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Review

Regulation of cardiac stem cells by microRNAs: State-of-the-art

Armita Mahdavi Gorabi[a], Vanessa Bianconi[b], Matteo Pirro[b], Maciej Banach[c,d], Amirhossein Sahebkar[e,f,g,*]

[a] Research Center for Advanced Technologies in Cardiovascular Medicine, Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran
[b] Unit of Internal Medicine, Angiology and Arteriosclerosis Diseases, Department of Medicine, University of Perugia, Perugia, Italy
[c] Department of Hypertension, WAM University Hospital in Lodz, Medical University of Lodz, Zeromskiego 113, Lodz, Poland
[d] Polish Mother's Memorial Hospital Research Institute (PMMHRI), Lodz, Poland
[e] Halal Research Center of IRI, FDA, Tehran, Iran
[f] Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
[g] Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

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ABSTRACT

Stem cells have a therapeutic potential in various medical conditions. In cases without sufficient response to conventional drug treatments, stem cells represent a next generation therapeutic strategy in cardiovascular diseases. Cardiac stem cells (CSCs), among a wide variety of stem cell sources, have been identified as a valid option for stem cell-based therapy in cardiovascular diseases. CSCs mainly act as a cell source to supply the physiological need for cardiovascular cells. However, they have been demonstrated to reproduce the myocardial cells under pathological settings. Despite their roles and functions have somewhat been clarified, molecular pathways underlying the regulatory mechanisms of CSCs are still not fully elucidated. Several studies have recently shown that different microRNAs (miRNAs) play a substantial role in regulating and controlling both the physiological and pathological proliferation and differentiation of stem cells. MiRNAs are small non-coding RNA molecules that regulate gene expression and may undergo aberrant expression levels during pathological conditions. Understanding the way through which miRNAs regulate CSC behavior may open up new horizons in modulating these cells *in vitro* to devise sophisticated approaches for treating patients with cardiovascular diseases. In this review article, we tried to discuss available evidence about the role of miRNAs in regulating CSCs.

1. Introduction

MicroRNAs (miRNAs) are endogenous, small, non-coding RNAs that play a crucial role in the post-transcriptional regulation of mRNA expression. It has been established that miRNAs have a crucial role in different physiological processes like cell proliferation and differentiation, cell metabolism, and apoptosis, as well as in different pathological conditions [1–11]. Over the course of past few decades, stem cells have been studied as a potential treatment strategy in patients with cardiovascular diseases who show insufficient response to the conventional treatments [12,13]. Stem cells are multipotent progenitor cells that are involved in the formation of new tissues through a number of asymmetric cell divisions resulting in the generation of variably differentiated daughter cells [14]. In recent preclinical studies, cardiac stem cells (CSCs) have shown the potential of reproducing tissues of diseased hearts [15–17]. In spite of difficulties in harvesting an enough amount of cells as well as invasive processes of obtaining CSCs, these cells seem to be the preferred stem cell source in stem cell-based therapies for the treatment of cardiovascular diseases [15,17]. Nevertheless, little has been understood with respect to the molecular mechanisms that regulate the physiology of CSCs. Here, we intended to go over the basic features of CSCs, and then to discuss the role of different miRNAs in controlling CSC function.

2. MicroRNAs

MiRNAs are short non-coding RNA molecules within eukaryotic cells containing about 22 nucleotides. MiRNAs are regarded as post-transcriptional regulatory molecules that function by binding to the complementary regions of target mRNAs, leading either to their transcriptional suppression or degradation. Through controlling the expression of several genes, actually, miRNAs are considered as crucial regulatory elements of various biological cellular processes, such as early commitment to a specific lineage, differentiation, proliferation,

* Corresponding author at: Biotechnology Research Center, Mashhad University of Medical Sciences, Mashhad 9177948564, Iran.
E-mail address: sahebkara@mums.ac.ir (A. Sahebkar).

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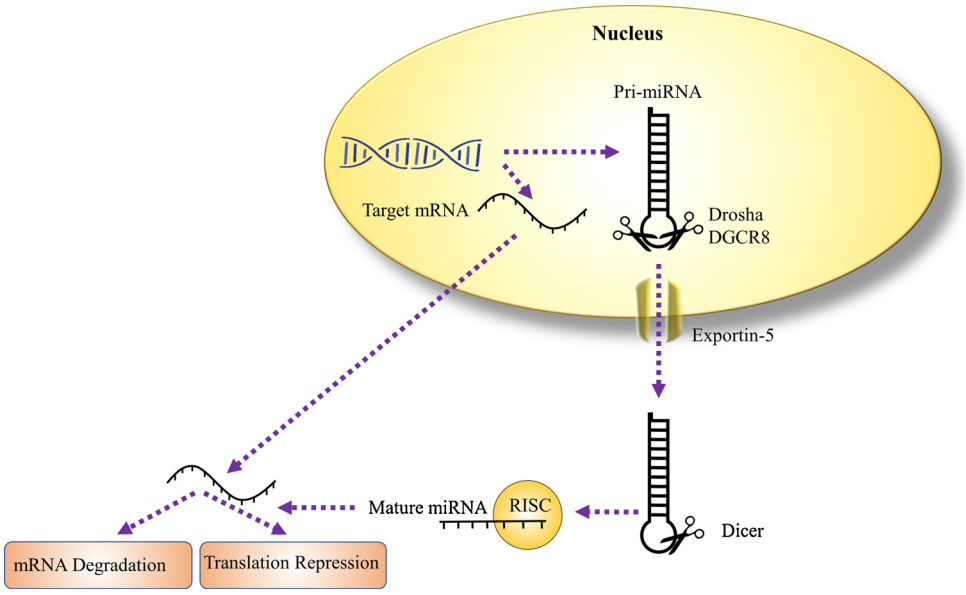

Fig. 1. Mechanisms of miRNA actions. miRNAs are endogenous, small, non-coding RNAs that are involved in the post-transcriptional regulation of mRNA expression. Generation and maturation of miRNAs include a number of steps that start in the nucleus with the transcription of primary miRNAs by RNA polymerase II. Subsequently, primary miRNAs are processed *via* an RNase III (also called Dorsha) and Pasha and maturate into stem-loop forms with a length of almost 70–100 nucleotides, namely pre-miRNAs. Pre-miRNAs are then delivered into the cytoplasm via Exportin 5 located in the membrane of nucleus. In the cytoplasm, pre-miRNAs are processed by an RNase III (also called Dicer) and maturate into double-strand 18–42 bp miRNA molecules. Upon separation of the two strands in the cytoplasm, one of them functions as a mature miRNA by binding to the RISC. This complex includes the mature single-strand miRNA and suppresses the expression of mRNAs. In fact, the final function of miRNAs in suppression of gene expression depends on the complementary miRNA-mRNA interaction. If the sequence of miRNA matches completely with the target mRNA, the result is the degradation of target mRNA. Instead, a partial complementary sequence results in the temporary suppression of mRNA translation.

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3. Cardiac stem cells

Over the course of recent years, CSCs have gained a great deal of attraction to be used in the clinical practice because of their potential in differentiating towards cardiovascular cells with normal functions. In the adult human myocardium and epicardium, there is a reservoir of resident CSCs that can be triggered in response to pathological stimuli, such as ischemic injuries [18,19]. Actually, these resident CSCs have the potential to differentiate into several cardiovascular cell types, including cardiomyocytes [20–22] and endothelial cells [23,24]. This ability is required for maintaining the normal physiological turn-over of cardiac cells [25,26]. For clinical applications, CSCs could be isolated from myocardial or epicardial tissues of patients with cardiovascular diseases, expanded *in vitro* to attain a sufficient number of cells, and then transplanted back into patients to repair the injured heart tissue [27–29]. After the discovery of CSCs [30], several studies have been performed to attain different subsets of CSCs in mice and humans [30]. With respect to their ability to differentiate into cardiomyocytes, CSCs are functionally the same in both mice and humans. However, *in vitro* studies have shown that mice CSCs can be expanded in a slower pace when compared with human CSCs [31]. Cardiac progenitor cells (CPCs) are another subgroup of stem cells that can be found within myocardium. Although both CSCs and CPCs show identical surface markers as well as functional characteristics, these cells can be distinguished on the basis of their behavior during myocardial differentiation in physiological conditions. Accordingly, CSCs possess great proliferative and differentiation abilities. Instead, CPCs have been shown to differentiate only toward mature cardiomyocytes and to exhibit a little proliferative ability [32] (Fig. 2).

3.1. Subsets of CSCs

To date, a number of subsets of CSCs have been characterized according to the expression of surface molecules, including multidrug resistance protein 1 (MDR-1), stem cell antigen 1 (Sca-1), islet1 (Isl1), and c-kit protein [29]. Almost 70% of CSCs express the Sca-1 marker in murine cardiovascular tissues [33,34]. Sca-1 expressing CSCs show a mesenchymal phenotype and can expedite the cardiac remodeling process after myocardial infarction (MI) [35]. In spite of lack of sufficient data in characterization of the human ortholog Sca-1 molecule, Sca-1-like CSCs have been isolated from the adult human heart by applying an anti-mouse Sca-1 antibody. Human Sca-1-like CSCs have been shown to express early cardiac transcription factors and have the potential to differentiate into cardiomyocytes that possess contractile abilities [28]. Also, human Sca-1-like CSCs were reported to express some mesenchymal stem cell (MSC) surface markers, including CD90 and CD105. When cultured in the cardiac differentiation medium, human Sca-1-like CSCs expressed cardiac specific genes [36].

CSCs typically express c-kit on their surface. C-kit is utilized as the major marker for the isolation of human CSCs from heart [29,31]. By comparing the different CSC subsets, it was found that c-kit-positive cells were the primitive sup-population in the heart [37]. Nonetheless, endogenous c-kit-expressing CSCs are recruited to ischemic areas and then differentiate toward cardiomyocytes. In mice, it was demonstrated that the suppression of endogenous c-kit-expressing cells within myocardium impaired the process of heart repairing after an induced myocardial injury [38]. Furthermore, preclinical studies [39–41] reported a remarkable improvement in heart repair upon transferring of exogenous c-kit-expressing CSCs into injured myocardial tissue. However, a little functional importance of the c-kit protein as the primary surface marker of CSCs has been reported [42]. As a result, functional studies need to be performed to establish the precise role of c-kit-expressing CSCs.

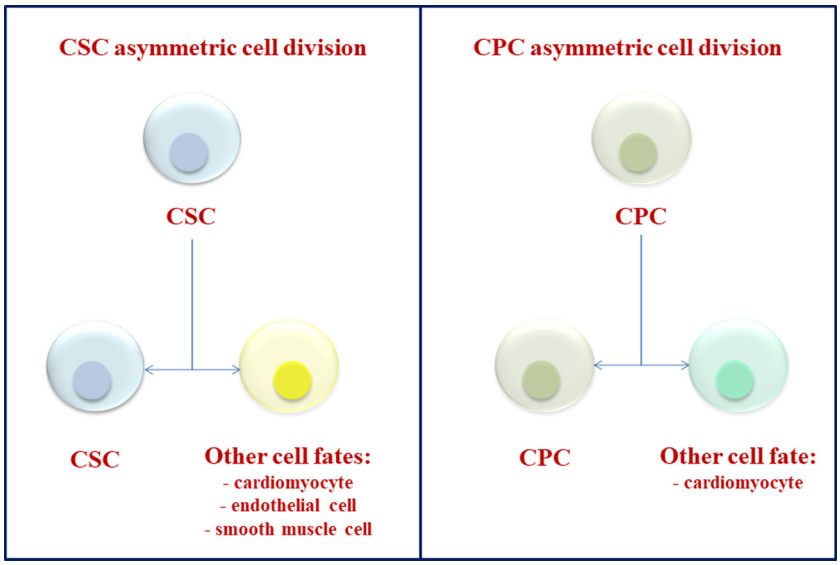

Fig. 2. Cardiac stem cell (CSC) and cardiac progenitor cell (CPC) asymmetric cell division. Both CSCs and CPCs show identical surface markers as well as functional characteristics, these cells can be distinguished on the basis of their behavior during myocardial differentiation in physiological conditions. CSCs present proliferative and differentiation abilities. CPCs have been shown to differentiate only toward mature cardiomyocytes and to exhibit a little proliferative ability.

Isl1 was first identified as a specific surface marker for the second heart field (SHF), a population of multipotent progenitor cells which are involved in the elongation of heart tube during the looping morphogenesis. Nonetheless, studies have reported that Isl1 expression may be found within common cardiac progenitors and may play a critical function during the development of heart tissues [43]. Isl1-positive CSCs overexpress angiogenic-associated genes. Moreover, it was reported that *Isl1* gene delivery into cardiomyocytes culminated in an expedited myocardium functional improvement and decreased myocardial fibrosis in murine injured hearts [44]. Finally, it was shown that Isl1-expressing cardiac progenitors found in the human myocardium had the ability to differentiate into several heart cell lineages, including smooth muscle cells, cardiomyocytes, and endothelial cells [45].

3.2. Potential of CSCs to be used as a cell source for stem cell-based therapies

Heart regeneration may be significantly ameliorated with the autologous engraftment of CSCs into injured heart tissues through two major pathways, including either the direct differentiation of CSCs into cardiovascular cells or the generation of paracrine mediators that stimulate the processes of heart regeneration. In a study by Beltrami et al, in which CSCs were transplanted into infarcted myocardium, a thickened myocardium was detected within the transplantation area. In this study, CSCs were labelled through an enhanced green fluorescent protein (EGFP) before the injection. After the transplantation, these labeled cells were observed to proliferate, as detected by a great deal of fluorescence [27]. Moreover, the engraftment of CSCs ameliorated the function of transplanted human heart. Transplantation of autologous cardiosphere-derived cells resulted in a remarkable improvement in the viable myocardium in subjects with MI [46]. Even though these studies did not provide data about the efficacy of transfusion of other stem cell types, observations from other studies imply that CSCs may serve as an acceptable option for cardiac regeneration in comparison with other stem cell subtypes originated from other sources. Such result may due to the nature of CSCs, that are primarily programmed to generate cardiomyocytes and, therefore, enhance the viability of cardiac tissue [47–49]. Furthermore, resident CSCs that are found in the proximity of the injured region are located primarily in the specialized areas in the myocardium, which selectively contribute to their tissue viability [50]. As a consequence, CSCs are able to be recruited to the injured region and quickly expand and differentiate, leading to a more expedited and efficient reproduction of the myocardial tissue rather than other stem cell types [51]. Beyond these pathways, it was hypothesized that stem cells primarily carry out their advantageous roles through paracrine mediators [52,53]. Many studies were performed to investigate the impact of various paracrine mediators in the differentiation of stem cells [54–56], such as CSCs [57,58]. Moreover, it was indicated that the exosomes obtained from the CPCs possessed the potential of protecting the ischemic myocardium in mice [59].

4. Physiological functions of miRNAs in CSCs

4.1. MiRNAs, expansion of CSCs, and regulation of myocardial differentiation

MiR-1 and miR-133 have been shown to play a crucial role in controlling the differentiation of stem cells. It has been reported that there is a downregulated expression of miR-1 and miR-133 in mouse embryonic stem cells (ESCs) upon stimulation of myocardial differentiation. In addition, the upregulation of miR-1 and miR-133 was indicated to result in the downregulation of *Nkx2.5* (a cardiac specific gene) in ESCs. Moreover, the upregulation of miR-1 was reported to result in a decreased translation of cyclin-dependent kinase 9 (cdk9), which is involved in the activation of cardiac-specific genes [60]. Hand2, which is a transcription factor involved in the development of ventricular cardiomyocytes, was shown to be a targeted by miR-1 [61]. These observations show a crucial involvement of miR-1 and miR-133 in the control of myocardial differentiation *via* regulating the expression of cardiac-specific genes.

However, there are controversial findings with respect to the regulatory role of miR-1 and miR-133 in controlling the functions of CSCs and CPCs [61,62]. Accordingly, it was indicated that miR-1 overexpression, by suppressing the translation of delta-like protein 1 precursor (DLL1), promoted the differentiation of CPCs [62]. By contrast, miR-133 was reported to suppress the differentiation of CPCs [62]. Despite the molecular mechanisms of this suppression are not fully understood, it was shown that miR-133 targeted the negative elongation factor (NELF)-A, a factor involved in the cardiogenesis [63].

Moreover, it was demonstrated that miR-1 and miR-499 decreased proliferative potency and increased differentiation ability of human CPCs. In such context, miR-1 was shown to suppress the expression of histone deacetylase 4 (HDAC4), involved in the silencing of muscle gene expression. Instead, miR-499 was reported to target the sex determining region Y (SRY)protein involved in muscle differentiation [64]. In addition, the silencing of miR-1 and miR-499 culminated in the inhibition of CPC differentiation [64]. These observations imply that the expression of both miR-1 and miR-499 is mandatory for CPCs and

provide evidence for the inevitable involvement of miRNAs in controlling the differentiation and expansion of the CPCs.

In CPCs of species other than humans like Drosophila, miR-1 was identified to target Notch ligand and, therefore, to suppress Notch signaling [65]. It was shown that Notch signaling was involved in cardiogenesis during ESC differentiation. This is in line with previous findings showing that in Drosophila the differentiation of CPCs was inhibited when miR-1 was silenced [65,66]. Other than Notch signaling pathway, it is hypothesized that miR-1 may target other molecular pathways that are critical during cardiogenesis [65].

A bulk of investigations provide evidence on the involvement of other miRNAs, including miR-23a, miR-23b, miR-193a, miR-204, miR-218, and miR-669a in promoting CPC differentiation [67,68]. It was reported that miR-204 silencing enhanced the expansion of human CPCs, even though no effect was detected on cell survival. Moreover, miR-204 silencing was correlated with a decreased differentiation capacity and a downregulation of cardiac-specific proteins, including β-myosin heavy chain, c-actin, and troponin T. Activating transcription factor 2 (ATF2) was recognized as a target of miR-204, as the upregulation of ATF2 in human CPCs improved the expansion capacity of CPCs. As a consequence, miR-204/ATF2 is considered as another molecular pathway involved in the expansion of CPCs [67]. Moreover, it was observed that the expression of miR-193a was downregulated in insulin-like growth factor (IGF)-1-stimulated CSCs. On the other side, c-kit-expressing CSCs transfected with lentivirus carrying miR-193a downregulated c-kit expression and decreased migration and proliferation abilities of CSCs [69]. Additionally, the upregulation of miRNA-21 was observed to enhance the migration and proliferation of Sca-1 expressing CSCs and to enhance the ability of these cells to repair damaged myocardium [70]. A negative regulator of the Wnt signaling, secreted frizzled related protein 2 (sFRP2), was observed to be a direct target of miR-218. CSC transfection with the miR-218 mimic was observed to culminate in the expression of sFRP2 and to intensify Wnt signaling. The downregulation of sFRP2 by shRNA potentiated the Wnt signaling, contributing to CSC proliferation and differentiation into cardiac cells [71].

The function of miR-669a and miR-669q was studied by extracting neonatal CPCs from mice mutant for β-sarcoglycan, that have a downregulated expression of miR-669a and do not express miR-669q. After the engraftment of CPCs into infarcted hearts, these cells generated skeletal muscle fibers. Nonetheless, the upregulation of miR-669a and miR-669qdecreased CPC potential to differentiate toward skeletal muscle fibers by suppressing the expression of MyoD [68].

Some miRNAs have been identified to be expressed in clusters in CPCs [72]. The cluster of miR-17-92, including miR-17, miR-18, miR-19a, miR-19b, miR-20a, and miR-92a, has been observed to be expressed in CPCs and to increase their expansion potential. In order to shed further validation light on this observation, lentiviral-mediated upregulation of miR-17-92 cluster was carried out in mouse heart cells. The upregulation of miR-17-92 cluster enhanced the proliferation potential of CPCs [73]. Therefore, it seems that miRNA clusters (like miR-17-92) may play a critical role in modulating the proliferative capacity of CPCs, suggesting a novel therapeutic potential with regard to stem cell therapy [73]. Bone morphogenic protein (BMP)4 has been reported to regulate the expression of miR-17-92 cluster. Particularly, BMP4 knocking down was reported to result in the downregulation of miR-17-92 cluster expression, which ultimately led to a decreased capacity of CPCs to differentiate into myocardial cells [74].

In different pathological conditions like hypertension and diabetes, there is a small capacity of myocardial differentiation as well as proliferation of CSCs because of an increased apoptosis rate [75]. Nonetheless, miRNAs can be manipulated to trigger the differentiation and expansion capacity of CSCs.

4.2. MiRNAs, neovasculogenesis, and angiogenesis via CSCs and CPCs

It has been reported that the overexpression of miR-1 in CPCs is involved in promoting the angiogenic differentiation. Moreover, the upregulation of miR-1, by suppressing the antiangiogenic sprouty-related, EVH1 domain-containing protein 1 (spred1), was shown to cause an increased vascular tube generation, spheroid sprouting, and recruitment of CPCs [76]. As a consequence, miR-1 possesses the potential to be used as a therapeutic tool in promoting angiogenesis in ischemic heart disease [77]. As a proangiogenic miRNA, miR-132 play a role in promoting neovasculogenesis by CPC commitment [78,79]. It has been demonstrated that saphenous vein-derived progenitor cells (SVPs) were able to produce miR-132 that targeted p120RasGap (an inhibitor of proangiogenic VEGF) and, therefore, promoted their differentiation into vascular cells. Moreover, the infusion of SVPs into the infarcted myocardium of mice upregulated significantly the expression of miR-132, thereby ameliorating angiogenesis in ischemic area. Furthermore, released miR-132 triggered endogenous CSCs, which then further enhanced angiogenesis *via* differentiation of CSCs toward vascular cells [80].

5. Pathological functions of miRNAs in CSCs

5.1. miRNAs and vascular remodeling via CSCs

Several investigations have reported that miRNAs are involved in the process of vascular remodeling in different pathological settings (Fig. 3) [81]. Inhibition of dicer was observed to result in the suppressed growth and expansion of vascular smooth muscle cells. In addition, knocking out of *dicer* gene in mice was observed to led to a decreased thickness of aorta medial layer of smooth muscle cells because of an aberration in actin stress fibers [82].

It has reported that miR-221 and miR-222, through the direct targeting of c-kit and the indirect downregulation of endothelial nitric oxide synthase (eNOS) expression, caused the inhibition of endothelial cell proliferation, endothelial cell migration, and vascular remodeling [83]. Moreover, miR-221 and miR-222 downmodulated c-kit expression in hematopoietic progenitor cells, resulting in a decreased rate of cell proliferation [84]. C-kit is a critical marker of CSCs, and since miR-221 and miR-222 target this molecule, it seems that it also plays an essential role in CSC differentiation [31]. The crucial role of eNOS in the migration and function of stem cells has been established [85]. Moreover, it should be noted that a number of chronic pathological conditions, including hyperlipidemia or diabetes can negatively influence the function of these miRNAs in CSCs. Accordingly, it has been reported that there is an upregulated expressions of miR-221 [86] and miR-222 [87] in diabetic patients. Therefore, it is possible that these miRNAs are overexpressed in CSCs from heart tissue of diabetic patients. As a consequence, manipulating the expression of miR-221 and miR-222 in CSCs may be useful to control vascular remodeling in diabetic patients.

5.2. MiRNAs and potassium channels in CPCs

Two potassium channels, KCNQ1 and KCNE1, are expressed on the CPC surface and play an important role in cell repolarization [88]. Through the down-regulation of the expression of potassium channels on the surface of cardiomyocytes, miR-1 overexpression was shown to trigger cardiac arrhythmias [89]. Also, CPC exposure to high glucose levels was reported to culminate in the upregulation of miR-1 and miR-133, leading to a reduced expression of KCNQ1 and KCNE1 channels on the cell surface [90]. Hence, miR-1 and miR-133 seem to play an important role in the modulation of potassium channels in CPCs and the aberrant expression of these miRNAs seems to interfere with cardiac cell function (Fig. 3).

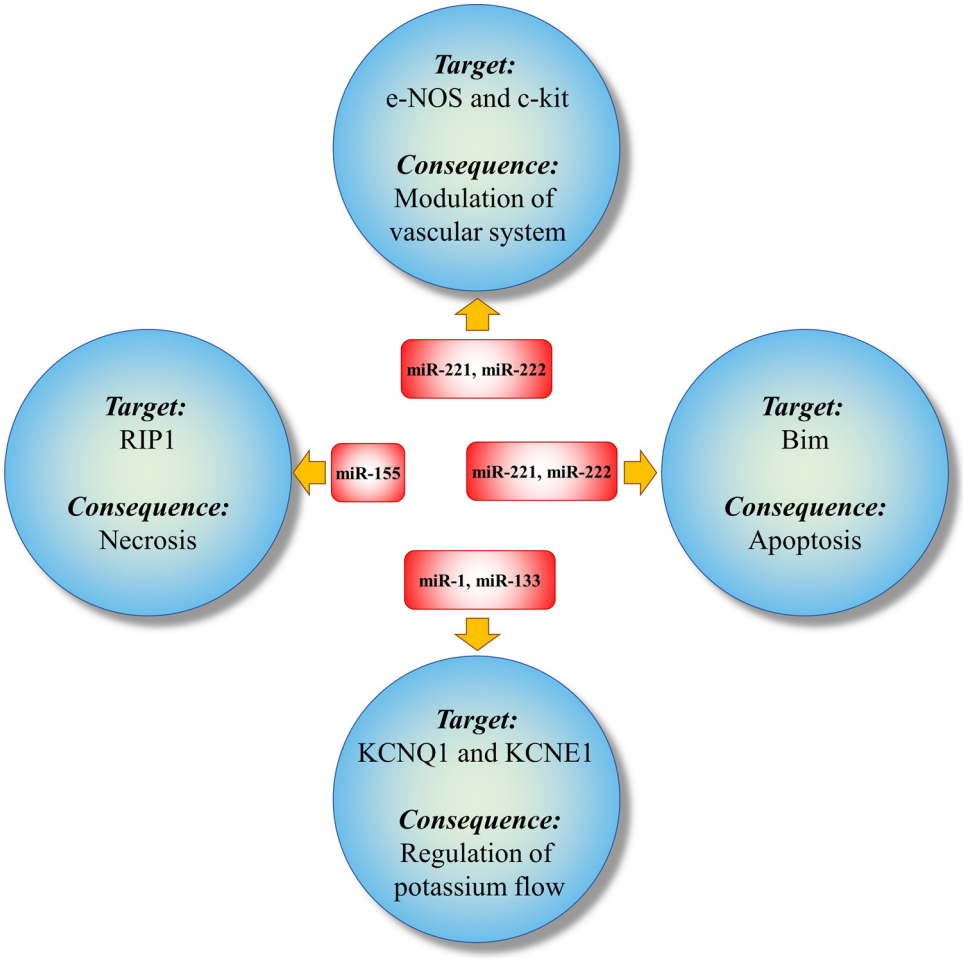

Fig. 3. Different miRNAs, by targeting various molecular pathways in CSCs, might modulate vascular system, potassium channel remodeling, apoptosis, and necrosis and, thereupon, play a critical role in the fate of cardiovascular system.

5.3. MiRNAs and survival of CSCs and CPCs

Different miRNAs have been reported to regulate the survival and apoptosis of CSCs. CPC exposure to miR-21, miR-221, and miR-24 increased cell survival by modulating the expression of the B cell lymphoma 2 interacting mediator of cell death (Bim), which plays a crucial role in the programmed cell death [91]. The exposure of c-kit-expressing CSCs to miR-21 inhibited the phosphatase and tensin homolog (PTEN) expression and reduced the oxidative stress-triggered cell death [92,93]. Furthermore, when murine CPCs were treated with a miRNA cocktail including miR-21, miR-221, and miR-24 and were injected into infarcted hearts, a prolonged CPC survival rate was observed [91]. MiR-125a plays a central role in the maintenance of the CSC reservoir, as it has been shown to be upregulated in CSCs and involved in the regulation of CSC apoptosis [94]. Beyond apoptosis, it has been reported that some miRNAs play a crucial role in the necrotic cell death of CSCs. When CSCs were exposed to pro-oxidant hydrogenperoxide, an upregulation of miR-155 was observed [95]. Continuous exposure of miR-155-treated CSCs to oxidative stress suppressed the necrotic cell death through the inhibition of a necrosis activator protein, namely receptor interacting protein 1 (RIP1) [95]. The engraftment of transplanted CSCs in diabetic cardiomyopathy depends largely on their survival [96,97]. Thus, the use of miRNAs involved in the repression of apoptosis and necrosis might be a promising strategy in increasing the survival of stem cells and improving their regenerative potential (Fig. 3). Nonetheless, further investigations are still needed to find a precise miRNA network involved in the regulation of CSC death and survival.

6. MiRNA modulation in CSCs and CPCs for therapeutic purposes

With respect to the involvement of different miRNAs in both physiological and pathological conditions in CSCs, researchers have focused on the potential of some miRNAs in ameliorating the regenerative activity of CSCs and enhance their efficacy in the treatment of cardiovascular diseases. It was observed that the suppression of miR-378 expression improved the survival of CSCs by promoting the connective tissue growth factor (CTGF) expression. CTGF has a crucial role in the protection against tissue ischemic injury [98], since it promotes tissue repair, fibrosis [99] and survival of endothelial cells [100]. Specifically, when CSCs were provoked by an electrical impulse, miR-378 was downregulated and, thereupon, CTGF was overexpressed. This observation suggests that the suppression of miR-378 might increase the CSC vitality [101]. It was reported that miR-499 was involved in the differentiation of CSCs into cardiomyocytes. In physiological conditions miR-499 is poorly expressed in CSCs, while it is upregulated in cardiomyocytes. Nonetheless, in case of necessity, miR-499 is upregulated in CSCs and, by targeting the regulator of differentiation 1 (Rod1) and Sox6, stimulates them to differentiate into cardiomyocytes. Similarly, when miR-499-expressing CSCs were engrafted into rat infarcted hearts, the differentiation of CSCs into cardiomyocytes was expedited and cardiac function was ameliorated [102].

The regenerative potential of CPCs was demonstrated to be modulated by miR-133. When CPCs were cultured in different differentiation media, the expression of miR-133 was shown to be significantly upregulated. Furthermore, the administration of miR-133-overexpressing CPCs into injured heart tissues *in vitro* ameliorated cardiomyocyte

function [103]. Although no clinical trial has been conducted to investigate the efficacy of miR-133, miR-378, and miR-499-overexpressing CSCs in treating cardiovascular diseases, there have been promising results in animal studies. Actually, the potential utility of these miRNAs in modulating CSC function with the aim of treating cardiac diseases is under investigation; yet, we still need to better explore the precise mechanisms of the miRNA regulatory pathways in CSCs.

Certain miRNAs have been successfully delivered in stem cells and in cancer cells using nanoparticles to restore endogenous levels in order to change the phenotypic behavior of cells [104–108]. It was found that magnetic nanoparticles-mediated transfection of miRNAs into stem cells may provide a long-term beneficial effect for genetic modulation [109]. As a consequence, such approaches in efficient delivery of miRNAs to CSCs or CPCs may become of critical importance for future *in vivo* and clinical applications.

7. Conclusions and perspectives

Different miRNAs play a critical role in modulating the proliferation, differentiation and function of CSCs. Over the course of past few years, it has been surveyed the potential impact of some miRNAs in improving the regenerative efficacy of CSCs by enhancing their expansive and differentiative capacities. Controlling the expression of cardiac-specific miRNAs in CSCs might provide an advantageous strategy in stem cell-based therapies for cardiovascular diseases. Studies conducted in animal models investigating the treatment of cardiovascular diseases with the modulation of miRNAs in CSCs have shown promising results. Nonetheless, clinical trials are still mandatory to be performed to gain clear vision about the efficacy of miRNA regulation in CSCs in treating cardiovascular diseases. Also, there are several unclear aspects that needs to be clarified with respect to the regulation and biological role of miRNAs in CSCs. For instance, few data are currently available about the influence of age, gender, concomitant diseases, medications, and environmental factors on the biological activity of miRNAs in CSCs. Future research could provide promising understandings with respect to the precise function of miRNAs in the biology of CSCs, which might hopefully culminate in the devising of novel therapeutic approaches.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Banach has served on speaker's bureau and as an advisory board member for Amgen, Sanofi-Aventis and Lilly. Other authors have no competing interests to disclose.

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None.

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