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MINI REVIEW ARTICLE

# Do exosomes play role in cardiovascular disease development in hematological malignancy?

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## Abstract

Exosomes play a role in the pathogenesis and treatment of malignancies as a double-edged sword. Recently, researchers discussed about two new roles, cardiomyocyte function impairment and cardiovascular disease (CVD) genesis. Data were collected from PUBMED at various time points up to the 2019 academic year. The related key words are listed as following; "Arsenic trioxide", "acute promyelocytic leukemia" and "cardio toxicity" and "molecular pathway" and "biomarker". This study has shown that exosomes secreted substances stimulate angiogenesis and cardiomyocytes repairment; cited process depended on the kinds of released substances. Generally, exosomes may involve in the pathogenesis of CVD; although CVD can prevented by identifying the pathways that induce angiogenesis.

**Keywords** Exosome · Cardiovascular disease · Hematological malignancy · Angiogenesis

## Introduction

According to the reports of World Health Organization (WHO), the rate of mortality related to hematological malignancies is increasing. Despite progression in the diagnostic method and introducing new prognostic factors many of involved patients die, as a result of disease [1]. Occurrence of cardiovascular disease (CVD) as an underlying disease or malignancy induced is much [2]. The researches which are done recently has shown that mammalian cells exosomes, have a role not only in proliferation of malignant cells but also in pathogenesis of CVD [3]. Vesicles are categorized in three size including small, media and large; the small ones are called exosomes, which contain [4] different substances such as, Micro RNAs (miRs), cytokine, chemokines and coagulant factors [5]. Given that, exosomes have both coagulation activity and releasing cytokines and chemokines; they lead to immune system function impairment. We can say that these vesicles simultaneously promote malignancy and CVD. Thus, designing proper therapies, regarding to exosomes content, can prevent CVD and malignant cells proliferation simultaneously [6, 7]. Therefore, we investigated

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the role of exosomes in the CVD pathogenesis in hematological malignancies.

## Structure of exosomes

Exosomes are vesicles derived from different cells which are found in body fluids such as amnion fluid, milk, and blood; the diameter is 30–100 nm [8]. These vesicles are cup-shaped and surrounded by a series of proteins and lipids such as sphingomyelin and cholesterol [9]. They contain a variety of proteins, including chaperones, kinase and GTPase, and many CD markers such as CD81 and CD82 [10]. Furthermore, they have a number of miRs that are effective in cellular communication in normal and pathogenic states. Many of exosomes released from cardiomyocytes and other cardiac cells along with endothelial cells exosome, lead to connection between the cardiac components; the linkage will improve cardiac function and ultimately supply energy for body's metabolic activity [11, 12]. The exosomes have a series of miRs that not only disrupt cell signaling, but also activate thrombosis and inflammation by coagulation factors. These Processes simultaneously lead to disease progression with cardiac origin.

## Exosome proteins

Proteins is one of the components displaced by exosomes and are present in the external structure of exosomes. Exosomes surface proteins not only interact with other cells, but also stimulate molecular pathways by binding to receptors at the target cell surface [13, 14]. S100-A9 is one of the serum proteins secreted by Exosomes in hematological malignancies. The S100-A9 receptor is an extracellular matrix metalloproteinase inducer (EMMPRIN) which expresses on the surface of many cells [15]. In addition, S100-A9 interaction with EMMPIRIN lead to activate NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway and trigger inflammation [16]. On the opposite side, EMMPRIN expression at the surface of some exosomes and, its interaction with Matrix metalloproteinase (MMPs) can cause cardio myocytes progenitors cells (CPCs) displacement and cardio myocytes repairmen. It also increases angiogenesis through vascular endothelial growth factor (VEGF) secretion [17, 18]. Thus in hematological malignancies, CVD occurrence and progression are preventable by expressing EMMPIRIN on heart cells but not malignant cells. This finding needs to identify signaling pathways that activate EMMPRIN in cardiac tissue and prevent angiogenesis in the malignant cells. Also, when inflammatory responses are triggered by NF-κB pathway activation and the inflammatory mediators production increased, Tumor growth factor-β (TGF-β) production is increased too; these events prevent overproduction of mediators as well as damage healthy tissues [19]. During a malignancy procedure, malignant cells secrete vesicles containing TGF-β, after inflammation; they grow and proliferate by suppressing immune cells [20]. Also exosomes contain TGF-β ccccsis of cardiomyocytes and cardiomyopathy in CVD [21]. Furthermore, researches have shown that exosomes contain TGF-β are accompanied with increased expression of high-mobility group box 1 (HMGB-1); HMGB-1 enhances TGF-β production by activating NF-κB pathway [22]. Therefore, targeting HMGB-1 in malignant cells reduces the secretion of exosomes containing TGF-β. TGF-β inhibits the proliferation of malignant cells and cardiomyocytes fibrosis. Another study, emphasize on the cardio protection role of HMGB-1, the results of these studies show that HSP70 expresses on exosomes; Interaction of HSP70 with Toll-like receptor 4 (TLR4) activates the ERK/MAPK pathway which cause cardio protection by preventing apoptosis [22, 23]. HMGB-1 enhances TLR4 expression by activating the NF-κB pathway. In addition, it activates the PI3k/AKT/mTOR pathway in malignant cells. It induces the malignant cells resistance to chemotherapy; activating the PI3k/AKT/mTOR pathway by HMGB-1, promotes proliferation and growth of cardiomyocytes, in CVD condition (Fig. 1) [24, 25].

Finally, we can say that HMGB-1 is a key factor at the center of signaling pathways; it has a dual role in hematologic malignancies in malignant cell proliferation and CVD. Identifying pathways that jointly Prevents cell proliferation and cardiomyocytes dysfunction could be a suitable therapeutic design for hematological malignancy patients with CVD.

## Exosome microRNA

Exosomes also excrete microRNAs (miRNAs). These miRNAs involved in various processes, including cell-to-cell and cell-to-extracellular communication, as well as the association between heart and stem cells [26, 27]. MiRNAs are short noncoding RNAs which are effective in the regulation of expression as well as the translation of many mRNAs in the cell [28]. Recent studies imply that exosomes secreted miRNAs of leukemia patients, are effective in in promoting malignant cell proliferation and development of CVD. On the contrary, recent studies have reported that induction of some miRNAs by exosomes in patients, causes cardiac repair and regeneration, it prevents CVD too. For instance, miR-26a prevents cardiac

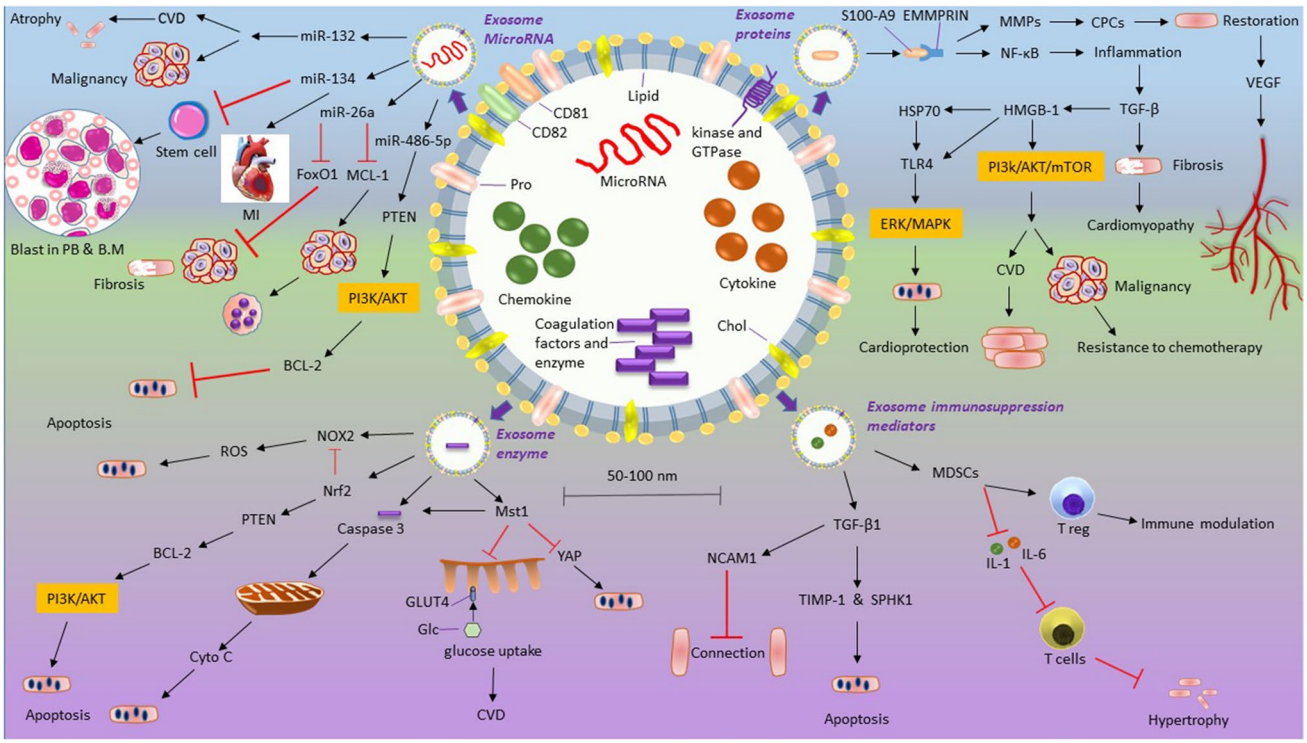


**Fig. 1** Multiple functions of exosomes associated with CVD in hematologic malignancies, with regard to their proteins, miRNAs, immunomodulators, and enzymes. According to the signaling aspect, interactions between exosome proteins, as well as secretory cytokines (such as TGF-β), induce diverse effects on cardiac tissue, angiogenesis, and malignant cell proliferation. Alongside these effects, miRNAs as a double-edged sword, are capable of stimulating leukemic cell proliferation (or even CVD development) and some of them inhibit leukemic cell proliferation by increasing their susceptibility to chemotherapy drugs. Similar to the consequences of miRNAs function, exosomal immunomodulators, despite causing leukemic cell resistance against host immune responses, are considered an appropriate strategy for repair damaged heart cells and CVD prevention. Exosomal enzymes generally affect inflammatory and apoptosis processes, which can be involved in the pathogenesis of CVD through their powerful weapons (such as ROS and NOX2). Accurate identification of each of these aspects can be useful indesigning therapeutic strategies to reduce the progression of CVD in hematologic malignancies. *CVD* cardiovascular disease, *MIR* microrna, *PB* peripheral blood, *BM* bone marrow, *MI* myocardial infarction, *PI3K/AKT* phosphoinositide 3-kinases, *FOXO1* forkhead box protein O1, *MCL-1* myeloid cell leukemia-1, *PTEN* phosphatase and tensin homologue, *Bcl-2* B-cell lymphoma 2, *NOX2* NADPH oxidase 2, *ROS* reactive oxygen species, *NRF2* nuclear factor erythroid 2-related factor 2, *CYTO C* cytochrome c, *MST1* mammalian sterile 20-like kinase 1, *YAP* yes-associated protein, *GLUT4* glucose transporter 4, *Glc* glucose, *CD* cluster of differentiation, *PRO* protein, *CHOL* cholesterol, *GTP* guanosine-5′-triphosphate, *MMP* matrix metalloproteinase, *CPC* myocytes progenitors cells, *NF-Kb* nuclear factor kappa-light-chain-enhancer of activated B cells, *HSP70* heat shock protein 70, *HMGB-1* high-mobility group box 1, *TGF-β* tumor growth factor-β, *VEGF* vascular endothelial growth factor, *TLR4* toll-like receptor 4, *ERK* extracellular-signal-regulated kinase, *MAPK* mitogen activated protein kinase, *MTOR* mammalian target of rapamycin, *MDSC* myeloid-derived suppressor cells, *TGF-β1* transforming growth factor beta 1, *NCAM1* neural adhesion molecule 1, *SPHK1* sphingosine kinase 1, *TIMP-1* TIMP metallopeptidase inhibitor 1, *IL-1* interleukin-1, *TREG* T regulatory cell

cell fibrosis by reducing FoxO1 and TRIM63/MuRF1 expression. In addition, evidences suggest that miR-26a expression is decreased, in chronic lymphocytic leukemia (CLL) patients. MCL-1 inhibition induces miR-26a expression which promotes apoptosis process of leukemic cell [29–31]. On the other hand, miR-486-5p inhibits leukemia cell proliferation by targeting FoxO1 and increasing their susceptibility to chemotherapy drugs [32]. On the contrary, miR-486-5p by targeting PTEN and enhancing PI3K/AKT pathway induces BCL-2 expression and prevents cardiomyocyte apoptosis, in the ischemia patients [33]. MiR-134 is another miRs that increases in the serum of myocardial infarction patients; it has been introduced as a biomarker in patients with myocardial infarction [34]. MiR-134 increases blast in peripheral blood and bone marrow by preventing stem cell differentiation; its expression is associated with poor prognosis in leukemic patients [35]. MiR-132 expression is decreased in CVD patients and results in cardiomyocyte atrophy; induction of miR-132 expression leads to increased angiogenesis and prevents myocardial infraction. It is not protective on leukemic cells and leads to increased proliferation of malignant cells [36, 37]. Finally, each miRs, can both promote the proliferation of cancer cells and impair cardiomyocyte function, depending on the biological function. Some are known for the protective effect for cardiomyocytes and

**Table1** Correlation between miR expression in leukemia and heart disease

| MiR | Target | Leukemia patients | Possible function in heart cells | References |
|---|---|---|---|---|
| miR-125b | Block p53<br>Expression VEGF | Inhibition of apoptosis and differentiation of myeloid progenitor<br>Increased angiogenesis | Inhibition apoptosis of and repair cardiomyocytes | [40, 41] |
| miR-215 | P53<br>P21 | Increased senescence leukemia cell<br>Increased sensitive leukemia cell to chemotherapy | Protective cardiac cell by negative regulation of Act1/IL-17RA signaling | [42, 43] |
| miR-21 | RhoB | Increased angiogenesis | Expression of miR-21 predictive of heart failure | [44, 45] |
| miR-150 | CTNNB1<br>Notch2 | Downregulation of proliferation leukemia cell | May be predictive of coronary heart disease | [46, 47] |
| miR-126 | CXCL12<br>VCAM-1 | Downregulation adhesion leukemia cell to endothelial cell | As risk factor for progression CVD | [48, 49] |
| miR-29c | DNMT3a<br>DNMT3b | Correlated with relapse disease | Suppress Wnt signaling in cardiac cell | [50, 51] |

*VEGF* vascular endothelial growth factor, *CVD* cardiovascular disease , *DNMT* DNA methyl transferase, *VCAM-1* vascular cell adhesion molecule 1, *CXCL12* C-X-C motif chemokine 12, *CTNNB1* catenin beta 1

induces leukemic cell resistance to chemotherapy (Fig. 1) [38, 39]. Therefore, screening and detection of miRs as a prognostic marker can be used in the plasma of leukemia patients; they can predict therapy resistance and CVD incidence in the patients (Table 1).

## Exosome immunosuppression mediators

Secretion of exosomes that contain immunosuppressive factors is one of the mechanisms which causes leukemia cells resistance to host immune responses; these factors provide the conditions for proliferation and development of leukemic cells, by modulating the immune system [52, 53]. For instance, studies show that increased myeloid-derived suppressor cells (MDSCs) inhibit the production of inflammatory cytokines such as IL-1 and IL-6; this mechanism prevents cardiomyocyte hypertrophy and CVD by preventing T-cell from functioning [54]. MDSCs modulate the immune system from pro-inflammatory to anti-inflammatory state by inducing T regulatory cells (Treg) differentiation and blocking access of T-cells to L-arginine [55]. TGF-β1 is another secreted immunosuppressive agent by exosomes in leukemic patients. Studies have shown that TGF-β1 secretion unlike MDSC does not induce cardiomyocyte repairing; it increases the expression of both sphingosine kinase 1 (SPHK1) and TIMP metallopeptidase inhibitor 1 (TIMP-1). These two factors cause angiogenesis and regulate metabolism, normally, but increasing expression by TGF-β1 leads to cardiomyocyte apoptosis and CVD [56]. It has been proven that, TGF-β1 leads to increased expression of neural adhesion molecule 1 (NCAM1) in CVD patients; NCAM1 expression leads to impaired cardiomyocyte adhesion and impaired cardiac function, consequently (Fig. 1) [57].

It can be concluded that some factors are protective for cardiomyocytes, although they increase leukemia cells survival and proliferation. Therefore, identifying these pathways can be a way to design a suitable treatment strategy to prevent CVD development.

## Exosome enzyme

Enzymes are other factors released from exosomes secreted by leukemic cells. These factors play an important role in inflammation and apoptosis and the pathogenesis of CVD through the reactive oxygen species (ROS) production. Caspase-3 is one of the enzymes released by exosomes, which induces cardiomyocytes apoptosis by releasing cytochrome C from mitochondria [58, 59]. Mammalian sterile 20-like kinase 1 (Mst1) is a component of the Hippo signaling pathway which has a role in cell apoptosis and autophagy to regulate. Results have shown that Mst1 induces cardiomyocytes apoptosis by activating caspase-3 and inhibition of the yes-associated protein (YAP) (involved in cell cycle progression). In addition, Mst1 inhibits glucose uptake and insulin resistance by impairing Glucose transporter 4 (GLUT4) function, which results in cardiomyocyte hypertrophy and CVD, ultimately [60–62]. NADPH oxidase 2 (NOX2) is another effective enzyme in the CVD development due to ROS production. This enzyme induces cardiomyocyte apoptosis by increasing ROS production. Nuclear factor erythroid 2-related factor 2 (Nrf2) is one of the antioxidant factors that inhibits ROS production due to NOX2 dysfunction. Furthermore, given that Mst1 has been shown to decrease Nrf2 expression, it can be said that increased

Mst1 expression by increasing ROS production lead to CVD [63, 64]. Another prominent role of Nox2 is apoptosis prevention. Nox2 inhibits apoptosis by targeting PTEN and enhancing BCL-2 expression through activating PI3K/AKT pathway [65]. According to the dual role of NOX2 in cardiomyocyte apoptosis induction and suppression, it can be said that accurate identification of signaling pathways which activated or inactivated by NOX2 could be suitable for designing a therapeutic strategy.

## Conclusion

Some researchers believed that exosomes secreted substances are able to impair cardiomyocyte function and cause CVD; the events occur by stimulating the immune system as well as producing ROS. Contradictory results from other studies revealed that CVD can be prevented by angiogenesis and stimulation of cardiomyocyte precursor's differentiation; some studies have cited that secreted miRs and lncRNAs are responsible for these events. Therefore, the reconnaissance of angiogenesis pathways can be used as an appropriate therapeutic strategy for the treatment of CVD in hematologic malignancies.

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### Compliance with ethical standards

**Conflict of interest** The authors declare no conflict of interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

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