



# MiR-125 Family in Cardiovascular and Cerebrovascular Diseases

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Cardiovascular and cerebrovascular diseases are a serious threaten to the health of modern people. Understanding the mechanism of occurrence and development of cardiovascular and cerebrovascular diseases, as well as reasonable prevention and treatment of them, is a huge challenge that we are currently facing. The miR-125 family consists of hsa-miR-125a, hsa-miR-125b-1 and hsa-miR-125b-2. It is a kind of miRNA family that is highly conserved among different species. A large amount of literature shows that the lack of miR-125 can cause abnormal development of the cardiovascular system in the embryonic period. At the same time, the miR-125 family participates in the occurrence and development of a variety of cardiovascular and cerebrovascular diseases, including myocardial ischemia, atherosclerosis, ischemia-reperfusion injury, ischemic stroke, and heart failure directly or indirectly. In this article, we summarized the role of the miR-125 family in the development and maturation of cardiovascular system, the occurrence and development of cardiovascular and cerebrovascular diseases, and its important value in the current fiery stem cell therapy. In addition, we presented this in the form of table and diagrams. We also discussed the difficulties and challenges faced by the miR-125 family in clinical applications.

**Keywords:** cardiovascular and cerebrovascular diseases, mir-125, atherosclerosis, myocardial ischemia, ischemia-reperfusion, ischemic stroke, mesenchymal stem cell

## INTRODUCTION

Cardiovascular disease is one of the leading causes of death in the world. A retrospective study from 204 countries around the world found that from 1990 to 2019, the total number of cardiovascular diseases increased from 271 million to 523 million, and the number of cardiovascular deaths increased from 12.1 million to 18.6 million (Roth et al., 2020). Therefore, we should actively explore the occurrence and development mechanism of cardiovascular disease, which is of great significance to alleviate the pressure of health system and improve the quality of life on a global scale.

Although it has been nearly 30 years since the first microRNA (miRNA) was discovered, the research on miRNA is still hot. Earlier studies found that miRNA expression was tissue-specific, that is, specific miRNAs were expressed only in specific cells or tissues (Lagos-Quintana et al., 2002). It was discovered that most miRNAs could be expressed in different organs or cells, and some of them were highly expressed among different species (Ludwig et al., 2016). Many studies have shown that miRNAs play an important regulatory role in the occurrence and development of diseases, and

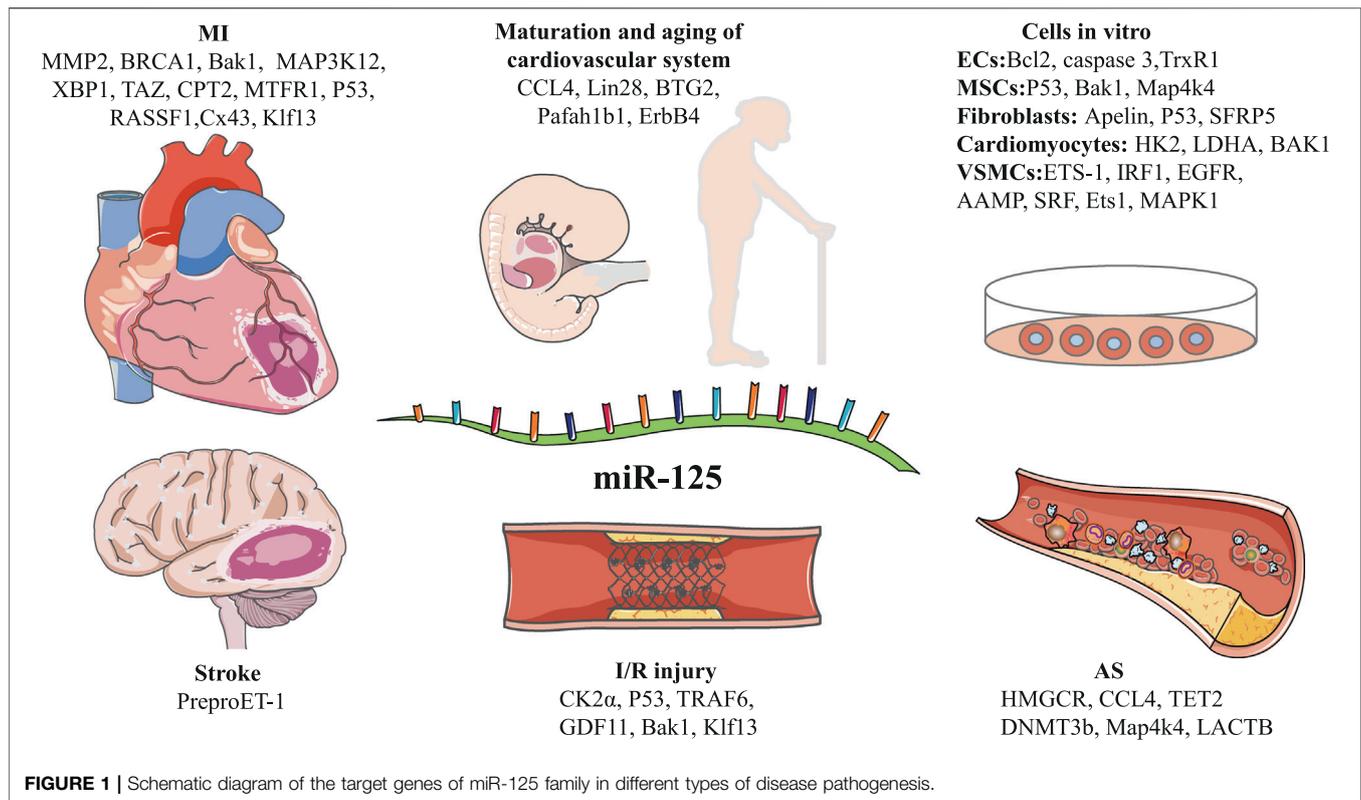
**TABLE 1 |** Summary of studies investigating the regulators and effectors of miR-125 family in cardiovascular and cerebrovascular diseases.

Reference	miRNA	Target cells/ tissues/organs	Disease or phenotype	Intervention	Experimental setting	Species	Target genes
Li et al. (2018)	miR-125	H9c2	Oxidative stress	H <sub>2</sub> O <sub>2</sub>	<i>In vitro</i>	Rat	MMP2
Gródecka-Szwajkiewicz et al. (2020)	miR-125	Plasma	Premature birth	N	<i>In vivo</i>	Human	N
Díaz et al. (2017)	miR-125a	Myocardial cells	I/R injury	I/R, Urocortin	<i>In vitro, In vivo</i>	Rat	BRCA1, MAP3K12, XBP1, TAZ, CPT2, MTFR1
Svensson et al. (2014)	miR-125a	HUVECs, Arterial endothelial cells	Endothelial cell proliferation and viability	Growth factors	<i>In vitro</i>	Human	Bcl2, caspase-3
Maitrias et al. (2015)	miR-125a	Carotid plaque	Carotid plaque	N	<i>In vivo</i>	Human	N
Zhang and Niu, (2020)	miR-125a	Plasma	Acute ischemic stroke	N	<i>In vivo</i>	Human	N
Chen et al. (2018)	miR-125a	HUVECs	Oxidative stress	H <sub>2</sub> O <sub>2</sub>	<i>In vitro</i>	Human	TrxR1
Ye et al. (2020)	miR-125a	VSMCs	AS, VSMCs proliferation and migration	High glucose	<i>In vitro</i>	Rat	HMGCR
Li et al. (2020)	miR-125a	Plasma	Acute ischemic stroke	N	<i>In vivo</i>	Human	N
Hu et al. (2019)	miR-125a-3p	VSMCs	VSMCs proliferation and migration	Carotid artery balloon injury, Platelet derived growth factor	<i>In vitro, In vivo</i>	Rat	MAPK1
Wang et al. (2019b)	miR-125a-5p	VSMCs	AS	Oxidized low-density lipoprotein	<i>In vitro</i>	Human	CCL4
Zhou et al. (2021)	miR-125a-5p	VSMCs	VSMCs proliferation, migration and invasion	High glucose	<i>In vitro</i>	Rat	EGFR
Hendgen-Cotta et al. (2017)	miR-125a-5p	Heart	I/R injury	I/R, Nitrite	<i>In vivo</i>	Mouse	N
Che et al. (2014)	miR-125a-5p	Arterial endothelial cell	Aging	N	<i>In vitro</i>	Mouse	RTEF-1
Galluzzo et al. (2021)	miR-125a-5p	Serum	Advanced heart failure	N	<i>In vivo</i>	Human	N
Gareri et al. (2017)	miR-125a-5p	VSMCs, A10	Carotid artery balloon injury	Carotid artery balloon injury	<i>In vitro, In vivo</i>	Rat	ETS-1
Zheng et al. (2019)	miR-125a-5p	VSMCs	VSMCs proliferation	Platelet derived growth factor-BB, Vein graft	<i>In vitro, In vivo</i>	Rat	IRF1
Zhaolin et al. (2019)	miR-125a-5p	HUVECs	AS	Oxidized low-density lipoprotein	<i>In vitro</i>	Human	TET2
Kjipaisalratana et al. (2020)	miR-125a-5p, miR-125b-5p	Serum	Posterior circulation stroke/Peripheral vertigo	N	<i>In vivo</i>	Human	N
Tiedt et al. (2017)	miR-125a-5p, miR-125b-5p	Plasma	Acute ischemic stroke	N	<i>In vivo</i>	Human	N
Li et al. (2010)	miR-125a-5p, miR-125b-5p	H5V, b.END.3, VSMCs, NIH3T3	Oxidative stress	Oxidized low-density lipoprotein	<i>In vitro, In vivo</i>	Stroke-prone spontaneously hypertensive rats	PreproET-1
Ke et al. (2019)	miR-125a-5p, miR-125b-5p	Hippocampal tissues	I/R injury	I/R	Bioinformatics analysis	Rat	N
Wang et al. (2021)	miR-125b	VSMCs	Vascular smooth muscle cells proliferation	N	<i>In vitro</i>	Rat	AAMP, SRF
Nagpal et al. (2016)	miR-125b	Cardiac fibroblasts	Myocardial fibrosis	Angiotensin II, TGF-β2	<i>In vitro, In vivo</i>	Human, Mouse	Apelin, P53
Xu and Fang, (2021)	miR-125b	Myocardial cells	Diabetic cardiomyopathy/ Myocardial cell death	High glucose	<i>In vitro, In vivo</i>	Human, Rat	HK2, LDHA

(Continued on following page)

**TABLE 1 |** (Continued) Summary of studies investigating the regulators and effectors of miR-125 family in cardiovascular and cerebrovascular diseases.

Reference	miRNA	Target cells/ tissues/organs	Disease or phenotype	Intervention	Experimental setting	Species	Target genes
Zhang et al. (2021)	miR-125b	Myocardial cells	Heart failure/ Cardiomyocyte apoptosis	Transverse aortic constriction	<i>In vitro, In vivo</i>	Mouse	Bak1
Liang et al. (2018)	miR-125b	PC12	I/R injury	I/R,OGD	<i>In vitro</i>	Rat	CK2 $\alpha$
Cheng et al. (2015)	miR-125b	Immune cells	Aging	N	<i>In vivo</i>	Human	CCL4
Sun et al. (2020)	miR-125b	Cardiac fibroblasts	AMI	Circ-LAS1L overexpression vector	<i>In vitro</i>	Human	SFRP5
Bie et al. (2016)	miR-125b	Cardiac fibroblasts	Cardiac fibroblasts growth and activation	N	<i>In vitro</i>	Human	SFRP5
Wang et al. (2014)	miR-125b	H9c2	I/R injury	I/R	<i>In vitro, In vivo</i>	Transgenic mice with overexpression of miR-125b + Rat	P53, Bak1, TRAF6
Wen et al. (2014)	miR-125b	VSMCs	VSMCs transdifferentiation and calcification	$\beta$ -glycerophosphoric acid	<i>In vitro</i>	Rat	Ets1
Cao et al. (2016)	miR-125b	VSMCs	AS, VSMCs proliferation	Homocysteine, Methionine diet	<i>In vitro, In vivo</i>	Human, ApoE <sup>-/-</sup> mouse	DNMT3b
Xiao et al. (2018)	miR-125b	MSCs, cardiomyocytes	MI, Autophagic Flux	MI, OGD, Co-culture	<i>In vitro, In vivo</i>	Mouse	P53
Wong et al. (2012)	miR-125b	ESCs	Embryo differentiation	N	<i>In vitro</i>	Human	Lin28
Fan et al. (2020)	miR-125b	H9c2, Cardiomyocytes	Cardiomyocyte injury	Hypoxia	<i>In vitro</i>	Rat	HK2
Ding et al. (2015)	miR-125b	Plasma	Coronary heart disease	N	<i>In vivo</i>	Human	N
Zhu et al. (2018)	miR-125b	Bone marrow mesenchymal stem cells, H9C2	MI	MI, Hypoxia, Co- culture, Reactive dibenzylcyclootyne	<i>In vitro, In vivo</i>	Mouse	P53, Bak1
Xiaochuan et al. (2020)	miR-125b	Myocardial cells	AMI	AMI, Adenoviruses containing RASSF1 siRNA, hypoxia	<i>In vivo</i>	Rat	RASSF1
Chen et al. (2021)	miR-125b-1	Heart	Birth defects	Cardiac-specific miR- 125b-1 KO	<i>In vivo</i>	Cardiac specific miR-125b-1 KO mouse	BTG2, Pafah1b1
Szabó et al. (2020)	miR-125b-1-3p	Heart	Hypercholesterolemia, I/ R injury	Special Diet, I/R	<i>In vitro, In vivo</i>	Rat	N
Deng et al. (2015)	miR-125b-2	Embryonic stem cells, E14TG2A	Birth defects	All-trans-retinoic acid	<i>In vitro</i>	Mouse	N
Dufeys et al. (2021)	miR-125b-5p	Cardiac fibroblasts	MI/Myocardial fibrosis	Myofibroblasts -specific AMPK $\alpha$ 1 KO	<i>In vitro, In vivo</i>	Human, AMPK $\alpha$ 1 KO mouse	Cx43
Nazari-Shafti et al. (2020)	miR-125b-5p	MSCs extracellular vehicles	N	N	<i>In vitro</i>	Human	N
Ben-Zvi et al. (2020)	miR-125b-5p	Serum	Systolic heart failure	N	<i>In vivo</i>	Human	N
Lee et al. (2015)	miR-125b-5p	Embryonic stem cells, H9	Embryonic stem cells maturation	Co-culture	<i>In vitro</i>	Human, Mouse, Rat	ErbB4
Chen et al. (2020)	miR-125b-5p	HT-22	I/R injury	Oxygen Glucose Deprivation	<i>In vitro</i>	Mouse	GDF11
Bayoumi et al. (2018)	miR-125b-5p	HL-1, H9c2, Ventricular cardiomyocytes	AMI, I/R injury	AMI, I/R, Carvedilol	<i>In vitro, In vivo</i>	Mouse, Rat	Bak1, Klf13
Jia et al. (2016)	miR-125b-5p	Plasma	Acute myocardial infarction	N	<i>In vivo</i>	Human	N
Lin et al. (2021)	miR-125b-5p	Bone marrow mesenchymal stem cells, VSMCs, Aortic tissues	AS	High fat diet, Tail vein injection	<i>In vitro, In vivo</i>	ApoE <sup>-/-</sup> mouse	Map4k4
Lu et al. (2016)	miR-125b-5p	THP-1, Atherosclerotic plaques	AS	LPS	<i>In vitro, In vivo</i>	Human	LACTB



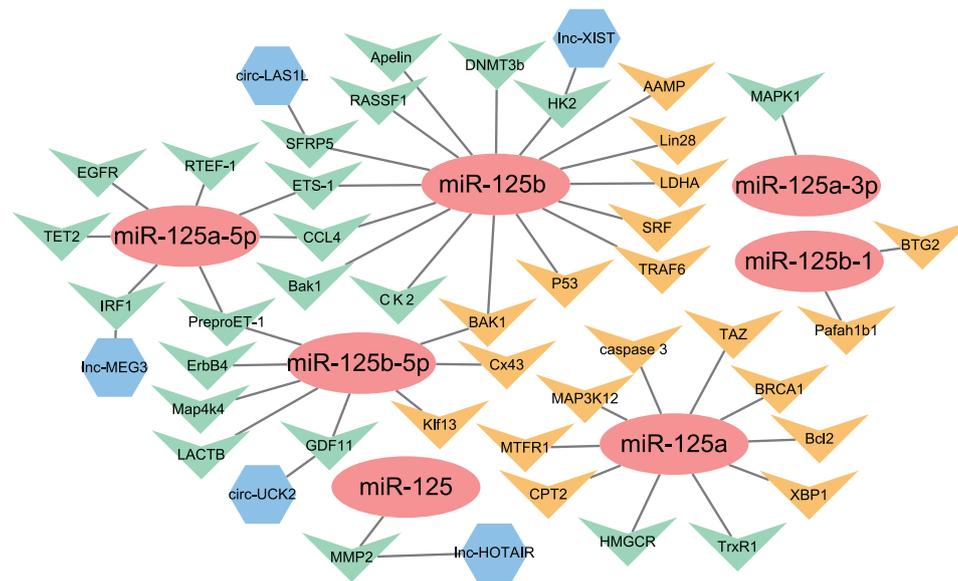
sometimes even in different stages in the same disease. Many miRNAs were highly conserved between different species (Perge et al., 2017). In different species, this provides us with the possibility to study whether the same miRNA plays the same role in the same disease, including cardiovascular and cerebrovascular diseases. For example, in both early and late stages, miR-19a/19b could protect cardiomyocytes in mice after myocardial infarction (MI) (Gao et al., 2019). Therapeutic silencing miR-146b-5p improved cardiac remodeling in porcine and mouse model of MI (Liao et al., 2021). MiR-21 from exosomes in human cardiomyocytes could be used to treat MI injury models in mice (Qiao et al., 2019).

MiR-125 family is widely expressed in mammals and its sequence is highly conserved. It is composed of three homologs hsa-miR-125a, hsa-miR-125b-1 and hsa-miR-125b-2 (Sun et al., 2013). hsa-miR-125a was discovered to be located at 19q13, while hsa-miR-125b-1 was verified on chromosomes 11q23 and hsa-miR-125b-2 on chromosomes 21q21 (Rodriguez et al., 2004). The miR-125 family plays an important role in the growth and development of animals, as well as the occurrence and development of cancer (Kim et al., 2016; Wang et al., 2019a). In addition, the role of miR-125 in cardiovascular and cerebrovascular diseases cannot be ignored. This article will review the role and mechanism of miR-125 family in the occurrence and development of cardiovascular and cerebrovascular diseases, including the role of the miR-125 family in the development and maturation of cardiovascular system, the occurrence and development of cardiovascular and

cerebrovascular diseases, and its value in the stem cell therapy. Furthermore, we presented this in the form of tables and diagrams (Table 1; Figures 1, 2). Finally, we also discussed the challenges faced by the miR-125 family in clinical applications in the future.

## MIR-125 FAMILY AND THE MATURATION AND AGING OF CARDIOVASCULAR SYSTEM

It was reported that when miR-125b-1 was specifically knocked out in the mouse heart, the mortality rate of perinatal mice was as high as 60%. Even in the surviving mice, their hearts were hypertrophy to varying degrees, and the mitochondria of the cardiomyocytes of these mice experienced varying degrees of morphological changes and loss of function in terms of morphology and function (Chen et al., 2021). Coincidentally, overexpression of miR-125b-2 in mouse embryonic stem cells (ESCs) inhibited the differentiation of mouse ESCs into endoderm and ectoderm, but it did not affect mesoderm differentiation, self-renewal and proliferation of mouse ESCs (Deng et al., 2015). Since the mesoderm was the origin of heart development, this study also indirectly showed that miR-125b-2 may play a role in maintaining the normal development of the heart in early mouse embryos. If murine and human embryonic-stem-cell-derived cardiomyocytes (m/hESC-CMs) were co-cultured with endothelial cells or endothelial cell



**FIGURE 2 |** The network of miR-125 family members with their upstream genes and downstream genes. (●) = miRNA-125 family members; (▼) = Downstream target genes verified by luciferase assay; (▲) = Downstream target genes without luciferase assay; (●) = Upstream target genes verified by luciferase assay.

lysates, it could improve the maturity and increase the expression of cardiomyocyte maturation markers in m/hESC-CMs. The reason for this phenomenon was that four miRNAs targeting ErbB4, including miR-125b-5p, overexpressed in m/hESC-CMs during the period when they were co-cultured with endothelial cells (Lee et al., 2015). This was probably because miRNAs from endothelial cells were released in the form of cell vesicles and absorbed by m/hESC-CMs during the co-cultivation process, thus increasing the maturity of m/hESC-CMs.

In another study on human ESCs (Wong et al., 2012), researchers found that miR-125b was an important regulator of human ESCs differentiation and development (including myocardium). Overexpression of miR-125b led to early heart disease. The upregulation of transcription factors, GATA4 and Nkx2-5, accelerated the progress of human embryonic stem cell-derived myocardial precursors to the phenotype of embryonic cardiomyocytes. In recent years, with the popularization of second-generation sequencing technology, more and more studies have shown that when the body was in a damaged state, large numbers of miRNAs would be released into the circulatory system from the damaged part (Cheng et al., 2019). Therefore, when the myocardium was damaged, the miRNA in the blood could be used as a marker of heart damage to a certain extent (Akat et al., 2014). Dorota Gródecka-Szwajkiewicz et al. analyzed the miRNA profile of umbilical cord blood of the peripheral blood mononuclear cells during the delivery of term infants and preterm infants. Many angiogenesis related miRNAs, including miR-125, decreased significantly in cord blood miRNAs of preterm infants. This may increase the risk of abnormal development and function of the cardiovascular system after these premature infants reached adulthood (Gródecka-Szwajkiewicz et al., 2020).

With the continuous aging, various components in the cell will change, and the cell function will also degrade. The increased expression of miR-125a in arterial endothelial cells of aging mice could regulate angiogenesis by targeting RTEF-1 and regulating the expression of eNOS and VEGF. The low expression of miR-125a in endothelial cells may be the “youth code” that maintained the normal operation of endothelial cells (Che et al., 2014). In addition, compared with the immune cells of young people, miR-125b was lowly expressed in the elderly. The expression of CCL4 was negatively correlated with the expression of miR-125b. CCL4 was an important chemokine of immune cells, which may be one of the reasons why aging had lower immunity compared with young people (Cheng et al., 2015).

## MIR-125 FAMILY AND ISCHEMIA-REPERFUSION INJURY

After analyzing GSE82146 in the GEO database, Hong Ke et al. found that miR-125a and miR-125b may be the key genes that mediate ischemia-reperfusion (I/R) damage (Ke et al., 2019). In another study on I/R injury, more than half of the changes in miRNA expression including miR-125a-3p occurred in the nitrite treatment group compared with the control group 30 min after myocardial ischemia and 5 min after reperfusion (Hendgen-Cotta et al., 2017). These studies showed the high sensitivity of miR-125 family to I/R injury, which also provided a favorable reference value for miR-125 family to evaluate the therapeutic effect of I/R injury in the future. NF- $\kappa$ B signal pathway is the key to mediate myocardial injury after I/R injury. Overexpression of miR-125b in I/R injured mice could effectively reduce I/R-induced cardiomyocyte apoptosis, caspase-3/7 and

caspace-8 activities, and prevent the activation of NF- $\kappa$ B pathway after I/R injury (Wang et al., 2014). In the rat I/R injury model, miR-125b could inhibit the expression of CK2 $\alpha$  and regulate the CK2 $\alpha$ /NADPH oxidation signal pathway to protect the rat brain from I/R damage directly (Liang et al., 2018).

In addition to directly targeting downstream mRNA for regulation, ceRNA bonded by miRNA and circRNA influence the expression of mRNA to produce regulation. Cheng Luo et al. found that the expression of circPVT1 in rats with I/R injury increased significantly. It could inhibit the expression of miR-125b and miR-200a by targeting them, increase cardiomyocytes apoptosis after I/R injury, and weaken their protective effect on heart muscles (Luo et al., 2021). MiR-125a, together with miR-139 and miR-324, could cooperate with urocortin to protect rat myocardium after I/R injury (Díaz et al., 2017). By targeting MAPK1, miR-125a-3p could also inhibited intimal thickening and the function of vascular smooth muscle cells (VSMCs), thereby reducing the degree of restenosis (Hu et al., 2019). In addition, miR-125a could participate in the proliferation of endothelial cells by acting on Bcl2, caspase-3 and TrxR1 *in vitro* experiments (Svensson et al., 2014; Chen et al., 2018). Interventional therapy is the traditional treatment for vascular stenosis. However, I/R injury and restenosis after interventional therapy have always been a major problem for clinicians. All the above studies provide potential targets for the treatment of I/R injury and vascular restenosis after injury from the gene level.

## MIR-125 FAMILY AND MYOCARDIAL ISCHEMIA

Currently, the number of studies of miR-125b is the most among miRNAs related to myocardial ischemia in the miR-125 family. Researchers found that the expression of miR-125b in the plasma of coronary heart disease patients was lower than that of non-coronary heart disease patients. As the Gensini score increased, the level of miR-125b reduced significantly (Ding et al., 2015). Diabetic cardiomyopathies is a special type of heart disease. miR-125b and miR-34a could protect cardiomyocytes in high glucose environment. Their action on the HK2 in glucose metabolism and LDHA in lactate metabolism respectively inhibited the glucose metabolism, glucose uptake and lactate metabolism of cardiomyocytes (Xu and Fang, 2021).

Hypercholesterolemia is one of the causes of myocardial ischemia. Ischemic preconditioning could up-regulate the expression of miR-125b-1-3p and activate cardiac self-protection mechanisms. However, rats with hypercholesterolemia could attenuate the up-regulation of miR-125b-1-3p level through ischemic preconditioning, which was related to the loss of cardioprotection (Szabó et al., 2020). Myocardial infarction (MI) is one of the main types of myocardial ischemia. Accurate and timely diagnosis of acute myocardial infarction (AMI) is particularly important for a good prognosis of patients. After analyzing the plasma miRNA data of AMI patients, it was found that miR-125b-5p and miR-30d-5p could be used to diagnose AMI effectively. Compared with the

existing diagnostic methods of CK-MB, cTnI and myoglobin, the diagnostic performance of miRNA could be comparable to or even exceed the potential of existing diagnostic indicators (Jia et al., 2016). All of these contribute a new idea to the diagnosis of myocardial ischemia in our clinical work. Cardiomyocyte apoptosis is a common pathological process after myocardial ischemia. Up-regulation of miR-125b in cardiomyocytes could reduce the protein levels of apoptosis-related markers c-caspase-3 and Bax significantly, and increase the expression of anti-apoptotic protein Bcl-2 to increase the survival rate of cardiomyocytes (Zhang et al., 2021). In addition, miR-125b could also inhibit cardiomyocytes apoptosis by inhibiting the expression of RASSF1 and KLF3 (Bayoumi et al., 2018; Xiaochuan et al., 2020). lncRNA is another non-coding RNA which has the similar function with circRNA. It can form ceRNA with miRNA to weaken the post-transcriptional modification effect of miRNA on mRNA. In H9C2 cells, lncRNA-XIST could form ceRNA with miR-125b to affect the downstream HEK2 gene, which could weaken the cardioprotective effect of miR-125b and result in cardiomyocytes damage (Fan et al., 2020).

Myocardial fibrosis is an important cause of decreased heart function after myocardial ischemia. When heart was injured, the Ang II-TGF- $\beta$  axis could influence the expression of miR-125b, and then inhibit the expression of apelin and p53, leading to the proliferation of fibroblasts and the conversion of fibroblasts to myofibroblasts. The final outcome of the increase in miR-125b level was the occurrence of myocardial remodeling (Nagpal et al., 2016). The effect of miR-125a did seem to be opposite to that of miR-125b. Similarly, in H9C2 cells, miR-125a mimics reduced the expression of MMP2 and the proliferation of it, while promoting its apoptosis. However, lnc-HOTAIR could restore the expression of MMP2 by targeting miR-125a. At the same time, it could also promote the proliferation and survival of H9C2 (Li et al., 2018). In cardiac fibroblasts from patients with AMI, circ-LAS1L could bind to miR-125b to relieve the inhibitory effect on downstream SFRP5. Furthermore, it could inhibit the activation, proliferation and migration, and promote apoptosis of cardiac fibroblasts (Bie et al., 2016; Sun et al., 2020). Compared with WT mice, the MI model of AMPK $\alpha$ 1 knocked out conditionally showed more severe myocardial remodeling. Interfering with AMPK $\alpha$ 1 expression in fibroblasts could also reduce the expression of Cx43 protein significantly. However, deletion of AMPK $\alpha$ 1 could only reduce the activity of Cx43 promoter by about 40%, which was inconsistent with the expression of Cx43 protein. By using a preliminary quantitative PCR microRNA array, the authors showed that AMPK $\alpha$ 1, in addition to binding directly to Cx43, could perform post-transcriptional control of Cx43 by upregulating miR-125b in its own absence (Dufeyes et al., 2021).

## MIR-125 FAMILY AND ATHEROSCLEROSIS

As we all know, atherosclerosis (AS) is a chronic and complex disease involving multiple factors, and it is one of the main causes of coronary heart disease, myocardial ischemia, and cerebral infarction. By comparing the miRNA in

symptomatic with asymptomatic atherosclerotic plaques after surgical resection Pierre Maitrias et al. found that miR-125a was significantly different between the two groups (Maitrias et al., 2015). This implies that miR-125a plays an important role in the changes of atherosclerotic plaques at different stages of the disease. Macrophages are important participants in the AS process. It is of great significance to reduce the aggregation of macrophages and protect damaged endothelial cells from inflammation in the control of AS. MCP-1 is an important chemokine for macrophages. In THP-1 macrophage cell line, miR-125b-5p could inhibit the expression of MCP-1 by targeting LACTB and attenuate the chemotaxis of macrophages (Lu et al., 2016). Pyroptosis is a new mode of programmed cell death that has been discovered and confirmed in recent years, and its development is often accompanied by the release of massive inflammatory factors. TET2 was an important member of the TET enzyme family and played an important role in epigenetics (Shen et al., 2018). After treating the endothelial cell surface with oxLDL *in vitro*, the increased expression of miR-125a-5p could reduce the expression of TET2. Inactivation of TET2 could result in abnormal DNA methylation, NF- $\kappa$ B nuclear transposition, inflammatory response, and subsequent pyroptosis (Zhaolin et al., 2019).

With the development of the disease, VSMCs subjected to inflammatory stimulation will proliferate, migrate, and invade. This is one of the causes of plaque formation, arterial calcification, and stenosis. As we mentioned before, miR-125b had a targeting relationship with CCL4 (Cheng et al., 2015). Interestingly, in VSMCs, miR-125a also had a targeting relationship with CCL4. This combination could inhibit the expression of NLRP3 and alleviate the inflammatory process (Wang et al., 2019b). Ping Wen et al. treated primary rat VSMCs cultured *in vitro* with  $\beta$ -glycerophosphate and found that the  $\beta$ -glycerophosphate promoted the phenotypic transition and calcification of VSMCs. Besides, they found that the expression of miR-125b decreased significantly. After the VSMCs transfected with miR-125b mimics, they could resist  $\beta$ -glycerophosphate-mediated cell differentiation and calcification (Wen et al., 2014). The effect on inhibiting the proliferation of VSMCs of miR-125b was also confirmed in previous study. In the cell model of homocysteine-induced VSMCs proliferation, miR-125b could counteract the proliferation of VSMCs by targeting DNMT3b and mediating p53 DNA methylation (Cao et al., 2016). In addition, miR-125b could also inhibit the proliferation and migration of VSMCs by inhibiting the expression levels of AAMP and SRF (Wang et al., 2021). The function of miR-125a on VSMCs was the same as miR-125b, and both of them could inhibit the proliferation and migration of VSMCs. miR-125a could play a role by inhibiting EST1, which was related to cell proliferation and migration in the PDGF-BB pathway (Gareri et al., 2017). In addition, miR-125a could also work by targeting IRF1, EGFR and HMGcr in VSMCs (Zheng et al., 2019; Ye et al., 2020; Zhou et al., 2021).

## MIR-125 FAMILY AND OTHER CARDIOVASCULAR AND CEREBROVASCULAR DISEASES

At present, many of the cardiovascular and cerebrovascular patients would develop heart failure gradually as the diseases progress (Sulo et al., 2020). In patients with heart failure, the expression of miR-125b would rise significantly (Ben-Zvi et al., 2020). And in patients with advanced heart failure, there were significant differences in the expression of three miRNAs including miR-125a-5p, which were related to the composite end point of cardiac death, cardiac transplantation, or mechanical circulatory support implantation (Galluzzo et al., 2021). These studies had important predictive reference value for the prognosis of patients with heart failure.

In terms of pathogenesis, there are many similarities between ischemic stroke and myocardial ischemia. For example, in addition to being a marker of myocardial ischemia, the miR-125 family could also be used as a potential biomarker for acute vertigo, posterior circulation stroke and acute ischemic stroke (Tiedt et al., 2017; Kijpaisalratana et al., 2020). In a large case-control study (210 participants in the control group, 210 participants in the acute ischemic stroke group), the researchers found that the expression of miR-125a decreased in the plasma of the experimental group. The reason for this decline was that lnc-NEAT1 inhibited its expression (Li et al., 2020). The other lnc-ITSN1-2 inhibited the expression of miRNA such as miR-125a via inactivating its anti-angiogenesis and anti-inflammatory effects. The ultimate result was changes in alter vascular structure as well as inflammation related NF- $\kappa$ B pathway and TRL pathway activation (Zhang and Niu, 2020). In addition, the reduction of miR-125a-5p and miR-125b-5p expression was also related to the expression of preproET-1 in the aorta of stroke-susceptible spontaneous hypertensive rats (SHR-SPs) (Li et al., 2010). This provided new and strong evidence for the miR-125 family to participate in the maintenance of vascular homeostasis in the body. In the process of ischemic stroke, circ-UCK2 could act as an endogenous miR-125b-5p sponge to inhibit the activity of miR-125b-5p, which in turn led to an increase in GDF11 expression and improved neuronal damage subsequently (Chen et al., 2020).

## MIR-125 AND MESENCHYMAL STEM CELLS AND THEIR EXTRACELLULAR VESICLES

The current treatments for cardiovascular and cerebrovascular diseases, such as interventions and drugs, have certain therapeutic effects. However, in many cases, conventional treatments cannot save the dying tissues. Mesenchymal stem cells (MSCs) are a kind of stem cells with multiple differentiation potentials and a promising treatment for cardiovascular and cerebrovascular diseases. By far, stem cell therapy has been partially applied to the clinical work of cardiovascular and cerebrovascular diseases (Hu et al., 2011). miR-125b-5p was highly expressed in the miRNA profiles of extracellular vesicles isolated from MSCs

derived from cord blood and adipose tissues (Nazari-Shafti et al., 2020). This is the basis of MSCs and their vesicles in the treatment of cardiovascular and cerebrovascular diseases.

In the ApoE<sup>-/-</sup> mice model of AS, the researchers found that the exosomal miR-125b-5p from mouse bone marrow mesenchymal stem cells (BMSCs) inhibited the formation of atherosclerotic plaques by inhibiting the expression of Map4k4 (Lin et al., 2021). P53 was an important apoptosis-regulating gene in organisms, and it could regulate the apoptosis process of cells in a variety of ways (Hafner et al., 2019). Studies have found that transplantation of MSCs or their exosomes could effectively inhibit the autophagy flux, cell death and P53 gene expression of cardiomyocytes after MI. And the therapeutic effect of the MSCs-exosome treatment group is significantly better than that of the MSCs-exosome-antimiR-125b group. Therefore, stem cells and their exosomes were likely to inhibit autophagy flux and target P53 through miR-125b, thereby inhibiting the apoptosis process of cardiomyocytes mediated by P53 gene and protecting cardiomyocytes (Xiao et al., 2018). It has been reported that when they were used to treat ischemic mouse body models, MSCs could improve their ability to promote functional angiogenesis after undergoing a hypoxia process (Huang et al., 2013). So, if the MSCs are pretreated with hypoxia, will their ability to treat cardiovascular and cerebrovascular diseases be improved? The answer is yes. MI mice treated with exosomes of BMSCs after 72 h of hypoxia culture had a significant reduction in the area of MI. Next-generation sequencing showed that hypoxia treatment could significantly increase the content of miR-125b-5p in exosomes of BMSCs, and this mechanism of action was due to the ability of miR-125b to inhibit the expression of pro-apoptotic genes P53 and BAK1 in cardiomyocytes (Zhu et al., 2018). This study proved the highly effective treatment effect of miR-125 family members on MI again.

## CONCLUSION

More and more studies have shown that miR-125 family is related to the development and differentiation of mammalian embryonic heart. Furthermore, they were found played an important role in diseases and pathophysiological processes such as, coronary heart disease, MI, I/R injury, stroke, myocardial fibrosis, endothelial cell injury and myocardial cell apoptosis. However, in different

diseases and different pathological processes, the same miR-125 family members play different roles. That is very interesting. For example, overexpression of miR-125b in cardiomyocytes can inhibit cardiomyocyte apoptosis and inflammatory response in pathological state to protect cardiomyocytes. But at the same time, miR-125b is also a regulator of cardiac fibrosis. Its overexpression in cardiac fibroblasts can enhance their proliferation and reduce their apoptosis. Therefore, excessive miR-125b will aggravate myocardial fibrosis and myocardial remodeling under pathological conditions, destroy the original morphological structure of the heart, increase the difficulty of neovascularization, and aggravate the apoptosis of cardiomyocytes in the damaged area.

As mentioned above, if miR-125 is used as a treatment target of cardiovascular and cerebrovascular diseases in clinical practice, further studies have to take the following two points into account. Firstly, because some miR-125 family members have ‘two sides’ in the role of cardiovascular and cerebrovascular diseases, we should find the best ‘balance point’ between harmful and beneficial to give full play to its maximum treatment and circumvent its negative effects. Secondly, in the future, it may not be enough to only study the optimal therapeutic dose of miR-125 in the process of diagnosis and treatment. It is also necessarily need to find a suitable miR-125 vector that can target our target cells for “precision treatment”. Only in this way can we give full play to the optimal therapeutic effect of miR-125 family members.

## AUTHOR CONTRIBUTIONS

YW, CF and QW designed and wrote the manuscript. LW, GP, HC, QZ, SW and CH revised the manuscript. JT drew the figures. CF and QW provided critical feedback and helped to shape the manuscript. All authors listed have made a substantial contribution to the work.

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