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REVIEW

Exosomes: Key Messengers Mediating the Interaction Between Tumor Cells and CD8$^+$ T Cells in the Tumor Microenvironment

Yilin Li[1,*], Qiwei Yang[1,*], Danni Li[2], Wenya Li[1], Wanfu Men[1]

[1]Department of Thoracic Surgery, the First Hospital of China Medical University, Shenyang, 110002, People's Republic of China; [2]Department of Medical Oncology, the First Hospital of China Medical University, Shenyang, 110002, People's Republic of China

*These authors contributed equally to this work

Correspondence: Wanfu Men; Wenya Li, Email 472581624@163.com; saint5288@hotmail.com

Abstract: In recent years, with an increasingly profound comprehension of the tumor microenvironment, it has been discovered that the constituent cells within the immune microenvironment, such as macrophages, CD4$^+$T cells, and CD8$^+$T cells, interact with tumor cells in manners conducive to tumorigenesis and progression. Exosomes play a pivotal role as essential mediators for intercellular material exchange and signal transmission in this context. Tumor cell-derived exosomes carrying cargo such as PD-L1 and ncRNAs engage with CD8$^+$T cells to induce cytotoxic responses and facilitate immune evasion, thereby promoting tumor advancement. When combined with current immune checkpoint inhibitors like anti-PD-L1/PD-1 therapy, enhancing CD8$^+$T cell function through exosomal pathways while monitoring and augmenting therapeutic effects can significantly improve efficacy. This review delineates the crucial role of exosomes derived from both tumor cells and CD8$^+$T cells within the tumor microenvironment along with their impact mechanisms on both tumor cells and CD8$^+$T cells. Furthermore, it summarizes the potential for clinical treatment in this realm when integrated with existing immunotherapy methods—particularly exploring the feasibility of clinical translation alongside engineering materials science techniques.

Keywords: CD8$^+$T, TME, exosome, EVs

Introduction

Exosomes are a type of extracellular vesicles with a diameter of approximately 30–150 nanometers, which are released by various cell types into the extracellular environment via an exocytic process. They serve as crucial mediators of intercellular communication and material exchange, facilitating the transportation of biological macromolecules such as proteins, lipids, glycoconjugates and nucleic acids between cells[1,2] (Figure 1). Consequently, they exert influence over the function and behavior of recipient cells.[3] Extracellular vesicles derived from tumors, known as tumor-derived exosomes, are produced and released by tumor cells and play a crucial role in the tumor microenvironment. They mediate communication and material exchange between tumor cells and immune cells, stromal cells, and other components within the tumor microenvironment (TME), further impacting the initiation and progression of tumors. In TME, various immune cells, including T cells, are involved in these responses, influencing tumor progression. T cells originate from hematopoietic stem cells in the bone marrow and differentiate into effector cells in the thymus. They are classified into CD4$^+$ T cells and CD8$^+$ T cells based on co-stimulatory factors. CD4$^+$ T cells are activated by complexes formed by antigen peptides and class II molecules, becoming helper T cells (Th cells). CD8$^+$ T cells are activated by complexes of antigen peptides and class I molecules, becoming cytotoxic T lymphocytes (CTLs), which can directly kill pathogen-infected cells and tumor cells.[4] Tumor cells can evade immune surveillance through various mechanisms, such as altering antigen presentation pathways and expressing immunosuppressive molecules. In cancer, clinical specimens often show dysregulation of CD8$^+$ T cells and activation of immunosuppressive signals.[5] A key challenge in cancer

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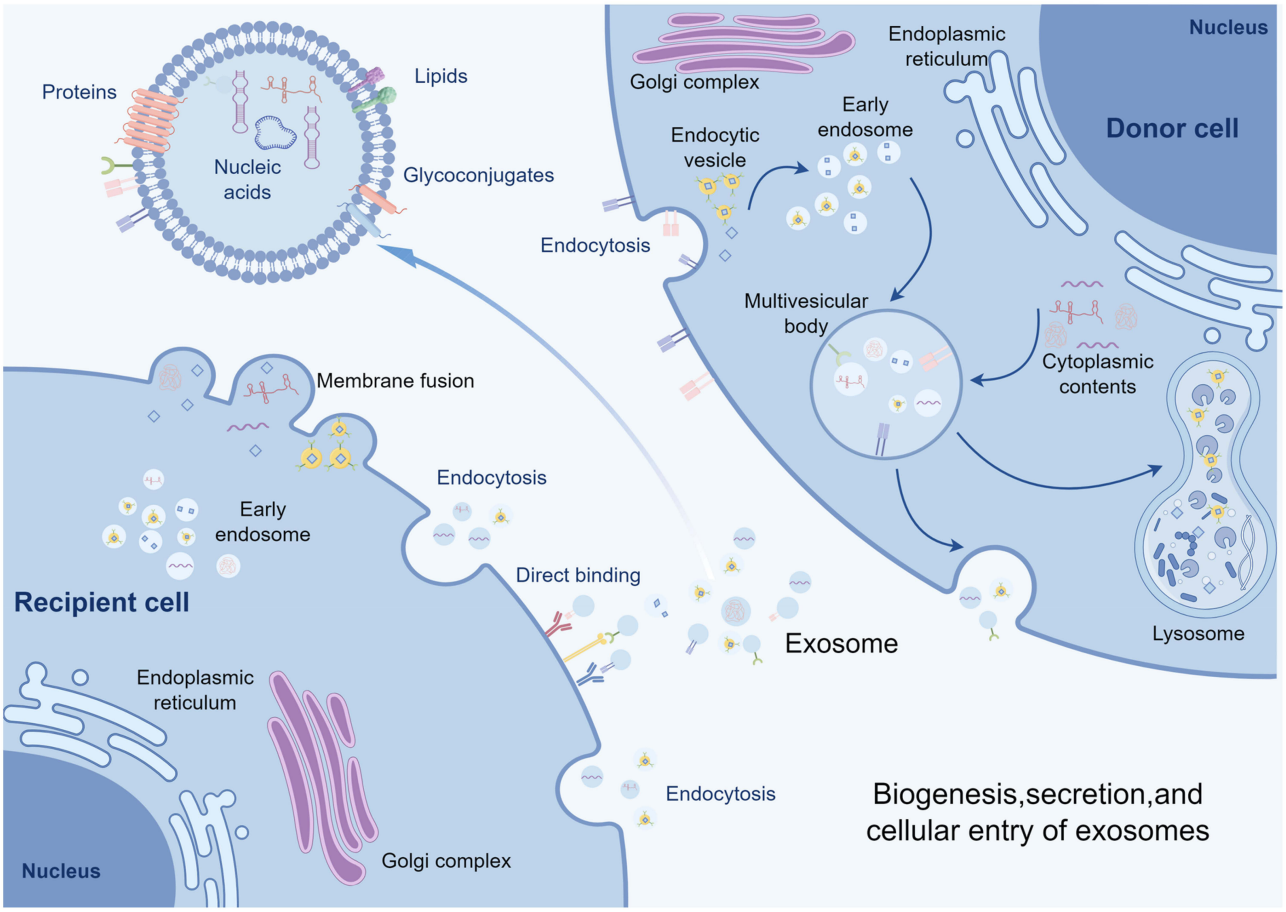

Figure 1 Biogenesis,Secretion,and Cellular Entry of Exosomes. The multivesicular body of the donor cell fuses with the cell membrane and releases exosomes to the outside of the cell; exosomes act on the recipient cell through endocytosis, direct binding to the receptor, or fusion with the membrane of the recipient cell. By Figdraw.

immunotherapy is to enhance the recognition and cytotoxic functions of $CD8^+$ T cells while overcoming tumor immune evasion strategies. Targeting the indirect communication pathways that mediate intercellular interactions and material exchange, particularly focusing on the role of exosomes in the interaction between tumor cells and $CD8^+$ T cells, holds potential for enhancing therapeutic efficacy in this field. This review will summarize the mechanisms and clinical translational prospects of exosomes in the tumor microenvironment as crucial pathways for intercellular communication and substance exchange between tumor cells and $CD8^+$ T cells, aiming to offer direction for future research.

Effects of Tumor-Derived Exosomes and Their Contents on $CD8^+$T Cells

Tumor-derived exosomes can enhance tumor proliferation, invasion, and apoptosis by modulating a range of immunomodulatory mechanisms, including antigen expression, immune activation, immune surveillance, immunosuppression, and intercellular communication.[6–8] Although the interaction and influence of tumor-derived exosomes with T cells and regulatory T cells are still under investigation, studies have revealed several modes of interaction between exosomes and T cells: 1. T cells metabolize exosomes through receptor-mediated endocytosis, leading to degradation by lysosomes and release of signaling molecules; 2. Exosomes initiate cascade signals in T cells by binding to membrane proteins on their surface; 3. Exosomes fuse with the plasma membrane of T cells, facilitating the transfer of their contents.[9,10] Through these interactions, exosome contents and cell signals can be transmitted to target cells, thus facilitating intercellular communication and mediating immunosuppression. Tumor-derived exosomes from various tumor types have been demonstrated to modulate T cell function.[10–12] It can either directly or indirectly inhibit T cell activation by promoting the activity of regulatory T cells.[13] In addition, in the context of tumor metastasis to the lymphatic system, exosomes

derived from tumors can be efficiently transported to draining lymph nodes via lymphatic vessels. These exosomes carry tumor antigens and are capable of presenting them on MHC-I molecules to endothelial cells in the lymph nodes, thereby triggering apoptosis of antigen-specific $CD8^+$ T cells. This process contributes to the establishment of a pre-metastatic niche for tumor lymphatic metastasis.[14] In this chapter, we will elucidate the mechanisms by which tumor-derived exosomes modulate the activity of $CD8^+$ T cells to facilitate malignant tumor behavior (Figure 2).

Exosomal PD-L1

One strategy employed by tumor cells to evade immune surveillance is the up-regulation of PD-L1 surface expression, which interacts with PD-1 on effector T cells to suppress their anti-tumor response. Despite the development of anti-PD -1/PD-L1 monoclonal antibodies targeting this pathological mechanism, overall efficacy remains limited due to drug resistance.[15] Evidence suggests that tumor-derived exosome PD-L1 exhibits equivalent functionality to intracellular PD-L1 and can bind to PD-1 with the same affinity, potentially serving as a critical factor in tumor immune evasion. Tumor cells elude immune surveillance by upregulating surface expression of PD-L1 and even binding to monoclonal antibodies targeting PD-L1.[16,17] In light of this, exosome PD-L1 may serve as a mechanism for facilitating immune evasion and tumor progression, potentially contributing to the development of immunotherapy resistance[18,19] (Figure 3). A retrospective study of patients with gastric cancer revealed that exosome PD-L1 served as an independent prognostic factor for gastric cancer: the overall survival rate was sig nificantly lower in the high-exosome PD-L1 group compared to the low-exosome PD-L1 group. Furthermore, exosome PD-L1 levels in plasma samples from patients with metastatic gastric cancer showed a negative correlation with $CD8^+$ T cell count, suggesting a link between exosome PD-L1 and

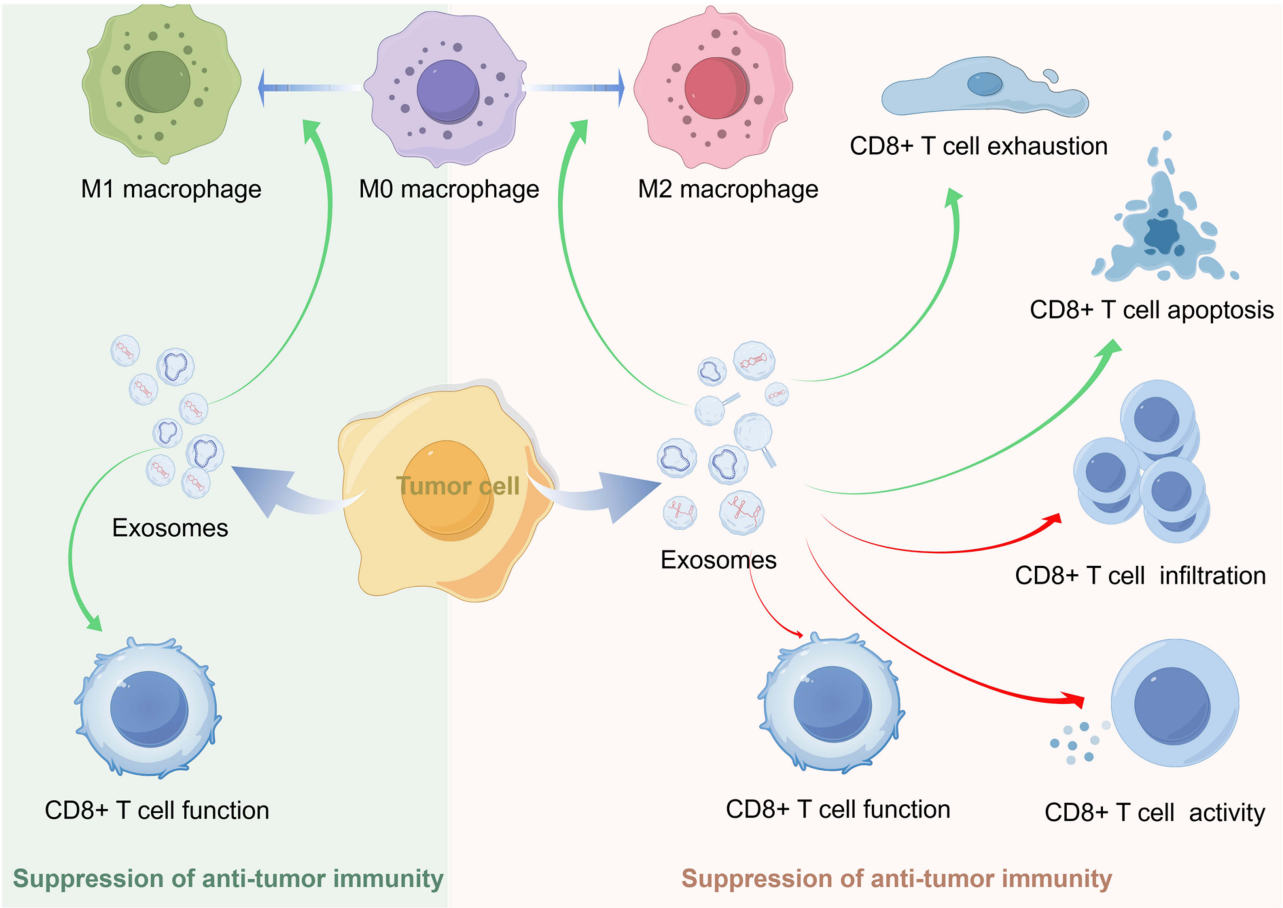

Figure 2 Comprehensive Overview of Tumor Cell-Derived Exosome Effects on $CD8^+$ T Cells and Macrophages. Exosomes originating from various tumor cells influence $CD8^+$ T cells and macrophages, either promoting or inhibiting anti-tumor immunity. In the illustration, green arrows indicate promotion, red arrows indicate inhibition, and blue arrows depict exosome secretion and macrophage polarization direction. By Figdraw.

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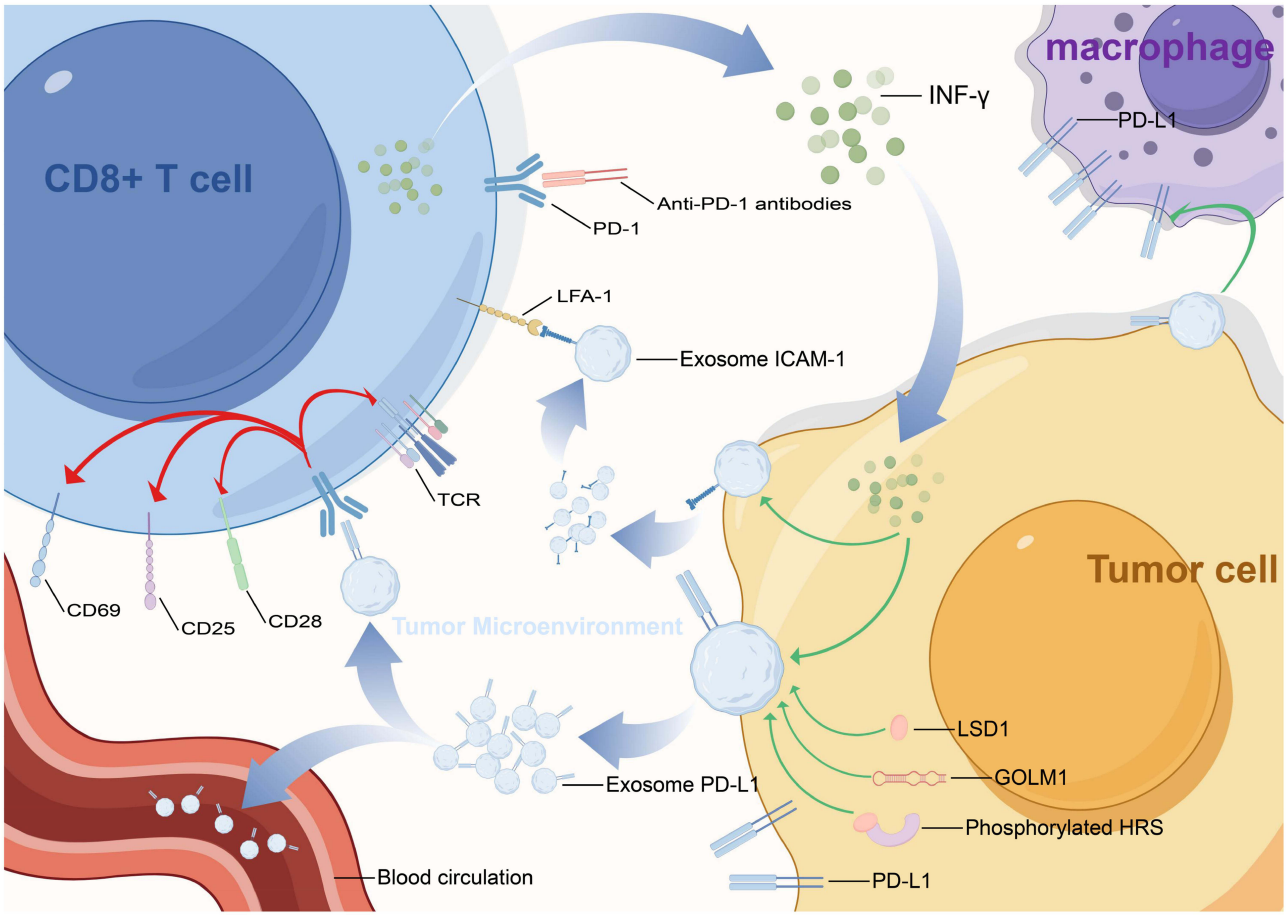

Figure 3 Comprehensive Overview of Immune Suppression Pathways Involving Tumor-Derived Exosomal PD-L1 and T Cell Interaction. Tumor-derived exosomes PD-L1 can bind to PD-1 receptors on T cells, leading to the inhibition of T cell activation and cytotoxic functions. In the diagram, green arrows indicate the promoting effects, red arrows indicate inhibitory effects, and blue arrows show the destinations of exosomes and protein molecules within the tumor microenvironment. By Figdraw.

immunosuppressive status in patients with gastric cancer.[20] In prostate cancer, the upregulation of exosome PD-L1 expression can directly interact with PD-1 on the surface of T cells, thereby suppressing the cytotoxic function of $CD8^+$T cells against tumor cells. Modulating exosome secretion or sorting PD-L1 into exosomes may enhance the therapeutic efficacy in treating prostate tumors with elevated PD-L1 levels.[21] Through the establishment of a mouse model for melanoma lung metastasis, it has been discovered that exosome PD-L1 plays a crucial role in the depletion of tumor-specific $CD8^+$ T cells, and the level of exosome PD-L1 is associated with the prognosis of mice. This indicates that pre-existing levels of circulating exosomal PD-L1 may serve as an important predictive biomarker for immune checkpoint inhibitor therapy prior to PD-1/PD-L1 blockade.[22]

During exosome biosynthesis, the endosomal sorting complexes required for transport (ESCRT) play a role in facilitating membrane synthesis and ultimately generating vesicles.[23,24] Hepatocyte growth factor-regulated tyrosine kinase substrate (HRS) is a crucial member of the ESCRT family. Phosphorylated HRS, regulated by ERK, spatially excludes $CD8^+$ T cells from infiltrating melanoma tumor tissue; in other words, phosphorylated HRS strongly interacts with PD-L1, selectively promoting PD-L1 loading into exosomes and thereby preventing $CD8^+$ T cell infiltration. Moreover, inhibiting HRS phosphorylation enhances the efficacy of PD-1 blocking in in vivo trials of immunotherapy resistance. Consequently, including exosome PD-L1 and functional HRS in clinical monitoring may aid in selecting patients who would benefit from immune checkpoint blocking therapy.[25] Marie-Nicole et al discovered that following co-incubation of activated T cells with PD-L1-carrying exosomes isolated from plasma of patients with head and neck squamous cell carcinoma, the PD-L1-mediated pathway is implicated in the downregulation of CD69 surface expression on activated T cells. Furthermore, pre-incubation of anti-PD-1 antibodies with T cells almost completely

reversed the inhibitory effect of PD-L1 exosomes on T cell activation.[26] In breast cancer, tumor-derived exosome PD-L1 significantly suppressed CD3/CD28-induced T cell ERK phosphorylation and NF-κB activation in a dose-dependent manner, thereby attenuating T cell cytotoxic activity.[27] The presence of transforming growth factor β (TGF-β) in the tumor microenvironment stimulates the expression of PD-L1 in exosomes derived from breast cancer cells in a dose-dependent manner. Exosomes with high PD-L1 expression further exacerbate T cell dysfunction by modulating early phosphorylation of T cell receptor (TCR) signaling cascades, thereby mediating immunosuppression.[28] Ricklefs et al also observed PD-L1 expression on the surface of glioblastoma-derived exosomes in glioblastoma, which inhibited the activation of $CD8^+$ and $CD4^+$ T cells by binding to PD-1 and suppressing the TCR-related pathway, leading to reduced expression of CD69 and CD25 (markers for early and late T cell activation).[29]

With the advancement of research, the role of exosome PD-L1 in facilitating immune evasion is gradually elucidated, and associated molecules are being unveiled one by one. Interferon γ (IFN-γ) plays a pivotal role in the immunosuppression mediated by exosome PD-L1, promoting tumor immune escape through inducing PD-L1 expression and exosome secretion. In melanoma, IFN-γ can enhance the quantity of PD-L1 on exosomes, leading to the release of a large number of PD-L1-positive exosomes into both the tumor microenvironment and circulation. Subsequently, PD-L1 binds to PD-1 on T cell surfaces, resulting in T cell inactivation and fostering tumor growth.[10] Jie et al also demonstrated that IFN-γ can upregulate the binding of PD-1 on exosome surface PD-L1 and $CD8^+$ T cells, thereby facilitating NPC immune evasion, whereas anti-PD-L1 antibodies can inhibit the interaction between PD-L1 and PD-1.[30] Subsequent research has demonstrated that IFN-γ amplifies the binding mechanism of PD-1 on exosome PD-L1 and $CD8^+$ T cells, as it not only upregulates exosome PD-L1 but also increases exosome ICAM-1 levels. Exosome ICAM-1 can then interact with LFA-1 on activated T cells, facilitating the adhesion of exosomes and T cells—a crucial step for exosome PD-L1-mediated immunosuppression.[31] Not only can INF-γ upregulate exosome PD-L1 and promote exosome and T cell adhesion, but conversely, exosome PD-L1 can also reduce INF-γ production thereby facilitating immune evasion. Dong et al discovered that PD-L1 is present on exosomes isolated from the plasma of patients with non-small cell lung cancer, and the quantity of exosomes is associated with PD-L1 positivity in tumor tissues. Exosomes can hinder immune function by diminishing the production of cytokines such as interferon-γ (IFN-γ) and inducing apoptosis of $CD8^+$ T cells. Both enforced expression of PD-L1 on cells lacking PD-L1 and treatment with exosomes containing PD-L1 promoted tumor growth in vivo.[32] In addition to IFN-γ, other molecules involved in this process have also been identified. Yunfeng et al discovered that O-GlcNAc transferase (OGT) present in the exosomes of esophageal cancer stem cells can be taken up by neighboring CD8 T cells, leading to increased expression of PD-1 in CD8 T cells, thus shielding esophageal cancer stem cells from killing by $CD8^+$T cells. Additionally, it has been reported that histone lysine-specific demethylase 1 (LSD1) enhances the secretion and accumulation of exosome PD-L1 in gastric esophageal cancer cells, thereby suppressing T cell activity.[33]

In hepatocellular carcinoma, Golgi membrane protein 1 (GOLM1) facilitates the deubiquitination of PD-L1, leading to an increase in its cellular expression and promoting its packaging into exosomes by inhibiting Rab27b in the trans-Golgi network region. Consequently, the elevated levels of exosomal PD-L1 derived from HCC cells upregulate PD-L1 expression on tumor-associated macrophages, thereby inducing immunosuppression of $CD8^+$ T cells through both direct binding to PD-1 on the surface of $CD8^+$ T cells and indirect modulation of tumor-associated macrophages.[34] Liu et al discovered that endoplasmic reticulum stress induced exosomes derived from hepatocellular carcinoma, which contained high levels of miR-23a-3p. These exosomes up-regulated the expression of PD-L1 in macrophages by activating the PTEN/AKT pathway, thereby reducing the ratio of CD8 T cells and promoting T cell apoptosis.[35] Similarly in breast cancer, endoplasmic reticulum stress has been reported to promote exosome secretion and elevate exosomal miR-27a-3p expression, upregulate PD-L1 levels on macrophages via the MAGI2/PTEN/PI3K axis, and decrease the ratio of immune cells such as $CD8^+$ T cells and promote T cell apoptosis.[36] Wei et al also found that prostate cancer cells undergoing endoplasmic reticulum stress showed upregulation of exosomal PD-L1 and PI3K/AKT pathways, thereby developing an immunosuppressive status[37] (Table 1).

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Table 1 Exosomal PD-L1 Promotes Tumor Immune Evasion by Interacting with $CD8^+$ T Cells

Cancer Type	Origin of Exosome	Potential Mechanism	References
Gastric cancer	Plasma from gastric cancer patients	Exosomal PD-L1 significantly reduces CD69 and PD-1 expression on T cells, levels of exosomal PD-L1 are inversely correlated with $CD8^+$ T cell count	[20]
Prostate cancer	Mouse prostate cancer model; Human prostate cancer xenograft model in nude mice; Human prostate cancer cell lines (PC3, LNCaP, 22RV1, DU145); Murine prostate cancer cell line (RM1)	Exosomal PD-L1 is absorbed by tumor cells with low PD-L1 expression, thereby inhibiting $CD8^+$ T cell cytotoxicity	[21]
Melanoma	Plasma from melanoma patients; murine melanoma cell lines (B16, B16-luc cells (B16 stably transduced with firefly luciferase) and B16-OVA cells (B16 cells stably expressing chicken OVA))	Exosomal PD-L1 is a key initiator of tumor-specific $CD8^+$ T cell exhaustion	[22]
Non-small cell lung cancer	Lung cancer cell lines (A549, H460, H1975, LLC-1)	The abundance of exosomal PD-L1 correlates with PD-L1 positivity in tumor tissues, exosomal PD-L1 promotes $CD8^+$ T cell apoptosis via PD-1/PD-L1 interaction	[32]
Melanoma	Human melanoma cell lines (WM9, WM164, A375)	Hepatocyte growth factor-regulated tyrosine kinase substrate (HRS) interacts with PD-L1 and mediates its selective loading into exosomes, exosomal PD-L1 inhibits $CD8^+$ T cell migration to tumors	[25]
Head and neck squamous cell carcinoma	Plasma from head and neck squamous cell carcinoma patients	Exosomal PD-L1 downregulates surface expression of CD69 on activated $CD8^+$ T cells; anti-PD-1 antibodies can reverse the inhibition of $CD8^+$ T cell activation caused by exosomes with high PD-L1 expression	[26]
Breast cancer	Human breast cancer cell lines (MDA-MB-231), murine mammary tumor cell lines 4T1	Exosomal PD-L1 significantly inhibits CD3/CD28-induced $CD8^+$ T cell extracellular regulated protein kinases (ERK) phosphorylation and nuclear factor kappa-B (NF-Kb) activation in a dose-dependent manner	[27]
Breast cancer	Triple negative breast cancer cell line (MDA-MB-231, ER^+PR^+HER2- T47D, RE-PR-$HER2^+$ MDA-MB-453)	Transforming growth factor-β (TGF-β) induces PD-L1 expression in exosomes, and high PD-L1 exosomes further promote $CD8^+$ T cell dysfunction by regulating early phosphorylation in the TCR signaling cascade	[28]
Glioblastoma	Human glioblastoma stem-like cell lines (G34, G35, G44, and G157)	Exosomal PD-L1 inhibits TCR-related pathways by binding to PD-1, reducing CD69 and CD25 expression, and suppressing $CD8^+$ T cell activation	[29]
Melanoma	Human melanoma cell lines (MEL624, WM1552C, WM35, WM902B, WM793, UACC-903, WM9, A375, WM164); Plasma from melanoma patients	Interferon-γ (IFN-γ) increases the amount of PD-L1 on exosomes, which then bind to PD-1 on $CD8^+$ T cells, leading to $CD8^+$ T cell inactivation	[10]
Nasopharyngeal cancer	Nasopharyngeal cancer cell lines (C666-1, HK-1, HNE3, NPC-TW01), human normal nasopharyngeal cell line (NP69), and human embryonic kidney cell line (HEK-293T); Plasma from nasopharyngeal cancer patients and healthy donors	IFN-γ promotes PD-L1 expression on exosomes and enhances the binding of exosomal PD-L1 to PD-1 on $CD8^+$ T cells, thereby weakening cytotoxic $CD8^+$ T cell function	[30]
Pan-cancer	Human melanoma cell lines (WM9, WM164); Murine melanoma cell line (YUMM1.7); Human lung cancer cell line (H1264, H1299); Human colon cancer cell line (HCT116); Murine colon cancer cell line (MC38)	IFN-γ upregulates PD-L1 and ICAM-1 on exosomes; Exosomal Intercellular adhesion molecule 1 (ICAM-1) interacts with Lymphocyte function-associated antigen-1 (LFA-1) on activated $CD8^+$ T cells, facilitating the binding of exosomal PD-L1 to PD-1 on activated $CD8^+$ T cells	[31]
Esophageal carcinoma	Esophageal cancer cell lines (Kyse-150, ECA-109)	Exosomal O-GlcNAc transferase (OGT) is absorbed by adjacent $CD8^+$ T cells, increasing PD-1 expression on these cells; PD-1 then binds to exosomal PD-L1, blocking $CD8^+$ T cell-mediated tumor cell killing	[38]
Gastric cancer	Human gastric cancer cell lines (AGS, BGC-823, HGC-27, MGC-803, MKN-45, NCI-N87); Murine gastric cancer cell line (MFC)	Lysine-specific demethylase 1 (LSD1) induces the accumulation of PD-L1 in exosomes, thereby inhibiting $CD8^+$ T cell responses in the tumor microenvironment	[33]
Hepatocellular carcinoma	Human hepatocellular carcinoma cell line (MHCC-97H)	Golgi membrane protein 1 (GOLM1) upregulates PD-L1 expression on cells and promotes PD-L1 sorting into exosomes, increasing exosomal PD-L1 levels; Exosomal PD-L1 upregulates PD-L1 expression on tumor-associated macrophages, leading to $CD8^+$ T cell immune suppression	[34]

Exosomal Non-Coding RNAs

In recent years, numerous studies have revealed that exosomes not only transport proteins, but also harbor a substantial amount of Non-coding RNA (ncRNA), including microRNA (miRNA), long non-coding RNA (lncRNA), and circular RNA (circRNA).[39,40] Although these ncRNAs do not encode proteins, they play pivotal roles in the regulation of gene expression, cell signaling, and immune modulation. Particularly in the process of tumor immune evasion, non-coding RNAs within tumor-derived exosomes influence $CD8^+$ T cell function through various mechanisms, aiding tumor cells in evading the immune system's attack, thereby promoting tumor growth and metastasis.[41,42]

Tumor-derived exosomal miRNAs exert profound regulatory effects on T cells. By transferring specific miRNAs directly or indirectly to T cells, tumor-derived exosomes modulate immune responses, contributing to the intricate interplay between tumor progression and immune evasion. For instance, in nasopharyngeal carcinoma, exosomal miR-24-3p inhibits T cell proliferation and the differentiation of Th1 and Th17 cells, while targeting FGF11 to promote Treg formation. Mechanistically, this phenomenon results from increased expression of phosphorylated ERK, STAT1, and

STAT3, coupled with decreased expression of phosphorylated STAT5. Moreover, hypoxic conditions within the tumor microenvironment elevate miR-24-3p levels, thereby intensifying T cell suppression.[43] The regulation of $CD8^+$ T cells in the tumor microenvironment by exosomal miRNA is gradually being unveiled. Exosomes derived from melanoma, containing specific miRNAs such as miR-3187-3p and miR-181a, can inhibit $CD8^+$ T cell activity by diminishing TCR signaling and reducing the secretion of cytokines and granzymes.[44] In colorectal cancer, hnRNPA2B1 facilitates the sorting of miR-1246 into exosomes, and exosomal miR-1246 can promote macrophage polarization towards the M2 phenotype, thereby hindering the infiltration and functional state of $CD8^+$ T cells in the tumor immune microenvironment.[45] In the investigation of distant metastatic mechanisms in papillary thyroid carcinoma, it was discovered that exosomal miR-519e-5p is significantly upregulated in distantly metastatic thyroid cancer. This miRNA can be transferred to $CD8^+$ T cells, suppressing the Notch signaling pathway by downregulating NOTCH2, thus facilitating immune evasion in distant tumor metastasis.[46] In cervical squamous cell carcinoma, miR-142-5p is transferred to lymphatic endothelial cells via tumor cell-secreted exosomes, inducing the expression of indoleamine 2.3-dioxygenase (IDO) through the ARID2-DNMT1-IFN-γ signaling pathway, thereby indirectly inhibiting and depleting $CD8^+$ T cells.[47] Li and colleagues discovered that miR-20a-5p is associated with poor prognosis in triple-negative breast cancer. It can be secreted by breast cancer cells in the form of exosomes, internalized into $CD8^+$ T cells, where it targets and inhibits the nuclear protein ataxia-telangiectasia, thereby suppressing $CD8^+$ T cell proliferation and mediating resistance to anti-PD-1 therapy.[48] In exosomes derived from colorectal cancer stem cells, miR-146a-5p has been identified as a major non-coding RNA. It targets the Numb receptor in recipient colorectal cancer cells, promoting stem cell-like traits and tumorigenicity. Among 53 colorectal cancer patients, those with high miR-146a-5p expression exhibited increased tumor-infiltrating $CD66^+$ neutrophils and decreased tumor-infiltrating $CD8^+$ T cells. The impact of miR-146a-5p on immune cells within the tumor microenvironment, particularly $CD8^+$ T cells, warrants further investigation to determine its potential effects on immunotherapy outcomes.[49]

Moreover, exosome-derived lncRNA and circRNA play crucial roles in modulating T cells within the tumor microenvironment, serving as key factors in immune evasion and resistance to immunotherapy. CircRNA often functions as a molecular sponge, binding specific miRNAs to regulate target genes, thereby altering gene expression and protein stability in T cells. Through intricate regulatory networks, they enhance tumor growth and metastasis. Shi and colleagues discovered that in bladder cancer, exosomal circRNA_0013936 can sponge miR-320a and miR-301b, respectively promoting FATP2 expression and inhibiting RIPK3 expression, thereby significantly suppressing IFN-γ production and $CD8^+$ T cell function.[50] High-throughput sequencing revealed that exosomal circTRPS1 from bladder cancer cells can sponge miR-141-3p, enhancing the function of the key glutamine metabolism enzyme GLS1. The overexpression of GLS1 boosts the proliferation and invasiveness of bladder cancer cells while inducing $CD8^+$ T cell exhaustion.[51] CircCCAR1 promotes the growth and metastasis of hepatocellular carcinoma and can be packaged into exosomes in an hnRNPA2B1-dependent manner. Exosomal circCCAR1 binds to PD-1 protein in $CD8^+$ T cells, inhibiting PD-1 ubiquitination and preventing its proteasomal degradation, thus shielding tumor cells from $CD8^+$ T cell attack.[52] In lung adenocarcinoma, exosomal circZNF451 promotes an anti–inflammatory phenotype in macrophages and depletes cytotoxic $CD8^+$ T cells through TRIM56-mediated FXR1 degradation, activating the ELF4-IRF4 pathway and reshaping the tumor immune microenvironment.[53] Additionally, lncRNAs play a significant regulatory role on $CD8^+$ T cells within the tumor microenvironment. HOTAIR, a well-studied lncRNA in tumors, can stabilize PKM2 and activate STAT3, enhancing PD-L1 expression and subsequently inhibiting $CD8^+$ T cell activity.[54] LncRNA KCNQ1OT1, also found to be significantly increased in colorectal cancer tissues and exosomes, regulates PD-L1 ubiquitination via the miR-30a-5p/USP22 pathway, suppressing $CD8^+$ T cell responses and promoting colorectal cancer progression.[55]

As understanding of the tumor immune microenvironment deepens, researchers are increasingly recognizing that tumor-derived exosomal ncRNAs do not solely suppress anti-tumor immunity. It has been reported that radiotherapy can enhance the release of exosomal circPIK3R3 from melanoma. Once absorbed by macrophages, this exosome promotes Type I interferon (I–IFN) secretion and M1 polarization via the miR-872-3p/IRF7 axis. The secreted I-IFN activates the JAK/STAT signaling pathway in $CD8^+$ T cells, promoting IFN-γ and GZMB secretion, thereby enhancing the anti-tumor immune response of $CD8^+$ T cells.[56] Xiang et al delivered tumor-derived exosomal miR-155-5p into an immunocompetent mouse model of ovarian cancer, which inhibited cancer progression and macrophage infiltration while activating

$CD8^+$ T cell function.[57] These complex regulatory roles of tumor-derived exosomal ncRNAs necessitate further investigation by researchers to select suitable types for improving current systemic cancer therapies.

Other Molecules

Over the past decades, researchers have increasingly focused on the role of cytokines in tumor growth suppression and immune stimulation within the tumor microenvironment. Interleukins (ILs) are crucial cytokines that regulate immune responses, and tumor-derived exosomes can utilize ILs, such as IL-10 and IL-8, to impact T cell activity, significantly influencing tumor development.[58] IL-10 itself can enhance $CD8^+$ T cell activation and proliferation independently of lymphoid tissue migration. In hepatocellular carcinoma, tumor-derived exosomes can inhibit $CD8^+$ T cell function through IL-10 secretion and immunosuppressive activity. These exosome-induced effects are associated with disease progression, leading to early recurrence and reduced survival rates in patients.[13] In prostate cancer, tumor-derived exosomes rich in IL-8 disrupt $CD8^+$ T cell function by altering energy metabolism. Mechanistically, they induce $CD8^+$ T cell starvation through PPARα overactivation, resulting in decreased glucose utilization and increased fatty acid catalysis.[59] TGF-β1 also plays a significant regulatory role on immune cells within the tumor microenvironment. For instance, in osteosarcoma, exosomes rich in immunosuppressive proteins like TGF-β1 significantly inhibit T cell proliferation and reduce CD25 expression on $CD8^+$ T cells, distinctly contrasting with exosomes derived from osteoblasts.[60]

Effects of $CD8^+$T Cell-Derived Exosomes and Their Contents on Tumor Cells

Overall, $CD8^+$ T cells primarily function as cytotoxic cells that secrete cytokines to directly exert tumor-killing effects. In recent years, extensive research has been conducted on exosomes derived from $CD8^+$ T cells as a direction for immunotherapy. Investigating the contents and surface receptor expression of these exosomes can further elucidate the mechanisms by which $CD8^+$ T cells exert their effects and provide more convincing directions for improving therapeutic strategies (Figure 4). Wang et al focused on the cytotoxic effects of exosomes derived from Vδ2 T cells (which carry more functional molecules from their parent cells) on Epstein-Barr virus (EBV)-associated tumors. In both in vitro and in vivo experiments, these exosomes effectively induced apoptosis in EBV-associated tumor cells through FasL- and TRAIL-dependent pathways, thereby inhibiting tumor progression. Regarding targeting capabilities, exosomes derived from allogeneic Vδ2 T cells stimulated an increase in CCR5 on T cells, leading to enhanced T cell infiltration into EBV-associated tumor tissues. This has significant implications for enhancing therapeutic efficacy in patients with immunosuppression due to systemic tumor treatment.[61] $CD8^+$ T cells are critical effector cells in the immune system's fight against tumor cells. They recognize specific antigens on the surface of tumor cells via their T cell receptors (TCRs). Upon recognizing these antigens, $CD8^+$ T cells secrete cytokines, release cytotoxic granules, and/or induce apoptosis in cancer cells through Fas/FasL interactions.[62] Exosomes derived from $CD8^+$ T cells play important roles in tumor immune infiltration and immune regulation, thereby inhibiting tumor progression. Studies have shown that exosomes from cytotoxic $CD8^+$ T cells co-cultured with lung cancer A549 cells for 48 hours can modulate the levels of metastasis-related genes MMP2, MMP9, TWIST, SNAI1, and CDH1. The results indicate that exosomes from $CD8^+$ T cells exhibit anti-proliferative and anti-metastatic effects, reducing the proliferation and metastasis of cancer cells.[63]

Increasing research indicates that non-coding RNAs are enriched in exosomes and play crucial roles in tumorigenesis and progression. Dysfunctional $CD8^+$ T cells secrete a large number of exosomes, which can be taken up by normal $CD8^+$ T cells, impairing their proliferation (Ki67), cellular activity (CD69), and cytokine production (such as interferon-γ and interleukin-2). Wang et al identified 257 abnormally expressed lncRNAs in exosomes from exhausted $CD8^+$ T cells using microarray sequencing. These lncRNAs may promote the aging of normal $CD8^+$ T cells and reduce their anti-tumor activity, contributing to the functional exhaustion of $CD8^+$ T cells.[64] As a miRNA closely associated with estrogen, miR-765 shows a significant downregulation trend in endometrial cancer. In order to further investigate the role of miR-765 in tumor immunity, Zhou et al used fluorescence in situ hybridization to confirm the significant upregulation of miR-765 in CD45RO-$CD8^+$ T cells. The expression of miR-765 was also upregulated in exosomes derived from CD45RO-$CD8^+$ T cells. Meanwhile, the expression of

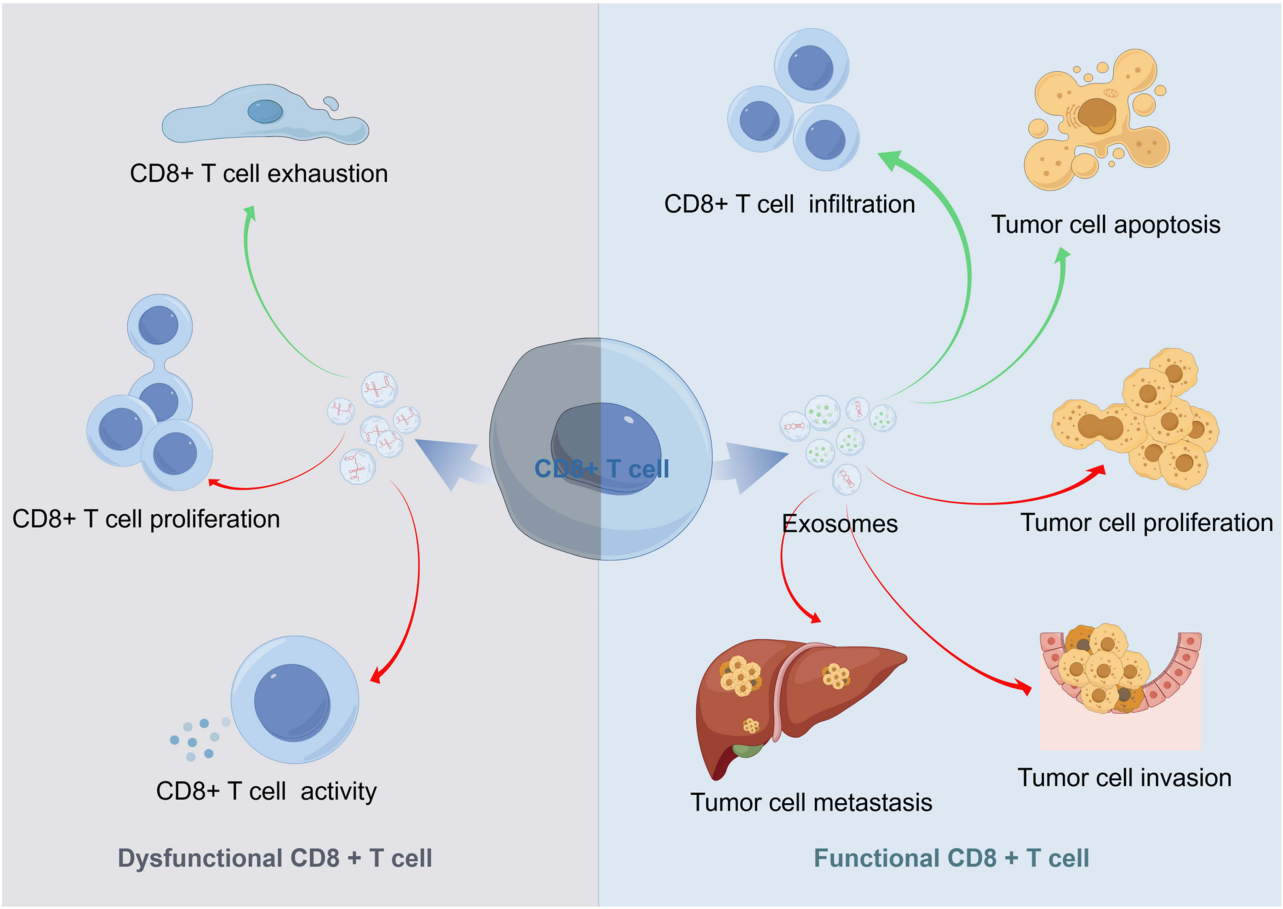

Figure 4 Comprehensive Overview of $CD8^+$ T Cell-Derived Exosome Effects on Tumor Cells and $CD8^+$ T Cells. Exosomes from dysfunctional/functional $CD8^+$ T cells interact with tumor cells and $CD8^+$ T cells, either inhibiting or enhancing anti-tumor immunity. In the illustration, green arrows indicate enhancement, red arrows indicate inhibition, and blue arrows represent exosome secretion. By Figdraw.

Proteolipid protein 2 (PLP2) showed a downregulation trend. PLP2, as a transmembrane protein, has been confirmed to be involved in regulating biological processes such as proliferation, migration, and invasion in tumor cells.In both in vivo and in vitro experiments, the results indicate that these exosomes deliver miR-765 to tumor cells, targeting the PLP2 gene and thereby eliminating the stimulating effects of estrogen on the Ki-67 expression, epithelial-mesenchymal transition (EMT) process, and invasive capacity in Ishikawa and KLE cells. This study sheds light on the potential therapeutic implications of miR-765 and exosome-mediated regulation of PLP2 in endometrial cancer.[65]

The Scheme of Clinical Application and Improvement by Engineering Material Science Methods

Current immunotherapy strategies for cancer, such as PD-1/PD-L1 immune checkpoint blockade therapy, are often closely associated with the reactivation of the cytotoxic effects of $CD8^+$ T cells,[66] $CD8^+$ T cells are able to recognize TCR antigens from cancer cells and developing malignant tumors, then rapidly proliferate and differentiate into cytotoxic T lymphocytes (CTL) to eliminate cancer cells through cell-to-cell contact. Therapeutic strategies derived from such immune response mechanisms have been increasingly studied by researchers, such as the recent hot topic of cancer immunotherapy, chimeric antigen receptor T cell (CAR-T).[67] Notably, exosomes offer significant advantages over other synthetic therapeutic approaches due to their endogenous nature, particularly in enhancing $CD8^+$ T cell-centered treatment strategies. As crucial mediators of material exchange and information transfer between tumor cells and $CD8^+$ T cells, exosomes show great promise in reflecting disease treatment status and identifying therapeutic targets (Figure 5). Circular non-coding RNA CCAR1 (CircCCAR1), which is overexpressed in hepatocellular carcinoma,

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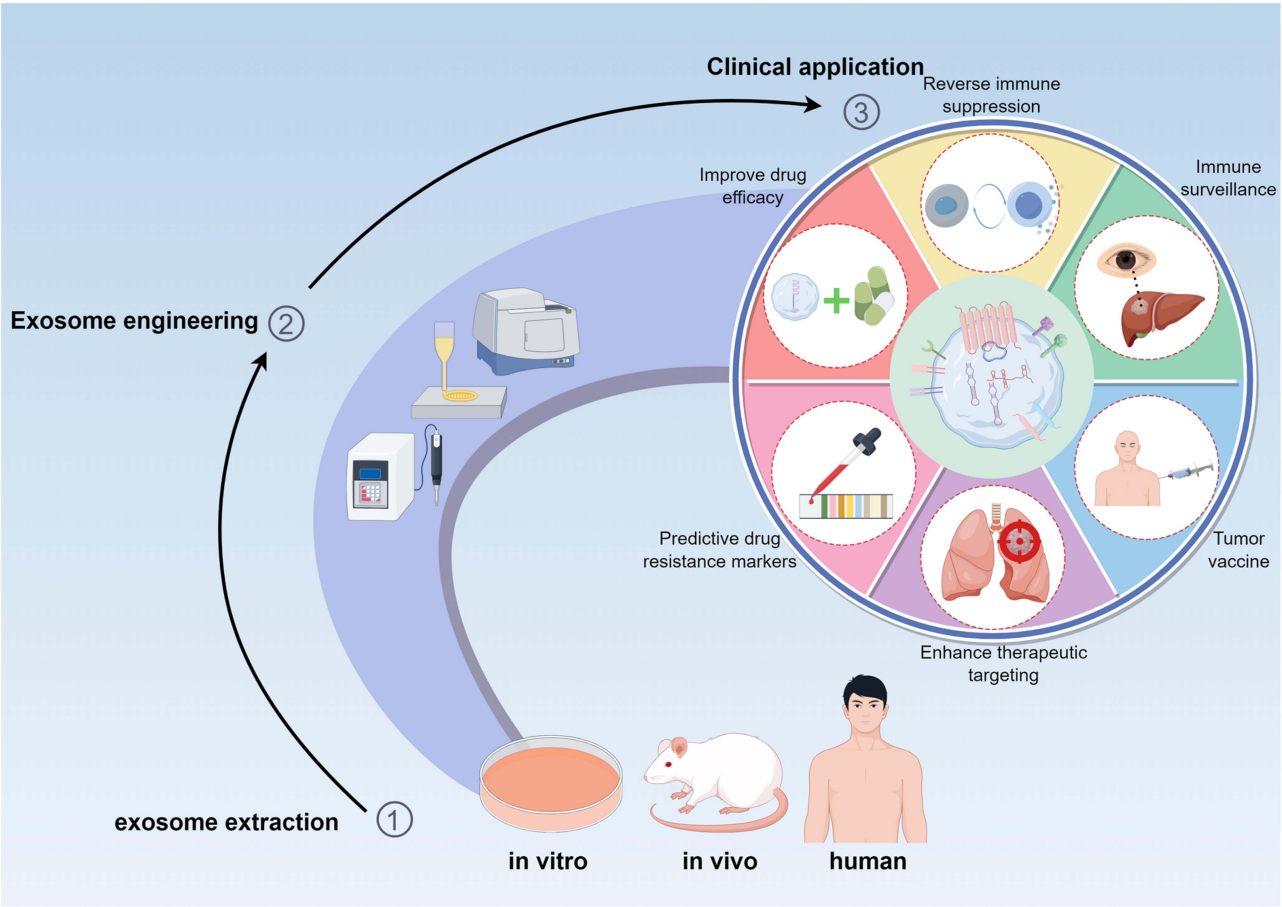

Figure 5 Comprehensive Overview of Clinical Applications of Exosome. Exosome engineering through in vitro, in vivo, and human extraction for clinical applications in prevention, diagnosis, and therapy. By Figdraw.

promotes malignant tumor behavior and can enter tumor cell-derived exosomes through hnRNPA2B1 mediation. Exosomal CircCCAR1 inhibits the ubiquitination and degradation of PD1, leading to $CD8^+$ T cell exhaustion and thereby reducing their cytotoxicity and ability to produce TNF-α, IFN-γ, granzyme B, and perforin. Researchers have further demonstrated that xenotransplant mice with high circCCAR1 expression exhibit resistance to PD-1 therapy and have significantly shortened survival times. Targeting exosomal CircCCAR1 may thus represent a novel strategy to enhance the efficacy of immunotherapy.[52] In another study, lung cancer-derived exosomal circular non-coding RNA USP7 (CircUSP7) was found to reduce the levels of TNF-α, IFN-γ, granzyme B, and perforin in $CD8^+$ T cells through the miR-934/SHP2 axis. In vivo experiments demonstrated that xenotransplant mice with high exosomal CircUSP7 expression exhibited significant resistance to PD-1 therapy. Clinical and pathological statistics revealed that patients with high levels of exosomal CircUSP7 were more likely to develop resistance to PD-1 therapy. Notably, the levels of exosomal CircUSP7 were not associated with TP53, KRAS, or ALK, which are potential predictors guiding anti-PD-1/PD-L1 immunotherapy, indicating that CircUSP7 could serve as a predictive marker for PD-1 resistance in lung cancer therapy.[68] Moreover, an increasing number of studies are integrating tools from materials engineering, such as 3D printing technology, enhanced hydrogel models, and engineered exosomes, to further advance research in this direction, significantly enhancing its potential for clinical translation.[69,70]

The unique properties of biomimetic nanomaterials offer numerous new possibilities for drug delivery and cancer immunotherapy. Combining nanoparticles with conventional therapies to specifically target $CD8^+$ T cells has become an effective approach in cancer immunotherapy. For example, Chen and colleagues developed mPEG-PLGA-PLL (PEAL) nanoparticles coated with PD-L1 blocking antibodies (P/PEALsiCD155), which not only enhanced early-stage $CD8^+$

T cell immune surveillance against breast cancer but also reversed the suppression of $CD8^+$ T cells in late-stage tumors. This process mediated immunogenic cell death (ICD), thereby further improving the efficacy of immune checkpoint therapy.[71] Advances in biomedical engineering have made it possible to use exosomes for the efficient delivery of therapeutic agents in cancer treatment. Engineered exosomes have garnered significant attention from researchers for their role in tumor immunotherapy. Exosomes derived from dying cancer cells and modified with MART-1 peptide and CCL22-siRNA serve as a prophylactic vaccine. This approach disrupts the CCR4/CCL22 axis between dendritic cells and Treg cells, inhibiting Treg cell proliferation and thus effectively treating pancreatic cancer.[72] As previously mentioned, exosomes play a crucial role in intercellular communication between tumor cells and $CD8^+$ T cells. By leveraging bioengineering materials to improve exosome-based therapies, this field shows immense research potential. Jung and colleagues developed interleukin-2-secreting extracellular vesicles (IL-2-sEVs) by using a flexible linker to combine IL-2 expression on the plasma membrane with engineered Jurkat T cells. These enhanced T cell-derived extracellular vesicles increased the autocrine effect of IL-2, upregulated the expression of miR-181a-3p and miR-223-3p, and reduced PD-L1 protein levels in tumor cells, thereby mediating $CD8^+$ T cell proliferation and activation. In in vivo models simulating cisplatin and anti-PD-L1 therapy, the combined use of IL-2-sEVs significantly improved the therapeutic outcomes compared to the use of cisplatin or αPD-L1 antibody alone.[73] Another study applies membrane-bound cytokine technology to exosomes derived from $CD8^+$ T cells, incorporating surface expression of interleukin-2 (IL-2) and the anti-epidermal growth factor receptor (EGFR) antibody cetuximab (CTX). These engineered exosomes not only enhance their targeting of lung cancer cells by binding to EGFR through CTX but also exert anti-tumor activity by directly killing cells and indirectly stimulating anti-tumor immunity through IL-2. As with other cytokines, ensuring that the overall effect of tumor treatment relies on providing a sufficiently high local concentration of cytokines while avoiding other autoimmune symptoms in the body. Thus, the engineered exosome therapy that balances targeting and treatment efficacy appears to outweigh the drawbacks. Furthermore, this engineered exosome downregulates the expression of Rab27a protein, which regulates vesicle secretion in lung cancer cells. This could potentially inhibit tumor immune escape by reducing tumor EVs mediated by Rab27a.[74]

Summary and Outlooks

$CD8^+$ T cells, as a crucial subset of effector T cells, play a significant role in the tumor microenvironment. After responding to tumor antigen signals, they undergo proliferation and enter tumors to exert anti-tumor activity, but over time, they become depleted. Exosomes have played a significant role in mediating the interaction between the two components of the tumor microenvironment. As previously mentioned, numerous studies have focused on investigating the impact of exosomes on tumor cell and $CD8^+$ T cells, contributing to a comprehensive understanding of this field from various perspectives, including content and receptor signaling binding. Understanding the specific mechanisms by which T cells receive signals, undergo alterations, and ultimately become exhausted is crucial for advancing current $CD8^+$ T cell immunotherapy strategies. In addressing the diminished efficacy of immunotherapy due to immune exhaustion, gene-engineered exosome pathways can effectively restore therapeutic outcomes. Exosomes engineered to carry the PD1 gene and encapsulate the immune adjuvant imiquimod (PD1-imi Exo) have demonstrated significant therapeutic effects in mouse models of melanoma and breast cancer. These modified exosomes release imiquimod, promoting the maturation of immature dendritic cells and reversing immune exhaustion by activating and restoring $CD8^+$ T cell function.[75] In summary, exosome therapy combined with immunotherapy presents a promising strategy, and further exploration by researchers could yield even more exciting results in this field.

In clinical therapy, advancing current research findings to clinical application requires overcoming numerous challenges, particularly in the extraction, purification, and characterization of exosomes. Utilizing exosome therapy as a strategy targeting $CD8^+$ T cells presents difficulties due to the diverse regulatory effects arising from exosomal content heterogeneity, as different contents may exert opposing effects on $CD8^+$ T cells, making therapeutic outcomes unpredictable This uncertainty necessitates further research. Advanced techniques such as machine learning models can analyze large datasets to refine the selection of therapeutic exosomes and more accurately predict patient responses. While advances in engineering materials have mitigated some limitations, further improvements are needed to maintain the ideal physicochemical properties of exosomes and enhance loading efficiency. Most engineering

methods struggle to balance stable loading and surface modification while preserving exosome biocompatibility. In terms of clinical translation, exosome therapy faces numerous challenges. Accurate exosome separation and characterization are crucial for developing exosome-based therapies, necessitating standardized analysis methods to ensure data consistency and comparability. Addressing these challenges will expedite the translation of exosome-related research into clinical practice, ultimately benefiting patients. Exosome yield heavily depends on parent cells, and the variability in exosome secretion capacity, along with the high difficulty and cost of large-scale cell culture, complicates the production of clinical-grade exosomes. The inefficiency of large-scale exosome isolation is another barrier to clinical-grade exosome development, with issues such as low separation efficiency, sample loss, and inter-batch variability needing resolution. Current clinical trials in this field, as searched on Clinicaltrials.gov, lack support from large-scale multicenter samples, indicating a need for further research efforts to enhance clinical translation feasibility.

Data Sharing Statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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