, which consists of miR-23 and the autophagy-related Mit-TFE transcription factor activated by oxidative stress (OS) and *GAS5*, can alleviate vascular oxidation and inflammatory damage in sepsis and maintain vascular barrier function [35]. Functional studies both *in vivo* and *in vitro* have implied that miR-23a can also improve sepsis-induced lung injury through the PTEN/PI3K/AKT/P53 pathway [36]. Moreover, miR-23a-3p is downregulated in the serum and lipopolysaccharide-treated HK-2 cells of patients with sepsis-associated acute kidney injury. The overexpression of miR-23a-3p inhibits the lipopolysaccharide-induced HK-2 cell proliferation inhibition, promotes apoptosis, and reduces cytokine production. miR-23a can alleviate the lipopolysaccharide-induced cell damage by targeting *wnt5a* to induce the Wnt/β-catenin pathway deactivation [37], as well as by directly binding *Rho associated coiled-coil containing protein kinase 1* (ROCK1) to inhibit its expression level. ROCK1 prevents the expression of *SIRT1* and stimulates the phosphorylation of the NF-κB signaling pathway, thereby inhibiting lipopolysaccharide-induced cell damage and inflammatory cytokine secretion [38].

The anti-inflammatory function of miR-23 was also observed in patients with obstructive sleep apnea (OSA) as well. Compared with 20 matched subjects with primary snoring (PS), the expression level of miR-23–3p was reduced and its target gene *TNF-α* was increased in OSA patients (40 samples), demonstrating that miR-23–3p directly targets the TLR/TNF-α pathway to cope with chronic intermittent hypoxia with re-oxygenation (IHR) injury [39]. Research has also revealed that exosomal miR-23a-3p from intestinal epithelial cells (IECs) knockdown intensified gut injury after intestinal ischemia/reperfusion (II/R) by targeting *MAP4K4* [40]. Additionally, in an established pig model of encephalopathy, it was observed that miR-23 was significantly upregulated within 6 h after hypoxic injury. The dynamic changes in expression patterns at different time points enable it to serve as a biomarker to distinguish and differentiate different states of inflammation, hypoxia, and inflammation sensitive hypoxia [41]. The above studies indicate that miR-23a has been popularly studied in immunity, and not only serve as a marker of inflammation but also improve related diseases by varying its expression levels, rendering it a potential therapeutic target.

4. miR-23 isoforms in cardiovascular disease: angiogenesis, apoptosis, and repair

4.1. Distinct roles of miR-23 isoforms in cardiovascular disease

Previous studies have discovered that miR-23 is a regulatory factor tightly linked with cardiovascular disease, which is essential for maintaining the balance of the vascular system and regulating the process of angiogenic. As early as 2011, a study discovered that miR-23-24-27 clusters are abundantly expressed in endothelial cells and highly vascularized tissues, targeting a multitude of endothelial junction proteins to protect vascular integrity through the functional regulation of endothelial cell junctions. Research has found that the two isoforms of miR-23 can facilitate angiogenesis and influence endothelial cell apoptosis by directly targeting *Sprouty2* [42,43], but they have different effects on endothelial cell function. Specifically, miR-23a mainly acts on permeability-related proteins, while miR-23b displays inhibition of angiogenesis by blocking cell cycle progression and reducing endothelial cell rejection signals [44,45]. This may be due to selective effects on their target proteins and differences in miRNA expression patterns, resulting in different functional types of miR-23 isoforms. miR-23 was increased in mouse laser-induced choroidal neovascularization models, and suppression of miR-23 reduced choroidal neovascularization development [46]. In fact, the pro- and anti-angiogenic factors derived from the retinal pigment epithelium are the primary cause of choroidal neovascularization pathogenesis. Therefore, the normal expression of *vascular endothelium growth factor* (VEGF) is crucial for maintaining the basic physiological state of this tissue, while current studies have shown that it can be regulated by miR-23. In another clinical study, miR-23 was found to be abundantly expressed in endothelial progenitor cells and plasma in over 300 patients with myocardial ischemia. The experiments performed *in vivo* also confirmed that the reduction of miR-23 can inhibit VEGF expression and endothelial progenitor cell activity, and then restore its blood flow in the ischemic limbs of mice [47]. It is worth noting that in the vascular injury repair study conducted on the arterial injury model of 57 BL/6 mice, miR-23a can be regulated by other transcription factors, such as *RUNX2* binding to the promoter of miR-23a to activate its expression. As a target gene of miR-23a, *TGF receptor type 2* (TGFR2) is subsequently downregulated, leading to an increase in the vitality of vascular smooth muscle cells (VSMCs) and a reduction in cell apoptosis [48]. Similarly, researchers have observed that miR-23 is also upregulated in the peripheral blood of patients with coronary heart disease (CHD). Overexpression of miR-23 can promote the proliferation of VSMCs and inhibit apoptosis through another target *BCL2L11* [49]. Among other upstream regulatory signals, angiotensin II and norepinephrine in the pro-hypertrophic signaling pathways can also regulate the proximal promoter of miRNA. Together, they can upregulate miR-23-24-27 cluster expression levels in hypertrophic cardiomyopathy and skeletal muscle atrophy [50]. Additionally, miR-23a was significantly reduced in human macular retinal pigment epithelial (RPE) cells, which derived from age-related macular degeneration (AMD) eyes. The overexpression of miR-23a could decrease H_2O_2-induced ARPE-19 cell death and apoptosis by targeting *Fas*, thus achieving the purpose of protecting RPE cells against oxidative damage [51].

4.2. Role of miR-23 in cardiomyocyte apoptosis and cardiac repair: mechanisms and therapeutic potential

The damage and apoptosis of myocardial cells are intricately associated with the precise regulation of miR-23a. It was confirmed that miR-23a increased in mediating the lysophosphatidic acid (LPA) -induced cardiomyocyte hypertrophy, *LPA1* was the direct target, however, miR-23a elevation can be restrained by PI3K inhibitors [52]. In models of cardiac dysfunction, researchers have revealed that miR-23 can regulate cell metabolism and reduce injury through two pathways: directly targeting *GLS* to restore glutamine metabolism and regulating *CX43* to modulate mitochondrial autophagy [53,54]. It has been shown that treatment for heart disease may involve the transplantation of bone marrow mesenchymal stem cells (MSCs), but their low survival rate limits their effectiveness. Overexpression of miR-23a can improve hypoxia/serum deprivation-induced MSC apoptosis and increase their survival rate; conversely, downregulation of miR-23 can exacerbate TNF-α-induced MSC apoptosis by regulating *caspase-7* [55,56]. Actually, miR-23 inhibitor therapy exhibited significant restoration of cardiac function in a rat model of myocardium lesions [57]. In another rat model of myocardial infarction, it was observed that the expression level of miR-23a in the heart is concerned with the modulation of VEGF derived from bone marrow mesenchymal stem cell (BM-MSC) therapy, improving cardiac function impairment caused by myocardial infarction through reducing cellular apoptosis [58]. It was also discovered that miRNA-23a-3p has a dose-dependent and time-dependent protective effect against high glucose-induced H9c2 cardiomyocyte injury [59]. These research findings indicate that in different models, the positive effects exerted by miRNA-23a on myocardial cell damage are dependent on dosage and intervention time. In cardiac pathology, myocardial cell apoptosis is an important aspect regulated by miR-23a. Additionally,

there are certain studies explicit that overexpression of miR-23a-3p can promote cell viability as well as repressed apoptosis. For instance, miR-23a inhibits cigarette smoke extract-induced pulmonary vascular endothelial cell apoptosis by targeting *DNAJB1*, thus alleviating pulmonary emphysema development; it also specifically binds to *p53* to stimulate its transcriptional activity in cardiomyocytes and promotes oxidative stress-induced cell apoptosis. In rats with myocardial ischemia-reperfusion injury, it can target *FoxO3a* to regulate cardiomyocyte growth, leading to increased cardiomyocyte apoptosis while the overexpression of miR-23 effectively reduced this phenomenon [60–62]. Furthermore, the proliferation of cardiac fibroblasts is also regulated by miR-23. Examination of right atrium tissue from 60 patients with atrial fibrillation sinus rhythm revealed that overexpression of miR-23 could target *transforming growth factor β1* (TGF-β1) in atrial fibrillation to enhance fibroblast proliferation and inhibit apoptosis [63]. The above research concludes that miR-23 can regulate the process of cardiac cell apoptosis through multiple target genes, including *DNAJB1*, *p53*, *FoxO3*, and *TGF-β1*, despite mouse models or human tissues.

4.3. *miR-23 regulates apoptosis, cognitive function and vascular integrity in cerebral hemorrhage, ischemia and hypertension*

Cerebral hemorrhage is a complex and deadly disease, and brain damage caused by cerebral hemorrhage or ischemia can greatly affect cognitive function. Up-regulated expression of miR-23a-3p has been identified both in the blood samples of acute cerebral hemorrhage patients and in a rat model of subarachnoid hemorrhage, leading to augmented apoptosis of cerebral vascular endothelial cells by suppressing the expression of the target gene *ZO-1*, as well as the formation of cerebral hematoma. Meanwhile, the suppression of miR-23a-3p can inhibit the apoptosis of cerebral microvascular endothelial cells by targeting *VCAN*, and thereafter promote cell activity and improve cognitive function after subarachnoid hemorrhage in rats [64,65]. On the other hand, the expression of miR-23a-5p in extracellular vesicles derived from M2 microglia is elevated after cerebral ischemia in mice, and it can advance white matter repair and brain function recovery after ischemic stroke by functioning on target gene *Olig3* [66]. Moreover, the experiment in mice confirmed that the treatment with M2 microglia-derived extracellular vesicles could reduce the area of cerebral infarction and edema. The vesicle-derived miR-23a-5p could directly target *TNF*, by down-regulating the expression of *MMP3* and *NF-κB p65* to regulate the integrity of hemoglobin and attenuates the destruction of the blood-brain barrier after cerebral ischemia [5]. In the realm of the research field of traditional Chinese medicine, acupuncture stimulation can down-regulate the expression of miR-23a-3p, thereby improving the neurological dysfunction stemming from intracerebral hemorrhage (ICH) in rats, alleviating inflammation, ferroptosis, and neuronal cell death [67].

In addition, miR-23 also participates in the regulation of hypertension. One of the common causes of hypertension is primary aldosteronism, and miR-23 can impact aldosterone production through the target gene *Twik associated acid sensitive K (+) channel 2* (TASK-2). The high expression of miR-23 can lead to a decrease in *TASK-2* activity, and then increase the expression of acute regulatory proteins and aldosterone synthase in steroid production [68]. Meanwhile, miR-23a belongs

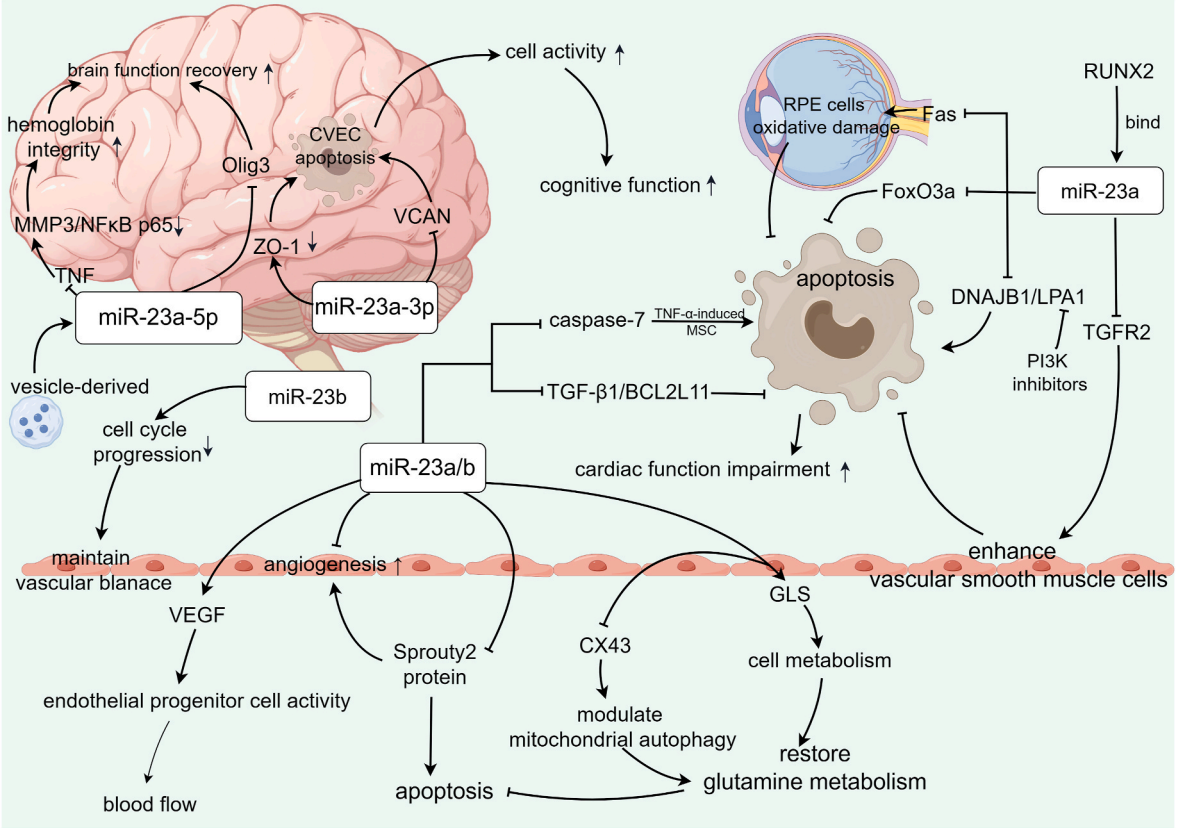

Fig. 3. The pivotal regulatory functions of miR-23 in brain and vascular cells. Specifically, the brain is mainly regulated by miR-23a-5p and miR-23a-3p, such as participating in CVEC apoptosis, and promoting brain recovery by enhancing cell activity and hemoglobin integrity. Moreover, miR-23a/b regulates cell cycle progression, maintaining vascular balance and fostering endothelial progenitor cell activity. In vascular cells, miR-23a/b inhibits apoptosis and stimulates vascular smooth muscle cell growth, promoting angiogenesis and endothelial function. Furthermore, it modulates mitochondrial autophagy and glutathione metabolism by targeting *Sprouty2*, ultimately restoring cellular metabolism. These intricate regulatory mechanisms underscore the significance of miR-23 in preserving brain function and vascular health. The figure was drawn by Figdraw (https://www.figdraw.com).

to one of the miRNAs related to the pathogenesis of salt sensitive hypertension. In hypertensive rats, it can regulate acid-base balance in the kidney through the target gene *sodium hydrogen exchanger 1* (NHE1) [69]. The above evidence fully demonstrates the role and importance of the miR-23 family in cardiovascular and cerebrovascular diseases (Fig. 3).

5. The complex functions of miR-23 in cancers

5.1. miR-23 in digestive system cancers: growth, metastasis, and immune regulation

Researchers have observed substantial alterations in miRNA profiles within the cancerous state, with certain miRNAs playing a causative role in tumorigenesis. For instance, in male Fisher rats fed a folate, methionine, and choline-deficient (FMD) diet and developing hepatocellular carcinoma (HCC), the expression pattern of miRNAs undergoes significant changes. In the context of digestive system-related cancers, there has been considerable focus on miR-23 in liver tissues. Investigation of miRNA profiles through *in vitro* microarray analysis has indicated that miR-23a/b are most probably derived from adipocytes and are upregulated. These miRNAs are then transferred to cancer cells via exosomes, thus promoting the growth and migration of HCC cells. This discovery highlights the complex role of miR-23 in the pathogenesis of liver cancer and suggests that it is a potential target for HCC therapy [70–72]. As a result, miR-23a can serve as a reliable biomarker for detecting HCC and making it a promising and reliable prognostic tool. Reliable biomarker screening is crucial for reducing the incidence and mortality rates of the disease. As mentioned earlier, miR-23 is a biomarker for T2DM. Not only that, it can also screen liver cirrhosis (LC) and HCC in patients with T2DM. Analysis of clinical serum samples from more than hundreds of patients with diabetes-associated LC and HCC revealed that, miR-23, identified through genetic screening, has been discovered as a key participant in both HCC and T2DM [73]. In HCC patients induced by hepatitis C virus genotype 2a Japanese fulminant hepatitis-1 (JFH-1), the low-expression differentially expressed gene *MSMO1* is a target of the miR-23 family. Meanwhile, miR-23a decreased in HCC patients infected with the hepatitis B virus, along with an increase in the target gene *CCL22*. The use of miR-23a inhibitors promotes tumor growth by upregulating target gene *CCL22* on the p65/miR-23a/CCL22 axis to regulate T cell recruitment in hepatitis B virus positive HCC [74,75]. Moreover, miR-23a-3p can promote the growth and metastasis of liver cancer cells and regulate chemotherapy sensitivity. It was subsequently found that miR-23a-3p promotes tumor growth by reducing the level of the target gene *procalcadherin 17* (PCDH17), promoting the transition of the HCC cell cycle [76]. As previously mentioned, miR-23 can act on immune cells to exert regulatory functions, which has also been confirmed in HCC. Abundant expression of miR-23a-3p was found in the exosomes of HCC cells treated with tetracycline, resulting in inhibition of *PTEN* mRNA level. The exosomes can effectively transmit the regulatory effects of miR-23 as a channel. Subsequently, it enhances the expression of phosphorylated *AKT* and *PD-L1* in macrophages and inhibits T cell function by functioning on the miR-23a-PTEN-AKT pathway [77]. In addition, upregulation of miR-23 expression has been detected in both colorectal cancer and gastric cancer patients, such as in serum exosomes, blood tissues, and gastric cancer tissues [78–80]. However, the opposite situation also occurs. The miR-23a-3p is downregulated in oral squamous cell carcinoma (OSCC) tissue, while its overexpression can inhibit the PTEN/PI3K/Akt signaling pathway by suppressing the target gene *Runx2*, thereby curbing the proliferation and metastasis of OSCC [81].

5.2. miR-23 in reproductive system cancers: growth, and metastasis and oncogenic regulation

In cancers related to the reproductive system, breast and ovarian cancers are common malignant tumors with high mortality rates in women. Research has found that all members of the miR-23-27-24 cluster are increased and act as oncogenes in breast cancer. It was noteworthy that the target gene *HIC1* of the miR-23 functional cluster also acts as a transcription inhibitor to negatively regulate their expression levels, forming a negative feedback loop. Specifically, overexpression of the miR-23 functional cluster accelerates tumor growth, whereas the recovery of *HIC1* can significantly inhibit tumor growth [82]. This study indicates that the regulation of miR-23 is not merely acting on target genes and downstream signaling pathways, but can also be directly regulated by the target gene, forming a regulatory feedback loop. Analysis and screening of miRNAs in 100 cases of breast cancer and 100 cases of normal adjacent samples also confirmed that miRNAs directly control the expression levels of *CFIm25*, subsequently regulating the expression of oncogenes and tumor proliferation [83]. In an in-depth exploration of the role of miR-23 in triple-negative breast cancer (TNBC), it has been found to regulate vitamin D receptor (VDR) activity, significantly influence breast cancer development, and modulate drug resistance during treatment [84,85]. Interestingly, in the tumor tissues of 50 patients with ovarian cancer (OC), researchers found that the expression levels of miR-23a/b were not identical in relation to the clinical pathological parameters and prognosis, suggesting there is a functional divergence among different family members. It is worth noting that the expression of miR-23a is negatively correlated with the expression of miR-23b. Specifically, the high expression of miR-23a and the low expression of miR-23b both determine the occurrence and progression of OC [86]. However, an in-depth study indicated that the decline of miR-23a-3p is crucial to the pathogenesis of OC. The lncRNA *LINC00909* is upregulated in the tumor and serum tissues and adsorbs miR-23a-3p, thereby promoting epithelial-mesenchymal transition (EMT) in OC cells, a crux process in cancer progression and metastasis [87]. In addition, miR-23a can regulate the PAK6-LIMK1 signaling pathway in prostate cancer, thereby significantly inhibiting cell migration and invasion. This result is verified from cancer cell lines, tumor tissues, as well as mouse models. The expression level of miR-23a displayed an abnormal decrease in this cancer cell lines, which is opposite to we mentioned previously in breast and ovarian cancers [88]. In general, although the abnormal expression of miR-23 in reproductive system-related cancers varies among different family members or displays cancers-independent, they can all impact on the development of cancer cells.

5.3. miR-23 in respiratory cancers: regulation of hypoxia-induced Oncogenesis, wnt/β-catenin pathway activation, and EMT process

The role of miR-23a in respiratory system-related cancers is increasingly being recognized by the scientific community. Research has shown that there is an inseparable functional link between tumor microenvironmental factors, particularly hypoxia, and miR-23a. By using microarray technology, researchers have revealed that miR-23a was induced under hypoxic circumstances and can ultimately act upon pro-apoptotic signals to promote tumor formation and oncogenic transformation [89]. Additionally, miR-23a can also be upregulated in human bronchial epithelial cells induced by radon exposure, leading to changes in cell cycle, oxidative stress, inflammation, oncogene suppression, and malignant transformation. However, further in-depth research is still limited [90]. Studies have indicated that members of the miR-23a functional cluster are overexpressed in tumors and associated with an increased risk of postoperative recurrence in non-small cell lung cancer (NSCLC) patients. The elevation of β-catenin and the methylation of the *p16* and *CDH13* promoters have also been linked to this over-expression. Furthermore, miR-23a activates the Wnt/β-catenin signaling pathway by targeting its inhibitors and promotes the silencing of tumor suppressor genes by affecting the expression of DNA methylation-related genes [91]. Similarly, miR-23 was decreased in respiratory system-related cancers, such as lung cancer. A clinical study

involving 109 cases of lung cancer tissue and 52 cases of normal tissue revealed that the expression of miR-23a is significantly reduced in HPV-positive lung cancer tissue. This phenomenon is closely associated with the epithelial-mesenchymal transition (EMT) process in lung cancer, a key step in cancer development and metastasis, involving changes in cell phenotype that confer invasive properties upon tumor cells [92].

5.4. miR-23 in other cancers: mechanisms of tumor progression, metastasis, and therapeutic potential

In the field of other cancers, the role of miR-23a is gradually being elucidated. Its characteristic is still elevated expression in cancer tissue, and its function is mostly to promote cell metastasis and proliferation, including co-regulation with lncRNA. Previous studies have found that miR-23 is among the differentially expressed miRNAs within 89 children cases with acute lymphoblastic leukemia (ALL) by high throughput sequencing, and *B-cell lymphoma 2* (BCL2) was its anti-apoptotic target [93]. The miR-23a assumes an essential part in the metabolic adaptation of leukemia cells. For example, over-expression of miR-23a reduces the expression of its target glutaminase *GLS*, induces mitochondrial dysfunction, and leads to leukemia cell death, while the expression of miR-23a is restrained by the *p65* subunit of *NF-κB*, confirms that miR-23a is a hub for regulating glutamine metabolism; besides, the miR-23a functional cluster can affect antioxidant response elements by targeting *KEAP1*, participates in oxidative phosphorylation of tumor cells, and affects mitochondrial activity [94,95]. Unlike the functional differentiation of miR-23a/miR-23b in OC, their expression levels are upregulated in radiation-induced thymic lymphoma model mice and share a common target gene *Fas*. Treatment by inhibitors of miR-23a/miR-23b can both boost cell death and apoptosis in lymphoma cells [96]. In addition, the expression levels of miR-23a-3p are also increased in abdominal aortic aneurysm (AAA), however, this observation is limited to clinical samples and lacks further investigation of its regulation mechanism [97]. Besides, miR-23a assumes a complex role in the pathogenesis and progression of glioma. Studies have shown that the expression level of miR-23a is elevated in postoperative glioma specimens of various grades, and this elevation is associated with the downregulation of *PTEN* expression, which may be related to the malignancy of the tumor. Furthermore, the expression changes of miR-23a are related to the angiogenesis of glioblastoma microvascular proliferation tissue. In this context, miR-23 is downregulated, while its target genes *ATP5A1* and *ATP5B* are highly expressed in endothelial cells. These discoveries imply that the expression and function of miR-23a in glioma might vary depending on the tissue type, revealing its potential role in tumor angiogenesis [98,99]. It has been discovered that in melanoma and pituitary tumors, miR-23a binds to lncRNA *Malat1* and *MEG3*. A downregulation of *Malat1* or *MEG3* leads to an increase in miR-23a levels, consequently promoting tumor cell proliferation, migration, and invasion [100,101]. It is important to note that the expression of miR-23a is reduced in osteosarcoma cells and tissues due to hypermethylation of its promoter region. However, demethylation treatment can restore miR-23a expression. Ectopic expression of miR-23a significantly inhibits the proliferation, migration, and invasion of osteosarcoma cells by targeting *RUNX2* and *CXCL12* in osteosarcoma, while overexpression of miR-23 can significantly inhibit the *uPA* expression and then repress the invasive ability of multiple myeloma cells under *in vitro* and *in vivo* conditions [102,103]. In brief, the expression of miR-23 is closely associated with the occurrence of a variety of cancers and tumors. Its abnormal expression can cause carcinogenesis of systems through different target genes (Table 2). The above studies shown that miR-23a/b can exhibit different expression patterns, such as in OC, or display a similar regulation role in thymic lymphoma. Meanwhile, even the members of the same miR-23 family may also exhibit opposite expression patterns, for example in OC. The reason for this phenomenon may be due to the complexity of the cancer development process. Therefore, as a potential biomarker, more standardized guidelines are needed. In summary, these studies provide a comprehensive generality of the complex regulatory networks involving miR-23a and miR-23b in tumor biology, emphasizing their potential as therapeutic targets for cancer treatment (Fig. 4).

6. Roles of miR-23 in organ development and functional regulation

6.1. Skeletal muscle differentiation, bone formation, and Osteoporosisv regulation

miRNAs were play important roles in tissues and functional development processes such as skeletal muscle, heart, and reproduction since been discovered. With the development of high-throughput sequencing technology, multitudinous development-related miRNAs have been identified, and miR-23 was one of them. Recently, the regulation of miR-

Table 2
Association analysis of expression patterns of miR-23 and its target genes in different cancers.

Disease	Name	Position	Target region	Validated target	miR- 23/ target	Ref.
hepatocellular carcinoma	miR-23a	serum exosomes and tumor tissue	3′UTR	von Hippel-Lindau/hypoxia-inducible factor axis	up/down	[70]
	miR-23	Huh7 cell	3′UTR	*MSMO1*	down/down	[74]
	miR-23a-3p	HCC tissue	3′UTR	*PCDH17*	up/down	[76]
	miR-23a	HBV tumor	3′UTR	*CCL22*	down/up	[75]
	miR-23a-3p	macrophage	unidentified	*PTEN*	up/down	[77]
gastric cancer	miR-23a/27a/24-2	gastric cancer tissue	3′UTR	*SOCS6*	up/down	[80]
oral squamous cell carcinoma	miR-23a-3p	oral squamous cell carcinoma tissue	3′UTR	*Runx2*	down/up	[81]
breast cancer	miR-23~27~24	breast cancer tissue	3′UTR	*HIC1*	up/down	[82]
	miR-23	breast cancer tissue	3′UTR	*CFIm25*	up/down	[83]
ovarian cancer	miR-23b-3p	ovarian cancer cell	unidentified	*ZNF839*、*LASP1*、*DEPDC1 and MRC2*	up/down	[87]
prostate cancer	miR-23a	tumor tissue	unidentified	*PAK6*	down/up	[88]
non-small cell lung cancer	miR-23a/27a/24-2	NSCLC cell	3′UTR	multiple suppressors of Wnt/β-catenin signaling	up/down	[91]
leukemic	miR-23	leukemic Jurkat cell	unidentified	*GLS*	down/up	[94]
thymic lymphoma	miR-23a	thymic lymphoma tissue sample	3′UTR	*Fas*	up/down	[96]
glioblastoma	miR-23	blood vessel	3′UTR	*ATP5A1/ATP5B*	down/up	[99]
melanoma	miR-23a	tumor tissue	3′UTR	lncRNA *Malat1*	down/up	[100]
pituitary tumors	miR-23b-3p	Pituitary tumor cell	unidentified	*FOXO4*	up/down	[101]
osteosarcoma	miR-23a	osteosarcoma cell and tissue	3′UTR	*RUNX2/CXCL12*	down/up	[102]
multiple myeloma	miR-23	intraosseous sample	3′UTR	*uPA*	down/up	[103]

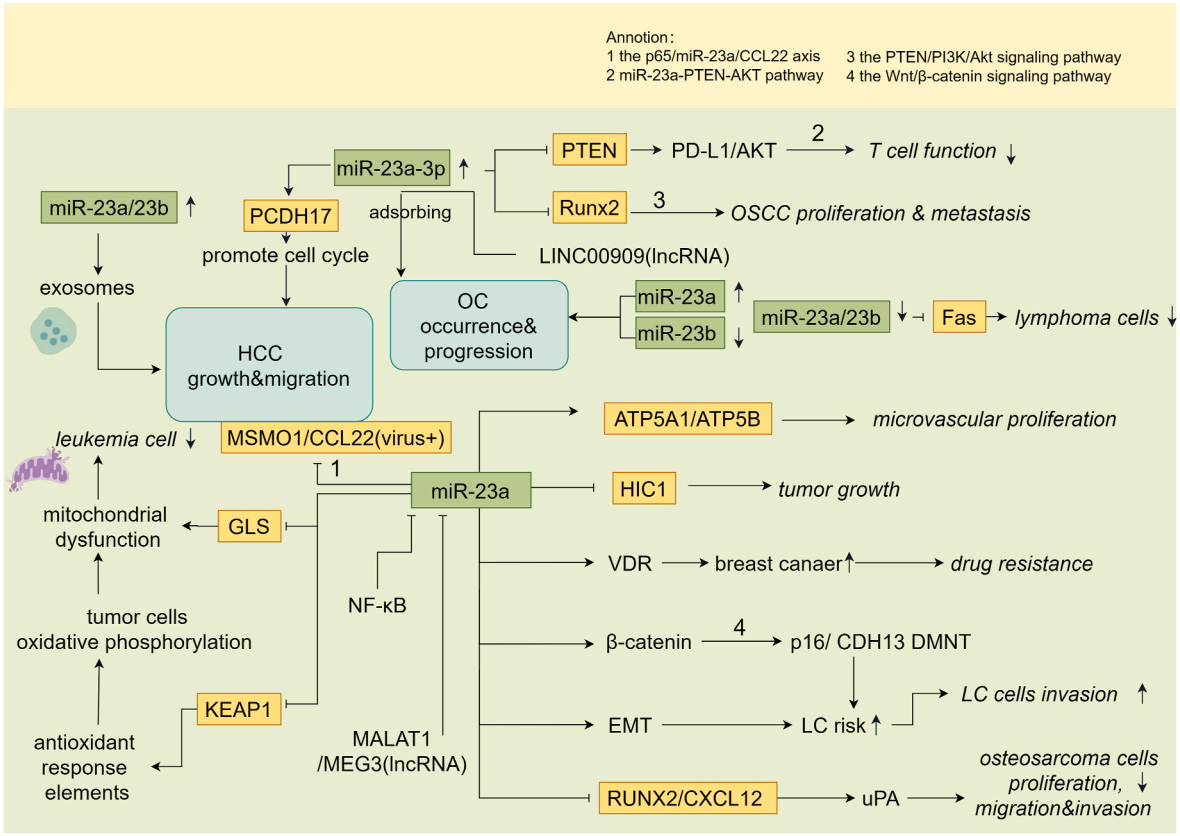

Fig. 4. The intricate signaling pathways and functional networks of miR-23 in tumor cell biology. miR-23a and miR-23b regulate various genes and pathways that affect tumor development and progression. Key pathways depicted include the p65/miR-23a/CCL22 axis, the PTEN/PI3K/Akt signaling pathway, the Wnt/β-catenin signaling pathway, and mitochondrial dysfunction mediated by *GLS*. The isoforms of miR-23 displayed different expression patterns in HCC, OC and lymphoma cells, but can all affect tumor growth. miR-23a undertake more roles in promotes tumor growth through multiple mechanisms, including its regulation of tumor proliferation and metastasis, cell cycle progression, and microvascular proliferation. The diagram also highlights the involvement of lncRNAs, such as LINC00909 *Malat1* and *MEG3*, in modulating miR-23a/23b function and tumor behavior. Moreover, the interactions between miR-23a/23b and genes like *NF-κB*, *β-catenin*, *p16/CDH13*, and *KEAP1* suggest their importance in tumor cell proliferation, invasion, and drug resistance. This figure was drawn by Figdraw (https://www.figdraw.com).

23 has been explored in the development of various organ, primarily involving the growth and development of bone tissue, teeth, heart, ovaries, and uterus, with experimental functional verification (Fig. 5).

The growth and development of organisms cannot be separated from pluripotent stem cells, which can differentiate into almost any type of biological cell. In the process of studying the cells reprogramming of horse, the expression level of miR-23 was decreased in induced pluripotent stem cells (iPSCs), which can recognize the breed characteristics of horses. Notably, miR-23a and miR-23b share a common target and have consistent functions, which can affect skeletal muscle differentiation by inhibiting *Thioredoxin reductase 1* (TrxR1) and participate in skeletal muscle generation [104–106]. In other species, such as pigeons and mice, miR-23 has also been found to be a hub for skeletal muscle development. However, the abundance of miR-23a functional clusters expressed in skeletal muscle is not stable enough, and mice lacking this functional cluster quickly downregulate the expression level of mature miR-23a [107,108]. Thus, the research on skeletal muscle development should also be paid attention to time constraints. Furthermore, miR-23 is also involved in the differentiation process of osteoclasts. miR-23a is highly expressed in osteoblasts, chondrocytes, and fibroblast cell lines. The experiments *in vitro* have demonstrated that it can control the progression of osteoblast and chondrocyte lineages and inhibit osteogenic differentiation by targeting the transcription factors *Runx2* and *Satb2* in mice. However, there existed no notable variance in the number of osteoblasts and osteoclasts between miR-23 transgenic and wild-type mice, along with their activity in the bone. Thus, it signifies that more precise experiments need to be designed to clarify the function of miR-23 in bone formation and maintenance [109,110]. Within the first 24 h of osteoclast formation, the miR-23 family displayed differential downregulation between undifferentiated cells and macrophages stimulated by receptor activator of nuclear factor-B ligand (RANKL). However, during human cartilage regeneration, the expression level of miR-23a-3p in small extracellular vesicles derived from umbilical cord mesenchymal stem cells was significantly ramped up, inhibiting the expression level of *PTEN*. Human hemoglobin combined with vesicles-derived miR-23a-3p overexpression through gel scaffold can repair and reconstruct bone through PTEN/AKT signal pathway, and promote osteogenesis and angiogenesis [111–113]. Furthermore, clinical analysis between osteoporosis patients and healthy controls revealed that overexpression of miR-23 can significantly reduce the expression levels of markers related to osteoblasts. miR-23 highly expressed in the pathological process of osteoporosis inhibits the osteogenic differentiation of human bone marrow mesenchymal stem cells, promotes bone resorption, and polarization of macrophage inflammation through the MAPK signaling pathway mediated by the target gene *MEF2C* [114–116]. Using a viral vector to transfect miR-23a-3p mimics or inhibitors into bone mesenchymal stem cells, and then injecting them into a steroid induced femoral head necrosis model, it was found that the inhibitor group could reduce the incidence of bone necrosis in the rat model [117]. This indicates that under normal physiological conditions of bone, miR-23 can maintain a stable low expression level, which is more beneficial for its growth and development.

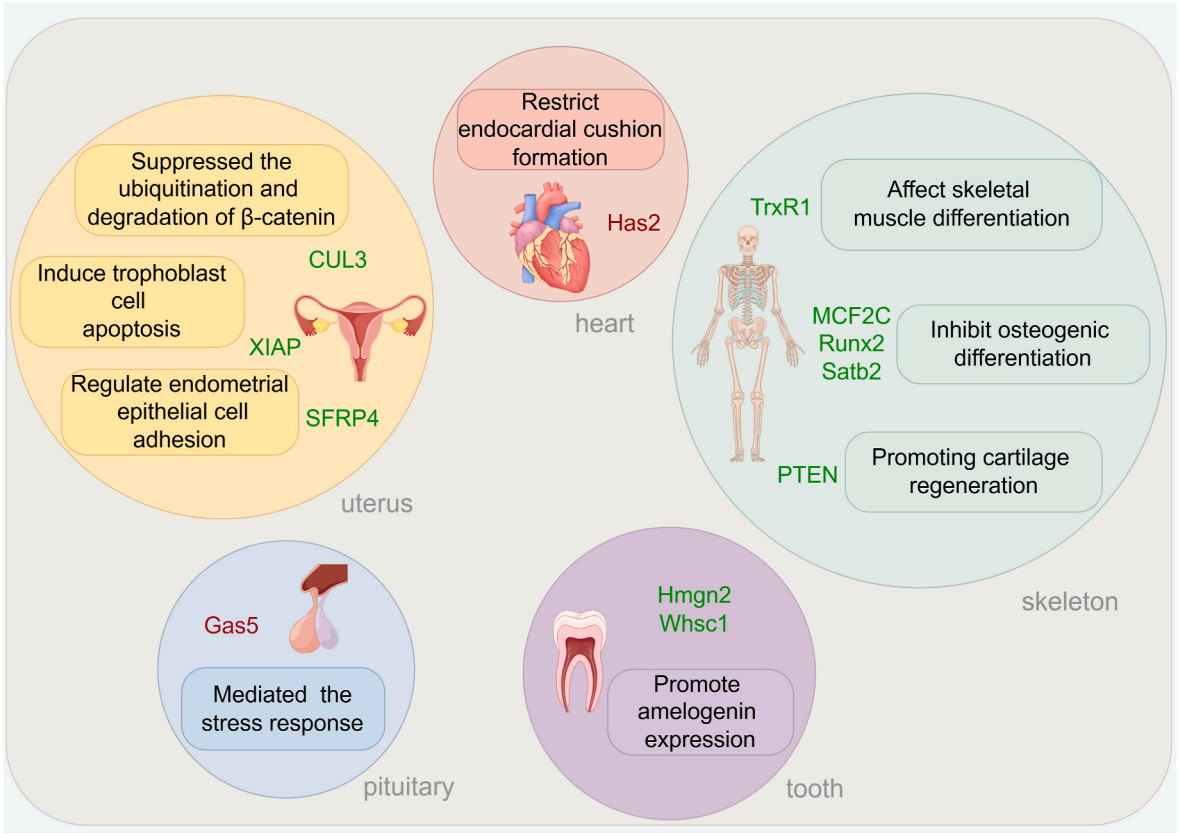

Fig. 5. Functional roles of miR-23 in organ development. This diagram illustrates the diverse functional roles of miR-23 in regulating various biological processes during organ development. Each circle represents the interaction genes and related pathways of miR-23 in different organs, which are displayed in yellow, red, green, purple, and blue for uterus, heart, skeleton, tooth, and pituitary tissues. The research on miR-23 in the skeleton is the most extensive among all the organs shown in the figure. This figure was drawn by Figdraw (https://www.figdraw.com).

6.2. Tooth development and cardiac formation

The isoforms of miR-23 exhibit consistent regulatory characteristics during tooth development. For instance, miR-23a/b are highly expressed in mature tooth germ, and they share common target genes, namely *high mobility group protein N2* (Hmgn2), and *Wolf-Hirschhorn syndrome candidate 1 gene* (Whsc1). The expression of miR-23 in mouse embryos leads to a decrease in *Hmgn2*, which subsequently boosts the amelogenin expression through multiple transcription factors, including *Pitx2*, *Dlx2*, *Lef-1*, and *FoxJ1* [118,119]. The studies provide evidences that the impact of miR-23 on organisms is long-lasting and can affect tooth growth during embryonic stages. Moreover, studies have discovered that miR-23 is involved in regulating the cardiac development in several species such as zebrafish, mice, and chickens. In zebrafish and mice, miR-23 within the embryonic heart is essential to confine endocardial cushion formation by inhibiting the expression of *hyaluronic acid synthase 2* (Has2) and extracellular hyaluronic acid production. Further evidence from chickens and mice has indicated that the over-expression of miR-23 during the early stages of myocardial formation hinders the generation of myocardium in the epicardial/transverse membrane [120, 121]. Myocardial cells differentiated from human pluripotent stem cells autonomously regulate during early development. miR-23 and lncRNA *Malat1* can regulate early expression of cardiac genes, thereby influencing cardiac development and contraction [122].

6.3. miR-23 in reproductive health, lactation, and spermatogenesis: insights from functional development and epigenetics

miR-23 is widely involved in the functional development of the ovaries, uterus, milk secretion, sperm, and testes. In a genome-wide analysis of ovarian miRNA expression profiles in humans, mice, cows, pigs, goats, and other mammals, the miR-23 functional cluster is upregulated in human ovarian follicles, showing species specificity, which assumes a part in follicular atresia and promotes granulosa cell apoptosis [123]. Lentivirus-mediated experiments *in vitro* also confirmed that overexpression of miR-23a could significantly induce trophoblast cell apoptosis through inhibiting X-linked inhibitor of apoptosis, and a substantial rise in the expression was also detected in placental tissue of pre-eclampsia patients, indicating that miR-23a may also be beneficial in the clinical treatment [124]. In addition to ovarian tissue, miR-23 can also regulate reproduction through other species. The expression of miR-23–3p is upregulated in endometrial epithelial cells of pregnant mice, and its expression level is positively correlated with pregnancy time. miR-23a-3p can suppress the ubiquitination and degradation of *β-catenin* by targeting *CUL3*, and the immunoprecipitation experiment confirmed that *CUL3* can directly interact with *β-catenin*. Therefore, overexpression of miR-23–3p is advantageous to endometrial receptivity and embryo implantation, enhancing the adhesion ability of trophoblast spheroids for normal conception. These results indicate that miR-23 may be a key regulator factor in endometrial epithelial adhesion and receptivity [4,125]. In the process of studying epigenetics, experts found that the regulatory function of miR-23 can also be transmitted through lactation behavior. For example, the change of stress response mediated by miR-23 can be inherited and intervened by methyl modulator during lactation. In the rats with the fetal malnutrition model, it has been confirmed that the expression of miR-23 was down-regulated in the rats with low birth weight, but the expression could be retrieved by methyl modulator after lactation. Moreover, by revealing the expression pattern characteristics of the miRNAs associated with donkey lactation, it was discovered that miR-23–3p can affect milk composition synthesis and

mammary gland development, which is achieved by targeting donkey mammary gland immunity and milk lipid, protein, and vitamin metabolism [126,127]. Additionally, miR-23 is also involved in the mechanism of spermatogenesis and can regulate male reproductive function. Retinoic acid (RA) signaling is fundamentally necessary for spermatogenesis and testis function. The miRNA expression profile of dysfunctional testis response induced by RA and Cyp26b1 inhibitors in dogs found that the miR-23 family was significantly downregulated [128]. The above study carried on in whole genome-wide sequencing analysis verified that miR-23 needs to be maintained at a certain expression level during the growth and development of organ tissues, and the lack of it may affect cell regeneration. Although overexpression of miR-23 can promote apoptosis, it can also promote embryo implantation in the reproductive progress, exhibiting a positive effect.

7. miR-23 in neural differentiation, neurogenesis, and neurological disorders: implications for epilepsy, spinal cord injury, and central nervous systemCNS tumor therapy

The development of the central nervous system is a complicated procedure involving extensively interacting factors, but it has been discovered nearly 20 years back that miR-23 has the ability to affect neural differentiation. NT2 cells originate from human embryonal tumor can differentiate into neuronal cells after treatment with all-trans-retinoic acid (ATRA). A basic helix-loop-helix transcriptional repressor, named *Hes1*, is an authentic target of miR-23. The decrease in miR-23 levels can lead to the accumulation of *Hes1* during retinal acid-induced neural differentiation in NT2 cells, which in turn affects neural differentiation. Subsequently, it was found that miR-23 is specifically expressed in astrocytes of the adult brain and is one of the miRNAs that are highly expressed in neurons during brain development. Interestingly, *Hes1* is also directly targeted by miR-124, and the knockdown of miR-124 levels mediated by locked nucleic acids is similar to the effect of miR-23 inhibition. The expression level of *Hes1* increases, ultimately hindering neuronal differentiation of P19 cells induced by the retinoic acid [129–131]. It indicates that the regulation of neural development by miR-23 is probably achieved through the combined action of other miRNAs. A recent study conducted experiments using neonatal cerebellum, PC12 cells, and newborn transgenic mouse cerebellum, observing that the levels of miR-23 declined in the cerebellum of transgenic mice with *α1ACT* overexpression, confirming its function on the neurogenesis and development promotion of dendritic synapses via MAPK signaling and cell death pathways, and controls the balance between cerebellar neuronal proliferation, differentiation, and cell death [132]. The above research confirms the impact of downregulation of miR-23 expression on the nervous system, while overexpression of miR-23 has a positive effect on the nervous system. For example, overexpressing miR-23a in mice was observed as the thickness of myelin increases, it can inhibit the expression of *lamin B1* to protect against leukodystrophy characterized by demyelination of the central nervous system. LncRNA *2700046G09Rik* was targeted by miR-23a to modulate phosphatase and tensin homolog and maintain normal myelin function [133,134]. Additionally, miR-23a-3p can be regulated in synapses or nearby nerve fibers induced by memory long-term potentiation (LTP) in adult SD rats. By conducting laser dissection and establishing miRNA expression profiling of nerve fibers induced by unilateral synaptic LTP, researchers found that upregulation of miR-23a-3p expression can promote the persistence of LTP by regulating the synaptic proteome [135].

In typical neurological diseases such as epilepsy and spinal cord injury, researchers have discovered that the expression differences of miR-23 are not consistent across different diseases. However, the isoforms of miR-23 exhibit similar expression patterns and functions within the same disease. For example, in a chronic temporal lobe epilepsy (TLE) rat model, the expression levels of miR-23a/b were upregulated and dysregulated with status epilepticus in the hippocampus. Clinical evidence has also confirmed elevated levels of miR-23a-3p in the blood tissues of refractory epilepsy patients. Researchers have investigated in more detail how miR-23 functions in brain learning and memory. Intracerebral injection of miR-23a-3p inhibitors can reduce brain damage and the related learning and memory deficits in valproic acid (VPA) resistance rat models. The influx drug transporter *organic anion-transporting polypeptide 2* (Oatp2), is a direct target of miR-23a-3p. The miR-23a-3p negatively regulates Oatp2 in the brain microvascular endothelial cells (BMECs), leading to reduced VPA uptake in intractable epilepsy [136,137]. Contrary to its expression pattern in epilepsy models, it was observed that miR-23a/b are down-regulated in the skeletal muscles of rats with spinal cord injury. Their targets comprise TGF- β Signal transduction which might impact changes in skeletal muscle mass and insulin responsiveness in paralyzed muscles caused by damage to upper motor neurons. However, this study lacks relevant experimental verification [138]. In the treatment of central nervous system tumors, radiation therapy is one of the most important clinical interventions, but it has significant side effects and can induce central nervous system toxicity. The miR-23a-3p was found downregulated in mice cortex, hippocampus, and neurons after brain radiation, while the expression of Bcl family members was upregulated, causing secondary DNA damage. On the contrary, intervention with overexpression of miR-23a-3p can protect nerves and attenuate the apoptotic process and neuronal cell death [139]. In addition, miR-23 is involved in the regulation of GABA synthase expression during retinal development in rats, and some cells in the ganglion cell layer can be labeled by miR-23 at different time points [140]. The research results presented above indicate that dysregulation of miR-23 expression levels is associated with neurological disorders. miR-23a-3p suppression in epilepsy can reduce brain damage, while its overexpression after brain radiation reduces neuronal apoptosis. It indicates that miR-23 exhibits different regulatory effects under different interventions, and whether it has a protective effect on the nervous system still needs to consider specific targets.

8. Conclusions

The miR-23 family is immensely conserved amidst diverse species and is capable of exerting a regulatory influence on organisms independently, either as a functional cluster or as a solitary regulator. In this review, the functions of miR-23 and its isoforms in metabolic disorders, cardiovascular and cerebrovascular diseases, cancer, as well as growth and development were elaborated in detail. Regulatory networks encompassing target genes were established, and the functional disparities among the isoforms were compared. Through this review, it can be concluded that miR-23 possesses the following characteristics. Firstly, it can serve as a biomarker for various diseases. Existing studies have indicated that miR-23 demonstrates a certain expression in different tissues, which can be detected, and diseased tissues can also have an impact on their expression level. In the regulation of cancer pathogenesis, a significant number of studies have detected an elevated expression of miR-23 in pathological tissues derived from clinical samples. Additionally, cerebral hemorrhage can also stimulate the upregulation of miR-23 expression. Secondly, treatments developed in the context of miR-23 could ameliorate the progression of the disease. Given the abnormal expression level of miR-23 in the disease, the most straightforward strategy is to intervene with inhibitors or overexpression, and the research findings also reveal a favorable therapeutic effect. Thirdly, different isoforms of miR-23 can target common target genes, yet their functions can vary. This implies that even if the miRNA seed sequence (2-8 nt) is highly conserved, other base mutations can have a decisive impact on the function, even if the difference amounts to only 1 base. This also validates the powerful fine-tuning role of miRNA on the side. Additionally, it should be noted that certain genes as targets of miR-23 have distinct specific action pathways in different diseases, such as *Fas*, and *PTEN*. Meanwhile, miR-23 can interact with the sequence of lncRNA *Malat1*, and participate in regulating macrophages during inflammation (Fig. 2), tumor cell proliferation (Fig. 4), and heart

cell development (Fig. 5). This suggests that miR-23 may have diverse regulatory functions through its fixed combination, making it a central regulatory hub for these processes. This necessitates us to consider the expression status of some key targets in different diseases when developing miR-23 therapies. In conclusion, this review accentuates the vast research potential of miR-23 in different diseases, which holds great significance for the study of the mechanism of action of miRNA isoforms, thus possessing important clinical application prospects.

CRediT authorship contribution statement

Xu Qian: Writing – original draft, Visualization. **Yongwei Jiang:** Writing – original draft. **Yadi Yang:** Visualization, Software. **Yukun Zhang:** Visualization, Investigation. **Na Xu:** Investigation. **Bin Xu:** Supervision. **Ke Pei:** Validation, Supervision, Investigation. **Zhi Yu:** Supervision, Funding acquisition. **Wei Wu:** Writing – review & editing, Supervision, Project administration.

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Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

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Abbreviations

AAA, abdominal aortic aneurysm; ALL, acute lymphoblastic leukemia; AMD, aged-related macular degeneration; ATRA, all-trans-retinoic acid; BCL2, B-cell lymphoma 2; BMECs, brain microvascular endothelial cells; BM-MSC, bone marrow mesenchymal stem cell; cGAS, Cyclic GMP-AMP synthase; CHD, coronary heart disease; CXCL12, C-X-C motif ligand 12; EMT, epithelial-mesenchymal transition; FAS, fatty acid synthase; FMD, folate, methionine, and choline-deficient; Has2, hyaluronic acid synthase 2; HCC, hepatocellular carcinoma; hDPSCs, Human dental pulp stem cells; Hmgn2, high mobility group protein N2; HSV-1, herpes simplex virus type 1; ICH, intracerebral hemorrhage; IECs, intestinal epithelial cells; IHR, intermittent hypoxia with re-oxygenation; II/R, intestinal ischemia/reperfusion; iPSCs, induced pluripotent stem cells; IRF1, interferon regulatory factor 1; JFH-1, hepatitis C virus; LAMP1, lysosomal-associated membrane protein 1; LC, liver cirrhosis; LCs, Langerhans cells; lncRNA, long non-coding RNA; LTP, long-term potentiation; Malat1, metastasis-associated lung adenocarcinoma transcript-1; miRNA, microRNA; MSCs, mesenchymal stem cells; NHE1, sodium hydrogen exchanger 1; NSCLC, non-small cell lung cancer; Oatp2, organic anion-transporting polypeptide 2; OC, ovarian cancer; OS, oxidative stress; OSA, obstructive sleep apnea; OSCC, oral squamous cell carcinoma; PC, phytosomal curcumin; PCDH17, procalcadherin 17; PGC-1α, peroxisome proliferator activated receptor-γ coactivator 1-α; pre-miRNAs, precursor miRNAs; pri-miRNAs, primary miRNAs; PTEN, phosphatase and tensin homolog; RA, Rheumatoid arthritis; RA, Retinoic acid; RANKL, nuclear factor B ligand receptor activator; RISC, RNA-induced silencing complex; ROCK1, Rho associated coiled-coil containing protein kinase 1; RPE, retinal pigment epithelial; SREBP-1, sterol regulatory element binding protein-1; T2DN, Type 2 diabetic nephropathy; TASK-2, Twik associated acid sensitive K (+) channel 2; TGFR2, TGF receptor type 2; TGF-β1, transforming growth factor β1; TLE, temporal lobe epilepsy; TNBC, TLE; TrxR1, Thioredoxin reductase 1; VDR, vitamin D receptor; VPA, valproic acid; VSMCs, vascular smooth muscle cells; Whsc1, Wolf-Hirschhorn syndrome candidate 1.

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