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Review

The role of exosomal shuttle RNA (esRNA) in lymphoma

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ABSTRACT

Lymphoma is a common primary hematologic malignancy of lymph nodes or other lymphoid tissues which can occur at any age. Exosomes are small membrane vesicles which emerge as a novel intercellular communication method and play an important role in the tumor proliferation and metastasis. Some ribonucleic acids, including mRNA, microRNA, long non-coding RNA and circle RNA, can be functionally transferred between cells via exosomes and are called 'exosomal shuttle RNA (esRNA)'. A growing body of evidences have shown that esRNA mediate a variety of pathological conditions related to the lymphoma development, progression and therapeutic failures. In this article, we will review the role of exosomes, with the focus on the role of exosomal shuttle RNA (esRNA) in lymphoma. The importance of esRNA in the pathogenesis, progression, drug resistance and the prospect of clinical application will be discussed in detail.

1. Introduction

Lymphoma represents a heterogeneous group of hematologic malignancies which originates from lymphocytes. According to the latest data published in 2018, lymphoma is accounted for 3–4% of all malignant tumors and lead to about 275 000 cancer-related deaths around the world, with a higher incidence rate in the developed world than the developing world (Bray et al., 2018).

Exosomes are 30–100 nanometer-sized membrane vesicles formed in the endosomes and secreted by various viable cells including tumor cells (van Niel et al., 2006). When firstly discovered by Johnstone and colleagues in the early 1980s, exosomes were mainly investigated for their role in eradicating useless membrane-associated proteins during the reticulocyte maturation (Harding et al., 1983; Pan et al., 1985). However, exosomes were then found to be a novel method of intercellular communication in a series of studies, such as immune regulation and tumor development (Zitvogel et al., 1998; Raposo et al., 1996; Taylor and Black, 1986). In 2007, functional microRNA (miRNA) and messenger RNA (mRNA) were observed in the exosomes and could be delivered to recipient cells and these RNAs were called "exosomal shuttle RNA" (esRNA) (Valadi et al., 2007). Over the last few years, an increasing body of evidences indicated that exosomes also carried abundant functional circular RNA (cirRNA), long noncoding RNA (lncRNA) and other non-coding RNA which could be transferred to another cells. Given this, we propose that esRNA include not only miRNA and mRNA, but also cirRNA, lncRNA and other non-coding RNA.

Previous studies have shown that extracellular vesicles were involved in many normal physiological processes: tissue regeneration (Quesenberry and Aliotta, 2008), coagulation (Aleman et al., 2011), reticulocyte maturation (Pan and Johnstone, 1983), immune regulation (Mastronardi et al., 2011) and pregnancy (Toth et al., 2007). Moreover, exosomes also play an important role in various pathological processes, such as cancer proliferation and metastasis (Fang et al., 2018), drug resistance (Boelens et al., 2014) and immunosuppression (Chen et al., 2018a). Recent studies demonstrated that exosomes involved the pathogenesis and progression of lymphoma and esRNA play a key role in this process (Feng et al., 2018; El-Saghir et al., 2016; Provencio et al., 2017; Rutherford et al., 2018; Koch et al., 2014). In this review, we will focus on the role of esRNA in the pathogenesis, progression, drug resistance, immunoregulation, and the potential clinical application of esRNA as biomarkers and therapeutic target in lymphoma.

2. The profile of the esRNA

Valadi et al. (2007) firstly reported that the mRNA expression in exosomes differed greatly from the RNA profile of the parental cells. The study also showed that mRNA and miRNA were abundant while

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much little 18S and 28S ribosomal RNA (rRNA) was present in the exosomes, which was totally different from the donor cells. The similar RNA profile was subsequently reported in many studies worldwide in exosomes from different body fluid, including plasma (Taylor and Gercel-Taylor, 2008; Skog et al., 2008), breast milk (Lasser et al., 2011a), saliva (Lasser et al., 2011a; Palanisamy et al., 2010), and amniotic fluid (Keller et al., 2011). Rich lncRNA and cirRNA were also identified in exosomes by subsequent studies over the last few years (Qu et al., 2016; Li et al., 2018a,b,c, 2015). ExoCarta is an internet-based exosome database based on the findings of 286 studies around the world. According to latest figure in the database, the total number of identified miRNAs and mRNAs were 2838 and 3408, respectively. In 2017, another database exoRBase aimed to collect and characterize all long RNA species in human blood exosomes was developed by Fudan University Shanghai Cancer Center (Li et al., 2018b). This database was based on the result of RNA-sequencing data analyses of human blood exosomes and experimental findings from the published literature, and a total of 58 330 circRNAs, 15 501 lncRNAs and 18 333 mRNAs were included. Recently, a group in Huazhong University of Science and Technology conducted small RNA sequencing in 17 sources/diseases derived extracellular vesicles and identified over 1000 miRNAs and specific miRNAs for each source/disease (Liu et al., 2018). Based on this data, they developed the EVmiRNA database, which primarily provides three functional modules, including the miRNA expression profile of EVs derived from different sources, the specific miRNA expression in different EVs, and the miRNA annotations. Searching the EVmiRNA database, a total of 394 miRNAs have been detected in the lymphoma exosomes and 23 miRNAs are specific for lymphoma. The lncRNA and cirRNA have not yet been investigated in lymphoma derived exosomes.

3. The specific sorting of RNA into exosomes

Some research data has shown that the expression level of mRNA (Valadi et al., 2007; Skog et al., 2008), miRNA (Valadi et al., 2007; Mittelbrunn et al., 2011), and lncRNA (Gezer et al., 2014) differs substantially between exosomes and their donor cells, suggesting that the sorting of esRNA into exosomes was a specific process. Although the concrete mechanism has not been clearly clarified, the discovery of EXOmotifs within RNA shed light into this problem (Statello et al., 2018) (Fig. 1). EXOmotifs are short specific sequences in the esRNAs which can form RNA–RBP (RNA-binding protein) complexes with RBP to guide the sorting of such RNA into exosomes. Some studies have shown that RNA-binding proteins such as hnRNPA2B1, hnRNPA1, YBX1 and SYNCRIP control the sorting of mRNA, lncRNA and siRNA into exosomes through binding to the specific sequence motifs present in exosomal shuttle RNA (Villarroya-Beltri et al., 2013; Santangelo et al., 2016; Kossinova et al., 2017). Several EXOmotifs were also associated with the transfer of miRNAs into lymphoma exosomes (Hoshina et al., 2016; Nanbo et al., 2018). In the gamma herpes virus infected lymphoma cells, the CCCG and CCCT were identified as nucleotide motifs which could guide the sorting of specific virus-encoded miRNAs into the exosomes (Hoshina et al., 2016). Another study indicated that the asymmetric distribution of miRNAs between exosomes and parental Burkitt lymphoma cells was partly caused by the EXOmotifs (Nanbo et al., 2018). Recently, a study identified 20 RNA-binding proteins in the exosomes and some of these proteins can facilitate the transit of RNAs into exosomes in human epithelial cells (HTB-177) (Statello et al., 2018). In this study, gene transcripts encoding six common exosomal RNA-binding proteins (HSP90AB1, XPO5, HNRNPH1, HNRNPM, HNRNPA2B1, and MVP) were silenced, however, only a significant reduction (50%) of total exosomal RNA were found in MVP- silencing cells, indicating that MVP play an important role in the sorting of RNA into exosomes .The above results suggest that EXOmotifs and RNA-binding proteins are key players in the load of esRNA and the role of RNA-binding proteins differs in different cells.

A large amount of RNA still exists in the exosomes after the knockdown or the silencing of gene transcripts of RNA-binding proteins, indicating that there are other mechanisms in the sorting of esRNA. GW182 and AGO2 protein are two main components of RNA-induced silencing complex (RISC). Gibbings et al. (2009) found that endosomes and multivesicular bodies were sites of miRNA-loaded RISC (miRISC) accumulation, however, the mature miRNAs in exosomes were accompanied by abundant GW182 and a small amount of AGO2 protein, while P-body components and miRNA-repressible mRNA were absent, suggesting that the miRNAs did not form miRISC in the exosomes. Consistent with the above results, little AGO2 was observed in the exosomes by a subsequent study (Ostenfeld et al., 2014). Instead of forming miRISC, the major function of AGO2 protein in exosomes may be associated with the stabilization of miRNA by forming miRNA-AGO2 complex (Beltrami et al., 2015). In addition, endogenous RNAs were also reported to be involved with the miRNA loading into exosomes and interruption of individual miRNAs expression accelerated miRNA relocation from cell cytoplasm to multivesicular bodies and controlled the exosomal miRNA sorting (Squadrito et al., 2014).

Together, these data suggests that the endogenous RNA, EXOmotifs, and some cooperative proteins such as RNA-binding proteins and AGO2 play a key role in the transfer of specific RNA into exosomes.

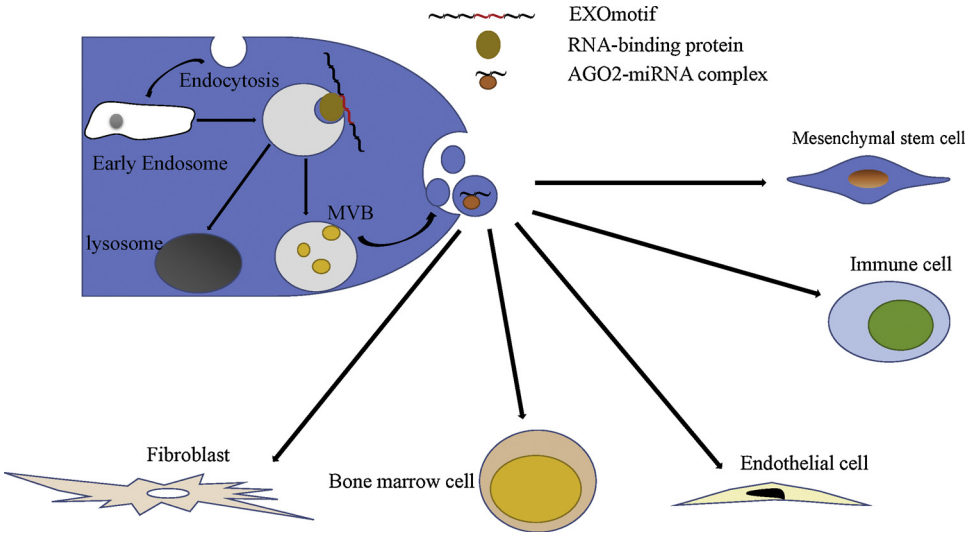

Fig. 1. Specific RNAs contained different EXOmotifs can be sorted into multivesicular bodies (MVBs) by different RNA-binding proteins. Exosomes produced in MVBs can be released into extracellular space and AGO2-miRNA complex is a more stable form for transferring miRNA. EsRNA can reprogram the mesenchymal stem cells, mast cells, and macrophages in the bone marrow, and thereby promote bone marrow invasion in lymphoma patients. At the same time, esRNA stimulate proliferation of endothelial cells and promote angiogenesis as well as re-program the stromal cells such as fibroblasts. In addition, the function of immune cells can also be inhibited by esRNA.

4. Exosome uptake and esRNA transfer

The uptake of exosomes by recipient cells has been recognized as a novel and important means of cell-to-cell communication. Two pathways have been reported in literatures regarding exosome internalization: membrane fusion and endocytosis. Fusion of exosomes and microvesicles with plasma membrane has been validated in the previous studies (Del Conde et al., 2005; Parolini et al., 2009). The mechanism of exosome–cell fusion has not been clearly understood and tetraspanins on the exosomes may play an important role in this process. Some research have reported that tetraspanins are related to the cell fusion in both physiological and pathological processes, such as egg-sperm fusion, the fusion of monocytes to form giant cell, and the microbial infections (Hassuna et al., 2009; Iwai et al., 2007; Levy and Shoham, 2005; van Spriel and Figdor, 2010; Rubinstein et al., 2006). Previous reports also suggested that exosomal adhesion molecules such as integrins were involved in target cell attachment and tetraspanin may promote exosome–cell fusion (Tian et al., 2010; Rana and Zoller, 2011).The concrete mechanism of exosome–cell fusion need further investigations.

Endocytosis was reported to be another mode of exosome internalization, including phagocytosis, macropinocytosis and receptor mediated endocytosis. Feng et al. (2010) found that the phagocytosis of exosome was dependent on the phosphatidylinositol 3-kinase (PI3K) and actin network, and knockdown of dynamin2 could inhibit this process. Macropinocytosis was also reported to be a method of exosome internalization in previous studies. It has been shown that exosomes from PC12 cells could be taken up by mesenchymal stromal cells (BMSCs) via clathrin-mediated macropinocytosis (Tian et al., 2014). However, another study showed that oligodendrocyte derived exosomes lack antigen presenting capacity and the macropinocytosis of exosomes by microglia represents a removal process of oligodendroglial membrane (Fitzner et al., 2011). Receptor mediated endocytosis was demonstrated to be a relatively common means of exosome internalization, including lipid raft-mediated endocytosis, Clathrin-mediated endocytosis and heparan sulfate proteoglycans (HSPGs)-mediated endocytosis (Tian et al., 2014; Christianson et al., 2013; Svensson et al., 2013). Christianson et al. (2013) reported that exosome uptake depended on the heparin sulfate proteoglycans of the cell surface and the inhibition of proteoglycan biosynthesis could substantially attenuate the exosome uptake. Mammalian cells could uptake exosomes via lipid raft-mediated endocytosis which was negatively regulated by caveolin-1 (Svensson et al., 2013). Clathrin-mediated endocytosis was also an important pathway for exosome to transfer information between different cells (Tian et al., 2014). In addition, exosomes from mantle cell lymphoma can be taken up by malignant and non-malignant B-lymphocytes in a cholesterol-dependent pathway, which differs from the above receptor mediated endocytosis (Hazan-Halevy et al., 2015).

Some factors were reported to have an important effect on the exosome internalization, including temperature, pH environment, glycoproteins and proteins in the exosomes, recipient cell types (Parolini et al., 2009; Hazan-Halevy et al., 2015; Shimoda et al., 2017). Shimoda et al. (2017) showed that glycan recognition was important for the uptake of exosomes from mesenchymal stem cells. It has been shown that various endocytic pathways were associated with exosome uptake by ovarian cancer cells and this process could be affected by several factors, such as low temperature, sialic acid-containing glycoproteins and proteins from the exosomes (Escrevente et al., 2011). A low pH environment was favorable for the exosome fusion with melanoma cell membrane, exosome release and uptake, and this phenomenon could be inhibited by proton pump inhibitors, suggesting the key role of microenvironmental pH for exosome traffic in cancer (Parolini et al., 2009). Horibe et al. (2018) indicated that the exosome uptake capability depends on the recipient cells by co-culturing exosomes derived from a donor cell line with three cell lines, respectively. The consistent conclusion was obtained in another study, which showed that exosomes from patients with mantle cell lymphoma were internalized rapidly and preferentially by both malignant and benign B cells, while no apparent internalization occurred in neither T lymphocytes nor NK cells (Hazan-Halevy et al., 2015).

When RNA was firstly identified in exosomes, Valadi et al. (2007) also indicated that exosomal miRNA and mRNA could be transferred to recipient cells. In this study, radioactive RNA could be measured in exosomes released from mast cells cultured with ^{3}H-uracil and recipient cells co-cultured with these exosomes also contained radioactive RNA, suggesting that exosomal RNA could be transferred between mast cells. The transfer of exosomal miRNA and mRNA was then identified in the subsequent researches through qRT-PCR (Tian et al., 2014; Kogure et al., 2011; Chiba et al., 2012). In the recent years, the transmission of lncRNAs and cirRNAs between different cells was also validated by qRT-PCR analysis (Qu et al., 2016; Dong et al., 2018; Kang et al., 2018; Zheng et al., 2018; Li et al., 2018d).

5. The function of transferred esRNA in the recipient cells

Previous studies have shown that the esRNA can produce some relevant biological effects on the recipient cells. The functionality of the exosomal mRNA was firstly uncovered by showing that isolated exosomal mRNAs could be translated into proteins in the vitro translation assay. Meanwhile, newly generated proteins were found in the human cells after postcoincubation with the mouse mast cell-derived exosomes, indicating that mRNA in the exosomes is functional in the recipient cells (Valadi et al., 2007). Skog et al. (2008) cultured the exosomes containing Gluc mRNA with human brain microvascular endothelial cells (HBMVEC) and found that Gluc activity increased continually over 24 hours in the recipient cells, which support the sustaining translation of the Gluc mRNA.

Recent studies also showed that not only mRNA can be transferred to recipient cells via exosomes, but also that functional miRNAs, lncRNA and cirRNA can be transferred to the recipient cells. The effect of internalized exosomal miRNAs on the recipient cells was detected by the luciferase activity after incubating the miRNA containing exosomes with cells transfected with a luciferase vector carrying a target sequence (Higuchi et al., 2018). Furthermore, some studies validate the function of exosomal miRNA by co-culturing the cells with target miRNA-poor and miRNA-rich exosomes, respectively (Fang et al., 2018; Higuchi et al., 2018). Similarly, the function of exosomal lncRNAs and circular RNAs can be proved by incubating recipient cells with target lncRNAs-containing exosomes and target lncRNAs-silencing exosomes (Li et al., 2018d,e). In addition, a luciferase screening assay was also used to confirm the function of exosomal cirRNA as a sponge for miRNAs in exosomes (Li et al., 2018c; Zheng et al., 2016).

In conclusion, the results of the above studies demonstrate that esRNAs can exert their functions in the recipient cells and play a key role in the intercellular communication.

6. The role of esRNA in lymphoma

Horizontal gene transfer is a common phenomenon between different cells and the transferred DNA or RNA sometimes play an important role in the recipient cells. However, horizontal gene transfer in human was once considered to be of little or no importance as most nucleic acids would be easily degraded if released into the blood. Exosomes are membrane vesicles which could shelter nucleic acids from degradation and transfer RNA to the distant organs to mediate different functions (Balaj et al., 2011; Baj-Krzyworzeka et al., 2006). Exosome seems to be a novel and important mode of intercellular cell communication between lymphoma cells and its microenvironment and may play an important role in the lymphomagenesis. In the following sections, we will focus on the role of esRNA in the lymphomagenesis, lymphoma spread, chemoresistance, immunoregulation and clinical application.

6.1. The role of esRNA in lymphomagenesis

As we have discussed above, the cell specific uptake of exosomes was also observed in lymphoma (Hazan-Halevy et al., 2015; Higuchi et al., 2018; Gutzeit et al., 2014). A group from Tel Aviv University in Israel found that B lymphocytes took up mantle cell lymphoma-derived exosomes rapidly and preferentially while few exosomes was internalized by T-cell leukemia and bone marrow stroma cells (Hazan-Halevy et al., 2015). Subsequent study indicated that functional messages could be transmitted from B lymphoma cells to human B cells via exosomes and led to some biological effects in the recipient cells (Gutzeit et al., 2014). Epstein-Barr virus (EBV) was considered as a oncogenic virus which play a key role in the development of various lymphoproliferative diseases, such as Hodgkin lymphoma (HL), Burkitt lymphoma (BL), and NK/T-cell lymphomas (Scott and Gascoyne, 2014; Shain et al., 2015). The characteristic and influence of exosomes derived from EBV infected Burkitt's lymphoma cells has been investigated (Gutzeit et al., 2014). In this study, B cells with EBV infection in vitro released exosomes that harbored the similar level of viral latent membrane protein 1 (LMP1) compared with the exosomes from LMP1-transfected DG75 cells. DG75 exosomes could be taken up efficiently by isolated B cells and promote the proliferation and generation of circle and germline transcripts for IgG1 in the B cells. Further study investigated the importance of EBV-associated lymphoma derived exosomes in the lymphomagenesis (Higuchi et al., 2018). Exosomes from EBV positive lymphoma cells could cause severe lymphoproliferative disease (LPD) in humanized mice model and the elevated expression level of an EBV-encoded miRNA was an adverse prognostic factor in elderly DLBCL patients, indicating that EBV-encoded miRNA may play an important role in the tumor development (Table 1). In vitro, exosomes mediated EBV-noncoding RNA delivery and produced immune regulatory effects by modulating the gene expressions of IL-10 and TNF-α in monocytes, and thereby facilitated tumor progression (Higuchi et al., 2018).

MYC is an oncogene associated with cell proliferation differentiation and apoptosis and previous studies showed that *MYC* rearrangement was an adverse predictor of clinical outcome in lymphoma patients (Rosenthal and Younes, 2017). Around 15% of all human genes are potential target genes of the MYC protein, including the genes related to cell proliferation, differentiation, and metabolism (Dang et al., 2006). *MYC* mRNA in exosomes was a predictor of adverse clinical outcome and poor response to therapy in B cell lymphoma (Provencio et al., 2017). The possible mechanism behind this is that *MYC* mRNA delivered to the other malignant or normal B cells was translated into MYC oncoprotein and thereby regulated the target gene expression to promote lymphomagenesis.

In addition, some Hodgkin lymphoma-related miRNAs such as miR155-5p and miR21-5p abundant in the plasma extracellular vesicles of Hodgkin lymphoma patients may be associated the tumorigenesis in the recipient cells (van Eijndhoven et al., 2016) (Table 1). MiR-21 and miR-155, which was associated with tumorigenesis in adult T-cell lymphoma/leukemia (ATLL) (Tomita, 2012; Pichler et al., 2008), were also upregulated in ATLL-derived exosomes and may play an important role in the lymphoma development (El-Saghir et al., 2016). Therefore, we propose that lymphoma derived exosomes can be internalized by specific cells such as malignant lymphoma cells and normal cells, and the transferred functional information can facilitate lymphomagenesis.

6.2. The role of esRNA in lymphoma spread

Lymphoma spread is a complicated process which consists of multiple steps. The interaction between cancer cells and the surrounding microenvironment was the basis for this process (Joyce and Pollard, 2009). Fibroblasts are the main components of the tumor stroma and the activation of fibroblasts play the vital role in promoting cancer invasion (Joyce and Pollard, 2009). A recent study reported that extracellular vesicles isolated from Hodgkin lymphoma (HL) cells could be internalized by fibroblasts and enhanced their migration capacity (Dorsam et al., 2018) (Fig. 1). Treated with these extracellular vesicles, fibroblasts transformed into cancer-associated fibroblasts which was able to secrete many soluble factors to promote HL progression, including pro-angiogenic factors (e.g., VEGF), growth factors (G-CSF and GM-CSF), and pro-inflammatory cytokines (e.g., IL-6, and TNF-α) (Dorsam et al., 2018). Angiogenesis is also required for the cancer metastasis as tumor vessels are important for providing oxygen and nutrients and eradicating the carbon dioxide and metabolic wastes produced by the tumor cells. Chen et al. (2018b) demonstrated that exosomes from diffuse large B cell lymphoma (DLBCL) cells could enhance the proliferation and angiogenesis of endothelial cells and stimulate the expression of matrix metalloproteinase 2 (MMP2) and

Table 1
The role of exosomal shuttle RNA in the lymphoma.

RNA	Target	Method	Notes	Reference
Pathogenesis				
Tax mRNA	–	qPCR	Induce the activation of NF-κB pathway in the MSC	El-Saghir et al. (2016)
BART miRNAs	ARG1, RILP, MEF2C, CD1c	qPCR	Transferred from EBV-infected cells to the non-infected cells by exosomes to regulate the function for the tumorigenesis in EBV-associated lymphoma	Higuchi et al. (2018)
miR155-5p, miR21-5p, Let7a-5p, miR127-3p, miR24-3p	–	qPCR	Overexpression in plasma exosomes of cHL	van Eijndhoven et al. (2016)
KSHV-miR-K12-11	IKKε	qPCR	Inhibit the host anti-viral immunity	Rainy et al. (2016)
Diagnosis				
miR155-5p, miR21-5p, Let7a-5p, miR127-3p, miR24-3p	–	qPCR	Expression in the HL plasma exosomes upregulated	van Eijndhoven et al. (2016)
BART miRNAs	–	qPCR	Overexpression in the EBV-associated lymphoma.	Higuchi et al. (2018)
Prognosis				
BART 13 miRNAs	–	qPCR	High levels correlate with better OS in elderly patients with EBV positive DLBCL	Higuchi et al. (2018)
MYC mRNA	–	RT-PCR	High expression correlate with worse PFS and OS in B cell lymphoma	Provencio et al. (2017)
BCL-6 mRNA	–	RT-PCR	High expression correlate with worse OS in B cell lymphoma	Provencio et al. (2017)
PTEN mRNA	–	RT-PCR	High expression correlate with better PTEN in B cell lymphoma	Provencio et al. (2017)
miR-99a-5p, miR-125b-5p	–	qPCR	High levels correlate with worse PFS in DLBCL patients	Feng et al. (2018)
Drug resistance				
miR-99a-5p, miR-125b-5p	–	qPCR	High levels correlate with chemoresistance in DLBCL patients	Feng et al. (2018)
BCL-6 mRNA	–	RT-PCR	Increased level in patients correlates with non-response to rituximab-based chemotherapy	Provencio et al. (2017)

MSC: mesenchymal cell; RG1: arginase1; RT-PCR: reverse transcription-polymerase chain reaction; cHL: classical Hodgkin lymphoma; KSHV: Kaposi's sarcoma-associated herpesvirus; BART 13 miRNAs: BamHI fragment A rightward transcript 13 micro-RNAs; OS: overall survival; PFS: progression-free survival.

MMP9 to facilitate invasion (Fig. 1). The above results indicate that lymphoma derived exosomes can reshape the extracellular matrix toward a microenvironmental niche which is favorable to the tumor growth and spread.

Lymphoma derived exosomes could also reprogram the bone marrow environment and cause tumor progression. Adult T-cell lymphoma/leukemia (ATLL) cells derived exosomes could transfer *Tax* mRNA to the mesenchymal stem cells (MSCs) to activate the NF-κB pathway and promote tumor proliferation, progression and angiogenesis (El-Saghir et al., 2016) (Fig. 1). Another study confirmed the presence of lymphoma derived exosomes in the bone marrow aspirates and these exosomes could reprogram bone marrow by activating pro-inflammatory signaling in mast cells and macrophages to induce cytokine expression (Mancek-Keber et al., 2018). Understanding the role of exosomes in bone marrow invasion will be beneficial to develop new drug.

6.3. EsRNA inhibits the immune response and interferes with the immunotherapy against lymphoma

Previous investigations have indicated that lymphoma derived exosomes are involved in the immune dysfunction, and thereby cause tumor progression (Higuchi et al., 2018; Rainy et al., 2016). Higuchi et al. (2018) demonstrated that exosomal EBV-coding RNAs from Akata-lymphoblastoid cells could transform the monocytes into the immune regulatory phenotype by regulating the gene expression of interleukin 10 (IL-10), tumor necrosis factor-α (TNF-α), and arginase1. Kaposi's sarcoma herpesvirus (KSHV) infected lymphoma cells could deliver exosomal KSHV-miR-K12-11 to the acceptor T cells in vitro and inhibit anti-viral immunity by regulating the transcription of target mRNAs (Rainy et al., 2016) (Table 1, Fig. 1).

Lymphoma derived **e**xosomes could also interfere with the immunotherapy and compromise therapeutic efficacy. Extracellular vesicles from blood cancer cells could express tumor associated antigens in a different degree, such as CD19 and CD20 in B-cell neoplasms, CD38 in multiple myeloma, and CD30 in HL (Caivano et al., 2015; Oksvold et al., 2014; Aung et al., 2011). It has been shown that plasma exosomes from B-cell lymphoma cells carried CD20 and bound therapeutic anti-CD20 antibodies, consumed complement, and thereby protected lymphoma cells against immunotherapy (Oksvold et al., 2014; Aung et al., 2011). These findings suggest that the lymphoma derived exosomes may reduce the effectiveness of immunotherapy against tumor-related antigens and cause treatment failure.

6.4. EsRNA serves as diagnostic and prognostic biomarker in lymphoma

Some properties of exosomes make them candidates as diagnostic biomarker in various diseases. Firstly, exosomes could be easily extracted from different fluids of patients, including plasma (Caby et al., 2005), urine (Street et al., 2017), breast milk (Qin et al., 2016), bronchoalveolar lavage fluid (BALF) (Admyre et al., 2003), saliva (Ogawa et al., 2011), and nasal secretions (NAL) (Lasser et al., 2011b). Secondly, compared with healthy population, the level of exosomes was detected to be much higher in the serum of various tumors, including lymphoma (Taylor and Gercel-Taylor, 2008; van Eijndhoven et al., 2016; Duijvesz et al., 2011). Thirdly, tumor-derived exosomal miRNA could reflect the miRNA profile in tumor tissue and the tumor-related miRNA was frequently upregulated in the exosomes (Taylor and Gercel-Taylor, 2008). Furthermore, some lymphoma exosomes express lymphoma-associated antigen, such as CD19 in B cell neoplasms, CD38 in MM and CD30 in Hodgkin's lymphoma (HL), making them specific biomarker for these cancers (Caivano et al., 2015). Shuttle RNAs were demonstrated to be excellent diagnostic biomarkers in lymphoma. The level of miRNAs in plasma extracellular vesicles (EVs) corresponded with the FDG-PET (positron emission tomography) status, indicating that lymphoma related miRNA levels in plasma EVs represent the tumor load and are potential biomarkers for monitoring therapy response in patients with Hodgkin lymphoma (van Eijndhoven et al., 2016). In addition, exosomal miRNAs could serve as biomarker for chemotherapy resistance in diffuse large B cell lymphoma as the expression level of some miRNAs in chemoresistant DLBCL cells-derived exosomes differs substantially from the parental cells, with 37 significantly upregulated and 17 downregulated (Feng et al., 2018). DLBCL patients with significantly high levels of miR-99a-5p and miR-125b-5p in the plasma exosomes had shorter progression-free survival time (PFS), suggesting that they may be predictors of chemotherapeutic efficacy (Feng et al., 2018) (Table 1).

Messenger RNA in plasma exosomes has been demonstrated to be a potential liquid biopsy method in non-Hodgkin Lymphoma patients (Provencio et al., 2017). Six studied mRNAs were identified in exosomes from B cell lymphoma patients with different proportions: 3% for *AKT*, 8% for *NK-κB*, 9% for *MYC*, 16% for *BCL-XL*, 25% for *PTEN* and 34% for *BCL-6*. The presence of *MYC* mRNA in the plasma exosomes from pretreatment patients was a predictor of adverse clinical outcome and poor response to the first-line therapy. Moreover, *BCL-6* mRNA and *PTEN* mRNA were also associated with the survival outcome (Provencio et al., 2017) (Table 1).

In addition, lncRNA are also enriched in exosomes and have proven to be potential biomarkers in many tumors, such as prostate cancer (Isin et al., 2015), colorectal cancer (Liu et al., 2016a), hepatocellular carcinoma (HCC) (Hou et al., 2018), and bladder cancer (Zhan et al., 2018). Several studies indicated that abundant circular RNAs present in exosomes are stable and may be promising biomarkers in cancer (Li et al., 2018b,c,d, 2015). The role of lncRNAs and cirRNAs as biomarkers in lymphoma has not been explored yet.

6.5. EsRNA mediate drug resistance

Chemoresistance is one of the most important mechanisms for treatment failure in cancer. Tumor derived exosomes could transfer drug resistance between cancer cells and have attracted large research attention. Delivery of exosomal miRNAs to cancer cells has proven to increase drug resistance in different cancers (Qin et al., 2017). The low expression level of serum exosomal miR-146a-5p was associated with high recurrence rates in lung cancer as miR-146a-5p could increase the chemosensitivity of cancer cells to cisplatin through inhibition of autophagy (Yuwen et al., 2017). The increased exosomal miR-155 level was demonstrated to induce gemcitabine resistance via promoting anti-apoptotic activity in pancreatic ductal adenocarcinoma (Mikamori et al., 2017). Several signaling pathways such as PI3K/AKT/MTOR were involved in cancer metastasis and drug resistance (Liu et al., 2016b). A study showed that exosomal shuttle miRNAs could alter target gene expression to modulate cell cycle and activate related pathways involved in tumorigenesis and lead to drug resistance in breast cancer (Chen et al., 2014). The downregulated level of miR-100-5p in exosomes from cisplatin-resistant A549 cells was associated with drug resistance and the mammalian target of rapamycin (MTOR) was the potential target (Qin et al., 2017). A recent study demonstrated that exosomal miR-21 from tumor-associated macrophages induced cisplatin resistance in gastric cancer cells by targeting PTEN, which was known as a PI3K inhibitor (Zheng et al., 2017). P-glycoprotein (P-gp) could mediate specific drug efflux from cancer cells and contribute to chemoresistance in some malignancies such as breast cancer and NK/T cell lymphoma (Lv et al., 2014; Drenou et al., 1997). Synthetic anti-miR-9 carried by mesenchymal stem cell derived exosomes was transmitted to glioblastoma cells and successfully overcame the chemoresistance via the inhibition of P-gp and achieved good efficacy (Munoz et al., 2013). Only few studies have demonstrated the role of exosomal miRNAs in chemoresistance in hematologic malignancies to date (Feng et al., 2018; Wang et al., 2014). Feng et al. (2018) found that miR-99a-5p and miR-125b-5p significantly upregulated in the exosomes of chemoresistant DLBCL cells were predictors for prognosis and

chemotherapy efficacy in DLBCL (Table 1). From the above, exosomal miRNA may induce lymphoma chemoresistance through the following mechanisms: (i) regulating the autophagy and apoptosis of cancer cells; (ii) interrupting associated signal pathways such as PI3K/AKT/MTOR; (iii) inhibiting the ATP binding cassette (ABC) transporter, such as P-glycoprotein. (iv) targeting genes to modulate cell cycle. In addition, *MYC* mRNA in the exosomes from pretreatment patients with B cell lymphoma was associated with poor response to the first-line therapy, indicating that exosomal *MYC* mRNA was crucial for the drug resistance (Provencio et al., 2017).

Although the role of exosomal lncRNA has not been investigated in lymphoma, increasing evidences indicated that exosomal lncRNAs and mRNAs mediated drug resistance in various cancers. The function of lncRNAs in cancer chemoresistance could be ascribed to the alteration of drug transporters leading to efflux of anticancer agents, the suppression of miRNA to promote expressions of oncogenes, modification of autophagy/apoptosis to enhance survival, activation of associated signal pathways and inhibition of apoptosis (Qu et al., 2016; Dong et al., 2018; Kang et al., 2018; Takahashi et al., 2014a,b).

6.6. Gene delivery vehicles

Based on the fact that exosomes could transfer gene materials such as esRNAs between different cells, exosomes may be potential gene therapy vehicles in various diseases. It has been found that many exosomal miRNAs, mRNAs, lncRNAs and cirRNA are involved in tumorigenesis, tumor metastasis and drug resistance (Fang et al., 2018; Li et al., 2018c,d,f; Dong et al., 2018; Zhang et al., 2018; Zhou et al., 2014). Some studies have verified the role of exosomes as gene therapy vectors in vitro and in vivo. According to the result from Oxford university, therapeutic siRNA-loaded exosomes could knock down the *BACE1* gene in the brain of mouse and reduce the level of *BACE1*, which was associated with Alzheimer's disease (Alvarez-Erviti et al., 2011). Recently, a study demonstrated that stellate cell-derived exosomes loaded with miR-335-5p could inhibit tumor growth, invasion, promote tumor cell apoptosis, and successfully induce the shrink of hepatocellular carcinoma, indicating that exosomes loaded with therapeutic miRNA may be effective in cancer treatment (Wang et al., 2018). Another study showed that exosomal lncRNA PTENP1, which downregulated in bladder cancer tissues and the plasma exosomes in patients with bladder cancer, could be transferred from normal cells to bladder cancer cells, and decreased the ability of cancer proliferation and invasion (Zheng et al., 2018). Exosomal mRNAs could exert anticancer functions through inhibiting the genes associated with tumor development (Mao et al., 2018). Although the therapeutical effect of esRNA has not been investigated in lymphoma yet, the exosomal RNA may be exploited as anti-lymphoma treatment through the following methods. On the one hand, siRNA, miRNA, mRNA and lncRNAs with tumor-suppressor activity could be loaded into exosomes and transferred to target cells to play an anti-lymphoma role. On the other hand, we could interrupt the process of the internalization of RNA into exosomes, especially those involved in cancer metastasis and drug resistance. Furthermore, the interference of the interaction between the tumor derived exosomal shuttle RNA and recepient cells may also be a good strategy. In addition, the eradication of exosomes which promote tumor development will also reduce the effects of esRNA in cancer. However, there are several challenges we should face. Firstly, in order to produce largest anti-cancer therapeutic efficacy with minimal side effects, the delivery of esRNA to cancer cells must be relatively specific. Secondly, the concrete mechanism of the sorting of RNA into exosomes remains unclear, making it difficult to develop new drugs. Thirdly, tumor derived exosomes could not be separated from normal cell exosomes as they lack specific markers.

7. Conclusion

Exosomes are a new means of intercellular communication which can exchange functional information between different cells. As nano-sized biological vesicles, exosomes protect the ribonucleic acid (RNA) against degradation in body fluid. RNA delivery via exosomes contribute to the exchange of genetic material between different cells and produce a profound biological effect on the recipient cells. Tumor derived exosomes enriched in the plasma provide a new insight into the pathogenesis and progression of lymphoma. We discussed the mechanisms of esRNA sorting, exosome internalization and esRNA transfer, and the function of esRNA in the recipient cells, which aids understanding of the shuttle RNA from lymphoma cells to other cells. Furthermore, the role of esRNA in the tumorigenesis, progression, and chemoresistance in lymphoma has also been demonstrated. In addition, the abundant tumor derived exosomes and esRNA may be excellent candidates as diagnostic and prognostic biomarkers in lymphoma. The prospect of using exosomes as vehicles to deliver therapeutic RNAi may be a new treatment strategy for some refractory/relapsed lymphoma patients. However, the study of esRNA in lymphoma is just in its infancy, efforts are required to gain a further understanding of its exact function. On the one hand, studies to elucidate the mechanism of specific esRNA biogenesis should continue; On the other hand, other shuttle RNA in exosomes such as lncRNA and cirRNA may also mediate various pathological processes in lymphoma and require further investigation in the future. With the in-depth study, we believe that significant progress will be achieved to better understand the biogenesis, regulation and function of esRNA in lymphoma.

Conflict of interest

None declared.

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