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Review article

miR-19 family: A promising biomarker and therapeutic target in heart, vessels and neurons

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ABSTRACT

The miR-19 family, including miR-19a, miR-19b-1 and miR-19b-2, arises from two different paralogous clusters miR-17-92 and miR-106a-363. Although it is identified as oncogenic miRNA, the miR-19 family has also been found to play important roles in regulating normal tissue development. The precise control of miR-19 family level is essential for keeping tissue homeostasis and normal development of organisms. Its dysregulation leads to dysplasia, disease and even cancer. Therefore, this review focuses on the roles of miR-19 family in the development and disease of heart, vessels and neurons to estimate the potential value of miR-19 family as diagnostic biomarker or therapeutic target of cardiac, neurological, and vascular diseases.

1. Introduction

MicroRNAs (miRNAs) are a class of single stranded small noncoding RNAs with 22 nucleotides in length. MiRNAs negatively regulate the expression of target genes by binding to 3'untranslated regions (3'UTRs) of genes mRNA and finetune intracellular homeostasis. The members of one miRNA family have high sequence homology, and are different from each other in one base variation. The miR-19 family includes miR-19a, miR-19b-1 and miR-19b-2, which are transcribed from miR-17-92 and miR-106a-363 clusters. The miR-19 family is widely distributed in vertebrates, and is vital to normal development of organism and pathology of disease. It has been found that miR-19 family is involved in regulating inflammation [1,2], tissue fibrosis [3,4], aging [5], metabolism [6], and tumorigenesis [7–9]. Besides, it regulates the development of heart, vessels, neurons, pancreas, etc. [10–13]. Abnormal expression of the miR-19 family members may lead to tissue and organ dysplasia, diseases, even cancer. The level of miRNA has been considered to be a marker or target of several diseases, such as tumorigenesis [14,15]. This review has summarized the roles of miR-19 family in the development and disease of heart, vessels and neurons. These research results make the potential value of miR-19 family as a promising biomarker or target of cardiac, vascular or neurological disease.

Abbreviations: miRNAs, microRNAs; 3'UTRs, 3'untranslated regions; TP53, tumor protein 53; Bax, Bcl2-associated X protein; P21, cyclin dependent kinase inhibitor 1A; TNF-α, tumor necrosis factor alpha; NF-κB, nuclear factor kappa B; RNF11, ring finger protein 11; Myc, myelocytomatosis oncogene; E2F1, E2 promoter binding factor 1; E2F2, E2 promoter binding factor 2; E2F3, E2 promoter binding factor 3; E2F, E2 promoter binding factor; SP1, transacting transcription factor 1; Hes1, hes family bHLH transcription factor 1; Pim-1, proviral integration site 1; PTEN, phosphatase and tensin homolog; BIM, BCL2 like 11; KCNE4, potassium voltage-gated channel subfamily E regulatory subunit 4; KCNQ1, potassium voltage-gated channel, KQT-like subfamily, member 1 (KCNQ1); Wnt, wingless and INT; Wnt1, wingless and INT1; Ctnnb1, catenin beta 1; MuRF-1, muscle ring finger protein 1; PDE5A, phosphodiesterase 5A; GJA1, gap junction alpha 1; CCNB1, cyclin B1; CCND1, cyclin D1; CDK1, cyclin dependent kinase 1; BCL6, cell death related genes B cell leukemia/lymphoma 6; PIK3AP1, phosphoinositide-3-kinase adaptor protein 1; XAF1, XIAP associated factor 1; Col1a1, fibrosis marker genes collagen type I alpha 1; Col3a1, collagen type III alpha 1; TGFBR2, transforming growth factor beta receptor 2; SOCS1, immune response related gene suppressor of cytokine signaling 1; CTGF, connective tissue growth factor; TSP-1, thrombospondin-1; VEGF, vascular endothelial growth factor; TGF-β, transforming growth factor beta; FGFR2, fibroblast growth factor receptor 2; FZD4, frizzled class receptor 4; LRP6, low density lipoprotein receptor related protein 6; ROS, reactive oxygen species; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1alpha; ABCA1, ATP-binding cassette transporter A1; ApoE$^{-/-}$ mice, apolipoprotein E deficient mice; PAI-1, plasminogen activator inhibitor-1; STAT3, signal transducer and activator of transcription 3; KLF10, Kruppel like factor 10; Apaf1, apoptotic peptidase activating factor 1; RAPGEF2, rap guanine exchange factor 2; PPARα, peroxisome proliferator activated receptor alpha; LRIG1, leucine rich repeats and immunoglobulin like domains1; Runx3, runt related transcription factor 3; RhoB, ras homolog family member B; MEG3, maternally expressed gene 3

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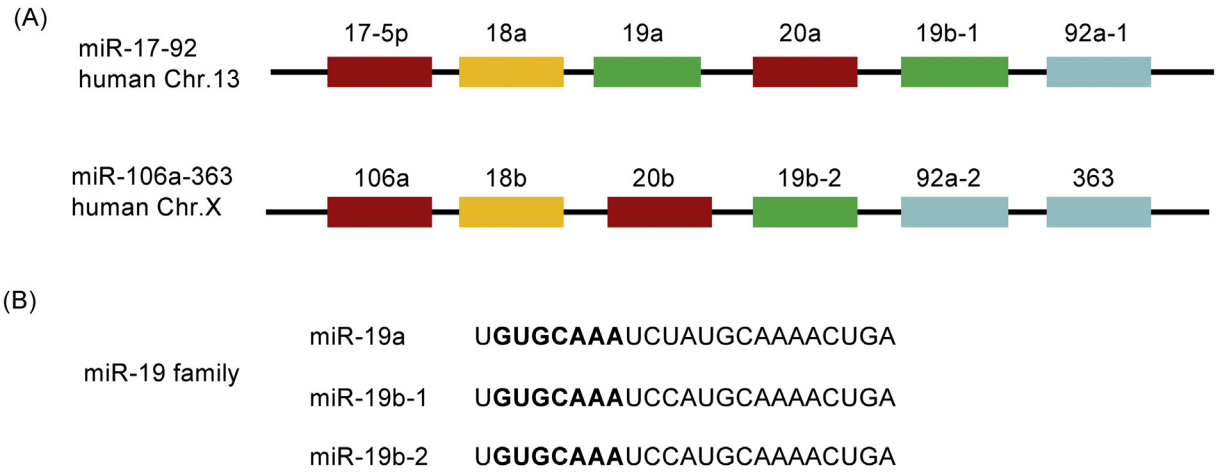

Fig. 1. Schematic of the miR-17-92, miR-106a-363 clusters and miR-19 family. (A) The location and organization of the miR-19 family. (B) The sequences of miR-19 family.

2. An outline of miR-19 family

The miR-19 family is an ancient and conserved miRNA specie, and it includes miR-19a, miR-19b-1 and miR-19b-2. The members of miR-19 family have identical seed region and arise from two different paralogous clusters miR-17-92 and miR-106a-363. MiR-19a and miR-19b-1 are encoded by miR-17-92 cluster, which is located in the intron 3 in the locus of MIR17HG/C13orf25 gene of human chromosome13 [16] (Fig. 1A). MiR-19b-2 is encoded by miR-106a-363 cluster, which is located on the X chromosome of human [16] (Fig. 1A). Although miR-19b-1 and miR-19b-2 are transcribed from different genes, they have the same mature sequence which is often referred to as miR-19b. Mature sequences of miR-19a and miR-19b are different by one nucleotide outside of the seed sequence (Fig. 1B). The miR-19a and miR-19b are considered to share a number of targeted genes, however, sometimes each has distinct targets. It is shown that miR-19b but not miR-19a directly targets tumor protein 53 (TP53), and diminishes the level of its downstream genes Bcl2-associated X protein (Bax) and cyclin dependent kinase inhibitor 1A (P21) in cancer cells [17]. MiR-19a, but not miR-19b, is found to target tumor necrosis factor alpha (TNF-α) [18], whereas mainly miR-19b is involved in the nuclear factor kappa B (NF-κB) pathway by targeting ring finger protein 11 (RNF11) [1]. In view of the above phenomena, we speculate that there may be other mechanisms for miRNAs to recognize their target sequence beyond “seed region”, which make miR-19a and miR-19b have different target genes and functions although they have the same seed sequence.

The miR-19 family members have abundant biological roles in regulating the development of nervous system, respiratory systems, cardiovascular systems, blood vessels formation, vertebrate axis, etc. Abnormal expression of miR-19 family members leads to multiple diseases, even promotes the initiation and progression of tumor [19,20]. It is well known that deletion of miR-17-92 cluster leads to neonatal lethality and specific defects in the development of heart, lung and B cells, however, deletion of miR-106b-25 and miR-106a-363 clusters do not affect the development of mice [21]. These phenotypes caused by miR-17-92 cluster deletion are largely responsible by the loss of miR-19a, miR-19b and miR-18 [21]. When miR-19 and miR-92a were knocked out in all the three clusters, miR-17-92, miR-106b-25 and miR-106a-363 clusters, the mice showed a reduced anterior-posterior axis and skull width, and their phenotypes were similar to that of miR-17-92 cluster knocked out mice [22]. The above evidences demonstrate that miR-19 family members are important for tissue and organ development.

3. Regulation of miR-19 family

To understand the transcriptional regulation of miR-19 family members, it is imperative to analyze the transcription regulators of miR-17-92 and miR-106a-363 cluster. Reports have shown that myelocytomatosis oncogene (Myc) binds directly to promoter of the miR-17- 92 cluster and activates transcription in HeLa cells [23] and primary cerebellar granule neuron precursors [24]. Myc binds to genomic regions upstream of the miR-106a-363 cluster in cytotrophoblasts and regulates cell differentiation [25]. Except for Myc, E2 promoter binding factor 1 (E2F1), E2 promoter binding factor 2 (E2F2), and E2 promoter binding factor 3 (E2F3) are found to directly bind to the promoter of the C13orf25 gene and activate transcription in HeLa cells [26]. E2F1 can also activate the transcription of miR-106a-303 cluster [27].

It is known that Myc could activate the expression of E2F gene, Myc and E2F are both inhibited by members of miR-17-92 cluster [28], thus they form negative feedback loop in the transcriptional regulatory network (Fig. 2). Moreover, the expression of miR-17-92 is also induced by other transcription factors, such as transacting transcription factor 1 (SP1) [29], hes family bHLH transcription factor 1 (Hes1) [30,31], NF-κB p65 [32] and proviral integration site 1 (Pim-1) [33], which could combine with the promoter of miR-17-92 cluster and induce a transcriptional activation.

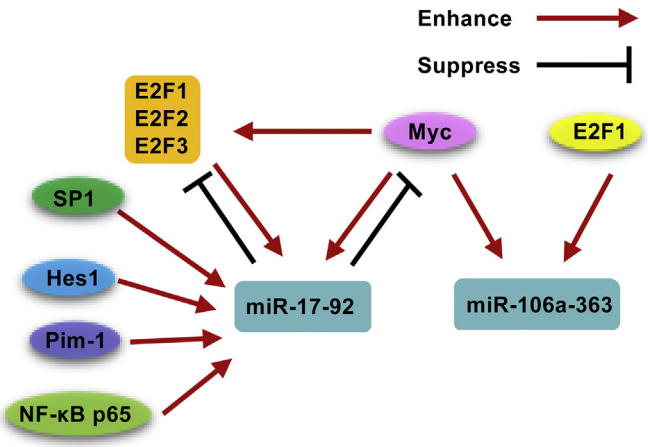

Fig. 2. The regulators of miR-17-92 and miR-106a-363 clusters. NF-κB P65, nuclear factor kappa B P65; Pim-1, proviral integration site 1; Hes1, hes family bHLH transcription factor 1; SP1, transacting transcription factor 1; E2F1, E2 promoter binding factor 1; E2F2, E2 promoter binding factor 2; E2F3, E2 promoter binding factor 3; Myc, myelocytomatosis oncogene.

The posttranscriptional regulation also affects the expression of miR-17-92 cluster. The secondary or tertiary structure of pri-miR-17-92, microprocessor or Dicer accessory factors has been identified to facilitate or inhibit the processing of miRNAs. Reports have shown that compact globular structure, which is formed by the tertiary structure between a non-miRNA stem-loop and the pre-miR-19b hairpin, impaired the access of Drosha enzyme to the 3′core domain of miR-19b and miR-92a. That is one reason why the internalized miRNAs, miR-18a, miR-19b and miR-92a, are processed less efficiently than those on the surface of the structure, miR-17, miR-20a and miR-19a [34–36]. A progenitor-miRNA, which is a miRNA biogenesis intermediate upstream of microprocessor, is identified to regulate the expression of miR-17-92 at posttranscriptional level [37].

4. Functions of miR-19 family in heart

MiR-19a and miR-19b are highly expressed in the heart [38], they promote proliferation and inhibit apoptosis in the cardiomyocytes. The myocardial hypoplasia in miR-17-92 cluster deficient mice is mainly caused by the absence of miR-19a and miR-19b [21], which leads to the stagnation of cardiac cells proliferation by regulating phosphatase and tensin homolog (PTEN) and BCL2 like 11 (BIM) [10,39]. The miR-19b deficient zebrafishes have developed severe bradycardia and reduced cardiac contractility, duing to the impairment of repolarization mediated by potassium voltage-gated channel subfamily E regulatory subunit 4 (KCNE4) upregulation [40]. The KCNE4 is a regulatory subunit of potassium voltage-gated channel, KQT-like subfamily, member 1 (KCNQ1), which mainly mediating Iks current in cardiac tissue during repolarization. MiR-19b protects against cell apoptosis and improves cell survival by targeting PTEN in H9C2 cardiomyocytes treated with hydrogen peroxide, which mimicking oxidative stress occurring during myocardial ischemia-reperfusion injury [41]. In rodent or cellular models of myocardial infarction, microvascular obstruction or cardiac hypertrophy, miR-19b and miR-19a protect cardiomyocytes against heart failure induced by ischaemia, hypoxia or endoplasmic reticulum stress through inhibiting apoptosis or activating autophagy by regulating BIM [42–44]. Furthermore, studies have implied that miR-19b may be regulator of heart regeneration and differentiation in zebrafish and mouse [39,45]. MiR-19b promotes the differentiation of mouse embryonic carcinoma P19 cells into mature cardiac cells through inhibiting the wingless and INT (Wnt)/β-catenin signaling by targeting wingless and INT1 (Wnt1) [46,47].

Abnormal spatio-temporal expression of miR-19b is accompanied by cardiac disease. The level of miR-19b has been found to be dysregulated in the serum or platelet microparticles of patients with cardiovascular diseases [48], such as atrial fibrillation [49], myocardial infarction [50], viral myocarditis [51], and unstable angina pectoris patients [52]. At the early stage of zebrafish embryos, overexpression of miR-19b causes severe pericardial edema, cardiac looping defects and irregular heart, through inhibiting canonical Wnt signaling by targeting catenin beta 1 (Ctnnb1) [53]. In rat neonatal cardiomyocytes, overexpression of miR-19b induces cardiomyocytes hypertrophy by targeting anti-hypertrophic genes atrogin-1 and muscle ring finger protein 1(MuRF-1) [44]. This phenotype is also found in cardiac-specific miR-17-92 transgenic mouse , which showed cardiac hypertrophy and arrhythmias [54]. However, miR-19 family functions as a anti-hypertrophic regulator in pressure overload induced hypertrophic hearts by targeting phosphodiesterase 5A (PDE5A) [55]. The level of miR-19b is upregulated in the mouse model of viral myocarditis [51]. Overexpression of miR-19b contributes to cardiac arrhythmia through repressing gap junction alpha 1 (GJA1), a regulator for the electrical synchrony of cardiomyocytes [51]. MiR-19b is downregulated in the heart from a murine model of ischemia-reperfusion injury [41]. The miR-19b level is increased in early phase of patients and mouse model of myocardial infarction [39,50,42], then it is downregulated and increased again during the pathological process, exhibiting dynamic changes [39,42]. MiR-19a and miR-19b have been confirmed to be an potential therapeutic targets for heart failure of mouse with myocardial infarction [39]. MiR-19a and miR-19b enhance cardiomyocyte proliferation and stimulate cardiac regeneration by reducing the expression of genes related to multiple cellular functions, including proliferation and apoptosis targeting gene PTEN and Bim, cell cycle related genes cyclin B1 (CCNB1), cyclin D1 (CCND1) and cyclin dependent kinase 1 (CDK1), cell death related genes B cell leukemia/lymphoma 6 (BCL6), phosphoinositide-3-kinase adaptor protein 1 (PIK3AP1) and XIAP associated factor 1 (XAF1), fibrosis marker genes collagen type I alpha 1(Col1a1), collagen type III alpha 1 (Col3a1) and transforming growth factor beta receptor 2 (TGFBR2), and target gene associated with immune response suppressor of cytokine signaling 1(SOCS1).

In addition, miR-19 is found to be related to the process of aging associated heart failure [56]. In the aged cardiomyocytes and hearts of old failure-prone mice, the levels of miR-19a and miR-19b are decreased, accompanied by the upregulation of cardiac extracellular matrix proteins connective tissue growth factor (CTGF) and thrombospondin-1 (TSP-1) [56,57]. The accumulation of CTGF is a major feature of cardiac fibrosis [58]. Studies have shown that miR-19b could also be served as potential biomarker for myocardial fibrosis in patients with hypertrophic cardiomyopathy, aortic stenosis and heart failure [59,60]. The regulation of miR-19 on the extracellular matrix proteins is cell specific, and occurs only in cardiomyocytes, but not in cardiac fibroblasts, a type of cells responsible for cardiac fibrosis [5661]. In the cardiac fibroblasts, miR-19b promotes cell proliferation, cell migration and accelerates the process of cardiac fibrosis by targeting PTEN [61]. MiR-19 is not only related with cardiac fibrosis, it has been linked to the pathogenesis of fibrosis in lung [62], liver [3,4] and intestine [3,63].

In view of the significant roles of miR-19 family in cardiac development and disease (Fig. 3), miR-19 family could be a potential therapeutic target for cardiac disease. Besides, circulating miR-19a and miR-19b have been suggested as novel potential biomarkers of a series of myocardial lesions, including heart failure, dilated cardiomyopathy, stable angina pectoris, diabetic cardiomyopathy etc. [64–67].

5. Functions of miR-19 family in angiogenesis

Endothelial cells are required for the growth of new blood vessels. In the process of neovascularization, endothelial cells proliferate, sprout, form tube-like structures, and generate branching microvessels from preexisting ones [68]. The functions of endothelial cells and angiogenesis are regulated by vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-β) signaling, miR-17-92 cluster, etc. [69,70]. Studies have shown that miR-19b family could inhibit the process of angiogenesis (Fig. 4). The molecular mechanisms for miR-19 to impede angiogenesis include reducing the sprout formation of endothelial cells [70], blocking the cell cycle progress by regulating the expression of cyclin D1 and fibroblast growth factor receptor 2 (FGFR2) [11], suppressing the Wnt signaling pathway by targeting frizzled class receptor 4 (FZD4) and low density lipoprotein receptor related protein 6 (LRP6) [71]. The miR-19a and miR-19b antagonisms stimulate arteriogenesis and improve blood flow recovery in aged mice after ischemia [71]. Although miR-19 family regulates the angiogenic activity and angiogenesis in endothelial cells, it has hardly impact on the differentiation of endothelial cells. Upon the induction of endothelial cells differentiation from murine embryonic stem cells or pluripotent stem cells, the expression of miR-19 is increased, but the expressions of endothelial marker genes do not change [72].

The miR-19 family promotes apoptosis of endothelial cells (Fig. 4). MiR-19-3p enhances the production of reactive oxygen species (ROS) via the impairment of mitochondrial function in human aortic endothelial, further leading to cell apoptosis [73]. The apoptosis of endothelial cells is an important early event in the pathogenesis of atherosclerosis [74]. It has been reported that miR-19b-3p expression was enriched in the intima of human atherosclerotic vessels, and it

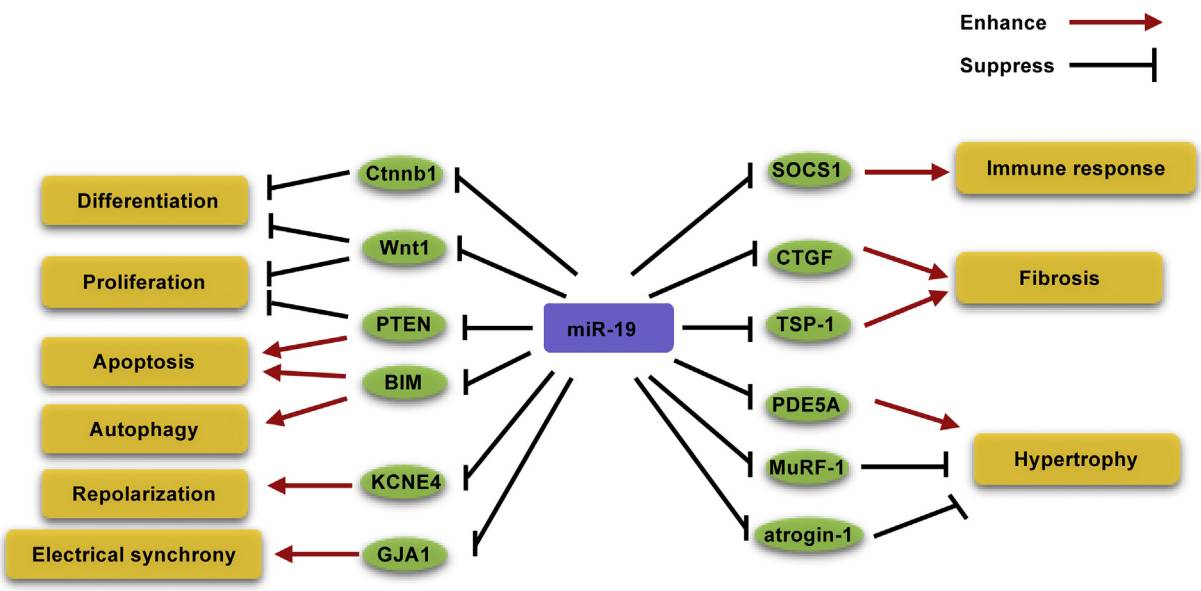

Fig. 3. The roles and targets of miR-19 in heart. Ctnnb1, catenin beta 1; Wnt1, wingless and INT1; PTEN, phosphatase and tensin homolog; BIM, BCL2 like 11; KCNE4, potassium voltage-gated channel subfamily E regulatory subunit 4; GJA1, gap junction alpha 1; SOCS1, immune response related gene suppressor of cytokine signaling 1; CTGF, connective tissue growth factor; TSP-1, thrombospondin-1; PDE5A, phosphodiesterase 5A; MuRF-1, muscle ring finger protein 1.

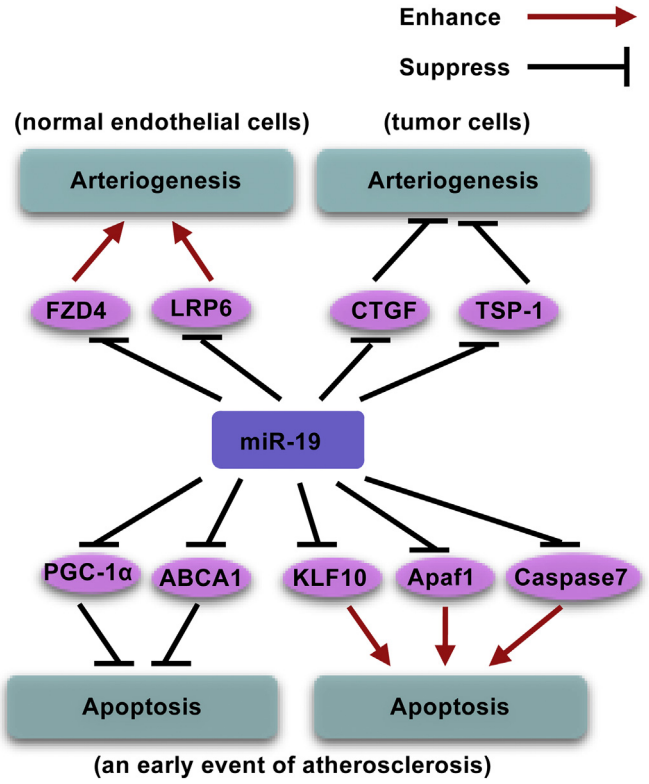

Fig. 4. The functions and targets of miR-19 in blood vessels. The miR-19 family exhibits opposing effects on angiogenesis in tumor cells versus normal endothelial cells. Different research works have presented that miR-19 family exerts anti-apoptotic or pro-apoptotic function in vascular endothelial cells. FZD4, frizzled class receptor 4; LRP6, low density lipoprotein receptor related protein 6; CTGF, connective tissue growth factor; TSP-1 thrombospondin-1; PGC-1a, peroxisome proliferator activated receptor γ coactivator 1alpha; ABCA1, ATP-binding cassette transporter A1; KLF10, Kruppel like factor 10; Apaf1, apoptotic peptidase activating factor 1.

could facilitate the development of atherosclerosis by decreasing the protein level of peroxisome proliferator-activated receptor γ coactivator 1alpha (PGC-1α), a transcriptional coactivator of lipid catabolism [73], and ATP-binding cassette transporter A1 (ABCA1), a membrane protein for effluxing cholesterol in macrophage [75]. Diosgenin inhibits the progression of aortic atherosclerosis by suppressing miR-19b expression and enhancing ABCA1 expression in the macrophage [76]. Mitochondria-targeted esculetin alleviates endothelial dysfunction, atherosclerotic plaque formation and inhibits plasminogen activator inhibitor-1(PAI-1) by modulating miR-19b and miR-30c levels via affecting the activation of Sirtuin3 and signal transducer and activator of transcription 3 (STAT3) pathways in apolipoprotein E deficient ($ApoE^{-/-}$) mice [77,78]. MiR-19 may be a therapeutic target for diosgenin and mitochondria-targeted esculetin. Moreover, the plasma concentration of miR-19a has been identified as a mortality predictor for patients with coronary artery [79].

Increasing evidences suggest that the biological functions of miRNAs may be either micro-environment or cell-type dependent, so miRNAs may have opposite functions in the same cell or organ in some cases (Fig. 4). Recently, other research works have presented that miR-19 family exerts anti-apoptotic or pro-proliferative function in vascular endothelial cells. The level of miR-19 is downregulated in the vascular epithelial tissues of ischemia-reperfusion injury rats [80]. The decreased miR-19 inhibits proliferation and promotes apoptosis in vascular endothelial cells of rats with lower limb ischemia reperfusion injury via the TGF-β/Smad signaling by suppression of Kruppel like factor 10 (KLF10) [80]. MiR-19b attenuates apoptosis induced by TNF-α in the primary human umbilical vein endothelial cells by inhibiting the apoptotic peptidase activating factor 1(Apaf1) and caspase7 [81]. Likewise, miR-19 family exhibits opposing effects on angiogenesis in tumor cells versus normal endothelial cells. Physiological expression of miR-19 represses endothelial cell sprouting, however aberrant elevation of miR-19 promotes angiogenesis in tumors. MiR-19b had been found to be significantly upregulated in Myc induced tumors and promotes angiogenesis by targeting TSP-1 and CTGF, the angiogenesis inhibitors [82]. The mechanisms of miR-19 family regulating cell functions and angiogenesis are complex, further researches should be performed to prove the cellular and environmental dependence of miR-19.

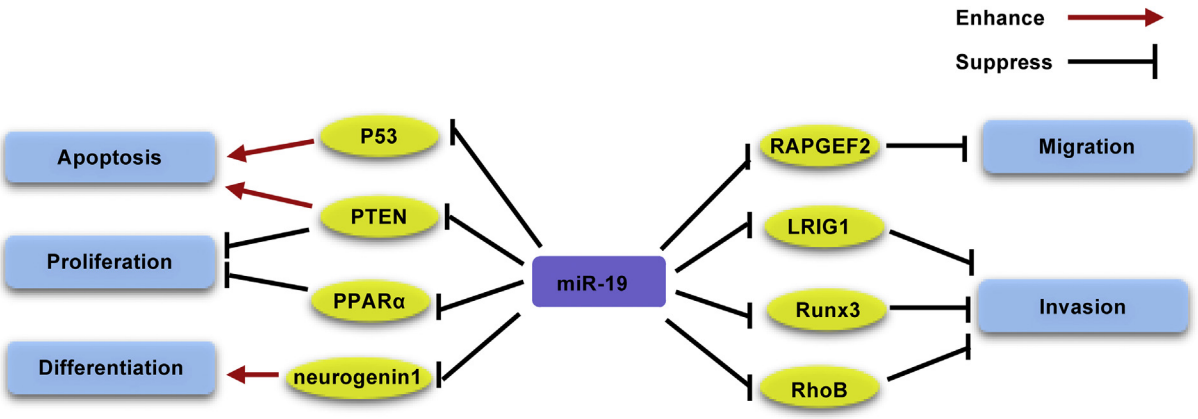

Fig. 5. The roles and targets of miR-19 in neural cells. PTEN, phosphatase and tensin homolog; PPARα, peroxisome proliferator activated receptor alpha; RAPGEF2, rap guanine exchange factor 2; LRIG1, leucine rich repeats and immunoglobulin like domains1; Runx3, runt related transcription factor 3; RhoB, ras homolog family member B.

6. Functions of miR-19 family in neurons

Emerging studies demonstrate that miR-19 family members play a key role in the differentiation, cell survival and migration of neurons (Fig. 5), and participate in regulating neurodegeneration diseases, such as spinocerebellar ataxia type 1 [83], Alzheimer's diseases [84], Parkinson's disease [84] and malignant brain tumor [85]. It has been revealed that miR-19a inhibits the differentiation of neural stem cells into neurons by negatively regulating neurogenin 1 [86]. MiR-19b promotes the proliferation of neural progenitor cell through altering PTEN expression [87,88]. MiR-19b is upregulated in neural progenitor cell in human stroke patients and rat models of ischemic stroke, meanwhile, the proliferation of neural progenitor cells is upregulated after stroke [87,88]. Aluminum maltolate could downregulate miR-19a and miR-19b, upregulate PTEN and its downstream apoptosis related proteins, and diminish cell proliferation in vitroin human neuroblastoma SH-SY5Y cells and rat brain tissue [84]. Overexpression of miR-19 attenuates apoptosis induced by aluminum maltolate [84]. Folic acid prevents miR-19a and miR-19b downregulation mediated by aluminum maltolate, thus suppresses cell apoptosis and the progress of Alzheimer's disease [89]. The miR-19 family may be a drug target of folic acid in Alzheimer's disease. A research , revealing the mechanism of neural cell proliferation impaired by sevoflurane , has pointed that abolishment of miR-19-3p upregulation protects the proliferation of neurons, and alleviates the impairment of neuron cell proliferation, learning and memory of neonatal rats with sevoflurane exposure [90].

In addition, dysregulation of miR-19 family in the brain is associated with neuropsychiatric disorders, such as schizophrenia and fragile X syndrome [91,92] . In the brains of schizophrenic patients, the expression of miR-19 is increased and aberrant cell migration is found [91,93]. It has been demonstrated that miR-19a and miR-19b facilitate cell migration of newborn neurons by targeting rap guanine exchange factor 2 (RAPGEF2) and affect the maturation of cells [12,93].

The miR-19 family, as oncogenic miRNA, is significantly upregulated in nervous system tumors [85,94]. Circulating miR-19 is regarded as potential prognostic biomarker of glioma and is associated with poor patient survival [95]. In the glioma cells, miR-19 inhibits apoptosis and promotes proliferation, invasion and migration by targeting PTEN [85,96], P53 [96,97], peroxisome proliferator activated receptor alpha (PPARα) [98], leucine rich repeats and immunoglobulin like domains1 (LRIG1) [99], runt related transcription factor 3 (Runx3) [100], ras homolog family member B (RhoB) [101]. The miR-19 inhibitor has reduced tumor growth in flank and brain allografts and prolonged the survival of mice [94]. The miR-19 is a potential target for gene and drug associated with nervous system tumors. Long noncoding RNA maternally expressed gene 3 (MEG3) acts as a competing endogenous RNA for miR-19a to suppress glioma cell proliferation, migration, and invasion [102]. Resveratrol could inhibit the growth of glioma cells via downregulating miR-19 and upregulating downstream pathway [96].

7. Conclusions and future perspective

In this review, we summarized the current knowledges about miR-19 family, and its physiology and pathology roles in heart, vessels and neurons (Fig. 6). The miR-19 family regulates the function of heart, vessels and neurons mainly through modulating proliferation, apoptosis, differentiation, repolarization, invasion and migration of cells by targeting multiple genes. The level of miR-19a or miR-19b in tissue, serum or plasma of patients or animal disease model has been proved changed in the early stage or the process of cardiac, vascular or neurological disease, making potential value of miR-19 family as diagnostic

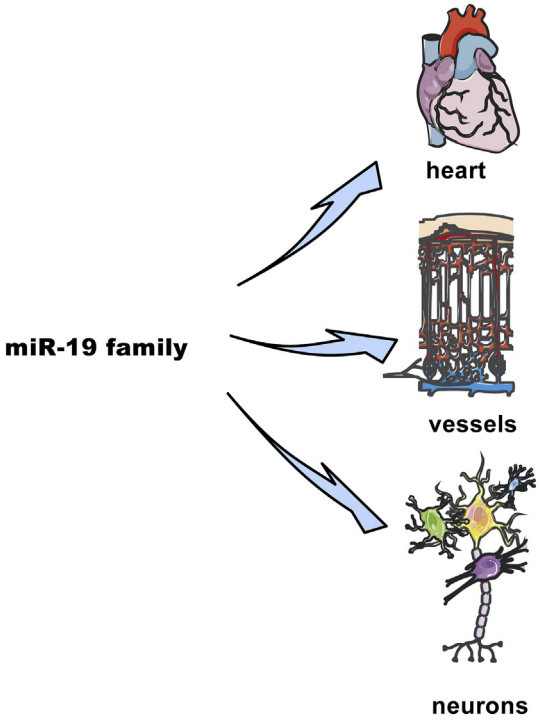

Fig. 6. This review focuses on the roles of miR-19 family in the development and disease of heart, vessels and neurons to estimate the potential value of miR-19 family as diagnostic biomarker or therapeutic target of cardiac, neurological, and vascular diseases.

or prognostic biomarker, although there is no clinical application at present. Some functional mechanisms of miR-19 to development and disease of heart, vessels and neurons have been revealed in vivo and in vitro experiments. When related drugs have been used in animal models of diseases, the expressions of miR-19 and its downstream genes are changed, suggesting the potential of miR-19 as target for the drugs. In conclusion, studies provide evidences to support the potential biomarker and therapeutic target of miR-19 family for cardiac, neurological, and vascular diseases. Despite recent extensive research in this field, there are still certain challenges and barriers that remain to be overcome before their clinical application. The delivery, specificity, side effects and security of miR-19 family need to be further studied before miR-19 can become effective therapeutic tools.

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Declaration of Competing Interest

The authors report no conflict of interest.

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