Critical Reviews in Oncology / Hematology 144 (2019) 102825

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

The opportunistic effect of exosomes on Non-Hodgkin Lymphoma microenvironment modulation

Mara Fernandes[a,b,c], Ana Luísa Teixeira[a], Rui Medeiros[a,b,c,d,*]

[a] Molecular Oncology and Viral Pathology Group, IPO-Porto Research Center (CI-IPOP), Portuguese Oncology Institute of Porto (IPO-Porto), Rua Dr António Bernardino de Almeida, 4200-072 Porto, Portugal
[b] Faculty of Medicine, University of Porto (FMUP), Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal
[c] Research Department, LPCC-Portuguese League against Cancer- Northern Branch (Liga Portuguesa Contra o Cancro-Núcleo Regional do Norte), Estrada Interior da Circunvalação 6657, 4200-172 Porto, Portugal
[d] CEBIMED, Faculty of Health Sciences, Fernando Pessoa University, Praça de 9 de Abril 349, 4249-004 Porto, Portugal

ARTICLE INFO

Keywords:
Non-Hodgkin Lymphoma
Lymphomagenesis
Microenvironment
Cell communication
Exosome

ABSTRACT

There has been a shift in the paradigm of Non-Hodgkin lymphomas, changing from the classical genetic aberration-based model to a more complex and dynamic model involving tumor microenvironment interactions. In this instance, exosomes have emerged as important mediators in intercellular communication by providing survival and proliferation signals, licensing immune evasion and acquisition of drug resistance. The capability to transfer molecular cargo made exosomes a focus of research to understand cancer pathogenesis and its progression pathways. Several studies identified exosomes transporting tumor-released components in peripheral blood and focused on understanding their clinical relevance in the diagnosis, prognostic and in monitoring cancer progression. Moreover, due to their biophysical properties and physiological function, exosomes have drawn attention as potential therapeutic target and drug delivery vehicles. This review will discuss the function of exosomes in Non-Hodgkin lymphomagenesis, highlight their potential as diagnosis and prognosis biomarkers, and as new therapeutic opportunities in lymphoma management.

1. Introduction

Lymphomas are a heterogeneous group of clonal neoplasms, characterized by infiltration of lymphoid tissues. They can arise from B and T lymphocytes, and natural killer (NK) cells, at different stages of differentiation (Swerdlow et al., 2016). In the latest World Health Organization (WHO) lymphomas classification, more than 80 lymphoma subtypes were categorized, according to morphology, immunophenotype, genetic alterations and clinical findings (Swerdlow et al., 2016). Moreover, the majority of lymphoma cases are B-cell lymphomas, which overall, are divided into Hodgkin's lymphoma (accounting for ~10 %) and non-Hodgkin lymphoma (NHL) (Elenitoba-Johnson and Lim, 2018). In the past years, diverse studies have focused on uncover the risk factors associated with the development of NHL. These factors include autoimmune disorders (rheumatoid arthritis, Sjögren syndrome, and systemic lupus erythematosus), infections (Helicobacter pylori, Epstein-Barr virus, Hepatitis C virus), obesity, genetics, ethnicity, family history and occupational factors (Cerhan et al., 2014; Fallah et al., 2014; Anderson et al., 2014).

Concerning the management of NHL, the recognition that the addition of rituximab to an anthracycline-containing chemotherapy regimen (cyclophosphamide, doxorubicin, vincristine, prednisone – R-CHOP) significantly improves treatment outcomes, was a major turning point (Armitage et al., 2017). However, despite the substantial percentage of patients who achieves durable remissions after R-CHOP treatment, this current standard of care is still associated with substantial toxicity and, more importantly, one-third of patients presents refractory disease or relapsed in the first 2–3 years after treatment (Roschewski et al., 2013; Larouche et al., 2010). Moreover, patients with relapsed or refractory disease often develop chemotherapy resistance and the ones that remain sensitive undergo high-dose chemotherapy followed by autologous stem cell transplantation (ASCT), but the success rate is still reduced (Roschewski et al., 2014). Therefore, there is an imperative need to broaden our knowledge about this pathology in order to enhance the ability to predict the efficacy, response rate, and safety of a selected drug. The inclusion of additional

* Corresponding author at: Molecular Oncology and Viral Pathology Group, IPO-Porto Research Center (CI-IPOP), Portuguese Oncology Institute of Porto (IPO-Porto), Rua Dr. António Bernardino de Almeida, 4200-072 Porto, Portugal.
E-mail address: ruimedei@ipoporto.min-saude.pt (R. Medeiros).

https://doi.org/10.1016/j.critrevonc.2019.102825
Received 24 August 2019; Received in revised form 20 October 2019; Accepted 22 October 2019

prognostic markers based on the biology of lymphoma and the development of novel treatment approaches are an imperative clinical need (Espirito Santo and Medeiros, 2013; Li et al., 2017a; Paiva et al., 2008).

In fact, recently our understanding of the complex biology of NHL has greatly improved. Not only NHL is considered a paradigm of translocation-based tumors, particularly B-cell NHL, but also, now it is established the role of tumor microenvironment (TME) in the acquisition of key characteristics that allow cancer development, progression and drug resistance development (Hanahan and Weinberg, 2011; Scott and Gascoyne, 2014). TME is highly diversify and dynamic, being composed by immune cells, stromal cells, blood vessels and extracellular matrix (Tarte, 2017).

The cell–cell contact-dependent mechanisms and/or soluble messengers have been long ago established as forms by which tumor cells can communicate and modulate TME composition (Ungefroren et al., 2011). Recently, a new system of cell communication was described involving transfer of information via extracellular vesicles (EVs) (Bebelman et al., 2018). EVs are involved in short and long-distance delivery of cellular contents, and their structure prevents cargo's destruction and it is essential to direct the horizontal information transfer (Maas et al., 2017). EVs consist of a heterogeneous group of lipid bilayer particles, which size can range from 15 nm to 10 microns and they are virtually released by all cell types (normal and tumor). Depending on their size they can be classified into exosomes, microvesicles (ectosomes), microparticles and oncosomes (Maas et al., 2017). Several studies have been shedding light on how EVs shape cell function. Recently it has been demonstrated that EVs are involved in the compartmental regulation of hematopoiesis in the bone marrow (BM) (Hornick et al., 2016; Kumar et al., 2018).

Particularly, the interest in circulating exosomes has been continuously increasing in the past few years. Since these entities can be detected in a variety of biological fluids and carry variable cellular constituents (proteins, nucleic acids and lipids), they represent a promising strategy to use as potential biomarkers with diagnostic and prognostic relevance, holding the potential to be used as cancer liquid biopsy (Halvaei et al., 2018). For example, studies showed that exosomes carry genomic DNA (exoDNA) as double-stranded DNA which reflects the mutational status of the derived cancer cells (Möhrmann et al., 2018). Driver mutations in *KRAS* and *TP53* were detected in exoDNA fragments in patients with pancreatic cancer (Yang et al., 2017; Katz et al., 2017). In another study involving the analysis of urinary exosomes from bladder cancer patients, were identified somatic mutations and copy number variations in exoDNA with similar pattern to those observed in the tumor tissue, underlining exoDNA as an useful source of information on genomic alterations in the tumor (Lee et al., 2018).Therefore, the better understanding of the interplay between lymphoma cells and their microenvironment is crucial to comprehend not only the differences observed between the pathogenesis and prognosis of NHL subtypes, but also has the potential as new therapeutic targets and/or exosome-based cancer therapy.

The focus of this review is to discuss recent advances in the field of exosomes as players in NHL development and uncover their role in the crosstalk tumor-TME, development of drug resistance, as well as their potential use as biomarkers and therapeutic opportunities.

2. Biogenesis and properties of exosomes

Contrary to the biogenesis of larger microvesicles, exosome's biogenesis initiates with the inward budding of endosomal membrane given rise to multivesicular bodies (MVBs), characterized by the accumulation of multiple small intraluminal vesicles (ILVs) (Colombo et al., 2014). Next, MVBs cargo is sorted during maturation, where some of the formed MVBs are directed to lysosomal degradation, while the remaining can dock and fuse with the plasma membrane, resulting in the release of ILVs into the extracellular milieu, after which they are called exosomes (Fig. 1) (Samanta et al., 2017). The ubiquitinated proteins present in ILVs are sorted by the endosomal sorting complexes required for transport (ESCRT) machinery (Fig. 1A) (Stoorvogel, 2015). The ESCRT machinery consists of four different complexes ESCRT-0, -I, -II, -III, together with the AAA ATPase vacuolar protein-associated sorting 4 (VPS4) complex (Christ et al., 2017). A study developed by Baietti et al. disclosed a little more about the role of ESCRTs in exosome biogenesis, by showing that syntenin interacts with ALIX, an ESCRT-III-binding protein, mediating the budding process and the production of exosomes (Baietti et al., 2012a). Moreover, syntenin-ALIX exosome pathway is responsible for mediating the sorting of syndecans into exosomes through their binding to syntenin (Baietti et al., 2012a). Vesicular transport and sorting can also be regulated by ESCRT-independent pathway which is less understood. Some authors showed that lipids are also involved in these processes, such as sphingosine-1-phosphate and ceramide, tetraspanin-enriched microdomains and sphingomyelinase (Bissig and Gruenberg, 2013). Trajkovic et al. showed that inhibition of neutral sphingomyelinase 2 (nSMase2), an enzyme involved in ceramide production, reduced exosomal release of proteolipid protein (PLP) and EGFP-CD63 from Oli-neu cells and EGFP-CD63-transfected PC-3 cells, respectively (Trajkovic et al., 2008). Moreover, phospholipase D2 (PLD2), an enzyme involved in phosphatidic acid (PA) production from phospholipids, was shown to function as an effector of small GTPase ADP ribosylation factor 6 (ARF6), in syntenin-ALIX exosome biogenesis and budding into MVs (Ghossoub et al., 2014).

Exosome secretion is an oriented process, however the specific molecular motors involved are still unknown. MVBs anchorage and fusion to the cell membrane seem to be mediated by RAB-GTPase family (such as Rab27 and Rab35), as well as their trafficking within the cell (Fig. 1B) (Ostrowski et al., 2010; Hsu et al., 2010). Proteins such as Rab27b and Rab27, synaptotagmin-like 4 and exophilin 5 are involved in the regulation of MVBs' docking at the plasma membrane (Ostrowski et al., 2010). Interestingly, RAB7 seems to be not only involved in targeting MVEs to lysosomes but also to be essential to exosome release (Baietti et al., 2012b; Rocha et al., 2009). This dual function is apparently mediated by the ubiquitylation status of RAB7 (Song et al., 2016). Some studies showed that SNARE proteins (soluble NSF attachment receptor) and synaptotagmin family members are apparently also involved in the process of MVEs fusion with the plasma membrane to release ILVs as exosomes (van den Bogaart and Jahn, 2011). Moreover, Ca^{2+} may have a regulatory role in the activation of the SNARE complexes leading to exosome secretion (Savina et al., 2005; Messenger et al., 2018).

Despite the diverse studies focusing in uncovering the molecular components of exosome biogenesis, the detailed mechanism needs to be further studied. For example, Mazzeo and colleagues observed that PKD1/2 regulates MVBs maturation and exosome secretion, by functioning as major effector of DGKα in the regulation of MVBs secretory traffic in T and B cells (Mazzeo et al., 2016).

Proteomic studies showed that secreted exosomes display a selective assemblage of membrane components such as cell surface receptors, antigen presentation proteins and major histocompatibility complex (MHC) and tetraspanins (CD63, CD81, CD9, and CD82) (Mathivanan et al., 2010; Colombo et al., 2013; van Niel et al., 2011).

The process of exosome biogenesis is extremely complex and there is still a lot to uncover. It is important to understand that this process can vary depending on the cell type and cargo and can be modulated by the different stimuli that the cell receives. Therefore, depending on the context, different machineries and sorting mechanisms can act concomitantly or sequentially on producing heterogeneous populations of ILVs and exosomes (Colombo et al., 2014; Lo Cicero et al., 2015).

After the release into the extracellular space, exosomes can act locally by altering the behavior of neighboring cells or enter in circulation and act at distant anatomic sites (Xu et al., 2018). After docking over plasma membrane of target cells, exosomes can promote functional responses and phenotypic changes in different ways. Exosomes can

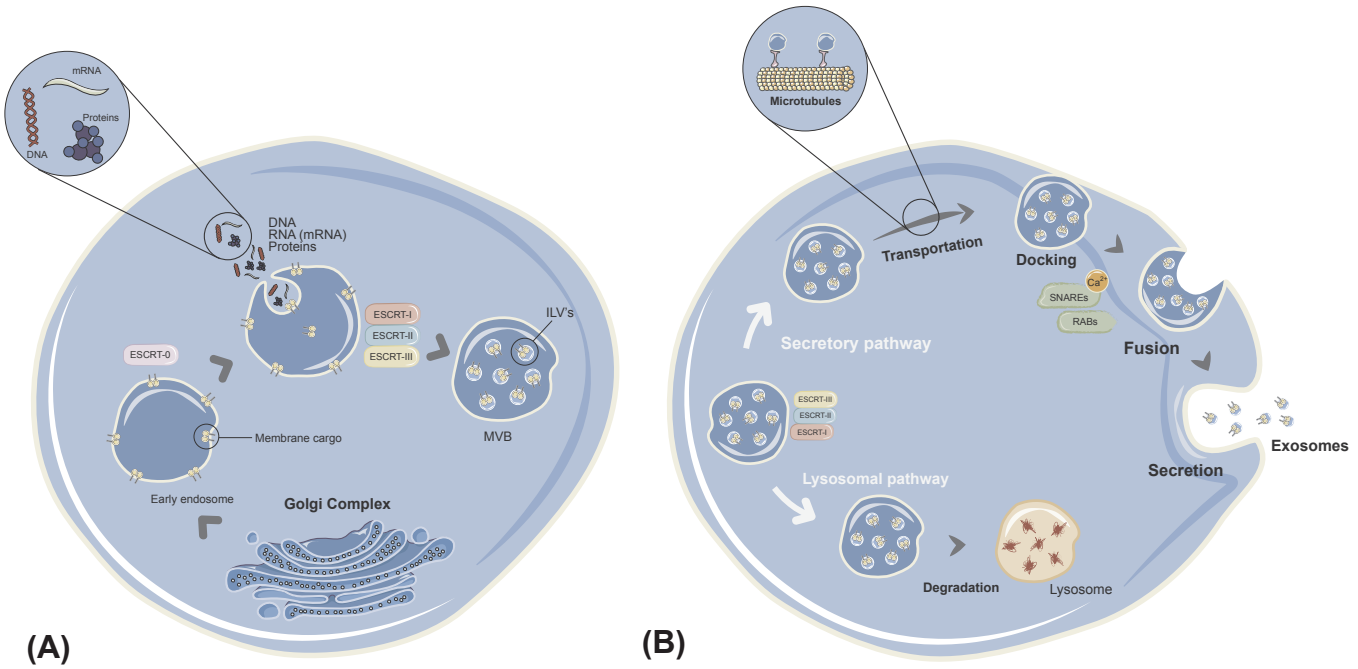

Fig. 1. Exosomes biogenesis pathway. (A) MVBs are originated by inward budding of endosomal membrane followed by accumulation of multiple ILVs. During maturation, selected protein are sorted to ILVs by ESCRT machinery, consisting of four different complexes ESCRT-0, -I, -II, -III. Ubiquitinated transmembrane proteins are recognized and sequestered in the endosomal membrane by ESCRT-0. ESCRT-I, ESCRT-II and ESCRT-III recognize and bind to the ubiquitinated cargo proteins driving membrane deformation into buds and subsequent vesicle scission. During the reverse budding, cytosolic DNA, RNAs and proteins are loaded into the interior of the forming vesicles. (B) MVBs can then follow the secretory or the lysosomal pathway where ILVs undergo lysosomal degradation. In the secretory route, MVBs are transported to the cell membrane, through the microtubules, where they dock and fuse with plasma membrane, and consequently releasing the ILVs into the extracellular milieu (now termed exosomes). The MVBs anchorage and fusion seems to be mediated by the activation of by RAB-GTPase family and SNARE complexes, leading to exosome secretion.

directly stimulate cell surface receptors of recipient cells as shown by exosomes derived from B cells and dendritic cells, which induce specific antigenic response by presenting antigens to T cells (Raposo et al., 1996; Zitvogel et al., 1998). Moreover, exosomes may directly fuse with plasma membrane or be endocytosed by the recipient cells, resulting in the release of intraluminal content in the cell cytoplasm. Some of the mediators involved in this process have been already identified including SNAREs, Rab proteins, SM-proteins, and several proton pumps (McKelvey et al., 2015). Additionally, exosome uptake by the recipient cells is dependent of sphingolipid- and cholesterol-enriched microdomains present in the plasma membrane known as lipid rafts (Simons and Vaz, 2004). When the integrity of these microdomains is disrupted by the depletion of plasma membrane cholesterol, cellular exosome uptake is inhibited (Svensson et al., 2013). A study by Vardaki et al. demonstrated that Bcl-xL present in stroma exosomes is a caspase-3 substrate and that its cleaved form is required for exosomes' uptake by myeloma and lymphoma cells, which in turn results in their increased proliferation (Vardaki et al., 2016).

These processes enable the direct exchange of proteins and lipids which can activate diverse responses and processes in target cells. For instance, bladder cancer–derived exosomes can transfer TGFβ to fibroblasts and induce SMAD pathway activation, triggering their differentiation into cancer-associated fibroblasts (CAFs) (Ringuette Goulet et al., 2018). Exosomes not only display an unique lipid membrane composition, but also can function as lipid carriers by transporting diverse lipid species including eicosanoids, fatty acids and cholesterol, as well as lipid related enzymes, therefore contributing to the regulation of various bioactive lipids (Record et al., 2014; Skotland et al., 2017). Additionally, the most fascinating aspect of exosome's cargo is their ability to transfer genetic information and induce epigenetic changes. Exosomes protect nucleic acids such as DNA, miRNA, other non-coding RNAs and mRNA, from extracellular degrading enzymes, and modulate the function of the recipient cells (Balaj et al., 2011; Valadi et al., 2007; Kalluri and LeBleu, 2016). For example, recent studies have reported that exoDNA not only can be transfer to recipient cells but apparently has pathophysiological significance. ExoDNA localized to and enter the nuclear membrane where increases the coding mRNA and protein levels in the recipient cells (Cai et al., 2015). When in the nucleus, exoDNA seems to recruit and combine with transcription factors, initiating its transcription (Cai et al., 2013; Chen et al., 2013). Moreover, the transferred DNA was reported to have pathophysiological implications *in vitro* and *in vivo*. Normal neutrophils begin to express BCR/ABL, involved in the pathogenesis of chronic myeloid leukemia (CML), after incubation with CML cell line K562 EVs, resulting in their decreased phagocytic activity *in vitro* (Chen et al., 2013). An *in vivo* study supported the previous results by inducing CML characteristics in mice after injection of K562 EVs carrying BCR/ABL hybrid gene (Cai et al., 2014). Transfer of exosomal RNAs, such as miRNAs, was shown to have a central role in the regulation of relevant biologic processes on the recipient cells. The internalization of exosomal miRNAs can induce phenotypic changes and modulate the activity of the recipient cells by regulating their mRNA and protein expression (Higuchi et al., 2018; Fang et al., 2018). Bayraktar et al. gives an interesting point of view by describing exosome-derived miRNAs as hormones given their ability to reach distant target cells and influence their behavior (Bayraktar et al., 2017). Depending on their targets, miRNAs can play oncogenic or oncosuppressor functions. Interestingly, tumor cells seem to exploit exosomes to shuttle oncogenic miRNAs that promote angiogenesis, induce epithelial mesenchymal transition and immune evasion; or to extrude tumor suppressor miRNAs, leading to the expression of cellular oncogenes (Pucci et al., 2018). In fact, exosomal miRNAs were proven to play a role during NHL lymphomagenesis, lymphoma progression and metastization and the development of chemoresistance (Li et al., 2019). For instance, exosomal miRNAs-derived from lymphoma cells can

induce the immune regulatory phenotype in macrophage by enhancing the expression of immune mediator factors, essential to the formation of an inflammatory niche (Higuchi et al., 2018; Li et al., 2019).

Therefore, it has been long gone the idea that exosomes are mere cellular garbage disposals, being now recognized as important players in intercellular communications, not only in normal physiological processes, like inflammation, cell proliferation and immune response, but also, implicated in the pathogenesis and progression of diseases such as cancer (Dalvi et al., 2017; Osada-Oka et al., 2016; La Shu et al., 2018; Li et al., 2018).

3. Microenvironment and Tumor crosstalk mediated by exosomes

Over the past decade, it has been established that tumor-derived exosomes influence non-neoplastic cells to support tumor initiation, progression and drug resistance, creating a permissive TME for tumor growth and metastasis establishment.

One of the main obstacles to tumor progression and metastasis formation is created by immune system surveillance. Briefly, cytotoxic T lymphocytes (CTL) and NK cells are recruited to tumor site where they undergo phenotypic and functional changes being redirected to a pro-tumoral activity through the expression of various immune mediators and modulators, in order to facilitate tumor invasion, spreading, and angiogenesis (Grivennikov et al., 2010). Therefore, the communication network designed to evade antitumor immune responses is essential for cancer development.

Actually, exosomes play a central role as important mediators of tumor immune escaping (Fig. 2). The presence of MHC class I and II proteins on exosomes' surface from B lymphocytes has been already extensively characterized in multiple studies, proving the antitumor activity of immune cells-derived exosomes (Lindenbergh and Stoorvogel, 2018). Klinker et al. reported that human B cell-derived lymphoblastoid cell lines induce antigen-specific apoptosis in autologous $CD4^+$ T cells by constitutively producing $MHCII^+FasL^+$ exosomes (Klinker et al., 2014). On the other hand, researchers are now focusing on how immune-modulating exosomes released from tumor cells support cancer development and progression. A study showed that T- and B cell leukemia/lymphoma constitutively express mRNA and protein NKG2D ligands (such as MICA/B and ULBP 1 and 2), which are then secreted via exosomes. NKG2D ligand-bearing exosomes seem to act as decoy through downregulation of the NKG2D receptor-mediated cytotoxicity, ultimately impairing NK-cell activity and facilitating the immune evasion of leukemia/lymphoma cells (Hedlund et al., 2011). Furthermore, another mechanism of exploiting the exosome pathway to modulate the activity of immune cells, particularly based on the induction of inhibitory B cells, was shown in Yang et al. work where exosomes released by melanoma and lymphoma cells promoted IL-10 expression in splenic B cells. In turn, the production of IL-10 promoted regulatory B cells and subsequent inhibition of T cell proliferation and TCR signaling (Yang et al., 2012). A study by Bohana-Kashtan et al. also demonstrated that B-lymphoma cells evade complement-mediated lysis through the phosphorylation of complement C9 by exosomal kinase casein kinase 2 (CK2) (Bohana-Kashtan et al., 2005). In chronic lymphocytic leukemia (CLL), tumor-derived exosomes trigger CLL-associated phenotypes in recipient monocytes by inducing cytokines release, such as C-C motif chemokine ligand 2 (CCL2), CCL4, and IL-6, and the expression of PD-L1, suggesting an exosome-related inflammation and concurrent immune escape (Haderk et al., 2017).

Recent research has provided insights into how chemotherapy-exposed cells exploit exosomes to alter their microenvironment and

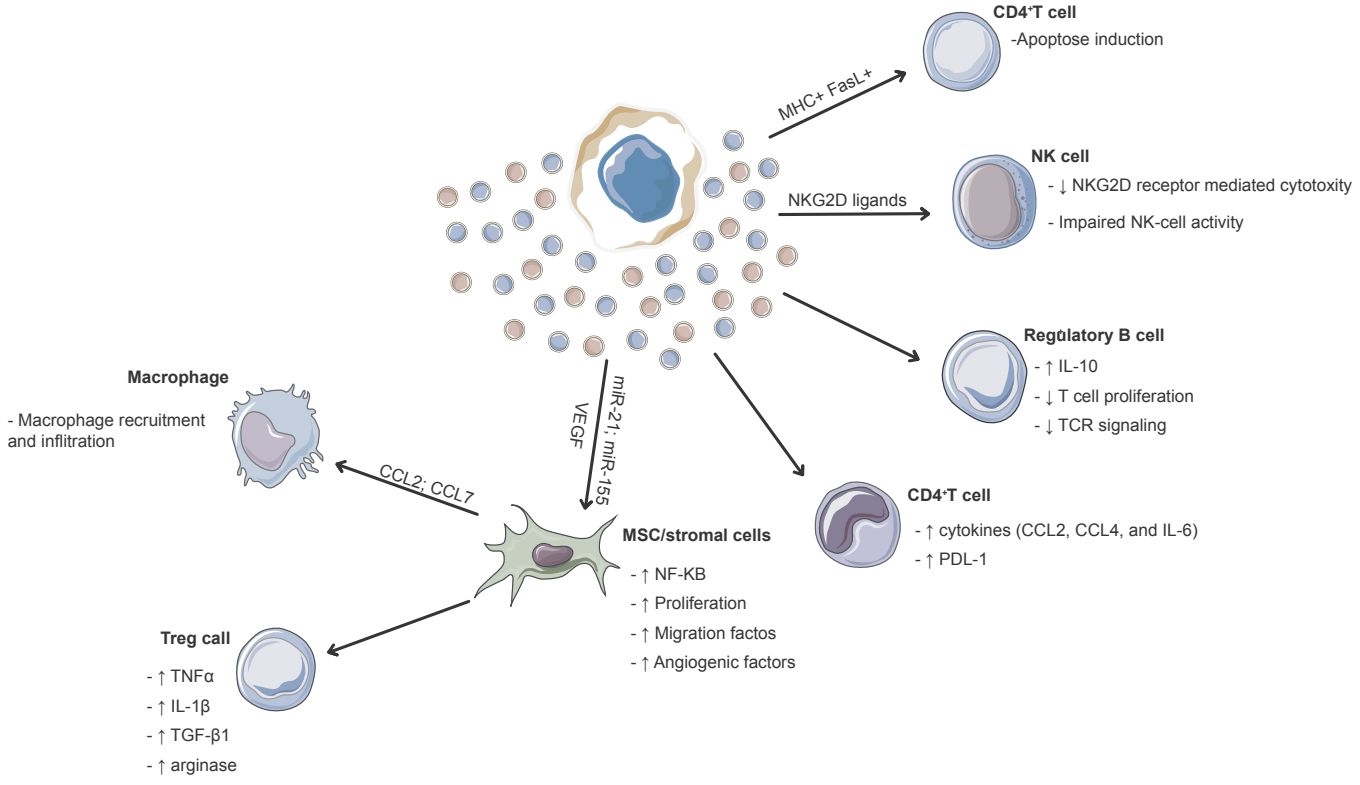

Fig. 2. Cross-talk between cancer cells and non-neoplastic cells via exosome release. Cancer cells can modulate surrounding and distant normal cells to create a immunosuppressive milieu and further promote tumor progression and metastasis. Tumor exosomes bearing imune-mediating factors can induce antigen-specific apoptosis in CD4 + T cells or even downregulate NK-cell cytotoxicity, therefore facilitating immune evasion. The induction of IL-10 production in splenic B cells promotes regulatory B cells and inhibition of T cell proliferation. Tumor exosomes trigger phenotypic changes in monocytes that release cytokines and PD-L1 promoting inflammation and immune escape. MSCs can be modulated to increase their proliferation and to express migration and angiogenic factors via NF-κB activation. In turn, exosome-stimulated MSCs promote Treg cells and the release of immune-related factors (TNF-α, IL-1β, TGF-β1), and can recruit macrophage to tumor site through the release of CCL2 and CCL7.

enhance tumor survival and progression. Myeloma cells exposed to chemotherapy enhanced exosome secretion and modified exosome's proteome profile, including a dramatic elevation of surface's heparinase levels. Therefore, chemotherapy-induced exosomes (chemoexosomes) bearing heparanase induced tumor cells' heparan sulfate degrading activity of the extracellular matrix. Moreover, chemoexosomes stimulated macrophage migration and their secretion of TNF-α, an important myeloma growth factor (Bandari et al., 2018).

The bone marrow hematopoietic niche consists of an important microenvironment in cancer pathogenesis, especially in hematological malignancies. In this context, it is not surprising that tumor cells take advantage of exosomes capabilities as vehicles of growth factors, cytokines, enzymes, angiogenic molecules, and genetic material to reprogram the bone marrow microenvironment. In fact, the 'proof of principle' that tumor-derived exosomes educate and transform the bone marrow environment was demonstrated by Peinado et al., who showed that exosomes secreted by murine metastatic melanoma cells promoted the formation of a pro-metastatic niche by mobilizing and reprograming bone marrow progenitors toward a pro-vasculogenic and pro-metastatic phenotype via induction of MET signaling which supports the metastatic progression of melanoma cells (Peinado et al., 2012). Mesenchymal stem/stromal cells (MSCs) represent one of the central cellular components of lymphoma microenvironment. Exosomes-derived from adult T-cell leukemia/lymphoma (ATL) cells modulate the properties of human MSCs by transferring miR-21, miR-155 and vascular endothelial growth factor (VEGF), resulting in NF-κB activation leading to a change in cellular morphology, increased proliferation and the induction of gene expression of migration and angiogenic markers (El-Saghir et al., 2016). A study by Lee et al. showed how MSCs help to create an immunosuppressive milieu that promotes tumor evasion of immune surveillance. The co-injection of MSCs with B lymphoma cells resulted in enhanced tumor growth in a murine model of lacrimal gland B-cell lymphoma. Importantly, bone marrow-derived MSCs promoted the increased of $CD4^+$ cells, $CD11b^+$ cells, $CD4^+Foxp3^+$ regulatory T cells and myeloid-derived suppressor cells, and upregulation of immune-related factors including TNF-α, IL-1β, TGF-β1, and arginase (Lee et al., 2017). Actually, a study showed that MSCs stimulated by TGF-β and IFN-γ secrete exosomes that promote the differentiation of peripheral blood mononuclear cells (PBMCs) into Tregs, which have an immune suppression effect (Zhang et al., 2018). Lin *et al.* reported a new mechanism in which MSCs are endowed with the ability to promote macrophage recruitment to tumor site, using a melanoma and lymphoma model. MSCs educated by tumor cell-derived exosomes produced CCR2 ligands, CCL2 and CCL7, responsible for macrophage infiltration, subsequently facilitating tumor growth (Lin et al., 2016). CLL cells stablish a bi-directional crosstalk with BM-MSCs through exosomes secretion, which induces platelet-derived growth factor receptor (PDGFR) activation and downstream ERK and AKT phosphorylation in BM-MSCs. In turn, PDGFR-induced BM-MSCs triggers VEGF secretion which promotes CLL tumor survival (Ding et al., 2010, 2009; Ghosh et al., 2010; Gehrke et al., 2011). Moreover, recent work has revealed that MSCs and endothelial cells acquire an inflammatory phenotype with the activation of NF-κB-dependent signaling induced by CLL exosomes. When analyzed the gene expression profiling of these cells, it was observed a transcriptional reprogramming into pro-inflammatory response similar to the gene signature of activated CAFs (Paggetti et al., 2015).

Recently, Manček-Keber and colleagues reported that exosomes derived from lymphoma B-cells harboring mutated MYD88 were able to trigger the activation of proinflammatory signaling in mast cells and macrophages, hence reprograming BM microenvironment into a tumor-promoter niche (Mancek-Keber et al., 2018).

4. Exosomes in virus-related lymphomas

The association between viral agents, such as EBV, the Kaposi's sarcoma-associated herpesvirus (KSHV), and human immunodeficiency virus type 1 (HIV-1), and the development of lymphomas, specially B-cell lymphomas, has been long established (Castillo et al., 2014). Viral-induced lymphomagenesis can be initiated by 3 main pathogenetic mechanisms: (1) direct carcinogenesis due to cancer cell infection by lymphotropic transforming viruses (EBV and KSHV) with consequent activation of main signaling pathways that results in increased B-cell proliferation and malignant transformation (Boshoff, 2011); (2) chronic antigenic activation of lymphocytes receptors by viral antigens and cytokines ultimately leading to clonal expansion of B-cell (Couronné et al., 2018); and (3) immunodeficiency or immunosuppression cause by virus-dependent Th and Tregs depletion, particularly HIV, inducing specific immunological defects and initiating malignant transformation (Carbone et al., 2014).

Several evidences have added a new level of complexity in virus-induced lymphomagenesis by showing that oncogenic viruses can use exosomes to modulate cellular microenvironment and evade immune system recognition to survive and accelerate tumor progression (Dolcetti, 2015).

Several studies have shown that EBV-infected B lymphocytes secrete exosomes harboring viral and cellular components. EBV-derived exosomes contain Fas ligand (FasL) which triggers apoptosis of recipient cells by the FasL-mediated extrinsic pathway (Ahmed et al., 2015). Exosomes released by EBV-infected B cells transport the viral latent membrane protein 1 (LMP1), which is proved to be a promoter of lymphomagenesis. In fact, internalization of $LMP1^+$ exosomes resulted in enhanced proliferation, induction of activation-induced cytidine deaminase (AID), production of circle and germline transcripts for IgG1 and B cell differentiation toward a plasmablast-like phenotype (Gutzeit et al., 2014). Another study supporting the presence of LMP1 protein in EBV-transformed cells reported that these exosomes also contain EBV-encoded latent phase mRNAs, such as LMP1, LMP2, EBNA1 (Epstein–Barr nuclear antigen 1), and EBNA2 (Epstein–Barr nuclear antigen 2). These results seem to suggest that the exosomal mRNAs will then be translated into the respectively oncogenic protein once internalized by the host recipient cells. Functionally, these EBV-encoded oncogenic proteins are responsible for altering cellular gene transcription and constitutively activating key signaling pathways, involved in cell growth, apoptosis, cell motility, and angiogenesis (Canitano et al., 2013).

Apart from oncoproteins, EBV-infected exosomes also transport several viral and cellular miRNAs which regulate cellular processes and manipulate TME. A study using Burkitt Lymphoma Mutu Cell Lines, characterized the expression profile of exosomal miRNAs, observing the expression of specific cellmiRNAs, such as miR-143, miR-877, miR-4516-5p, miR-6087-5p, and miR-7704-5p. Moreover, they observed that EBV-infected cells presented upregulation of exosomes biogenesis and that multiple viral miRNAs were transferred to epithelial cells via exosomes (Nanbo et al., 2018). Recently, Higuchi et al. reported that exosomes secreted by EBV^+ lymphoma cells, containing EBV-derived ncRNAs such as BamHI fragment A rightward transcript (BART) miRNAs and EBV-encoded RNA (EBER), induced an immune regulatory phenotype in macrophages characterized by the expression of IL-10, TNF-α and arginase 1. Additionally, the expression levels of EBV-encoded miRNAs were also associated with clinical outcome of diffuse large B-cell lymphoma patients (Higuchi et al., 2018).

The lymphotropic herpesvirus KSHV is responsible for distinct lymphoproliferative disorders including primary effusion lymphoma (PEL), multicentric Castleman disease (MCD) and MCD-associated plasmablastic lymphoma (Carbone and Gloghini, 2008). During KSHV infection, gamma interferon-inducible protein 16 (IFI16) acts as a nuclear pattern recognition receptor and interacts with ASC and procaspase-1 to form a functional inflammasome complex and induces the release of inflammatory cytokines (such as IL-1β and IL-18) to regulate immune responses (Kerur et al., 2011). Singh et al. reported that KSHV-infected cells release IFI16 and cleaved IL-1β via exosomes, probably as

a way of disrupting IL-1β functions in order to reduce immune defense (Singh et al., 2013). Global quantitative proteomics analysis of KSHV-infected B-cell exosomes showed exosomes highly enriched in proteins involved in the glycolysis pathway, cell death and survival, protein synthesis, mTOR signaling, and remodulation of epithelial adherents junctions, suggesting a role in cell anchorage or movement (Meckes et al., 2013).

As observed in EBV-infected exosomes, KSHV also altered not only the exosomal protein content but also the cellular and viral miRNAs profile that fine-tunes host gene expression in order to promote viral pathogenesis. Chugh et al. demonstrated for the first time the presence of both KSHV-encoded miRNAs and host miRNAs, including members of the miR-17–92 cluster, in exosomes of patients with KSHV-associated malignancies and isolated from KSHV mouse models (Chugh et al., 2013). The analysis of the exosomal miRNA targets showed the involvement of key signaling pathways in KSHV pathogenesis and enhanced cell migration and IL-6 secretion in endothelial cells (Chugh et al., 2013). A more recent study demonstrated that in order to manipulate the metabolic nature of the tumor microenvironment, KSHV infected cells transfer virus-encoded microRNAs via exosomes, which induce Warburg effect in the neighboring cells (Yogev et al., 2017). KSHV-infected endothelial cells release exosomes containing miR-K12-2-5p, miRK12-4-3p, miR-K12-4-5p, miR-K12-6-5p, miR-K12-8-3p, miR-K12-10a-3p, miR-K12-11-3p, and miR-K12-12, which participate in a metabolic shift toward aerobic glycolysis in non-infected cells, and ultimately supporting the growth of infected cells (Yogev et al., 2017; Hoshina et al., 2016). Rainy et al. demonstrated that KSHV-infected cells transfer miR-K12-11 via exosomes into T cells, where inhibits the innate type-I interferons response to viral dsRNAs in a non-cell-autonomous mode and consequently promotes oncogenesis (Rainy et al., 2016).

Taken together, the reported data clearly shows that oncogenic viruses take advantage of exosomes traffic to enhance viral pathogenesis by modulation of the lymphoma microenvironment towards angiogenesis, metabolic switch, and immune dysfunction.

5. Exosomes and therapy resistance

The major progresses on understanding NHL biology in the last decade have led to a great improvement in NHL treatment paradigm. Particularly, since Coiffier et al. demonstrated that the combination of rituximab and the established CHOP chemotherapy regime improve patients' therapy response, event-free survival (EFS) and overall survival (OS), when compared with CHOP regime alone (Coiffier et al., 2002). Since then, other studies have showed and supported Coiffier results, which resulted in the introduction of rituximab as a standard of care of NHL patients (R-CHOP regime) (Pfreundschuh et al., 2011; Fu et al., 2008; Coiffier et al., 2010).

Despite the major improvement in the outcome of NHL patients, therapy response still remains highly variable and there is a considerable high percentage of patients that are primarily refractory or experience short-term relapse, presenting a poor prognosis (Camus and Tilly, 2017; Li et al., 2017b). Moreover, the acquisition of chemotherapy resistance still remains a major obstacle in the treatment of these patients (Younes et al., 2016; Pérez-Callejo et al., 2015).

Diverse mechanisms of chemotherapy resistance have been already established such as drug efflux from cancer cells, alterations in drug metabolism and mutation of drug targets, microenvironment acidification and augmentation of DNA repair mechanisms (Holohan et al., 2013). Moreover, due to the exceptional adaptability of tumors, they have the ability to activate survival pathways and inhibit cell death mechanisms resulting also in drug resistance (Holohan et al., 2013). Recently, a new mechanism of chemoresistance has emerged involving exosomes. In fact, tumor exosomes have the ability to horizontally transfer multi-drug resistance (MDR)-associated proteins and miRNAs between tumor cells (Maia et al., 2018). Since the pioneer work of Corcoran et al. that showed that exosomes can induce docetaxel resistance in prostate cancer, more studies have been focused on uncovering this new mechanism of resistance in other tumors (Corcoran et al., 2012). In a recent study developed by Qin et al., exosomes released by cisplatin resistant lung cancer cells, induced drug resistance in recipient cells through downregulation of exosomal miR-100–5p levels and in turn increasing mTOR expression (Qin et al., 2017). On the other hand, exosomes can induce tumor resistance by mediating drug efflux, where drugs and their metabolites are extruded from the cell, diminishing their cytostatic action (Robey et al., 2018). One of the most studied mechanisms of drug resistance is the expression of ATP-binding cassette (ABC) transporters, such as the multidrug resistance protein 1 (MDR1, also known as P-glycoprotein or P-gp) which is associated with resistance to cytotoxic and targeted chemotherapy (Robey et al., 2018). Actually, a study in B-cell lymphoma showed that exosomes seem to be involved in the export of doxorubicin and pixantrone from the cell. Moreover, depletion of ABCA3 by indomethacin suppresses exosome biogenesis, and consequently enhances the nuclear trapping of the drugs, increasing their cytostatic efficacy against DLBCL cell lines (Koch et al., 2016). Therefore, the results suggest a potential alternative approach to overcome chemoresistance and increase drug efficacy by targeting exosome biogenesis.

Exosomes can also modulate the effect of antibody drugs used in target therapies, by interfering with their binding to tumor cells. Tumor-derived exosomes transporting HER2 sequestrate the antibody trastuzumab, attenuating its therapeutic action and resulting in tumor aggressiveness and progression (Battke et al., 2011; Ciravolo et al., 2012). Similar results were observed in lymphoma, demonstrating that lymphoma-derived exosomes carrying CD20 act as decoy and protect target cells from antibody action. In fact, exosomes carrying CD20 impaired therapeutic action of rituximab and antibody-dependent cell mediated cytotoxicity (ADCC) by reducing drug bioavailability (Aung et al., 2011).

As previously mentioned, tumors cells constantly communicate with neighboring cells by exchanging exosomes. Therefore, it is not surprising that exosomes secreted by stromal cells can also influence drug resistance. Bone marrow stromal cells (BM-SCs)-derived exosomes induce cell survival and chemoresistance of multiple myeloma cells to bortezomib, by the activation of several survival pathways, including c-Jun N-terminal kinase, p38, p53, and Akt (Wang et al., 2014). Another study conducted by Wang and colleagues showed that BM-SCs' exosomes protect human B-cell acute lymphoblastic leukemia cells from etoposide-induced apoptosis leading to exosome-induced drug resistance (Wang et al., 2017). Additionally, a recent work demonstrated that B cell-derived $CD19^+$ EVs enriched in CD39 and CD73 hydrolyze ATP released from tumor cells treated with chemotherapy into adenosine, which in turn inhibits $CD8^+$ T cell activity and proliferation and consequently reduces chemotherapy efficacy (Zhang et al., 2019)

Another obstacle to chemotherapy efficacy is the presence of cancer stem cells (CSC) subpopulation within the tumor. One of the features of CSCs is the induction of drug resistance in cancer cells. In fact, a study by Koch R. and colleagues demonstrated that exosomes transporting Wnt proteins induced a CSCs-like phenotype in cancer cells in a diffuse large cell B cell lymphoma model. Moreover, the induction of this phenotype is associated with increased expulsion of doxorubicin and therefore the acquisition of drug resistance (Koch et al., 2014).

6. Exosomes as biomarkers

Since the observation that several tumor-released components can be identified in peripheral blood, an increased number of studies have been focusing their attention on understanding their clinical value in the diagnosis, monitoring and as potential therapeutic targets in cancer. The concept of "liquid biopsies", encompassing the analysis of mRNA, microRNA, circulating-tumor DNA, proteins or cancer metabolites, emerges as a promising minimally invasive approach to assess tumor-

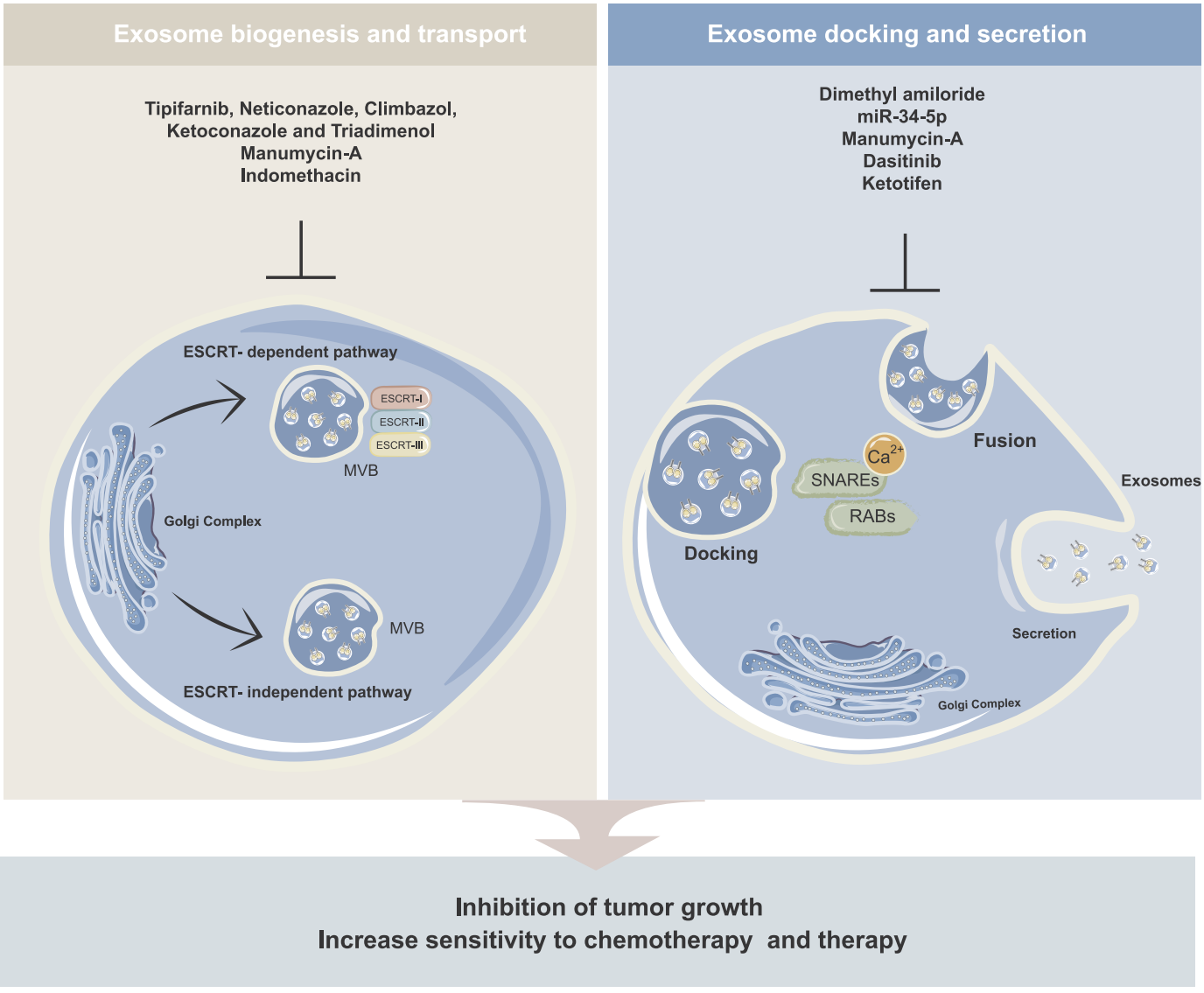

Fig. 3. Schematic illustration of strategies for exosomal modification and cargo loading for the development of exosome-based cancer therapy. Some compounds have been shown to interfere with exosomes either by silencing or inhibiting exosome biogenesis and trafficking or even by inhibit docking and secretion. Studies demonstrated that disruption of exosome pathway resulted in tumor suppression and appears to be a promising strategy to increase therapy efficacy and overcome drug resistance.

specific changes and as a most informative predictor of patients' outcome or therapy response (Bardelli and Pantel, 2017). In this context, exosomes have been viewed as a major step forward in the liquid biopsies field. In fact, resembling to what it was observed in solid tumors, FACS analysis showed that exosomes are also enriched in plasma of patients with hematological malignancies when compared to healthy individuals. Moreover, Caivano et al. identified tumor-related antigens expressed in the exosomes, such as CD19 in B cell neoplasms, CD38 in MM, CD13 in myeloid tumors, and CD30 in HL, and correlated exosome's levels with the clinical features showing the potential of exosomes as biomarkers in hematological malignancies (Caivano et al., 2015). Analysis of plasma samples from CLL patients also revealed significantly high plasma levels of exosomes which decreased following ibrutinib therapy (Yeh et al., 2015).

The RNA fraction represents the most abundant and diversified constituent of exosomal cargo, gaining great attention in the field of biomarkers discovery, especially exosomal miRNAs. Exosomal miRNAs are highly stable in various body fluids, and interestingly were found to remain stable at −208 °C for 5 years and to resist to freeze-thaw cycles (Weber et al., 2010). Moreover, their levels and composition not only differ between patients and healthy individuals but also between diseases (Tomasetti et al., 2017). The specificity and central role of miRNAs in post-transcriptional regulation in order to maintain the fine tuning of several biological processes, have established their potential as biomarkers.

In fact, accumulating evidence suggests that specific miRNA profiles characterized each tumor, and that important signaling pathways and exosome-released miRNAs change during carcinogenesis steps, indicating that exosomal miRNAs could be an important diagnostic and prognostic biomarker of cancer (Li et al., 2019; Palma et al., 2012; Cortez et al., 2011; Madhavan et al., 2015; Matsumura et al., 2015). Yeh et al. identified a distinct exosomal miRNA profile in plasma samples of CLL patients, which include miR-29 family, miR-150, miR-155, and miR-223 (Yeh et al., 2015). Analysis of plasma EV miRNA repertoire of untreated classical HL patients showed enriched levels of miR24-3p, miR127-3p, miR21-5p, miR155-5p, and let7a-5p. Interestedly, following to treatment miRNA levels decreased matching a complete metabolic response, and increased again in relapse patients (van Eijndhoven et al., 2016). Exosome-derived miR-15a-3p, miR-21-5p and miR-181a-5p seemed to be potential candidates miRNAs in the

differential diagnosis of DLBCL (Inada et al., 2014). In a study where the entire plasma mirnome of DLBCL patients was evaluated, including the exosomal counterpart, it was observed increased plasma levels of miR-124 and miR-532-5p and low levels of miR-425, miR-141, miR-145, miR-197, miR-345, miR-424, miR-128 and miR-122. Concerning the correlation between baseline plasma miRNA profiles and patients' outcome, they observed that plasma levels of miR-20a, 20b, 93 and 106a 106b were associated with higher mortality (Khare et al., 2017). Feng and colleagues identified increased levels of miR-99a-5p and miR-125b-5p in exosomes derived from DLBCL patients' serum. Additionally, exosomal miRNA levels were correlated with shorter progression-free survival time, and they can predict chemotherapeutic efficacy (Feng et al., 2019).

Exosomes analysis represents a major step forward in liquid biopsies since they provide important information about the circulating transcriptome. Exosomes' special features permit not only to detect miRNAs and lncRNAs, but also extracellular mRNA, which normally are promptly degraded by RNase activity when in circulation, allowing the identification of tumor-specific gene expression profiles (Siravegna et al., 2017). However, compared to miRNAs, less is known about the importance of exosomal mRNA as potential biomarker of cancer. A study by Provencio et al. evaluated the prognostic implications of pretreatment tumor-associated exosomal mRNA (C-MYC, BCL-XL, BCL-6, NF-κβ, PTEN and AKT) in B-cell lymphomas. They showed that the presence of BCL-6 and c-MYC mRNA was associated with worse progression-free survival (PFS) and overall survival (OS). Moreover, exosomal AKT mRNA positivity was associated with non-response to rituximab-based treatment (Provencio et al., 2017).

7. Exosomes as therapeutic target and drug delivery vehicles

Given the important role of tumor-derived exosomes in reprograming microenvironment to drive tumor progression and escape, it is rational to think that inhibition or silencing of tumor exosomes would be an interesting therapeutic strategy. Theoretically, either by silencing or inhibiting exosome production (biogenesis and/or release) (Fig. 3), by interfering with exosomes uptake by recipient cells, or by eliminating exosome from circulation (Vader et al., 2014).

The identification of key proteins involved in exosome biogenesis gives some light on the development of small-molecules inhibitors of enzymes or proteins involved in this process. For instance, in HeLa cells, the silencing of ESCRT machinery resulted in reduction of exosome secretion and modulated the content of their cargo (Colombo et al., 2013). Modulation of syndecan-syntenin-ALIX axis can emerge as another alternative to regulate the formation of exosomes (Baietti et al., 2012b). A recent study identified various compounds that modulate ESCRT-dependent and ESCRT-independent exosome biogenesis and/or release in aggressive prostate cancer cells. Using quantitative high throughput screen assay they validated tipifarnib, neticonazole, climbazole, ketoconazole, and triadimenol as potent inhibitors giving light on novel therapeutic strategies for advanced cancer (Datta et al., 2018). The use of dimethyl amiloride, a compound known for its anti-ischemic effects, was shown to also reduce exosome secretion in mice bearing EL4 lymphoma, while enhancing the *in vivo* antitumor efficacy of the chemotherapeutic drug. Moreover, the secretion inhibition of tumor exosomes carrying HSP70 resulted in suppression of myeloid-derived suppressor cells, followed by the inhibition of tumor growth (Chalmin et al., 2010). The study developed by Peng et al. showed that the simple upregulation of miR-34-5p, a downregulated miRNA in AML stem cells, results in disruption of exosome shedding by inhibition of RAB27B and promotes eradication of acute myeloid leukemia stem cells by inducing senescence (Peng et al., 2018). Moreover, Datta et al. reported that manumycin-A treatment, a natural product of microbes, resulted in decreased of exosome biogenesis and release in a prostate cancer cell line by supposedly interfering with the ESCRT machinery and Rab27a. Interestingly, Datta's results suggest that malignant and normal cells have different mechanisms of exosome biogenesis, since marumycin-A treatment did not affect exosome release from normal RWPE-1 cell line (Datta et al., 2017). Actually, this observation is particularly important since one of the major challenges of therapeutically interfere with exosome biogenesis and release is to find approaches that have sufficient specificity to tumor cells without altering normal cell function. A study performed using an imatinib resistant chronic myeloid leukemia cell line (K562IMT), revealed that dasitinib induces apoptosis by preventing exosome release and autophagy through inhibition of beclin-1 and Vps34 (Liu et al., 2016). Moreover, ketotifen, an antihistaminic mast cell stabilizer, was shown to reduce exosome release which resulted in an increase in the sensitivity to doxorubicin by attenuating drug exosomal export from the cell (Khan et al., 2018). Taking together these results and the ones reported by Koch et al. in lymphoma, previously described in this review, highlight the potential of targeting exosomes biogenesis and release as a promising strategy to overcome drug resistance and increase therapy efficacy (Koch et al., 2016). On the other hand, exosome uptake by recipient cells could also be targeted by blocking surface adhesion molecules which are essential for exosome docking and internalization, such as phosphatidylserine, ICAM1, sHS, proteoglycans (van Niel et al., 2018). For example, disruption of cholesterol-rich membrane microdomains located in lipid rafts by synthetic nanoparticles seems to inhibit cellular exosome uptake. Plebanek et al. developed a synthetic nanoparticle mimic of HDL which bonded to scavenger receptor type B-1 (SR-B1) and consequently activated cholesterol efflux and attenuated the influx of esterified cholesterol. Ultimately, SR-B1 disruption resulted in cholesterol imbalance in the plasma membrane potently inhibiting cellular exosome uptake (Plebanek et al., 2015).

Another approach has been proposed based on the idea of removing the exosomes from circulation as therapeutic adjuvant in cancer. The authors suggested the extracorporeal hemofiltration of exosomes from the entire circulation using an affinity plasmapheresis platform such as the ADAPT™ system. This technology has the ability to trap tumor-derived exosomes on a lectins or antibody-coated matrix during dialysis (Marleau et al., 2012). For example, this approach could be applied in breast cancer cases with overexpression of human epidermal growth factor receptor-2 (HER-2), where HER-2-bearing exosomes could be captured and removed using anti-HER-2 antibodies and thus improving therapy efficacy and patient outcome (Marleau et al., 2012). Recently, a new study regarding exosome depletion from circulation has emerged but this time as a method of suppressing cancer metastasis. Treatment with human-specific anti-CD9 and anti-CD63 antibodies reduced metastasis to the lungs, lymph nodes, and thoracic cavity in a human breast cancer xenograft mouse model. Additionally, *in vitro* and *in vivo* analysis suggested that antibody-tagged exosomes are internalized and eliminated by macrophages (Nishida-Aoki et al., 2017). Unfortunately, there are no studies employing this type of approach in hematological malignancies.

On the other hand, instead of looking into exosomes as therapeutic targets, researchers are now exploring their ability to transport cargo which makes them an attractive vehicle for therapeutic cargos delivery. Exosomes' "natural" features turn them into a desirable alternative of therapy-delivery vesicles: (1) exosomes nanometric-size facilitates their transfer between cells; (2) exosomes structure and composition protect molecules from the action of nucleases and proteases; (3) exosomes have low immunogenicity and toxicity when compared with other conventional delivery systems; and (4) the presence of specific surface proteins and lipids stabilize exosomes in circulation and confer them cell and tissue specific tropism (Luan et al., 2017).

Given their function, multiple studies have emerged evaluating and testing exosomes as transporters of miRNAs, mRNAs, proteins, peptides, and synthetic drugs (e.g., doxorubicin, curcumin, etc.) (Erkan et al., 2017; Barile and Vassalli, 2017). The first obstacle is how to load therapeutic agents into exosomes or exosomes mimetics. Active cargo molecules can be incorporated into exosomes using two approaches,

active or passive encapsulation (Luan et al., 2017). Passive loading methods are simpler but still lack on loading efficiency. Exosomes can be incubated directly with the substances (for example, curcumin, acridine orange, doxorubicin, or paclitaxel), and by concentration gradient pressure the molecules diffuse into the exosomes (Sun et al., 2010; Iessi et al., 2017; Srivastava et al., 2016; Kim et al., 2016a). Another passive method is by incubating donor cells with a drug prior to exosome isolation, which then will be secreted in drug-loaded exosomes (Pascucci et al., 2014). On the other hand, active methods rely on techniques such as sonication, extrusion, incubation with membrane permeabilizers or electroporation, which have as principal the disruption of exosome's membrane allowing the drug to diffuse into the exosomes (Kim et al., 2016b; Fuhrmann et al., 2015; Podolak et al., 2010; Kamerkar et al., 2017). Electroporation is the method of choice to load exosomes with siRNA or miRNA, for example Kamerkar et al. engineered exosomes derived from normal fibroblast-like mesenchymal cells to carry siRNA specific to oncogenic $Kras^{G12D}$, a common mutation in pancreatic cancer, resulting in cancer suppression and significantly increased overall survival (Kamerkar et al., 2017). Lunavat et al. developed a study where they generated exosomes carrying cMyc siRNA, which were able to reduce cMyc transcript and induced apoptosis in mouse λ820 lymphoma cells (Lunavat et al., 2016).

The second major obstacle in engineering exosomes as targeted vehicles is the selection and modification of surface peptides and proteins for better cell recognition. Donor cells can be engineer by inserting the gene encoding candidate proteins or peptides, which will fuse with exosomal membrane proteins securing its insertion into the exosome membrane (Stickney et al., 2016). Tian et al. modified dendritic cells to express exosomal membrane protein (Lamp2b) fused to αv integrin-specific iRGD peptide, which were then loaded with doxorubicin. iRGD exosomes showed high delivery efficiency and anti-tumor effect on αv integrin-positive breast cancer cells mouse model (Tian et al., 2014). Another recent study engineered paclitaxel-loaded exosomes with aminoethylanisamide-polyethylene glycol (AA-PEG) to directly target sigma receptor, an overexpressed receptor in lung cancer cells. These exosomes not only presented high loading capacity, high affinity to cancer cells upon systemic administration, but also demonstrated improved therapeutic effect (Kim et al., 2018). Qi et al. developed another approach linking transferrin-conjugated superparamagnetic nanoparticles to transferrin receptor on exosome membrane and placing an external magnet on the tumor site. This methodology allows the direct targeting of tumor cells by the magnetic exosomes (Qi et al., 2016).

7.1. Immunotherapy

The recent evidences that tumor-derived exosomes contain endogenous tumor antigens and that they interact with the immune system opens the door toward development of novel immunotherapy strategies. Based on these ideas, diverse studies are now emerging, and several clinical trials have already started using exosomal-mediated antitumor immunity as anticancer vaccines (Lener et al., 2015). A study by Chen et al. assessed the efficacy of exosomes derived from heat-shocked mouse B lymphoma cells (HS-Exo) in the induction of anti-tumor immune responses. They demonstrated that HS-Exo were enriched in HSP60 and HSP90 and had the ability to induce a strong antitumor immune response by activating T cell responses and functional maturation of dendritic cells (Chen et al., 2006). Moreover, exosomes isolated from ascites of T-Cell lymphoma-bearing mice expressing CD24 and HSP-90 induced tumor-specific humoral and cellular immune responses by activating tumor-specific CD4+ and CD8+ IFN-γ secreting cells (Menay et al., 2017). Chen et al. observed that dendritic cells pulsed with DLBCL-derived exosomes induced clonal expansion of T cells and secretion of IL-6 and TNFα, and inhibited secretion of immunosuppressive cytokine IL-4 and IL-10 by T helper 2 cells. Furthermore, exosomes-immunized T cells demonstrated a specific anti-lymphoma response (Chen et al., 2018).

In a clinical trial involving indolent NHL patients with measurable disease, patients were vaccinated with autologous tumor-loaded dendritic cells. Clinical results showed that from the eighteen patients engaged, 3 patients had continuous radiographic complete responses and 3 partial responses. The enhanced antitumor activity seemed to be associated with a reduction in $CD4^+CD25^+FOXP3^+$ regulatory T cells, an increase in $CD3^-CD56^{dim}CD16^+$ natural killer cells, and maturation of lymphocytes to the effector memory stage (Di Nicola et al., 2009).

8. Conclusion

In recent years, our understanding of the complexity of NHL lymphomagenesis has greatly improved. Studies' initial focus on understanding the underlying mechanisms only with regard to genetic alterations in primary lymphoma cells, was long put aside, and now directed their attention to TME contribution in tumor progression. In fact, cancer is no longer viewed as an isolated entity but as a dynamic and complex co-evolution of tumor cells and their reprogrammed microenvironment. The bystander cells present in the microenvironment enable the licensing of malignant transformation by promoting blasts' survival and resistance and suppressing anti-tumor function of immune cells. A fair example of the change in paradigm was the emerging role of immunotherapy in lymphoma treatment, which has greatly improved patients' outcome. Therefore, a profound understanding of the interplay between lymphoma cells and TME can lead to the development of more intricate approaches which re-educate host cells against lymphoma and pave the way to enhance treatment efficacy. Recent advances in the analysis of TME placed a spotlight on exosomes as vehicles of bidirectional transfer of molecules between tumor cells and the TME. In the era of liquid biopsies, circulating exosomes held a great promise as diagnostic and therapeutic tools and as such have become a prominent research topic in oncology. In fact, increasing evidences suggest a multifunctional role of exosomes not only in lymphomageneses but also in mediating immune dysfunction, virus infection, and drug resistance. However, the number of studies reporting exosomal biomarkers in lymphomas and their potential clinical value is still scarce. Moreover, exosomes' full potential for clinical application has yet to be reached much due to lack of standardization of isolation and quantification methods. Therefore, there is an urgent need to develop more sophisticated and efficient technics to improve quality and purity of the isolated exosomes, facilitating the validation of the results and their clinical application. Indeed, the future progress in lymphoma largely depends on uncovering the answers to the role of exosomes and will undoubtedly alter our view of lymphoma biology and will present a new window of opportunity to precision diagnostics and innovative therapies.

Authors' contributions

Mara Fernandes was involved in the drafting and editing of the manuscript. Ana L. Teixeira was involved in the revising of the manuscript critically for the important scientific content. Rui Medeiros was involved in the revising of the content and providing the final approval of the version to be published. All authors read and approved the final manuscript.

Funding

Mara Fernandes is a recipient of a research scholarship awarded by LPCC-NRN (Portuguese League Against Cancer- Northern Branch). Ana L. Teixeira is a post-doctoral fellow from FCT (Portuguese Foundation for Science and Technology) (SFRH/BPD/111114/2015).

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgements

We would like to thank Liga Portuguesa Contra o Cancro – Nucleo Regional do Norte – LPCC-NRN (Portuguese League Against Cancer-Northern Branch).

References

Ahmed, W., et al., 2015. Epstein-Barr virus-infected cells release Fas ligand in exosomal fractions and induce apoptosis in recipient cells via the extrinsic pathway. J. Gen. Virol. 96 (12), 3646–3659.
Anderson, L.A., et al., 2014. Common infection-related conditions and risk of lymphoid malignancies in older individuals. Br. J. Cancer 110 (11), 2796–2803.
Armitage, J.O., et al., 2017. Non-Hodgkin lymphoma. Lancet 390 (10091), 298–310.
Aung, T., et al., 2011. Exosomal evasion of humoral immunotherapy in aggressive B-cell lymphoma modulated by ATP-binding cassette transporter A3. Proc. Natl. Acad. Sci. U. S. A. 108 (37), 15336–15341.
Baietti, M.F., et al., 2012a. Syndecan–syntenin–ALIX regulates the biogenesis of exosomes. Nat. Cell Biol. 14, 677.
Baietti, M.F., et al., 2012b. Syndecan-syntenin-ALIX regulates the biogenesis of exosomes. Nat. Cell Biol. 14 (7), 677–685.
Balaj, L., et al., 2011. Tumour microvesicles contain retrotransposon elements and amplified oncogene sequences. Nat. Commun. 2, 180.
Bandari, S.K., et al., 2018. Chemotherapy induces secretion of exosomes loaded with heparanase that degrades extracellular matrix and impacts tumor and host cell behavior. Matrix Biol. 65, 104–118.
Bardelli, A., Pantel, K., 2017. Liquid biopsies, what we do not know (Yet). Cancer Cell 31 (2), 172–179.
Barile, L., Vassalli, G., 2017. Exosomes: Therapy delivery tools and biomarkers of diseases. Pharmacol. Ther. 174, 63–78.
Battke, C., et al., 2011. Tumour exosomes inhibit binding of tumour-reactive antibodies to tumour cells and reduce ADCC. Cancer Immunol. Immunother. 60 (5), 639–648.
Bayraktar, R., Van Roosbroeck, K., Calin, G.A., 2017. Cell-to-cell communication: microRNAs as hormones. Mol. Oncol. 11 (12), 1673–1686.
Bebelman, M.P., et al., 2018. Biogenesis and function of extracellular vesicles in cancer. Pharmacol. Ther. 188, 1–11.
Bissig, C., Gruenberg, J., 2013. Lipid sorting and multivesicular endosome biogenesis. Cold Spring Harb. Perspect. Biol. 5 (10), a016816.
Bohana-Kashtan, O., Pinna, L.A., Fishelson, Z., 2005. Extracellular phosphorylation of C9 by protein kinase CK2 regulates complement-mediated lysis. Eur. J. Immunol. 35 (6), 1939–1948.
Boshoff, C., 2011. Unraveling virus-induced lymphomagenesis. J. Clin. Invest. 121 (3), 838–841.
Cai, J., et al., 2013. Extracellular vesicle-mediated transfer of donor genomic DNA to recipient cells is a novel mechanism for genetic influence between cells. J. Mol. Cell Biol. 5 (4), 227–238.
Cai, J., et al., 2014. Transferred BCR/ABL DNA from K562 extracellular vesicles causes chronic myeloid leukemia in immunodeficient mice. PLoS One 9 (8), e105200.
Cai, J., et al., 2015. SRY gene transferred by extracellular vesicles accelerates atherosclerosis by promotion of leucocyte adherence to endothelial cells. Clin. Sci. (Lond.) 129 (3), 259–269.
Caivano, A., et al., 2015. High serum levels of extracellular vesicles expressing malignancy-related markers are released in patients with various types of hematological neoplastic disorders. Tumour Biol. 36 (12), 9739–9752.
Camus, V., Tilly, H., 2017. Managing early failures with R-CHOP in patients with diffuse large B-cell lymphoma. Expert Rev. Hematol. 10 (12), 1047–1055.
Canitano, A., et al., 2013. Exosomes released in vitro from Epstein-Barr virus (EBV)-infected cells contain EBV-encoded latent phase mRNAs. Cancer Lett. 337 (2), 193–199.
Carbone, A., Gloghini, A., 2008. KSHV/HHV8-associated lymphomas. Br. J. Haematol. 140 (1), 13–24.
Carbone, A., et al., 2014. Diagnosis and management of lymphomas and other cancers in HIV-infected patients. Nat. Rev. Clin. Oncol. 11 (4), 223–238.
Castillo, J.J., et al., 2014. Viral lymphomagenesis: from pathophysiology to the rationale for novel therapies. Br. J. Haematol. 165 (3), 300–315.
Cerhan, J.R., et al., 2014. Medical history, lifestyle, family history, and occupational risk factors for diffuse large B-cell lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J. Natl. Cancer Inst. Monogr. 2014 (48), 15–25.
Chalmin, F., et al., 2010. Membrane-associated Hsp72 from tumor-derived exosomes mediates STAT3-dependent immunosuppressive function of mouse and human myeloid-derived suppressor cells. J. Clin. Invest. 120 (2), 457–471.
Chen, W., et al., 2006. Efficient induction of antitumor T cell immunity by exosomes derived from heat-shocked lymphoma cells. Eur. J. Immunol. 36 (6), 1598–1607.
Chen, C., et al., 2013. Extracellular vesicle-mediated transfer of donor genomic DNA to recipient cells is a novel mechanism for genetic influence between cells. J. Mol. Cell Biol. 5 (4), 227–238.
Chen, Z., et al., 2018. Dual effect of DLBCL-derived EXOs in lymphoma to improve DC vaccine efficacy in vitro while favor tumorgenesis in vivo. J. Exp. Clin. Cancer Res. 37 (1), 190.
Christ, L., et al., 2017. Cellular functions and molecular mechanisms of the ESCRT membrane-scission machinery. Trends Biochem. Sci. 42 (1), 42–56.
Chugh, P.E., et al., 2013. Systemically circulating viral and tumor-derived MicroRNAs in KSHV-Associated malignancies. PLoS Pathog. 9 (7), e1003484.
Ciravolo, V., et al., 2012. Potential role of HER2-overexpressing exosomes in countering trastuzumab-based therapy. J. Cell. Physiol. 227 (2), 658–667.
Coiffier, B., et al., 2002. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse Large-B-Cell lymphoma. N. Engl. J. Med. 346 (4), 235–242.
Coiffier, B., et al., 2010. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 116 (12), 2040–2045.
Colombo, M., et al., 2013. Analysis of ESCRT functions in exosome biogenesis, composition and secretion highlights the heterogeneity of extracellular vesicles. J. Cell. Sci. 126 (Pt 24), 5553–5565.
Colombo, M., Raposo, G., Thery, C., 2014. Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. Annu. Rev. Cell Dev. Biol. 30, 255–289.
Corcoran, C., et al., 2012. Docetaxel-resistance in prostate cancer: evaluating associated phenotypic changes and potential for resistance transfer via exosomes. PLoS One 7 (12), e50999.
Cortez, M.A., et al., 2011. MicroRNAs in body fluids—the mix of hormones and biomarkers. Nat. Rev. Clin. Oncol. 8, 467.
Couronné, L., et al., 2018. From hepatitis C virus infection to B-cell lymphoma. Ann. Oncol. 29 (1), 92–100.
Dalvi, P., et al., 2017. Immune activated monocyte exosomes alter microRNAs in brain endothelial cells and initiate an inflammatory response through the TLR4/MyD88 pathway. Sci. Rep. 7 (1), 9954.
Datta, A., et al., 2017. Manumycin A suppresses exosome biogenesis and secretion via targeted inhibition of Ras/Raf/ERK1/2 signaling and hnRNP H1 in castration-resistant prostate cancer cells. Cancer Lett. 408, 73–81.
Datta, A., et al., 2018. High-throughput screening identified selective inhibitors of exosome biogenesis and secretion: a drug repurposing strategy for advanced cancer. Sci. Rep. 8, 8161.
Di Nicola, M., et al., 2009. Vaccination with autologous tumor-loaded dendritic cells induces clinical and immunologic responses in indolent B-cell lymphoma patients with relapsed and measurable disease: a pilot study. Blood 113 (1), 18–27.
Ding, W., et al., 2009. Bi-directional activation between mesenchymal stem cells and CLL B-cells: implication for CLL disease progression. Br. J. Haematol. 147 (4), 471–483.
Ding, W., et al., 2010. Platelet-derived growth factor (PDGF)–PDGF receptor interaction activates bone marrow–derived mesenchymal stromal cells derived from chronic lymphocytic leukemia: implications for an angiogenic switch. Blood 116 (16), 2984–2993.
Dolcetti, R., 2015. Cross-talk between Epstein-Barr virus and microenvironment in the pathogenesis of lymphomas. Semin. Cancer Biol. 34, 58–69.
Elenitoba-Johnson, K.S.J., Lim, M.S., 2018. New insights into lymphoma pathogenesis. Annu. Rev. Pathol. Mech. Dis. 13 (1), 193–217.
El-Saghir, J., et al., 2016. ATL-derived exosomes modulate mesenchymal stem cells: potential role in leukemia progression. Retrovirology 13 (1), 73.
Erkan, E.P., et al., 2017. Extracellular vesicle-mediated suicide mRNA/protein delivery inhibits glioblastoma tumor growth in vivo. Cancer Gene Ther. 24 (1), 38–44.
Espirito Santo, A., Medeiros, R., 2013. Pharmacogenetic considerations for non-Hodgkin's lymphoma therapy. Expert Opin. Drug Metab. Toxicol. 9 (12), 1625–1634.
Fallah, M., et al., 2014. Autoimmune diseases associated with non-Hodgkin lymphoma: a nationwide cohort study. Ann. Oncol. 25 (10), 2025–2030.
Fang, J.-H., et al., 2018. Hepatoma cell-secreted exosomal microRNA-103 increases vascular permeability and promotes metastasis by targeting junction proteins. Hepatology 68 (4), 1459–1475.
Feng, Y., et al., Exosome-derived miRNAs as predictive biomarkers for diffuse large B-cell lymphoma chemotherapy resistance. Epigenomics. 0(0): pp. null.
Fu, K., et al., 2008. Addition of rituximab to standard chemotherapy improves the survival of both the germinal center B-cell-like and non-germinal center B-cell-like subtypes of diffuse large B-cell lymphoma. J. Clin. Oncol. 26 (28), 4587–4594.
Fuhrmann, G., et al., 2015. Active loading into extracellular vesicles significantly improves the cellular uptake and photodynamic effect of porphyrins. J. Control. Release 205, 35–44.
Gehrke, I., et al., 2011. Bone marrow stromal cell-derived vascular endothelial growth factor (VEGF) rather than chronic lymphocytic leukemia (CLL) cell-derived VEGF is essential for the apoptotic resistance of cultured CLL cells. Mol. Med. 17 (7-8), 619–627.
Ghosh, A.K., et al., 2010. Circulating microvesicles in B-cell chronic lymphocytic leukemia can stimulate marrow stromal cells: implications for disease progression. Blood 115 (9), 1755–1764.
Ghossoub, R., et al., 2014. Syntenin-ALIX exosome biogenesis and budding into multivesicular bodies are controlled by ARF6 and PLD2. Nat. Commun. 5, 3477.
Grivennikov, S.I., Greten, F.R., Karin, M., 2010. Immunity, inflammation, and cancer. Cell 140 (6), 883–899.
Gutzeit, C., et al., 2014. Exosomes derived from Burkitt's lymphoma cell lines induce proliferation, differentiation, and class-switch recombination in B cells. J. Immunol. 192 (12), 5852–5862.
Haderk, F., et al., 2017. Tumor-derived exosomes modulate PD-L1 expression in monocytes. Sci. Immunol. 2 (13).
Halvaei, S., et al., 2018. Exosomes in Cancer liquid biopsy: a focus on breast cancer. Mol. Ther. Nucleic Acids 10, 131–141.
Hanahan, D., Weinberg, R.A., 2011. Hallmarks of cancer: the next generation. Cell 144 (5), 646–674.
Hedlund, M., et al., 2011. Thermal- and oxidative stress causes enhanced release of NKG2D ligand-bearing immunosuppressive exosomes in leukemia/lymphoma T and B cells. PLoS One 6 (2), e16899.
Higuchi, H., et al., 2018. Role of exosomes as a proinflammatory mediator in the

development of EBV-associated lymphoma. Blood 131 (23), 2552–2567.
Holohan, C., et al., 2013. Cancer drug resistance: an evolving paradigm. Nat. Rev. Cancer 13, 714.
Hornick, N.I., et al., 2016. AML suppresses hematopoiesis by releasing exosomes that contain microRNAs targeting c-MYB. Sci. Signal. 9 (444), ra88.
Hoshina, S., et al., 2016. Profile of exosomal and intracellular microRNA in gamma-herpesvirus-Infected lymphoma cell lines. PLoS One 11 (9), e0162574.
Hsu, C., et al., 2010. Regulation of exosome secretion by Rab35 and its GTPase-activating proteins TBC1D10A-C. J. Cell Biol. 189 (2), 223–232.
Iessi, E., et al., 2017. Acridine Orange/exosomes increase the delivery and the effectiveness of Acridine Orange in human melanoma cells: a new prototype for theranostics of tumors. J. Enzyme Inhib. Med. Chem. 32 (1), 648–657.
Inada, K., et al., 2014. Availability of circulating microRNAs As a biomarker for the early diagnosis of diffuse large B-Cell lymphoma. Blood 124 (21), 2988.
Kalluri, R., LeBleu, V.S., 2016. Discovery of double-stranded genomic DNA in circulating exosomes. Cold Spring Harb. Symp. Quant. Biol. 81, 275–280.
Kamerkar, S., et al., 2017. Exosomes facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer. Nature 546, 498.
Katz, M., et al., 2017. High prevalence of mutant KRAS in circulating exosome-derived DNA from early-stage pancreatic cancer patients. Ann. Oncol. 28 (4), 741–747.
Kerur, N., et al., 2011. IFI16 acts as a nuclear pathogen sensor to induce the inflammasome in response to Kaposi sarcoma associated herpesvirus infection. Cell Host Microbe 9 (5), 363–375.
Khan, F.M., et al., 2018. Inhibition of exosome release by ketotifen enhances sensitivity of cancer cells to doxorubicin. Cancer Biol. Ther. 19 (1), 25–33.
Khare, D., et al., 2017. Plasma microRNA profiling: exploring better biomarkers for lymphoma surveillance. PLoS One 12 (11), e0187722.
Kim, M.S., et al., 2016a. Development of exosome-encapsulated paclitaxel to overcome MDR in cancer cells. Nanomedicine 12 (3), 655–664.
Kim, M.S., et al., 2016b. Development of exosome-encapsulated paclitaxel to overcome MDR in cancer cells. Nanomed. Nanotechnol. Biol. Med. 12 (3), 655–664.
Kim, M.S., et al., 2018. Engineering macrophage-derived exosomes for targeted paclitaxel delivery to pulmonary metastases: in vitro and in vivo evaluations. Nanomedicine 14 (1), 195–204.
Klinker, M., et al., 2014. Human B cell-derived lymphoblastoid cell lines constitutively produce fas ligand and secrete MHCII + FasL + killer exosomes. Front. Immunol. 5 (144).
Koch, R., et al., 2014. Populational equilibrium through exosome-mediated Wnt signaling in tumor progression of diffuse large B-cell lymphoma. Blood 123 (14), 2189–2198.
Koch, R., et al., 2016. Nuclear trapping through inhibition of exosomal export by Indomethacin increases cytostatic efficacy of doxorubicin and pixantrone. Clin. Cancer Res. 22 (2), 395–404.
Kumar, B., et al., 2018. Acute myeloid leukemia transforms the bone marrow niche into a leukemia-permissive microenvironment through exosome secretion. Leukemia 32 (3), 575–587.
La Shu, S., et al., 2018. Metabolic reprogramming of stromal fibroblasts by melanoma exosome microRNA favours a pre-metastatic microenvironment. Sci. Rep. 8 (1), 12905.
Larouche, J.-F., et al., 2010. Lymphoma recurrence 5 years or later following diffuse large B-cell lymphoma: clinical characteristics and outcome. J. Clin. Oncol. 28 (12), 2094–2100.
Lee, M.J., et al., 2017. Mesenchymal stromal cells promote B-cell lymphoma in lacrimal glands by inducing immunosuppressive microenvironment. Oncotarget 8 (39), 66281–66292.
Lee, D.H., et al., 2018. Urinary exosomal and cell-free DNA detects somatic mutation and copy number alteration in urothelial carcinoma of bladder. Sci. Rep. 8 (1), 14707.
Lener, T., et al., 2015. Applying extracellular vesicles based therapeutics in clinical trials - an ISEV position paper. J. Extracell. Vesicles 4, 30087.
Li, J., et al., 2017a. EP300 single nucleotide polymorphism rs20551 correlates with prolonged overall survival in diffuse large B cell lymphoma patients treated with R-CHOP. Cancer Cell Int. 17 (1), 70.
Li, M., et al., 2017b. Model-based meta-analysis of progression-free survival in non-Hodgkin lymphoma patients. Medicine 96 (35), e7988.
Li, Q., et al., 2018. Exosomal miR-21-5p derived from gastric cancer promotes peritoneal metastasis via mesothelial-to-mesenchymal transition. Cell Death Dis. 9 (9), 854.
Li, J., Tian, T., Zhou, X., 2019. The role of exosomal shuttle RNA (esRNA) in lymphoma. Crit. Rev. Oncol. Hematol. 137, 27–34.
Lin, L.Y., et al., 2016. Tumour cell-derived exosomes endow mesenchymal stromal cells with tumour-promotion capabilities. Oncogene 35 (46), 6038–6042.
Lindenbergh, M.F.S., Stoorvogel, W., 2018. Antigen presentation by extracellular vesicles from professional antigen-presenting cells. Annu. Rev. Immunol. 36 (1), 435–459.
Liu, J., et al., 2016. Distinct dasatinib-induced mechanisms of apoptotic response and exosome release in imatinib-resistant human chronic myeloid leukemia cells. Int. J. Mol. Sci. 17 (4), 531.
Lo Cicero, A., Stahl, P.D., Raposo, G., 2015. Extracellular vesicles shuffling intercellular messages: for good or for bad. Curr. Opin. Cell Biol. 35, 69–77.
Luan, X., et al., 2017. Engineering exosomes as refined biological nanoplatforms for drug delivery. Acta Pharmacol. Sin. 38, 754.
Lunavat, T.R., et al., 2016. RNAi delivery by exosome-mimetic nanovesicles - Implications for targeting c-Myc in cancer. Biomaterials 102, 231–238.
Maas, S.L.N., Breakefield, X.O., Weaver, A.M., 2017. Extracellular vesicles: unique intercellular delivery vehicles. Trends Cell Biol. 27 (3), 172–188.
Madhavan, B., et al., 2015. Combined evaluation of a panel of protein and miRNA serum-exosome biomarkers for pancreatic cancer diagnosis increases sensitivity and specificity. Int. J. Cancer 136 (11), 2616–2627.
Maia, J., et al., 2018. Exosome-based cell-cell communication in the tumor microenvironment. Front. Cell Dev. Biol. 6, 18.
Mancek-Keber, M., et al., 2018. Extracellular vesicle-mediated transfer of constitutively active MyD88(L265P) engages MyD88(wt) and activates signaling. Blood 131 (15), 1720–1729.
Marleau, A.M., et al., 2012. Exosome removal as a therapeutic adjuvant in cancer. J. Transl. Med. 10, 134.
Mathivanan, S., Ji, H., Simpson, R.J., 2010. Exosomes: extracellular organelles important in intercellular communication. J. Proteomics 73 (10), 1907–1920.
Matsumura, T., et al., 2015. Exosomal microRNA in serum is a novel biomarker of recurrence in human colorectal cancer. Br. J. Cancer 113, 275.
Mazzeo, C., et al., 2016. Protein kinase D1/2 is involved in the maturation of multivesicular bodies and secretion of exosomes in T and B lymphocytes. Cell Death Differ. 23 (1), 99–109.
McKelvey, K.J., et al., 2015. Exosomes: mechanisms of uptake. J. Circ. Biomark. 4, 7.
Meckes, D.G., et al., 2013. Modulation of B-cell exosome proteins by gamma herpesvirus infection. Proc. Natl. Acad. Sci. U. S. A. 110 (31), E2925–E2933.
Menay, F., et al., 2017. Exosomes isolated from ascites of T-Cell lymphoma-bearing mice expressing surface CD24 and HSP-90 induce a tumor-specific immune response. Front. Immunol. 8, 286.
Messenger, S.W., et al., 2018. A Ca^{2+}-stimulated exosome release pathway in cancer cells is regulated by Munc13-4. J. Cell Biol.
Möhrmann, L., et al., 2018. Liquid biopsies using plasma exosomal nucleic acids and plasma cell-free DNA compared with clinical outcomes of patients with advanced cancers. Clin. Cancer Res. 24 (1), 181–188.
Nanbo, A., et al., 2018. Infection of Epstein–Barr virus in type III latency modulates biogenesis of exosomes and the expression profile of exosomal miRNAs in the burkitt lymphoma mutu cell lines. Cancers 10 (7), 237.
Nishida-Aoki, N., et al., 2017. Disruption of circulating extracellular vesicles as a novel therapeutic strategy against cancer metastasis. Mol. Ther. 25 (1), 181–191.
Osada-Oka, M., et al., 2016. Macrophage-derived exosomes induce inflammatory factors in endothelial cells under hypertensive conditions. Hypertens. Res. 40, 353.
Ostrowski, M., et al., 2010. Rab27a and Rab27b control different steps of the exosome secretion pathway. Nat. Cell Biol. 12 (1), 19–30 sup pp 1-13.
Paggetti, J., et al., 2015. Exosomes released by chronic lymphocytic leukemia cells induce the transition of stromal cells into cancer-associated fibroblasts. Blood 126 (9), 1106–1117.
Paiva, M., et al., 2008. FcgammaRIIa polymorphism and clinical response to rituximab in non-Hodgkin lymphoma patients. Cancer Genet. Cytogenet. 183 (1), 35–40.
Palma, J., et al., 2012. MicroRNAs are exported from malignant cells in customized particles. Nucleic Acids Res. 40 (18), 9125–9138.
Pascucci, L., et al., 2014. Paclitaxel is incorporated by mesenchymal stromal cells and released in exosomes that inhibit in vitro tumor growth: a new approach for drug delivery. J. Control. Release 192, 262–270.
Peinado, H., et al., 2012. Melanoma exosomes educate bone marrow progenitor cells toward a pro-metastatic phenotype through MET. Nat. Med. 18 (6), 883–891.
Peng, D., et al., 2018. miR-34c-5p promotes eradication of acute myeloid leukemia stem cells by inducing senescence through selective RAB27B targeting to inhibit exosome shedding. Leukemia 32 (5), 1180–1188.
Pérez-Callejo, D., et al., 2015. Action and resistance of monoclonal CD20 antibodies therapy in B-cell Non-Hodgkin Lymphomas. Cancer Treat. Rev. 41 (8), 680–689.
Pfreundschuh, M., et al., 2011. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. Lancet Oncol. 12 (11), 1013–1022.
Plebanek, M.P., et al., 2015. Nanoparticle targeting and cholesterol flux through scavenger receptor type B-1 inhibits cellular exosome uptake. Sci. Rep. 5, 15724.
Podolak, I., Galanty, A., Sobolewska, D., 2010. Saponins as cytotoxic agents: a review. Phytochem. Rev. 9 (3), 425–474.
Provencio, M., et al., 2017. mRNA in exosomas as a liquid biopsy in non-Hodgkin Lymphoma: a multicentric study by the Spanish Lymphoma Oncology Group. Oncotarget 8 (31), 50949–50957.
Pucci, M., et al., 2018. Extracellular vesicles As miRNA nano-shuttles: dual role in tumor progression. Target. Oncol. 13 (2), 175–187.
Qi, H., et al., 2016. Blood exosomes endowed with magnetic and targeting properties for cancer therapy. ACS Nano 10 (3), 3323–3333.
Qin, X., et al., 2017. Cisplatin-resistant lung cancer cell-derived exosomes increase cisplatin resistance of recipient cells in exosomal miR-100-5p-dependent manner. Int. J. Nanomedicine 12, 3721–3733.
Rainy, N., et al., 2016. Viral oncomiR spreading between B and T cells is employed by Kaposi's sarcoma herpesvirus to induce non-cell-autonomous target gene regulation. Oncotarget 7 (27), 41870–41884.
Raposo, G., et al., 1996. B lymphocytes secrete antigen-presenting vesicles. J. Exp. Med. 183 (3), 1161–1172.
Record, M., et al., 2014. Exosomes as new vesicular lipid transporters involved in cell-cell communication and various pathophysiologies. Biochim. Biophys. Acta 1841 (1), 108–120.
Ringuette Goulet, C., et al., 2018. Exosomes induce fibroblast differentiation into cancer-associated fibroblasts through TGFβ signaling. Mol. Cancer Res.
Robey, R.W., et al., 2018. Revisiting the role of ABC transporters in multidrug-resistant cancer. Nat. Rev. Cancer 18 (7), 452–464.
Rocha, N., et al., 2009. Cholesterol sensor ORP1L contacts the ER protein VAP to control Rab7-RILP-p150 glued and late endosome positioning. J. Cell Biol. 185 (7), 1209–1225.
Roschewski, M., Staudt, L.M., Wilson, W.H., 2013. Diffuse large B-cell lymphoma—treatment approaches in the molecular era. Nat. Rev. Clin. Oncol. 11, 12.
Roschewski, M., Staudt, L.M., Wilson, W.H., 2014. Diffuse large B-cell lymphoma-

treatment approaches in the molecular era. Nat. Rev. Clin. Oncol. 11 (1), 12–23.
Samanta, S., et al., 2017. Exosomes: new molecular targets of diseases. Acta Pharmacol. Sin. 39, 501.
Savina, A., et al., 2005. Rab11 promotes docking and fusion of multivesicular bodies in a calcium-dependent manner. Traffic 6 (2), 131–143.
Scott, D.W., Gascoyne, R.D., 2014. The tumour microenvironment in B cell lymphomas. Nat. Rev. Cancer 14, 517.
Simons, K., Vaz, W.L., 2004. Model systems, lipid rafts, and cell membranes. Annu. Rev. Biophys. Biomol. Struct. 33, 269–295.
Singh, V.V., et al., 2013. Kaposi's sarcoma-associated herpesvirus latency in endothelial and B cells activates gamma interferon-inducible protein 16-Mediated inflammasomes. J. Virol. 87 (8), 4417–4431.
Siravegna, G., et al., 2017. Integrating liquid biopsies into the management of cancer. Nat. Rev. Clin. Oncol. 14, 531.
Skotland, T., Sandvig, K., Llorente, A., 2017. Lipids in exosomes: Current knowledge and the way forward. Prog. Lipid Res. 66, 30–41.
Song, P., et al., 2016. Parkin modulates endosomal organization and function of the endo-lysosomal pathway. J. Neurosci. 36 (8), 2425–2437.
Srivastava, A., et al., 2016. Nanosomes carrying doxorubicin exhibit potent anticancer activity against human lung cancer cells. Sci. Rep. 6, 38541.
Stickney, Z., et al., 2016. Development of exosome surface display technology in living human cells. Biochem. Biophys. Res. Commun. 472 (1), 53–59.
Stoorvogel, W., 2015. Resolving sorting mechanisms into exosomes. Cell Res. 25 (5), 531–532.
Sun, D., et al., 2010. A novel nanoparticle drug delivery system: the anti-inflammatory activity of curcumin is enhanced when encapsulated in exosomes. Mol. Ther. 18 (9), 1606–1614.
Svensson, K.J., et al., 2013. Exosome uptake depends on ERK1/2-heat shock protein 27 signaling and lipid Raft-mediated endocytosis negatively regulated by caveolin-1. J. Biol. Chem. 288 (24), 17713–17724.
Swerdlow, S.H., et al., 2016. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 127 (20), 2375–2390.
Tarte, K., 2017. Role of the microenvironment across histological subtypes of NHL. Hematology Am. Soc. Hematol. Educ. Program 2017 (1), 610–617.
Tian, Y., et al., 2014. A doxorubicin delivery platform using engineered natural membrane vesicle exosomes for targeted tumor therapy. Biomaterials 35 (7), 2383–2390.
Tomasetti, M., et al., 2017. Exosome-derived microRNAs in cancer metabolism: possible implications in cancer diagnostics and therapy. Exp. Mol. Med. 49 (1), e285.
Trajkovic, K., et al., 2008. Ceramide triggers budding of exosome vesicles into multivesicular endosomes. Science 319 (5867), 1244–1247.
Ungefroren, H., et al., 2011. Interaction of tumor cells with the microenvironment. Cell Commun. Signal 9, 18.
Vader, P., Breakefield, X.O., Wood, M.J., 2014. Extracellular vesicles: emerging targets for cancer therapy. Trends Mol. Med. 20 (7), 385–393.
Valadi, H., et al., 2007. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat. Cell Biol. 9 (6), 654–659.
van den Bogaart, G., Jahn, R., 2011. Counting the SNAREs needed for membrane fusion. J. Mol. Cell Biol. 3 (4), 204–205.
van Eijndhoven, M.A.J., et al., 2016. Plasma vesicle miRNAs for therapy response monitoring in Hodgkin lymphoma patients. JCI Insight 1 (19), e89631.
van Niel, G., et al., 2011. The tetraspanin CD63 regulates ESCRT-independent and -dependent endosomal sorting during melanogenesis. Dev. Cell 21 (4), 708–721.
van Niel, G., D'Angelo, G., Raposo, G., 2018. Shedding light on the cell biology of extracellular vesicles. Nat. Rev. Mol. Cell Biol. 19, 213.
Vardaki, I., et al., 2016. Caspase-3–dependent cleavage of Bcl-xL in the stroma exosomes is required for their uptake by hematological malignant cells. Blood 128 (23), 2655–2665.
Wang, J., et al., 2014. Bone marrow stromal cell-derived exosomes as communicators in drug resistance in multiple myeloma cells. Blood 124 (4), 555–566.
Wang, J., et al., 2017. Exosomes derived from bone marrow stromal cells decrease the sensitivity of leukemic cells to etoposide. Oncol. Lett. 14 (3), 3082–3088.
Weber, J.A., et al., 2010. The microRNA spectrum in 12 body fluids. Clin. Chem. 56 (11), 1733–1741.
Xu, R., et al., 2018. Extracellular vesicles in cancer — implications for future improvements in cancer care. Nat. Rev. Clin. Oncol. 15 (10), 617–638.
Yang, C., et al., 2012. Exosomes released from Mycoplasma Infected tumor cells activate inhibitory B cells. PLoS One 7 (4), e36138.
Yang, S., et al., 2017. Detection of mutant KRAS and TP53 DNA in circulating exosomes from healthy individuals and patients with pancreatic cancer. Cancer Biol. Ther. 18 (3), 158–165.
Yeh, Y.-Y., et al., 2015. Characterization of CLL exosomes reveals a distinct microRNA signature and enhanced secretion by activation of BCR signaling. Blood 125 (21), 3297–3305.
Yogev, O., et al., 2017. Herpesviruses shape tumour microenvironment through exosomal transfer of viral microRNAs. PLoS Pathog. 13 (8), e1006524.
Younes, A., et al., 2016. The landscape of new drugs in lymphoma. Nat. Rev. Clin. Oncol. 14, 335.
Zhang, Q., et al., 2018. Exosomes originating from MSCs stimulated with TGF-beta and IFN-gamma promote Treg differentiation. J. Cell. Physiol. 233 (9), 6832–6840.
Zhang, F., et al., 2019. Specific decrease in B-Cell-Derived extracellular vesicles enhances post-chemotherapeutic CD8(+) t cell responses. Immunity 50 (3), 738–750 e7.
Zitvogel, L., et al., 1998. Eradication of established murine tumors using a novel cell-free vaccine: dendritic cell derived exosomes. Nat. Med. 4, 594.