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Review paper

miR-135b: An emerging player in cardio-cerebrovascular diseases

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ABSTRACT

miR-135 is a highly conserved miRNA in mammals and includes miR-135a and miR-135b. Recent studies have shown that miR-135b is a key regulatory factor in cardio-cerebrovascular diseases. It is involved in regulating the pathological process of myocardial infarction, myocardial ischemia/reperfusion injury, cardiac hypertrophy, atrial fibrillation, diabetic cardiomyopathy, atherosclerosis, pulmonary hypertension, cerebral ischemia/reperfusion injury, Parkinson's disease, and Alzheimer's disease. Obviously, miR-135b is an emerging player in cardio-cerebrovascular diseases and is expected to be an important target for the treatment of cardio-cerebrovascular diseases. However, the crucial role of miR-135b in cardio-cerebrovascular diseases and its underlying mechanism of action has not been reviewed. Therefore, in this review, we aimed to comprehensively summarize the role of miR-135b and the signaling pathway mediated by miR-135b in cardio-cerebrovascular diseases. Drugs targeting miR-135b for the treatment of diseases and related patents, highlighting the importance of this target and its utility as a therapeutic target for cardio-cerebrovascular diseases, have been discussed.

1. Introduction

MicroRNAs (miRNAs), a class of single-stranded non-coding RNA, have several intracellular regulatory roles [1]. They bind to the complementary target gene mRNA, inhibiting translation or degradation of the corresponding mRNA [2–4]. Previous studies have shown that one-third of human genes are directly regulated by miRNAs. As a member of miRNAs, miR-135b has attracted much attention due to its extensive involvement in human diseases. It is a conserved miRNA located in the *LEM domain containing 1 (LEMD1)* gene locus and is divided into miR-135b-3p and miR-135b-5p according to the origin of the 5′ and 3′ sequence of the pre-miRNA stem-loop structure [5]. miR-135b can affect biological processes associated with the cardiovascular and cerebrovascular systems by regulating the expression of multiple genes by promoting angiogenesis [6], regulating cardiomyocyte apoptosis and mediating inflammatory responses [7]. Therefore, abnormal expression of miR-135b may indicate the occurrence and development of cardiovascular and cerebrovascular diseases (CCDs) and is a potential therapeutic target.

Herein, we provide a comprehensive overview of the role of miR-135b in CCDs and the signaling pathways regulated by it. We discuss drugs targeting miR-135b and related patents. The review attempts to provide a reference for future prevention and treatment of clinical CCDs.

2. Biological characteristics of miR-135 and its family members

The miR-135 family comprises miR-135a (including miR-135A1 and miR-135A2) and miR-135b. miR-135a is transcribed from miR-135A1 (3p21.2) and miR-135A2 (12q23.1) [8]. miR-135b is transcribed from miR-135B (1q32.1) [8]. Fig. 1 illustrates the process of formation of miR-135a and miR-135b (Fig. 1). miR-135a and miR-135b are expressed in several tissues and organs, including the heart, brain, liver, spleen, lung, and kidney [9]. miR-135b critically affects the onset and progression of CCDs by modulating multiple signaling pathways.

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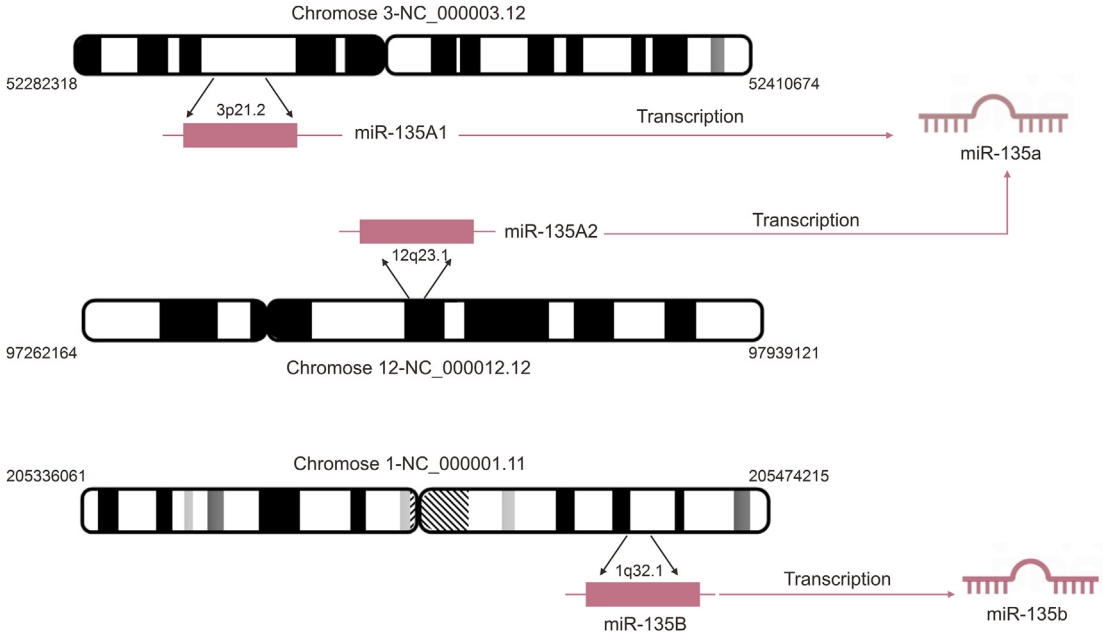

Fig. 1. Processes underlying the formation of miR-135a and miR-135b. miR-135a is transcribed from miR-135A1 (3p21.2) and miR-135A2 (12q23.1). miR-135b is transcribed from miR-135B (1q32.1).

3. Signaling pathways related to miR-135b

3.1. miR-135b-mediated downstream signaling pathways in CCDs

miR-135b directly suppresses multiple downstream targets and affects crucial signaling pathways. Through the inhibition of downstream targets, numerous studies have demonstrated the involvement of miR-135b in CCDs. In heart diseases, miR-135b can ameliorate myocardial infarction (MI) by inhibiting the NOD-like receptor thermal protein domain associated protein 3 (NLRP3)/cysteine-requiring aspartate protease-1 (caspase-1)/interleukin (IL)-1β pathway [10] and aggravate myocardial ischemia-reperfusion (MI/R) injury by inhibiting glutathione peroxidase 4 (GPX4) expression [11]. It improves pathological cardiac hypertrophy by inhibiting the expression of calcium voltage-gated channel subunit alpha1C (CACNA1C) [12] and promotes the formation of atherosclerotic plaque by inhibiting myocyte enhancer factor 2C (MEF2C) or erythropoietin receptor (EPOR) [13,14]. In brain diseases, it can alleviate the progression of cerebral ischemia/reperfusion (CI/R) injury, cerebral injury in cerebral palsy (CP) rats, post-stroke cognitive impairment, Parkinson's disease (PD), and Alzheimer's disease (AD) by inhibiting glycogen synthase kinase-3beta (GSK-3β), S100 calcium-binding protein B (S100B), mineralocorticoid receptor (NR3C2), forkhead Box O1 (FOXO1), and β-site APP-cleaving enzyme 1 (BACE1) [15–19]. In vascular diseases, it has been shown to promote angiogenesis in hypoxia/reoxygenation-exposed trophoblastic cells by inhibiting the expression of phosphoinositide-3-kinase regulatory subunit 2 (PIK3R2) [20]. Moreover, it has been observed to enhance angiogenesis in diabetic retinopathy mice by suppressing the expression of Von Hipp-el-Lindau protein (VHL) [21]. The above miR-135b-mediated signaling pathways in CCDs are summarized in Table 1 [10–21]. Taken together, miR-135b-mediated signaling pathways are indispensable in the development of CCDs.

3.2. Upstream factors regulating miR-135b in CCDs

ceRNAs constitute the most extensively studied mechanism of miR-135b regulation. Numerous reports have demonstrated that miR-135b is regulated by various long non-coding RNAs (lncRNAs) [22–28] (Fig. 2A) and circular RNAs (circRNAs) [29–39] (Fig. 2B). In CCDs, the lncSNHG14/miR-135b-5p/karyopherin subunit alpha 4 (KPNA4) [22] and lncMALAT1/miR-135b-5p/glycoprotein non-metastatic melanoma protein B (GPNMB) [23] axes can promote the progression of PD. The circRNA RSF1/miR-135b-5p/histone deacetylase 1 (HDAC1) axis alleviates atherosclerosis [33]. The circRNA CDR1as/miR-135b/heme oxygenase 1 (HMOX1) axis promotes heart failure [40]. In addition, various proteins [41–49] (Fig. 2C), such as specificity protein-1 (SP-1), paired box protein 6 (PAX6), IL-6/signal transducer and activator of transcription 3 (STAT3), IL-1α/β, Wnt, phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT), heat shock factor 1 (HSF1), and Yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ), can also regulate miR-135b. Notably, these regulatory factors exert complex and important effects on the expression of miR-135b in CCDs (Table 2) [22,23,33,40–42], suggesting the significance of these regulatory mechanisms for understanding disease development and implementing relevant treatment strategies.

4. The role of miR-135b in CCDs

4.1. MI

Endothelial cell injury can induce MI [50–52]. Yang et al. [41] reported that miR-135b was involved in the process of human umbilical vein endothelial cell (HUVEC) injury. In hypoxia-induced HUVECs, with the extension in the duration of hypoxia exposure (12 h, 24 h, 48 h, 72 h), miR-135b expression decreased gradually, and that of SP-1 increased. However, when SP-1 expression was inhibited, miR-135b level increased, while the expression of

Table 1
Downstream targets of direct inhibition by miR-135b in cardiovascular and cerebrovascular diseases (CCDs).

microRNA	Disease type	Expression	Target gene	Main function	Refs.
miR-135b	Myocardial infarction	↓	Caspase-1	Protective effect	[10]
miR-135b-3p	Myocardial ischemia/reperfusion injury	↑	GPX4	Damage effect	[11]
miR-135b	Cardiac hypertrophy	↓	CACNA1C	Protective effect	[12]
miR-135b-5p	Atherosclerosis	↑	MEF2C	Damage effect	[13]
miR-135b	Atherosclerosis	–	EPOR	Damage effect	[14]
miR-135b-5p	Cerebral ischemia/reperfusion injury	↓	GSK-3β	Protective effect	[15]
miR-135b	Cerebral palsy	↓	S100B	Protective effect	[16]
miR-135b	Parkinson's disease	↓	FOXO1	Protective effect	[17]
miR-135b	Alzheimer's disease	↓	BACE1	Protective effect	[18]
miR-135b-5p	Post-stroke cognitive impairment	↓	NR3C2	Protective effect	[19]
miR-135b-5p	Preeclampsia	↓	PIK3R2	Protective effect	[20]
miR-135b-5p	Diabetic retinopathy	–	VHL	Protective effect	[21]

Caspase-1: cysteine-requiring aspartate protease-1; GPX4: glutathione peroxidase 4; CACNA1C: calcium voltage-gated channel subunit alpha1C; MEF2C: myocyte enhancer factor 2c; EPOR: erythropoietin receptor; GSK-3β: glycogen synthase kinase-3beta; SB100: S100 calcium binding protein B; FOXO1: forkhead Box O1; BACE1: β-site APP-cleaving enzyme 1; NR3C2: mineralocorticoid receptor; PIK3R2: phosphoinositide-3-kinase regulatory subunit 2; VHL: Von Hipp-el-Lindau.

hypoxia inducible factor-1alpha (HIF-1α) was decreased. In this case, hypoxia-induced apoptosis and inflammation of HUVECs were significantly inhibited, and cell proliferation was enhanced. This finding reveals the importance of the SP-1/miR-135b/HIF-1α pathway in hypoxia-induced vascular endothelial injury [41] (Fig. 3A). Li et al. [10] elucidated the mechanism of miR-135b action in MI. miR-135b expression in the infarct margin region of mice with MI decreased. Upon miR-135b overexpression, miR-135b inhibited the occurrence of cardiomyocyte pyroptosis by inhibiting the NLRP3/caspase-1/IL-1β inflammatory response pathway, further exhibiting cardioprotective effects during MI [10] (Fig. 3B). Xiang et al. [7] and Hu et al. [53] verified the findings of Li et al. and confirmed the major role of miR-135b in the pathogenesis of MI. However, Mao et al. [54] reported that the lncGAS5/miR-135b axis is a better potential therapeutic target for MI than miR-135b alone. To this, Bai et al. [55] reported that there are currently no studies confirming that lncGAS5 can regulate miR-135b in MI. Therefore, more studies are required in the future to prove whether the lncGAS5/miR-135b axis is a better potential therapeutic target for MI than miR-135b alone. To summarize, miR-135b is a star factor in the treatment of MI, which is expected to become a new hope for the treatment of MI.

4.2. MI/R injury

The irreversible damage to the heart caused by MI/R has garnered widespread attention [56–58]. After MI/R injury, the upregulation of miR-135b-3p expression in cardiac tissue is a crucial cause of cardiac tissue damage. The knockdown of miR-135b-3p expression in rats with MI/R injury decreased the degree of cardiac injury [11]. Mechanistic studies have reported that miR-135b-3p induces ferroptosis by downregulating the expression of ferroptosis-related gene GPX4, further aggravating MI/R injury [11] (Fig. 4A). The study provided novel ideas and techniques for the

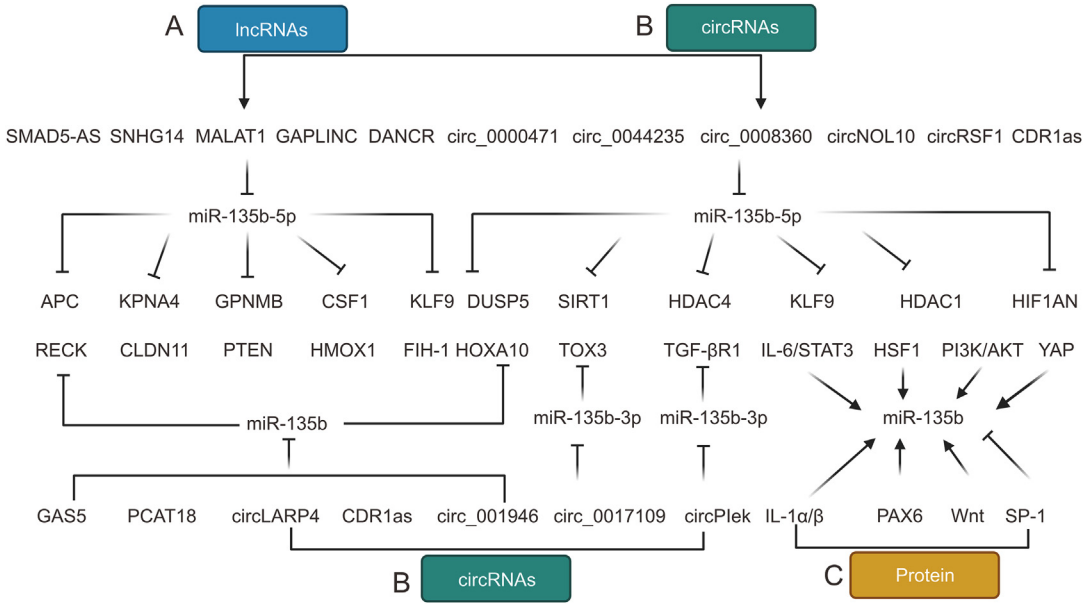

Fig. 2. miR-135b-mediated signaling pathways. (A) long non-coding RNAs (lncRNAs)/miR-135b/mRNA regulatory mechanisms. (B) circular RNAs (circRNAs)/miR-135b/mRNA regulatory mechanisms. (C) Upstream proteins that regulate miR-135b. APC: adenomatous polyposis coli; KPNA4: karyopherin subunit alpha 4; GPNMB: glycoprotein non-metastatic melanoma protein B; CSF1: colony-stimulating factor 1; KLF9: Krüppel-like factor 9; RECK: reversion-inducing cysteine-rich protein with Kazal motifs; CLDN11: claudin-11; PTEN: phosphatase and tension homolog; HMOX1: heme oxygenase 1; FIH-1: factor inhibiting hypoxia-inducible factor-1; DUSP5: dual specificity phosphatase 5; SIRT1: sirtuin 1; HDAC4: histone deacetylation 4; HDAC1: histone deacetylase 1; HIF1AN: hypoxia-inducible factor 1-alpha subunit suppressor; HOXA10: homeobox A10; TOX3: TOX high mobility group box family member 3; TGF-βR1: transforming growth factor-beta receptor-1; IL: interleukin; SIRT3: sirtuin 3; HSF1: heat shock factor 1; PI3K/AKT: phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT); YAP: Yes-associated protein; PAX6: paired box protein 6; SP-1: specificity protein-1.

Table 2
Upstream factors regulating miR-135b in cardiovascular and cerebrovascular diseases (CCDs).

Upstream factors	miR-135b expression	Signaling pathway	Main function	Refs.
lncRNA SNHG14	Inhibits expression	SNHG14/miR-135b-5p/KPNA4	The SNHG14/miR-135b-5p/KPNA4 axis promotes Parkinson's disease progression	[22]
lncRNA MALAT1	Inhibits expression	MALAT1/miR-135b-5p/GPNMB	The MALAT1/miR-135b-5p/GPNMB axis promotes Parkinson's disease progression	[23]
circRNA RSF	Inhibits expression	RSF1/miR-135b-5p/HDAC1	The RSF1/miR-135b-5p/HDAC1 axis inhibits atherosclerosis progression	[33]
CDR1as	Inhibits expression	CDR1as/miR-135b/HMOX1	The CDR1as/miR-135b/HMOX1 axis promotes heart failure progression	[40]
SP-1	Inhibits expression	SP-1/miR-135b/HIF-1α	The SP-1/miR-135b/HIF-1α axis mediates hypoxia-induced vascular endothelial injury	[41]
PAX6	Promotes expression	PAX6/miR-135b/TGF-β/BMP	PAX6 activates miR-135b to inhibit TGF-β and BMP signaling and promotes the differentiation of human embryonic stem cells toward a neural phenotype	[42]

KPNA4: karyopherin subunit alpha 4; GPNMB: glycoprotein non-metastatic melanoma protein B; HDAC1: histone deacetylase 1; HMOX1: heme oxygenase 1; HIF-1α: hypoxia inducible factor-1alpha; SP-1: specificity protein-1; PAX6: paired box protein 6; TGF-β: transforming growth factor beta; BMP: bone morphogenetic protein.

treatment of MI/R injury. However, this study has only explored the relationship between miR-135b and MI/R injury. Therefore, further studies are required to confirm its effect.

4.3. Cardiac hypertrophy

Cardiac hypertrophy is a major cause of arrhythmia and heart failure [59–61]. miR-135b expression is reduced in angiotensin II and transverse aortic constriction-induced cardiac hypertrophy models [12]. When miR-135b is overexpressed, the marker genes of hypertrophy, including atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and beta-myosin heavy chain (β-MHC) concomitantly decrease [12]. Mechanistic studies have shown that miR-135b decreases cardiac hypertrophy is associated with suppressed CACNA1C expression [12]. Chen et al. [28] reviewed the aforementioned studies and confirmed the crucial role of miR-135b in cardiac hypertrophy. However, the upstream molecules regulating miR-135b remain unclear. lncGAS5 can promote the apoptosis of cardiomyocytes and exacerbate pathological cardiac hypertrophy by targeting miR-135b [28]. The report by Chen et al. [28] that lncGAS5 may be an upstream regulator of miR-135b is consistent with the presence of the lncGAS5/miR-135b axis in the MI model proposed by Mao et al. [54]. Therefore, based on the prediction of Chen et al. [28] and Mao et al. [54], we hypothesize that lncGAS5 is an upstream regulator of miR-135b. However, this hypothesis merits further experimental confirmation. Nevertheless, this provides further directions and ideas for subsequent studies on miR-135b.

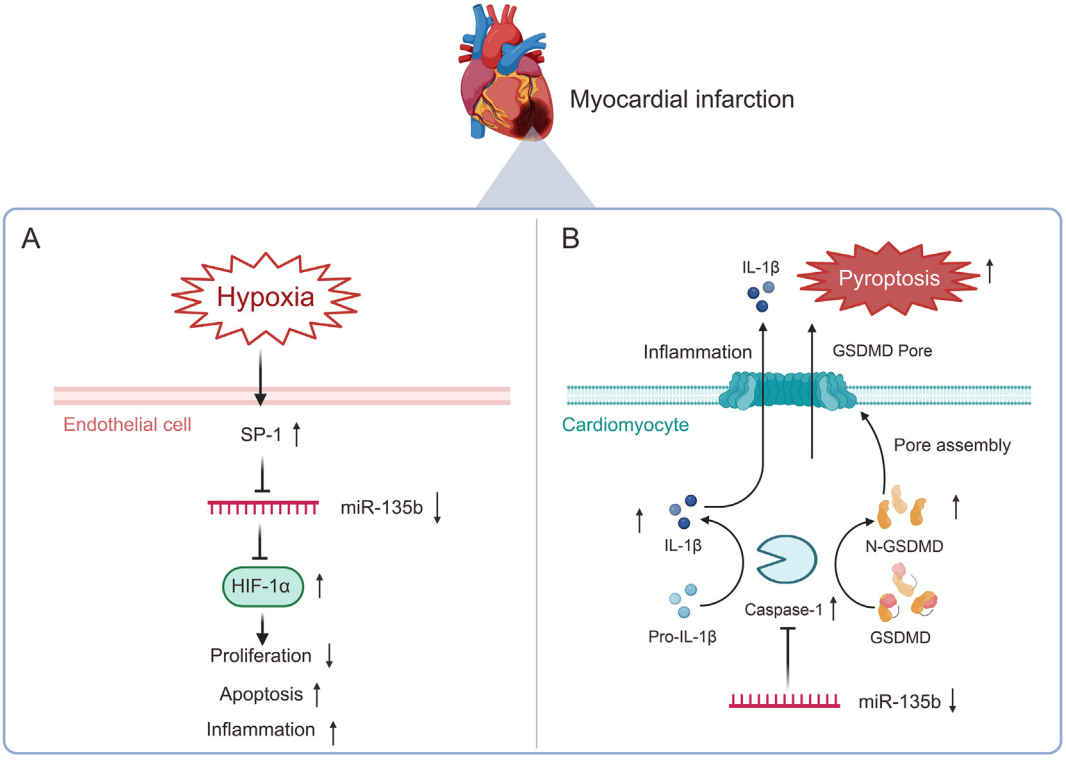

Fig. 3. The role and mechanism of miR-135b in regulating myocardial infarction (MI). (A) The specificity protein-1 (SP-1)/miR-135b/hypoxia-inducible factor-1alpha (HIF-1α) axis aggravates MI. (B) miR-135b inhibits pyroptosis by targeting cysteine-requiring aspartate protease-1 (caspase-1) during MI. IL-1β: interleukin-1β; GSDMD: gasdermin D.

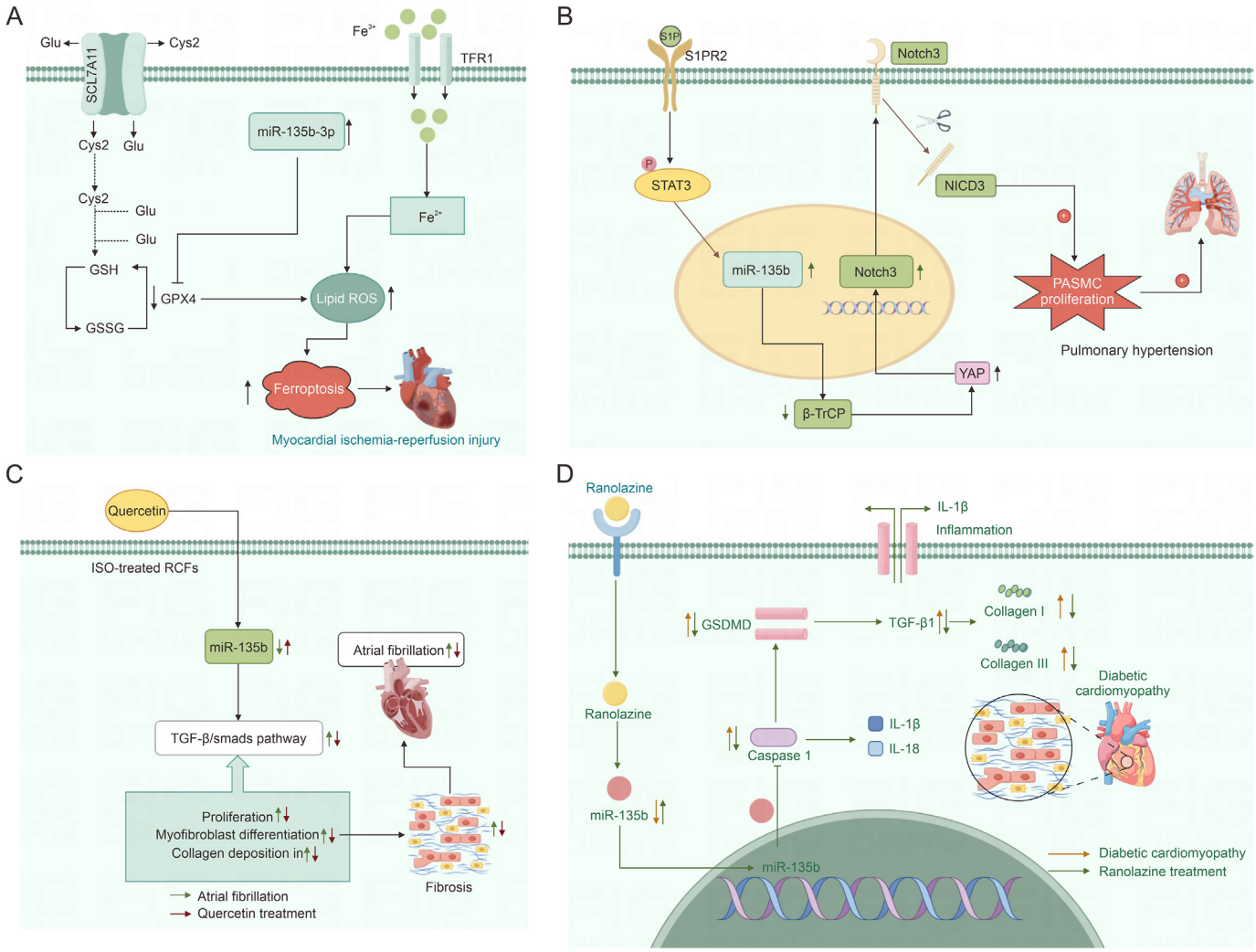

Fig. 4. The role and mechanism of miR-135b action in regulating myocardial ischemia-reperfusion (MI/R) injury, pulmonary hypertension (PH), atrial fibrillation (AF), and diabetic cardiomyopathy (DCM). (A) miR-135b-3p aggravates MI/R injury by inhibiting glutathione peroxidase 4 (GPX4)-mediated ferroptosis. (B) miR-135b activation aggravates PH progression. (C) Quercetin ameliorates AF by regulating the miR-135b-transforming growth factor-beta (TGF-β)/Smads axis. (D) Ranolazine exerts therapeutic effects against DCM by up-regulating miR-135b expression. GSH: glutathione; GSSG: glutathione disulfide; S1P: sphingosine 1-phosphate; S1PR2: sphingosine 1-phosphate receptor 2; STAT3: signal transducer and activator of transcription 3; β-TrCP: β-transduction repeat-containing protein; Notch3: neurogenic locus notch homolog protein 3; NICD3: Notch3-ICD; YAP: Yes-associated protein; SMAD: suppressor of mother against decapentaplegic; GSDMD: gasdermin D; Caspase-1: cysteine-requiring aspartate protease-1; IL: interleukin; RCFs: rat cardiac fibroblasts; ROS: reactive oxygen species; ISO: isoprenaline; TFR1: transferrin receptor 1.

4.4. Pulmonary hypertension (PH)

PH occurs when the pulmonary blood vessel pressure exceeds the normal range [62]. PH can cause pulmonary vasospasm, occlusion, and proliferation, eventually forming pathological changes similar to malignant tumors; therefore, PH is called "cardiovascular cancer" [63–65]. Excessive proliferation of pulmonary artery smooth muscle cells (PASMCs) is the hallmark of pulmonary vascular remodeling [66,67]. A recent study suggested that miR-135b is involved in the excessive proliferation of sphingosine-1-phosphate (S1P)-mediated PASMCs [68]. Notably, S1P promotes the massive proliferation of PASMCs by activating the STAT3↑–miR-135b↑–β-transduction repeat-containing protein (β-TrCP)↓–YAP↑–neurogenic locus notch homolog protein 3 (Notch3)↑ signaling pathway, further exacerbating PH [68] (Fig. 4B). Therefore, targeting this signaling pathway may inhibit the abnormal proliferation of PASMCs, potentially beneficial for PH.

4.5. Atrial fibrillation (AF)

AF is a frequently occurring sustained cardiac arrhythmia that increases the risk of several conditions, including cerebral embolism and heart failure [69–71]. In cases of AF, miR-135b expression is downregulated, and those of transforming growth factor-β receptor type 1/2 (TGFBR1/2, confirmed targets of miR-135b) and Smad family member 2 (Smad2, confirmed targets of miR-135b) are up-regulated in atrial tissues [72]. Overexpression of miR-135b can inhibit isoproterenol-induced AF occurrence and development, and this protective effect is mediated by quercetin and inhibition of the TGF-β/Smads pathway [72] (Fig. 4C). The above findings indicate that drugs targeting miR-135b possess the potential to treat AF.

4.6. Diabetic cardiomyopathy (DCM)

DCM refers to the cardiovascular complications caused by diabetes, resulting in arrhythmia, heart failure, and even sudden death

[73–75]. Currently, there are no specific clinical treatments options for DCM, and existing ones include drugs for treating heart diseases or diabetes. Ranolazine (an US Food and Drug Administration (FDA)-approved drug for the treatment of angina) exerts a therapeutic effect on DCM, and its target is miR-135b [76]. The specific regulatory mechanism is as follows: ranolazine up-regulates the expression of miR-135b, and miR-135b directly binds to caspase-1 to degrade it and inhibit myocardial fibroblast pyroptosis to alleviate myocardial fibrosis in DCM [76] (Fig. 4D). This finding provides new ideas and targets for identifying effective anti-DCM drugs. Ranolazine has a certain protective effect on myocardial damage in rats with DCM *in vivo*; however, the study of its target miR-135b was limited to cardiac fibroblasts treated with high glucose, and no relevant experiments were conducted *in vivo*. Therefore, further investigation into the regulatory mechanism and therapeutic potential of miR-135b is expected to help better understand and manage DCM.

4.7. Atherosclerosis (AS)

AS is a common cardiovascular disease causing serious harm [77–79]. It can lead to stenosis and occlusion of target organs and blood vessels, resulting in an insufficient blood supply to the target organs, which can cause ischemia, hypoxia, and even necrosis [80–82]. In the course of AS, the proliferation and migration of HUVECs and vascular smooth muscle cells (VSMCs) are key factors in disease progression. The expression of miR-135b-5p is high in the serum of patients with AS, which exerts a superimposed enhancement effect on the proliferation and migration of HUVECs and VSMCs [13] (Fig. 5A). This implies that highly expressed miR-135b-5p may promote the progression of AS lesions. Therefore, miR-135b may be a potential treatment target against AS. Further studies showed that miR-135b-5p expression was significantly upregulated in HUVECs treated with oxidized low-density lipoprotein (ox-LDL) [33]. Overexpression of miR-135b-5p can reverse the protective effect of circRSF1 on HUVECs treated with ox-LDL, specifically by promoting HUVECs proliferation and inhibiting apoptosis and inflammation [33] (Fig. 5B). Therefore, miR-135b-5p is a promoter of AS pathogenesis. Additionally, Wu et al. [14] found a significant up-regulation of miR-135b expression in AS mice; inflammatory responses were alleviated when the expression was downregulated, and the formation of AS plaques was inhibited. Mechanistic studies have shown that miR-135b can inhibit macrophage autophagy in AS mice by inhibiting EPOR expression and activating the PI3K/AKT signaling pathway, further exacerbating the progression of AS [14] (Fig. 5C). miR-135b has a crucial regulatory role in complex processes involved in the occurrence and development of AS. Therefore, targeting miR-135b regulation may be a novel approach to treat AS.

4.8. Brain diseases

Brain diseases pose a major global public health challenge and a heavy burden on patients and their families [83–85]. The therapeutic potential of miR-135b in brain diseases has been discussed. Reduced miR-135b levels have been reported in 1-methyl-4-phenylpyridinium (MPP^+)-induced PD *in vitro* models; miR-135b overexpression relieved the PD symptoms [17]. Mechanistically, miR-135b can alleviate PD damage through suppressing FOXO1-induced NLRP3 inflammasome and pyroptosis [17] (Fig. 6A), and regulate MPP^+ mediated apoptosis, inflammation and proliferation of neuronal cells by suppressing the expression of KPNA4, GPNMB, GSK-3β to alleviate the development of PD [22,23,86] (Fig. 6B). Additionally, miR-135b also is pivotal in the progression of AD. The levels of miR-135b are reduced in the peripheral blood of patients with AD [18]. Overexpression of miR-135b in the SAMP8 mice

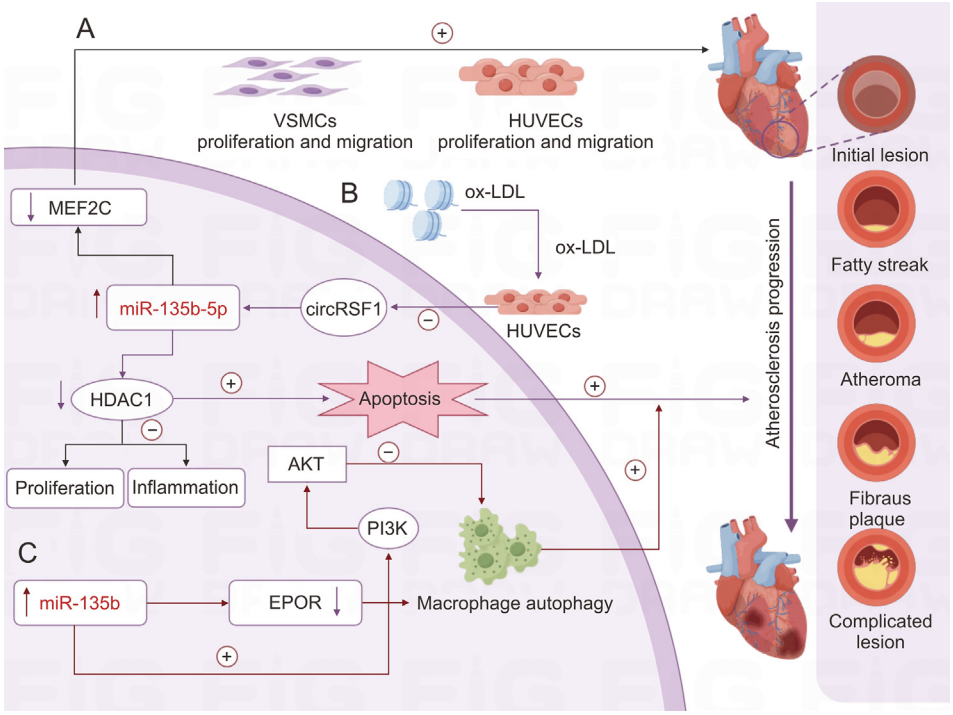

Fig. 5. The role and mechanism of miR-135b in regulating atherosclerosis (AS). (A) miR-135b-5p exacerbates AS progression by inhibiting myocyte enhancer factor 2c (MEF2C) expression. (B) The circRSF1/miR-135b-5p/histone deacetylase 1 (HDAC1) axis regulates AS progression. (C) miR-135b accelerates AS progression by inhibiting the expression of erythropoietin receptor (EPOR) and promoting the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway. VSMCs: vascular smooth muscle cells; HUVECs: human umbilical vein endothelial cells; ox-LDL: oxidized low-density lipoprotein.

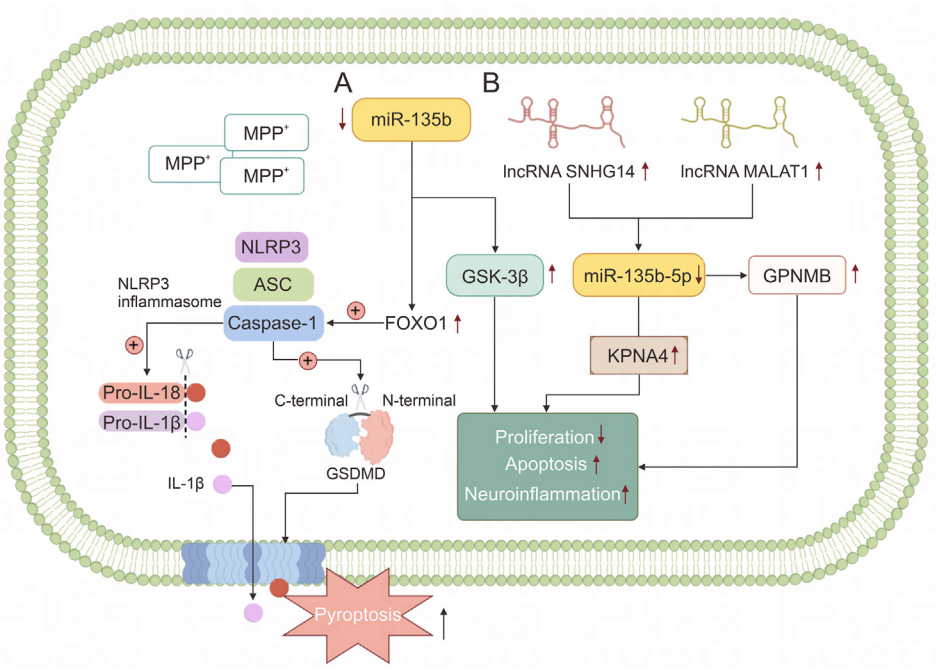

Fig. 6. The role and mechanism of miR-135b in 1-methyl-4-phenylpyridinium (MPP^+)-induced Parkinson's disease (PD). (A) miR-135b alleviates PD damage through inhibiting forkhead Box O1 (FOXO1)-induced NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome and pyroptosis. (B) miR-135b exerts neuroprotective effects against PD by inhibiting the expression of glycogen synthase kinase-3beta (GSK-3β), karyopherin subunit alpha 4 (KPNA4), or glycoprotein non-metastatic melanoma protein B (GPNMB). ASC: apoptosis associated speck like protein containing a CARD; caspase-1: Cysteine-requiring aspartate protease-1; GSDMD: gasdermin D; IL-1β: interleukin-1β.

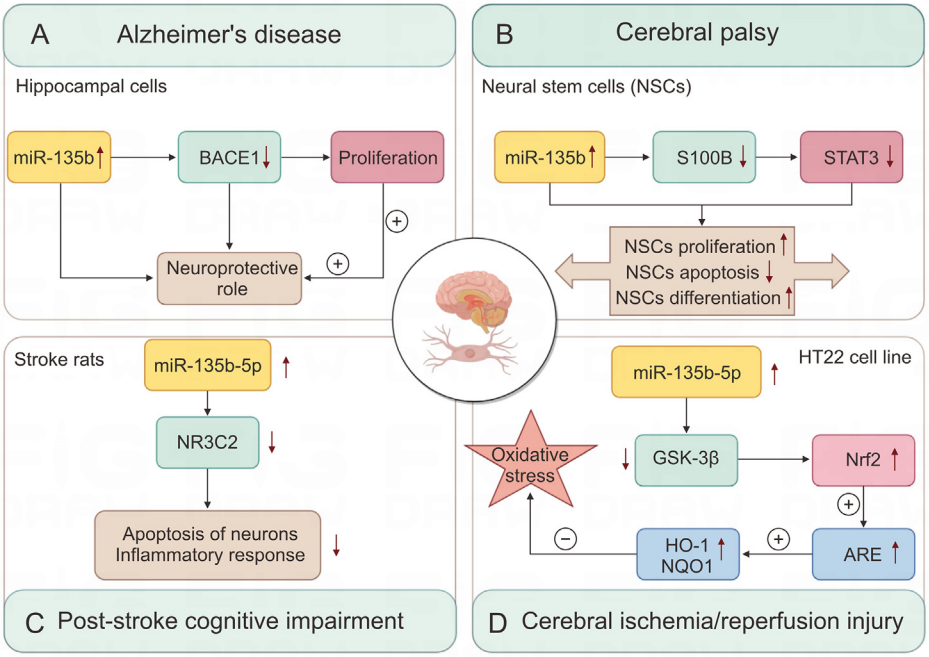

Fig. 7. The role and mechanism of miR-135b in Alzheimer's disease (AD), cerebral palsy (CP), post-stroke cognitive impairment, and cerebral ischemia/reperfusion (CI/R) injury. (A) miR-135b exerts neuroprotective effects against AD by directly targeting β-site APP-cleaving enzyme 1 (BACE1). (B) miR-135b reduces brain damage in rats with CP by inhibiting the S100 calcium binding protein B (S100B)-signal transducer and activator of transcription 3 (STAT3) pathway. (C) miR-135b-5p relieves post-stroke cognitive impairment by targeting mineralocorticoid receptor (NR3C2). (D) miR-135b-5p activates the nuclear factor erythroid 2-related factor (Nrf2)/antioxidant response element (ARE) signaling pathway by inhibiting glycogen synthase kinase-3beta (GSK-3β) to alleviate CI/R injury. HO-1: Heme oxygenase-1; NQO1: NADPH quinone oxidoreductase 1.

enhances learning and memory, indicating the neuroprotective effect of miR-135b in AD [18]. This neuroprotective effect was correlated to the direct inhibition of BACE1 expression and the promotion of hippocampal cell proliferation [18] (Fig. 7A).

Moreover, miR-135b exerts a protective effect on rats with CP, stroke, and CI/R injury. Specifically, miR-135b inactivates the STAT3 pathway by targeting S100B, thereby promoting neural stem cell differentiation, and reducing brain damage in rats with CP [16] (Fig. 7B). Furthermore, it reduced post-stroke cognitive impairment by inhibiting the expression of NR3C2 [19] (Fig. 7C), and activating the nuclear factor erythroid 2-related factor (Nrf2)/antioxidant response element (ARE) signaling pathway to reduce CI/R injury by inhibiting GSK-3β expression [15] (Fig. 7D). Therefore, miR-135b plays a protective role against PD, AD, CP, stroke, and CI/R injury by targeting different regulatory pathways. The findings provide potential therapeutic strategies for treating related diseases and insights into the mechanisms underlying the occurrence of these diseases.

In conclusion, miR-135b is a protective factor in MI, cardiac hypertrophy, DCM, and AF. It may serve as a pathogenic factor in MI/R injury, AS, and PH. A reason for this dual effect may be that miR-135b targets different target genes and participates in several cell death pathways. miR-135b has two kinds of shear mature forms, namely miR-135b-5p and miR-135b-3p, which may play different roles in the same kind of cells. For example, in MI, miR-135b is a protective factor as it inhibits pyroptosis in cardiomyocytes by targeting NLRP3 [10]; however, in MI/R injury, miR-135b-3p is damaging as it induces ferroptosis in cardiomyocytes by targeting GPX4 [11]. miR-135b participates in the pathogenic regulation of different functions in various types of cells. For example, in AS, miR-135b acts by inhibiting autophagy in macrophages [14]; in PH, miR-135b worsens the condition by promoting excessive proliferation of PASMCs [68]. Notably, miR-135b shows consistent protective effects against PD, AD, stroke, CI/R injury, and cerebral palsy, providing important theoretical support for further research and application of miR-135b in the treatment of brain diseases. The studies also provide new ideas and possibilities for the development of related treatment strategies and drugs.

5. Drugs targeting miR-135b and related patents

Various miRNA-related drugs in clinical trials are in the preclinical research stage [87–89]. As an emerging factor, miR-135b is a crucial target for therapy using drugs, such as melatonin, quercetin, ranolazine, desflurane, morin, gypenosides, estradiol, and cisplatin (Table 3) [38,72,76,90–95]. Specifically, melatonin inhibits lung adenocarcinoma cell proliferation by enhancing miR-135b expression [38], and quercetin ameliorates AF by promoting miR-135b expression [72]. Ranolazine helps treat DCM by enhancing miR-135b expression [76]. Desflurane reduces liver ischemia-reperfusion injury by inhibiting the expression of miR-135b-5p [90], and morin pigment inhibits the survival of lung cancer cells by inhibiting miR-135b expression [91]. The inhibitory effect of total gypenosides on renal interstitial fibrosis has been studied, and

Table 3
Drugs targeting miR-135b.

Drug name	miR-135b expression	Signal pathway	Functional disease
Melatonin	Promotes expression	hsa_circ_0017109/miR-135b-3p/TOX3	Lung adenocarcinoma [38]
Quercetin	Promotes expression	miR-135b/TGF-β/Smads	Atrial fibrillation [72]
Ranolazine	Promotes expression	miR-135b/caspase-1/TGF-β1	Diabetic cardiomyopathy [76]
Desflurane	Inhibits expression	miR-135b-5p/JAK2	Liver ischemia/reperfusion injury [90]
Morin	Inhibits expression	miR-135b-CCNG2	Lung cancer [91]
Gypenosides	Inhibits expression	–	Renal fibrosis [92]
Estradiol	Inhibits expression	ER-β/miR-135b/MMR	Colorectal cancer [93]
Cisplatin	–	miR-135b/MST1/MAPK	Cisplatin resistant gastric cancer [94]
Cisplatin	–	miR-135b/PTEN	Ovarian cancer [95]

TOX3: TOX high mobility group box family member 3; TGF-β: transforming growth factor beta; Smad: suppressor of mother against decapentaplegic; Caspase-1: cysteine-requiring aspartate protease-1; JAK2: Janus kinase-2; CCNG2: clinical significance of cyclin G2; ER-β: estrogen receptor-beta; MMR: mismatch repair gene; MAPK: mitogen-activated protein kinase; PTEN: phosphatase and tension homolog.

Table 4
Patents related to miR-135b.

Patent name	Publication number	Application	Publication date
An exosome containing miR-135b-5p and its application against anti-rotavirus infection	CN114469996B	Anti-rotavirus infection	2023-10-20
Use of miR-135b inhibitors as drugs for the treatment of lung metastasis and recurrent osteosarcoma	CN106692987A	Osteosarcoma	2017-05-24
Methods and compositions involving miR-135b for distinguishing pancreatic cancer from benign pancreatic disease	US20180066316A1	Pancreatic cancer	2018-03-08
A primer combination for detecting miR-135b and its application	CN111961728A	Gastric cancer	2020-11-20
A biomarker combination for detecting the efficacy of FOLFIRI as a second-line chemotherapy agent against metastatic colorectal cancer and its application	CN105779571A	Chemotherapy for metastatic colorectal cancer	2016-07-20
A prognostic marker for locally advanced esophageal squamous cell carcinoma and its application	CN109897899A	Advanced esophageal squamous cell carcinoma	2019-06-18
A tumor migration and invasion ability and/or proliferation ability evaluation kit	CN110438225B	Gastric cancer	2023-05-12
A microRNA marker composition, detection reagent, and detection kit for diagnosing colorectal cancer	CN116219019A	Colorectal cancer	2023-06-06
A peripheral blood miRNA lung cancer diagnostic marker combination and detection kit	CN112695095A	Lung cancer	2021-04-23

https://patents.qizhidao.com/search/simple-result?from=simple&searchBtntype=searchBtn&businessSource=PC%E6%9F%A5%E4%B8%93%E5%88%A9&statement=miR-135b&current=1.

miR-135b inhibition is an underlying mechanism involved in the therapeutic effect [92]. Estradiol's anti-colorectal cancer effect is correlated with the inhibition of miR-135b expression [93]. The inhibition of miR-135b reduces the resistance of gastric cancer [94] and ovarian cancer [95] cells to cisplatin, indicating that miR-135b plays a certain role in gastric cancer and ovarian cancer treatment, and suppressing its expression can improve chemotherapeutic effects. In addition to the drugs targeting miR-135b, patent research on miR-135b covers various aspects (Table 4). For instance, Xu et al. utilized miR-135b as a therapeutic target and employed inhibitors, including antisense or antagomiR, or plasmids expressing miR-135b antisense, to suppress lung metastases and overcome the recurrence of osteosarcoma (CN106692987A). Zhou et al. engineered exosomes containing miR-135b-5p with anti-rotavirus properties (CN114469996B). Several patents involve the use of miR-135b as a marker for tumor treatment or prognosis (Table 4). In conclusion, miR-135b has high application value as a therapeutic target and can provide new directions and possibilities for developing related drugs.

6. Conclusion and prospects

Although basic research demonstrates the potential of miR-135b for the treatment of CCDs, its translation into clinical application still faces many challenges. Technical and safety issues, such as effectively targeting miR-135b to cardiovascular and cerebrovascular tissues, ensuring that the therapeutic dose is within a safe range, and avoiding related adverse reactions, are difficult problems that merit consideration. Therefore, more clinical studies are needed to verify the feasibility and safety of targeting miR-135b for therapeutic purposes. As demonstrated in the findings discussed in this review, the potential of miR-135b as a therapeutic target for CCDs cannot be ignored. Targeting miR-135b expression can effectively alleviate the pathological process of CCDs and improve related symptoms. Therefore, miR-135b is a new potential target for the treatment of CCDs, and the findings lay a theoretical foundation for developing innovative treatment strategies and drugs. Moving forward, we believe that future research should be devoted to in-depth exploration of the potential mechanism of miR-135b in CCDs and its correlation with other factors. This will help reveal the specific role of miR-135b in the development of the disease and provide a more precise scientific basis for further optimization of treatment options and its clinical application in this field. In addition, clinical epidemiological surveys and clinical trials can be used to evaluate the correlation between the expression of miR-135b and clinical characteristics of patients with CCDs to explore its utility as a biomarker. At the same time, combined with pharmacological studies, the feasibility and safety of miR-135b as a therapeutic target will be further verified. In conclusion, with the in-depth research on miR-135b, we believe that this microRNA is expected to emerge as an important innovative breakthrough for treating CCDs.

CRediT authorship contribution statement

Yingchun Shao: Conceptualization, Writing - Original draft preparation, and Reviewing and Editing, Investigation; **Jiazhen Xu**: Writing - Reviewing and Editing; **Wujun Chen**: Writing - Reviewing and Editing; **Minglu Hao**: Writing - Reviewing and Editing; **Xinlin Liu**: Conceptualization; **Renshuai Zhang**: Conceptualization; **Yanhong Wang**: Conceptualization, Investigation, Writing - Reviewing and Editing; **Yinying Dong**: Conceptualization, Investigation, Writing - Reviewing and Editing.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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