Published in final edited form as:

Adv Exp Med Biol. 2017 ; 998: 113–138. doi:10.1007/978-981-10-4397-0_8.

Pathological Effects of Exosomes in Mediating Diabetic Cardiomyopathy

Esam S.B. Salem and Guo-Chang Fan, Ph.D.

Department of Pharmacology and Cell Biophysics, University of Cincinnati College of Medicine,
5872 Care Mail Loc-0575, Cincinnati, OH 45267, USA

8.1 Introduction

Diabetes mellitus (DM) is a chronic endocrine and metabolic disorder characterized by hyperglycemia due to defective insulin secretion, action, peripheral insulin resistance or all of them [1, 2]. The global prevalence has reached epidemic proportions and approximately 285 million cases were diagnosed with diabetes in 2010, and this figure is estimated to reach 439 million in 2030 [3]. Recent studies suggest that 26 million people in the USA are suffering from diabetes, and by 2030 the estimated economic burden would reach to \$490 billion [4]. Most cases of diabetes can be classified into two groups: type 1 (T1DM) and type 2 (T2DM) with annual estimation of 150,000 newly diagnosed patients with type 1 and 1.3 million with type 2 in the USA [5]. T1DM was previously known as “insulin dependent diabetes mellitus” (IDDM) [6]. It occurs in 0.3–0.5% of the population, and is characterized by insidious and sudden onset [7]. T1DM is a chronic autoimmune disorder characterized by an absolute deficiency of insulin caused by selective destruction of pancreatic β -cells [8]. T2DM was previously known as “non-insulin-dependent diabetes mellitus” (NIDDM) [9]. It occurs in 3–5% of the population, and typically is characterized by slow and progressive onset [10]. T2DM is often associated with obesity, lack of exercise and family history [11]. Moreover, the pathogenesis of T2DM involves a combination of insulin resistance and diminished insulin secretion from pancreatic β -cells [12]. Notably, patients with diabetes are at two to three folds higher risk of developing heart disease [13]. Indeed, the main cause of mortality and morbidity among subjects with diabetes is cardiovascular disease [14], accounting for more than 60% of death [15]. Although comorbidity factors such as chronic systemic hypertension and vascular atherosclerosis contribute to development of cardiovascular disease among diabetic patients, but chronic hyperglycemia itself is considered as an independent risk factor for cardiac damage [16]. In diabetic animal models, cardiac dys-function could be occurred without systemic hypertension, coronary artery disease, or blood vessel atherosclerosis [17, 18]. Furthermore, the incidence of suffering from heart failure is still high even after pharmacological controlling of hypertension or ischemic heart disease in diabetic patients [19]. High levels of inflammatory cytokines, adrenergic and renin-angiotensin hormones in the blood circulation, augmented sympathetic outflow, hyperlipidemia and hyperglycemia enhance toxic effects on the myocardium and

cause cardiac dysfunction and damage, and that pathological disorder together known as diabetic cardiomyopathy (DCM) [20–25].

More than a decade has passed since DCM was first described with a substantial amount of research; nonetheless, how DCM develops is still largely complex and remained unclear [26]. The heart is the most active and life-long beating organ, which continuously keeps pumping the blood to perfuse the whole tissues of the body with sufficient amount of oxygen and nutrient [27]. In fact, coordination, synchronization and communication between different cell types of the heart are essential and required to maintain effective myocardial function and normal structure [28]. Histologically, the heart of an adult murine is composed of two to three billion cardiomyocytes, which accounts one-third of the total cellular mass of the heart [29]. However, it should be emphasized that, not only cardiomyocytes are important to maintain normal function and structure of myocardium, but also smooth muscle cells, endothelial cells, cardiac stem cells, fibroblasts, and immunological cells such as macrophages [30–33]. Therefore, it becomes clear that local or long-distance cell-to-cell communications have a major contribution to maintain normal cardiac homeostasis [34]. These include several pathways that are mediated via paracrine or autocrine growth factors, cell matrix interactions, cell gap junctions or adhesion molecules that control physiological cardiac homeostasis [35–38].

Large amount of evidence has suggested that extracellular vesicles generated and released from different mammalian cells' have a potential role for cardiac cells communication [39, 40]. These extracellular vesicles composed of a phospholipid bilayer and contain a specific code of genetic materials, proteins and lipids [40–43]. Several types of extracellular vesicles can be produced by different cells of the heart, including apoptotic bodies, microvesicles and exosomes [43–45]. These different sorts of vesicles are distinguished from each other on the basis of their site of origin, diameter and contents. For example, apoptotic bodies are originated from the plasma membrane of cells when they undergo the last stage of apoptosis with 1–5 μm in diameter [46]. They harbor different cytoplasmic organelles, and many nuclear DNA fragments. Even though the precise role of apoptotic bodies is not completely emphasized, but it is widely accepted that apoptotic bodies can induce the elimination of other damaged cells [47]. On the other hand, microvesicles are 200–1000 nm in diameter and synthesized from cells by a direct external budding (Exocytosis) of the plasma membrane when they are exposed to physiological or pathological stimuli such as cellular proliferation or differentiation, and cellular apoptosis or necrosis [48–50]. Microvesicles can be derived from non-nucleated cells include platelets and red blood corpuscles, or nucleated endothelial and other viable cells [49]. Microvesicles contain variable amounts of bioactive molecules, including cytokines and chemokines, cytoplasmic proteins, plasma membrane proteins and lipids, non-coding RNAs (e.g., miRNAs, lncRNAs, circRNAs) and mRNAs [48, 49, 51]. Whereas, exosomes are defined as types of extracellular vesicles whose diameter ranges between 10 and 200 nm. They are characterized by very unique properties that distinct them from apoptotic bodies or microvesicles (Fig. 8.1) [52, 53]. Synthesis and release of exosomes from viable cells was considered as a mechanism through which their waste products can be discard into extracellular environment. However, accumulated reports have suggested that exosomes are appeared to have an important function as biological messengers in mediating inter-cellular communication both in physiological (e.g.

myocardial angiogenesis) and pathological conditions (e.g. metastasis of malignant cancer) [54–56]. This chapter will focus and summarize the available data concerning the detrimental effects of exosomes in diabetic cardiomyopathy.

8.2 Diabetic Cardiomyopathy: What We Have Known and Do Not Know

8.2.1 Concept and Characterizations of Diabetic Cardiomyopathy

In 1972, diabetic cardiomyopathy (DCM) was first identified by Rubler et al. based on postmortem observations of the cardiac autopsy from diabetic patients who were diagnosed with heart failure without other cardiovascular complications [57]. These observations were suggested as specific impairment of the heart muscle itself [57]. DCM has a higher 12% prevalence in type 2 diabetic patients compared to healthy subjects [58], and been described as a long-term and serious complication of sustained toxic effects of hyperglycemia that leads to enhance cardiac oxidative stress [59, 60], inflammation [61], abnormal Ca^{2+} handling and mitochondrial function [62–64], myocardial apoptosis and fibrosis [65, 66]. Type 1 diabetic patients have also been clinically diagnosed with reduced cardiac function, left ventricular hypertrophy [67], and eventually heart failure independent of other comorbidities including blood vessel atherosclerosis, coronary arteries disease or chronic systemic hypertension [68]. Moreover, development of cardiomyopathy has also been reported in animal models which are rodents resistant to atherosclerosis with type 1 or 2 diabetes, providing strong evidence for the occurrence of DCM comparable with that seen in human diabetic subjects [69].

While multiple and different signaling pathways are involved in the onset and development of DCM, it is difficult to distinguish between a pure hyperglycemic toxic effect and other cardiovascular comorbidity factors effect [70]. Consequently, the medical diagnosis or terminology of DCM as an independent cardiac disease has been unpopular among physicians [71], and even the existence of DCM has been disproved among some scholars for a long time [72, 73]. However, large accumulation of data from *in vivo* and *in vitro* studies, both have shown that hyperglycemia itself can cause functional abnormalities and structural changes of the heart. These studies strongly support the existence of DCM [74, 75]. In diabetic heart, cardiomyocytes have to increase β -oxidation of fatty acids in order to generate ATP, which results in an elevation of reactive oxygen species (ROS) production [76]. ROS have harmful effects on cell homeostasis by damaging DNA, proteins, plasma membrane lipids, subcellular organelles, and inhibiting enzymes of the oxidative-phosphorylation mechanism, thereby further reducing efficiency of ATP generation [77–81]. During the early stage, intracellular anti-oxidant buffers counteract the effects of increased levels of ROS, but these buffering agents are depleted quickly. The cardiomyocytes thereafter undergo an energy deficit, alteration of gene transcription and protein translation, certainly leading to apoptosis [82–85].

DCM clinical presentation can be divided into an initial stage which is preceded by abnormal myocardial metabolism, and the early stage that is characterized by diastolic dysfunction [86]. Then, the late well-established stage which is presented with systolic dysfunction or heart failure [17, 18]. In clinical practice, the initial stage of DCM is asymptomatic and difficult to be diagnosed, but the early stage of DCM is characterized by

diastolic dysfunction (including: ventricular hypertrophy and stiffness, high end-diastolic volume and pressure) [87, 88], and cardiac inter-cellular matrix remodeling (including: an accumulation of insoluble type VI collagen and fibrous connective tissue) [89, 90]. Several mechanisms contribute to ventricular stiffness in diabetic heart mainly due to hyperglycemia and formation of advanced glycation end-products (AGEs) [91]. Consequently, AGEs can interact and bind with extracellular matrix proteins including collagen and elastin, leading to a change in the properties of myocardium compliance and eventually impairing ventricular relaxation [92–94]. Also, the diastolic dysfunction prevalence is much higher in type 2 diabetic patients compared to healthy subjects with same age and gender [95, 96]. A diabetic subject with DCM is clinically diagnosed as the impairment of his left ventricle (LV) function in the absence of other concomitant risk factors, including coronary artery disease (CAD), chronic systemic hypertension, or other congenital cardiac anomalies [74]. Additionally, many studies have demonstrated that there is a link between cardiac systolic dysfunction and sustained hyperglycemia [97]. Other studies have indicated that systolic function during the physical rest was not altered in the most patients with type 2 diabetes, as clinically evaluated by measuring the left ventricular ejection fraction (LVEF) [98, 99]. However, some diabetic subjects have cardiac systolic dysfunction during an extensive exercise, which suggests that LVEF is not a sensitive indicator of myocardium contraction to detect early changes in myocardial function during rest [100].

In fact, during the course of hyperglycemia, these processes are exacerbated and led to hypertrophy, apoptosis and fibrosis of myocardium. When the hypertrophy of myocardium can't overcome or compensate for apoptosis and fibrosis, systolic dysfunction appears, indicating the irreversible stage of DCM towards congestive heart failure [101]. At the beginning, DCM is similar and diagnosed as restrictive cardiomyopathy with normal left ventricle ejection fraction [102, 103]. After that, the late stage of DCM is similar and diagnosed as dilated cardiomyopathy with reduced left ventricle ejection fraction [103, 104]. In general, human subjects or animal models with cardiac systolic dysfunction have a worse prognosis and could be exacerbated further in the presence of diabetes [105–107]. Therefore, the main pathophysiological features of DCM include the metabolic changes of cardiomyocytes during the initial stage, followed by increased ROS production and ATP deficiency, altered intracellular calcium transport and recycling, enhanced myocardial hypertrophy, and then cardiac apoptosis and fibrosis, leading to ultimate congestive heart failure [108, 109].

8.2.2 The Mechanisms Underlying the Development of Diabetic Cardiomyopathy

At present, it has been elucidated that diabetes-induced cardiac dysfunction correlates with abnormal changes in Ca^{2+} handling that reduce efficiency of the sarco-mere and thereby the electromechanical coupling mechanism, resulting in impairment of myocardium contraction [110]. Furthermore, the cardiac sarcoendo-plasmic reticulum Ca^{2+} -ATPase 2 (*SERCA2*), the $\text{Na}^+/\text{Ca}^{2+}$ exchanger 1 (*NCX1*), and ryanodine receptor (*RyR*) functions are significantly inhibited in DCM, causing to a reduction in release and slow in recycling of Ca^{2+} from and to endoplasmic reticulum during the relaxation phase [62, 111–115]. Using diabetic animal models to investigate underlying mechanisms, and to understand how hyperglycemia damages the myocardium would be beneficial to develop therapeutic agents to protect or

retard onset of heart failure in human diabetic subjects [59, 77]. Hyperglycemia, hyperlipidemia, oxidative stress, apoptosis, autophagy, non-coding RNAs, and epigenetic effects have been investigated as underlying etiologies and mechanisms of DCM [116–118]. For example, there is an evidence that hyperglycemia directly activates caspase-3 resulting in increased cardiac fibrosis due to apoptosis of cardiomyocytes. So enhanced myocardium apoptosis is an essential etiology in the development and progression of heart failure from reversible compensated to irreversible decompensated stage [77, 119]. Recently, studies have been reported that insulin-resistance contributes to the development of DCM. Even though the myocardial insulin signaling is impaired in patients with DCM; however, the underlying mechanisms that could be involved in the insulin resistance are not extensively investigated or deeply understood [17, 120, 121]. Based on previous results, medical therapeutic interventions were developed to treat DCM. For example, administration of antioxidant buffers was failed to protect diabetic heart in the clinical practice [122, 123]. Furthermore, tight control of hyperglycemia also failed to retard the onset or progression of DCM towards heart failure in diabetic patients [124]. To highlight more on the same theme, we will briefly discuss about several sorts of miRNAs and their potential roles in DCM pathogenesis [116]. Structurally, miRNAs are a family of small (~22 nucleotide) and single-strand noncoding RNAs that act as post-transcriptional regulators of target genes via degradation or translation inhibition of their targeted mRNAs [125]. For instance, a recent study has found that miRNA-195 levels were higher in the hearts of STZ-induced diabetic mice, which was negatively correlated with lower expression levels of its targeted molecules including Sirtuin 1 (*SIRT-1*) and B-cell leukemia/lymphoma 2 (*BCL-2*) in comparison to wild type mice. In addition, inhibition of miRNA-195 reduced hypertrophy, oxidative stress, and apoptosis in STZ diabetic myocardium [126]. Moreover, same study has observed that restoration of normal cardiac function, improvement of coronary blood flow, an elevation of expression levels of *SIRT-1* and *BCL-2* and SIRT-1 after miRNA-195 blockade, demonstrating that reduction of miRNA-195 levels can retard the onset or propagation of DCM towards complete heart failure [126]. In the same context, a study has shown that expression levels of miRNA-133a/b were participated in diminishing the protein expression of glucose co-transporter isoform 4 (GLUT4) and then the rate of glucose uptake into neonatal rat cardiomyocytes (NRCMs) [127]. Of interest, another study has emphasized that miRNA-133a expression levels were significantly decreased in diabetic hearts, and simultaneously there was an elevation in the expression levels of cardiac fibrosis markers. Additionally, the same study has found that higher levels of miRNA-133a ameliorate cardiac fibrosis and prevent development of HF in diabetic hearts [128]. In spite of the controversial between these two previous studies that have been conducted on different animal models, more investigations are required to explore the function of miRNAs in DCM pathogenesis [129–131]. Furthermore, higher levels of miRNA-223 in NRCMs were significantly increased the glucose uptake with a similar rate of glucose uptake that measured in cells stimulated with insulin [132]. Overexpression of miRNA-223 in cardiomyocytes also observed to enhance total GLUT4 expression levels and translocation of GLUT4-contained vesicles from the cytoplasm to the cell membrane [132]. By contrast, blockage of myocardial miRNA-223 caused a reduction in expression levels of insulin-regulated glucose transporter, GLUT4 [132]. Another study has revealed that miRNA-141 levels were significantly higher in a diabetic mouse heart, which was associated with a significant

decrease in the phosphate transporter/solute carrier family 25 member 3 (*Slc25a3*) of inner-mitochondrial membrane in the mouse atrial cardiomyocyte cell line (HL-1), demonstrating that miRNA-141 can impact the mitochondrial function of myocardium [133]. In the same context for the importance of miRNAs in the pathogenesis of DCM, miRNA-451 expression levels were highly increased in palmitate-stimulated NRCMs and high fat diet (HFD)-induced obesity mice hearts [134]. Furthermore, cardiac hypertrophy was improved in miRNA-451 knockout mice fed with HFD via inhibition of the LKB1/AMPK signaling cascade. As well as, *in vitro* miRNA-451 knockdown protein expression was protected from toxic and harmful effects of the lipid via the inhibition of LKB1/AMPK pathway [134]. Additionally, induction of miRNA-143 in cardiomyocytes via release activin-(A) from adipose tissue of epicardium membrane can attenuate insulin action due to inhibition the AKT signaling pathway through down-regulation of ORP8. However, further studies are needed to confirm the functional role of miRNA-143/ORP8 in the pathogenesis of DCM [135]. In regard to insulin action, a study has exhibited that miRNA-29 was participated in the development of DCM. In the same context, a recent study has shown that insulin inhibits the expression levels of miRNA-29a, b and c, which was associated with an increase of the mRNA levels of the pro-survival protein myeloid cell leukemia 1 (MCL-1) in (*HL-1*)-cells [136]. Also, the same study has revealed that dis-balance of the (miRNA-29)-(MCL-1) levels due to mTORC1 inhibition or lower insulin levels in Zucker Diabetic Fatty (ZDF) rats was involved in the myocardium destruction, and contributed to cardiac malfunction [136]. Additionally, a recent study has found that miRNA-322 modulates the insulin signaling cascade, protects the myocardium against the malfunction and structural damage detected in HFD-fed mice, revealing that overexpression of miRNA-322 attenuated insulin-induced AKT phosphorylation [137]. Indeed, miRNA-322 can modulate insulin signaling, protect the cardiac function and structure against pathological effects of hyperinsulinemia as seen in pre-diabetic subjects and patients with type 2 diabetes [137]. On the other hand, a recent study has demonstrated that detrimental effects of cardiac miRNAs induced by sustained hyperglycemia were irreversible even after the normalization of hyperglycemia with anti-diabetic medications because altered levels of miRNAs profile in the diabetic heart were involved in autophagy, oxidative stress, apoptosis, fibrosis and eventually HF. Based on the *in vitro* and *in vivo* data presented above, miRNAs are clearly involved in the pathophysiology mechanisms of DCM. Nonetheless, further studies are needed to investigate the underlying mechanisms of DCM, and thus clear understanding of these mechanisms will control their therapeutic potential by protecting the heart from the toxic effects of hyperlipidemia and hyperglycemia.

8.3 Role of Exosomes in Diabetes: What We Have Known and Do Not Know

8.3.1 Diabetes Affects the Exosome Generation and Exosomal Compositions

Exosomes are generated from inward invagination of the cell plasma membrane to form and produce an early endosome [138]. During the maturation of an early endosome, the inward luminal buddings of the endosomal membrane form and produce multi-vesicular bodies (MVBs) that contain intraluminal vesicles (ILVs) [139]. These newly formed vesicles contain different cytoplasmic components, including proteins, lipids, DNA and several types

of RNAs [140]. Then, the endosomal sorting complexes required for cellular transport machinery are essential for the formation of ILVs in MVBs [141]. When MVBs are formed, the ILVs (exosomes) are released to the extracellular environment by docking and fusion of the MVBs with the cell plasma membrane, which is mediated by small GTPase-dependent proteins such as Rab-proteins (e.g., Rab27, Rab35) [142–145]. Alternatively, MVBs can fuse with a lysosome, where the contents of the MVBs are degraded as cell waste products [146, 147]. The functions of secreted exosomes can be exerted directly via interaction of their transmembrane integral proteins or lipid with receptors of recipient cells, or indirectly by delivering their contents, including transcription factors, cytoplasmic proteins, mRNAs, miRNAs into cytoplasm of recipient cells via an endocytosis mechanism (e.g., cell drinking or eating) [148]. Several of the regulatory exosomes are sensitive and regulated by changing of glucose concentration levels [149, 150]. Expression levels of miRNA-9, miRNA-15a, miRNA-30d and miRNA-133a were up-regulated, whereas expression levels of miRNA-375 was down-regulated, by high glucose levels [151, 152]. Also, fatty acids can affect miRNA expression levels; for example, miRNA-34a and miRNA-146 expression levels were up-regulated by increased levels of fatty acids concentrations [153, 154]. Functionally, biologic effects of exosomes can be local or remote by delivering coded messages from the cell of origin to recipient cell via releasing them into inter-cellular fluid or blood circulation [155].

8.3.2 Detrimental Effects of miRNAs and Exosomes in the Development of Diabetes Mellitus

Currently, exosomes have been implicated as pathological factors in the pathogenesis of several diseases, including malignant tumors, autoimmune and inflammatory diseases; as well as, cardiovascular and chronic metabolic disorders [156–158]. Indeed, recent studies have also demonstrated that exosomes can orchestrate insulin signaling cascade in peripheral tissues and different organs, indicating the pivotal role of exosomes in regulation of glucose metabolism in T2DM [159–161]. Large amount of data has shown that miRNAs regulate pancreatic β -cell activity, but recently some studies reported that these miRNAs are also can be transferred from β -cells to another recipient cells via exosomes [162, 163]. Additionally, exosomes-enriched miRNAs regulate a wide spectrum of genes that are important for pancreatic β -cell homeostasis, and a chronic exposure to high concentrations of glucose and fatty acids impact negatively on their synthesis and secretion of insulin hormone. Therefore, exosomes-enriched with a specific set of miRNAs can participate in progressive β -cell dysfunction or devastation in both types of diabetes [164, 165]. In order to investigate if miRNAs directly involved in mediating pancreatic β -cells dysfunction and apoptosis, miRNAs expression levels have been investigated indifferent cell lines, type 1 and type 2 diabetic animal models, exploring the functional roles of several miRNAs in β -cells dysfunction, and their potential roles in the apoptosis of pancreatic β -cells under hyperglycemic condition [166–168]. For instance, cytokine-treated Min6B1 cells (pancreatic β -cell line) secrete exosomes containing miRNAs that are transferred to neighboring β -cells, leading to apoptosis [169, 170]. Exosomes were also isolated from the culture media of pancreatic islet cells of human and non-obese diabetic (NOD) mice (type 1 diabetes model); as well as, Min6B1-cells treated with pro-inflammatory cytokines (TNF α , IL-1 β , IFN γ). Then, by incubating these isolated exosomes with untreated mice pancreatic β -cells or Min6B1-cells leads to apoptosis in the recipient cells [169–171]. The pro-inflammatory

cytokines induce β -cells expression of miRNA-21, miRNA-29, miRNA-34a and miRNA-146a, thereby an increase levels of these miRNAs can contribute at least partially in destroying of insulin-secreting pancreatic β -cells and then in the development of diabetes [153, 162, 164, 172]. Additionally, over-expression of miRNA-29, miRNA-34a, miRNA-146a or miRNA199a-5p in Min6B1-cells enhance apoptosis [173], while knockdown of miRNA-34a, miRNA-203, miRNA-210 and miRNA-383 diminishes β -cell apoptosis [173, 174]. High levels of miRNA-34a were also negatively associated with the anti-apoptotic protein Bcl-2 (B-cell lymphoma 2), demonstrating that pro-apoptotic effects of miRNA-34a could be exerted via inhibition of Bcl-2 [175]. Whereas, the pro-apoptotic effect of miRNA-29 was due to its ability to block translation of another pro-survival protein Mcl-1 (Myeloid Cell Leukemia 1) [136]. On the other hand, mRNA translation of the tumor suppressor programmed cell death protein 4 (PDCD4) in pancreatic β -cells was reduced by miRNA-21. Additionally, PDCD4 expression levels were significantly attenuated as result of higher miRNA-21 expression levels in NOD mice [176]. Subsequently, the same study has shown that inhibition of miRNA-21 activity significantly increased β -cell apoptosis. Moreover, β -cells-specificPDCD4Knockoutwas correlated with an elevation in the expression levels of the anti-apoptotic genes (e.g., Bcl-xL), whereas with a reduction in the expression levels of the pro-apoptotic genes (e.g., Bax family), leading to the delay in the onset of diabetes development. Therefore, over-expression of miRNA-21 could be a pivotal protective mechanism of pancreatic β -cells after exposure to pathological stimuli via shifting the balance from pro-apoptotic to anti-apoptotic proteins [176]. In the same route, a recent study has reported that higher expression levels of miRNA-200 in a mouse pancreatic β -cells promote apoptosis of β -cells and development of diabetes via inhibition of tumor suppressor (Trp53) and amelioration of pro-apoptotic (Bax) signaling pathway [177]. Mocharla et al., was successfully able to detect that CD34⁺ peripheral blood mono-nuclear cells (PBMCs) release higher levels of miRNA-126 containing exosomes than CD34⁻ PBMC, and to observe that these exosomes enriched higher miRNA-126 levels had higher pro-angiogenic effects on endothelial cells (ECs) in comparison to lower miRNA-126 levels enriched exosomes [178]. At the same time, same author also reported that treatment of CD34⁺ PBMC with anti-miRNA-126 or inhibition of their release diminished their pro-angiogenic effects on ECs. In addition, same study has revealed that treatment of CD34⁺ PBMCs with high glucose concentration was associated with impairment of their pro-angiogenic properties, which could be rescued by miRNA-mimic-126 treatment [178]. Even though there is still a gap of knowledge and limitation of studies that clearly demonstrate the biological nature of several types extracellular vesicles (EVs), but also there are several studies reported that the levels of EVs are higher in the plasma of type 2 diabetic subjects compared to healthy subjects [179–181]. In specific, the membrane proteins or lipids of EVs which are released from skeletal muscle, platelets, or T lymphocytes increase the risk of metabolic dysfunction and cardiovascular diseases [182, 183]. In addition, an elevation levels of EVs has been reported and positively linked with obesity, diabetic micro or macrovascular complications, and inflammations, suggesting that the exosomes quantity can be clinically used as an early indicator (e.g.; urinary or blood marker) of previous diseases and their complications [184–187]. For example, exosomes released from visceral adipose tissue (VAT) in diabetic mice can fuse with blood monocytes and stimulate their differentiation into mature and active macrophages [160]. Various studies have provided an

interesting attention into the way miRNA-containing endothelial micro-particles (EMPs) influence inflammatory effects under hyperglycemic condition [188]. Studies both *in vitro* and *in vivo* have shown that extracellular membrane-bonded micro-vesicles (EMVs) contribute to anti-inflammatory effects by diminishing endothelial ICAM-1 expression since they act as carriers to transfer functional miRNA-222 into recipient cells. Interestingly, their anti-inflammatory effects were reduced under hyperglycaemic condition due to a reduce of miRNA-222 levels of newly generated EMPs [170]. Exosomes released from VAT in type 2 diabetic mice also induce the development of insulin resistance when they were administered to wild type healthy mice. Adipocyte-derived exosomes contain numerous sorts and sets of proteins, which is indicated the important roles of exosomes in the extracellular and intercellular transmission of signals [189]. Further, exosomes released from skeletal muscle, which is another critical tissue regulating blood glucose metabolism, have an auto-regulation effect on skeletal muscle homeostasis as well as on other organs, including the pancreas and liver [159]. Barutta et al., also has provided additional information about the role of exosomes and underlying mechanisms that taking place in diabetes. The author reported that urinary exosomes from micro-albuminuric patients contain higher concentrations of miRNA-130a and miRNA-145, whereas the concentrations of miRNA-155 and miRNA-424 were lower [190]. In a mouse model of diabetic nephropathy, urinary levels miRNA-145-enriched exosomes were elevated while miRNA-145 were overexpressed within the glomeruli, which was simultaneously associated with higher levels of urinary miRNA-145-containing exosomes as detected in the urine specimens from type 2 diabetic patients, reflecting a higher shedding rate of exosomes from the renal parenchyma into the urine [191, 192]. In addition, renal mesangial cells cultured with high glucose concentration showed an increase in miRNA-145 levels in these mesangial cells and their released exosomes [191]. Human β -cells exhibit specific miRNAs sets and profiles which are involved in activation or inhibition specific genes associated with the development of type 2 diabetes [193–196]. Moreover, similar miRNAs setting and profiling of β -cells from diabetic Goto-Kakizaki rat (non-obese type 2 diabetes model) have been identified and detected upregulation levels of miRNA-130a, miRNA-132, miRNA-212 and miRNA-335 [197]. In 2010, Zampetaki et al., investigated and generated an expression profile of miRNAs in plasma of type 2 diabetic subjects. The author observed a significant decrease in plasma levels of miRNA-15a, miRNA-20b, miRNA-21, miRNA-24, miRNA-126, miRNA-191, miRNA-197, miRNA-223, miRNA-320, and miRNA-486, whereas a moderate increase of miRNA-28 and miRNA-3p levels. Additionally, high glucose concentration was attributable to the reduction of miRNA-126 levels in endothelial apoptotic bodies [198]. Furthermore, it has been suggested that type 1 and 2 diabetes are associated with multiple variations of mouse miRNA-encoding genes and miRNA-binding sites in 3'-UTR of mRNA-encoding genes, speculating the importance of preceded alteration in the miRNAs profile that incorporated in diabetes pathogenesis [199, 200]. Fundamentally, the ongoing research are still at the early phase of understanding the ultimate role of exosomes in pathogenesis of both types of diabetes, and demonstrating how we can use them clinically as an effective therapy for the prevention or retardation onset of diabetes, or as an early and sensitive biomarker for its long-term complications including DCM [187, 201].

8.4 Role of Exosomes in Diabetic Cardiomyopathy

The cellular cross-talk mechanisms involving exosomes are often multidirectional and multifunctional rather than unidirectional and unifunctional [55, 202]. Exosomes enclose and carry both numerous species of miRNAs and different types of proteins, of which transfer several and specific signaling codes from the cell of origin to another cells of different tissues and organs at the adjacency, at the proximity or at the distance [203, 204]. In this context, accumulated evidence has emphasized that a major portion of the plasma miRNAs are enveloped in exosomes [205, 206]. On the another hand, a study has suggested that plasma miRNAs can be bound to high density lipoproteins in the blood circulation in addition to exosomes [207]. Recently, based on the multiple properties of cardiac-derived exosomes from all different cell types of the heart, scientific community has speculated that exosomes can be involved in the pathophysiology of cardiovascular disorders including DCM [49]. However, the available data on a such context is still limited due to either gap of knowledge or technical difficulties on exosomes. In fact, we will cover and summarize the present studies that investigated the roles of exosomes in diabetes-induced cardiomyopathy, as reviewed below.

8.4.1 Diabetic Cardiomyocytes Secrete Antiangiogenic Exosomes

During the initial course of diabetes, hyperglycemia can lead to endothelial and microvascular dysfunctions [208, 209]. Interestingly, it has been reported that dys-regulation of myocardial angiogenesis is the pivotal cause of diabetic cardiovascular disease [210–212]. Indeed, cardiac endothelial cells play a critical role in cardiomyocyte contraction and structure [213, 214]. However, under hyperglycemic condition, whether cardiomyocytes have an ability to modulate cardiac endothelial cell function remains uncertain [215, 216]. In the context of understanding the mechanism, recent studies have shown that cardiomyocytes-derived exosomes contain variable amounts of mRNAs and miRNAs, proteins and lipids, all of which can transfer to the adjacent cardiac endothelial cells and regulate their functions [217–220]. In prior study by Dr. Fan's team has provided an evidence that cardiomyocyte-derived exosomes can affect cardiac endothelial cells' contents and release (ECs) in the variable ways that are dependent upon the condition to which the cardiomyocytes were exposed to or cultured with. As an example, isolated exosomes from diabetic Goto-Kakizaki (GK) rat's cardiomyocytes diminished the migration and proliferation of cardiac ECs. In contrast, isolated exosomes from control non-diabetic Wistar rat's cardiomyocytes promoted the migration and proliferation of cardiac ECs (Fig. 8.2) [220]. Further, the effects of generated exosomes from both diabetic GK and non-diabetic Wistar rat's cardiomyocyte on cardiac ECs were reversed by blocking their release using an inhibitor of neutral sphingomyelinase/ceramide GW4869. Consequently, previous results suggest that pathological exosomes can transfer and distribute harmful molecules that participating in the development of diabetic cardiomyopathy [220–222].

In addition, the same study has emphasized that cardiomyocytes-derived exosomes from diabetic GK cardiomyocytes enriched with higher levels of miRNA-320, and lower levels of miRNA-126 and heat shock protein 20 (Hsp20) in comparison to non-diabetic Wistar rat's cardiomyocyte-derived exosomes [220]. They also observed that the cardiomyocyte

enriched-miRNA-320 exosomes can transfer to cardiac ECs, and subsequently downregulate the expression of IGF-1, Hsp20, and Ets-2, resulting in impairment of angiogenic function of adjacent cardiac ECs (Fig. 8.2). Therefore, these observations provide a strong evidence that exosomes-isolated from diabetic cardiomyocytes reduced the angiogenesis in the diabetic myocardium via transferring detrimental factors that are able to induce, amplify and spread the downstream cascade of anti-angiogenic effects to cardiac ECs [220]. Garcia et al., has been recently shown that exosomes-derived from contractile cardiomyocytes can regulate glucose transport into the cardiac ECs. Same study reported that under hypoglycemic condition, cardiomyocytes produced larger amount of exosomes-enriched with glucose transporters and enzymes involved in glucose metabolism, resulting in increased in the rate of glucose uptake and glycolysis in cardiac ECs under condition of glucose deprivation [223].

8.4.2 Beneficial Effects of Gene-Modified Exosomes in Diabetic Cardiomyopathy

It has recently been elucidated that loaded contents of exosomes could be directly mediated by gene transfection or indirectly modified in parental cells, thereby we can convert diseased exosomes to be beneficial ones [224]. Along this line, it has been reported that Hsp20, an important chaperone protein involves in cellular defense mechanisms against multiple pathological stimuli, can promote the production of exosomes from cardiomyocytes via interacting with tumor susceptibility gene 101 (Tsg101) [225, 226]. Tsg101 is an upstream and integral protein of regulated endosomal membrane transport, thereby it involves in the exosome biogenesis, trafficking, sorting and secretion pathways [139, 222, 227]. An interesting study by Wang et al., has revealed that Hsp20 expression levels were decreased in diabetic cardiomyocytes and inhibited by miRNA-320 post-transcriptionally. In addition, Hsp20 response was sensitive to both acute and chronic course of hyperglycemia in a mouse heart, implying that reduced levels of Hsp20 could be involved in the development of DCM and propagation towards heart failure [226]. Consequently, chemical-induced type 1 diabetes in transgenic mice with cardiac-specific Hsp20 overexpression were generated and used to investigate the underlying mechanisms regard the functional role of Hsp20 in diabetic heart. In fact, this study also observed that deleterious effects of exosomes released from diabetic cardiomyocytes can be transformed to beneficial exosomes after Hsp20 overexpression via altering contents and the secretion pattern of cardiomyocyte-generated exosomes, as result restoring normal cardiac functions under hyperglycemic condition. Importantly, the same author also reported that altered exosomes contain cellular protective proteins, including phosphorylated AKT, SOD1, and Survivin, all of which distributed to adjacent cardiac cells promoting myocardial angiogenesis, alleviating oxidative stress, ameliorating fibrosis and apoptosis in a mouse diabetic heart (Fig. 8.2) [226]. Even though it has been confirmed that beneficial exosomes deliver functionally active Hsp20 to the recipient cardiac cells of type 1 diabetic mouse, but also it is interesting to further investigate in-depth the molecular alterations induced in Hsp20 transgenic cardiomyocytes under hyperglycemia and emphasize what are the pivotal mediators that mediate a such deviation from releasing detrimental exosomes to beneficial exosomes [222]. In the same avenue, a study reported that cardiomyocyte-derived exosomes do not have only local cardiac effects, but also have systemic effects. Interestingly, a study by Pironti et al., revealed that both *in vitro* cellular stretch and *in vivo* pressure overload promote the cardiomyocytes to produce exosomes-

enriched with angiotensin II type 1 receptor (AT1R) into the culture media and blood circulation, respectively [228]. Transferring functionally active AT1R to other distinct tissues and organs, principally mesenteric vasculature and skeletal muscles can modulate peripheral vascular resistance and thus blood pressure, when these specific exosomes were injected into the tail vein of AT1 knockout mice [228]. Clearly, the functional role of exosomes in the regulation of different cellular mechanisms can be altered in diabetes and contribute to the onset and development of cardiovascular complications. Finally, the exosomes can deliver and distribute sustained information between distinct cardiovascular cells under hyperglycemic condition has large-scale clinical implications in terms of diabetic cardiomyopathy pathogenesis [222, 226, 229]. Considering all the previous data and taken these findings together, exosomes have potential and functional roles on the pathophysiology of DCM; as well as, promising and possible roles for exosomes to act as therapeutic targets or agents that can be used in the treatment of diabetic cardiomyopathy.

8.5 Conclusion and Future Directions

DCM is still the main cause of morbidity and mortality among diabetic patients. The complete understanding of DCM pathophysiology and the role of exosomes in this pathologic disorder are still under investigations. However, there has been emerging *in vitro*, *ex-vivo* and *in vivo* experimental data about different underlying mechanisms that might be helpful to answer important questions during the study of DCM. In addition, exosomes are considered and studied as microRNA-carriers that are essential for local tissue-specific or inter-systemic cells' communication. Of interest, miRNAs-enriched exosomes play an important role in the development of DCM based on present evidences such as alteration of miRNAs profile in the diabetic heart, suggesting their sustained detrimental effects on DCM despite normalization of hyperglycemia. As matter of fact, exosomes can be generated and derived from different cell types of the body under different pathological conditions, implicating that molecular pathological messages can be spread throughout the body organs via exosomes. Clearly, exosomes are involved in all stages of DCM, including altered insulin signaling and glucose metabolism, hypertrophy, apoptosis and fibrosis of the myocardium. In this context, the functional and expressional pheno-type of exosomes from different sort of cells contributing to the onset and propagation of DCM to HF can be an alternative medical therapy, in which external artificial exosomes will be administered in order to counteract the molecular defects in DCM. Nonetheless, further studies are necessary to emphasize and elucidate the complete molecular mechanisms underlying the development of DCM and the biological nature of exosomes: First, could we be able to isolate normal exosomes from the blood of healthy subjects?; Second, could isolated normal exosomes reverse the phenotype and restore normal cardiac function in patients diagnosed with DCM?; Third, could we be able to use host cells to overexpress beneficial factors that can be loaded and delivered via exosomes?; Fourth, is it clinically possible to intervene the generation or secretion of harmful exosomes?; also, we do not know if blockade of harmful exosomes generation or secretion during DCM pathogenesis is able to have beneficial effects? In general, deep understanding of mechanisms that are contributed to exosome generation, secretion or uptake will be important to modulate the quality and quantity of exosomes in order to develop an effective therapy and improve efficacy of therapeutic intervention for the

treatment of DCM. To sum up, there are clear evidence that exosomes play a critical role in the regulation of tissue-specific and/or whole body glucose metabolism. Future studies in the understanding of cell-to-cell communication pathways via exosomes in the setting of diabetic cardiomyopathy will facilitate clinical research towards the identification of effective medical therapy for DCM.

References

1. Eriksson J, Franssila-Kallunki A, Ekstrand A, Saloranta C, Widen E, Schalin C, Groop L (1989) Early metabolic defects in persons at increased risk for non-insulin-dependent diabetes mellitus. *N Engl J Med* 321(6):337–343 [PubMed: 2664520]
2. Shepherd PR, Kahn BB (1999) Glucose transporters and insulin action—implications for insulin resistance and diabetes mellitus. *N Engl J Med* 341(4):248–257 [PubMed: 10413738]
3. Egede LE, Ellis C (2010) Diabetes and depression: global perspectives. *Diabetes Res Clin Pract* 87(3):302–312 [PubMed: 20181405]
4. Farag YM, Gaballa MR (2011) Diabetes: an overview of a rising epidemic. *Nephrol Dial Transplant* 26(1):28–35 [PubMed: 21045078]
5. Greenberg RA, Sacks DB (2002) Screening for diabetes: is it warranted? *Clin Chim Acta* 315(1–2): 61–69 [PubMed: 11728411]
6. Castano L, Eisenbarth GS (1990) Type-I diabetes: a chronic autoimmune disease of human, mouse, and rat. *Annu Rev Immunol* 8:647–679 [PubMed: 2188676]
7. American Diabetes Association (2010) Diagnosis and classification of diabetes mellitus. *Diabetes Care* 33(Suppl 1):S62–S69 [PubMed: 20042775]
8. Hanafusa T, Imagawa A (2007) Fulminant type 1 diabetes: a novel clinical entity requiring special attention by all medical practitioners. *Nat Clin Pract Endocrinol Metab* 3(1):36–45 [PubMed: 17179928]
9. Reaven GM (1988) Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 37(12):1595–1607 [PubMed: 3056758]
10. Fajans SS (1989) Maturity-onset diabetes of the young (MODY). *Diabetes Metab Rev* 5(7):579–606 [PubMed: 2689121]
11. American Diabetes Association (2006) Diagnosis and classification of diabetes mellitus. *Diabetes Care* 29(Suppl 1):S43–S48 [PubMed: 16373932]
12. Sacks DB, McDonald JM (1996) The pathogenesis of type II diabetes mellitus. A polygenic disease. *Am J Clin Pathol* 105(2):149–156 [PubMed: 8607437]
13. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, Mitch W, Smith SC, Jr, Sowers JR (1999) Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation* 100(10):1134–1146 [PubMed: 10477542]
14. Zimmet P, Alberti KG, Shaw J (2001) Global and societal implications of the diabetes epidemic. *Nature* 414(6865):782–787 [PubMed: 11742409]
15. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L (2001) Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 24(4):683–689 [PubMed: 11315831]
16. Ryden L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer MJ, Cosentino F, Jonsson B, Laakso M, Malmberg K, Pioro S, Ostergren J, Tuomilehto J, Thrainsdottir I, Vanhorebeek I, Stramba-Badiale M, Lindgren P, Qiao Q, Pioro SG, Blanc JJ, Budaj A, Camm J, Dean V, Deckers J, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo J, Zamorano JL, Deckers JW, Bertrand M, Charbonnel B, Erdmann E, Ferrannini E, Flyvbjerg A, Gohlke H, Juanatey JR, Graham I, Monteiro PF, Parhofer K, Pyorala K, Raz I, Scherthaner G, Volpe M, Wood D, Task Force on D, Cardiovascular Diseases of the European Society of C, European Association for the Study of D (2007) Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur Heart J* 28(1):88–136 [PubMed: 17220161]

17. Boudina S, Abel ED (2007) Diabetic cardiomyopathy revisited. *Circulation* 115(25):3213–3223 [PubMed: 17592090]
18. Boudina S, Abel ED (2010) Diabetic cardiomyopathy, causes and effects. *Rev Endocr Metab Disord* 11(1):31–39 [PubMed: 20180026]
19. Poirier P, Bogaty P, Garneau C, Marois L, Dumesnil JG (2001) Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes: importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy. *Diabetes Care* 24(1):5–10 [PubMed: 11194240]
20. Atlas SA (2007) The renin-angiotensin aldosterone system: pathophysiological role and pharmacologic inhibition. *J Manag Care Pharm* 13(8 Suppl B):9–20 [PubMed: 17970613]
21. Bahrami H, Bluemke DA, Kronmal R, Bertoni AG, Lloyd-Jones DM, Shahar E, Szklo M, Lima JA (2008) Novel metabolic risk factors for incident heart failure and their relationship with obesity: the MESA (Multi-Ethnic Study of Atherosclerosis) study. *J Am Coll Cardiol* 51(18):1775–1783 [PubMed: 18452784]
22. Floras JS (2009) Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. *J Am Coll Cardiol* 54(5):375–385 [PubMed: 19628111]
23. Lymperopoulos A, Rengo G, Koch WJ (2013) Adrenergic nervous system in heart failure: pathophysiology and therapy. *Circ Res* 113(6):739–753 [PubMed: 23989716]
24. Privratsky JR, Wold LE, Sowers JR, Quinn MT, Ren J (2003) AT1 blockade prevents glucose-induced cardiac dysfunction in ventricular myocytes: role of the AT1 receptor and NADPH oxidase. *Hypertension* 42(2):206–212 [PubMed: 12847113]
25. Wende AR, Abel ED (2010) Lipotoxicity in the heart. *Biochim Biophys Acta* 1801(3):311–319 [PubMed: 19818871]
26. Schilling JD, Mann DL (2012) Diabetic cardiomyopathy: bench to bedside. *Heart Fail Clin* 8(4): 619–631 [PubMed: 22999244]
27. Skrzypiec-Spring M, Grotthus B, Szelag A, Schulz R (2007) Isolated heart perfusion according to Langendorff—still viable in the new millennium. *J Pharmacol Toxicol Methods* 55(2):113–126 [PubMed: 16844390]
28. Kakkar R, Lee RT (2010) Intramyocardial fibroblast myocyte communication. *Circ Res* 106(1):47–57 [PubMed: 20056945]
29. Banerjee I, Fuseler JW, Price RL, Borg TK, Baudino TA (2007) Determination of cell types and numbers during cardiac development in the neonatal and adult rat and mouse. *Am J Physiol Heart Circ Physiol* 293(3):H1883–H1891 [PubMed: 17604329]
30. Frangogiannis NG (2008) The immune system and cardiac repair. *Pharmacol Res* 58(2):88–111 [PubMed: 18620057]
31. Orlic D, Hill JM, Arai AE (2002) Stem cells for myocardial regeneration. *Circ Res* 91(12):1092–1102 [PubMed: 12480809]
32. Souders CA, Bowers SL, Baudino TA (2009) Cardiac fibroblast: the renaissance cell. *Circ Res* 105(12):1164–1176 [PubMed: 19959782]
33. Williams AR, Hare JM (2011) Mesenchymal stem cells: biology, pathophysiology, translational findings, and therapeutic implications for cardiac disease. *Circ Res* 109(8):923–940 [PubMed: 21960725]
34. Tirziu D, Giordano FJ, Simons M (2010) Cell communications in the heart. *Circulation* 122(9): 928–937 [PubMed: 20805439]
35. Blankenberg S, Rupprecht HJ, Bickel C, Peetz D, Hafner G, Tiret L, Meyer J (2001) Circulating cell adhesion molecules and death in patients with coronary artery disease. *Circulation* 104(12): 1336–1342 [PubMed: 11560847]
36. Re RN (1989) The cellular biology of angiotensin: paracrine, autocrine and intracrine actions in cardiovascular tissues. *J Mol Cell Cardiol* 21(Suppl 5):63–69 [PubMed: 2697759]
37. Sapir Y, Kryukov O, Cohen S (2011) Integration of multiple cell-matrix interactions into alginate scaffolds for promoting cardiac tissue regeneration. *Biomaterials* 32(7):1838–1847 [PubMed: 21112626]
38. van der Velden HM, Wilders R, Jongsma HJ (2002) Atrial fibrillation-induced gap junctional remodeling. *J Am Coll Cardiol* 39(10):1709 [PubMed: 12020511]

39. Thery C (2011) Exosomes: secreted vesicles and intercellular communications. *F1000 Biol Rep* 3:15 [PubMed: 21876726]
40. Turturici G, Tinnirello R, Sconzo G, Geraci F (2014) Extracellular membrane vesicles as a mechanism of cell-to-cell communication: advantages and disadvantages. *Am J Physiol Cell Physiol* 306(7):C621–C633 [PubMed: 24452373]
41. Gupta S, Knowlton AA (2007) HSP60 trafficking in adult cardiac myocytes: role of the exosomal pathway. *Am J Physiol Heart Circ Physiol* 292(6):H3052–H3056 [PubMed: 17307989]
42. Record M, Carayon K, Poirot M, Silvente-Poirot S (2014) Exosomes as new vesicular lipid transporters involved in cell-cell communication and various pathophysiologicals. *Biochim Biophys Acta* 1841(1):108–120 [PubMed: 24140720]
43. Waldenstrom A, Genneback N, Hellman U, Ronquist G (2012) Cardiomyocyte microvesicles contain DNA/RNA and convey biological messages to target cells. *PLoS One* 7(4):e34653 [PubMed: 22506041]
44. Ibrahim AG, Cheng K, Marban E (2014) Exosomes as critical agents of cardiac regeneration triggered by cell therapy. *Stem Cell Rep* 2(5):606–619
45. Sharov VG, Sabbah HN, Shimoyama H, Goussev AV, Lesch M, Goldstein S (1996) Evidence of cardiocyte apoptosis in myocardium of dogs with chronic heart failure. *Am J Pathol* 148(1):141–149 [PubMed: 8546201]
46. Hristov M, Erl W, Linder S, Weber PC (2004) Apoptotic bodies from endothelial cells enhance the number and initiate the differentiation of human endothelial progenitor cells in vitro. *Blood* 104(9):2761–2766 [PubMed: 15242875]
47. Elmore S (2007) Apoptosis: a review of programmed cell death. *Toxicol Pathol* 35(4):495–516 [PubMed: 17562483]
48. Buzas EI, Gyorgy B, Nagy G, Falus A, Gay S (2014) Emerging role of extracellular vesicles in inflammatory diseases. *Nat Rev Rheumatol* 10(6):356–364 [PubMed: 24535546]
49. Sluijter JP, Verhage V, Deddens JC, van den Akker F, Doevendans PA (2014) Microvesicles and exosomes for intracardiac communication. *Cardiovasc Res* 102(2):302–311 [PubMed: 24488559]
50. Zhu H, Dardick CD, Beers EP, Callanhan AM, Xia R, Yuan R (2011) Transcriptomics of shading-induced and NAA-induced abscission in apple (*Malus domestica*) reveals a shared pathway involving reduced photosynthesis, alterations in carbohydrate transport and signaling and hormone crosstalk. *BMC Plant Biol* 11:138 [PubMed: 22003957]
51. Ling H, Fabbri M, Calin GA (2013) MicroRNAs and other non-coding RNAs as targets for anticancer drug development. *Nat Rev Drug Discov* 12(11):847–865 [PubMed: 24172333]
52. Johnsen KB, Gudbergsson JM, Skov MN, Pilgaard L, Moos T, Duroux M (2014) A comprehensive overview of exosomes as drug delivery vehicles—endogenous nanocarriers for targeted cancer therapy. *Biochim Biophys Acta* 1846(1):75–87 [PubMed: 24747178]
53. Vlassov AV, Magdaleno S, Setterquist R, Conrad R (2012) Exosomes: current knowledge of their composition, biological functions, and diagnostic and therapeutic potentials. *Biochim Biophys Acta* 1820(7):940–948 [PubMed: 22503788]
54. Johnstone RM, Adam M, Hammond JR, Orr L, Turbide C (1987) Vesicle formation during reticulocyte maturation. Association of plasma membrane activities with released vesicles (exosomes). *J Biol Chem* 262(19):9412–9420 [PubMed: 3597417]
55. Johnstone RM, Bianchini A, Teng K (1989) Reticulocyte maturation and exosome release: transferrin receptor containing exosomes shows multiple plasma membrane functions. *Blood* 74(5):1844–1851 [PubMed: 2790208]
56. Kharaziha P, Ceder S, Li Q, Panaretakis T (2012) Tumor cell-derived exosomes: a message in a bottle. *Biochim Biophys Acta* 1826(1):103–111 [PubMed: 22503823]
57. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A (1972) New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Cardiol* 30(6):595–602 [PubMed: 4263660]
58. Kiencke S, Handschin R, von Dahlen R, Muser J, Brunner-Larocca HP, Schumann J, Felix B, Berneis K, Rickenbacher P (2010) Pre-clinical diabetic cardiomyopathy: prevalence, screening, and outcome. *Eur J Heart Fail* 12(9):951–957 [PubMed: 20581103]

59. Cai L, Kang YJ (2001) Oxidative stress and diabetic cardiomyopathy: a brief review. *Cardiovasc Toxicol* 1(3):181–193 [PubMed: 12213971]
60. Liu Q, Wang S, Cai L (2014) Diabetic cardiomyopathy and its mechanisms: role of oxidative stress and damage. *J Diabetes Investig* 5(6):623–634
61. Westermann D, Rutschow S, Jager S, Linderer A, Anker S, Riad A, Unger T, Schultheiss HP, Pauschinger M, Tschope C (2007) Contributions of inflammation and cardiac matrix metalloproteinase activity to cardiac failure in diabetic cardiomyopathy: the role of angiotensin type 1 receptor antagonism. *Diabetes* 56(3):641–646 [PubMed: 17327431]
62. Choi KM, Zhong Y, Hoit BD, Grupp IL, Hahn H, Dilly KW, Guatimosim S, Lederer WJ, Matlib MA (2002) Defective intracellular Ca(2+) signaling contributes to cardiomyopathy in Type 1 diabetic rats. *Am J Physiol Heart Circ Physiol* 283(4):H1398–H1408 [PubMed: 12234790]
63. Duncan JG (2011) Mitochondrial dysfunction in diabetic cardiomyopathy. *Biochim Biophys Acta* 1813(7):1351–1359 [PubMed: 21256163]
64. Lebeche D, Davidoff AJ, Hajjar RJ (2008) Interplay between impaired calcium regulation and insulin signaling abnormalities in diabetic cardiomyopathy. *Nat Clin Pract Cardiovasc Med* 5(11):715–724 [PubMed: 18813212]
65. Asbun J, Villarreal FJ (2006) The pathogenesis of myocardial fibrosis in the setting of diabetic cardiomyopathy. *J Am Coll Cardiol* 47(4):693–700 [PubMed: 16487830]
66. Singh VP, Le B, Khode R, Baker KM, Kumar R (2008) Intracellular angiotensin II production in diabetic rats is correlated with cardiomyocyte apoptosis, oxidative stress, and cardiac fibrosis. *Diabetes* 57(12):3297–3306 [PubMed: 18829990]
67. Raev DC (1994) Which left ventricular function is impaired earlier in the evolution of diabetic cardiomyopathy? An echocardiographic study of young type I diabetic patients. *Diabetes Care* 17(7):633–639 [PubMed: 7924771]
68. Fang ZY, Prins JB, Marwick TH (2004) Diabetic cardiomyopathy: evidence, mechanisms, and therapeutic implications. *Endocr Rev* 25(4):543–567 [PubMed: 15294881]
69. Bugger H, Abel ED (2009) Rodent models of diabetic cardiomyopathy. *Dis Model Mech* 2(9–10):454–466 [PubMed: 19726805]
70. Rodrigues B, McNeill JH (1992) The diabetic heart: metabolic causes for the development of a cardiomyopathy. *Cardiovasc Res* 26(10):913–922 [PubMed: 1486584]
71. Mizamtsidi M, Paschou SA, Grapsa J, Vryonidou A (2016) Diabetic cardiomyopathy: a clinical entity or a cluster of molecular heart changes? *Eur J Clin Invest* 46(11):947–953 [PubMed: 27600276]
72. Bugger H, Abel ED (2014) Molecular mechanisms of diabetic cardiomyopathy. *Diabetologia* 57(4):660–671 [PubMed: 24477973]
73. Holscher ME, Bode C, Bugger H (2016) Diabetic cardiomyopathy: does the type of diabetes matter? *Int J Mol Sci* 17(12):2136
74. Aneja A, Tang WH, Bansilal S, Garcia MJ, Farkouh ME (2008) Diabetic cardiomyopathy: insights into pathogenesis, diagnostic challenges, and therapeutic options. *Am J Med* 121(9):748–757 [PubMed: 18724960]
75. Galderisi M, Anderson KM, Wilson PW, Levy D (1991) Echocardiographic evidence for the existence of a distinct diabetic cardiomyopathy (the Framingham Heart Study). *Am J Cardiol* 68(1):85–89 [PubMed: 2058564]
76. Maisch B, Alter P, Pankuweit S (2011) Diabetic cardiomyopathy—fact or fiction? *Herz* 36(2):102–115 [PubMed: 21424347]
77. Cai L, Li W, Wang G, Guo L, Jiang Y, Kang YJ (2002) Hyperglycemia-induced apoptosis in mouse myocardium: mitochondrial cytochrome C-mediated caspase-3 activation pathway. *Diabetes* 51(6):1938–1948 [PubMed: 12031984]
78. Huynh K, Kiriazis H, XJ D, Love JE, Gray SP, Jandeleit-Dahm KA, McMullen JR, Ritchie RH (2013) Targeting the upregulation of reactive oxygen species subsequent to hyperglycemia prevents type 1 diabetic cardiomyopathy in mice. *Free Radic Biol Med* 60:307–317 [PubMed: 23454064]
79. Liu ZW, Zhu HT, Chen KL, Dong X, Wei J, Qiu C, Xue JH (2013) Protein kinase RNA-like endoplasmic reticulum kinase (PERK) signaling pathway plays a major role in reactive oxygen

species (ROS)-mediated endoplasmic reticulum stress-induced apoptosis in diabetic cardiomyopathy. *Cardiovasc Diabetol* 12:158 [PubMed: 24180212]

80. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J (2007) Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem Cell Biol* 39(1): 44–84 [PubMed: 16978905]
81. Ye G, Metreveli NS, Ren J, Epstein PN (2003) Metallothionein prevents diabetes-induced deficits in cardiomyocytes by inhibiting reactive oxygen species production. *Diabetes* 52(3):777–783 [PubMed: 12606520]
82. Cai L, Wang J, Li Y, Sun X, Wang L, Zhou Z, Kang YJ (2005) Inhibition of superoxide generation and associated nitrosative damage is involved in metallothionein prevention of diabetic cardiomyopathy. *Diabetes* 54(6):1829–1837 [PubMed: 15919806]
83. Haidara MA, Yassin HZ, Rateb M, Ammar H, Zorkani MA (2006) Role of oxidative stress in development of cardiovascular complications in diabetes mellitus. *Curr Vasc Pharmacol* 4(3):215–227 [PubMed: 16842139]
84. Hamblin M, Friedman DB, Hill S, Caprioli RM, Smith HM, Hill MF (2007) Alterations in the diabetic myocardial proteome coupled with increased myocardial oxidative stress underlies diabetic cardiomyopathy. *J Mol Cell Cardiol* 42(4):884–895 [PubMed: 17320100]
85. Li CJ, Lv L, Li H, Yu DM (2012) Cardiac fibrosis and dysfunction in experimental diabetic cardiomyopathy are ameliorated by alpha-lipoic acid. *Cardiovasc Diabetol* 11:73 [PubMed: 22713251]
86. Schannwell CM, Schneppenheim M, Perings S, Plehn G, Strauer BE (2002) Left ventricular diastolic dysfunction as an early manifestation of diabetic cardiomyopathy. *Cardiology* 98(1–2): 33–39 [PubMed: 12373045]
87. Connelly KA, Gilbert RE, Krum H (2008) Letter by Connelly et al regarding article, “Diastolic stiffness of the failing diabetic heart: importance of fibrosis, advanced glycation end products, and myocyte resting tension”. *Circulation* 117(23):e483 [PubMed: 18541748]
88. van Heerebeek L, Hamdani N, Handoko ML, Falcao-Pires I, Musters RJ, Kupreishvili K, Ijsselmuiden AJ, Schalkwijk CG, Bronzwaer JG, Diamant M, Borbely A, van der Velden J, Stienen GJ, Laarman GJ, Niessen HW, Paulus WJ (2008) Diastolic stiffness of the failing diabetic heart: importance of fibrosis, advanced glycation end products, and myocyte resting tension. *Circulation* 117(1):43–51 [PubMed: 18071071]
89. Khaidar A, Marx M, Lubec B, Lubec G (1994) L-arginine reduces heart collagen accumulation in the diabetic db/db mouse. *Circulation* 90(1):479–483 [PubMed: 8026034]
90. Spiro MJ, Crowley TJ (1993) Increased rat myocardial type VI collagen in diabetes mellitus and hypertension. *Diabetologia* 36(2):93–98 [PubMed: 8458534]
91. Bodiga VL, Eda SR, Bodiga S (2014) Advanced glycation end products: role in pathology of diabetic cardiomyopathy. *Heart Fail Rev* 19(1):49–63 [PubMed: 23404649]
92. Candido R, Forbes JM, Thomas MC, Thallas V, Dean RG, Burns WC, Tikellis C, Ritchie RH, Twigg SM, Cooper ME, Burrell LM (2003) A breaker of advanced glycation end products attenuates diabetes-induced myocardial structural changes. *Circ Res* 92(7):785–792 [PubMed: 12623881]
93. Liu J, Masurekar MR, Vatner DE, Jyothirmayi GN, Regan TJ, Vatner SF, Meggs LG, Malhotra A (2003) Glycation end-product cross-link breaker reduces collagen and improves cardiac function in aging diabetic heart. *Am J Physiol Heart Circ Physiol* 285(6):H2587–H2591 [PubMed: 12946933]
94. Vasan S, Foiles P, Founds H (2003) Therapeutic potential of breakers of advanced glycation end product-protein crosslinks. *Arch Biochem Biophys* 419(1):89–96 [PubMed: 14568012]
95. From AM, Scott CG, Chen HH (2010) The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction a population-based study. *J Am Coll Cardiol* 55(4): 300–305 [PubMed: 20117433]
96. von Bibra H, St John Sutton M (2010) Diastolic dysfunction in diabetes and the metabolic syndrome: promising potential for diagnosis and prognosis. *Diabetologia* 53(6):1033–1045 [PubMed: 20349347]

97. Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Lee ET, Welty TK, Fabsitz RR, Robbins D, Rhoades ER, Howard BV (2000) Impact of diabetes on cardiac structure and function: the strong heart study. *Circulation* 101(19):2271–2276 [PubMed: 10811594]
98. Patil VC, Patil HV, Shah KB, Vasani JD, Shetty P (2011) Diastolic dysfunction in asymptomatic type 2 diabetes mellitus with normal systolic function. *J Cardiovasc Dis Res* 2(4):213–222 [PubMed: 22135479]
99. Paulus WJ, van Ballegoij JJ (2010) Treatment of heart failure with normal ejection fraction: an inconvenient truth! *J Am Coll Cardiol* 55(6):526–537 [PubMed: 20152557]
100. Zhang X, Wei X, Liang Y, Liu M, Li C, Tang H (2013) Differential changes of left ventricular myocardial deformation in diabetic patients with controlled and uncontrolled blood glucose: a three-dimensional speckle-tracking echocardiography-based study. *J Am Soc Echocardiogr* 26(5):499–506 [PubMed: 23562087]
101. MacDonald MR, Petrie MC, Hawkins NM, Petrie JR, Fisher M, McKelvie R, Aguilar D, Krum H, McMurray JJ (2008) Diabetes, left ventricular systolic dysfunction, and chronic heart failure. *Eur Heart J* 29(10):1224–1240 [PubMed: 18424786]
102. Reisinger J, Dubrey SW, Falk RH (1997) Restrictive cardiomyopathy. *N Engl J Med* 336(26):1917
103. Seferovic PM, Paulus WJ (2015) Clinical diabetic cardiomyopathy: a two-faced disease with restrictive and dilated phenotypes. *Eur Heart J* 36(27):1718–1727 [PubMed: 25888006]
104. Kuethe F, Sigusch HH, Bornstein SR, Hilbig K, Kamvissi V, Figulla HR (2007) Apoptosis in patients with dilated cardiomyopathy and diabetes: a feature of diabetic cardiomyopathy? *Horm Metab Res* 39(9):672–676 [PubMed: 17846975]
105. Dries DL, Sweitzer NK, Drazner MH, Stevenson LW, Gersh BJ (2001) Prognostic impact of diabetes mellitus in patients with heart failure according to the etiology of left ventricular systolic dysfunction. *J Am Coll Cardiol* 38(2):421–428 [PubMed: 11499733]
106. Shiomi T, Tsutsui H, Ikeuchi M, Matsusaka H, Hayashidani S, Suematsu N, Wen J, Kubota T, Takeshita A (2003) Streptozotocin-induced hyperglycemia exacerbates left ventricular remodeling and failure after experimental myocardial infarction. *J Am Coll Cardiol* 42(1):165–172 [PubMed: 12849678]
107. Song GY, Wu YJ, Yang YJ, Li JJ, Zhang HL, Pei HJ, Zhao ZY, Zeng ZH, Hui RT (2009) The accelerated post-infarction progression of cardiac remodelling is associated with genetic changes in an untreated streptozotocin-induced diabetic rat model. *Eur J Heart Fail* 11(10):911–921 [PubMed: 19789393]
108. Miki T, Yuda S, Kouzu H, Miura T (2013) Diabetic cardiomyopathy: pathophysiology and clinical features. *Heart Fail Rev* 18(2):149–166 [PubMed: 22453289]
109. Voulgari C, Papadogiannis D, Tentolouris N (2010) Diabetic cardiomyopathy: from the pathophysiology of the cardiac myocytes to current diagnosis and management strategies. *Vasc Health Risk Manag* 6:883–903 [PubMed: 21057575]
110. Morgan JP (1991) Abnormal intracellular modulation of calcium as a major cause of cardiac contractile dysfunction. *N Engl J Med* 325(9):625–632 [PubMed: 1861696]
111. Hattori Y, Matsuda N, Kimura J, Ishitani T, Tamada A, Gando S, Kemmotsu O, Kanno M (2000) Diminished function and expression of the cardiac Na⁺-Ca²⁺ exchanger in diabetic rats: implication in Ca²⁺ overload. *J Physiol* 527(Pt 1):85–94 [PubMed: 10944172]
112. Lanner JT (2012) Ryanodine receptor physiology and its role in disease. *Adv Exp Med Biol* 740:217–234 [PubMed: 22453944]
113. Periasamy M, Bhupathy P, Babu GJ (2008) Regulation of sarcoplasmic reticulum Ca²⁺ ATPase pump expression and its relevance to cardiac muscle physiology and pathology. *Cardiovasc Res* 77(2):265–273 [PubMed: 18006443]
114. Teshima Y, Takahashi N, Saikawa T, Hara M, Yasunaga S, Hidaka S, Sakata T (2000) Diminished expression of sarcoplasmic reticulum Ca(2⁺)-ATPase and ryanodine sensitive Ca(2⁺)Channel mRNA in streptozotocin-induced diabetic rat heart. *J Mol Cell Cardiol* 32(4):655–664 [PubMed: 10756121]

115. Trost SU, Belke DD, Bluhm WF, Meyer M, Swanson E, Dillmann WH (2002) Overexpression of the sarcoplasmic reticulum Ca(2+)-ATPase improves myocardial contractility in diabetic cardiomyopathy. *Diabetes* 51(4):1166–1171 [PubMed: 11916940]
116. Asrih M, Steffens S (2013) Emerging role of epigenetics and miRNA in diabetic cardiomyopathy. *Cardiovasc Pathol* 22(2):117–125 [PubMed: 22951386]
117. Chavali V, Tyagi SC, Mishra PK (2013) Predictors and prevention of diabetic cardiomyopathy. *Diabetes Metab Syndr Obes* 6:151–160 [PubMed: 23610527]
118. Finck BN, Han X, Courtois M, Aimond F, Nerbonne JM, Kovacs A, Gross RW, Kelly DP (2003) A critical role for PPARalpha-mediated lipotoxicity in the pathogenesis of diabetic cardiomyopathy: modulation by dietary fat content. *Proc Natl Acad Sci U S A* 100(3):1226–1231 [PubMed: 12552126]
119. Narula J, Pandey P, Arbustini E, Haider N, Narula N, Kolodgie FD, Dal Bello B, Semigran MJ, Bielsa-Masdeu A, Dec GW, Israels S, Ballester M, Virmani R, Saxena S, Kharbanda S (1999) Apoptosis in heart failure: release of cytochrome c from mitochondria and activation of caspase-3 in human cardiomyopathy. *Proc Natl Acad Sci U S A* 96(14):8144–8149 [PubMed: 10393962]
120. Rutter MK, Parise H, Benjamin EJ, Levy D, Larson MG, Meigs JB, Nesto RW, Wilson PW, Vasan RS (2003) Impact of glucose intolerance and insulin resistance on cardiac structure and function: sex-related differences in the Framingham Heart Study. *Circulation* 107(3):448–454 [PubMed: 12551870]
121. Witteles RM, Tang WH, Jamali AH, Chu JW, Reaven GM, Fowler MB (2004) Insulin resistance in idiopathic dilated cardiomyopathy: a possible etiologic link. *J Am Coll Cardiol* 44(1):78–81 [PubMed: 15234411]
122. Johansen JS, Harris AK, Rychly DJ, Ergul A (2005) Oxidative stress and the use of antioxidants in diabetes: linking basic science to clinical practice. *Cardiovasc Diabetol* 4:5 [PubMed: 15862133]
123. Vassort G, Turan B (2010) Protective role of antioxidants in diabetes-induced cardiac dysfunction. *Cardiovasc Toxicol* 10(2):73–86 [PubMed: 20458637]
124. Fein FS (1990) Diabetic cardiomyopathy. *Diabetes Care* 13(11):1169–1179 [PubMed: 2261838]
125. Bartel DP (2004) MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 116(2):281–297 [PubMed: 14744438]
126. Zheng D, Ma J, Yu Y, Li M, Ni R, Wang G, Chen R, Li J, Fan GC, Lacefield JC, Peng T (2015) Silencing of miR-195 reduces diabetic cardiomyopathy in C57BL/6 mice. *Diabetologia* 58(8):1949–1958 [PubMed: 25994075]
127. Horie T, Ono K, Nishi H, Iwanaga Y, Nagao K, Kinoshita M, Kuwabara Y, Takanabe R, Hasegawa K, Kita T, Kimura T (2009) MicroRNA-133 regulates the expression of GLUT4 by targeting KLF15 and is involved in metabolic control in cardiac myocytes. *Biochem Biophys Res Commun* 389(2):315–320 [PubMed: 19720047]
128. Chen S, Puthanveetil P, Feng B, Matkovich SJ, Dorn GW II, Chakrabarti S (2014) Cardiac miR-133a overexpression prevents early cardiac fibrosis in diabetes. *J Cell Mol Med* 18(3):415–421 [PubMed: 24428157]
129. Chavali V, Tyagi SC, Mishra PK (2012) MicroRNA-133a regulates DNA methylation in diabetic cardiomyocytes. *Biochem Biophys Res Commun* 425(3):668–672 [PubMed: 22842467]
130. Feng B, Chen S, George B, Feng Q, Chakrabarti S (2010) miR133a regulates cardiomyocyte hypertrophy in diabetes. *Diabetes Metab Res Rev* 26(1):40–49 [PubMed: 20013939]
131. Yildirim SS, Akman D, Catalucci D, Turan B (2013) Relationship between downregulation of miRNAs and increase of oxidative stress in the development of diabetic cardiac dysfunction: junctin as a target protein of miR-1. *Cell Biochem Biophys* 67(3):1397–1408 [PubMed: 23723006]
132. Lu H, Buchan RJ, Cook SA (2010) MicroRNA-223 regulates Glut4 expression and cardiomyocyte glucose metabolism. *Cardiovasc Res* 86(3):410–420 [PubMed: 20080987]
133. Baseler WA, Thapa D, Jagannathan R, Dabkowski ER, Croston TL, Hollander JM (2012) miR-141 as a regulator of the mitochondrial phosphate carrier (Slc25a3) in the type 1 diabetic heart. *Am J Physiol Cell Physiol* 303(12):C1244–C1251 [PubMed: 23034391]

134. Kuwabara Y, Horie T, Baba O, Watanabe S, Nishiga M, Usami S, Izuhara M, Nakao T, Nishino T, Otsu K, Kita T, Kimura T, Ono K (2015) MicroRNA-451 exacerbates lipotoxicity in cardiac myocytes and high-fat diet-induced cardiac hypertrophy in mice through suppression of the LKB1/AMPK pathway. *Circ Res* 116(2):279–288 [PubMed: 25362209]
135. Blumensatt M, Greulich S, Herzfeld de Wiza D, Mueller H, Maxhera B, Rabelink MJ, Hoeber RC, Akhyari P, Al-Hasani H, Ruige JB, Ouwens DM (2013) Activin A impairs insulin action in cardiomyocytes via up-regulation of miR-143. *Cardiovasc Res* 100(2):201–210 [PubMed: 23812417]
136. Arnold N, Koppula PR, Gul R, Luck C, Pulakat L (2014) Regulation of cardiac expression of the diabetic marker microRNA miR-29. *PLoS One* 9(7):e103284 [PubMed: 25062042]
137. Marchand A, Atassi F, Mougenot N, Clergue M, Codoni V, Berthuin J, Proust C, Tregouet DA, Hulot JS, Lompre AM (2016) miR-322 regulates insulin signaling pathway and protects against metabolic syndrome-induced cardiac dysfunction in mice. *Biochim Biophys Acta* 1862(4):611–621 [PubMed: 26775030]
138. Thery C, Zitvogel L, Amigorena S (2002) Exosomes: composition, biogenesis and function. *Nat Rev Immunol* 2(8):569–579 [PubMed: 12154376]
139. Stoorvogel W, Kleijmeer MJ, Geuze HJ, Raposo G (2002) The biogenesis and functions of exosomes. *Traffic* 3(5):321–330 [PubMed: 11967126]
140. Simons M, Raposo G (2009) Exosomes—vesicular carriers for intercellular communication. *Curr Opin Cell Biol* 21(4):575–581 [PubMed: 19442504]
141. Fevrier B, Raposo G (2004) Exosomes: endosomal-derived vesicles shipping extracellular messages. *Curr Opin Cell Biol* 16(4):415–421 [PubMed: 15261674]
142. Babst M (2011) MVB vesicle formation: ESCRT-dependent, ESCRT-independent and everything in between. *Curr Opin Cell Biol* 23(4):452–457 [PubMed: 21570275]
143. Ostrowski M, Carmo NB, Krumeich S, Fanget I, Raposo G, Savina A, Moita CF, Schauer K, Hume AN, Freitas RP, Goud B, Benaroch P, Hachohen N, Fukuda M, Desnos C, Seabra MC, Darchen F, Amigorena S, Moita LF, Thery C (2010) Rab27a and Rab27b control different steps of the exosome secretion pathway. *Nat Cell Biol* 12(1):19–30 [PubMed: 19966785]
144. Raiborg C, Stenmark H (2009) The ESCRT machinery in endosomal sorting of ubiquitylated membrane proteins. *Nature* 458(7237):445–452 [PubMed: 19325624]
145. Slagsvold T, Pattni K, Malerod L, Stenmark H (2006) Endosomal and non-endosomal functions of ESCRT proteins. *Trends Cell Biol* 16(6):317–326 [PubMed: 16716591]
146. Blott EJ, Griffiths GM (2002) Secretory lysosomes. *Nat Rev Mol Cell Biol* 3(2):122–131 [PubMed: 11836514]
147. Luzio JP, Rous BA, Bright NA, Pryor PR, Mullock BM, Piper RC (2000) Lysosome-endosome fusion and lysosome biogenesis. *J Cell Sci* 113(Pt 9):1515–1524 [PubMed: 10751143]
148. Raposo G, Stoorvogel W (2013) Extracellular vesicles: exosomes, microvesicles, and friends. *J Cell Biol* 200(4):373–383 [PubMed: 23420871]
149. de Jong OG, Verhaar MC, Chen Y, Vader P, Gremmels H, Posthuma G, Schiffelers RM, Gueck M, van Balkom BW (2012) Cellular stress conditions are reflected in the protein and RNA content of endothelial cell-derived exosomes. *J Extracell Vesicles* 1. doi:10.3402/jev.v1i0.18396
150. Rice GE, Scholz-Romero K, Sweeney E, Peiris H, Kobayashi M, Duncombe G, Mitchell MD, Salomon C (2015) The effect of glucose on the release and bioactivity of exosomes from first trimester trophoblast cells. *J Clin Endocrinol Metab* 100(10):E1280–E1288 [PubMed: 26241326]
151. Dehwah MA, Xu A, Huang Q (2012) MicroRNAs and type 2 diabetes/obesity. *J Genet Genomics* 39(1):11–18 [PubMed: 22293113]
152. Williams MD, Mitchell GM (2012) MicroRNAs in insulin resistance and obesity. *Exp Diabetes Res* 2012:484696 [PubMed: 22851965]
153. Guay C, Roggli E, Nesca V, Jacovetti C, Regazzi R (2011) Diabetes mellitus, a microRNA-related disease? *Transl Res* 157(4):253–264 [PubMed: 21420036]
154. Kong L, Zhu J, Han W, Jiang X, Xu M, Zhao Y, Dong Q, Pang Z, Guan Q, Gao L, Zhao J, Zhao L (2011) Significance of serum microRNAs in pre-diabetes and newly diagnosed type 2 diabetes: a clinical study. *Acta Diabetol* 48(1):61–69 [PubMed: 20857148]

155. Salido-Guadarrama I, Romero-Cordoba S, Peralta-Zaragoza O, Hidalgo-Miranda A, Rodriguez-Dorantes M (2014) MicroRNAs transported by exosomes in body fluids as mediators of intercellular communication in cancer. *Onco Targets Ther* 7:1327–1338 [PubMed: 25092989]
156. Esteller M (2011) Non-coding RNAs in human disease. *Nat Rev Genet* 12(12):861–874 [PubMed: 22094949]
157. Ha TY (2011) MicroRNAs in human diseases: from cancer to cardiovascular disease. *Immune Network* 11(3):135–154 [PubMed: 21860607]
158. Iborra M, Bernuzzi F, Invernizzi P, Danese S (2012) MicroRNAs in autoimmunity and inflammatory bowel disease: crucial regulators in immune response. *Autoimmun Rev* 11(5):305–314 [PubMed: 20627134]
159. Aswad H, Forterre A, Wiklander OP, Vial G, Danty-Berger E, Jalabert A, Lamaziere A, Meugnier E, Pesenti S, Ott C, Chikh K, El-Andaloussi S, Vidal H, Lefai E, Rieusset J, Rome S (2014) Exosomes participate in the alteration of muscle homeostasis during lipid-induced insulin resistance in mice. *Diabetologia* 57(10):2155–2164 [PubMed: 25073444]
160. Deng ZB, Poliakov A, Hardy RW, Clements R, Liu C, Liu Y, Wang J, Xiang X, Zhang S, Zhuang X, Shah SV, Sun D, Michalek S, Grizzle WE, Garvey T, Mobley J, Zhang HG (2009) Adipose tissue exosome-like vesicles mediate activation of macrophage-induced insulin resistance. *Diabetes* 58(11):2498–2505 [PubMed: 19675137]
161. Karolina DS, Armugam A, Tavintharan S, Wong MT, Lim SC, Sum CF, Jeyaseelan K (2011) MicroRNA 144 impairs insulin signaling by inhibiting the expression of insulin receptor substrate 1 in type 2 diabetes mellitus. *PLoS One* 6(8):e22839 [PubMed: 21829658]
162. Guay C, Jacovetti C, Nesca V, Motterle A, Tugay K, Regazzi R (2012) Emerging roles of non-coding RNAs in pancreatic beta-cell function and dysfunction. *Diabetes Obes Metab* 14(Suppl 3):12–21 [PubMed: 22928560]
163. Ventriglia G, Nigi L, Sebastiani G, Dotta F (2015) MicroRNAs: novel players in the dialogue between pancreatic islets and immune system in autoimmune diabetes. *Biomed Res Int* 2015:749734 [PubMed: 26339637]
164. Guay C, Regazzi R (2013) Circulating microRNAs as novel biomarkers for diabetes mellitus. *Nat Rev Endocrinol* 9(9):513–521 [PubMed: 23629540]
165. Rottiers V, Naar AM (2012) MicroRNAs in metabolism and metabolic disorders. *Nat Rev Mol Cell Biol* 13(4):239–250 [PubMed: 22436747]
166. Lovis P, Roggli E, Laybutt DR, Gattesco S, Yang JY, Widmann C, Abderrahmani A, Regazzi R (2008) Alterations in microRNA expression contribute to fatty acid-induced pancreatic beta-cell dysfunction. *Diabetes* 57(10):2728–2736 [PubMed: 18633110]
167. Roggli E, Britan A, Gattesco S, Lin-Marq N, Abderrahmani A, Meda P, Regazzi R (2010) Involvement of microRNAs in the cytotoxic effects exerted by proinflammatory cytokines on pancreatic beta-cells. *Diabetes* 59(4):978–986 [PubMed: 20086228]
168. Roggli E, Gattesco S, Caille D, Briet C, Boitard C, Meda P, Regazzi R (2012) Changes in microRNA expression contribute to pancreatic beta-cell dysfunction in prediabetic NOD mice. *Diabetes* 61(7):1742–1751 [PubMed: 22537941]
169. Guay C, Menoud V, Rome S, Regazzi R (2015) Horizontal transfer of exosomal microRNAs transduce apoptotic signals between pancreatic beta-cells. *Cell Commun Signal* 13:17 [PubMed: 25880779]
170. Pfeifer P, Werner N, Jansen F (2015) Role and function of microRNAs in extracellular vesicles in cardiovascular biology. *Biomed Res Int* 2015:161393 [PubMed: 26558258]
171. Patel D, Ythier D, Brozzi F, Eizirik DL, Thorens B (2015) Clic4, a novel protein that sensitizes beta-cells to apoptosis. *Mol Metab* 4(4):253–264 [PubMed: 25830089]
172. Zhao X, Mohan R, Ozcan S, Tang X (2012) MicroRNA-30d induces insulin transcription factor MafA and insulin production by targeting mitogen-activated protein 4 kinase 4 (MAP4K4) in pancreatic beta-cells. *J Biol Chem* 287(37):31155–31164 [PubMed: 22733810]
173. Osmi M, Osmi Y, Bang-Berthelsen CH, Pallesen EM, Vestergaard AL, Novotny GW, Pociot F, Mandrup-Poulsen T (2016) MicroRNAs as regulators of beta-cell function and dysfunction. *Diabetes Metab Res Rev* 32(4):334–349 [PubMed: 26418758]

174. Nesca V, Guay C, Jacovetti C, Menoud V, Peyot ML, Laybutt DR, Prentki M, Regazzi R (2013) Identification of particular groups of microRNAs that positively or negatively impact on beta cell function in obese models of type 2 diabetes. *Diabetologia* 56(10):2203–2212 [PubMed: 23842730]
175. Lin X, Guan H, Huang Z, Liu J, Li H, Wei G, Cao X, Li Y (2014) Downregulation of Bcl-2 expression by miR-34a mediates palmitate-induced Min6 cells apoptosis. *J Diabetes Res* 2014:258695 [PubMed: 24829923]
176. Ruan Q, Wang T, Kameswaran V, Wei Q, Johnson DS, Matschinsky F, Shi W, Chen YH (2011) The microRNA-21-PDCD4 axis prevents type 1 diabetes by blocking pancreatic beta cell death. *Proc Natl Acad Sci U S A* 108(29):12030–12035 [PubMed: 21730150]
177. Belgardt BF, Ahmed K, Spranger M, Latreille M, Denzler R, Kondratiuk N, von Meyenn F, Villena FN, Herrmanns K, Bosco D, Kerr-Conte J, Pattou F, Rulicke T, Stoffel M (2015) The microRNA-200 family regulates pancreatic beta cell survival in type 2 diabetes. *Nat Med* 21(6): 619–627 [PubMed: 25985365]
178. Mocharla P, Briand S, Giannotti G, Dorries C, Jakob P, Paneni F, Luscher T, Landmesser U (2013) AngiomiR-126 expression and secretion from circulating CD34(+) and CD14(+) PBMCs: role for proangiogenic effects and alterations in type 2 diabetics. *Blood* 121(1):226–236 [PubMed: 23144172]
179. Cocucci E, Racchetti G, Meldolesi J (2009) Shedding microvesicles: artefacts no more. *Trends Cell Biol* 19(2):43–51 [PubMed: 19144520]
180. Gyorgy B, Szabo TG, Pasztoi M, Pal Z, Misjak P, Aradi B, Laszlo V, Pallinger E, Pap E, Kittel A, Nagy G, Falus A, Buzas EI (2011) Membrane vesicles, current state-of-the-art: emerging role of extracellular vesicles. *Cell Mol Life Sci* 68(16):2667–2688 [PubMed: 21560073]
181. Schattteman GC, Hanlon HD, Jiao C, Dodds SG, Christy BA (2000) Blood-derived angio-blasts accelerate blood-flow restoration in diabetic mice. *J Clin Investig* 106(4):571–578 [PubMed: 10953032]
182. Lawson C, Vicencio JM, Yellon DM, Davidson SM (2016) Microvesicles and exosomes: new players in metabolic and cardiovascular disease. *J Endocrinol* 228(2):R57–R71 [PubMed: 26743452]
183. Tabit CE, Chung WB, Hamburg NM, Vita JA (2010) Endothelial dysfunction in diabetes mellitus: molecular mechanisms and clinical implications. *Rev Endocr Metab Disord* 11(1):61–74 [PubMed: 20186491]
184. Burger D, Thibodeau JF, Holterman CE, Burns KD, Touyz RM, Kennedy CR (2014) Urinary podocyte microparticles identify prealbuminuric diabetic glomerular injury. *J Am Soc Nephrol* 25(7):1401–1407 [PubMed: 24676640]
185. Fais S, O'Driscoll L, Borrás FE, Buzas E, Camussi G, Cappello F, Carvalho J, Cordeiro da Silva A, Del Portillo H, El Andaloussi S, Ficko Trcek T, Furlan R, Hendrix A, Gursel I, Kralj-Iglic V, Kaeffer B, Kosanovic M, Lekka ME, Lipps G, Logozzi M, Marcilla A, Sammar M, Llorente A, Nazarenko I, Oliveira C, Pocsfalvi G, Rajendran L, Raposo G, Rohde E, Siljander P, van Niel G, Vasconcelos MH, Yanez-Mo M, Yliperttula ML, Zarovni N, Zavec AB, Giebel B (2016) Evidence-based clinical use of nanoscale extracellular vesicles in nanomedicine. *ACS Nano* 10(4):3886–3899 [PubMed: 26978483]
186. Kranendonk ME, de Kleijn DP, Kalkhoven E, Kanhai DA, Uiterwaal CS, van der Graaf Y, Pasterkamp G, Visseren FL, Group SS (2014) Extracellular vesicle markers in relation to obesity and metabolic complications in patients with manifest cardiovascular disease. *Cardiovasc Diabetol* 13:37 [PubMed: 24498934]
187. van der Pol E, Boing AN, Harrison P, Sturk A, Nieuwland R (2012) Classification, functions, and clinical relevance of extracellular vesicles. *Pharmacol Rev* 64(3):676–705 [PubMed: 22722893]
188. Jansen F, Yang X, Franklin BS, Hoelscher M, Schmitz T, Bedorf J, Nickenig G, Werner N (2013) High glucose condition increases NADPH oxidase activity in endothelial microparticles that promote vascular inflammation. *Cardiovasc Res* 98(1):94–106 [PubMed: 23341580]
189. Lakhter AJ, Sims EK (2015) Minireview: emerging roles for extracellular vesicles in diabetes and related metabolic disorders. *Mol Endocrinol* 29(11):1535–1548 [PubMed: 26393296]

190. Barutta F, Tricarico M, Corbelli A, Annaratone L, Pinach S, Grimaldi S, Bruno G, Cimino D, Taverna D, Deregibus MC, Rastaldi MP, Perin PC, Gruden G (2013) Urinary exosomal microRNAs in incipient diabetic nephropathy. *PLoS One* 8(11):e73798 [PubMed: 24223694]
191. Li R, Chung AC, Yu X, Lan HY (2014) MicroRNAs in diabetic kidney disease. *Int J Endocrinol* 2014:593956 [PubMed: 24550986]
192. Mann JF, Rossing P, Wiecek A, Rosivall L, Mark P, Mayer G (2015) Diagnosis and treatment of early renal disease in patients with type 2 diabetes mellitus: what are the clinical needs? *Nephrol Dial Transplant* 30(Suppl 4):iv1–iv5 [PubMed: 26209731]
193. Joglekar MV, Joglekar VM, Hardikar AA (2009) Expression of islet-specific microRNAs during human pancreatic development. *Gene Expr Patterns* 9(2):109–113 [PubMed: 18977315]
194. Melkman-Zehavi T, Oren R, Kred-Russo S, Shapira T, Mandelbaum AD, Rivkin N, Nir T, Lennox KA, Behlke MA, Dor Y, Hornstein E (2011) miRNAs control insulin content in pancreatic beta-cells via downregulation of transcriptional repressors. *EMBO J* 30(5):835–845 [PubMed: 21285947]
195. Tang X, Muniappan L, Tang G, Ozcan S (2009) Identification of glucose-regulated miRNAs from pancreatic {beta} cells reveals a role for miR-30d in insulin transcription. *RNA* 15(2):287–293 [PubMed: 19096044]
196. Wang Y, Liu J, Liu C, Naji A, Stoffers DA (2013) MicroRNA-7 regulates the mTOR pathway and proliferation in adult pancreatic beta-cells. *Diabetes* 62(3):887–895 [PubMed: 23223022]
197. Esguerra JL, Bolmeson C, Cilio CM, Eliasson L (2011) Differential glucose-regulation of microRNAs in pancreatic islets of non-obese type 2 diabetes model Goto-Kakizaki rat. *PLoS One* 6(4):e18613 [PubMed: 21490936]
198. Zampetaki A, Kiechl S, Drozdov I, Willeit P, Mayr U, Prokopi M, Mayr A, Weger S, Oberhollenzer F, Bonora E, Shah A, Willeit J, Mayr M (2010) Plasma microRNA profiling reveals loss of endothelial miR-126 and other microRNAs in type 2 diabetes. *Circ Res* 107(6):810–817 [PubMed: 20651284]
199. Horikawa Y, Oda N, Cox NJ, Li X, Orho-Melander M, Hara M, Hinokio Y, Lindner TH, Mashima H, Schwarz PE, del Bosque-Plata L, Horikawa Y, Oda Y, Yoshiuchi I, Colilla S, Polonsky KS, Wei S, Concannon P, Iwasaki N, Schulze J, Baier LJ, Bogardus C, Groop L, Boerwinkle E, Hanis CL, Bell GI (2000) Genetic variation in the gene encoding calpain-10 is associated with type 2 diabetes mellitus. *Nat Genet* 26(2):163–175 [PubMed: 11017071]
200. Wicker LS, Clark J, Fraser HI, Garner VE, Gonzalez-Munoz A, Healy B, Howlett S, Hunter K, Rainbow D, Rosa RL, Smink LJ, Todd JA, Peterson LB (2005) Type 1 diabetes genes and pathways shared by humans and NOD mice. *J Autoimmun* 25(Suppl):29–33 [PubMed: 16257508]
201. Lai RC, Yeo RW, Tan KH, Lim SK (2013) Exosomes for drug delivery—a novel application for the mesenchymal stem cell. *Biotechnol Adv* 31(5):543–551 [PubMed: 22959595]
202. Simpson RJ, Lim JW, Moritz RL, Mathivanan S (2009) Exosomes: proteomic insights and diagnostic potential. *Expert Rev Proteomics* 6(3):267–283 [PubMed: 19489699]
203. Camussi G, Deregibus MC, Bruno S, Cantaluppi V, Biancone L (2010) Exosomes/microvesicles as a mechanism of cell-to-cell communication. *Kidney Int* 78(9):838–848 [PubMed: 20703216]
204. Lee Y, El Andaloussi S, Wood MJ (2012) Exosomes and microvesicles: extracellular vesicles for genetic information transfer and gene therapy. *Hum Mol Genet* 21(R1):R125–R134 [PubMed: 22872698]
205. Cortez MA, Calin GA (2009) MicroRNA identification in plasma and serum: a new tool to diagnose and monitor diseases. *Expert Opin Biol Ther* 9(6):703–711 [PubMed: 19426115]
206. Ge Q, Zhou Y, Lu J, Bai Y, Xie X, Lu Z (2014) miRNA in plasma exosome is stable under different storage conditions. *Molecules* 19(2):1568–1575 [PubMed: 24473213]
207. Vickers KC, Palmisano BT, Shoucri BM, Shamburek RD, Remaley AT (2011) MicroRNAs are transported in plasma and delivered to recipient cells by high-density lipoproteins. *Nat Cell Biol* 13(4):423–433 [PubMed: 21423178]
208. Di Carli MF, Janisse J, Grunberger G, Ager J (2003) Role of chronic hyperglycemia in the pathogenesis of coronary microvascular dysfunction in diabetes. *J Am Coll Cardiol* 41(8):1387–1393 [PubMed: 12706936]

209. Hink U, Li H, Mollnau H, Oelze M, Matheis E, Hartmann M, Skatchkov M, Thaiss F, Stahl RA, Warnholtz A, Meinertz T, Griendling K, Harrison DG, Forstermann U, Munzel T (2001) Mechanisms underlying endothelial dysfunction in diabetes mellitus. *Circ Res* 88(2):E14–E22 [PubMed: 11157681]
210. Chen JX, Zeng H, Reese J, Aschner JL, Meyrick B (2012) Overexpression of angiopoietin-2 impairs myocardial angiogenesis and exacerbates cardiac fibrosis in the diabetic db/db mouse model. *Am J Physiol Heart Circ Physiol* 302(4):H1003–H1012 [PubMed: 22180648]
211. Pandey AK, Agarwal P, Kaur K, Datta M (2009) MicroRNAs in diabetes: tiny players in big disease. *Cell Physiol Biochem* 23(4–6):221–232 [PubMed: 19471090]
212. Wang XH, Qian RZ, Zhang W, Chen SF, Jin HM, Hu RM (2009) MicroRNA-320 expression in myocardial microvascular endothelial cells and its relationship with insulin-like growth factor-1 in type 2 diabetic rats. *Clin Exp Pharmacol Physiol* 36(2):181–188 [PubMed: 18986336]
213. Brutsaert DL (2003) Cardiac endothelial-myocardial signaling: its role in cardiac growth, contractile performance, and rhythmicity. *Physiol Rev* 83(1):59–115 [PubMed: 12506127]
214. Narmoneva DA, Vukmirovic R, Davis ME, Kamm RD, Lee RT (2004) Endothelial cells promote cardiac myocyte survival and spatial reorganization: implications for cardiac regeneration. *Circulation* 110(8):962–968 [PubMed: 15302801]
215. Shantikumar S, Angelini GD, Emanuelli C (2014) Diabetes, microRNAs and exosomes: Les liaisons dangereuses. *J Mol Cell Cardiol* 74:196–198 [PubMed: 24874423]
216. Westermeier F, Riquelme JA, Pavez M, Garrido V, Diaz A, Verdejo HE, Castro PF, Garcia L, Lavandero S (2016) New molecular insights of insulin in diabetic cardiomyopathy. *Front Physiol* 7:125 [PubMed: 27148064]
217. Das S, Halushka MK (2015) Extracellular vesicle microRNA transfer in cardiovascular disease. *Cardiovasc Pathol* 24(4):199–206 [PubMed: 25958013]
218. Loyer X, Vion AC, Tedgui A, Boulanger CM (2014) Microvesicles as cell-cell messengers in cardiovascular diseases. *Circ Res* 114(2):345–353 [PubMed: 24436430]
219. Vrijnsen KR, Sluijter JP, Schuchardt MW, van Balkom BW, Noort WA, Chamuleau SA, Doevendans PA (2010) Cardiomyocyte progenitor cell-derived exosomes stimulate migration of endothelial cells. *J Cell Mol Med* 14(5):1064–1070 [PubMed: 20465578]
220. Wang X, Huang W, Liu G, Cai W, Millard RW, Wang Y, Chang J, Peng T, Fan GC (2014) Cardiomyocytes mediate anti-angiogenesis in type 2 diabetic rats through the exosomal transfer of miR-320 into endothelial cells. *J Mol Cell Cardiol* 74:139–150 [PubMed: 24825548]
221. Guo BB, Bellingham SA, Hill AF (2015) The neutral sphingomyelinase pathway regulates packaging of the prion protein into exosomes. *J Biol Chem* 290(6):3455–3467 [PubMed: 25505180]
222. Sahoo S, Emanuelli C (2016) Exosomes in diabetic cardiomyopathy: the next-generation therapeutic targets? *Diabetes* 65(10):2829–2831 [PubMed: 27659226]
223. Garcia NA, Ontoria-Oviedo I, Gonzalez-King H, Diez-Juan A, Sepulveda P (2015) Glucose starvation in cardiomyocytes enhances exosome secretion and promotes angiogenesis in endothelial cells. *PLoS One* 10(9):e0138849 [PubMed: 26393803]
224. Tan A, Rajadas J, Seifalian AM (2013) Exosomes as nano-theranostic delivery platforms for gene therapy. *Adv Drug Deliv Rev* 65(3):357–367 [PubMed: 22820532]
225. Ribeiro MF, Zhu H, Millard RW, Fan GC (2013) Exosomes function in pro- and anti-angiogenesis. *Current Angiogenesis* 2(1):54–59
226. Wang X, Gu H, Huang W, Peng J, Li Y, Yang L, Qin D, Essandoh K, Wang Y, Peng T, Fan GC (2016) Hsp20-mediated activation of exosome biogenesis in cardiomyocytes improves cardiac function and angiogenesis in diabetic mice. *Diabetes* 65(10):3111–3128 [PubMed: 27284111]
227. Kowal J, Tkach M, Thery C (2014) Biogenesis and secretion of exosomes. *Curr Opin Cell Biol* 29:116–125 [PubMed: 24959705]
228. Pironti G, Strachan RT, Abraham D, Mon-Wei Yu S, Chen M, Chen W, Hanada K, Mao L, Watson LJ, Rockman HA (2015) Circulating exosomes induced by cardiac pressure overload contain functional angiotensin II type 1 receptors. *Circulation* 131(24):2120–2130 [PubMed: 25995315]

229. Ailawadi S, Wang X, Gu H, Fan GC (2015) Pathologic function and therapeutic potential of exosomes in cardiovascular disease. *Biochim Biophys Acta* 1852(1):1–11 [PubMed: 25463630]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Fig. 8.1.

The mechanisms of cell-to-cell communication through several types of extracellular vesicles. Microvesicles are originated by outward budding of plasma membrane. Exosomes are formed and released from the multivesicular endosomal compartment. Apoptotic bodies are generated during the late stage of cell apoptosis

Fig. 8.2.

Schematic representation of healthy cardiomyocytes can release Hsp20 and miRNA-126 enriched exosomes, which transfer Hsp20 and miRNA-126 to adjacent endothelial cells, leading to normal angiogenesis and cardiac functions. By contrast, exosomes release from type 2 diabetic cardiomyocytes contain higher levels of miRNA-320 and lower levels of Hsp20, compared with those from non-diabetic healthy cardiomyocytes. Accordingly, miRNA-320 enriched exosomes are transported to endothelial cells, resulting in impairment of angiogenesis and cardiac functions. In Hsp20 overexpressed diabetic cardiomyocytes, Hsp20 promotes quantitative and qualitative changes in cardiomyocyte-derived exosomes, transforming diseased exosomes to beneficial exosomes, and resulting in improvement of angiogenesis and amelioration of cardiac functions