Li et al. ExRNA (2019) 1:31
https://doi.org/10.1186/s41544-019-0025-x

ExRNA

REVIEW Open Access

Exosomal miRNA: an alternative mediator of cell-to-cell communication

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Abstract

Mounting evidence show that miRNAs are loaded into exosomes and secreted by almost all types of cells. miRNAs are selectively sorted into exosomes, and transferred to recipient cells, where they manipulate cell function. Thus, exosomal miRNAs are believed to be an alternative cell-to-cell communication mediator. Exosomal miRNAs under different pathological or physiological stimuli show different signature, indicating exosomal miRNAs are highly associated with certain diseases. Although the mechanism governing selective sorting of miRNAs are largely unclear, several mechanisms have been reviewed here. Once exosomal miRNAs released, they enter and delivery exosomal miRNAs into recipient cells, where exosomal miRNAs use cellular machinery to reduce target gene expression and manipulate cell function. Exosomal miRNAs have been proven to be implicated in the development of tumorigenesis, angiogenesis, insulin resistance and atherosclerosis. This review reveals the current understanding of exosomes miRNAs.

Background

MicroRNAs (miRNAs) are a class of small, non-coding RNAs with a length of approximately 22 nucleotides [1]. MicroRNAs play a role in vast range of physiological and pathological processes by post-transcriptionally regulating target genes [2]. Since the discovery of miRNAs in 1993, a great number of studies proved that intracellular miRNAs serve as critical mediators in metabolic disease, cardiovascular disease, development, tumour growth, and cellular stress [1, 2]. Nevertheless, the function of miRNAs has been confined in a particular cell until the year of 2010, when extracellular microRNAs have been reported to stably exist in circulating system [3]. This discovery hugely extended the conventional view of miRNAs. Immediately after that, extracellular miRNAs were proved to be carried by exosomes, a class of 30–150 nm vesicles that are released from many cell types in extracellular space [4–6]. Besides, miRNAs were not randomly loaded into exosomes. Rather, with the different treatment of pathological stimuli, the profiles of exosomal miRNAs varied in content and abundance accordingly [7]. This means exosomal miRNAs are selectively and actively sorted into exosomes upon a particular treatment. Once release, exosomal miRNAs are delivered into recipient cell, where they manipulate cell function by the way the intracellular miRNAs do [7]. Given these effects, it is convincible that exosomal miRNAs are highly associated with disease and may participate the pathogenesis. Here, we aim to review the pathological profiling of exosomal miRNAs and the outcome of exosomal miRNAs communication.

The release of exosomal miRNAs

As we described above, the selective export is the most important property of exosomal miRNAs. The selective sorting is first presented by the distinctive profiling of miRNAs in exosomes and their parent cells. When analysed in exosomes derived from cells in response to the stimuli of H_2O_2, AGE and OA/PA., miRNA expressions were different. Cells exposed to AGE stimuli showed upregulation of miR-30d, miR-26b, miR-21, miR-148a, miR-24, miR-27b, and miR-27a in cells, but these miRNAs remained unchanged in exosomes upon the treatment; miR-26a, miR-29a, miR-181b, miR-150, and miR-222 were upregulated both in donor cell and exosomes; miR-25, miR-122, miR-23a, miR-103 miR-211, although upregulated in cells, were not secreted via exosomes. With the treatment of H_2O_2, miR-26b, miR-29a, and miR-222 were upregulated in cells but not released

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into circulating; miR-21a, miR-150, miR-181b and miR-23a, either upregulated or downregulated in cells, were upregulated into exosomes. Under high level FFAs conditions, although miR-24, miR-29a, miR-150 and miR-222 were downregulated in cell, they were increased in exosomes [7]. Another study by Goldie et al. also confirmed that the proportion of small RNAs were abundant in exosomes than that in their parent cell [8]. The selectivity of exosomal miRNAs are also proved by the miRNAs profiling varying in type and level upon different pathological stimuli. THP-1 secreted miR-30d were increased upon the treatment of AGE and OA/PA but remain unchanged upon the treatment of H_2O_2 [7]; miR-29a specially responded to the stimuli of AGE and was secreted via exosomes. These finding suggest that miRNAs are not passively released and packaged into exosomes. Quite the contrary, they are actively and selectively loaded into exosomes. Further, the profiling of secreted miRNAs varies due to the different stimuli, which are linked to a certain type of disease. Thus, this indicate that secreted miRNAs are highly associated with the pathological process.

The profiles of exosomal miRNAs are also present tissue specificity. Through comparing miRNAs profiling in exosomes among a wide range of cancer cell lines, let-7 miRNA family were found specifically increased in gastric cancer cell line, remaining unchanged in lung cancer cell line SBC-3/DMS35/NCI-H69, the colorectal cancer cell line SW480/SW620, and the stomach cancer cell line AZ-521 [9]. Besides, some miRNAs are preferentially sorted into exosomes. miR-320 family are enriched in exosomes derived from a wide range of normal or tumours cells [10–12]. miR-451 are highly expressed in exosomes derived from normal cells, such as the HMC-1 cell line, the HEK293T cell line, and Epstein-Barr virus-transformed lymphoblastic B-cell [10, 13, 14]. Microarray analysis of activation-induced miRNAs released from primary T lymphoblast found that miRNAs modulated upon activation are not the same in cells and exosomes. miR-575, miR-451, miR-125-3p, miR-198, miR-601 and miR887 were more highly expressed in exosomes than in cells. Conversely, some miRNAs, such as miR-17, miR-29a, let-7a, miR-142-3p, miR-181a, miR-18a, were more preferentially not loaded into exosomes [13].

Despite the specificity of exosomal miRNAs has been well established, the mechanisms governing the selective sorting of miRNAs into exosomes remained largely unclear. However, several promising mechanism has been proposed (Fig. 1). Neutral sphingomyelinase 2 (nSMase2) was believed to trigger secretion of exosomes via regulating the biosynthesis of ceramide. Reducing the activity of nSMase2 with a chemical inhibitor GW4869 or siRNA resulted in the decreased amount of miRNAs in exosomes [15]. Although this study proposed a mechanism governing miRNAs secretion, the reason for the selectivity of miRNAs secretion from different types of cell is still not quite clear. Villarroya-Beltri et al. found that miRNAs that are preferentially sorted to exosomes contain the specific short motifs (EXOmotifs). Sumoylated heterogeneous nuclear ribonucleoprotein A2B1 (hnRNPA2B1) has been demonstrated to control the loading of specific miRNAs into exosomes by binding to the motif. HnRNPA2B1 is an ubiquitous protein. According to previous reference, hnRNPA2B1 is able to bind to a RNA trafficking sequence (RTS) with a length of 21 nt and regulate mRNA trafficking to axons in neural cell. Through comparing the RTS and the EXOmotifs identified in Villarroya-Beltri study, both two EXOmotifs are contained in this sequence. Interestingly, the hnRNPA2B1 protein in exosomes is largely sumoylated. Artificially reducing this sumoylation inhibited the binding of miRNAs to hnRNPA2B1 [15]. Interestingly, a consistent result is found in the exosome of glioblastoma multiform cells by Bolukbasi et al. They assayed the sequence of mRNAs in exosomes and found that exosomal mRNA shared a 5-nt core sequence “CTGCC” (or variations CTGC, CTCCC, CGCCC, TGCC). Moreover, miR-1289 can bind to the core sequence and mediate the mRNA secretion. A closer check of miR-1289 sequence could reveal that the EXOmotif GGAG occurred in the 5′-end of this miRNAs sequence [16]. This may explain why mRNAs that are able to bind to miR-1289 can be sorted into exosomes. To be specific, miR-1289 might be sorted to exosomes via sumoylated hnRNPA2B1 noted in above mentioned study, simultaneously taking complementary mRNA into exosomes. Pre-miRNA-10a, pre-miR-10b, pre-miR-21, pre-miR27a, pre-miR-155, and pre-miR-373, along with RISC-loading complex (RLC) which consists of Dicer, AGO2, and TRBP, are present in exosomes of cancer cells [17]. These pre-miRNAs can be processed into mature miRNAs by RLC in exosomes [17–19]. This study provide a new mechanism of exosomal miRNA sorting.

The uptake of exosomal miRNA by recipient cells

Once released, exosomal miRNAs, after circulating in body fluids for a short period of time, will be delivered to recipient cells, where they appear to use a range of mechanisms to bind on target cell and undergo internalization [20, 21]. Surface protein on exosomes facilitate exosomes first adhere to target cell, which is thought to be a fundamental step for exosomes-target cell communication [22, 23]. Tetrapanins are thought to have a role in adhesion, motility, signal transduction and cell activation, and they are highly abundant on the exosomes surface [24–26]. These tetrapanins include CD9, CD53, CD63, CD81 and CD82, which may contribute to the spatial assemble for antigen recognition and may partially dictate the signal induced by the exosomes [26–31].

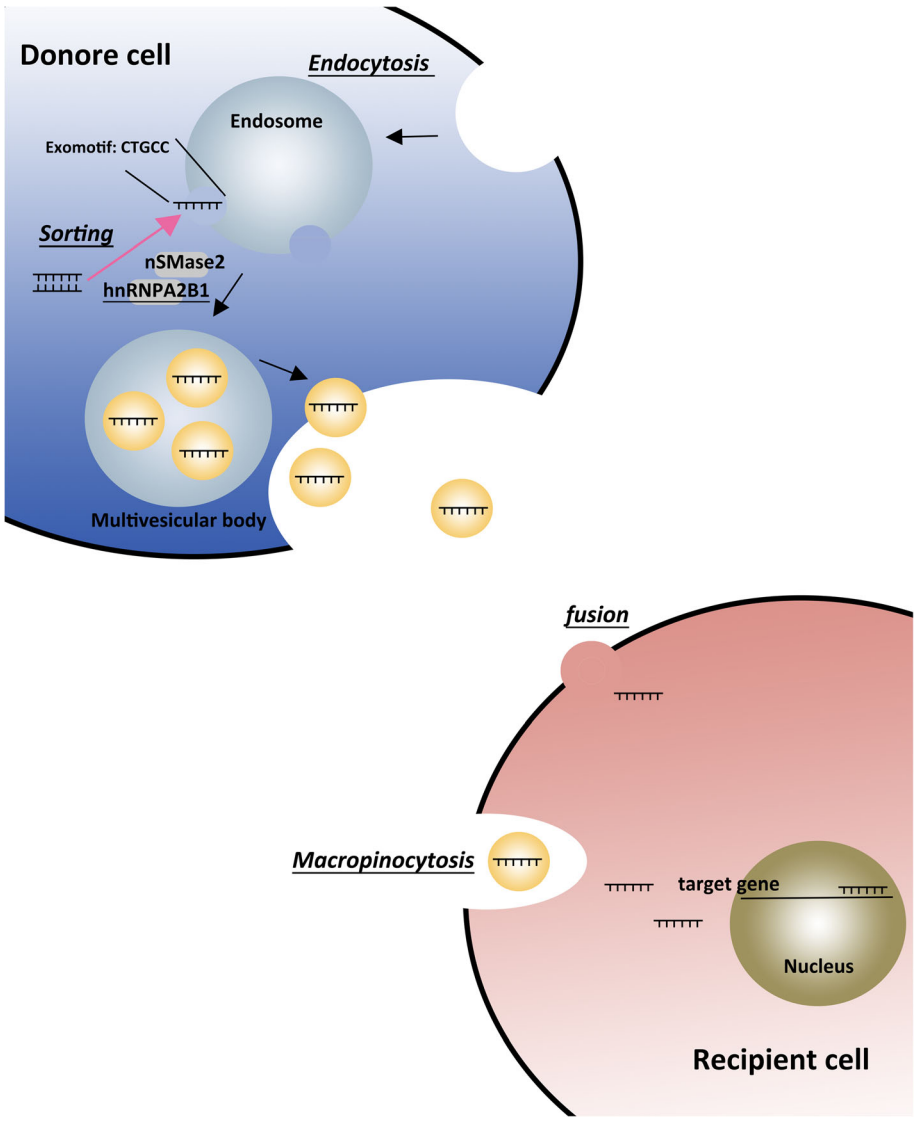

Fig. 1 The machanism of extracellular release and uptake

Treatment of antibodies on recipient cells against the tetraspanins CD81 or CD9 can reduce the uptake of exosomes by dentritic cells, which suggest that tetraspanins have a role in exosomes uptaking and function [32, 33]. Intergrin is another type of adhesion protein playing a role in exosomes binding. The treatment of antibodies against integrins αv (CD51) and β3 (CD61) on the dentritic cell surface reduce the uptake of exosomes [32]. When adhering, intergrins change to a high affinity status and assist the high avidity binding of cell to the integrin-bound cell [34, 35]. Inducing a high-affinity state of LFA-1 by manganese chloride on resting T-cells cause a significant increase of exosomes uptake [35, 36]; conversely, using an antagonistic antibody to hinder the formation of high-affinity state inhibit this process [37].

Internalization is the next step in exosomes' destiny, and also the fundamental process for exosomes delivering miRNAs into target cell and cellular response [5, 38–40]. The capacity of cells up-taking exosomes dramatically reduced at 4 C, which suggest that exosome uptake is an energy-dependent process [41]. The mechanism underlying internalization of exosomes are still being subject to debate. Nevertheless, there are four pathways have been implicated in exsomes uptake, including: fusion of the exosome membrane with the plasma membrane [42, 43]; Phagocytosis [44] and micropinocytosis; macropinocytosis [45, 46]; Clathrin-mediated endocytosis (CME) [47–49]; and Caveolin-dependent endocytosis [50–53], and lipid raft-mediated endocytosis [54–56].

The cellular response of exosomal miRNAs in recipient cells

Exosomal miRNAs can cause a range of response in recipient cell, where they are internalized and play function through post-transcriptionally silencing target gene [7, 57]. Exosomal miRNAs has been widely implicated in many steps of tumorigenesis. Zhang et al. discovered that exosomal monocytic miR-150 released by AGE-treated THP-1 serving as inflammatory factor can enter endothelial cells and enhance endothelial cell migration [7]. Endothelial cell migration is one of the important step of angiogenesis, which play a role in tumorigenesis. The following study continued to demonstrate that exosomal miR-150 from monocyte increase the angiogenesis by targeting c-Myc, which in turn result in enhanced tumour growth [58]. Further study demonstrated exosomal miR-150 from monocyte increase VEGF secretion of tumour-associated macrophage, which induce angiogenesis by recruiting endothelial cell [59]. The series of research demonstrate that, under chronic inflammation condition, THP-1 derived exosomal miR-150 contribute to tumorigenesis. miR-223, a tumour-associated macrophage (TAM) specific miRNA, can be released and transferred to breast cancer cell, where they activate the Mef2c-b-catenin pathway and enhance the invasiveness [60]. Tumours also are able to release miRNAs to manipulate microenvironment and facilitate the growth of themselves. MiR-214, which is thought to be onco-miRNAs has been reported to be released by tumour cells and travel to T regular cell. They reduce the expression of PTEN and activate the T regular cell, which in turn promote the immune escape [57]. Exosomal miRNAs also have a role in tumour metastasis outgrowth. In tumour cells disseminating to brain, the expression level of PTEN specifically reduced compared to primary tumour or other organ metastases. Further investigation found that astrocyte-derived exosomal miR-19a down-regulate PTEN expression in metastatic tumour cells, which in turn cause CCL2 up-regulation and enhance the outgrowth of brain metastatic tumour cells [61]. Another study also demonstrated exosomal miRNAs enhance the metastasis of cancer cell. Breast cancer cell lines MCF-10A and MDA-MB-231 released miR-105 reduced ZO-1 gene expression in endothelial cells and enhance the metastases to the lung and brain [62].

Exosomal miRNAs are also implicated metabolic diseases including, insulin resistance, and cardiovascular disease. Adipose tissue, a major organ for energy balancing, has been demonstrated by a number of studies that it can release considerable amount of exosomal miRNAs which manipulate metabolism [63]. Recent study demonstrate that adipose tissue secreted not only adipokines, but also exosomal miRNAs [64]. Specifically impairing the maturation of miRNAs in adipose tissue by knocking out the miRNAs-processing enzyme Dicer results in a substantial decrease in levels of exosomal miRNAs in circulating. In parallel experiments, the transplantation of white and brown adipose tissue into KO mice restore the level of insulin resistance [64]. This study proposed a conclusion that adipose tissue is a major source of circulating exosomal miRNAs. Further investigation into the

Table 1 The type of exosomal miRNAs and their involvements in the pathogenesis of diseases

Names of miRNA	Donor cell	Recipient cell	intercellular Target gene and function	Ref.
miR-150	Monocyte (THP-1)	Endothelial cell	c-myc, promoting angiogenesis	[7, 58, 59]
miR-19a	Brain astrocyte	Tumour cells metastasis to brain	PTEN, prime brain metastasis outgrowth	[61]
miR-214	Tumour cell	Regulatory T cell	PTEN, induce immune escape	[57]
miR-155	Adipose tissue macrophage (obese)	Liver, Muscle, adipose tissue	PPARγ	[65]
miR-223	tumour-associated macrophage	Tumour cells (breast cancer)	Activate Mef2c-b-catenin pathway	[60]
miR-105	Breast cancer	Endothelial cell	ZO-1, promote the metastasis to brain and lung	[62]
miR-143/miR-145	Endohelial cells	Vascular smooth muscle	Atheroprotective role	[67, 68]
miR-26a, miR-29a, miR-181b, miR-222	Monocyte (THP-1) exposed to AGE	–	–	[7]
miR-21, miR-150, miR-181b, miR-23a	Monocyte (THP-1) exposed to H_2O_2	–	–	[7]
miR-29a, miR-24a, miR-222	Monocyte (THP-1)	–	–	[7]
miR-451	HMC-1 HEK293T lymphoblastic B-cell	–	–	[10, 13, 14]
miR-320	Normal cell and tumour cells	–	–	[10–12]
miR-575, miR-451, miR-125-3p, miR-198, miR-601 , miR887	primary T lymphoblast	–	–	[13]

exosomal miRNAs found that adipose tissue macrophage release miR-155, which enter liver, muscle and adipocyte and modulate insulin sensitivity [65]. Large adipocytes transfer to small adipocytes, which in turn induce lipid storage [66]. Exosomal miRNAs also involved in the development of atherosclerosis [67]. A study found that endothelial cells also are able to secrete exosomal miR-143 and miR-145, which then alter the phenotype of vascular smooth muscle, playing an atheroprotective role in the development of sclerosis [68].

Conclusion

As the study of exosomal miRNAs mounting recent years, a novel miRNA-based communication network is forming in several defined diseases. Exosomal miRNAs, which are selectively and actively loaded into exosomes, are highly implicated in many pathogenesis process (Table 1). Despite not investigated comprehensively, exosomal miRNAs are considered as an alternative cell-to-cell communication mediator, which may play a role in pathogenesis. Further investigating the function of exosomal miRNAs can lead to the brand new understanding of many defined diseases. Nevertheless, due to the finite study strategy, the secretion of exosomal in health and disease in vivo is rarely understood. It is easy to observe the communication of exosomal miRNAs in vitro, but it is hard to grab the direct evidence of the transfer of exosomal miRNAs in vivo. The new research strategy and new cutting-edge technologies should be improved and utilized in this filed. More deep investigation into exsomal miRNAs physiological and pathological function in vivo should be performed.

Abbreviations

CME: Clathrin-mediated endocytosis; hnRNPA2b1: heterogenous nuclear ribonucleoprotein A2B1; LFA-1: Lymphocyte function associated antigen-1; miRNAs: microRNA; mRNA: messenger RNA; nSMase2: sphingomyelinase 2; OA: Oleic acid; PA: Palmitic acid; pre-miRNA: precursor microRNA; RLC: RISC-loading complex; TAM: Tumour-associated macrophage

Acknowledgments

Not applicable

Funding

This work was supported by the National Natural Science Foundation of China. (Grant No. 31741066), the Fundamental Research Funds for the Central Universities. (Grant No. 020814370087, 020814370094).

Availability of data and materials

Not applicable

Authors' contributions

JL and XJ conducted the literature search and drafted the manuscript. KW revised the text to produce the final version of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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Received: 20 July 2018 Accepted: 15 March 2019
Published online: 11 July 2019

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