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Stem cell-derived exosomes, autophagy, extracellular matrix turnover, and miRNAs in cardiac regeneration during stem cell therapy

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Abstract

Stem cell therapy (SCT) raises the hope for cardiac regeneration after ischemic heart disease. However, the molecular mechanisms underlying repair of dead myocardium in the ischemic heart is poorly understood. Growing evidences suggest that cardiac matrix stiffness and differential expressions of miRNAs play a crucial role in stem cell survival and differentiation. However, their roles on transplanted stem cells, for the myocardial repair of the ischemic heart, remain unclear. Transplanted stem cells may act in an autocrine and/or paracrine manner to regenerate the dead myocardium. Paracrine mediators such as stem cell-derived exosomes are emerging as a novel therapeutic strategy to overcome some of the limitations of SCT. These exosomes carry microRNAs (miRNAs) that may regulate stem cell differentiation into a specific lineage. MicroRNAs may also contribute to stiffness of surrounding matrix by regulating extracellular matrix (ECM) turnover. The survival of transplanted stem cell depends on its autophagic process that maintains cellular homeostasis. Therefore, exosomes, miRNAs, extracellular matrix turnover, and autophagy may have an integral role in improving the efficacy of SCT. This review elaborates the specific roles of these regulatory components on cardiac regeneration in ischemic hearts during SCT.

Keywords

Exosomes; microRNA; extracellular matrix; trans-differentiation; MMP9; autophagy

Introduction

Ischemic heart disease is a leading cause of mortality in the world. As per the 2012 World Health Organization report 7.4 million people die due to ischemic heart disease (http://www.who.int/mediacentre/factsheets/fs310/en/). Restricted blood supply to the ventricular muscles, due to narrowing of coronary arteries, results in ischemia that compromises oxygen

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supply to cardiomyocytes and other cells in the myocardium. Severe ischemia leads to acute myocardial infarction (MI) that results into massive loss of cardiomyocytes (1). The adult mammalian heart does not have adequate regenerative capacity to replenish the loss of damaged myocardium after MI. Therefore, MI leads to heart failure (2). Stem cell therapy (SCT) provides a strategy to regenerate new myocardium to replenish dead/damaged myocardium of MI hearts by using exogenous stem cell transplantation (3, 4). However, the survival, proliferation, and differentiation of transplanted stem cells depend on several factors including the stiffness of extracellular matrix (ECM) surrounding the stem cells (5-10). Proteolysis of ECM by matrix metalloproteinase (MMPs) is common in cardiovascular diseases (CVD) (11). MMP9 plays an important role in ECM degradation in pathological hearts that leads to cardiac fibrosis, a stiffer ECM, that may influence cardiac stem cell survival and differentiation (8). MMPs are regulated by microRNAs (miRNAs) (12, 13). MiRNAs are tiny non-coding RNAs that regulate biological functions of a cell by modulating expression of genes (14). MiRNAs have emerged as a novel therapeutic target for CVD (15-17). MiRNAs may play a pivotal role in stem cell survival because they regulate stem cell autophagy (18, 19). Autophagy is a lysosomal degradation process that regulates cellular homeostasis (20). MiRNAs may regulate cardiac stem cell proliferation and differentiation (21) by acting in an autocrine and/or a paracrine fashion (22, 23). MiRNAs encapsulated in an exosome circulate through blood and may have paracrine effects (24). Exosomes are lipid bilayer nanovesicles released by different types of cells when endosomes carrying multivesicles fuse with plasma membrane. Exosomes exert their therapeutic actions by involving in cell-cell interactions and transferring proteins, RNAs (25), and miRNAs (23). Exosomes derived from cardiac stem cells are promising therapeutic candidate because in one hand it may regulate survival, proliferation and differentiation of the transplanted stem cells whereas on the other hand it may overcome the limitations of SCT due to immune rejections, teratoma, or ethical concerns. In this review, we elaborated the roles for exosomes, miRNAs, autophagy, and extracellular matrix turnover in cardiac regeneration during stem cell therapy in ischemic hearts.

Stem cells characteristics and types

Stem cells are pluripotent cells that can differentiate into different lineages to regenerate different types of cells (26). Based on origin, stem cells are classified into embryonic stem cells (ESCs) and adult stem cells (ASCs). ESCs can be maintained in tissue culture, while retaining their pluripotency (27). ESCs in cell culture express the intrinsic transcription factor Oct4 and constitutively receive the extrinsic signal from the leukemia inhibitory factor (LIF) to maintain their pluripotent state (28, 29). Adult stem cells (ASCs) are slow cycling cells that are able to respond to specific environmental signals to either proliferate or differentiate. During differentiation, these ASCs enter into a transient state of rapid proliferation (30), withdraw from cell-cycle, and execute terminal differentiation. ASCs are localized in specific niches, where they utilize many of the extrinsic and intrinsic cues used by their embryonic counterparts in selecting a specific fate. ASCs are roughly categorized into bone marrow stem cells (BM-SCs), circulating pool of progenitor cells such as endothelial progenitor cells (EPCs), and tissue-resident stem cells such as cardiac stem cells (CSCs). BM-SCs are further categorized into mesenchymal stem cells (MSCs) and

hematopoietic stem cells (HSCs) (31). According to the expression of surface markers and properties, resident CSCs were classified into different subsets such as c-Kit-positive (c-Kit^{+}) cells, Sca-1-positive (Sca-1^{POS}) cells, side population (SP) cells, cardiosphere cells, and Isl1-positive (Isl1^{POS}) cells (32). CSCs are multipotent cells that can differentiating into multiple lineages; such as cardiomyocytes, smooth muscle cells, and endothelial cells (33, 34).

Regulators of CSCs proliferation and differentiation

The adult heart has small number of CSCs that may have potential for cardiac regeneration (35-37). Stem cells can be differentiated into cardiomyocyte with the treatment of a specific combination of factors (38). CSCs were identified and validated using various markers such as c-kit, MDR-1, and Sca-1 (38, 39). They are heterogeneous and expresses 7%-10% of important cardiogenic transcription factors like Nkx2.5, GATA4, and MEF2 (36). CSCs can divide both symmetrically and asymmetrically, however, asymmetrical division is predominant (40). They regulate myocytes turnover, which is heterogeneous across the heart. Myocytes turnover is faster at the apex and atria and slower at the base-and mid-regions of the ventricle (38, 41). The studies on CSCs differentiation were performed primarily on mice and chick embryos. The formation of cardiomyocytes from mesoderm is regulated by Wnts, BMPs, and Nodal (42, 43). Inhibition of Nodal (a family member of TGF-β), and Wnt promotes formation of cardiomyocytes in xenopus and chick embryos (44-46). Inhibition of Nodal and Wnt is also important for differentiation of mouse ESC into cardiomyocytes (46-48). The transmembrane receptor Notch induces a combination of growth factors that up regulates differentiation of ESC-derived mesoderm subpopulations into cardiac progenitors (49). These growth factors include Wnt5a, BMP6, and secreted frizzled-related protein1 (Sfrp1) (50). The differentiation of committed cardiac progenitors into cardiomyocytes is the last step of differentiation, and is poorly understood. It is believed that Wnt11 plays a crucial role in this last step (48, 51). The transduction of Wnt11 promotes mesenchymal stem cell trans-differentiation into cardiac phenotypes *in vitro* (52). Several transcription factors regulates differentiation of pluripotent stem cells (PSCs) into cardiac fate. These transcription factors include T Brachyury for primitive streak mesoderm, mesoderm posterior 1(Mesp-1) for cardiogenic mesoderm, and Nkx2.5, T-box (Tbx5/20), GATA4, MEF2C, and Hand1/2 for cardiac mesoderm (53-57). Cardiac development is a complex process that is tightly controlled by the sequential expression of multiple signal transduction proteins and transcription factors working in a synergistic manner. The most studied of these growth factors and signaling pathways include FGFs, BMPs, and Wnts/Nodal (58-61). We have summarized the important regulators of stem cells proliferation and differentiation in Figure 1.

Role of autophagy in homeostasis of stem cells

Autophagy is an evolutionary conserved adaptive process required for cellular homeostasis and protecting against various pathological conditions including CVD. During autophagy defective cytoplasmic cargoes are sequestered into double membrane autophagosome which after fusion with lysosome are degraded and recycled (62). Autophagy maintains the quality control of stem and progenitor cells (63). Various properties of the stem cells such as

pluripotency, quiescence, differentiation and self-renewal depends on autophagy activation (64, 65). Therefore, autophagy plays an important role in normal functions of stem and progenitor cells (66). Suppression of autophagy through fibroblast growth factor (FGF) signaling inhibits CSC differentiation (67). Autophagy may have different roles in different types of stem cells. It induces apoptosis in BM-MSCs of non-obese diabetic (NOD) mice (68) but promotes MSC-mediated hepatic regeneration in CC14-injured rat liver model (69) and MSC-mediated wound healing in diabetic mellitus patients (70).

Trans-differentiation of cells

Although differentiation of stem cells into a particular lineage is canonically the strategy for SCT, recent studies revealed that differentiated adult cells can be transdifferentiated into another phenotype by using certain factors. Fibroblasts are present in a large pool in the postnatal heart and they contribute to pathological remodeling via fibrosis. It is observed that by using developmental transcription factors (Gata4, Mef2c, and Tbx5), somatic fibroblast can be reprogrammed into cardiomyocytes in mouse heart (71). In neonatal and adult humans' fibroblasts addition of Gata4, Hand2, Tbx5, myocardin, miR-1 and miR-133 causes trans-differentiation of fibroblast into cardiomyocyte phenotype (72). There are several other factors are involved in this trans-differentiation process (73, 74). However, whether these cardiomyocytes can maintain the cardiomyocytes properties including contractility for prolong time and can maintain synchronous beating with resident cardiomyocytes, is unclear and requires further investigation.

Effect of extracellular matrix turnover on stem cell differentiation

The mechanical force of ECM may influence survival, proliferation, and differentiation of stem cells, and also trans-differentiation of other cells into cardiomyocytes. The mechanical load of the ECM contributes to differentiation of MSCs (75-78). Transforming growth factor- beta (TGF-β) promotes MSC differentiation into a smooth muscle lineage on stiff substrates (79, 80). Soft matrix promotes MSC differentiation into chondrogenic and adipogenic lineages. However, matrix stiffness may not be specific for only one lineage. Biochemical factors such as TGF-β are required to define a unique differentiation pathway (81). ECM stiffness depends on matrix turnover, which is determined by the balance between MMPs and tissue inhibitors of metalloproteinases (TIMPs) (82). MMP-9 and TIMP-4 are predominantly involved in cardiac remodeling. MMP-2 and MMP-9 are collagenases that degrade ECM and contribute to fibrosis (82, 83), where ECM is stiffer (Figure 2). Stiffness of cardiac ECM may play a pivotal role in stem cell therapy (84). MMP9 is also involved in inhibiting EPCs-mediated increase in vessel density in the peri-infarct area in the mouse brain (85). Moreover, it is implicated in migration of c-Kit$^+$ CSCs, which is partially mediated by stem cell factor (SCF) via the activation of PI3K/AKT/MMP-2/-9 signaling pathway (86). These reports indicate the diverse roles of MMPs. Along with MMPs, it was reported that various miRNA family members also regulate ECM. These miRNAs have either pro-, or anti-fibrotic roles in various tissues (87).

MicroRNAs in stem cell proliferation and differentiation

MiRNAs are 22 nucleotide long, non-coding RNAs that modulate gene expression and stem cell proliferation and differentiation (88). They have emerged as a biomarker and a therapeutic target for cardiovascular diseases (15, 89, 90). MiR-29 was found to be an important component of TGF-β signaling, which also regulates collagen synthesis (87). MiR-1, miR-24, miR-29b, miR-101, and miR-200b are anti-fibrotic, whereas miR-15 family, miR-21, miR-34a, miR-192, miR-199b, and miR-208 are pro-fibrotic miRNAs (87). As discussed above, fibrosis changes the ECM tensile properties and ECM related miRNAs can influence stem cell physiology in normal and pathological conditions. In Table 1, we have shown the list of miRNAs targeting important ECM regulators including MMPs, TIMPs, CTGF, and TGF-β (91-137). The information is obtained from online database miRTarbase (http://mirtarbase.mbc.nctu.edu.tw/).

MicroRNAs (miRNAs) regulate differentiation of stem cells into cardiomyocyte (138). MiR-1 induces differentiation of mESCs and hESCs into cardiac phenotype (51, 139). MiR-1 promotes differentiation of stem cell by targeting HDAC4, which is a negative regulator of MEF2, whereas miR-133 promotes stem cell proliferation by targeting SRF. The differential expression of miRNAs in ESCs and CSCs is nicely reviewed by Kuppusamy et al (140). MiR-1, miR-21, miR -133a, miR -133b, and miR -145 are upregulated both in mouse and human ESC differentiation into cardiac lineage, whereas miR-20b is downregulated during this process in both species (140). Empirical evidences demonstrate that several miRNAs are deregulated during differentiation of embryonic stem cells into cardiac stem cell lineage (140-143). It is also reported that miR-499 along with miR-1 and miR-208 regulates cardiomyocyte differentiation (143). MiR-133-a, -b, miR-125-a, -b, miR-126, miR-23-a, -b, miR-24, miR -30C, miR-132 are differentially expressed during mouse CSC differentiation (144). There are several miRNAs that regulate both ECM turnover (Table 1) and stem cell proliferation and differentiation (Table 2). MiR-1, miR-21-5p, miR-26a-5p, miR-26b-5p, miR-30c-2-3p, miR-126-3p, miR-126-5p, miR-145-5p, miR-30a, miR-30b, miR-99b, miR-125a-5p, miR-129-3p, miR-133a, miR-133b, miR-148a, miR-181b, miR-652 are upregulated whereas miR-17-5p, miR-124-3p, miR-200c-3p, miR-205-5p, miR-20a, miR-20b, miR-106a, miR-106b, miR-182, miR-183, miR-183*, miR-302c, miR-302c* are downregulated during differentiation of SC into cardiomyocytes (140, 143). MiRNAs which are involved in regulating ECM turnover include let-7e-5p (124), miR-100-5p (106), miR-103a-3p (121), miR-125b-5p (109), miR-132-3p (111), miR-140-5p (108), miR-143-3p (110), miR-144-3p (121), miR-16-5p (124), miR-181b-5p (119), miR-18a-5p (132), miR-18b-5p (124), miR-19a-3p (137), miR-19b-3p (132), miR-203a (104), miR-221-3p, miR-222-3p (119), miR-24-3p (125), miR-27a-3p (108), miR-27b-3p (107), miR-29b-3p (145), miR-335-5p (99), miR-338-3p (96), miR-375 (136), miR-423-5p (124), miR-451a (94), miR-491-5p (95), miR-519a-3p, miR-519c-3p, miR-519d-3p (112), miR-633, miR-663a (128), miR-9-5p (105). Therefore, miRNAs play an integral role in SCT (Figure 3).

MicroRNAs in trans-differentiation

Cardiac fibroblasts can be reprogrammed to cardiomyocytes using combination of different miRNAs (miR-1, miR- 133, miR- 208 and miR- 499) (146). Administration of these miRNAs into ischemic boarder zone of MI hearts induces trans-differentiation of cardiac fibroblasts into cardiomyocytes. Although miR-1 may be sufficient to induce cardiomyocyte trans-differentiation, the combination of miR-133, -208, and -499 is much more effective in the trans-differentiation process. Fibroblast-turned cardiomyocytes have all the properties of functional cardiomyocytes including contractility and spontaneous calcium oscillations (146). Therefore, trans-differentiation of fibroblast to cardiomyocytes by miRNAs provides a novel opportunity in SCT.

Stem cell therapy for cardiac regeneration

Stem cell therapy (SCT) is one of the propitious approaches to promote cardiac regeneration or repair myocardium after MI (147, 148). In vitro and in vivo studies have shown the transformation of various types of stem cells such as ESC (149), iPSCs (150), BM-SCs(151, 152), and adult tissue derived MSCs(14, 152, 153), HSCs (154), CSCs (155), adipose stem cells (156), and EPCs (157, 158) into cardiomyocyte lineage. Growing evidence suggest that cardiac regeneration by SCT is influenced by several paracrine factors (159, 160). Moreover, the homing of transplanted stem cells is dictated by the cytokines released from the damaged tissue (161). Broad range of cytokines, chemokines, growth factors such as vascular endothelial growth factors (VEGF), fibroblast growth factors (FGF), insulin-like growth factor-1 (IGF-1), and hepatocyte growth factor (HGF) have been shown to stimulate regeneration. Exosomes are one of the various paracrine mediators, which play an important role as regulators in cell autonomous repair mechanisms (162).

Role of miRNA containing exosomes in cardiac regeneration

Exosomes originate from inward folding of cell membranes which results in the formation of multiple intraluminal vesicles in the endosome called multivascular bodies (MVBs). These MVBs fuse with the plasma membrane releasing intraluminal vesicles into the extracellular matrix in the form of exosomes (163-165). They are present as extracellular space as vesicles (163). The diameter of exosome range from 30-120 nm. Exosome was first reported in sheep reticulocytes in early 1950s (165, 166). Exosomes are secreted from various types of cells including stem cells (167), cardiomyocytes (168), B cells (169), T cells (170), dendritic cells (171), platelets (172), Schwann cells (173), endothelial cells (174), and tumor cells (175). They are present in various body fluids such as blood, urine, plasma, semen, and broncho-alveolar lavage, and play an important role in intercellular communication (176, 177). They also play a pivotal role in modulation of immune responses and cell signaling pathways (178-180).

Different types of exosomes behave differently based on their origin. Stem cell exosomes are released by different types of stem cells such as pluripotent stem cell (embryonic stem cell and induced pluripotent derived exosomes) and adult stem cell (mesenchymal, endothelial progenitor and cardiac progenitor cell derived exosomes). The role of stem cell exosomes on

cardiac repair along with their roles in normal and infarcted heart is reviewed by others (165, 181). Exosomes released during stress or pathological conditions behave differently compared to healthy conditions (182). ESCs serve as a promising source of exosomes due to their unique microRNA and protein content to augment endogenous CPCs proliferation and differentiation. Mir-290 family is highly expressed in ESC-derived exosomes in the mouse cardiomyocytes, which is evident from the elevated levels of miR-291, miR-294 and miR-295. These exosomes might have an important role in ESC exosome-mediated cardiac repair. Therefore, these exosome are implicated in stem cell survival, proliferation and differentiation into cardiomyocyte lineage (183). Few studies have reported cardioprotective effects of CPC-derived exosomes in myocardial ischemia/reperfusion (I/R) injury and MI model. CPC exosomes with miR-451/144 might exert beneficial effects (184). They also enhanced endothelial cell migration through extracellular matrix metalloproteinase inducer (EMMPRIN) (185). Exosomes with various miRNAs derived from CPCs in hypoxic conditions improve cardiac function in the injured heart (186). Cardiosphere derived cell (CDC) exosomes with miR-146a have elicited signature beneficial effects in MI model by improving global function and decreasing scar mass. Though therapeutic regeneration was observed with miR-146a-treated hearts but CDC exosomes excel in having more promising effects (187). CDC exosomes carrying miR-22 and miR-24, and play a prominent role in cardiac regeneration (188, 189). Exosomes are also released from mature cells present in the heart like cardiomyocytes and fibroblasts (190, 191). MiR-320 enriched exosomes in diabetic cardiomyocytes transfer miR-320 into endothelial cells and inhibit endothelial cell proliferation, migration, and myocardial angiogenesis in diabetics (191).

Stem cell therapy and stem cell-derived exosomes in clinical trial

The first stem cell based clinical trial with intracoronary infusion was “transplantation of progenitor cells and regenerative enhancement in acute myocardial infarction (TOPCARE)”, where bone marrow-derived mononuclear cells (BMMNCs) were used (192). Although, there was initial success with this population of cells for acute myocardial infarction (AMI) and chronic heart failure (CHF) but later in larger trials, no significant improvement in heart conditions was observed (193). Subsequent clinical trials were based on purified cell population. In Act34-CMI trial, CD34+ EPCs were used for chronic myocardial infarction (CMI) and reduction in frequency of angina was reported. However, in another trial (POSEIDON) using purified BM derived human MSCs, no improvement in ejection fraction was observed in patients (193). Cardiac specific stem cells were used in recently concluded SCIPIO trial. It is reported that c-kit-positive, lineage negative CSCs improve post-infarction left ventricle function (194). However, another group found that c-kit^{+} cells have minimal contribution to cardiomyocytes in the adult heart (195). There is controversy on whether c-kit positive cells are the marker of cardiac stem cells (196). CADUCEUS clinical trial used CSC cardiosphere and observed no cardiac benefits in AMI patients whereas C-CURE trial used cardiopoietic hMSCs and reported positive results in ischemic cardiomyopathy patients (193). Apart from various phase-I and II clinical trials, there are few ongoing phase-III clinical trials – BMI, CHART-1, CHART-2. The BMI trial used BMMNCs whereas CHART-1 and 2 used MSCs isolated from patient's bone marrow (197). Clinical trials on human ESCs and iPSCs in various ailments is reviewed by others (198).

Transcoronary infusion of CPCs in patients with hypoplastic left heart syndrome, the (HLHS)- TICAP trial showed improvement in right ventricular ejection fraction that persisted during 36-month follow up (199). A list of existing and ongoing stem cell clinical trials are summarized in a recent review article by Poulin et al (200).

Limitations and Future perspective of stem cell therapy

Although several types of stem cells were used in clinical trials, they were successful only at different phases of clinical trials but mostly failed in larger trials, may be due to inappropriate choice of endpoints and/or less considerations for regulatory pathways involved in myocardial regeneration (201). Careful analyses of results from clinical trials will help us to understand the challenges to get success in stem cell therapy for heart failure (202, 203). To understand the cause of failure of larger clinical trial, it is imperative to evaluate the gene expression profiles of the transplanted stem cells after engraftment and to develop strategies that can facilitate the engraftment and differentiation of transplanted stem cells. The success of stem cell therapy may depend on homing and differentiation of transplanted stem cells to cardiac lineages that contribute to myocardial regeneration, the effect of paracrine factors that stimulate endogenous resident stem cell's differentiation to contribute to myocardial regeneration, and the microenvironment surrounding the niche of the stem cells that facilitate survival and differentiation of stem cells (88, 204). Recent studies demonstrated that stem cell exosomes could be a promising target for myocardial regeneration, and several preclinical trials reported improvement in myocardial regeneration by stem cell exosomes (205-208). Therefore, exosomes could be a novel approach for cardiac regeneration (209), and are given in pre-clinical studies for evaluating its safety and efficacy. MiRNAs from these exosomes can be also used as a biomarker for clinical outcome of the patients (210). Although miRNAs are now in clinical trials (211), stem cell-derived exosomes need further investigations to translate its role in SCT. One of the limitations of exosome-mediated cardiac regeneration is specificity and yield of exosomes (212). Developing techniques to isolate cardiac specific exosomes, and to deliver them to the border zone of the ischemic heart, understanding the mechanism of action of exosomes delivered to the ischemic heart, are some of the strategies for successful use of exosomes in regenerating damaged myocardium. An alternative strategy for replenishing the dead myocardium could be trans-differentiation of fibroblast into functional cardiomyocytes or inducing cardiomyocyte to reenter into cell cycle (213). Considering of ECM stiffness and its impact on stem cells, regulation of MMPs especially inhibition of MMP9 can be an important approach. Similarly, regulating of autophagy of stem cells is crucial for their survival and differentiation.

In summary, we can harness the basic science knowledge and clinical outcomes from the previous clinical trials to understand the factors that regulate survival of transplanted stem cells, differentiation of engrafted stem cells into a specific lineage such as cardiomyocytes, maintenance of cardiomyocyte's properties for prolong time. At the same time, we need to use systematic approach to improve cardiac regeneration in MI hearts and it may include autophagy, exosome, miRNAs, ECM stiffness, and trans-differentiation (Figure 4).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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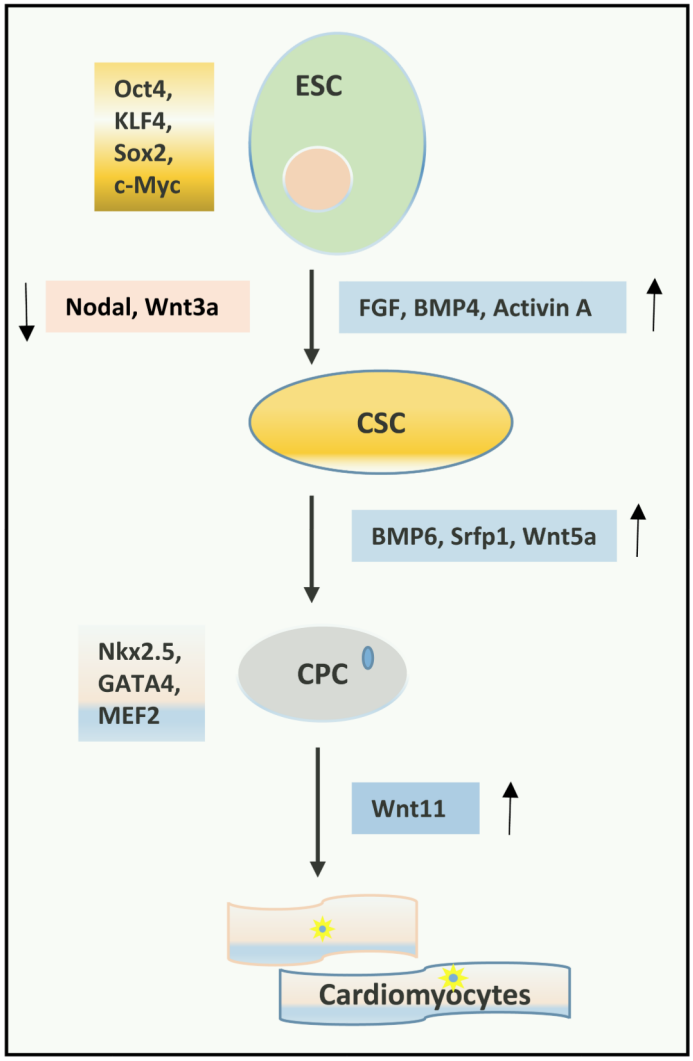

Figure 1.

Regulators for embryonic stem cell (ESC) differentiation into cardiomyocytes. Transcription factors Oct4, KLF4, Sox2 and c-Myc are required for maintaining embryonic stem cell pluripotency. Inhibition of signaling molecules Wnt3a, and nodal while upregulation of FGF, BMP4, and Activin A are required for differentiation of ESC into cardiac stem cell (CSC). Activity of BMP6, Srfp1, and Wnt5a are required for differentiation of CSC into cardiac lineage specific cardiac progenitor cell (CPC). Nkx2.5, GATA4 and MEF2 maintain cardiac lineage specificity. Wnt11 is involved in differentiation of CPC into cardiomyocytes.

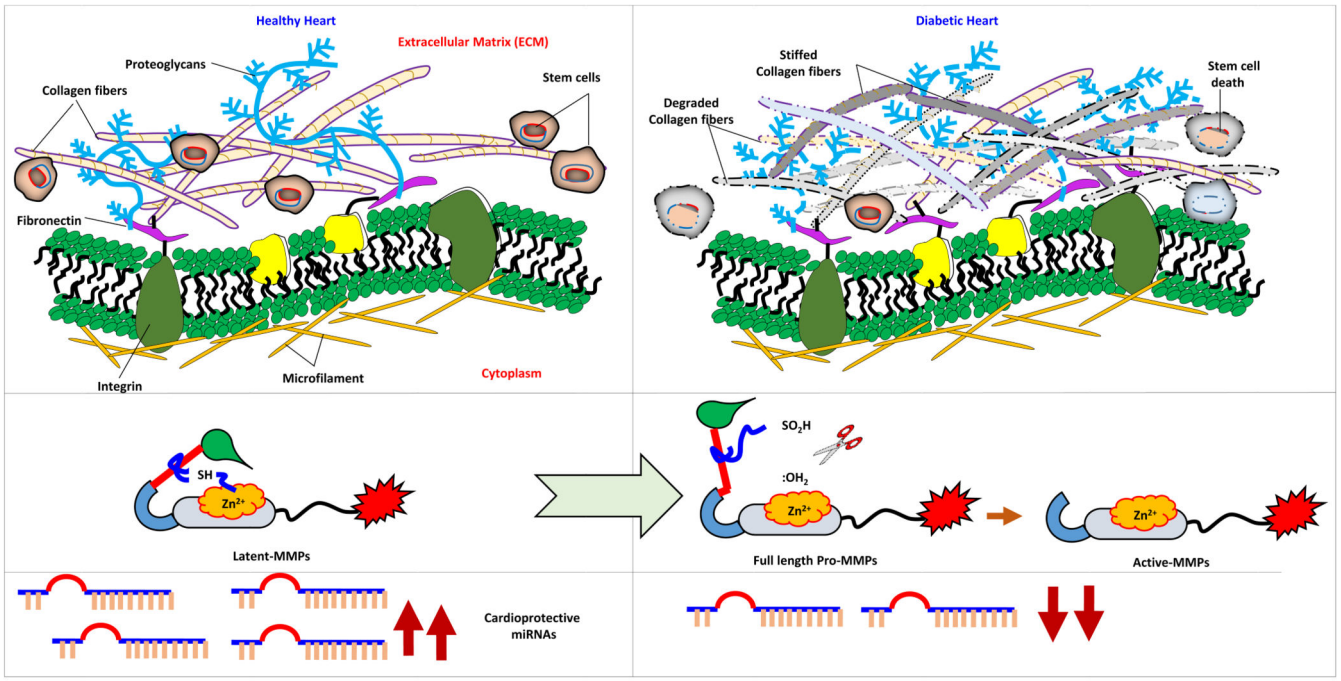

Figure 2.

Extracellular matrix (ECM) remodeling in diabetic heart. In healthy heart collagen and elastin are present in optimal ratio which might help in maintaining the integrity of the ECM and niche of stem cells. In pathological heart such as diabetic heart, activity of MMPs is augmented, expression of cardio-protective miRNAs is attenuated, stiffness of ECM, and apoptosis of stem cells are induced.

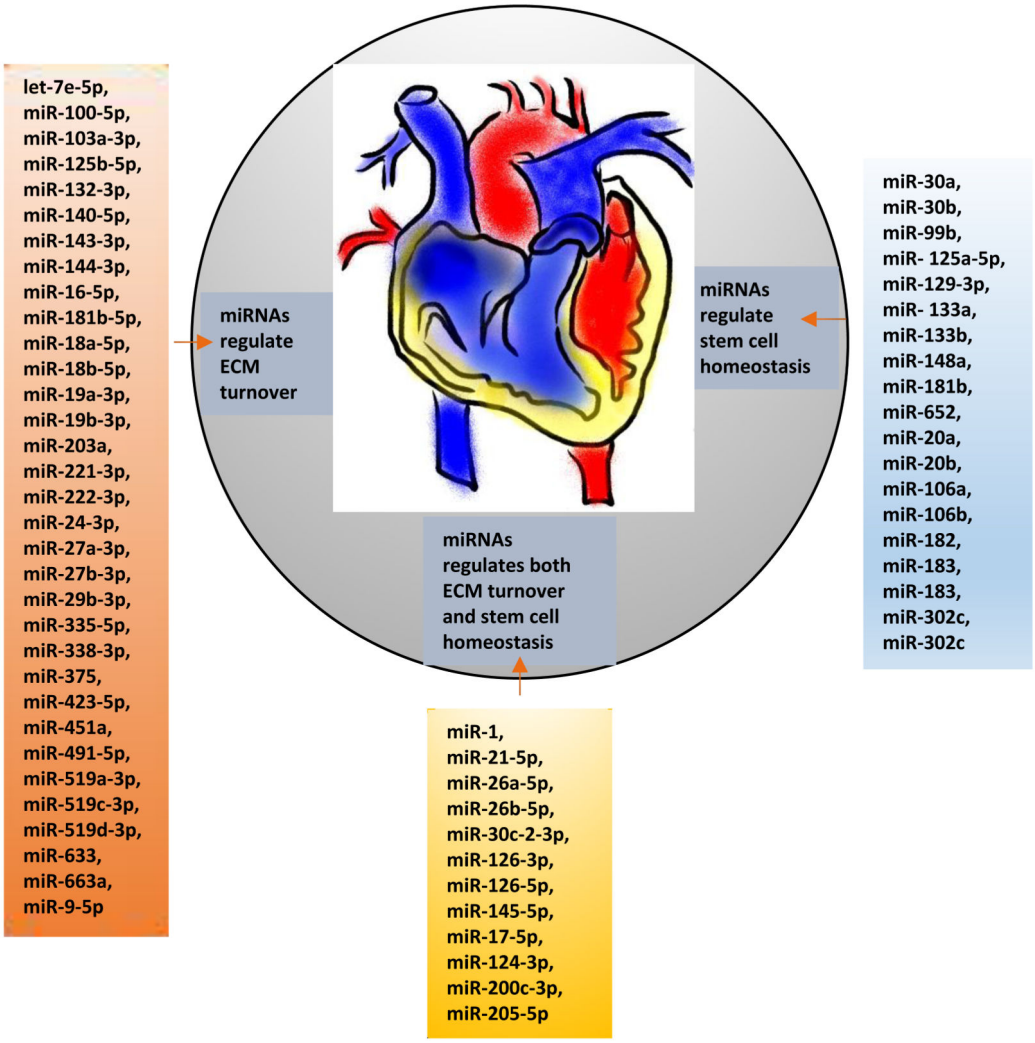

Figure 3.

MiRNAs involve in ECM turn over and stem cell differentiation. Left panel shows 33 miRNAs that regulate ECM turnover, right panel shows 19 miRNAs that regulate stem cell homeostasis, and middle panel represents miRNAs that regulate both stem cell homeostasis and ECM turnover.

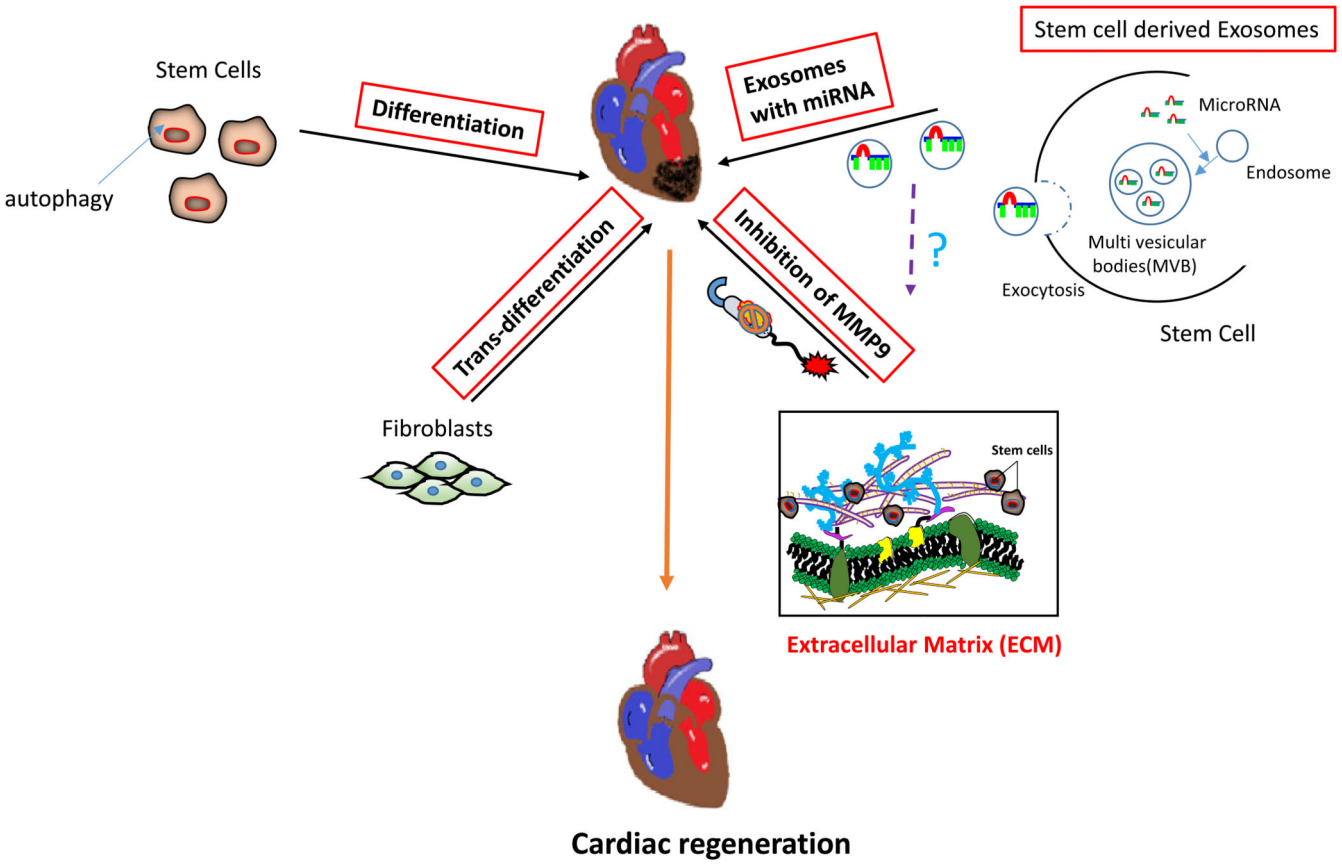

Figure 4.

Schematics for systemic approach for stem cell therapy. Cardiac regeneration can be achieved by using different approaches such as regulating autophagy in stem cells, using stem cell-derived exosomes, inhibiting matrix metalloproteinase-9 (MMP9) that may reduce stiffness of extracellular matrix to promote stem cell proliferation and differentiation, inducing trans-differentiation of fibroblasts into cardiomyocytes.

Table 1

MiRNAs that regulates extracellular matrix turn over in mouse and human hearts.

Genes involved in ECM turn over	miRNA (Mouse)	Ref.	miRNA (Human)	Ref.
MMP9	miR-204-5p, miR-212-3p, miR-132-3p, miR-320-3p	(91-93)	miR-451a, miR-491-5p, miR-338-3p, miR-21-5p	(91, 94-97)
MMP2	---	---	miR-29b-3p, miR-451a, miR-335-5p, miR-338-3p, miR-21-5p, miR-17-5p	(94, 96-100)
MMP7	---	---	miR-126-5p, miR-126-3p	(101)
MMP12	---	---	miR-145-5p	(102)
MMP-14	---	---	miR-335-5p, miR-145-5p	(99, 102)
MMP1	---	---	miR-222-3p, miR-203a, miR-145-5p	(102-104)
MMP13	---	---	miR-9-5p, miR-100-5p, miR-27b-3p, miR-140-5p, miR-27a-3p, miR-125b-5p, miR-143-3p, miR-132-3p	(105-111)
TIMP-1	---	---	miR-519a-3p, miR-26b-5p	(112, 113)
TIMP2	---	---	miR-519d-3p, miR-519c-3p, miR-200c-3p	(112, 114)
TIMP3	miR-181b-5p, miR-206-3p, miR-7b-5p, miR-181a-5p, miR-149-5p, miR-124-3p	(115-118)	miR-181b-5p, miR-21-5p, miR-1, miR-222-3p, miR-221-3p, miR-103a-3p, miR-335-5p, miR-124-3p, miR-423-5p, miR-30c-2-3p, miR-18b-5p, miR-16-5p, let-7e-5p	(99, 119-124)
TGF-β	---	----	miR-24-3p, miR-29b-3p, miR-144-3p, miR-633, miR-663a, miR-21-5p	(124-129, 145)
CTGF	miR-122-5p, miR-425-5p, miR-297a-5p, miR-9-5p	(117, 130)	miR-124-3p, miR-18a-5p, miR-26a-5p, miR-205-5p, miR-145-5p, miR-375, miR-19b-3p, miR-19a-3p	(117, 131-137)

Abbreviations: MMPs, Matrix metalloproteinases; TIMPs, Tissue inhibitor of metalloproteinases; TGF-β, Transforming growth factor-β; CTGF, Connective tissue growth factor; ECM, Extra cellular matrix.