Trends in Cancer

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REVIEWS

Review

Immune Cell-Derived Exosomes in the Cancer-Immunity Cycle

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Cells can communicate through extracellular vesicle (EV) secretion and uptake. Exosomes are lipid bilayer-enclosed EVs of 30–150 nm in diameter, which can transfer RNA, functional proteins, lipids, and metabolites to recipient cells *in vivo*. Most cell types, including immune cells, can secrete and uptake exosomes. Biogenesis, secretion, and uptake of immune cell-derived exosomes are regulated by intracellular proteins and extracellular stimuli. Immune cell-derived exosomes can mediate crosstalk between innate and adaptive immunity and regulate cancer progression and metastasis. The dichotomous roles of immune cell-derived exosomes towards tumor cells can induce suppressive or active immune responses. Hence, immune cell-secreted exosomes may have applications in cancer diagnosis and immunotherapy and could potentially be developed for vaccination and chemotherapy drug transportation.

Highlights

Immune cell-derived exosomes can mediate crosstalk between innate and adaptive immunity and regulate cancer progression and metastasis.

Immune cell-secreted exosomes may have applications in cancer diagnosis and immunotherapy and could potentially be developed for vaccination and chemotherapy drug transportation.

Current evidence has indicated that the messages delivered by exosomes may provide an alternative and highly efficient means of delivering information, which could have long-term effects in regulating anticancer immune responses.

Future studies are required to fully characterize exosomes that originate from immune cells and to learn how to precisely engineer exosomes for further therapeutic antitumor treatments.

Exosomes and the Regulation of Cancer Progression

Cell-released vesicles with membranous structures, collectively referred to as EVs, are widely reported to be involved in cell–cell communication [1]. Subtypes of EVs include: microvesicles, ectosomes, oncosomes, apoptotic bodies, and exosomes [2]. Exosomes are defined as a subclass of small EVs (sEVs; 30–150 nm in diameter) with a high content of cholesterol and glycoconjugates [3]. These nanoparticles are actively involved in crosstalk between cells and organs in hosts and pathogens.

Over the past decade, exosomes have been studied in relation to oncology, autoimmune syndromes, metabolic reprogramming, and infections [4–6]. Research has greatly expanded our knowledge of immune cell-derived exosomes [7,8], and accumulating evidence highlights their active engagement in the regulation of cancer progression [8]. Identification of immune cell-derived exosomes has enabled the development of a new class of cancer immunotherapy that specifically blocks immune effector inhibition on tumor cell growth, which reinvigorates and potentially expands pre-existing anticancer immune responses. The presence of immune cell-derived factors, such as exosomes, in the tumor microenvironment may explain the limited activity observed with previous immune-based therapies and why these therapies might be more effective in combination with agents that could target several key steps of the cancer-immunity cycle. In order to elicit an antitumor immune response, a series of seven steps comprising the cancer immunity-cycle must be initiated. Through this cycle tumor growth is precisely controlled by the innate and adaptive immune systems (Figure 1). Cancer cell-associated antigens (Ags) are captured and presented by dendritic cells (DCs), B cells, and macrophages, which migrate to lymph nodes where they prime and finally activate tumor-specific cytolytic $CD8^+$ T cells. These activated effector T cells migrate and infiltrate the tumor microenvironment, where they are able to recognize and eliminate tumor cells. T cell-mediated cytotoxic responses release new cancer cell Ags, refueling the cancer-immunity cycle. Exosomes play an important role in the crosstalk between tumor cells and immune systems. Tumor Ag presentation, immune cell activation, and

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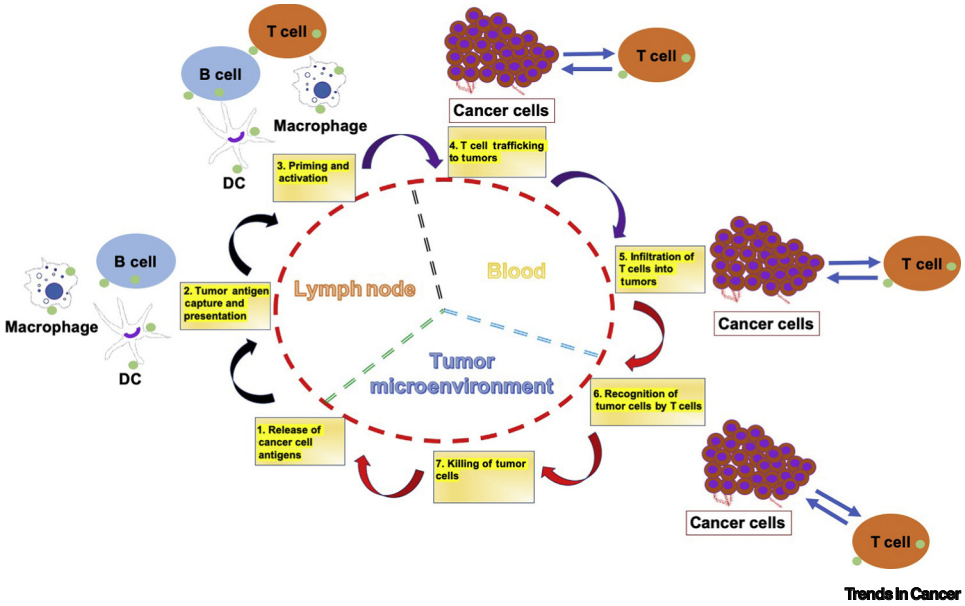

Figure 1. Immune Cell-Derived Exosomes in the Cancer-Immunity Cycle. Immune cell-derived exosomes contribute to cancer in a cyclic process that could be divided into seven main steps, which start with the release of cancer cell antigens (Ags) and end with the killing of tumor cells. After the release of cancer cell Ags (step 1) Ag presenting cells (APCs), including B cells, macrophages, and dendritic cells (DCs), present the captured Ags on MHC-I and MHC-II molecules to T cells (step 2). APCs and T cells prime and activate effector T cell responses against the cancer-specific Ags (step 3). The activated T cells traffic to the tumor site (step 4) where they infiltrate the tumor cells (step 5). The activated T cells recognize the tumor cells through the interaction between the T cell receptor (TCR) and its cognate Ags bound to MHC-I or MHC-II (step 6). The killing of the tumor cells (step 7) releases additional tumor cell Ags thus perpetuating the cycle.

immunosuppression can be considered the result of interactions between immune cell-derived exosomes and cancer cells.

In the present review, we primarily focus on the latest findings regarding immune cell-derived sEVs, particularly exosomes. Specifically, we discuss biogenesis and secretion of exosomes by different immune cells, extraction and characterization of immune cell-derived exosomes, the function of immune cell-derived exosomes in both innate and adaptive immunity, how immune cell-derived exosomes interact with cancer cells, exosome-mediated immunosuppression in cancer cell-bearing hosts, exosome-mediated activation of anticancer immune responses, and potential uses in cancer diagnosis and treatment.

Biogenesis and Secretion of Exosomes by Immune Cells

Biogenesis

Immune cells – like all other exosome-producing cells, including tumor cells – generate exosomes through an inward budding process of the plasma membrane and endosome membrane [9]. Plasma membrane invagination results in endosome formation, and subsequent endosome membrane invaginations lead to more intraluminal vesicles (ILVs) being pinched off [10]. Late endosomes are termed multivesicular bodies (MVBs). MVBs can either fuse with the plasma membrane and release ILVs as exosomes through a secretory pathway, or fuse with lysosomes and release ILVs into the lysosomal lumen for degradation through the lysosome pathway [11].

Importantly, exosomes can encapsulate proteins, lipids, RNAs, and metabolites [12]. The endosomal sorting complex for transport (ESCRT) can recruit ubiquitylated proteins [13], and

monoubiquitylation of the cytosolic domains of transmembrane proteins guides proteins into ILVs [14]. However, ESCRT and protein ubiquitination are not required for all proteins to be sorted into exosomes. For example, MHC class II molecules are sorted into exosomes independently of both ESCRT and protein ubiquitination. Since this information has previously been reviewed [15], here we briefly summarize some key factors affecting the packaging of immune cell-derived exosomes.

The development stage of parent cells can affect their released exosome content [16]. Exosomes reportedly contain distinct sets of miRNAs derived from mature, immature, and interleukin (IL)-10/nitric oxide (NO)-producing regulatory DCs [17–19]. Immature DCs (imDCs) sort MHC molecules into ILVs in MVBs for lysosomal degradation, whereas mature DCs sort MHC molecules for secretion and transfer to interact with T cells, indicating the existence of different MVB pathways in naïve and active DCs [19].

Exosome packaging can also be affected by intracellular proteins or surface markers [20]. For instance, hypoxia-induced factor 1-α (HIF-1α) can enhance Rab27a transcription and thus induce B cells to release more $CD19^+$ exosomes [21]. Additionally, functional Unc-93 homolog B1 (UNC93B1) facilitates syntenin-1 recruitment, enabling sorting of Toll-like receptor 7 (TLR7) into ILVs of MVBs, whereas TLR7 is absent from Raw264.7 macrophages expressing dysfunctional UNC93B1 [22]. Exosomes from human primary monocyte-derived DCs (moDCs) are highly heterogeneous and exhibit a large range of sizes [23]. As an endocytic receptor, lysosome-associated membrane protein 2 (LAMP-2) can selectively enrich Ags within exosomes by routing cargo into unusual Ag-processing pathways on human moDCs [24].

Extracellular environmental stimuli can also regulate components of immune cell-derived exosomes. For example, contact with bystander T cells enhances the release of EV-associated proteins by moDCs, leading exosomes to encapsulate more proteins, such as CD63, ICAM-1, and noncoding RNAs, including miR-155 [25].

Secretion

The manner of exosome secretion varies among immune cells of different types and statuses [26], and exosome secretion can be regulated by extracellular stimuli and intracellular proteins [27]. DCs and B cells exhibit enhanced exosome release upon T cell interaction, radiation exposure, or senescence induction [28,29]. Some immune cells, including DCs and macrophages, can spontaneously and constitutively secrete exosomes, and the amount of exosome secretion differs between mature and imDCs [29]. Moreover, CC chemokine receptor 7 (CCR7) regulates the accumulation of mature DC-derived exosomes (DEX) in the spleen, which can be taken up by splenetic DCs and T cells, thereby triggering inflammation responses [30]. Similarly, vacuolar ATPase (V-ATPase) can stimulate cell-producing clusters of EVs, while treatment with its inhibitor BafA1 can cause increased exosome release from HeLa cells [31].

Uptake

EV uptake is the final step in the delivery of content to recipient cells [32]. Once released, exosomes can be taken up by nearby cells, or may enter bodily fluids, including blood and saliva [33]. Circulating exosomes can fuse with recipient cells in various organs and tissues, displaying local and systemic regulation. The uptake process is regulated at multiple levels. For example, uptake may require assistance from membrane surface markers. Follicular DCs (FDCs) can recruit B cell exosomes via the Fc receptor (FcR) and/or complement receptors (CRs). Functional integrin α4β1 is highly enriched on B cell-secreted exosomes and can enhance exosome binding to Ags [34]. Additionally, tetherin (BST2) can maintain HeLa cell-derived exosomes on the cell surface through its glycophosphatidyl-inositol (GPI) anchor, and thus can help determine whether

exosomes participate in long- or short-range interactions [28]. Future, more in depth studies of the regulation of exosome biogenesis, secretion, and uptake may enable the engineering of exosomes for use as a drug vehicle in cancer immunotherapy.

Extraction and Characterization of Immune Cell-Derived Exosomes

Any study of EVs requires proper extraction and careful re-evaluation and validation. The International Society for Extracellular Vesicles (ISEV) has published updated methods for EV analysis twice over the past 5 years to match the fast-paced research field [35]. Ultracentrifugation is currently the most popular method for exosome isolation and is widely used in many laboratories. Although it is time consuming and labor intensive, it can provide high-purity exosomes, especially when combined with sucrose gradient ultracentrifugation [36]. However, drawbacks are emerging, such as substantial product loss during each spin and contamination. One cause of contamination is that ultracentrifugation can copurify miRNAs from serum-free media [37].

Other well-recognized methods for exosome isolation include size-based and affinity-based exosome isolation and polymer-based precipitation. These techniques can be applied for analysis of valuable samples, but at high cost. Electron microscopy (EM) and protein immunoblotting (IB) of exosome markers are widely used for exosome characterization [38,39,104]. EM is considered the gold standard for EV characterization, but alternative methods include: nanoparticle tracking analysis (NTA), microfluidic resistive pulse sensing (MRPS), ExoView, NanoView, and advanced imaging flow cytometry (IFCM). Among these techniques, IFCM exhibits high capacity for detection of submicron particles and sEVs [40–43]. After isolation and characterization, immune cell-derived exosomes can be applied for downstream *in vitro* or *in vivo* treatment. Importantly, the amount of exosomes should be properly controlled to precisely mimic physiological conditions *in vivo*.

The Role of Immune Cell-Derived Exosomes in Innate Immunity

The first-line defense against infection and cancer is innate immunity [43], which includes: mast cells (MCs), neutrophils, macrophages, eosinophils, basophils, and natural killer (NK) cells. Different types of innate immune cells can mutually secrete and take up exosomes among each other and can interact with adaptive immune cells, including DCs, T cells, and B cells. Moreover, pathogen-, leukocyte-, and nonhematopoietic cell-derived EVs can either stimulate or inhibit innate immune responses via multiple mechanisms [44]. The downstream effects may include: regulation of differentiation, polarization, activation, tissue recruitment, cytokine/chemokine production, or the ability to transfer Ags to different types of innate immune cells.

Under certain specific treatments, exosomes can transfer information from donor cells to other types of innate immune cells. For example, NK cells that were previously exposed to neuroblastoma (NB) can secrete exosomes containing NK cell receptors, for example, CD56, NKG2D, and KIR2DL2 receptors [45,46]. These exosomes can subsequently educate normal NK cells, generating greater and more efficient cytotoxicity against NB tumor cells [46]. Additionally, innate immune cells can be educated by exosomes secreted by adaptive immune cells. T cell-derived EVs can be taken up by MCs within 24 h, which induces MCs to secrete more cytokines, including IL-24 [47,105]. Proteomic analysis has revealed that T cell-derived exosomes are enriched with a small GTPase/mitogen-activated protein kinase (RAS/MAPK) signaling proteins, which induce extracellular signal-regulated kinase (ERK) phosphorylation in recipient MCs [48].

The Role of Immune Cell-Derived Exosomes in Adaptive Immunity

When innate immunity alone is insufficient to eliminate invading pathogens or to eradicate pathogen-infected or neoplastic cells, adaptive immunity is required. Virtually all innate immune cells can communicate with DCs, T cells, and B cells [49]. DEX can induce recipient Ag-specific

$CD8^+$ T cells and promote Ag-specific IgG production more efficiently than microvesicles (a larger subclass of EVs with diameters of 100–1000 nm) [50]. Regulatory T cell (Treg)-derived exosomal miRNAs, including miR-150-5p and miR-142-3p, can be delivered to DCs, prompting those DCs to produce more IL-10 and decreasing IL-6 upon lipopolysaccharide stimulation. In this context, these exosomes inhibit immune cell activities in tissues [51].

Tumor-associated macrophage (TAM)-delivered miR-21-5p and miR-29-3p induce Treg/T helper (Th)17 imbalance by suppressing signal transducer and activator of transcription (STAT)3, which facilitates the progression and metastasis of epithelial ovarian cancer cells [52]. Moreover, MC-derived exosomes induce phenotypic and functional maturation of DCs and elicit specific immune responses *in vivo* [53]. Let-7 is critical for both B cell activation and macrophage responses [54,106]. Through EVs, Treg cells can transfer let-7d to Th1 cells, which further suppresses their proliferation and cytokine secretion, thus preventing systemic diseases [55]. Furthermore, TAM-derived EVs (TAM-EVs) can promote T cell proliferation and activation [56]. EVs from mouse bone marrow-derived $CD63^+$ DCs (BMDCs) enhance Ag-specific antibody responses of $CD8^+$ T cells and follicular helper T cells [57]. *Mycobacterium tuberculosis*-infected DCs from Rab27a-deficient mice exhibit limited ability to present Ag to $CD4^+$ T cells, suggesting that Rab27a-dependent secretion of exosomes by these DCs is important for acquiring adaptive immune responses against tuberculosis [58]. Programmed death-ligand 1 (PD-L1) has been detected on the surface of EVs [59] and is reportedly specifically secreted within exosomes [60]. Exosomal PD-L1 from tumor suppressive T cells can be activated in draining lymph nodes [61].

EV release by primary B cells is induced by peptide-laden (p)MHC-II ligation with cognate T cell receptor (TCR) on $CD4^+$ T cells. B cell-derived exosomes impair antitumor T cell responses by hydrolyzing ATP from chemotherapy-treated tumor cells into adenosine via CD39 and CD73 [62]. T cell-derived exosomal CD40L can sustain signaling cues, which can promote B cell proliferation and differentiation [63]. Interferon-γ (IFN-γ)-stimulated DC-derived EVs induce strong adaptive immune responses [50]. Thymic stromal lymphopoietin (TSLP) induces DCs to secrete exosomes containing OX40 ligand (OX40L), which promotes $CD4^+$ T cell proliferation, enhances IL-4 production, and induces Th2 T cell differentiation [64]. Overall, immune cell-derived exosomes are important for both mediating communications between innate and adaptive immune cells and serving as a bridge between immune responses and tumor cells.

Immune Cell-Derived Exosomes Interact with Cancer Cells

Both innate and adaptive immune cell-derived exosomes can directly interact with cancer cells, and their uptake by tumor cells can induce various immune responses [65]. Bioactive lipids and biosynthetic enzymes carried by TAM-EVs can reportedly alter proinflammatory signaling in tumor cells [56]. For example, TAM-EVs can deliver HIF-1α-stabilizing long noncoding (lnc) RNA, which enhances the aerobic glycolysis and apoptotic resistance of breast cancer cells [66]. Additionally, TAM-derived exosomal miR-365 significantly decreases the sensitivity of pancreatic ductal adenocarcinoma (PDAC) cells to gemcitabine through upregulation of the triphosphonucleotide pool, and induction of enzyme cytidine deaminase in PDAC cells [67]. M2 macrophage-derived exosomal miR-21-5p and miR-155-5p enhance colorectal cancer cell mobility, migration, and invasion [68]. Alveolar macrophages (AM) secrete suppressors of cytokine signaling 3 (SOCS3) in EVs and regulate STAT-induced inflammatory responses in neighboring epithelial cells (ECs). EVs containing SOCS3 can exert endogenous antitumor functions, inhibiting proliferation and survival of lung cancer cells [69].

DEX can also mediate immune responses through interaction with tumor cells. For example, DEX can reportedly promote tumor progression in hepatocellular carcinoma (HCC) cells [70].

Exosomes derived from mature DCs with membrane expression of confirmed tumor necrosis factor (TNF)-α can increase human umbilical vein endothelial cell (HUVEC) inflammation through activation of the nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) signaling pathway [71]. Endowed with many immune function-associated molecules from DCs, DEX can stimulate $CD3^+$ T cells to produce more IFN-γ upon interaction with SK-BR-3 breast adenocarcinoma cells [72]. When taken up by tumor cells, immune-derived exosomes can either inhibit or stimulate immune responses in the cancer-immunity cycle.

Exosome-Mediated Immunosuppression in Cancer Cell-Bearing Hosts

The exosomes released by some immune cells exert protumor effects that facilitate carcinogenesis by suppression of immune responses [73]. $CD8^+$ T cell-derived exosomes with membrane expression of Fas ligand (FasL) can promote invasion and metastasis of Fas^+ tumor cells through matrix metalloproteinase-9 (MMP-9)-mediated degradation of extracellular matrix proteins [74]. Additionally, in acute myeloid leukemia (AML) patients, plasma exosomes that carry leukemia-associated Ags and multiple inhibitory molecules can inhibit tumor activities by interfering with NK-92 cells [75]. Interestingly, NB-derived exosomes can pre-educate NK cells, which can, in turn, provide a tumor-supporting niche through EVs (Figure 2) [46].

Exosome-Mediated Activation of Anticancer Immune Responses

When provoked by tumor cells, immune responses can be induced to clear cancer cells – a process known as immune surveillance [76]. Likewise, many immune cells, including NK cells, can secrete exosomes that activate immune responses, contributing to cancer cell clearance. Exosomes released by NK cells exhibit membrane expression of FasL and exert strong cytotoxicity against tumor cells by clearing Fas^+ tumor cells [77]. NK-92 cell-derived exosomal TNF-α exerts cytotoxic effects against melanoma cells, blocking the cell proliferation signaling pathway [78]. In addition to exosomal proteins, NK cell-derived exosomal miR-186 exhibits cytotoxicity towards MYCN-amplified NB tumors by directly targeting MYCN, AURKA, TGFBR1, and TGFBR2 [79].

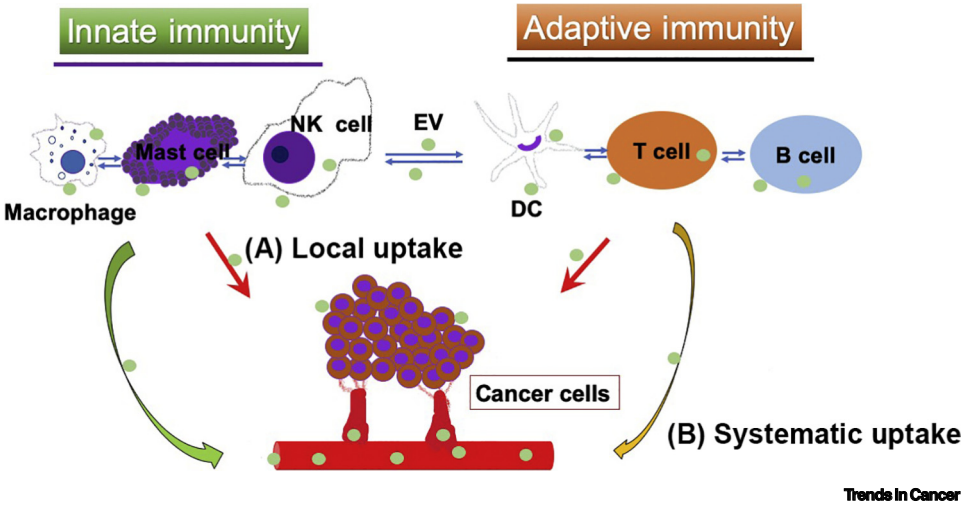

Figure 2. Exosomes Mediate the Communication between Different Types of Immune Cells across the Innate and Adaptive Immune System. Both innate and adaptive immune cells, including macrophages, mast cells (MCs), natural killer (NK) cells, dendritic cells (DCs), T cells, and B cells, can secrete and take up exosomes, mediating crosstalk between different immune cell types. Tumor cells can take up nearby immune cell-released exosomes or immune cell-derived exosomes that systematically travel through blood. Abbreviation: EV, extracellular vesicle.

Altogether, different types of innate and adaptive immune cells are either directly or indirectly helping or blocking the effective killing of cancer cells in each step of the cancer-immunity cycle (Figure 1). Immune cell-derived exosomes are involved from steps two to six in one intact cycle. Deeper understanding of the biological functions of immune cell-derived exosomes might allow us to better design an antitumor therapy strategy based on the cancer-immunity cycle.

Potential of Immune Cell-Derived Exosomes in Cancer-Immune Therapy

Recent reports describe the use of exosomes as natural nanoparticles for drug delivery in cancer immunotherapeutic applications [80–82]. Both macrophage-derived exosomes and DEX have been applied for anticancer immunotherapy [83]. DCs act in the first step of the cancer-immunity cycle, eliminating tumor cells through T cell activation [84]. As they share surface membrane components that interact with other immune cells, DC-derived EVs (especially exosomes) can potentially be engineered to act as cell-free antitumor vaccines, providing a novel immunotherapy in the fight against cancer [85]. In a clinical Phase I trial, DEX displayed NK cell effector functions [82]. During the Phase II trial, IFN-γ-matured DEX loaded with MHC class I and II tumor peptides were able to boost NK cell activity in non-small cell lung cancer (NSCLC) patients [28,81]. Over 32% of participants experienced stabilization over 4 months [86].

EVs derived from imDCs can also deliver chemotherapeutic agents, such as doxycycline (DOX), to triple-negative MDA-MB-231 breast cancer cells *in vitro*. *In vivo* injection of imDCs reportedly inhibits tumor growth in mice [87]. DEX that express A-fetoprotein (AFP) can reshape the tumor immune microenvironment and elicit competent Ag-specific immune responses in autochthonous HCC mouse models [88]. Raw264.7 macrophages can produce exosomes that are loaded with the potent anticancer agent paclitaxel (PTX), which can significantly increase drug cytotoxicity in drug-resistant MDCK cells [89,107]. Incorporation of an aminoethylanisamide-polyethylene glycol (AA-PEG) vector further enhances exoPTX (exosomes released by macrophages with PTX), such that it exhibits high-loading capacity with accumulation in cancer cells and displays greater anticancer effect [90].

In addition to regulating the cancer-immunity cycle, immune cell-derived exosomes also appear to play roles in diabetes, fibrosis, aging, transplantation, and cardiovascular disease [8,91,92]. For example, in obese mice, adipose tissue macrophages (ATMs) can secrete exosomal miR-155, which causes glucose intolerance and insulin resistance in lean mice [93]. T lymphocytes can release exosomal miR-142-3p, miR-142-5p, and miR-155, which promotes apoptosis in islet β cells [94]. Additionally, it was recently reported that M2 macrophage-derived exosomes can contain lncRNA-ASLNCS5088. This lncRNA can be delivered to fibroblasts to adsorb miR-200c-3p, resulting in increased glutaminase (GLS) and α-(SMA) smooth muscle actin expression, and thus increased tissue fibrosis after wound healing *in vivo* [95]. Macrophage-derived EVs can promote survival after injury by delivering WNT into intestinal stem cells [96]. Exosomes derived from imDC cells may express miR-682, which promotes immune tolerance in renal transplantation via suppression of Rho-associated protein kinase (ROCK) [97].

Concluding Remarks and Future Perspectives

The investigation of immune cell-secreted exosomes in the cancer-immunity cycle is a rapidly evolving field. It has been traditionally thought that immune cells secrete cytokines to regulate the immune response against cancer. However, emerging evidence indicates that they can secrete many genetic materials and proteins, encapsulated by exosomes, and can thus regulate recipient immune cells and cancer cells in local or remote tissues (Table 1, Key Table). Likewise, exosomes were initially thought to function in transferring unnecessary proteins from donor

Outstanding Questions

The functions and mechanisms of immune cell-derived exosomal metabolites are poorly defined. What are the physiological roles of exosomal metabolites in the cancer-immunity cycle?

The circulating exosomes in body fluid should be very heterogenous, comprising a mixture of different types of immune cell-derived exosomes. How can we develop an effective tracking system to monitor specific immune cell-derived exosomes under physiological and pathological conditions? How can we isolate other types of EVs, and how can we better purify and distinguish various class of EVs *in vivo*?

Although many reports have dissected the roles of tumor cell-derived exosomes in innate immunity, the effects of immune cell-derived exosomes on macrophages remain poorly characterized. For example, do M1 macrophage-derived exosomes educate M2 macrophages or *vice versa*?

The interaction between the immune cell secretion of EVs and cytokine secretion is poorly studied. Do EV biogenesis and secretion affect the processes of cytokine production and secretion?

Key Table

Table 1. Exosomes – Mediators of Immune Regulation

Immune cell of origin	Target cells	Influences of exosomes	Related key molecules involved	Refs
Mature DEX	Splenetic DCs and T cells	Triggering inflammation responses	CCR7	[30]
B cell exosomes	FDCs	Enhancing binding to Ags	FcR and/or CRs; integrin α4β1	[34]
NK cells that were previously exposed to NB	Normal NK cells	Generating greater and more efficient cytotoxicity against NB tumor cells	NK cell receptors, for example, CD56, NKG2D, and KIR2DL2 receptors	[46]
T cell-derived EVs	MCs	Inducing MCs to secrete more cytokines	IL-24	[47]
T cell-derived exosomes	MCs	Inducing ERK phosphorylation	RAS/MAPK/ERK	[48]
DEX	Ag-specific $CD8^+$ T cells	Promoting Ag-specific IgG production	IgG	[50]
Treg-derived exosomes	DCs	Prompting those activated DCs to produce more IL-10 and decreasing IL-6	miR-150-5p and miR-142-3p	[51]
TAM-delivered exosomes	Treg/Th17 cells	Facilitating the progression and metastasis of epithelial ovarian cancer cells	miR-21-5p and miR-29-3p	[52]
MC-derived exosomes	DCs	Eliciting specific immune responses *in vivo*	MHC class II, CD80, CD86, and CD40	[53]
Treg cell-derived exosomes	Th1 cells	Suppressing Th1 cell proliferation and cytokine secretion	Let-7d	[55]
TAM-EVs	T cell	Promoting T cell proliferation and activation	CSF1R	[56]
DCs (BMDCs)-derived extracellular vesicles	$CD8^+$ T cells and follicular helper T cells	Enhancing Ag-specific antibody responses	CD63	[57]
M. tuberculosis-infected DCs-derived exosomes	$CD4^+$ T cells	Acquiring adaptive immune responses against tuberculosis	Rab27a	[58]
B cell-derived exosomes	T cell	Impairing antitumor T cell responses	CD39 and CD73	[62]
T cell-derived exosomes	B cell	Promoting B cell proliferation and differentiation	CD40L	[63]
TSLP-activated DCs	$CD4^+$ T cell	Promoting $CD4^+$ T cell proliferation, enhancing IL-4 production, and inducing Th2 T cell differentiation	OX40L	[64]
TAM-EVs	Breast cancer cells	Enhancing the aerobic glycolysis and apoptotic resistance of breast cancer cells	HIF-1α-stabilizing lncRNA	[66]
TAM-derived exosomes	PDAC cells	Decreasing the sensitivity of PDAC cells to gemcitabine	miR-365	[67]
M2 macrophage-derived exosomes	Colorectal cancer cell	Enhancing colorectal cancer cell mobility, migration, and invasion	miR-21-5p and miR-155-5p	[68]
DEX	HCC cells	Promoting tumor progression in HCC cells	Tumor growth factor-β and IL-10	[70]
DEX	HUVEC	Increasing HUVEC inflammation	NF-κB	[71]
$CD8^+$ T cell-derived exosomes	Fas^+ tumor cells	Promoting invasion and metastasis of Fas^+ tumor cells	MMP-9	[74]
NK cell-derived exosomes	Fas^+ tumor cells	Exerting strong cytotoxicity against tumor cells	FasL	[77]
NK-92 cell-derived exosomes	Melanoma cells	Exerting cytotoxic effects against melanoma cells	TNF-α	[78]
NK cell-derived exosomes	NB tumor cells	Exhibiting cytotoxicity towards MYCN-amplified NB tumors	miR-186	[79]
imDCs-derived EVs	MDA-MB-231 breast cancer cells	Delivering chemotherapeutic agents, such as DOX	DOX	[87]
Raw264.7 macrophage-derived exosomes	Drug-resistant MDCK cells	Increasing drug cytotoxicity	Anticancer agent PTX	[89]

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Table 1. (continued)

Immune cell of origin	Target cells	Influences of exosomes	Related key molecules involved	Refs
ATM-derived exosomes	Lean murine cells	Causing glucose intolerance and insulin resistance	miR-155	[93]
T lymphocyte-derived exosomes	Islet β cells	Promoting apoptosis	miR-142-3p, miR-142-5p, and miR-155	[94]
M2 macrophage-derived exosomes	Fibroblasts	Increasing tissue fibrosis after wound healing *in vivo*	lncRNA-ASLNCS5088	[95]
Macrophage-derived EVs	Intestinal stem cells	Promoting survival after injury	WNT	[96]
imDC cell-derived exosomes	Treg cell	Promoting immune tolerance in renal transplantation	miR-682; ROCK	[97]

cells. However, current evidence indicates that the messages delivered by exosomes may provide an alternative and highly efficient means of delivering information, which could have long-term effects in regulating anticancer immune responses.

Studies in immunometabolism will have a significant impact in the field of cancer immunology. Metabolites, such as succinate and α-ketoglutarate (α-KG), have been reported to play a role in regulating immune cell functions, such as macrophage responses [98,99]. The functions and mechanisms of immune cell-derived exosomal metabolites are poorly defined. Functions of immune cell-derived exosomal metabolites in immunity will help deepen our understanding of the regulation and function of metabolite-reactive immune cells. Further research on the physiological and pathological roles of exosomal metabolites in the cancer-immunity cycle will allow for deeper elucidation of the precise role of exosomes in both physiological and pathophysiological processes, ultimately accelerating the use of exosomes as therapeutics and diagnostics in cancer.

The circulating exosomes in body fluid should be very heterogenous, consisting of a mixture of different types of immune cell-derived exosomes [100,101]. Various subpopulations may exist within EV populations. This heterogeneity might introduce an extra level of complexity in the study of EV biology and function in cancer and immunity. As current isolation and tracking techniques are ill-equipped to determine the heterogeneity of secreted EV populations, it will be necessary to find a better way to isolate EVs, such as microvesicles, ectosomes, oncosomes, and apoptotic bodies, and to purify and distinguish various class of EVs *in vivo* and to develop an effective tracking system to monitor specific immune cell-derived exosomes (see Outstanding Questions). Although several research groups have reported the roles of tumor cell-derived exosomes in innate immunity [83,102,103], the effects of immune cell-derived exosomes on certain innate immune cell types, such as macrophages, remain poorly characterized. There are many questions that remain to be addressed. For instance, do M1 macrophage-derived exosomes educate M2 macrophages or vice versa? Do B cell-derived exosomes affect B cell activation, B cell differentiation, class switching, VDJ recombination, somatic hypermutation, and plasma cell antibody production? Shedding light on the effects and mechanisms of exosomes in mediating B cell or T cell diversity and macrophage/DC activation will also allow for a better understanding of the physiological roles of exosomes in both innate and adaptive immune bioprocesses, ultimately further dissecting the role of exosomes as a mediator in immunity.

In addition, the interaction between the immune cell secretion of EVs and cytokine secretion is still obscure. It is still unclear whether EV biogenesis and secretion influence the processes of cytokine production by either M1 macrophages or activated B cells. It will be necessary to examine the *in vivo* functions of exosomes in different types of immune cells and knock out of a key component

in exosome biogenesis in different immune cells; for example, a LysM-cre^{+} Rab27a/b$^{flox/flox}$ engineered mouse model might be utilized to address this question.

Future studies are required to fully characterize exosomes that originate from immune cells, and to learn how to precisely engineer exosomes for further therapeutic antitumor treatments. Importantly, the involvement of researchers from different fields could greatly enrich our knowledge about immune exosomes and facilitate the development of better strategies for applying these naturally equipped nanocarriers as drug vehicles in anticancer immunotherapy. Collectively, these small particles play large roles in the regulation of multiple biological processes, especially in the cancer-immunity cycle *in vivo*.

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