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Exosomes as Mediators of Immune Regulation and Immunotherapy in Cancer

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Abstract

Exosomes are nanosized extracellular vesicles of endosomal origin that enclose a multitude of functional biomolecules. Exosomes have emerged as key players of intercellular communication in physiological and pathological conditions. In cancer, depending on the context, exosomes can oppose or potentiate the development of an aggressive tumor microenvironment, thereby impacting tumor progression and clinical outcome. Increasing evidence has established exosomes as important mediators of immune regulation in cancer, as they deliver a plethora of signals that can either support or restrain immunosuppression of lymphoid and myeloid cell populations in tumors. Here, we review the current knowledge related to exosome-mediated regulation of lymphoid (T lymphocytes, B lymphocytes and NK cells) and myeloid (macrophages, dendritic cells, monocytes, myeloid-derived suppressor cells and neutrophils) cell populations in cancer. We also discuss the translational potential of engineered exosomes as immunomodulatory agents for cancer therapy.

Keywords

Exosomes; cancer; immunotherapy; lymphoid cells; myeloid cells

Introduction

Exosomes are lipid bilayer-enclosed extracellular vesicles (EVs) ranging from 40 to 160 nm in diameter [1]. They are formed as intraluminal vesicles (ILVs) through the inward budding of endosomal membranes into multivesicular bodies (MVBs). After biogenesis, MVB-resident ILVs can follow the secretory pathway for release into the extracellular milieu

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Author contributions

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Conflict of interest

MDACC and R.K. hold patents in the area of exosome biology that are licensed to Codiak Biosciences, Inc. MDACC and R.K. are stock equity holders in Codiak Biosciences, Inc. R.K. is a consultant and scientific adviser for Codiak Biosciences, Inc. F.G.K. has no conflict of interest to declare.

as exosomes; or, as an alternative fate, they can merge with lysosomes for degradation [1–3]. Exosomes harbor multiple types of biomolecules, including nucleic acids (e.g. DNA, mRNA, miRNA, lncRNA) [4–7], lipids [8], metabolites [9, 10], proteins [11, 12] and carbohydrates [13]. Exosomes mediate intercellular communication through the transfer of their functional constituents to the target cells, or through engagement of membrane receptor-mediated signaling [14–16]. From a translational perspective, pre-clinical studies harnessing exosomes for cancer treatment have shown promising results [17–19]. Moreover, exosomes derived from body fluids and circulation can serve as non-invasive liquid biopsies, which allow for the early detection of pathologies, and for the assessment of patient prognosis and response to therapy [16, 20–22]. Of note, exosomes have been shown to harbor proteins that protect them from phagocytosis and complement-mediated lysis, mechanisms that may contribute to their stability [18, 23].

Microvesicles (MVs) are a class of EVs generated through direct budding from the plasma membrane. Their diameter ranges from 50 to 1,000 nm, and like exosomes, MVs were shown to mediate intercellular communication in physiological and pathological conditions [1, 2, 24].

The role of exosomes in shaping the immune landscape of tumors is an evolving area of research. An effective cycle of anti-tumor immune response begins with the release of antigens by cancer cells, and is followed by antigen-presenting cell (APC)-mediated processing and presentation of antigens to T lymphocytes. In turn, primed T lymphocytes infiltrate the tumor to perform their anti-tumor functions [25]. A broad spectrum of cell(s)-intrinsic and microenvironmental mechanisms orchestrate each stage of this cycle to determine whether a pro- or an anti-tumor immune response is mounted [25, 26]. Accordingly, exosome-derived signals can act to suppress or promote different aspects of immune responses in cancer [27–31].

Here, we discuss the current knowledge pertaining the contribution of exosomes in modulating lymphoid and myeloid cell functions in cancer. Moreover, we provide an overview on the role of engineered exosomes in cancer immunotherapy.

Exosomes regulate lymphoid cell functions in cancer

Exosomes modulate fundamental functional aspects of the lymphoid components of the tumor microenvironment (TME), and exert direct impact in immunosuppression, tumor progression and response to existing cancer therapies. In this section, we review the mechanisms of exosome-mediated regulation of T lymphocytes, B lymphocytes, and natural killer (NK) cell functions in cancer (Figure 1). A summary of these mechanisms is described in Table 1.

T lymphocytes

T cells mediate key immune responses in the context of infection, cancer and autoimmune diseases. Cytotoxic $CD8^+$ T lymphocytes and $CD4^+$ T helper 1 (T_H1) cells are major players of anti-tumor immune responses [32, 33]. On the other hand, regulatory T cells (T_{regs}) are an immunosuppressive subset of $CD4^+$ T cells in the tumor microenvironment [34]. Therefore,

mechanisms that favor the recruitment and expansion of cytotoxic $CD8^+$ T lymphocytes and T_H1 cells over T_{regs} support an efficient anti-tumor immune response. T helper 17 (T_H17) cells have a dual role in cancer, as they can either accelerate tumor progression through induction of angiogenesis and immunosuppression, or foster anti-tumor immunity through recruitment and activation of immune cells [35].

Several T cell-intrinsic and -extrinsic factors can promote dysfunction and exhaustion of $CD4^+$ and $CD8^+$ T lymphocytes in cancer. These factors include persistent T cell receptor (TCR) engagement, immune-checkpoint signals, cytokine milieu, nutrient and oxygen availability [26, 36]. Exosomes are often an overlooked component contributing to T cell dysfunction in cancer. However, a growing body of evidence has demonstrated that exosomes derived from cancer and from TME cells can engage an array of functional responses in T cells, which include inducing apoptosis, suppressing proliferation and activation, and fostering a T_{reg} phenotype [16, 27, 37, 38].

The interaction between Fas ligand (FasL) with Fas receptor initiates T cell apoptosis through activation of a caspase cascade [39]. FasL was identified in MVs and exosomes derived from different sources, including melanoma [40, 41], prostate cancer [37], squamous cell carcinoma of the head and neck (SCCHN) [41], ovarian cancer [42], oral squamous cell carcinoma (OSCC) [43], and activated T cells [41, 44, 45]. Strikingly, exosomes and MVs harboring FasL have been implicated in inducing apoptosis of T lymphocytes [37, 40–43]. In addition to FasL, MVs isolated from colorectal cancer (CRC) cells and patient plasma were decorated with TNF-related apoptosis-inducing ligand (TRAIL), and induced T cell apoptosis in a FasL- and TRAIL-dependent manner [46]. In addition to promoting T cell apoptosis, FasL in serum-derived membrane vesicles correlated with tumor burden and nodal involvement in OSCC patients, thus suggesting a potential role as a biomarker [43]. The T cell apoptosis induced by FasL-containing tumor derived-MVs could be prevented upon pre-treatment with IRX-2, an immunotherapeutic agent that contains physiological amounts of various cytokines [47]. Additionally, IRX-2 prevented the MV-induced up-regulation of Fas receptor, abrogated caspase 8 activation, and promoted nuclear translocation of nuclear factor kappa B (NF-κB) in T cells [48]. The cytoprotection conferred by IRX-2 was dependent on phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) axis and on protein synthesis, as the use of an Akt inhibitor or cycloheximide abrogated the anti-apoptotic effects of IRX-2 in T lymphocytes [47, 48].

Another mechanism of immune evasion in cancer is initiated by the interaction between the programmed death-ligand 1 (PD-L1), found in cancer cells and in TME cell populations, with the programmed cell death protein 1 (PD-1) receptor, expressed on activated T cells [49, 50]. Notably, exosomal PD-L1 has emerged as an additional mechanism of tolerance in cancer [31, 51]. *In vitro*, exosomal PD-L1 dramatically suppressed T cell activation and proliferation [16, 52, 53]; decreased the levels of T_H1 cytokines and granzyme B [16]; inhibited cell killing and the activation of extracellular signal-regulated kinase (ERK) and NF-κB in T cells [54]. Moreover, exosomes can transfer the PD-L1 protein to cancer and TME cells and convert them from PD-L1-negative to PD-L1-positive, suggesting a mechanism whereby exosomes can amplify immunosuppression in the tumor microenvironment through horizontal transfer of PD-L1 protein to cells [54]. *In vivo*,

exosomal PD-L1 enhanced B16-F10 tumor growth and suppressed anti-tumor immunity systemically [16]. Moreover, in the TRAMP-C2 and MC-38 tumor models, exosomal PD-L1 enhanced tumor progression and suppressed the activity of $CD8^+$ T cells in the draining lymph nodes, a phenotype that was rescued upon blockage of exosome secretion or upon PD-L1 deletion [55]. Exosomal PD-L1 also accelerated the growth of orthotopic 4T1 tumors, and the blockage of exosome secretion with GW4869 or Rab27a knockout (KO) had a synergistic effect with anti-PD-L1 treatment to suppress 4T1 tumor growth [54]. In addition to fostering tumor progression and immune tolerance, exosomal PD-L1 has been shown to provide prognostic value to several types of cancer. In head and neck squamous cell carcinoma (HNSCC), the levels of PD-L1 in plasma-derived exosomes were significantly higher in patients with active disease in comparison to patients with no evidence of disease after therapy [52]. In glioblastoma (GBM) patients, the levels of PD-L1 DNA in serum and plasma-derived EVs correlated with tumor volume [53]. In non-small cell lung cancer (NSCLC), the levels of PD-L1 in serum-derived exosomes were higher in patients with progressed disease features, including advanced tumor stage, larger tumor size, positive lymph node status and metastasis, thereby suggesting that exosomal PD-L1 can be used to monitor NSCLC progression [56]. In addition, the abundance of PD-L1 in exosomes isolated from plasma of NSCLC patients correlated with PD-L1 positivity in tumor tissues [57]. In metastatic melanoma patients, changes in the levels of circulating exosomal PD-L1 at early stages of anti-PD1 therapy could stratify patients into clinical responders from non-responders [16]. Moreover, the levels of exosomal PD-L1 inversely correlated with the response of melanoma patients to immune and targeted therapies [22]. A recent study found that the use of 5-fluorouracil (5-FU) may influence the levels of exosomal PD-L1 in circulation. In stage III–IV gastric cancer patients undergoing repeated cycles of 5-FU treatment, the levels of exosomal PD-L1 increased in comparison to baseline [58].

In addition to FasL and PD-L1, exosomes isolated from cancer patients and from cancer cells induced immunosuppressive traits in the target T cells through several mechanisms. Exosomes isolated from plasma of Epstein-Barr virus (EBV)-associated nasopharyngeal carcinoma (NPC) patients or mice transplanted with NPC tumors, harbored Galectin-9. Upon binding to the receptor T-cell immunoglobulin and mucin-domain containing-3 (Tim-3), exosomal Galectin-9 promoted apoptosis of EBV-specific $CD4^+$ T cells. The neutralization of Galectin-9 or Tim-3 reversed the exosome-induced apoptosis [59]. Exosomes derived from NPC cells and patients inhibited T cell proliferation, induced a T_{reg} phenotype and hindered T_H1 and T_H17 differentiation. Specifically, the NPC exosomes reduced the levels of interleukin-2 (IL-2), interferon gamma (IFNγ) and interleukin-17 (IL-17) and increased the levels of interleukin-1β (IL-1β), interleukin-6 (IL-6) and interleukin-10 (IL-10) released from $CD4^+$ and $CD8^+$ T cells [60]. The exosome-mediated transfer of 14–3-3ζ (or 14–3-3 protein zeta) from hepatocellular carcinoma (HCC) cells to T cells elicited immunosuppression, as demonstrated by impaired T cell activation and proliferation, and enhanced exhaustion and T_{reg} phenotype [61]. Exosomes from ascites fluid of ovarian cancer patients harbored the ganglioside GD3 at their surface, which contributed to the suppression of T cell activation. This finding was validated via addition of GD3 in liposomes, which also inhibited T cell activation; and through the use of GD3 blocking antibody or sialidase treatment, which ameliorated the exosome-induced T

cell phenotype [62]. In addition, exosomes isolated from ascites fluid of ovarian cancer patients inhibited TCR-dependent activation of T cells, a phenotype that was transient and reversible upon exosomes removal [63]. Exosomes isolated from plasma of melanoma patients suppressed activation and proliferation, and enhanced apoptosis of $CD8^+$ T cells. The melanoma-derived exosomes had increased levels of the immunosuppressive proteins FasL and TRAIL and decreased levels of the immunostimulatory proteins OX40 ligand (OX40L), OX40 and CD40 ligand (CD40L) [64]. Exosomes isolated from plasma of head and neck cancer patients with active disease enhanced apoptosis of $CD8^+$ T cells and suppressed the proliferation of $CD4^+$ T cells. The precise mechanism of action of the exosomes was not determined; however, the levels of several immunosuppressive proteins were increased, namely cyclooxygenase-2 (COX-2), transforming growth factor beta 1 (TGFβ1), PD-1, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and TRAIL [65]. B16-F10-derived exosomes enhanced tumor growth and apoptosis of $CD4^+$ T cells. The exosomes increased the levels of Fas on T cell surface and enhanced caspase activation. Moreover, miRNAs that suppress the levels of anti-apoptotic proteins may be responsible for the effect of B16-F10-derived exosomes on $CD4^+$ T cells [66]. Furthermore, melanoma-derived exosomes harboring tumor necrosis factor (TNF) transmitted redox signaling to recipient T lymphocytes [67].

In cancer, several reports have shown that EVs can foster a T_{reg} phenotype. Surface-bound TGFβ1 in exosomes isolated from malignant effusions of cancer patients supported tolerance through the maintenance of T_{reg} number and suppressive function [38]. Tumor-derived MVs induced the expansion of $CD4^+$ $CD25^+$ $FoxP3^+$ T_{regs}, as opposed to MVs derived from DCs, which were not implicated in promoting the T_{reg} phenotype [41]. Cancer cell-derived MVs transferred miR-214 to $CD4^+$ T cells to suppress phosphatase and tensin homolog (PTEN) expression and promote T_{reg} expansion. Notably, the miR-214-induced $CD4^+$ $CD25^+$ $FoxP3^+$ T_{regs} increased the levels of secreted IL-10 and promoted tumor growth *in vivo* [68]. Exosomes isolated from mutant KRAS NSCLC cell lines and patient serum promoted the conversion of naïve $CD4^+$ T cells into T_{regs}. The transfection of naïve T cells with mutant KRAS cDNA mirrored the phenotype, suggesting a role for exosome-mediated transfer of mutant KRAS DNA in driving the conversion. Accordingly, tumor tissues from mutant KRAS patients were enriched in $FoxP3^+$ T_{regs} in comparison to the WT KRAS counterparts [69]. Breast cancer-derived exosomes induced $CD73^+\gamma\delta1$ T_{reg} cells through exosome-mediated delivery of the lncRNA SNHG16. In the recipient cells, lncRNA SNHG16 competitively bound to miR-16–5p, enabling the activation of TGFβ1/SMAD5 pathway and promoting the expression of CD73 [70].

Exosomes derived from TME cells also contribute to the suppression of T cell functions. The exosome-mediated transfer of the miRNA Let-7d from T_{regs} to T_H1 cells decreased T_H1 proliferation and IFNγ secretion [71]. In epithelial ovarian cancer (EOC) patients, the T_{reg}/T_H17 ratio was higher in tumors and in metastatic tissues in comparison to benign tumors and peritoneum. Notably, the imbalance in the T_{reg}/T_H17 ratio occurred through exosome-mediated transfer of miR-29a-3p and miR-21–5p from macrophages to $CD4^+$ T cells, which suppressed signal transducer and activator of transcription 3 (STAT3) signaling [14].

Exosomes can suppress T cell function not only directly, but also indirectly through the processing of intermediates that elicit tolerance. In fact, cancer-derived exosomes harboring CD39 and CD73 mediated the hydrolysis of extracellular adenosine triphosphate (ATP) to generate adenosine, which in turn suppressed T cell functions [72]. Chemotherapeutic treatments trigger tumor cell death and release vast amounts of ATP to the extracellular milieu. $CD19^+$ B cell-derived EVs hydrolyzed extracellular ATP via CD39 and CD73 into adenosine, which then suppressed $CD8^+$ T cell responses in the post-chemotherapy setting. Notably, serum-derived $CD19^+$ EVs were increased in tumor-bearing mice and in cancer patients, and had an inverse correlation with improved patient prognosis post-chemotherapy. Hypoxia-inducible factor-1α (HIF-1α) supported the release of $CD19^+$ EVs from B cells through increase of Rab27a expression. *In vivo*, the silencing of Rab27a in B cells improved the efficacy of chemotherapy and increased the infiltration of $CD8^+$ T cells [73, 74]. Of note, adenosine can also induce a tolerogenic phenotype in dendritic cells (DCs) [75, 76]. Therefore, the exosome-mediated conversion of ATP into adenosine likely foster immunosuppression in distinct cell populations of the tumor microenvironment.

Exosomes can also transmit activating signals to T cells. Indeed, APC-derived exosomes carrying antigenic peptide/major histocompatibility complex (MHC) and costimulatory proteins were shown to directly present antigens to T cells and induce their activation. However, the potency of exosome-induced T cell activation was weaker than the one elicited by APCs [77–79]. Of note, exosomes can also mediate indirect antigen presentation through the transfer of antigenic peptide/MHC complexes to APCs [78, 80–82]. Mechanisms of direct and indirect antigen presentation mediated by EVs have been previously reviewed [27, 83].

B lymphocytes

B cells have multiple roles in the context of cancer immunity. They can produce immunoglobulins, present antigens, provide costimulatory signals and release cytokines. Importantly, the TME contain functionally heterogeneous B cell populations, which can either support or suppress anti-tumor immunity [84].

HCC-derived exosomes promoted the expansion of the $TIM\text{-}1^+$ regulatory B cell (B_{reg}) population, which expressed IL-10, and suppressed $CD8^+$ T cell proliferation, tumor necrosis factor-α (TNF-α) and IFNγ production. Mechanistically, exosome-bound high mobility group box-1 (HMGB1) engaged the toll-like receptor 2/4 (TLR2/4) and mitogen-activated protein kinase (MAPK) signaling in B cells to drive the B_{reg} phenotype. This mechanism can contribute to immune tolerance in HCC patients, as the accumulation of B_{regs} in HCC tumors correlated with poor clinical outcome [85]. MVs isolated from esophageal cancer cells induced the conversion of naïve B cells into TGFβ-producing B_{regs}, which in turn suppressed the proliferation of $CD8^+$ T cells [86].

Mycoplasma-infected cancer cells released exosomes that modulated B cell functions. Specifically, the exosomes enhanced the activation and expansion of inhibitory B cells, which suppressed T cell proliferation and impaired TCR signaling. This finding suggests a potential exosome-mediated mechanism implicated in mycoplasma-dependent immunosuppression [87].

A study has shown that pancreatic ductal adenocarcinoma (PDAC)-derived exosomes harbor tumor antigens able to induce autoantibodies and to bind to circulating immunoglobulins. Moreover, the PDAC-derived exosomes inhibited PDAC serum-mediated complement-dependent cytotoxicity against cancer cells. Taken together, the authors suggest that PDAC-derived exosomes can function as decoys to oppose complement-mediated cytotoxicity towards cancer cells [88].

A treatment modality in the setting of B-cell lymphoma corresponds to the administration of the anti-CD20 antibody rituximab. Exosomes have been shown to function as decoys that impair rituximab therapy. Specifically, B-cell lymphomas released exosomes containing CD20, which bound to the therapeutic anti-CD20 antibodies and protected the cancer cells from targeting and consequent cell death [89].

Recent studies revealed that B cells and tertiary lymphoid structures are associated with improved clinical outcome in metastatic melanoma, sarcoma and renal cell carcinoma patients undergoing immune checkpoint blockade (ICB) therapy [90–92]. In this setting, exosomes can be used to distinguish responders from non-responders to ICB therapy through the evaluation of B cell markers at exosome surface. Indeed, B cell-related exosomes positive for CD20 and CD27, were significantly increased in responders in comparison to non-responders to ICB therapy [92].

NK cells

NK cells are an innate lymphoid cell population with cytolytic function towards microbial agents and tumors [93].

Several reports have shown that exosomes can reduce the levels of the activating receptor natural killer group 2 member D (NKG2D) in NK cells. Indeed, NKG2D levels were decreased in NK cells treated with exosomes from melanoma [64], head and neck cancer patients [65], and acute myeloid leukemia (AML) patients and patient-derived xenografts (PDX) [94]. Shedding light into the potential mechanisms of exosome-mediated downregulation of NKG2D, a study has shown that cancer exosomes harbored TGFβ1 and several NKG2D ligands (MICA, MICB, ULBP-1, ULBP-2, or ULBP-3). The exosome-mediated reduction of NKG2D in NK cells was partially rescued upon MICA neutralization, and almost abolished upon TGFβ1 neutralization, suggesting a dominant role for TGFβ1 in this mechanism [95]. Similarly, HeLa-derived exosomes carried the full-length membrane-bound MICA*008 protein, and the treatment of NK cells with exosomal MICA*008 decreased surface levels of NKG2D [96].

Exosomes derived from mammary carcinoma enhanced tumor growth and inhibited NK cytotoxic activity, release of perforin, expression of cyclin D3 and activation of Jak3 pathway, suggesting that cancer-derived exosomes can favor tumor growth through impairment of NK functions [97]. HCC-derived exosomes promoted NK cell exhaustion through circular ubiquitin-like with PHD and ring finger domain 1 (circUHRF1) RNA, which suppressed miR-449c-5p and induced TIM-3 expression in NK cells. Notably, in HCC patients, higher circUHRF1 levels were associated with resistance to anti-PD1 therapy, and in subcutaneously implanted HCCLM3 tumors, the knockdown of circUHRF1 enhanced

the sensitivity to anti-PD-1 therapy [98]. Exosomal miR-378a-3p from irradiated U87 cancer cells impaired NK cytotoxicity through down-regulation of granzyme B. In line with this finding, the expression of miR-378a-3p in exosomes derived from GBM and cervix cancer patients treated with radiotherapy inversely correlated with the serum levels of granzyme B [99].

Exosomes have also been shown to potentiate NK cell functions. Cancer-derived exosomes enhanced NK activation, migration and cytolytic activity in a heat shock protein 70 (Hsp70)-dependent manner. Mechanistically, exosomal Hsp70 elicited apoptosis of cancer cells through NK release of granzyme B [100]. DC and 293T-derived exosomes harboring the protein HLA-B-Associated Transcript-3 (BAT3) bound to NKp30 receptor in NK cells and enhanced the secretion of TNF-α and IFNγ. The dependency of exosomal BAT3 in mediating this phenotype was confirmed through overexpression and silencing experiments [101]. The intratumoral injection of exosomes from irradiated melanoma cells delayed B16F10GP tumor growth and enhanced the infiltration of NK cells producing IFNγ. The depletion of NK cells abrogated the exosome-mediated anti-tumor phenotype, as opposed to the depletion of $CD8^+$ T cells, which had no effect [102]. DC-derived exosomes from murine and human origin enhanced NK cell proliferation and activation through IL-15Rα and NKG2D, respectively. Accordingly, in a phase I clinical trial testing DC-derived exosomes as cancer vaccine, a subset of melanoma patients restored the number and the NKG2D-dependent functions of NK cells [103].

Exosomes regulate myeloid cell functions in cancer

In the cancer setting, exosomes modulate key aspects of myeloid cell functions. In this section, we describe exosome-mediated mechanisms implicated in the functional reprogramming of tumor-associated macrophages (TAMs), DCs, monocytes, myeloid-derived suppressor cells (MDSCs), and neutrophils (Figure 2). A summary of these mechanisms can be found in Table 2.

Macrophages

Macrophages are cells from the mononuclear phagocytic system involved in the clearance of cells, pathogens and substances through phagocytosis. In addition, macrophages secrete a plethora of immunomodulatory cytokines and mediate key functions of innate and adaptive immune responses. In cancer, macrophages display exceptional functional plasticity and are traditionally classified as tumor-restraining M1, and tumor-promoting M2 population [104, 105].

Several studies reported that cancer cell-derived exosomes mediate the polarization of macrophages towards the tumor-promoting M2 phenotype. Exosomes isolated from EOC cells and patient serum were enriched with miR-222–3p, which was transferred to macrophages to induce M2 polarization. Mechanistically, miR-222–3p enhanced STAT3 activation through targeting of suppressor of cytokine signaling 3 (SOCS3). *In vivo*, miR-222–3p induced the M2 phenotype, promoted tumor growth, and increased the density of $CD31^+$ microvessels and LYVE-1^+ lymphatic vessels. Accordingly, the levels of miR-222–3p in serum-derived exosomes from EOC patients were higher than

healthy individuals [106]. p53-mutant cancer cells reprogrammed macrophages to a tumor-supporting anti-inflammatory state through exosome-mediated transfer of miR-1246. In macrophages, miR-1246 enhanced the secretion of anti-inflammatory cytokines and epithelial to mesenchymal transition (EMT)-promoting factors. *In vivo*, cancer cells co-transplanted with the mutant p53-reprogrammed macrophages or with macrophages transfected with miR-1246 enhanced tumor growth and metastasis. In CRC patients, mutant p53 positively correlated with TAMs and with miR-1246 expression [107]. Melanoma-derived exosomes transferred miR-125b-5p to macrophages and suppressed the expression of lysosomal acid lipase A (LIPA). In turn, this contributed to tumor-promoting properties and enhanced survival of macrophages [108]. Hypoxic pancreatic cancer cells shuttled miR-301a-3p to macrophages through exosomes. In macrophages, miR-301a-3p promoted M2 polarization via PTEN/PI3K signaling. The M2 polarized macrophages enhanced the metastatic ability of pancreatic cancer cells, both *in vitro* and *in vivo* [109]. Exosomes from the human PDAC cells AsPC-1 induced macrophage polarization towards the immunosuppressive M2 phenotype. Moreover AsPC-1 exosomes contained high levels of arachidonic acid, which can regulate inflammatory responses upon conversion to prostaglandin. Indeed, macrophages treated with AsPC-1-derived exosomes enhanced the secretion of prostaglandin 2, and of several other factors implicated in tumor progression, including vascular endothelial growth factor A (VEGFA), IL-6, IL-1β, monocyte chemoattractant protein-1 (MCP-1), TNF-α and matrix metalloproteinase-9 (MMP-9) [110]. Pancreatic cancer cells undergoing autophagy-dependent ferroptosis released exosomes containing oncogenic $KRAS^{G12D}$ protein, which was transferred to macrophages to promote M2 polarization through STAT3-dependent fatty acid oxidation. The blockage of $KRAS^{G12D}$ release or uptake abrogated the macrophage-mediated pancreatic tumor growth *in vivo*. In pancreatic cancer patients, high $KRAS^{G12D}$ in macrophages correlated with decreased survival [111]. Exosomes released by metastatic osteosarcoma cells, but not from non-metastatic osteosarcoma cells, induced M2 polarization and impaired phagocytosis, efferocytosis, and macrophage-dependent tumor cell killing [112]. Exosomes derived from lung cancer cells promoted M2 polarization and remodeling of macrophage metabolism, as demonstrated by enhanced oxygen consumption rate [113]. The exosome-mediated transfer of miR-25–3p, miR-130b-3p and miR-425–5p from CRC cells to macrophages induced M2 polarization through suppression of PTEN. In turn, the M2 macrophages induced EMT and angiogenesis, and enhanced the metastatic dissemination of cancer cells to the liver. Accordingly, in CRC patients, the expression levels of miR-25–3p, miR-130b-3p and miR-425–5p in serum-derived exosomes correlated with tumor progression and metastasis [114].

Exosomes released from breast cancer cells transferred gp130 to bone marrow-derived macrophages (BMDMs), which in turn promoted the activation of STAT3 signaling, enhanced the levels of pro-tumorigenic cytokines and the survival of BMDMs. The inhibition of gp130 or blockage of exosome uptake in BMDMs rescued the exosome-mediated phenotype, thus confirming that exosomal gp130 is involved in the polarization of BMDMs to a tumor-supporting phenotype [115].

Endoplasmic reticulum (ER) stress can impede the development of anti-tumor immune responses through reprogramming of several immune cell populations [116, 117]. In

macrophages, exosomes derived from liver cancer cells undergoing ER stress promoted the secretion of IL−6, MCP−1, IL−10 and TNF-α through STAT3 signaling [118]. Another study has shown that exosomal miR-27a-3p released from breast cancer cells undergoing ER stress promoted immune evasion through up-regulation of PD-L1 expression in macrophages [119]. These two studies may indicate that exosomes can contribute to ER stress-mediated reprogramming of macrophages.

Cancer cell-derived exosomes have been shown to activate NF-κB signaling in macrophages [120–122]. Breast cancer-derived exosomes promoted the activation of NF-κB and enhanced the levels of IL-6, TNF-α, granulocyte colony-stimulating factor (GCSF) and C-C motif chemokine ligand (CCL2) in macrophages; a phenotype dependent on TLR2 and MyD88, but not on TLR4 or TLR3/7/8/9. In addition, palmitoylated proteins at the exosome surface also contributed to the exosome-mediated NF-κB activation [120]. Exosomes derived from gastric cancer cells induced the activation of NF-κB and the expression of the pro-inflammatory factors IL-6, TNF-α, and CCL2 in macrophages. In turn, the exosome-reprogrammed macrophages enhanced the invasive, migratory and proliferative capabilities of cancer cells *in vitro* [121].

In macrophages, exosomal miRNAs were shown to function as agonists of TLR receptors to elicit a pro-metastatic inflammatory response. Specifically, miR-21 and miR-29a in exosomes from cancer cells operated as ligands of TLR receptors in macrophages, promoting NF-κB activation and increasing the secretion of IL-6 and TNF-α. This mechanism enhanced the formation of lung multiplicities *in vivo,* using a model of tail vein injection of Lewis lung cancer (LLC) cells in mice [122].

Lung cancer cells deployed exosomes to lower the host innate antiviral immunity. This occurred through the transfer of activated epidermal growth factor receptor (EGFR) from exosomes to the host macrophages. Using the LLC model combined with viral infection, the authors observed an increased viral load and impaired innate immunity upon exosome administration, which was dependent on EGFR and mitogen-activated protein kinase kinase kinase 2 (MEKK2). Mechanistically, MEKK2 phosphorylated interferon regulatory factor 3 (IRF3), mediated IRF3 poly-ubiquitination and inhibited IRF3 dimerization, nuclear translocation and transcriptional activity in the setting of viral infection [15].

DCs

DCs are regarded as specialized antigen-presenting cells mediating pivotal functions in innate and adaptive immune responses. In cancer, an array of signals can impair the differentiation and maturation of DCs, thereby favoring the emergence of DCs with tolerogenic potential [123].

Exosomes derived from cancer cells can contribute to the emergence of dysfunctional DCs. miR-212–3p was transferred from pancreatic cancer cells to DCs through exosomes. In DCs, miR-212–3p targeted the regulatory factor X-associated protein (RFXAP) and decreased MHCII expression, contributing to immune tolerance. *In situ* hybridization and immunohistochemistry (IHC) analyses of PDAC patient tissues revealed a negative correlation between miR-212–3p and RFXAP [124]. The exosome-mediated transfer of

miR-203 from pancreatic cancer cells to DCs decreased the expression of TLR4 and reduced the secretion of TNF-α and interleukin-12 (IL-12) [125]. Exosomes derived from murine and human breast cancer cells suppressed DC differentiation. *In vivo*, the exosomes from TS/A murine mammary adenocarcinoma cells targeted myeloid precursor cells in the bone marrow. Mechanistically, TS/A exosomes enhanced the levels of IL-6 and activation of Stat3 signaling in $CD11b^+$ cells. The involvement of IL-6 in the exosome-mediated impairment of DC differentiation was confirmed using bone marrow cells from IL-6 KO mice. In that setting, the tumor exosomes only partially inhibited DC differentiation, and the treatment with recombinant IL-6 restored the exosome-dependent inhibition of DC differentiation [126]. Exosomes released by LLC and 4T1 cancer cells inhibited differentiation, induced apoptosis, and enhanced the expression of PD-L1 in DCs. Moreover, the exosomes inhibited DC migration to lymph nodes, decreased T_H1 differentiation and induced a T_{reg} phenotype. The treatment with anti-PD-L1 partially rescued the $CD4^+$ T cell functions suppressed by the exosome-treated DCs [127]. In addition to cancer cells, T_{regs} have been shown to release exosomes that impair DC functions. The levels of miR-150–5p and miR-142–3p were elevated in DCs upon interaction with T_{regs} or treatment with their shed exosomes. In turn, this induced a tolerogenic DC phenotype, as measured by increased IL-10 and reduced IL-6 levels [128].

Exosomes have also been shown to support DC immunity through activation of cyclic GMP–AMP synthase (cGAS)/stimulator of interferon genes (STING) pathway [129–131]. The cytosolic DNA-sensing pathway cGAS/STING is a crucial defense mechanism against infections, which promotes the transcription of type I interferons and the activation of NF-κB [132]. In cancer, the role cGAS/STING pathway is context-dependent, as reports have shown that this pathway can either promote or suppress anti-tumor immunity [133, 134]. Breast cancer cells treated with Topocan shed exosomes containing DNA, which promoted DC activation through engagement of cGAS/STING pathway [129]. Exosomes derived from irradiated mouse breast cancer cells transferred double-stranded DNA (dsDNA) to DCs and enhanced the levels of costimulatory molecules and STING-mediated activation of IFN-I in DCs. *In vivo*, the exosome-mediated transfer of dsDNA engaged $CD8^+$ T cell responses, and had a protective role in tumor development [130]. Accordingly, T cell-derived EVs transferred genomic and mitochondrial DNA to DCs, which engaged the cGAS/STING pathway and promoted expression of IRF3-dependent interferon regulated genes in DCs. Notably, this EV-dependent DNA priming, mediated resistance of DCs to subsequent viral infections [131].

Monocytes

Monocytes are an innate immune cell population able to differentiate into tumor-associated macrophages and dendritic cells, promote angiogenesis, remodel the extracellular matrix, kill tumor cells, and recruit lymphocytes. Notably, this versatile cell population can either suppress or promote anti-tumor immunity depending on the context [135].

Cancer cell-derived exosomes have been shown to foster immunosuppressive functions of monocytes. In pancreatic cancer patients, immunosuppressive monocytes (defined as $CD14^+HLA\text{-}DR^{lo/neg}$) in circulation were increased in comparison to controls.

Notably, pancreatic cancer-derived exosomes mediated the downregulation of HLA-DR in monocytes, induced arginase expression and ROS [136]. The overexpression of the EMT transcriptional factor Snail in HNSCC cells enhanced the production of miR-21, which was released in exosomes. Exosomal miR-21 was transferred to monocytes, where it suppressed the expression of M1 and increased the levels of M2 macrophage markers. *In vivo*, the knockdown of miR-21 in cancer cells decreased tumor growth, M2 infiltration and angiogenesis in subcutaneous tumors. In HNSCC patient samples, a high expression of miR-21 correlated with increased SNAI1 and with M2 polarization, as measured by the marker MRC1 [137]. Exosomes isolated from plasma of chronic lymphocytic leukemia (CLL) patients were enriched with the noncoding Y RNA hY4 in comparison to exosomes from healthy donors. The treatment of monocytes with hY4 induced expression of PD-L1, as well as the release of CCL2, C-C motif chemokine ligand 4 (CCL4), and IL-6. This monocyte reprogramming occurred in a TLR7-dependent manner, and the use of chloroquine ameliorated the effects induced by hY4 and inhibited CLL development *in vivo* [138]. Exosomes from glioblastoma-derived stem cells (GSC) also induced an immunosuppressive phenotype by promoting monocyte differentiation into M2 macrophages and enhancing the levels of PD-L1 [139]. Similarly, exosomes from gastric cancer mediated monocytes differentiation into $PD1^+$ TAMs with M2 characteristics *in vitro* and *in vivo*. Notably, the $PD1^+$ macrophages correlated with poor prognosis in gastric cancer, and suppressed $CD8^+$ T cell functions, as measured by decreased proliferation, IFNγ and perforin levels [140].

Exosomes can also signal to monocytes to elicit anti-tumor immunity. In fact, pigment epithelium-derived factor (PEDF) on the surface of exosomes from non-metastatic melanoma cells promoted activation of an innate immune response that prevented the formation of melanoma metastasis in the lungs. The mechanism was mediated through Nr4a1 induction in monocytes, which mediated patrolling monocytes expansion, recruitment, and differentiation into $TRAIL^+$ macrophages with M1 features, able to kill and phagocyte cancer cells [141].

MDSCs

MDSCs are a population of immature myeloid cells with strong immunosuppressive ability in the tumor microenvironment [142].

Cancer cell-derived exosomes have been shown to potentiate the immunosuppressive nature of MDSCs though distinct mechanisms. Exosomal Hsp72 enhanced MDSCs suppressive functions through engagement of TLR2 and activation STAT3 signaling [143]. Likewise, renal cancer cell-derived exosomes harboring HSP70 promoted MDSC proliferation and activation through engagement of TLR2 signaling. Notably, the MDSCs primed by the renal cancer cell-derived exosomes enhanced renal tumor growth and promoted immunosuppression [144]. Exosomes released from breast cancer cells supported the expansion of early-stage MDSCs (eMDSCs) through the transfer of miR-9 and miR-181a. Mechanistically, miR-9 and miR-181a activated the janus kinase (JAK)/signal transducer and activator of transcription (STAT) axis in eMDSCs through the targeting of SOCS3 and protein inhibitor of activated STAT3 (PIAS3), respectively. The amplification of immature

eMDSCs suppressed murine and human T cell immunity. In 4T1 tumors, the enhanced infiltration of eMDSCs supported tumor growth and immune escape [145]. Exosomes derived from murine breast tumors induced the accumulation of MDSCs, accelerated tumor growth and decreased survival. Mechanistically, exosomal TGFβ1 and prostaglandin E2 (PGE2) were implicated in this phenotype, as their neutralization attenuated the exosome-mediated induction and accumulation MDSCs, as well as the enhanced tumor growth [146]. Hypoxic glioma exosomes promoted MDSCs expansion and activation through miR-10a/Rora/IκBα/NF-κB and miR-21/Pten/ PI3K/AKT axis. *In vivo*, orthotopic tumors generated from miR-10a or miR-21 knockout cells had less MDSC infiltration than the ones generated from control cells [147]. In line with this finding, exosomes shed by hypoxic OSCC enhanced the suppressive effect of MDSCs on γδ T cells through miR-21/PTEN/PD-L1 axis in MDSCs. Accordingly, the simultaneous targeting of miR-21 and PD-L1 in tumor-bearing mice delayed tumor growth, decreased MDSCs and favored γδ T cell infiltration into tumors [148].

Neutrophils

Neutrophils are regarded as the first line of defense during inflammation and infections and are the most abundant leukocyte population in circulation. Notably, neutrophils can infiltrate into tumors and be instructed by cancer and TME cells to either promote or restrain tumor progression. The functional plasticity of neutrophils in tumors prompted their classification into tumor-restraining N1 population, and tumor-promoting N2 population [149, 150].

Gastric cancer cell-derived and tissue-derived exosomes harboring HMGB1 skewed neutrophils toward a protumor N2 phenotype and induced autophagy through activation of TLR4/NF-κB signaling. Notably, HMGB1 expression was also increased in gastric tumor tissues and was associated with poor prognosis in gastric cancer patients [151].

In the context of CRC, RNA contained in exosomes released by tumor stem-like cells educated neutrophils towards a pro-tumorigenic state. Colorectal cancer stem cells (CRCSCs)-derived exosomes localized in the bone marrow and sustained the survival of neutrophils through delivery of tri-phosphate RNAs that enhanced the expression levels of IL-1β via a pattern recognition-NF-κB axis. Then, CRCSCs secrete CXCL1 and CXCL2 to recruit the exosome-primed neutrophils and promote tumorigenesis. The depletion of neutrophils using a Ly6G antibody abrogated CRCSC-induced tumorigenesis [152].

Cancer-derived exosomes may contribute to cancer-associated thrombosis through neutrophil extracellular traps (NETs). 4T1-bearing mice had higher number of circulating neutrophils and increased levels of plasma DNA and myeloperoxidase. Using models of venous and arterial thrombosis, the authors observed an accelerated thrombus formation in tumor-bearing mice in comparison to tumor-free control animals. *In vitro*, 4T1-derived exosomes enhanced the formation of NETs, and *in vivo,* 4T1-derived exosomes administered intravenously in G-CSF-treated mice accelerated the formation of venous thrombosis [153].

Exosomes as therapeutic agents for cancer immunotherapy

As discussed in the previous sections, exosomes derived from several cell types harbor functional molecules able to elicit immune responses in cancer. Due to their biocompatibility, long circulatory half-life and amenability to modification, exosomes have emerged as promising therapeutic delivery systems [154–157]. They have been successfully used as delivery vehicles for nucleic acids, proteins, antibodies, nanobodies, compounds and chemotherapeutic drugs, and can be produced in large-scale using good manufacturing practices [18, 154, 158–168]. Likely due to the fact that exosomes are naturally generated in living organisms, their administration to mice and humans displayed low toxicity [169–172]. Moreover, exosomes are efficiently internalized by recipient cells through several mechanisms, including clathrin-dependent endocytosis and clathrin-independent pathways, namely phagocytosis, macropinocytosis, lipid raft–mediated uptake, caveolin-mediated internalization, direct membrane fusion, and receptor-mediated entry [1, 173]. Altogether, these features make exosomes an attractive delivery system for cancer immunotherapy. Indeed, the concept of exploiting exosomes to engage anti-tumor immune responses is starting to emerge, as preclinical and clinical studies have shown the feasibility to engineer exosomes that deliver tumor-associated antigens (TAAs) or engage immunostimulatory pathways in lymphoid and myeloid cells.

Exosomes were engineered to deliver activating signals to T lymphocytes. A platform called synthetic multivalent antibodies retargeted exosome (SMART-Exo) was designed to redirect and activate T lymphocytes toward cancer cells. SMART-Exo displaying anti-CD3 together with anti-EGFR [174] or anti-HER2 antibodies [161] enabled simultaneous activation and redirection of T cells toward EGFR- or HER2-expressing breast cancer cells, respectively. The SMART-Exo therapy promoted anti-tumor immune responses both *in vitro* and *in vivo* [161, 174] (Figure 3a). Leukemia cells were engineered to produce exosomes carrying the B7 costimulatory proteins: B7–1 (CD80), B7–2 (CD86), or both. The exosomes carrying both leukemia cell-associated antigens and the B7 costimulatory signals enhanced T cell proliferation, T_H1 cytokines secretion, fostered cytotoxic responses, and generated protective immunity in mice challenged with L1210 cells [175] (Figure 3b).

Tumor peptide-pulsed DC-derived exosomes were used as cell-free vaccines to treat cancer and showed encouraging results in the preclinical setting [79]. In the clinical setting however, concluded phase I and II clinical trials exploiting exosome-based cell-free vaccines in advanced cancer patients showed limited therapeutic benefit, albeit excellent safety and tolerability were observed [170–172, 176] (Figure 3c). More information on the therapeutic use of DC-derived exosomes in cancer can be found in published reviews on the topic [83, 177, 178].

The activation of the CD40 receptor by CD40 ligand (CD40L) promotes DC differentiation, maturation and enhances the secretion of immunostimulatory cytokines [179]. 3LL Lewis lung cells were engineered to produce exosomes harboring CD40L (CD40L-EXO). The CD40L-EXO promoted the activation of bone marrow-derived DCs *in vitro*. Splenocytes isolated from mice immunized with CD40L-EXO showed enhanced secretion of T_H1 cytokines, and increased cytotoxic activity against 3LL cells, but not towards B16 cells. In

mice immunized with CD40L-EXO and challenged with 3LL tumors, the tumor burden was decreased and the survival prolonged in comparison to controls. Moreover, CD40L-EXO also elicited anti-tumor responses in established 3LL tumors [180] (Figure 3d).

Aiming at improving the efficacy of DC-based vaccines, a study exploited cancer cell-derived exosomes to prime DCs through the simultaneous delivery of TAA and of a TLR4 adjuvant signal. For that, the N-terminus domain of HMGN1 (N1ND) was covalently bound to exosomes. DCs pulsed with the engineered exosomes (called $DC_{TEX\text{-}N1ND}$) displayed increased activation and enhanced the cancer killing potential of T cells. In subcutaneous HCC, pancreatic and breast tumor models, $DC_{TEX\text{-}N1ND}$ delayed tumor growth and induced anti-tumor immunity. In orthotopic HCC tumors, $DC_{TEX\text{-}N1ND}$ decreased tumor mass, increased survival, and abolished metastasis to the lungs. Importantly, $DC_{TEX\text{-}N1ND}$ amplified effector and memory T cell populations, generating a robust and persistent anti-tumor immunity [19] (Figure 3e).

A protein anchoring approach based on the immobilization of streptavidin-tagged IFNγ at the membrane of biotinylated exosomes was used to develop an exosome-based vaccine for prostate cancer treatment. The basis for this approach consists in simultaneously promoting antigen presentation (by exosomal TAAs) and in enhancing maturation of APCs (by exosomal IFNγ). The vaccine promoted M1 macrophage polarization and enhanced their ability to engulf pro-tumorigenic and immunosuppressive exosomes shed by cancer cells. In subcutaneous RM-1 tumors, the administration of the exosome-based vaccine delayed tumor growth and prolonged survival. The vaccine also induced a remodeling in the populations of circulating immune cells, as demonstrated by the increase in $IFN\gamma^+$ $CD8^+$ T cells and the decrease in T_{regs}. Finally, the exosome-based vaccine had a synergistic effect with a tumor cell-based vaccine to induce anti-tumor immune responses [181] (Figure 3f).

Exosomes were also engineered to antagonize TNF-α-mediated inflammation by acting as decoys that display the binding domain of TNF receptor-1 on their surface. The efficacy of the engineered exosomes in antagonizing TNF-α was demonstrated *in vitro* [182] (Figure 3g).

From a translational perspective, exosomes can be engineered not only to elicit anti-tumor immune responses as exemplified above, but also to suppress/normalize the exacerbated activation of the immune system, which commonly occur in the setting of autoimmune diseases.

Concluding remarks and future directions

As discussed in this review, exosomes provide signals that interfere in each stage of the cancer immunity cycle. They can modulate the various lymphoid and myeloid cell populations of the TME to support or restrain anti-tumor immunity, and can be harnessed for therapeutic purposes in cancer immunotherapy. Despite the advances in basic biology and translational science achieved in the field, several aspects of exosome-mediated immunoregulation in cancer are thus far unexplored, and when addressed, they have the potential to provide valuable functional insights to the field, to advance the development of

novel cancer therapies, and to pinpoint additional biomarker candidates for cancer diagnosis, prognosis and assessment of therapy response.

Thus far, the field has majorly focused on how exosomes derived from a specific type of cancer cell modulate a specific subset of lymphoid or myeloid cell population. Nevertheless, a systematic evaluation of how exosomes derived from different types of cancer cells and TME sub-populations affect the immune landscape of tumors is lacking. In fact, studies that determine the functional contribution of exosomes from cancer-associated fibroblasts, endothelial cells, pericytes, and from the distinct subsets of immune cells in cancer deserve further attention. The advent of technologies allowing for the study of the immune landscape of tumors at a single cell level can help to solve this puzzle. In fact, these technologies can provide a comprehensive map on how exosomes from a specific source signal to the various populations of the immune microenvironment, thus guiding the field to uncover aspects of exosome-mediated regulation of the immune system previously overlooked. Collectively, breakthroughs in these areas will not only allow for the mapping of complex circuits of exosome-mediated signaling in tumor immunity, but also open new avenues for translational intervention.

Much of the work available in the field was performed with exosomes generated *in vitro*, and the development of systems allowing for the *in vivo* study of exosome-mediated regulation of the immune system is an open field of research that needs further attention.

From a biomarker perspective, several studies have demonstrated the value in exploiting exosome-resident immunomodulatory molecules derived from patients to monitor disease status and therapy response. This is an extremely exciting field of research that can be further developed and potentially impact cancer diagnosis and decision making in the clinical setting.

Finally, the therapeutic application of exosomes to elicit anti-tumor immunity has the potential to offer novel options for cancer treatment. So far, exosomes have been exploited to develop therapies that engage T lymphocyte- and APC-mediated immunity. Nevertheless, exosomes can also be engineered and harnessed to engage anti-tumor immune responses in other cell populations of the tumor microenvironment.

The field of exosome-mediated immunoregulation in cancer is an evolving area of research that holds great potential to decipher additional mechanisms contributing to cancer aggressiveness. Targeting these mechanisms may provide new avenues to treat cancer patients.

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Abbreviations:

Akt	protein kinase B
AML	acute myeloid leukemia
APC	antigen-presenting cell
ATP	adenosine triphosphate
BAT3	HLA-B-Associated Transcript-3
BMDM	bone marrow-derived macrophage
B_{reg}	regulatory B cell
CCL2	C-C motif chemokine ligand 2
CCL4	C-C motif chemokine ligand 4
CD40L	CD40 ligand
cGAS	cyclic GMP–AMP synthase
circUHRF1	circular ubiquitin-like with PHD and ring finger domain 1
CLL	chronic lymphocytic leukemia
COX-2	cyclooxygenase-2
CRC	colorectal cancer
CRCSC	colorectal cancer stem cell
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DC	dendritic cell
dsDNA	double-stranded DNA
EBV	Epstein-Barr virus
EGFR	epidermal growth factor receptor
eMDSC	early-stage MDSC
EMT	epithelial-to-mesenchymal transition
EOC	epithelial ovarian cancer
ER	endoplasmic reticulum
ERK	extracellular signal-regulated kinase
EVs	extracellular vesicles
FasL	Fas ligand

GBM	glioblastoma
GCSF	granulocyte colony-stimulating factor
GSC	glioblastoma stem cell
HIF-1α	hypoxia-inducible factor-1α
HCC	hepatocellular carcinoma
HMGB1	high mobility group box-1
HNSCC	head and neck squamous cell carcinoma
Hsp70	heat shock protein 70
ICB	immune checkpoint blockade
IFNγ	interferon gamma
IHC	immunohistochemistry
IL-1β	interleukin-1β
IL-2	interleukin-2
IL-6	interleukin-6
IL-10	interleukin-10
IL-12	interleukin-12
IL-17	interleukin-17
ILVs	intraluminal vesicles
IRF3	interferon regulatory factor 3
JAK	janus kinase
KO	knockout
LIPA	lysosomal acid lipase A
LLC	Lewis lung cancer
MCP-1	monocyte chemoattractant protein-1
MDSC	myeloid-derived suppressor cell
MEKK2	mitogen-activated protein kinase kinase kinase 2
MHC	major histocompatibility complex
MMP-9	matrix metalloproteinase-9
MVBs	multivesicular bodies

MVs	microvesicles
NETs	neutrophil extracellular traps
NF-κB	nuclear factor kappa B
NK	natural killer
NKG2D	natural killer group 2 member D
NPC	nasopharyngeal carcinoma
NSCLC	non-small cell lung cancer
OSCC	oral squamous cell carcinoma
OX40L	OX40 ligand
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PDAC	pancreatic ductal adenocarcinoma
PDX	patient-derived xenografts
PEDF	pigment epithelium-derived factor
PGE2	prostaglandin E2
PI3K	phosphoinositide 3-kinase
PIAS3	protein inhibitor of activated STAT3
PTEN	phosphatase and tensin homolog
RFXAP	regulatory factor X-associated protein
ROS	reactive oxygen species
SCCHN	squamous cell carcinoma of the head and neck
SMART-Exo	synthetic multivalent antibodies retargeted exosome
SOCS3	suppressor of cytokine signaling 3
STAT	signal transducer and activator of transcription
STAT3	signal transducer and activator of transcription 3
STING	stimulator of interferon genes
TAA	tumor-associated antigen
TAM	tumor-associated macrophage
TCR	T cell receptor

TGFβ1	transforming growth factor beta 1
TH1	T helper 1
TH17	T helper 17
Tim-3	T-cell immunoglobulin and mucin-domain containing-3
TLR	toll-like receptor
TME	tumor microenvironment
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor-α
TRAIL	TNF-related apoptosis-inducing ligand
T_{reg}	regulatory T cell
VEGFA	vascular endothelial growth factor A
5-FU	5-fluorouracil

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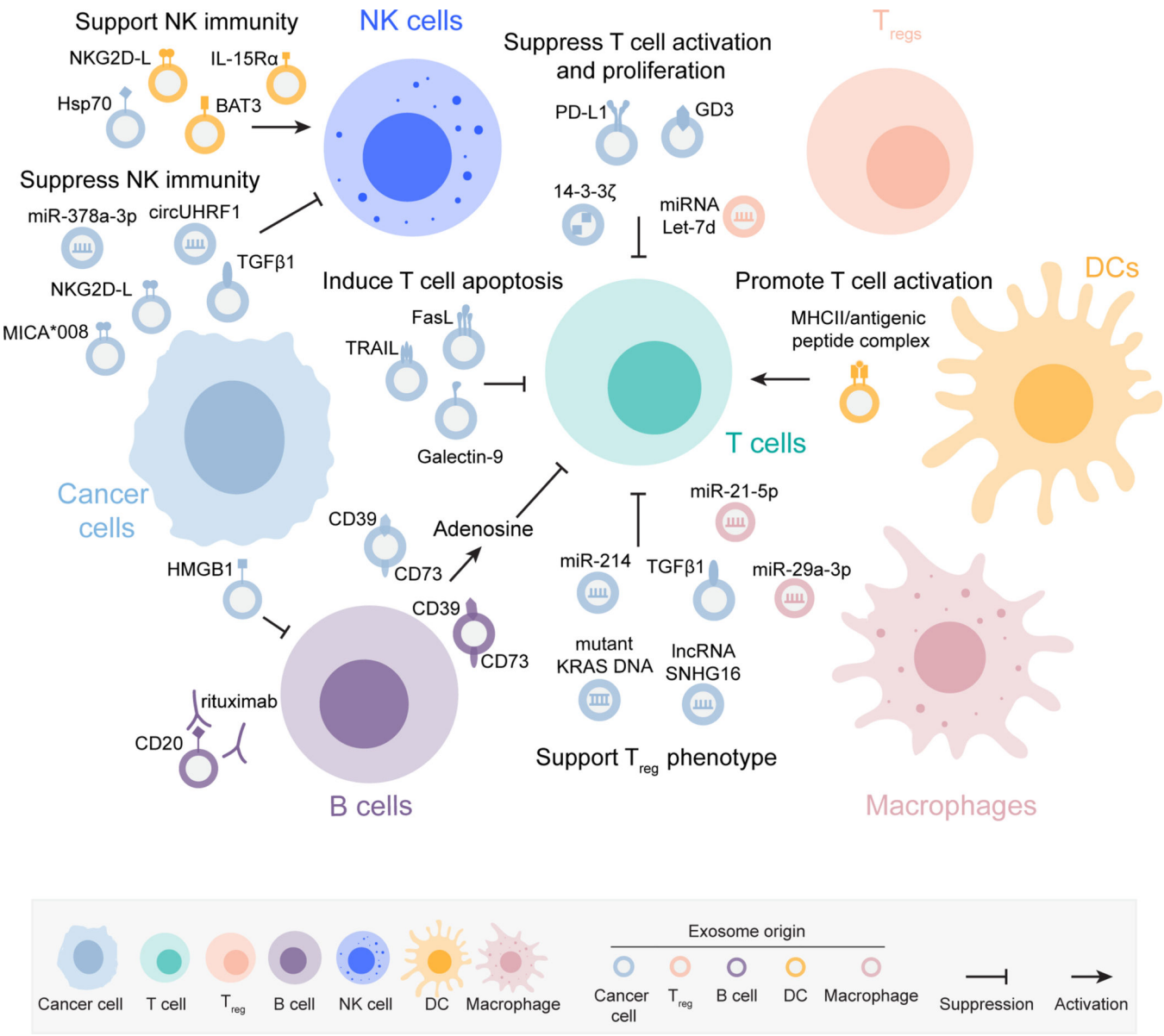

Figure 1: Exosome-mediated signaling modulate lymphoid cell functions in cancer.

Exosomes derived from cancer cells and from various immune cell populations engage immunosuppressive signaling in recipient T cells, which impair T cell activation and proliferation, induce apoptosis and support a T_{reg} phenotype. Antigen-presenting cell (APC)-derived exosomes harboring major histocompatibility complex II (MHCII)/antigenic peptide complex can present antigens to the target T cells and promote their activation. Exosomes derived from cancer cells suppress B cell functions. Exosomes from cancer cells and dendritic cells (DCs) signal to natural killer (NK) cells and can either promote or suppress NK cytotoxic function. The molecular cargoes in the exosomes mediating the immunomodulatory phenotypes in the lymphoid cells are indicated in the figure. The exosomes are color coded to represent the cell of origin, as described in the figure key.

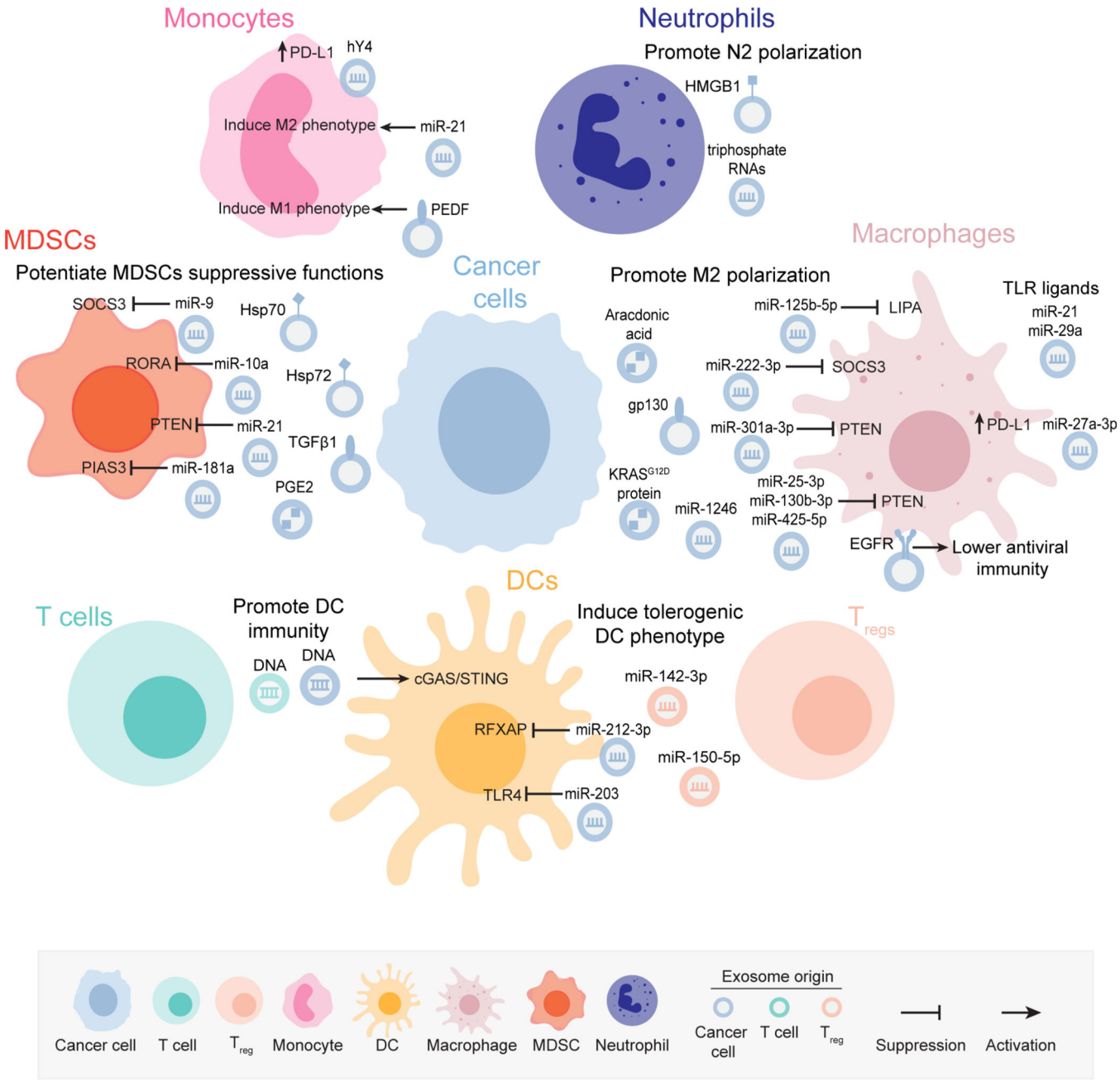

Figure 2: Exosome-mediated signaling modulate myeloid cell functions in cancer.

Cancer cell-derived and immune cells-derived exosomes mediate the reprogramming of several myeloid cell populations towards a tumor-promoting and immunosuppressive phenotype through the delivery of nucleic acids and proteins or via engagement of receptor-mediated signaling. Certain exosomal cargoes also trigger anti-tumor immune responses via myeloid cell targeting. The molecular cargoes in the exosomes mediating the immunomodulatory phenotypes in the myeloid cells are indicated in the figure. The representation of the exosomes is color coded to depict the cell of origin, which is shown in the figure key.

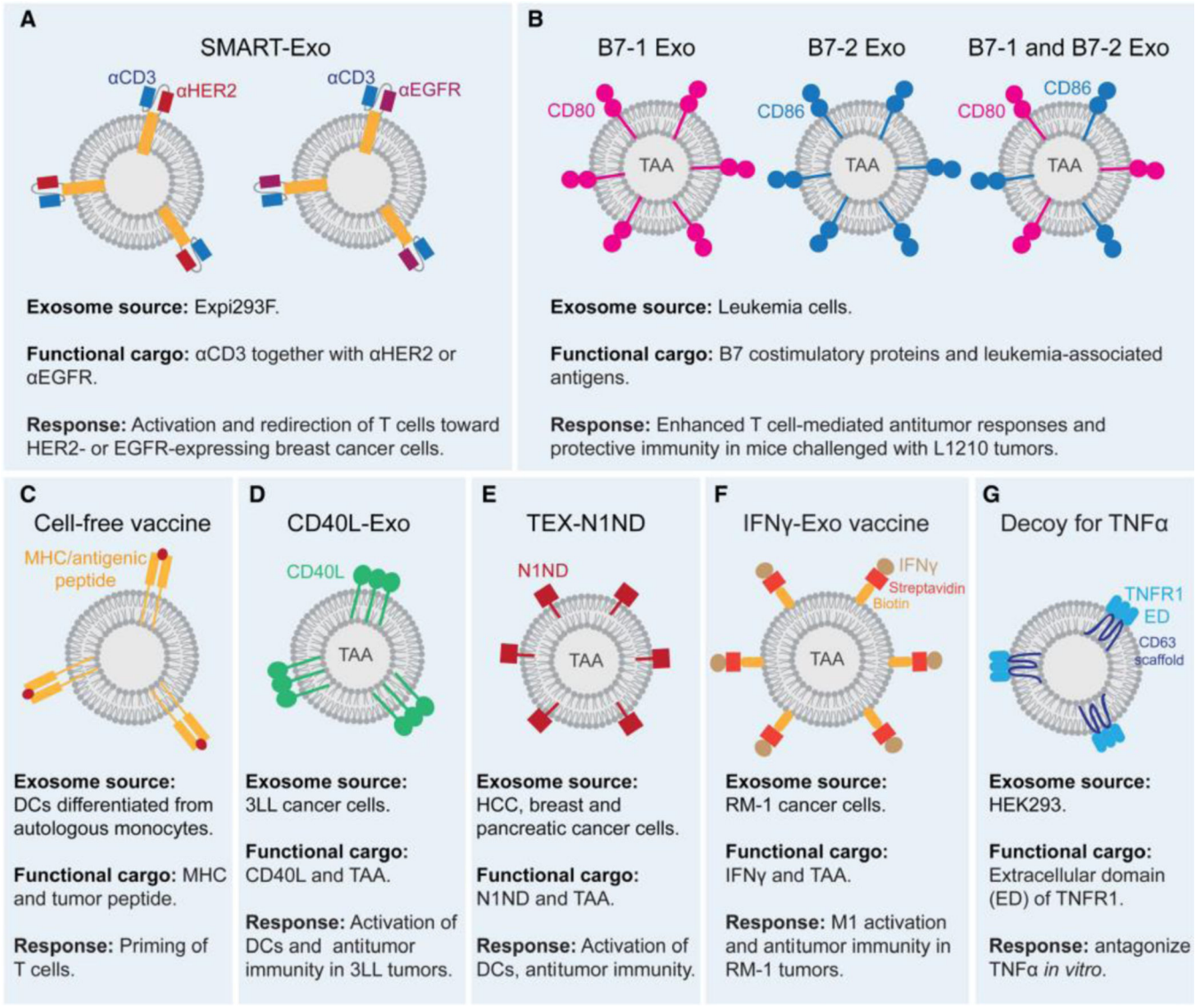

Figure 3: Engineered exosomes for cancer immunotherapy.

(a) Engineered exosomes displaying anti-CD3 together with anti-human epidermal growth factor receptor 2 (HER2) or anti-epidermal growth factor receptor (EGFR) activate and retarget T cells toward $HER2^+$ and $EGFR^+$ breast cancer cells. **(b)** Leukemia-derived exosomes containing tumor-associated antigens (TAAs) and harboring the B7 costimulatory proteins confer protective immunity. **(c)** Exosome-based cell-free vaccine from autologous monocytes isolated from advanced cancer patients. Monocytes are differentiated into dendritic cells (DCs) and loaded with tumor-associated antigens. Then, DCs are used to produce exosomes for patient administration. **(d)** Engineered 3LL-derived exosomes harboring CD40 ligand (CD40L) promote DC activation, T cell priming, and induce anti-tumor immunity. **(e)** Engineered cancer cell-derived exosomes harboring TAA and N1ND enhance DC activation and promote anti-tumor immunity. **(f)** A vaccine for prostate cancer treatment based on streptavidin-tagged interferon gamma (IFNγ) immobilized at the membrane of biotinylated cancer-derived exosomes. The engineered exosomes induce

macrophage polarization towards the M1 phenotype and promote anti-tumor immunity. **(g)** Exosomes containing the binding domain of tumor necrosis factor receptor 1 (TNFR1) were engineered to antagonize tumor necrosis factor alpha (TNF-α).

Table 1:

Exosome-mediated regulation of lymphoid cell functions in cancer.

Source	Functional molecule (s)	Target cell/molecule	Response in the target cell/molecule	Reference
Prostate cancer cells	FasL	$CD8^+$ T cells	Exosomal FasL promoted apoptosis of $CD8^+$ T cells.	[37]
Melanoma cells	FasL	T cells	MV-derived FasL induced apoptosis of Jurkat cells.	[40]
Melanoma and SCCHN	FasL	T cells	MVs induced apoptosis of $CD8^+$ T cells and promoted T_{reg} expansion.	[41]
Ovarian cancer	FasL	T cells	Membrane vesicles induced T cell apoptosis and suppressed TCR.	[42]
OSCC patient sera	FasL	T cells	MV-derived FasL induced T cell apoptosis and correlated with poor patient prognosis.	[43]
CRC cells and patient plasma	FasL and TRAIL	T cells	MV-derived FasL and TRAIL induced T cell apoptosis.	[46]
Metastatic melanoma	PD-L1	$CD8^+$ T cells	Exosomal PD-L1 impaired T cell functions, enhanced tumor growth and stratified patients into responders and non-responders to ICB therapy.	[16]
Plasma of HNSCC patients	PD-L1	$CD8^+$ T cells	Exosomal PD-L1 correlated with disease progression in HNSCC patients. Decreased $CD8^+$ T cell activation.	[52]
GBM cancer cells and patient serum/plasma	PD-L1	T cells	EV-resident PD-L1 suppressed T cell activation and proliferation. PD-L1 DNA in EVs from GBM patients correlated with tumor volume.	[53]
Breast cancer cells	PD-L1	T cells	Exosomal PD-L1 impaired the activation and cancer killing potential of T cells, and enhanced tumor growth.	[54]
Prostate and melanoma cells	PD-L1	$CD8^+$ T cells	PD-L1 in exosomes suppressed T cell activity in the draining lymph node.	[55]
NSCLC patient serum	PD-L1	-	Exosomal PD-L1 levels correlated with NSCLC disease progression.	[56]
Lung cancer cells and NSCLC patient plasma	PD-L1	$CD8^+$ T cells	Exosomal PD-L1 displayed immunosuppressive properties and correlated with PD-L1 levels of tumor tissues.	[57]
Cancer cells and melanoma patient-derived plasma	PD-L1	T cells	Exosomal PD-L1 suppressed T cell functions and had predictive value in the response of melanoma patients to targeted and ICB therapies.	[22]
Plasma of gastric cancer patients	PD-L1	T cells	5-FU enhanced the levels of circulating exosomal PD-L1 in gastric cancer patients. *In vitro*, exosomal PD-L1 induced apoptosis of Jurkat cells and reduced activation of PBMCs.	[58]
NPC patient plasma of NPC-bearing mice	Galectin-9	$CD4^+$ T cells	Exosomal Galectin-9 induced apoptosis of EBV-specific $CD4^+$ T cells upon binding to Tim-3.	[59]
NPC patient-derived serum and NPC cells	miRNAs	T cells	Exosomes inhibited T cell proliferation, induced a T_{reg} phenotype and impaired T_H1 and T_H17 differentiation.	[60]
HCC cells	14–3-3ζ	T cells	Exosomal 14–3-3ζ engaged an immunosuppressive phenotype in recipient T cells.	[61]
Ascites from ovarian cancer patients	Ganglioside GD3	T cells	Exosomal GD3 decreased T cell activation.	[62]
Ascites from ovarian cancer patients	-	T cells	Exosomes from ascites suppressed T cell functions.	[63]

Source	Functional molecule (s)	Target cell/molecule	Response in the target cell/molecule	Reference
Plasma of melanoma patients	-	$CD8^+$ T cells and NK cells	Enhanced apoptosis and suppressed proliferation and activation of $CD8^+$ T cells, decreased NKG2D in NK cells.	[64]
Plasma of head and neck cancer patients	-	T cells and NK cells	Enhanced apoptosis of $CD8^+$ T cells, suppressed the proliferation of $CD4^+$ T cells and decreased NKG2D in NK cells.	[65]
Melanoma cancer cells	miRNAs	$CD4^+$ T cells	Exosomes reduced the levels of BCL-2, BCL-xL and MCL-1 and enhanced apoptosis of $CD4^+$ T cells.	[66]
Melanoma	TNF	T cells	Exosomes enhanced ROS levels in T lymphocytes.	[67]
Malignant effusion	TGFβ1	T_{reg}	Exosomal TGFβ1 supported maintenance of T_{reg} number and suppressive function.	[38]
Lung cancer cells	miR-214	T_{reg}	MV-derived miR-214 suppressed PTEN and promoted T_{reg} expansion.	[68]
NSCLC cells or patient serum	mutant KRAS DNA	$CD4^+$ T cells	Exosomal mutant KRAS DNA promoted the conversion of naïve $CD4^+$ T cells into T_{reg}-like cells.	[69]
Breast cancer	lncRNA SNHG16	T cells	Exosomes induced $CD73^+\gamma\delta1$ $T_{regs.}$	[70]
Regulatory T cells	Let-7d	T_H1 cells	Exosomal Let-7d decreased T_H1 cells proliferation and IFNγ secretion.	[71]
Macrophages	miR-29a-3p and miR-21–5p	$CD4^+$ T cells	Exosomal miR-29a-3p and miR-21–5p suppressed STAT3 and regulated T_{reg}/T_H17 ratio.	[14]
Various cancer cells	CD39 and CD73	ATP/T cells	Exosomes mediated hydrolysis of ATP and generated adenosine.	[72]
B cells	CD39 and CD73	ATP/T cells	B-cell-derived EVs hydrolyzed ATP into adenosine and restrained post-chemotherapeutic $CD8^+$ T cell responses.	[73]
B cells	MHC class II/ antigenic peptide complex	T cells	The exosomes from mouse and human B cells induced antigen-specific MHC class II T cell responses.	[77]
Engineered mast cells	HLA-DR1-HA	T cells	Exosomes harboring MHC/antigenic peptide complex activated T cells weakly in comparison to DCs incubated with the exosomes.	[78]
DCs	MHCI, MHCII, CD86, tumor peptide	T cells	DC-derived exosomes pulsed with tumor antigens primed cytotoxic T cells to mediate anti-tumor responses.	[79]
HCC cells and patients	HMGB1	B cells	HMGB1 in exosomes promoted expansion of B_{regs} via TLR2/4-MAPK signaling pathway.	[85]
Esophageal cancer	-	B cells	MVs induced the conversion of naïve B cells into B_{regs}, which in turn suppressed the proliferation of CD8+ T cells.	[86]
Melanoma and thymoma cells infected with mycoplasma	-	B cells	Exosomes enhanced the activation and expansion of inhibitory B cells.	[87]
PDAC cells and patient plasma	Tumor-associated antigens	Immunoglobulins	Exosomes operated as decoys against complement-mediated cytotoxicity.	[88]
B-cell lymphoma	CD20	anti-CD20 antibody	Exosomal CD20 bound to rituximab and protected B-cell lymphoma from antibody attack.	[89]
Serum from melanoma patients on neoadjuvant ICB trial	CD20 and CD27	-	B cell-related exosomes $CD20^+$ and $CD27^+$ were increased in responders compared to non-responders to ICB therapy.	[92]

Source	Functional molecule (s)	Target cell/molecule	Response in the target cell/molecule	Reference
Acute myeloid leukemia patients and PDX	-	NK and $CD8^+$ T cells	Enhanced apoptosis of $CD8^+$ T cells and decreased NKG2D levels in NK cells.	[94]
B lymphoblastoid, mesothelioma, and prostate, cancer cells	TGFβ1 and NKG2D ligands	NK and $CD8^+$ T cells	Exosomes reduced NKG2D in NK and $CD8^+$ T cells in a MICA and TGFβ1-dependent manner.	[95]
Cervical cancer cells	MICA*008	NK cells	Exosomal MICA*008 decreased surface levels of NKG2D.	[96]
Mammary carcinoma cells	-	NK cells	Murine and human cancer-derived exosomes suppressed NK functions.	[97]
HCC	circUHRF1	NK cells	Exosomes induced NK cell exhaustion and may be linked to resistance to anti-PD-1 therapy.	[98]
Irradiated U87 cells	miR-378a-3p	NK cells	Exosomes impaired NK cytotoxicity through down-regulation of granzyme B.	[99]
Pancreatic and colon cancer cells	Hsp70	NK cells	Exosomal Hsp70 enhanced NK activation, migration and cytolytic activity.	[100]
DCs and 293T cells	BAT3	NK cells	Exosomal BAT3 enhanced TNFα and IFNγ secretion from NK cells.	[101]
Irradiated melanoma cells	-	NK cells	Exosomes from irradiated melanoma cells enhanced the infiltration of NK cells producing IFNγ into tumors and delayed tumor growth in an NK-dependent manner.	[102]
DCs	IL-15Rα and NKG2D ligands	NK cells	DC-derived exosomes enhanced NK cell proliferation and activation via IL-15R and NKG2D.	[103]

Table 2:

Exosome-mediated regulation of myeloid cell functions in cancer.

Source	Functional molecule (s)	Target cell	Response in the target cell	Reference
EOC cells	miR-222–3p	Macrophages	Exosomal miR-222–3p suppressed SOCS3, activated STAT3, induced M2 polarization and enhanced tumor progression.	[106]
p53-mutant cancer cells	miR-1246	Macrophages	Exosomal miR-1246 reprogramed macrophages to a tumor-promoting state.	[107]
Melanoma cells	miR-125b-5p	Macrophages	Exosomal miR-125b-5p targeted LIPA in macrophages and promoted survival.	[108]
Hypoxic pancreatic cancer cells	miR-301a-3p	Macrophages	Exosomal miR-301a-3p induced M2 phenotype through PTEN/PI3K signaling.	[109]
Pancreatic cancer cells	Arachidonic acid	Macrophages	Exosomes shuttled arachidonic acid and promoted M2 phenotype.	[110]
Pancreatic cancer cells undergoing ferroptosis	$KRAS^{G12D}$ protein	Macrophages	Exosomes promoted M2 polarization through STAT3-dependent fatty acid oxidation.	[111]
Metastatic osteosarcoma cells	-	Macrophages	Exosomes induced M2 polarization and impaired phagocytosis, efferocytosis, and macrophage-dependent tumor cell killing.	[112]
Lung cancer cells	-	Macrophages	Exosomes induced M2 polarization and enhanced macrophage oxygen consumption rate.	[113]
CRC cells	miR-25–3p, miR-130b-3p and miR-425–5p	Macrophages	Exosomes induced M2 polarization through suppression of PTEN and activation of PI3K/Akt signaling and contributed to the establishment of liver metastasis.	[114]
Breast cancer cells	gp130	Macrophages	Exosomal gp130 promoted activation of STAT3 signaling, enhanced the levels of pro-tumorigenic cytokines and the survival of BMDMs.	[115]
Liver cancer cells undergoing ER stress	-	Macrophages	Exosomes promoted the secretion of IL−6, MCP−1, IL−10 and TNFα in macrophages through STAT3 signaling.	[118]
Breast cancer cells undergoing ER stress	miR-27a-3p	Macrophages	Exosomes promoted immune evasion through increase in PD-L1 expression in macrophages.	[119]
Breast cancer cells	-	Macrophages	Exosomes promoted activation of NF-κB pathway in macrophages and enhanced the levels of IL-6, TNFα, GCSF and CCL2 in a TLR2-dependent manner.	[120]
Gastric cancer cells	-	Macrophages	Exosomes induced the activation of NF-κB and the expression of the pro-inflammatory factors IL-6, TNFα, and CCL2 in macrophages to promote tumor progression.	[121]
Lung cancer cells	miR-21 and miR-29a	Macrophages	Exosomal miR-21 and miR-29a favored a pro-metastatic inflammatory response by serving as ligands of TLR receptors in macrophages, promoting NF-κB activation and increasing the secretion of IL-6 and TNFα.	[122]
Lung cancer cells	EGFR	Macrophages	Activated EGFR in exosomes lowered the host innate antiviral immunity through MEKK2/IRF3 axis.	[15]
Pancreatic cancer cells	miR-212–3p	DCs	Exosomal miR-212–3p targeted RFXAP, decreased MHC II levels and induced immune tolerance in DCs.	[124]
Pancreatic cancer cells	miR-203	DCs	Exosomal miR-203 decreased the expression levels of TLR4 and the secretion of TNFα and IL-12 in DCs.	[125]
Breast cancer cells	-	DCs	Exosomes suppressed the differentiation of myeloid precursor cells into DCs in an IL-6-dependent manner.	[126]
LLC and 4T1 cells	-	DCs	Inhibited DC maturation.	[127]
Regulatory T cells	miR-150–5p and miR-142–3p	DCs	Induced tolerogenic phenotype in DCs.	[128]

Source	Functional molecule (s)	Target cell	Response in the target cell	Reference
Breast cancer cells	DNA	DCs	Breast cancer cells treated with Topocan released exosomes containing DNA, which activated the cGAS/STING pathway in DCs.	[129]
Breast cancer cells	DNA	DCs	Exosomal DNA primed DCs to elicit anti-tumor responses through cGAS/STING pathway.	[130]
T cells	DNA	DCs	EV-derived DNA engaged cGAS/STING pathway in DCs.	[131]
Pancreatic cancer	-	Monocytes	Exosomes decreased HLA-DR expression in monocytes, and induced arginase and ROS.	[136]
Snail-Expressing Cancer Cells	miR-21	Monocytes	Exosomal miR-21 induced M2 polarization and tumorigenesis.	[137]
Chronic lymphocytic leukemia	noncoding Y RNA hY4	Monocytes	Exosomal hY4 enhanced the expression of PD-L1 and the release of cytokines in a TLR7-dependent manner.	[138]
GBM stem cells	-	Monocytes	Exosomes skewed monocytes toward M2 phenotype and enhanced PD-L1 expression.	[139]
Gastric cancer cells	-	Monocytes	Exosomes mediated monocytes differentiation into PD1+ TAMs with M2 phenotype, which suppressed $CD8^+$ T cell functions.	[140]
Non-metastatic melanoma cells	PEDF	Monocytes	Exosomal PEDF promoted patrolling monocytes differentiation into TRAIL+ M1 macrophages with cancer killing potential.	[141]
Thymoma, mammary carcinoma, and colon carcinoma cells	Hsp72	MDSCs	Exosomal Hsp72 elicited immunosuppressive signaling in MDSCs via TLR2/STAT3 axis.	[143]
Renal cancer cells	HSP70	MDSCs	Exosomes promoted MDSC proliferation and activation via TLR2 signaling to promote tumor growth and immunosuppression.	[144]
Breast cancer cells	miR-9 and miR-181a	MDSCs	Exosomes activated JAK/STAT signaling in eMDSCs through the targeting of SOCS3 and PIAS3.	[145]
Breast tumors	TGFβ1 and PGE2	MDSCs	Exosomal TGFβ1 and PGE2 promoted MDSCs accumulation and accelerated tumor growth.	[146]
Hypoxic glioma cancer cells	miR-10a and miR-21	MDSCs	Exosomes promoted MDSCs expansion and activation through miR-10a/Rora/IκBα/NF-κB and miR-21/Pten/PI3K/AKT pathways.	[147]
OSCC cells	miR-21	MDSCs and γδ T cells	Hypoxic exosomes inhibited γδ T cells functions through MDSCs.	[148]
Gastric cancer cells	HMGB1	Neutrophils	Exosomal HMGB1 induced autophagy and pro-tumor activation of neutrophils via TLR4/NF-κB signaling	[151]
CRC stem cells	tri-phosphate RNAs	Neutrophils	Exosomes enhanced the expression of IL-1β via NF-κB signaling to promote tumorigenesis. The depletion of neutrophils abrogated CRCSC-induced tumorigenesis.	[152]
Breast cancer cells	-	Neutrophils	Exosomes enhanced the formation of NETs *in vitro*, and accelerated the formation of thrombosis *in vivo*.	[153]