REVIEW ARTICLE

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The Role of Exosomes in the Pathogenesis of Chemotherapy-induced Cardiotoxicity: A Diagnostic and Prognostic Approach

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Abstract

Exosomes are a subtype of natural extracellular vesicles that transfer a great number of biomolecules, released by almost all types of cells, and can be specifically taken up by recipient cells in order to maintain homeostasis and induce a proper response to stress or harsh environmental conditions. Since the heart is part of complex systems which involve various cell types, exosome-mediated communication plays a crucial role in the cardiovascular field. Given the extended studies on the molecular mechanisms mediated by exosome cargos, leading to cardiovascular diseases, we focus on the most important data that report the roles of proteins and microRNAs (miRNAs) transferred by exosomes and whether they possess cardiotoxicity or cardioprotection and also the potential of these biomolecules as therapeutic tools or diagnostic biomarkers.
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Introduction

One of the most formidable challenges in medicine is cancer and its treatment. It is the second reason for death among the human diseases [1]. The mortality and morbidity of this fatal disease affect all aspects of the patient's life. There are widespread methods for the treatment of cancer and it depends on the type and stage of cancer. Among these different ways, chemotherapy is one of the main basic treatments of cancer but it is like a double edge sword and its harmful damages cannot be ignored. Except for the general complications of these drugs like vomiting, hair loss, and cachexia, any medication has its own side effects. Cardiotoxicity is one of these lethal complications and it happens more as a result of consuming these drugs: 5-fluorouracil, Paclitaxel, Anthracyclines, monoclonal antibodies, and tyrosine kinase inhibitors [2]. Cardiotoxicity can happen in every stage of

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treatment even many years after cure and it can appear with different symptoms like cardiac failure, arrhythmia, changing blood pressure, etc. cardiotoxicity limited our possibility to continue the treatment. Exosomes are extracellular plasma membrane vesicles that can be produced by all types of the cells even cancer cells. Exosomes contain a composition of proteins, lipids, RNA, and DNA [3]. Exosomes play a significant role in the progress of tumor cells and facilitate tumor to further its angiogenesis, cancer cell enlargement, migration, and repel of the immune system attacks [4] and modulate the intercellular communications that it is vital for cells [5]. One of these target cells are cardiomyocytes. Exosomes by influencing their content and delivering signaling molecules present their effects and modulate the intercellular communications that is vital for cells function [6]. Final effects of exosomes in recipients cells depend on the many factors. Some situations like hypoxia, inflammation, or chemotherapy lead to the harmful effects of exosomes. miRNAs in exosomes can lead to detrimental alteration in cardiac cells like hypertrophy that lead to one of the perilous outcomes [7]. In this study we aim to describe that how exosomes play role in expedite of toxicity in cardiac cells.

Exosomes

Exosomes, as a member of extracellular vesicles (EVs), that have a size range of 30-150 nm are spherical vesicles with lipid bilayer, secreted by almost all types of the cells in physiological and pathological situations. Exosomes originate from the endocytic pathway.and their formation initiate with invagination of cytoplasmic membrane and shaping an early endosome followed by formation of intraluminal vesicles (ILVs) through inward germination. Then endosmes go through maturation by acidification and at last, fuse with plasma membrane and release from cell. It is known that, endosomal-sorting complex required for transport (ESCRT) play vital role in packaging of proteins into the intraluminal vesicles and composed of four complexes : ESCRT-0 to ESCRT-III. First, in endosome, ESCRT-0 binds to the phosphatidylinosi-

Table 1. The Most Common Composition of Exosomes

	Type of biomolecules	Markers
Protein	MHC molecule and costimulatory molecules	MHC-I, MHC-II, CD86
	Rab family	Rab11, Rab27a, Rab27b
	Adhesion molecules	CD54, CD11b
	Heat shock proteins	HSP70, HSP90
	tetraspanins	CD9, CD82, CD81, CD63
	ADP ribosylation factors (ARFs)	ARF6
	Annexins	Annexin A2
Lipids	Phospholipids	phosphatidic acid, Cardiolipin
	Sphingolipids	Ceramide
	phosphatidylinositols	Phosphatidylinositol-3,5-biphosphate
	Cholesterol	-
Nucleic acid	DNA	mitochondrial DNA, Genomic DNA
	miRNA	miR-1, miR-21, miR-1, miR-151, miR-181, miR-16

Table 2. Diagnostic and Prognostic Value of Exosomes in CVD

Source	Biomarker	Disease	application	Ref.
VSMCs	miR-155	Atherosclerosis	Diagnostic	[14]
Blood	miR-423-5p	DCM-AHF myocardial necrosis	Diagnostic	[15]
Serum	miR-92b-5p	DCM-AHF	Diagnostic	[16]
Serum	miR-9 miR-124	AIS	Diagnostic	[17]
Serum	miR-133a/ miR-199a-3p/ miR-221/miR590-5p/miR-25	Valvular heart diseases Predictor of recovery from mitral regurgitation	Prognostic	[18]
Plasma	Cystatin C CD14	Stroke Predictor of atrophy progression and vascular changes	Prognostic	[19]

VSMCs=Vascular smooth muscle cells, **KLF5**=Kruppel Like Factor 5, **HF**=heart failure, **DCM**=idiopathic dilated cardiomyopathy, **AIS**=acute ischemic stroke

tol-3-phosphate (PI3P) and to the ubiquitinated protein as cargo. Then ESCRT-I and ESCRT-II initate formation of buds containing the cargo by deformation of membrane and separation of the payload. Eventually, releasing the exosomes from the cytoplasmic membrane is executed by ESCRT-III [8, 9]. Exosomes contain the materials like proteins, nucleic acids and lipids[10]. There are many different types of proteins and biomolecules in exosomes. The most common composition of exosomes is listed in Table-1 and 2 [11-13]. Function and the possible effects of exosomes mainly depends on the nature of their content. It has been demonstrated that exosomes have major roles in induction of immune responses by presenting antigens, regulation of tumor advancements and cell-cell communications [8].

Exosome Proteins and Cardiotoxicity

Recent study have shown the effect of exosomes in cardiovascular disease [20]. In addition to the usual composition, exosomes present special DNA, RNA, and protein contents in a cell-dependent manner. Generally, protein content of exosomes can be divided in to groups, common proteins and type-specific proteins. The latter group are placed into exosomes exclusively by cells in particular pathophysiological or physiological situations. While some of these proteins are advantageous for cells, the others may be detrimental. Based on remarkable studies conducted in the evaluation and identification of protein content in exosomes that originated from cardiac cells, some protein's presence has been demonstrated that they participate in causing cardiotoxicity.

study showed that Hsp60 released from exosomes derived from cardiac myocytes [21] by binding to innate immunity receptor, Toll-like receptor4 (TLR4), and through JNK and NF-kB pathway, stimulates the production of TNFα and IL-6 which leads to activation of Caspase cascade apoptosis. In fact Hsp60 can be a great biomarker representing cardiovascular disease progression, and also a diagnostic and prognostic tool [22]. Another study reported that exosomal Hsp60, targets cardiomyocytes and after binding to the TLR4, which is the most abundant subtype of TLRs in cardiomyocytes, rapidly activates the NF-kB pathway. After activation of TLR4, two adaptor-associated proteins, MyD88 and TIRAP regulate activation of IL-1 Receptor-Associated Kinases (IRAKs) and TRAF6 which leads to activation of both IKKs' signaling pathway and MAPK pathway. IKK induces NF-kB transcription factor and p38MAPK which

eventually lead to the production of IL-6 ad TNF-α. Eventually apoptosis in cardiomycets is mediated by TNF-α through releasing Cytochrome C, AIF, and endonuclease G, followed by activation of caspase -3 and DNA cleavage [23, 24]. Taken together, Hsp60 derived from cardiomyocytes exosomes, has a harmful role in cardiac injuries and is valuable biomarker.

Although AngII has vital roles in maintaining normal functions of body, but excessive amounts of it have cardiotoxicity effects. Exosomes derived from Cardiac fibroblasts, thorough activation of MAPK and Akt, enhance the expression of renin, AT1R and AT2R, and angiotensinogen which leads to an elevation in Ang II production and subsequently hypertrophy and heart dysfunction. Overexpression of Ang II activates several signaling pathways leading to hypertrophy in cardiomyocytes. Binding of Ang II to Ang II receptor type 1(AT1R) leads to activation of epidermal growth factor receptor (EGFR) plus NAD(PH) complex on cardiac myocytes, resulting in the production of Reactant oxygen species (ROS) by transferring electrons from NADPH to molecular oxygen leads to an oxidative stress situation [25]. Ultimately, activated AT1R through activation of protein kinase C (PKC), the MAPK pathways that include p38 kinases, JNK, and ERK 1/2 leads to NF-kB transactivation which results in hypertrophy, proliferation, hypercontractility, and cardiac remodeling [26]. Furthermore, it has been reported that activation of AT1R directs to higher expression and activation of NADPH oxidases (Noxs), specially Nox2 and Nox4. Participation of Nox2 in Ang II-induced hypertrophy is due to increased generation of ROS, which consequently activates ERK1/2, Akt, MMP, and NF-kB signaling pathways. In addition, Nox4 is a great source of oxidative stress and is the only member of the Nox family that generates H2O2, resulting in the oxidation of histone deacetylase4 (HDAC4). This enzyme has preventive interaction with the nuclear factor of activated T cells (NFAT) and myocyte enhancer factor 2(MEF2),families of transcription factors that regulate cell proliferation and differentiation. Upon intracellular Ca+2 elevation , calcineurin complex is activated which dephosphorylates NFAT and results in NFAT translocation to the nucleus and induction in gene expression [27, 28]. Moreover, elevated intracellular calcium results in the transactivation of MEF2 through the p38MAPK pathway which leads to cell differentiation [29]. In overall, therapeutic approaches that inhibit the release of harmful exosomes can reducethe cardiac dysfuntion severity caused by AngII.

Datta and *et al* elucidated the cross-talk mechanisms in the regulation of collagen synthesis by evaluation of Hsp90 proteins derived from cardiomyocytes exosomes. Collagen synthesis alteration in fibroblasts is due to cardiac myocytes hypertrophy. Interaction of Hsp90 and IKKβ leads to IL-6 production in cardiomyocytes. This IL-6 is transformed via cardiac myocytes-derived exosomes containing Hsp90 into cardiac fibroblast and through activation of STAT3 pathway and excessive expression of collagen result in cardiac fibrosis [30, 31]. Also increased expression of IL-6 in cardiomyocytes and phosphorylation of STAT3, on one hand leads to inflammation and on the other hand potentiates EndoG suppression of MEF2A, which eventually leads to hypertrophy [32]. Furthermore, Hsp90 by activating Ras/Raf/MEK/Erk signaling results in C-myc expression followed by cell proliferation and cardiac fibrosis [33, 34]. In overall, upon inflammation ,cardiomyocyte-derived exosomes carrying Hsp90, regulate generation and degradation of collagen in cardiac tissue.Although intracellular Hsp70 has cardioprotective properties, but increased extracellular levels of this protein are an interesting prognostic marker of heart failure. Hsp70 by binding to the damage-associated molecular pattern receptors (DAMPS),

TLR2 and TLR4, activates p38-MAPK and the NF-κB signaling pathways, resulting in increase expression of IL-1, IL-6, IL-17, and TNF-α, that leads to chronic inflammation and chronic apoptosis in cardiomyocytes [35]. Also as a result of activation of NF-kB signaling pathway by Hsp70, the expression level of TGF-β is elevated. This over-expressed TGF-β binds to TGFβ receptor complex and upon activation of TGFβ-R , Smad3 is phosphorylated and forms a complex with Smad4 which later translocate to the nucleus and increase expression of α-smooth muscle actin (α-SMA), which is the most important mark-

er of myofibroblasts, collagens and fibronectin, leading to cardiac fibrosis. Furthermore, activation of TGFβ-R leads to induction of TRAF6, which subsequently through activation of TGF-β-activated kinase 1 (TAK1)/JNK/p38-MAPK pathway results in apoptosis. Also, TGF-β via recruiting partitioning-defective 6 (Par6) and Smad-specific E3 ubiquitin protein ligase (Smurf1), degrades RhoA which results in tight junction dissolution and Epithelial-to-mesenchymal transition (EMT)[36].

In addition to Hsp70 function, in hypoxic cardiac myocytes (after MI) the Hypoxia inducing factor-1alpha (HIF1-α) is activated and translocated to the nucleus and increased TNF-α expression leads to inflammation and apoptosis by activation of caspase cascade [37]. Since TNF-α has an extensive role in pathways that lead to heart failure, has the potential ability to use as a biomarker in diagnostic approaches. Taken together, according to studies, blocking transcription of intracellular Hsp70 developed cardiomyocyte hypertrophy while conversely, blocking extracellular Hsp70 with anti-HSP70 antibodies weakened hypertension-induced cardiac hypertrophy and fibrosis [38].

Arginase 1 is another protein that originated from serum exosomes, is an enzyme catalysis conversion of Arginine to ornithine, thereby reducing available arginines, the rate-limiting factor, for Nitric oxide (NO) production by Nitric oxide synthase (NOS) in endothelium cells leads to oxidative stress [39]. On other hand, in cardiomyocytes under oxidative stress, RASSF1A translocates Mammalian sterile 20-like kinase 1 (Mst1) to mitochondria. Mst1 is derived from Cardiac microvascular endothelial cells (CMES) exosomes, is involved in the HIPPO signaling pathway. Upon Mst1 activation, the formation of Bcl-xL-Bax complex is inhibited, leading to activation of Bax and apoptosis [40, 41]. In conclusion, increased cardiac cells apoptosis due to exosome-derived Arginase 1, leading to a decrease in the number of cardiomyocytes in MI, reperfusion injury, ischemic heart disease, cardiomyopathy, heart failure. Cheow and *et al* reported that the plasma of patients who are suffering from MI contains exosomes rich in Apolipoprotein C-III (APOC3) protein. This protein through enhancing the affinity of LDL for binding to proteoglycans of the artery wall , causes the accumulation of Lipoproteins in the subendothelial region which leads to atherogenic hyperglyceridemia [42]. Also, APOC3 has the potency to activate sphingomyelinases (SMase) which leads to arachidonic acid(AA) release as a pro-inflammatory metabolite. I

ncreasing levels of AA, increase expression of the c-jun transcription factor in a CPK-independent pathway, results in TNF-α generation which contributes to inflammation or apoptosis at sites of lipoprotein retention [43, 44]. Furthermore, APOC3 by activation of protein kinase C-beta and NF-kB enhances the expression of VCAM-1 and ICAM-1in endothelial cells and contributes to cell adhesions and atherogenesis promotion [45]. In addition, a recent study, demonstrated that APOC3 by binding to TLR2 and TLR4 activates TLR–SCIMP–Lyn–Syk–TRPM2 axis in monocytes,ROS production, and NLRP3 inflammasome assembly which eventually results in induction of Caspase-1 followed by inflammatory cell death and IL-1β production [46].

Exosome miRNAs and Cardiotoxicity

In the matter of cardiovascular disease, miRNAs are the most important nucleic acid materials identified in exosomes. Mounting data suggests that miRNAs are involved in the progression of heart dysfunction. miR-21 is a significant regulator of cardiac diseases which vastly exists in almost all subtypes of cardiac cells, including Cardiomyocytes, endothelial cells, vascular smooth muscle cells, and cardiac fibroblasts. It has been reported that exosomal miR-21 derived from cardiac fibroblast, targets SORBS2 and PDLIM5, proteins involves in cytoskeleton organization and cell-cell adhesion in cardiomyocytes and through down-regulating these factors resulting in increasing cardiomyocyte size and consequently hypertrophy [47, 48]. Overexpressed exosomal miR-217 in cardiomyocytes by targeting and suppressing PTEN results in activation of AKT/ERK pathway and cardiac hypertrophy. Also, exosomal miR-217 originated in cardiomyocytes and transferred into fibroblasts enhance the expression of Fibronectin, colα1and

colα2 genes, main markers of cardiac fibrosis, through AKT/mTOR pathway leading to fibrosis [49].

It has been reported that miR-320 originated from cardiomyocytes and transfer to endothelial cells via exosomes.in recipient cells, miR-320 targets and down-regulates IGF-1, Hsp20, and Ets2, angiogenesis genes, leading to reduction in angiogenesis and proliferation. miR-320 downregulates the expression of IGF-1, the inhibitor of apoptosis-related factors including p-ASK, p38, Bax, p-JNK, and caspace3, which results in endothelial apoptosis. Also, Hsp-20 through activation of VEGFR2 /AKT/ERK pathway promotes angiogenesis, thereby miR-320 by down-regulation of Hsp-20 presents its anti-angiogenic activity [50]. In addition, miR-320 along with miR-652 by inhibiting NOX2 expression leading to NO level reduction and consequently Cardiovascular diseases [51]. miR-146a originated from cardiomyocytes and targets endothelial cells. Exosomal miR-146a by suppressing NRAS , blocks PI3K/AKT/mTOR and RAF/ERK signaling pathways leading to endothelial cells proliferation reduction and microvasculature impairment. Also, miR-146a by down-regulation of Erbb4 expression, which has a critical role in the regulation of metabolic profiles by enhancing glucose uptake, results in heart failure and peripartum cardiomyopathy as a consequence of metabolic perturbation [52]. miR-146a similar to most of the cardiac exosomal miRNAs presents cardioprotection activity too. miR-146a through down-regulation of cyclophilin D in cardiomyocytes mitochondria results in inhibition of cytochrome c/ caspase 3 apoptosis pathway and myocardial infarction (MI) [53]. Also, in a recent study, it has been reported that in patients with Acute myocardial infarction(AMI) the plasma levels of miR-146a along with miR-199a and miR-26a significantly increased and they present considerable potential as diagnostic biomarkers of AMI [54].

Exosomal miR-200 which is derived from adipocytes as a result of PPAR-γ activation and uptake by cardiomyocytes through the mTOR signaling pathway and protein synthesis leads to cardiomyocytes hypertrophy(55). Exosomal miR-199a-5p in cardiomyocytes blocks the expression of PPAR gamma coactivator 1 alpha (PGC-1a), a transcriptional co-activator of genes involved in the regulation and promotion of muscle tissue to fiber composition. Suppressing PGC-1a leads to down-regulation of ERRa, a critical regulator of mitochondrial metabolism, results in the reduction of NRF2 and downstream antioxidant factors that protect myocardial against hypertrophy [56]. NRF2 suppresses MEF2A transcription, a key transcription factor that promotes the expression of cardiac hypertrophy genes. Also, NRF2 by preventing IL-6 secretion and thereby reducing STAT3 activation suppresses the production of TNFa and IL-10, the inflammatory cytokines which result in cardiac injury. Eventually, suppression of NRF2 leads to oxidative stress, hypertrophy, and inflammation in cardiomyocytes [57]. In addition, miR-199a-5p by binding to 3'-UTR of Sirt1 mRNA inhibits the blocking activity of Sirt1 on smad3. Following activation of smad3, expression of COL1A1, COL3A1, and a-SMA significantly increase and leads to cardiac fibrosis [58]. Likewise, Exosomal miR-199a-3p through blocking smad1 results in activation of smad3 pathway and leads to cardiac fibrosis. Also, miR-199a-3p targets and suppresses RB transcriptional corepressor 1 (Rb1), which have inhibitory effects on E2F2, a transcription factor that regulates cardiomyocytes cell cycles by enhancing the expression of cyclin A, and leads to cardiac hypertrophy [59-61].

Degradation of p27, Cyclin-dependent kinase inhibitor, activates CK2- α' followed by activation of HDAC2 and subsequently promotes expression of cardiac hypertrophy related genes. Likewise exosomal miR-221 by down regulation of p27, and activation of HDAC2 results in cardiac hypertrophy [62, 63]. Furthermore, it has been reported that down regulation of p27 by exosomal miR-221 promotes activation of CDK2-dependent mTOR pathway which suppresses autophagy kinase complex ULK1/2, eventually inhibits autophagy in cardiomyocytes, and leads to heart failure [64].

It has been reported that exosomal miR-15 by targeting Bcl2, the apoptosis regulator, results in cardiomyocytes death after ischemia, and miR-195, another member of the miR-15 family, by blocking SIRT1 and down-regulation

of Bcl2 leads to enhancing expression and activity of caspase 3 and consequently cardiomyocyte apoptosis [65, 66]. It has been identified that cardiomyocytes induced by AngII release exosomes enriched in miR-132 which through suppressing FOXO3 expression, the anti-hypertrophic factor, results in cardiac hypertrophy. FOXO3 promotes expression of Atrogin-1, a tissue-specific ubiquitin-proteasome, which proteolysis calcineurin and consequently inhibits calcineurin/NFAT signaling pathway and down-regulation of MCIP1.4 expression, which prevents further hypertrophic growth [67-70]. In addition, another function of FOXO3 in cardiomyocytes is promoting autophagy after a long period of starvation by enhancing the expression of LC3-II, the essential autophagosome membrane-bound protein, and BINP3, a powerful inducer of autophagy. Thereby inhibition of FOXO3 by Exosomal miR-132 in cardiomyocytes has anti-autophagic effects, and since autophagy is a critical process for regular cardiac tissue development, size adjustments and final differentiation in cardiomyocytes, suppressing autophagy results in heart failure [68, 71-73]. Furthermore, cardiac fibroblasts induced by AngII, generate miR-132 which targets and suppresses MMP9 expression, which leads to severe deposition of extracellular matrix in cardiac tissue due to lack of MMP9 collagen degrading activity [74, 75].

Also, it has been reported that miR-132 by suppressing FOXO3 expression leads to a significant increase in fibrotic genes, specifically COL1A1, and eventually cardiac fibrosis [76]. Recently Lie and *et al* reported that over expressed exosomal miR-132 through binding to 3'-UTR of sarcoplasmic-endoplasmic reticulum Ca2+ ATPase 2 (SERCA2a) mRNA , a key pump that transferes calcium from the cytoplasm to the sarcoplasmic reticulum in order to regulate heart contraction relaxation, results in perturbation in Calcium re-uptake and heart failure [77, 78]. It is noteworthy to mention that miR-132 directly targets and suppresses PTEN that further antagonizes PI3Kγ, which normally prevents generation of cAMP, thereby excess cAMP results in hypercontractility and cardiac inotropy [77, 79]. Another critical role of miR-132 in cardiovascular diseases is repressing MeCP2, the transcriptional factors that block the expression of Arginine vasopressin (AVP), a factor that promotes water reabsorption, thereby leading to Hyponatremia, and also this excessive AVP generation could result in enhanced systolic and diastolic wall stress and presents detrimental activity on myocardial contractility [80-82]. Plus recently Hinkel and *et al* reported that, in I/R myocardial tissue miR-132 is highly expressed and by suppressing the expression of SIRT1which significantly reduces the levels of PGC-1α and Nrf2 , factors involved in oxidative stress pathway, and also pyroptosis- related factors including NLRP3, caspase-1, and interleukin (IL)-1β, ultimately results in oxidative stress and endothelial inflammation [83, 84]. Finally, it is noteworthy to point advantages of miR-132 as a remarkable and unique cardiovascular disease biomarker, since the levels of miRNAs in plasma are completely stable and common cardiovascular drugs also do not alter the plasma level of miR-132. It has been reported that during the early phase of after MI, the plasma level of miR-132-5p is low and can serve as a good diagnostic biomarker of MI [85, 86].

Exosomes as Therapeutic Agents in Cardiovascular Disease

Given that the extend of processes in which exosomes are playing key roles in cardiovascular pathways is significantly wide, they have great potential for application as remarkable tools in therapeutic approaches. Exosomes have several advantages over other therapeutic nanoparticles as they are biocompatible, have the ability to cross physiological barriers and they are not immunogenic and tumorigenic. Therapeutic principles based on exosomes can be studied in two main groups: approaches that neutralize the detrimental activity of exosomes in recipient cells and approaches that derive benefits from cardioprotective features of exosomes (Table-3). It has been reported that exosomes derived from mesenchymal stem cells (MSCs) have the ability to provide proteomic shortage in ischemic/reperfused myocardium through presenting their protein contents. Since the critical factors that are involved in reperfusion injury include lack of ATP/NADH, enhancing oxidative stress, and apoptosis. Exosomal protein content refills im-

Table 3. Exosomes for Cardiac Therapy

Exosome source cells	Active agents	Target	effects	Ref.
H/R myocardial cells	↑miR-144	FOXO1	Reduction of myocardial ischemic injury and apoptosis	[87]
CPCs	↑miR-146a-5p	↓Traf6, ↓Mpo, ↓Smad4, ↓Irak1, ↓Nox4	Reduction of inflammatory and cell death in Dox-treated cells	[88]
hMSCs	↑miR-21-5p	↑PI3K	Increase calcium handling and heart contractility via PI3K signaling pathway	[89]
CPCs	↑miR-210, ↑miR-132	↓ephrin A3, ↓PTP1b, ↓RasGAP-p120	Induce anti- apoptotic and pro-angiogenis activity in cardiomyocytes	[90]
Hypoxia-induced myocytes	↑miR-99a	↓mTOR	Prevention of cardiomyocytes apoptosis and autophagy after MI	[91]
CDCs	↑miR-181b	↓PKCδ	Regulation of macrophage polarization, promotion of M1 to M2 macrophage shift after MI	[92]

H/R=hypoxia/reoxygenation, **FOXO1**=Forkhead box protein O1, **CPC**=cardiac progenitor cells, **Traf6**= TNF receptor-associated factor 6, **Mpo**=Myeloperoxidase, **Irak1**=Interleukin 1 Receptor Associated Kinase 1, **Nox4**=NADPH Oxidase 4, **hMSCs**=human mesenchymal stem cells, **PI3K**=Phosphoinositide 3-kinases, **CDCs**=cardiosphere-derived cells, **PKCδ**=Protein kinase C-δ

paired glycolytic enzymes thereby increasing levels of ATP and NADPH, and also provides peroxiredoxins and glutathione S-transferases for cardiomyocytes in order to minimize oxidative stress and moreover exosomal surface protein CD73 by generating adenosine from extracellular ATP activates RISK pathway, which enhances phosphorylation of Akt and GSK3 and improves cardiomyocytes viability [93, 94].

In a study conducted by Yu and *et al*, exosomes derived from MSC which genetically modified to overexpress GATA-4 protein, a transcription factor that is involved in myocardial differentiation, transfer miR-19a to cardiomyocytes which down-regulates the translation of PTEN and also BIM, a pro-apoptotic protein in destination cells and ultimately activates Akt/Erk signaling pathway and results in cardiomyocytes apoptosis reduction, decreasing infarct size and left ventricular remodeling and improving overall cardiac function [95, 96]. In addition in a recent study, it has been reported that in MI injury direct injection of miR-19a by suppressing PTEN, prevents apoptosis and induce cardiomyocytes proliferation which are the major causes of heart failure [97]. Also, Liu and *et al* reported that miR-19a/b through repressing expression of PDE5A, a phosphodiesterase that catabolizes cGMP in the myocardium, protects the heart from cardiac hypertrophy. Reduction in cGMP and subsequently decreasing level of protein kinase G(PKG), results in augmentation of hypertrophy through CaMKII and calcineurin pathway [98-100]. It has been reported that following ischemic preconditioning, exosomes originated from MSCs and enriched in miR-22 which directly targets Mecp2, a protein that induces apoptosis, presents anti-apoptosis and protective effects in cardiomyocytes [101]. Likewise, MCS- derived exosomes include miR-221 by suppressing PUMA, a subclass of Bcl-2 family, prevents apoptosis and results in cardiomyocytes survival [102]. In another study, treatment with exosomes originated from human umbilical cord blood-derived CD133+ cells, enriched in miR-126, significantly ameliorate cardiac action in type 2 diabetes mellitus (T2DM) stroke mice. miR-126 by suppressing SPRED1, a factor that inhibits angiogenesis through RAF1/ERK/NOS3 in endothelial cells, and also PIK3R2, a protein that inhibits

VEGF signaling through PI3K/AKT/VEGF pathway, results in angiogenesis improvement. Also, miR-126 represses VCAM and MCP-1, cell adhesion proteins that regulate vascular adhesion inflammation and increase migration of inflammatory cells to the heart, eventually resulting in reduced cardiac inflammation after stroke [103, 104]. It has been demonstrated that miR-126 by blocking RGS16, protein that inhibits CXCL12/CXCR4 signaling, increases endothelial progenitor cells migration and consequently enhance vascular wall repair [105]. Finally exosomal miR-126 by repressing TRAF7, a protein that induces pro-apoptotic pathway, prevents palmitate-induced apoptosis in endothelial cells, and presents atheroprotection feature [106, 107]. Wang and *et al* reported that exosomes derived from MSCs which are enriched in miR-223 by blocking inflammation -related genes, Sema3A and STAT3, prevents macrophages responses and cardiomyocytes death in sepsis-induced mice [108]. Also, miR-223-5p blocks TNFR1 and DR6 , two important cell death receptors and thereby blocking RIP1/RIP3/MLKL necroptotic pathway and attenuating I/R induced necrosis. Likewise, miR-223-3p through blocking expression of NLRP3 and IκB kinase α, factors that have major roles in I/R-induced inflammation and cell necroptosis, present cardioprotective feature [109]. Intriguingly, it has been reported that elevated levels of miR-223-3p identified in the serum of atherosclerosis patients and also in hypertension associated with hyperlipidemia cases which make miR-223 a remarkable biomarker of atherosclerosis-related diseases [110].

In a recent studies, it has been demonstrated that Exosomal miR-210 by targeting CDK10, a subclass of protein kinase family, APC protein, the antagonist of Wnt signaling pathway, EFNA3, a family of receptor tyrosine kinase which are essential in vascular and epithelial cells differentiation and finally PTPN1, an enzyme that involved in insulin-mediated signaling, regulates cardiomyocytes proliferation and apoptosis and have the potential to be applied as a therapeutic target molecule [111, 112].

Conclusion

Over the last decade, exosomes have been applied and evaluated as drug delivery carriers, diagnostic and prognostic biomarkers, communication tools between adjacent and distant cells, and even for the design of new targets of treatment approach. As a result of conducted studies, exosomes roles and involved molecular mechanisms in cardiovascular diseases became more clear. As reviewed above, in different conditions, exosomes have various content which directly affects the final physiological profile and determine whether they are helpful or detrimental. Exosomes are released almost from all types of cardiac cells including cardiomyocytes, cardiac fibroblasts, endothelial cells, and Cardiac-Derived Progenitor Cells. Proteins and miRNA content of each of these cells can be involved in the pathological mechanism, therapeutic pathways, and diagnostic approaches which provide opportunities to exploit exosomes as therapeutic tools and biomarkers. Since the exosomes are very specific, sensitive, easy to obtain from blood or urine samples, and possess a long half-life, they are an excellent candidate as diagnostic biomarkers. Although exosomes present interesting potential as new cardiovascular diseases treatment and diagnosis methods, but there are technical challenges that limit their practical application including, difficulties in exosomes isolation methods, characterization, and standardization.

In conclusion, despite the challenges ahead of application of exosomes as personalized exosome-based therapies, diagnostic targets, or in but the hope is that as our knowledge expands on exact molecular mechanisms, in the near future be able to overcome the limitations.

Conflict of Interest

none declared.

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