Exosomes, which are well-known nanoscale extracellular vesicles, are multifunctional biomaterials derived from endosomes and perform various functions. The exosome is a critical material in cell-cell communication. In addition, it regulates the pathophysiological conditions of the tumor microenvironment in particular. In the tumor microenvironment, exosomes play a controversial role in supporting or killing cancer by conveying biomaterials derived from parent cells. Innate immunity is a crucial component of the host defense mechanism, as it prevents foreign substances, such as viruses and other microbes and tumorigenesis from invading the body. Early in the tumorigenesis process, the innate immunity explicitly recognizes the tumor via Ags and educates the adaptive immunity to eliminate it. Recent studies have revealed that exosomes regulate immunity in the tumor microenvironment. Tumor-derived exosomes regulate immunity against tumor progression and metastasis. Furthermore, tumor-derived exosomes regulate polarization, differentiation, proliferation, and activation of innate immune cells. Exosomes produced from innate immune cells can inhibit or support tumor progression and metastasis via immune cell activation and direct cancer inhibition. In this study, we investigated current knowledge regarding the communication between tumor-derived exosomes and innate immune cell-derived exosomes (from macrophages, dendritic cells, NK cells, and neutrophils) in the tumor microenvironment. In addition, we discussed the potential development of exosomal immunotherapy using native or engineered exosomes against cancer.

Keywords: Exosomes; Tumor microenvironment; Cancer; Innate immunity

INTRODUCTION

Exosomes are vesicles composed of a lipid bilayer membrane ranging 50–150 nm and are produced by most types of cells, including tumor and immune cells (1). Exosomes, which reflect the internal environment of cells, have been investigated extensively over the past decade in relation to metabolic reprogramming, infection, immunology, and the tumor microenvironment, among other aspects (2). The role of exosomes in cell-to-cell communication has been a primary focus of research in this field. Exosomes are produced
by parental cells to control the functions of other cells, and studies on the modulation of cancer progression, particularly in the tumor microenvironment, have been performed in recent years. Now, we have a better understanding of tumor-derived and immune cell-derived exosomes. In particular, abundant evidence indicating that these exosomes contribute to tumor progression and have anti-cancer functions is available (3).

The relationship between tumors and immunity is essential for tumor growth and suppression. The cancer immunity cycle summarizes the 7 communication phases between the tumor and innate and adaptive immunity to control tumor occurrence (4). Ags produced in the early stages of cancer are recognized by dendritic cells (DCs), macrophages, and B cells, which comprise the innate immunity and then move to the lymph nodes to activate Ag-specific CD8+ T cells. Activated CD8+ T lymphocytes move to the tumor microenvironment and then infiltrate to detect and eradicate the tumor via the Ags. Exosomes play a crucial role in tumor and immune cross-communication, especially in tumor Ag presentation, immune cell activation, and immune repression (5,6).

This review focuses on new research trends in exosomes related to tumors and immune system cross-communication. This review aims to present reports on the regulation of immunity by exosomes produced from tumors, the mechanism of tumor microenvironment regulation by the immune cell-derived exosome, and the phenomenon of tumorigenesis, tumor development, and tumor inhibition. Furthermore, we expect to identify how tumors and immunity regulate each other via exosomes and, additionally, to understand the potential use of exosomes for cancer treatment.

**EXOSOME CHARACTERISTICS**

**Exosome biogenesis**

Exosomes are derived from the endosomal pathway (7,8), and their biogenesis begins with endosome formation on the plasma membrane. The endosome enters the interior and creates intraluminal vesicles (ILVs), forming multivesicular bodies (MVBs). Lastly, MVBs undergo acidification and maturation, fuse with the plasma membrane, and secrete ILVs from the cell. These processes are generally accomplished through the endosomal sorting complex required for transport (ESCRT). Thus, endosomes play a significant role in MVB and ILV generation. The ESCRT complex comprises ESCRT-0, ESCRT-1, ESCRT-2, ESCRT-3, and associated proteins such as ALIX, TSG101, and syntenin. The ESCRT complex functions by sequentially connecting its components. The ESCRT-0 complex then moves ubiquitinated proteins to the endosomal membrane. The ESCRT-1 and ESCRT-2 complexes prepare ILVs by isolating the payload and modifying the endosomal membrane to insert the payload into the endosomal membrane. The ESCRT-3 complex completes the MVB using an isolated payload to create ILVs. Additionally, ESCRT-independent pathways exist, including microRNA (miRNA) post-transcriptional 3'-end modification, RNA-induced silencing complex pathways, and neutral sphingomyelinase-dependent pathways, which are not entirely differentiated from the ESCRT-dependent pathways. Thus, exosomes are composed of proteins, lipids, and nucleic acids, all of which are essential cellular constituents. The exosome membrane contains components from the plasma membrane of the parent cell; the formation of ILVs through the ESCRT complex enables protein and nucleic acid transport to ILVs through the intracellular signal transduction system (Fig. 1) (9,10).

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https://immunenetwork.org
**Exosome contents**

The exosome is composed of a biomaterial representing the parent cell environment and contains proteins, lipids, DNA, and ribonucleic acid species (i.e., mRNA, long non-coding RNA [miRNA, and lncRNA]) (Fig. 1) (11). Since the lipid bilayer membrane of the exosome is produced via endocytosis of the parent cell membrane, proteins such as CD9, CD63, and CD81, which are tetraspanin superfamily proteins, constitute the exosomal membrane (12). In addition, exosomes contain tetraspanin-associated protein integrins, growth factor receptors, MHC, and costimulatory molecules. Exosome biogenesis-related proteins, ESCRT machinery-associated proteins, ALIX, HRS, and TSG101 are also enriched (13).

In addition, exosomes contain proteins associated with each specific cellular function. For example, heat shock proteins and MHC molecules are also found in the exosomes of most cell types, contributing to Ag presentation and innate immune activation via exosomes (14,15). The tumor-derived exosome usually comprises tumor Ag and immunosuppressive protein (i.e., PD-L1) (16). The exosome contains mRNA and non-coding RNAs, such as miRNA, tRNA, lncRNA, and circular RNA. RNA transfer through exosomes influences epigenetic features of target cells via gene regulation (17,18).

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**EXOSOMAL COMMUNICATION BETWEEN THE TUMOR AND INNATE IMMUNE SYSTEM**

Innate immunity is the earliest mechanism to prevent cancer; it consists of macrophages, DCs, NK cells, and neutrophils. In addition, specific Ag-presenting cells (APC) recognize...
cancer development via Ags and various chemicals and activate adaptive immunity to suppress cancer. For example, exosomes released by neuroblastoma (NB) contain NK-cell receptors, NKG2D, and KIR2DL2 receptors and can be transferred to NK cells and activated to induce cytotoxicity in NB cells (19). Therefore, this review investigates the regulation of innate immunity by exosomes in the tumor microenvironment and the functions associated with tumor regulation (Fig. 2).

**Macrophages**

Macrophages are innate immune cells, and depending on their activity, they can be classified into M1 macrophages (M1s) of a pro-inflammatory phenotype and M2 macrophages...
M2s of an anti-inflammatory type (20). M1s are classically activated macrophages that play an essential role in the direct host defense mechanism during early infection and tumorigenesis and initiate phagocytosis and pro-inflammatory cytokine release (21). M2s are alternatively activated macrophages that regulate inflammation following wound healing (22). Among macrophages, tumor-associated macrophages (TAMs) are one of the most critical components of tumors, accounting for around 30%–50% of the overall tumor mass. TAMs are commonly classified into pro-tumorigenic M2s and anti-tumorigenic M1s (23). Therefore, the polarization of M2s to M1s in the tumor microenvironment is a highly vital strategy for cancer treatment. Tumor-derived exosomes produced from specific cancers trigger macrophage M1 polarization (24). Exosomes released from epigallocatechin gallate (EGCG)-treated breast cancer convert M2s to M1s. EGCG is an active compound in green tea that causes cancer cell apoptosis (25). EGCG therapy boosts the level of miRNAs inside breast cancer cell-derived exosomes. In particular, EGCG increases the level of miRNA-16 to polarize TAMs to M1s. miRNA-16 decreases IL-6 and TGF-β, M2-associated proteins, and increases levels of TNF-α, an M1-associated protein (26). Exosomes released from colorectal cancer (CRC) polarize liver resident macrophages to M1s. In the CRC-derived exosome, the levels of miRNA-21 are increased and that of the pro-inflammatory cytokines TNF-α and IL-6 are increased when exosomes with miRNA-21 are treated with macrophage cell lines (RAW264.7 and THP-1). However, the levels of the anti-inflammatory cytokines IL-10 and Arg1 do not change considerably. MiRNA-21 binds to the macrophage Toll-like receptor-7 and is implicated in M1 polarization (27). Exosomes have been found in oral squamous cell carcinoma (OSCC). When THP-1 cells are treated with exosomes isolated from the conditioned media of SCC25 and Cal27 OSCC cell lines, M1 polarization occurs with the increasing levels of inflammatory cytokines TNF-α, IL-1β, and IL-6. In particular, thrombospondin 1 (THBS1) in exosomes is considered an essential regulator of M1 polarization. Furthermore, when exosomes isolated from THBS1-knockdown OSCC cells are treated with THP-1, the levels of pro-inflammatory proteins TNF-α, IL-1β, and IL-6 are suppressed relative to that in control (28).

After tumorigenesis, the tumor microenvironment develops into a form that supports tumor growth (29). Macrophages stimulated by tumor-derived exosomes are critical factors for tumor growth and metastasis. Exosome-activated macrophages promote tumor progression by promoting tumor growth, metastasis, tissue inflammation, and angiogenesis (30). Tumor-derived exosomes can generate TAMs through macrophage education in the tumor microenvironment (24). They have the M2 phenotype and contribute to tumor growth and metastasis by secreting anti-inflammatory proteins and pro-angiogenic factors (30). Recent studies indicate a link between M2 polarization and tumor growth via tumor-derived exosomes. For example, treating triple-negative breast cancer (TNBC)-generated exosomes with macrophages develops M2 polarization and increases lymph node metastases. During co-culture with cancer-derived exosomes, the expression of the M2 markers Arg1, CD206, and Fizz1 increased in macrophages, as determined through quantitative real-time PCR. Thus, TNBC-derived exosomes might regulate macrophage polarization to M2 to accelerate cancer growth and lymph node metastasis (31). Hypoxia refers to a low oxygen status in the tissue and is commonly induced within the tumor microenvironment. Hypoxia in the tumor microenvironment increases tumor-derived exosome production and contributes to tumor development by regulating peripheral macrophage polarization. In addition, hypoxia-triggered lung cancer can promote metastasis by secreting exosomes rich in miRNA-103a to induce angiogenesis. miRNA-103a inhibits the expression of the PTEN protein, and the reduced PTEN protein suppresses the immune response through IL10, CCL2, and VEGF-A via
activation of the STAT3 and PI3K/AKT signaling pathways. Recent studies have demonstrated macrophage M2 polarization by hepatocellular carcinoma cell (HCC)-derived exosomes. LncRNA-TUC339 is widely found in HCC-generated exosomes. TUC339 function was confirmed using the THP-1 macrophage cell line; when the TUC339 expression of THP-1 cells is elevated, the induction of M1 marker proteins TNF-α and IL-1β by LPS treatment decreases compared to that of the control. Reduction in TUC339 expression in THP-1 cells boosts the M1 phenotype. This suggests that when lncRNA TUC339 is transferred by HCC-derived exosomes to macrophages, the macrophages are polarized to the M2 phenotype, boosting tumor promotion (32). This phenomenon has also been observed in other patients. For example, blood analysis of patients with CRC revealed that miRNA-203 is highly expressed in exosomes, and miRNA-203 is associated with distant metastases and poor prognosis. Furthermore, in vitro experiments showed that miRNA-203 is involved in monocyte differentiation and enhances TAM differentiation via M2 polarization. Through additional in vivo xenograft experiments, it was shown that liver metastasis is exacerbated in CRC overexpressing miRNA-203 and that CRC patient-derived exosomes reinforce M2 polarization through miRNA-203 to increase metastasis and deteriorate the prognosis (33). Thus, tumors manipulate macrophages via exosomes to produce a favorable tumor microenvironment, thereby promoting tumor growth and metastasis.

As tumors predominantly employ tumor-derived exosomes to establish a favorable environment, macrophages use macrophage-derived exosomes according to the M1 and M2 states to improve anti-tumor immunity or promote tumor growth. M1-derived exosome-treated macrophages, DCs, and T cells largely increased the expression of pro-inflammatory proteins. In particular, exosomes produced from macrophages treated with IFN-γ create a pro-inflammatory milieu and exhibit anti-cancer potential (34). In addition, M1-derived exosomes directly act on cancer cells, suppressing the expression of PD-L1 in gastric cancer and increasing the number of IFN-γ+ T cells, consequently demonstrating anti-cancer properties. Exosome-expressed miRNA-16-5p plays an essential role in reducing PD-L1 expression (35).

In contrast, tumor-derived exosomes boost M2 polarization, whereas M1-derived exosomes limit tumor growth by polarizing M2s to M1s. M1-derived exosome treatment led to the differentiation of M2s into M1s; among miRNAs present in exosomes, miRNA-21, miRNA-125, and miRNA-155 were identified as notably contributing to the polarization of M2 to M1 (36). As the exosome activity reflects the activity of the parent cell, the M2-derived exosome promotes tumor growth or enhances metastasis in the same way as the M2. The M2-derived exosome assists in cell migration and invasion in colon cancer. By targeting colon cancer, miRNA-21-5p and miRNA-155-5p contained in exosomes are delivered to colon cancer cells and increase metastasis by suppressing BRG-1 protein expression. The M2-derived exosome modulates cancer metabolism, has pro-tumorigenic properties and increases aerobic glycolysis and chemoresistance in lung cancer. miRNA-3679-5p overexpressed in M2-derived exosomes suppresses the expression of NEDD4L, also known as an E3 ligase, thereby enhancing the stability of oncogene c-Myc and altering cancer metabolism to promote glycolysis and chemoresistance (37). In the pancreatic ductal adenocarcinoma microenvironment, M2-derived exosomes do not directly target tumors but target endothelial cells, thus enhancing angiogenesis and tumor progression. This mechanism is mediated by miRNA-155-5p and miRNA-221-5p overexpression in the exosomes. miRNAs in exosomes are transferred to endothelial cells and target the E2F2 protein to decrease its expression and promote angiogenesis (38).
Exosome communication induces macrophage M1/M2 polarization, boosts tumor promotion, or induces anti-tumor action in the tumor microenvironment. By boosting the polarization to M2, a pro-tumorigenic macrophage state, the tumor-derived exosome aims to establish a favorable environment for tumors. Exosomes produced from M1s improve anti-tumorigenic activity by promoting M1 polarization. M2-derived exosomes can produce a pro-tumorigenic milieu that promotes metastasis or can act directly on the tumor to regulate metabolism and improve chemoresistance and cell survival. The functions of macrophage-derived exosomes in the tumor microenvironment remain controversial, and more research is needed.

DCs

DCs are innate immune cells widespread throughout tissues and differentiate from myeloid cells and lymphoid progenitors. Several DCs have been identified, of which conventional DCs (cDCs) and plasmacytoid DCs (pDCs) are the most representative. pDCs predominantly synthesize and secrete Type-I interferons, whereas cDCs serve as APCs, contributing to the T cell response, which is adaptive immunity. Therefore, cDCs, as APCs, recognize foreign Ags through Ag capture and internalization and can stimulate CD4+ and CD8+ T cells through activated MHC-I and MHC-II molecules (39,40). The differentiation of DCs around the tumor microenvironment is not normal, and the infiltration of mature DCs is reduced in many carcinomas (41,42). The aberrant differentiation of DCs, abnormal maturation, and improper functions have been observed in the tumor microenvironment, and tumor-derived exosomes contribute to the development of these abnormal DCs (43). First, it has been shown that tumor-derived exosomes increase the number of undifferentiated myeloid progenitors, increase the number of immunosuppressive myeloid-derived suppressor cells (MDSCs) around the tumor, and decrease the quantity of DCs. The release of IL-6, which prevents DC differentiation by acting on CD34+ bone marrow progenitor cells, is elevated upon treatment with tumor-derived exosomes. IL-6 also stimulates the proliferation of MDSCs and prevents their apoptosis (42,44). In addition to IL-6, HLA-G, a non-classical MHC-I protein, suppresses DC differentiation by binding to inhibitory receptors. Cancer stem cell-produced exosomes contain HLA-G, which restricts monocyte-derived DC differentiation. In addition, when an Ab blocks HLA-G, the efficacy of exosomes disappears, suggesting that HLA-G plays a crucial role in DC differentiation via exosomes (45). DCs are typically present in immature conditions. In the presence of pathogen-associated molecular patterns and damage-associated molecular patterns, they are activated to a mature state through receptors, such as IL-R, TLRs, and TNF-R. To have potent Ag-presenting potential, mature DCs exhibit high MHC-I and MHC-II molecular expression levels and increased CD80 and CD86, which are costimulatory signaling C7 family molecules (46). In the tumor microenvironment, when mature DCs infiltrate the tumor, anti-tumor immunity is stimulated by augmenting T cell infiltration (47). However, DCs are generally present at an immature stage in the tumor microenvironment. Hence, it is difficult to demonstrate an anti-cancer immune response via adaptive immunity, such as CD8+ T cell activation and expansion. In addition, tumor-derived exosomes have been reported to contribute to DC maturation. T cell immunoglobulin mucin-domain containing-3 (TIM-3) and galectin-9 in tumor-derived exosomes bind to the TIM-3 receptors of tumor-infiltrating DCs. These proteins activate inhibitory signals and interfere with Ag recognition, suppressing DC maturation (48). The exosome in the cerebrospinal fluid of patients with glioblastoma multiforme has high galectin-9, binds to the TIM-3 receptors of DCs, impairs Ag recognition, and interferes with the anti-tumor function through cytoxic T cell activation. As such, galectin-9 in tumor-derived exosomes can be a primary regulator that promotes tumor progression by preventing DC maturation (49). In addition, tumor-derived exosomes can promote TGF-β1 synthesis, which restricts
the activation of DC and lymphocytes and inhibits DC maturation by diminishing the levels of MHC-II and CD86 (50). Advanced tumor-infiltrating DCs are mainly present in low numbers and exhibit high levels of expression of co-inhibitory molecules. These DCs are called regulatory DCs and contribute to tumor development by dampening immunity via T cell exhaustion (42). Tumor-derived exosomes are involved in the formation of regulatory DCs. For example, indoleamine-pyrrole 2,3-dioxygenase-positive tumor-derived exosomes were delivered to DCs to decrease CD40, CD80, CD86, and MHC-II expression levels and boost anti-inflammatory protein secretion (51). PD-L1 plays a key role in immune escape in the tumor microenvironment and interacts with PD-1 to suppress myeloid cell, B cell, and T cell activation (52). When the PD-L1-expressing tumor-derived exosomes are treated with DCs, they develop an immunosuppressive phenotype, which can be reversed when treated with a PD-L1 Ab (53). The exosomes derived from 4T1 cells, a mouse breast cancer cell line, increases PD-L1 expression and apoptosis and decreases differentiation in DCs (54). Decreased extracellular arginine levels induce DC dysfunction through decreased MHC-II levels (55). Arginase-1 (ARG-1) decreases the amount of arginine in the tumor microenvironment and is found in tumor-derived exosomes. ARG-1-expressing tumor-derived exosomes are transported to DCs in the draining lymph node, inducing DC dysfunction and suppressing cytotoxic CD8+ T cell proliferation (56). In particular, PGE-2 and TGF-β exosomes transferred to DCs induce anti-inflammatory extracellular adenosine levels via CD39 and CD73 (57). Tumor-derived exosomal miRNAs may contribute to DC dysfunction. miRNA-212-3p supplied through tumor-derived exosomes targets the DC regulatory factor X-associated protein and contributes to immunological tolerance by suppressing the expression of MHC-II molecules (58). miRNA-203 from pancreatic cancer-derived exosomes was administered to DCs to reduce TLR4 expression and decrease TNF-α and IL-12 production (59). DCs are APCs that play a crucial role in bridging the innate and adaptive immunities. Therefore, the role of DCs in the early recognition of tumor Ags in the cancer immunity cycle is significant, and DC-derived exosomes have been demonstrated to play an essential role in this process. Efforts have been made to alter DC-generated exosomes and exploit them in cancer immunotherapy (4,60). DC-produced exosomes contain MHC molecules and T cell costimulatory molecules, such as those in DCs, and can control tumors by inducing T cell activation (61). Research on immune cell communication through DC-derived exosomes has also been conducted. DC-generated exosomes administered to T cells enhance cytokine secretion. Uptake of exosomes in these T cells occurs in a C-C chemokine receptor 7-dependent manner. In addition, LFA-1 on the T cell surface is implicated in the uptake of MHC-II-expressing DC-derived exosomes (62,63). DC-derived exosome secretion and function are increased in DCs stimulated by an immune enhancer (i.e., Toll-like receptor and LPS), and the anti-tumor efficacy is increased. LPS-induced mature DCs can produce exosomes with increased MHC-II expression and activate more potent cytotoxic T lymphocytes (64). Cancer treatment can boost DC-derived exosome function, and breast cancer-Ag treated DC-generated exosomes and gastric cancer Ag-treated DC-derived exosomes dramatically improve T cell responsiveness to enhance anti-tumor T cell immunity (65,66). DC-derived exosomes can directly recognize and eliminate malignancies in a specific tumor microenvironment. For example, exosomes induce apoptosis in murine melanoma cells via TNF superfamily ligands expressed on the surface of DC-derived exosomes, and gastric cancer proliferation is likewise suppressed by DC-derived exosomes, which cause apoptosis (67).

DC-derived exosomes can be transmitted directly to the surrounding immune cells to improve anti-cancer immunity and promote tumor cell death. In addition, DC-derived exosomes can be used as therapeutic agents because of their high stability and safety benefits compared to those of DCs.
NK cells

NK cells are cytotoxic innate immune cells that contribute to tumor surveillance. NK cells operate as initial responders during cancer development, recognize tumor cells early in tumorigenesis, and destroy cells via cytotoxic proteins, granzyme A/B, perforin, and granulysin. NK cells are classified as innate immune cells that kill tumor cells in a way different from that of the adaptive immune cells (68). Unlike cytotoxic CD8⁺ T lymphocytes, NK cells can recognize and combat cancer early in tumorigenesis without Ags. In particular, NK cells express proteins such as activation receptors NKG2D, NKp30, NKp40, and NKp46 on the cell surface, and CD94-NKG2A, KIR, and inhibitory proteins can detect and destroy tumor cells (69). The activating receptor of NK cells binds to the activating ligand expressed in tumor cells, thereby triggering tumor cell death. However, the inhibitory receptor of NK cells cannot be attached because the MHC-I molecule, a ligand of the inhibitory receptor, is barely present in the tumor (70). To decrease the NK cell-mediated immune surveillance system in the tumor microenvironment, tumor-derived exosomes induce NK cell malfunction (71,72).

Tumor-derived exosomes reduce NK cell recruitment, cytokine production, protein expression, and cytolytic function through their surface ligands and biomolecules (73). Tumor-derived exosomes increase tumor promotion through NK cell-mediated immune suppression (74). Inhibition of NK cell recruitment by tumor-derived exosomes in the tumor microenvironment is an excellent strategy for limiting cell elimination by NK cells. Exosomes obtained from patients with acute myeloid leukemia (AML) can limit NK-92 cell migration. CCL5, CXCL4, and CXCL7 have overexpressed in AML patient-derived exosomes, while CXCR3 expression in exosome-treated NK-92 cells is reduced, consequently limiting NK-92 cell motility (74).

Reducing the number of NK cells near the tumor microenvironment can also facilitate tumor growth, and a recent study reported that tumor-derived exosomes diminish the number of NK cells. When murine mammary carcinoma (TS/A)-derived exosomes are used, the amount and proportion of NK cells decrease. In an in vivo mouse model using TS/A-derived exosomes, the NK cell number and percentage in the lung are significantly reduced, but not in the liver and lymph nodes. In particular, the proportion of NK cells in the spleen is decreased. Thus, the possibility of inhibiting NK cell proliferation via TS/A-derived exosomes was confirmed. Furthermore, when other tumor cell lines, murine breast cancer (4T1), human melanoma (A2058) and human breast cancer (MDA231) cell-line-derived exosomes are treated with NK cells, their proliferation by IL-2 stimulation is effectively reduced. Thus, TS/A tumors can inhibit NK cell-mediated immune surveillance (75). Another study indicated that AML-derived exosomes decrease NK-92 proliferation and that gastric cancer-derived exosomes reduce NK cell frequency in the tumor microenvironment; however, AML-derived exosomes did not induce NK cell apoptosis (74,76).

The cytolytic function of NK cells can destroy solid tumors from the early stages of tumor formation, and many studies have shown that tumor cells restrict cytotoxic NK cell capabilities. In a recent study, tumor-derived exosomes impaired NK cell function. When pancreatic cancer-derived extracellular vesicles (EVs) were treated with NK cells, the suppression of pancreatic cancer stem cells by NK cells was reduced, and saliva exosomes also inhibited the cytolytic action of NK cells via TGF-β1 (77,78). Patient cases confirmed the relationship between NK cell activity and tumor-derived exosomes. Head and neck cancer patient-derived exosomes reduce the cytolytic function of CD3⁺, CD56⁺ NK cells, and AML
and glioblastoma-derived exosomes reduce human NK cell function (74,79,80). Clear cell renal cell carcinoma (ccRCC)-derived exosomes also deactivate NK cells, and advanced stage (III/IV) ccRCC-derived exosomes show a higher suppressive effect on NK cell function than early stage ccRCC-derived exosomes (81).

In the tumor microenvironment, tumor-derived exosomes mainly operate as immune suppressors to accelerate tumor progression, whereas NK cell-derived exosomes do strengthen anti-tumor immunity in the tumor microenvironment. NK cell-derived exosomes show anti-tumor potential through cytotoxic proteins, cytokines, and non-coding RNA. After NK cell-derived exosomes were isolated using NK cells purified from healthy human blood, their cytotoxic activity was confirmed in cancer cells. NK cell-derived exosomes express NK cell marker and cytotoxic proteins as ligands and perforin molecules and exhibit anti-tumor activity in various carcinomas. In addition, NK cell-derived exosomes induce cancer cell apoptosis through caspase-9/12 and inhibit melanoma cell development through TNF-α, a pro-inflammatory cytokine. Furthermore, no effect on PBMCs was observed (82-84).

Upon treatment with IL-2 or IL-15, the NK cell-derived exosomes demonstrate significant cytotoxic activity. In cytokine-treated NK cell-derived exosomes, the expression of NK cell function-related proteins IFN-γ, DNAX accessory molecule-1 (DNAM1), lymphocyte function-associated Ag, and PD-1 is elevated. In particular, an experiment using a DNAM Ab confirmed that exosomal DNAM1 is necessary for the cytotoxic activity (85). miRNAs from NK cell-derived exosomes also contribute to tumor suppression. miRNA-186 in NK cell-derived exosomes causes NB cell death and prevents TGF-β1-dependent immune escape. In addition, miRNA-3607-3p in NK cell-derived exosomes reduces tumor migration by reducing IL-26, which promotes tumor progression and metastasis (86,87). Thus, it was confirmed that NK cell-generated exosomes perform anti-tumor functions through various mechanisms. Although it is still not feasible to entirely dismiss the immunosuppressive role of NK cell-derived exosomes, the possibility of cancer immunotherapy using NK cell-derived exosomes can be highlighted.

NK cells, innate immune cells, were previously assumed to lack immunologic memory; however, recently, memory-like NK cells with immunologic memory have been discovered. In addition, NK cells have a re-stimulation property that boosts the response following pre-activation from lasting for weeks to months. After pre-activation with the cytokines IL-12, IL15, and IL-18, for example, re-stimulation produced a more significant response, boosting IFN-γ production in particular. In clinical trial 1, memory-like NK cells were adoptively transferred to patients with AML, proliferated adequately within the patient's body, and were found to have anti-cancer activities (88,89). In addition to cytokines, after murine cytomegalovirus (MCMV) infection, mouse NK cells acquired immunologic memory against MCMV and provided more efficient protection compared to naive NK cells (90).

Memory-like NK cells also secrete exosomes. According to a recent study, exosomes of NK cells that had encountered NB cells expressed more NK cell receptors than naive NK cell-derived exosomes, resulting in more effective education of NK cells and inhibition of cancer progression (19). According to another study, memory-like NK cell exosomes exhibit better direct anti-cancer activity. Purified NK cell-derived EVs that were pre-activated by IL-15 demonstrated better cytolytic capability for glioblastoma, breast cancer, and thyroid cancer compared to control EVs (91). In addition, when we evaluated the anti-cancer activity of the differentiated memory-like NK cell exosome on treatment with IL-15 or IL-12, -15, and -18, the anti-cancer effect was sufficient in breast, glioblastoma, ovarian, and prostate tumor cell
line spheroids. In particular, there are challenges with poor drug penetration in solid tumors. In an experiment using spheroids mimicking solid tumors, the penetration of exosomes by spheroids was demonstrated to be adequate (92).

**Neutrophils**

Neutrophils generate one of the first defensive immune responses against infection or cancer and are the most abundant leukocytes in the blood. Neutrophil infiltration occurs in the tumor microenvironment, and neutrophils exhibit functional plasticity comparable to that of macrophages and are classified as N1 neutrophils, which suppress tumor progression, and N2 neutrophils, which facilitate tumor growth (93). Tumor-derived exosomes have been observed to cause N2 polarization in neutrophils. Gastric cancer-derived exosomes generate a neutrophil N2 phenotype via high mobility group box 1 (HMGB-1). HMGB-1 expression is mainly increased in gastric cancer, which is associated with poor prognosis in clinical patients (94). Colorectal cancer stem cell (CRCSC)-derived exosomes also induce pro-tumorigenic conditions in neutrophils. CRCSC-derived exosomes improve neutrophil survival in the bone marrow and increase the expression of inflammatory proteins such as IL-1β. Subsequently, CRCSCs recruit educated neutrophils through CXCL1 and promote tumor growth (95). Unlike tumor-generated exosomes that cause pro-tumorigenic neutrophil polarization, neutrophil-derived exosomes display anti-tumorigenic functions by modulating macrophages, neutrophils, and tumors. miRNA-30d-5p from neutrophil-derived exosomes causes M1 polarization (96). In addition, neutrophil-derived exosome-like vesicles are directly delivered to tumors and can trigger tumor cell apoptosis via the caspase pathway. In addition, when an exosome-like vesicle was used as a cytotoxic drug delivery system, the tumor selectivity and anti-tumor efficacy improved, and the survival rate increased in an *in vivo* mouse model (97).

**MDSC**

In the tumor microenvironment, MDSCs play a crucial role as immune regulators and are usually composed of immature heterogeneous myeloid cells. MDSCs comprise granulocytes, immature macrophages, DCs, and myeloid progenitor cells. MDSCs can negatively impact patient prognosis by producing an immunosuppressive environment around the tumor through communication with surrounding immune cells. MDSCs cannot be maturated and exist as MDSCs owing to factors that exist in various pathological conditions. These MDSCs show a pattern of expansion in the blood, tumors, lymph nodes, and spleen of cancer patients. Particularly, heterogeneous MDSC populations worsen patient prognosis by accelerating tumor growth via immunosuppressive functions. Immunosuppressive functions of MDSCs inhibit not only native anti-cancer immunity but also the effectiveness of cancer immunotherapy (98,99). MDSCs are divided into 2 subtypes based on the membrane protein profile and morphology: (i) granulocytic MDSCs are also known as polymorphonuclear MDSC, resemble neutrophils morphologically, and are characterized as CD11b+, Ly6G+, and Ly6Clow; (ii) monocytic MDSCs are characterized as CD11b+, Ly6G-, and Ly6Chi (100).

The immunosuppressive activity of MDSCs in the tumor microenvironment, such as the induction of Treg, which inhibits anti-cancer immunity (101), the increase in M2 differentiation, which are pro-tumorigenic macrophages (102), and the suppression of NK-cell immune activity, promotes tumor progression by inhibiting anti-cancer immunity (103).

Exosomes generated from MDSCs also contribute to immunosuppression, angiogenesis, tumor progression, and metastasis for cancer survival (104). Numerous studies have
established the immunosuppressive effect of MDSC-derived exosomes. The major role of MDSCs is to inhibit T cell function in the tumor microenvironment. In an in vivo mouse model treated with MDSC-derived exosomes, the depletion of CD8 T cells and M1 in the spleen demonstrated the immunosuppression and tumor progression functions of MDSC-derived exosomes (105). Angiogenesis is the most fundamental process in tumor formation, progression, and metastasis (106). Hypoxia and starvation can emerge during tumor development, and angiogenesis is essential to overcome these challenges. Thus, tumors drive vascular endothelial cell proliferation and blood vessel development through VEGF, a pro-angiogenic agent, and numerous growth factors (107). According to a recent study, MDSCs can boost angiogenesis by producing pro-angiogenic factors. One study discovered that MDSC-derived exosomes contribute to angiogenesis by promoting MDSC recruitment (108). It was also found that MDSC-derived exosomes induce tumor angiogenesis through miRNA-126a and promote lung metastasis in breast cancer. In mice with breast cancer treated with doxorubicin (dox), the production of miRNA-126a-positive MDSC-derived exosomes was found to be increased. In vitro and in vivo investigations indicated that the increased MDSC-derived exosomes interacted with endothelial cells and promoted angiogenesis (109). MDSC-derived exosomes also directly enhance tumor progression. For example, it has been reported that when a prostate cancer cell line was treated with MDSC-derived exosomes, cell proliferation, migration, and invasion activities of the cell line were enhanced. In particular, S100A9 of the MDSC-derived exosome was essential; it enhances tumor progression by increasing the expression of the MIDI protein (110).

Tumor-derived exosome modulates MDSCs to foster a survival-friendly environment. Exosomes from breast cancer promote MDSC development at an early stage by stimulating the JAK/STAT signaling cascade via miRNA-9 and miRNA-181a. In addition, this condition promotes tumor development by inhibiting T cell immunity (111). Through miRNA-10a and miRNA-21, glioma-derived exosomes enhance immunosuppressive MDSC activation and growth in the tumor microenvironment, ultimately establishing an immunosuppressive environment. In rat experiments, hypoxia-purified glioma-derived exosomes promoted MDSC activation more effectively than normoxia-purified exosomes. In cases of gliomas devoid of miRNAs 10a and 21, the tumor and spleen had fewer MDSCs than that observed in a typical glioma (112). Another tumor-derived exosomal miRNA-107 has been identified as promoting MDSC proliferation in gastric cancer by inhibiting DICER1 and activating the PI3K pathway by reducing PTEN (113). miRNA-29a and -92a of glioma-derived exosome target high-mobility group box transcription factor 1, protein kinase cAMP-dependent type 1 regulatory subunit alpha to augment immune suppression by activating and expanding MDSC activity. Furthermore, it was discovered that hypoxia-generated exosomes activated MDSC more efficiently than normoxia-induced exosomes (114). In addition to miRNAs found in tumor-derived exosomes, proteins also regulate MDSCs. For example, exosomes from breast cancer promote tumor growth by accumulating MDSCs via TGF-β and prostaglandin E2. Conversely, when neutralized with an Ab, the Ab reduced MDSC accumulation (44).

Reducing the number and activity of MDSCs in the tumor microenvironment is integral to establishing anti-cancer immunity. We showed the possibility of an approach to activate immunity in the tumor microenvironment by targeting MDSCs.
THERAPEUTIC APPLICATIONS OF EXOSOMES

As exosomes have the features of high stability in circulation, minimal toxicity, and low immunogenicity, they offer sufficient potential for medicinal administration or use in clinical practice. The exosome is secreted from the cell and controls the microenvironment by contributing to cell-cell communication using a bimolecular system. Specifically, in the tumor microenvironment, cell-cell communication occurs through tumor-derived and immune cell-derived exosomes. Each exosome demonstrates pro-tumorigenic and anti-tumorigenic functions, depending on the environment and their contents (115,116). However, tumor-derived exosomes are transported to immune cells and generally exhibit pro-tumorigenic functions. Therefore, therapeutic applications targeting tumor-derived exosomes require: 1) tumor-derived exosome secretion inhibitors; 2) elimination of circulating tumor-derived exosomes; 3) inhibition of tumor-derived exosome interactions with recipient cells (Fig. 3A) (117).

The development of therapeutic applications using immune cell-derived exosomes is challenging because of the controversial functions of immune cell-derived exosomes. However, a current approach uses pure and engineered exosomes.

One immunotherapy approach against cancer using immune cell-derived exosomes is cancer vaccination (118,119). Cancer vaccine development employing exosomes is a beneficial and successful anti-cancer immunotherapy based on exosome immunogenicity and cancer

Figure 3. Therapeutic application via exosomes. (A) Tumor-derived exosomes are known to promote tumor progression by modulating the immune system. Therefore, inhibiting them is a potentially effective anti-cancer strategy. This could be realized by inhibiting exosome biogenesis as well as exosome secretion, removing exosomes from blood, and inhibiting the interaction between exosomes and immune cells. (B) Immunotherapy may utilize immune cell-derived exosomes. Notably, exosomes derived from M1s and neutrophils induce M1 polarization, and through Ag presentation and immune activation, tumor-derived as well as DC-derived exosomes can cause T cell-dependent tumor cell death via Ag loading and presentation. Further, exosomes derived from NK cells directly induce cancer cell death; thus, they can be used as immunotherapy to stimulate immunity and have the potential for administration in combination with conventional cancer treatments. In particular, exosomes show the ability to increase the response rate when combined with immune checkpoint inhibitors.
Ag delivery (34,120,121). Cancer vaccines have received considerable attention, ongoing research and clinical applications have increased (122). A recent study showed that M1-derived exosomes could be used as vaccine adjuvants. In vitro and in vivo studies using NK cell-derived exosomes exhibit anti-tumor effectiveness against melanoma. In addition, a cancer vaccine using engineered exosomes has proven its efficacy and entered a phase 1 clinical trial (34,84,119). Unlike macrophages and neutrophils, DC-derived exosomes primarily promote anti-tumor immunity and suppress malignancy. Therefore, DC-derived exosomes have sufficient potential for anti-cancer immunotherapy. In addition, DCs are the most effective APCs. Therefore, for T cells to have sufficient anti-cancer immune activity, DCs that are sufficiently activated and educated as cancer APCs are necessary. DC-based cancer vaccination has been explored for a long time, and sipuleucel-T immunotherapy has been approved by the Food and Drug Administration and used to treat castration-resistant prostate cancer. However, cell therapy's cost and side effects pose a challenge (4,60,123). DC-derived exosomes have the potential to be alternatives to DC-based cancer vaccines. DC-derived exosomes express an adequate level of MHC-II complex molecules, similar to the parental DCs, can exhibit immune activation efficiency, can be frozen for more than 6 months maintaining high stability, and are less expensive than cell therapy. In addition, exosomes are more easily infiltrated into the tumor microenvironment than cells; therefore, they can provide more efficient Ag presentation and T cell priming and have no side effects such as immune dysfunction development. An early exosome study demonstrated that tumor Ag-pulsed DC-derived exosomes suppress tumor development and eradicate tumors through sufficient in vivo cytotoxic T cell priming. In fact, after 6 months of a single intradermal injection, 40%-60% of mice demonstrated tumor eradication (61). A powerful immune response targeting cancer was activated when a synthetic cytotoxic lymphocyte-defined epitope was loaded onto a DC-derived exosome and exploited as a cancer vaccine (121). The clinical significance was established by immunotherapy after chemotherapy using DC-derived exosomes loaded with MHC-I- and MHC-II-restricted cancer Ags in phase 2 clinical trial. However, another clinical case showed that the relevance associated with tumor progression could not be demonstrated in patients with inoperable non-small cell lung cancer. One reason for this controversial result is that DC-derived exosomes express PD-L1 and PD-L2, demonstrating an immunosuppressive phenotype (124,125). Therefore, adopting a cancer vaccine using DC-derived exosomes for treatment, combined with an immune checkpoint inhibitor therapy such as PD-1/PD-L1 blockade, can provide more clinical benefits and induce a sufficient immune response against cancer (126,127). To boost the efficacy of cancer vaccination by increasing immunogenicity, the G protein of the vesicular stomatitis virus was added to exosomes coupled with ovalbumin. Engineered exosomes exhibit improved uptake, DC maturation, greater Ab production capacity, Ag-specific CD8 T cell expansion, and in vivo CTL reactivity (128). Therefore, cancer vaccines using cancer DC-derived exosomes can overcome the immunosuppressive environment as a new approach to immunotherapy and may show adequate therapeutic relevance in combination with immune checkpoint inhibitors (Fig. 3B).

Tumor-derived exosomes can also prevent tumor progression by enhancing T cell priming through tumor Ag delivery (129). Dai et al. (122) conducted a phase 1 clinical study using tumor-derived exosomes. Exosomes were isolated from the ascites of patients with advanced CRC and administered in combination with GM-CSF to the patients with CRC. As a result of the clinical test, only grades 1-2 were reported, and a more effective tumor-specific cytotoxic T lymphocyte response was generated than in the group administered tumor-derived exosomes alone. However, the production of cancer vaccines using tumor-derived exosomes
requires further investigation. The immunosuppressive and tumor-promoting functions of tumor-derived exosomes are still difficult to overcome (Fig. 3B).

Nevertheless, immune cell-derived exosomes, especially DC-derived exosomes and tumor-derived exosomes, are considered acceptable materials to generate an anti-cancer immune response through immune regulation, and further studies on immune cell-tumor cell communication using exosomes are needed (Table 1).

**CONCLUSION**

Exosomes were shown to regulate cells by contributing to cell-cell communication via a specific mechanism rather than waste disposal after discovering exosome secretion for the first time in rat reticulocytes (130). This review shows that exosomes play a crucial role in tumor and immune cell communication, particularly of innate immune cells, in the tumor microenvironment. Furthermore, the anti-tumor immune response of exosome was validated through Ag transfer to APCs and the activation of innate immunity for tumor eradication using lymphocytes (61). Exosome-based cancer immunotherapy has been evaluated in phase 1 and 2 clinical trials, and its safety and efficacy have been assessed. In nonclinical animal studies, a cancer vaccine exploiting exosomes exhibited a high clinical outcome with tumor eradication, indicating a considerable potential for new immune-modulating immunotherapies and the development of new cancer treatment approaches (122,131).

Immunotherapy is an innovative cancer treatment that enhances immunity. In particular, exosome-based immunotherapy has several drug-development benefits, such as superior tumor infiltration, BBB penetration, biocompatibility, and serving as additional drug carriers. High tumor infiltration efficiency by size and immune enhancer activity can overcome the immunity suppression present in the current tumor microenvironment and generate anti-tumor immunity. In addition, exosomal immune activation can be achieved with additional treatments, such as immune checkpoint inhibitors and chemotherapy to boost anti-cancer efficacy. As a result, cancer immunotherapy using exosomes as immune modulators can be developed.

However, there are still issues to be solved in the therapeutic development of exosomes. Exosomes derived from immune cells and tumors can induce off-target damage. Although there has been no evidence of toxicity caused by specific exosomes having an off-target effect, adverse effects caused by immunological rejection or a severe immune response caused by exosomes present in the blood after transfusion have not been reported. Nevertheless, it is impossible to rule out the possibility of side effects when a drug is administered for an extended period. Excessive immunological activation, such as in the cytokine release syndrome, has not been described clinically when using immune cell-derived exosomes, but
it may occur. Therefore, drug development using immune-modulating exosomes should be approached more carefully because side effects may occur owing to immune regulation (132).

In addition, one of the critical issues in drug development using exosomes is the heterogeneous nature of exosomes. A recent study revealed that exosomes of 50–150 nm diameter could be divided into 3 types according to size, with each type having a different protein marker (133). Therefore, to develop an exosomal drug for immunotherapy, it should be possible to isolate the functional exosome through exosomal marker analysis and to develop a homogeneous exosome drug. Homogeneous exosome drugs are safer than heterogeneous exosome drugs because they can suppress side effects due to the characteristics of non-functional exosomes and will be more cost-efficient as we can use only potent drugs.

Significant advancements in tumor-immunity communication via exosomes in the tumor microenvironment have been reported, and it has been established that exosomes have the potential to be developed as cancer treatments. Recently, there has been a great deal of interest in immunity, and scientific progress has shown the prospect of tumor eradication through immune control, such as by CAR-T cell therapy. In addition, immune-modulating exosomes have also been presented as new therapeutic alternatives for cancer. With engineered exosomes, further exosome therapy will grow into a more effective, patient-specific, and individualized form.

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