Proceedings of ICMMGH 2026 Symposium: Cell and Molecular Biology: Understanding Immune Cell Functions
DOI: 10.54254/2753-8818/2026.PJ30830

The Role of Tumor-Derived Exosomes in Immune Evasion

Yanfei He

School of Life Sciences and Technology, China Pharmaceutical University, Nanjing, China
hyf@stu.cpu.edu.cn

Abstract. Tumor-derived exosomes (TDEs) are nanoscale extracellular vesicles secreted by cancer cells that directly or indirectly orchestrate immune evasion. Enriched with diverse bioactive cargos (e.g., cytokines, miRNAs, enzymes), they are critical mediators of intercellular communication, enabling cancer cells to evade immune surveillance. Beyond their established functions in tumor growth and metastasis, recent research highlights TDEs as key modulators of metabolic and signaling pathways across distinct immune cell types. By simultaneously undermining anti-tumor functions of different immune cells, like inhibiting T cell proliferation and activation, and reprogramming macrophages, TDEs establish a multifaceted barrier to anti-tumor immunity. Although recent research investigated these mechanisms, the accurate molecular pathways and their temporal dynamics remain incompletely understood. With targetability and excellent biocompatibility, TDEs hold considerable promise for overcoming immune evasion and enhancing the efficacy of immunotherapies. By synthesizing current knowledge and critical gaps, this review provides an integrated framework for the rational development of novel therapeutic approaches.

Keywords: TDEs, cancer, immune cells, immunotherapy.

1. Introduction

Composed of cytotoxic T cells, macrophages, and other effector cells, the human immune system serves a vital function in recognizing and clearing malignant pathologies like cancer, thereby maintaining immune homeostasis. However, specific genetic features of a cancer cell and the interaction between cancer cells enable the cancer to evade immune detection and destruction—typically known as immune evasion. This process allows tumors to avoid detection and attack by immune cells, remaining a major obstacle in cancer treatment [1]. A central challenge in clinical oncology is that the remarkable efficacy of many immunotherapies is frequently tempered by the development of treatment resistance or disease relapse, a phenomenon largely attributable to the dynamic capacity of tumors for immune evasion [2].

Within the tumor microenvironment (TME), TDEs are critical mediators that extensively regulate the process of immune evasion. TDEs are nanoscale extracellular vesicles secreted by cancer cells and possess a diameter within 30-150 nm2. Owing to their membrane composition, TDEs readily fuse with or are internalized by recipient cells. TDEs act as intercellular couriers that deliver a

© 2026 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2026.PJ30830

diverse array of bioactive molecules, notably immunosuppressive molecules, like immune checkpoint proteins, cytokines, and specific microRNAs (miRNAs) to recipient cells [3,4].

Recent reports demonstrate that, besides their capacity to directly induce tumor growth and metastasis, TDEs directly suppress anti-tumor immune responses and modify the TME. The process is fundamentally operated through regulating or reprogramming different types of immune cells. These mechanisms include both adaptive and innate immunity. For instance, in adaptive immunity, TDEs induce the apoptosis of cytotoxic T cells, while in innate immunity, TDEs polarize macrophages towards a pro-tumorigenic M2 phenotype [3].

Because of their unique physical characteristics and wide range of biological roles, TDEs have substantial therapeutic potential. However, a number of basic issues hinder its translational implementation. These include continuous technical obstacles in the separation, standardization, and scalable production of exosome-based therapies, as well as an inadequate comprehension of the molecular mechanisms controlling particular cargo loading and targeted transport to recipient immune cells.

This review critically evaluates the translational gap impeding clinical use after first summarizing the molecular processes by which TDEs influence different immune cells, such as T cells and macrophages. In the end, it suggests a comprehensive framework for the logical advancement of immunotherapies based on TDE.

2. Direct suppression of T cell function by TDEs

By utilizing multiple mechanisms, TDEs directly impair T cell function, leading to the effective dismantling of anti-tumor immunity.

2.1. Structure

A key mechanism involves the modulation of T cell signaling pathways via exosomal surface ligands (e.g., FasL, PD-L1). While PD-L1–PD-1 signaling is a well-recognized pathway in TME, the contribution of exosomal versus membrane-bound PD-L1 remains under investigation. A study shows that this process induces T cell apoptosis and anergy, as well as through ectoenzymes (CD39/CD73) [4] that catalyze the production of extracellular adenosine, a potent inhibitor of T cell proliferation and effector functions. Besides PD-L1, PD-L2 shows lower affinity binding to PD-1. But a recent study suggests an unexpected role for PD-L2-enriched exosomes in modulating T cell activity [5]. This pathway subsequently attenuates critical activation signals, including the phosphorylation of AKT and ERK1/2, thereby inducing a state of functional paralysis. This direct engagement potently suppresses T cell activation, proliferation, and effector functions.

2.2. Metabolic suppression

TDEs also present other typical pro-tumor pathways beyond receptor-ligand interactions, such as the delivery of oncogenic proteins like mutant p53. Upon internalization by T cells, mutant p53 cargo disrupts their metabolic fitness by downregulating key glycolytic enzymes, thereby reducing the bioenergetic and biosynthetic resources required for effector functions and promoting apoptosis under metabolic stress [6].

DOI: 10.54254/2753-8818/2026.PJ30830

2.3. Promotion of regulatory T cells (Tregs)

Concurrently, TDEs facilitate Treg expansion and support their functional activity. The systemic dissemination of TDE-PD-L2, for instance, has been shown to alter the immune landscape. Within both the TME and peripheral lymphoid organs, TDEs-PD-L2 increases the proportion of immunosuppressive Tregs while decreasing the frequency of cytotoxic CD8+ T cells [5].

Collectively, the effectiveness of immunotherapeutic interventions is significantly hampered by the intricate tumor-intrinsic program that these exosome-triggered responses represent to subvert adaptive immunity.

3. Reprogramming of macrophages by TDEs

TDEs show an essential role in reprogramming tumor-associated macrophages (TAMs), a pivotal process for establishing an immunosuppressive TME. This reprogramming generates an immunosuppressive environment through the shift of macrophages from M1 to M2, a change between opposing functional profiles [1]. The function of adaptive immunity is substantially affected by the stage of macrophages. The M2 phenotype is distinguished by its function in tissue healing, immunological control, and ultimately, the promotion of tumor growth [7]. By transporting certain chemical cargo to macrophages and triggering pro-tumor pathways, TDEs aid in this polarization.

Several different pathways are reported to be induced by TDEs from diverse types of cancer. For instance, the PDGFRA pathway in colon cancer [7], Notch signaling pathway in cholangiocarcinoma (CCA) [8], the pyruvate kinase M2 (PKM2) pathway in gastric cancer [9], and the JAK/STAT6 pathway in hepatoma [10]. In colon cancer, TDEs mediate the sequestration of miR-17-5p by delivering the long non-coding RNA XIST, which functions as a competitive endogenous RNA (ceRNA). This sequestration of miR-17-5p leads to the upregulation of its target, PDGFRA, a receptor tyrosine kinase that acts as a central node activating multiple key signaling pathways, thereby driving M2 polarization [7]. In gastric cancer, a distinct mechanism involves exosomal delivery of the metabolic enzyme PKM2. Once internalized by macrophages, PKM2 from TDEs promotes M2 polarization by inhibiting SREBP-cleavage activating protein (SCAP) polyubiquitination, which triggers the nuclear accumulation of the transcription factor SREBP1. This, in turn, enhances the expression of key fatty acid synthesis enzymes like FASN, ACACA and ACLY, reprogramming macrophage lipid metabolism to support an M2-like state [9]. The consequent dominance of M2 macrophages profoundly supports tumor growth by secreting a repertoire of growth factors (e.g., EGF, TGF-β) and immunosuppressive cytokines like IL-10 to promote angiogenesis, tumor cell proliferation, and direct suppression of cytotoxic T cells [2]. Furthermore, these TDE-reprogrammed M2 macrophages enhance the extracellular matrix remodeling that facilitates cancer cell invasion and metastasis, thereby fostering a permissive environment for cancer progression [1].

In conclusion, TDEs induce the polarization of TAMs from an M1 to an M2 phenotype, which propels the formation of an immunosuppressive niche. TDEs transporting certain chemical cargo, such metabolic enzymes and lncRNAs, are the essential cause of this polarization. Different pro-tumor signaling pathways may be activated. Ultimately, the ensuing dominance of M2 macrophages promotes angiogenesis, inhibits cytotoxic T-cell activity, secretes growth factors and immunosuppressive cytokines, and facilitates extracellular matrix remodeling, all of which promote the evolution of tumors.

DOI: 10.54254/2753-8818/2026.PJ30830

4. TDEs' effect on TME beyond T cells and macrophages

Besides T cells and macrophages, TDEs have been shown to concurrently control other immune cells in the TME in addition to T cells and macrophages. Together with tumor cells and other immune-suppressive chemicals, these modulation pathways contribute to the overall inhibitory effect on the anti-tumor immune response.

4.1. Natural Killer (NK) cells

TDEs thereby compromise an essential element of the innate antitumor immune response by considerably reducing the cytotoxicity of NK cells. There are several ways in which this suppression is mediated. Suppressive cargo, such as TGF-β1 from pancreatic cancer, which causes Smad2/3 phosphorylation, lowers IFN-γ production, and hinders glucose uptake, can be delivered directly to NK cells by TDEs, hence reducing NK cell cytotoxicity [1]. Furthermore, proliferation is targeted since TDEs from melanoma and breast cancer can block IL-2-induced proliferation by disrupting the IL-2R/Jak3/Stat5 signaling pathway [1]. As a result, these TDE-mediated deficiencies limit NK cells' capacity to identify and eradicate tumor cells, hence restricting their potential to control the progression of cancer.

4.2. Dendritic Cells (DCs)

TDEs have an immunomodulatory effect on DCs as well, severely impairing their function as professional antigen-presenting cells and adaptive immune response initiators. The whole lifecycle of DCs, including their differentiation, maturation, and subsequent functions, is modulated by this action. First, components such as COX-2 enzymes and their byproduct PGE2 have been demonstrated to interfere with the differentiation of several DC lineages in TDEs [11]. Another way that TDEs hinder DC development is by downregulating important markers such as S100A9 [12]. Additionally, TDEs contribute to circumstances that fundamentally prevent DCs from maturing. As an example, TDEs supply glycolytic enzymes that raise extracellular lactate and ATP levels in the tumor microenvironment. These are necessary circumstances that actively limit DC development. Finally, TDE cargo can stimulate DCs to produce TGF-β, resulting in an autocrine cycle that maintains a tolerogenic, immature state. TDEs facilitate the generation of adenosine, which plays a crucial role in tumor progression by creating an immunosuppressive environment and encouraging tumor growth and dissemination, by inducing a DC subpopulation that expresses CD39 and CD73 [13].

4.3. Myeloid-Derived Suppressor Cells (MDSCs)

TDEs result in an increment of MDSCs, which is a hallmark of defects in DC differentiation for its concurrence with the decrease of DCs [11]. TDEs are potent inducers of MDSCs' expansion and activation, a process critically dependent on specific protein cargo. According to a recent study, one key mediator is macrophage migration inhibitory factor (MIF), which is highly enriched in TDEs from cancers such as pancreatic ductal adenocarcinoma. The immunosuppressive function of exosomal MIF is contingent upon its enzymatic activities, including its N-terminal proline-dependent tautomerase and its cysteine-dependent thiol-protein oxidoreductase (TPOR) activities [14]. This illustrates a precise mechanism whereby TDEs utilize enzymatic proteins to orchestrate a profoundly immunosuppressive niche.

DOI: 10.54254/2753-8818/2026.PJ30830

5. TDEs' effect on TME beyond T cells and macrophages

The multifaceted roles of TDEs in TME infer their potential applications in significant clinical practice. Their inherent stability, bioavailability in biofluids, and ability to modulate molecular reflections of tumor cells also enhance their great prospects in all stages from diagnosis to cancer treatment.

5.1. TDEs as biomarkers for diagnosis and prognosis

The molecular composition of TDEs, which encompasses nucleic acids, proteins, as well as lipids, serves as a dynamic and rich source for identifying novel biomarkers. Moreover, their presence in easily accessible biofluids like plasma, urine, and saliva enables non-invasive liquid diagnosing approaches, which are particularly valuable for cancers where traditional tissue biopsies are challenging [2]. For instance, exosomal glypican-1 (GPC1) shows considerable promise for detecting early-stage pancreatic cancer. It was proved to be a reliable biomarker that could accurately identify PDAC patients among healthy individuals [15]. The profiling of TDE cargo offers critical information on tumor heterogeneity, mutational status, and adaptive responses to therapy. By analyzing changes in exosomal biomarkers over time, clinicians can monitor disease progression, predict recurrence early by biomarker signs, and stratify patients based on anticipated disease aggressiveness and potential response to treatment. As a result, patients can receive more dynamic and personalized clinical management.

5.2. Therapeutic targeting of TDE biogenesis or uptake

TDEs are important mediators of tumor growth, immune evasion, and metastasis. Thus, inhibiting the synthesis, secretion, or cellular absorption of TDEs represents a promising therapeutic approach that is presently being thoroughly investigated. This strategy aims to interfere with the harmful cell-to-cell communication that TDEs orchestrate. Promising pharmaceutical targets include important molecular regulators of the exosome system, such as the enzyme neutral sphingomyelinase (n-SMase), which is essential for the ceramide-dependent production of intraluminal vesicles [2]. Preclinical research has shown that TDE release can be considerably decreased by blocking these regulators. Although this approach has therapeutic potential, it must be developed carefully to prevent interfering with the vital physiological processes of exosomes made from healthy cells.

5.3. Exosome-based drug delivery and vaccines

Conversely, the innate biological properties of exosomes are being harnessed for therapeutic benefit. Engineered exosomes represent a promising vehicle for targeted therapies, as their natural origin supports extended circulation and enhances tissue penetration, thereby improving the therapeutic index [3]. TDEs, or exosomes from other sources, show prospects of carrying diverse therapeutic agents, including chemotherapeutic drugs (e.g., docetaxel, paclitaxel) or small interfering RNAs (siRNAs), and their surfaces are modifiable towards a more tumor-specific targeting status [1]. A clinical trial (NCT01159288) showed that exosomes loaded with tumor antigens can activate NK cells and induce antitumor immunity. Furthermore, exosomes are being developed as a novel class of anti-cancer vaccines that induce immune-mediated tumor clearance. By loading exosomes with tumor-specific antigens or immunostimulatory molecules, TDEs have the potential to prime the host

DOI: 10.54254/2753-8818/2026.PJ30830

immune system, activating DCs and cytotoxic T cells to induce a robust and specific antitumor immune response.

In summary, the clinical translation of TDE research is multifaceted, spanning from their utilization as non-invasive diagnostic and prognostic tools to the development of innovative therapies that either inhibit their pathogenic functions or repurpose their natural delivery capabilities for targeted treatment and immunization.

6. Conclusion and future perspectives

6.1. Summary of key findings

Several pivotal mechanisms, through which TDEs act as central mediators of immune evasion, are synthesized in this analysis. The evidence confirms that TDEs directly suppress anti-tumor immunity by delivering diverse bioactive cargo to recipient cells, especially immune cells. Key mechanisms on immune cells include the direct inhibition of cytotoxic functions and reprogramming certain types of immune cells to an anti-tumor status. Collectively, these multifaceted actions establish a profoundly immunosuppressive tumor microenvironment that facilitates cancer progression and resistance to therapies.

6.2. Current challenges and unanswered questions

TDEs have demonstrated significant potential in the entire clinical practice, involving immunotherapy, drug administration, and diagnostics. Despite these developments, there are still major obstacles to the complete comprehension and therapeutic use of TDE research. It is yet unclear what molecular mechanisms control the precise targeting of recipient immune cells and the loading of payload into TDEs. The lack of standardized, effective, and scalable techniques for exosome purification, quantification, and heterogeneity analysis limits the area technically. Furthermore, more thorough preclinical and clinical validation is needed for the safety and effectiveness of therapeutic approaches that either block TDE synthesis or use exosomes as drug delivery vehicles.

6.3. Future research directions

Finding new molecular mechanisms underlying TDE-mediated immune regulation should be a top priority for future research. At the same time, it is essential to develop and apply emerging technologies including the creation of AI-driven databases to incorporate complicated TDE data for predictive modeling and biomarker discovery, single-vesicle analysis to detect exosomal heterogeneity, and spatial multi-omics to map TDE dynamics within the tumor microenvironment. Overcoming these scientific and technical hurdles is necessary for translating the mechanistic understanding of TDEs into effective diagnostic tools and therapeutic interventions in clinical oncology.

References

[1] Tang, Q., Yang, S., He, G., Zheng, H., Zhang, S., Liu, J., Wei, S., Fan, Q., Peng, X., Li, X., Zhang, D., Yang, L., and Li, H. (2022). Tumor-derived exosomes in the cancer immune microenvironment and cancer immunotherapy. Cancer Letters, 548, 215823. https: //doi.org/10.1016/j.canlet.2022.215823

[2] Javdani-Mallak, A., Mowla, S. J., and Alibolandi, M. (2025). Tumor-derived exosomes and their application in cancer treatment. Journal of Translational Medicine, 23(1), 751. https: //doi.org/10.1186/s12967-025-06814-7

DOI: 10.54254/2753-8818/2026.PJ30830

[3] Chen, S., Sun, J., Zhou, H., Lei, H., Zang, D., and Chen, J. (2024). New roles of tumor-derived exosomes in tumor microenvironment. Chinese Journal of Cancer Research, 36(2), 151–166. https: //doi.org/10.21147/j.issn.1000-9604.2024.02.05

[4] Gui, Y., Peng, M., Huang, Y., Chen, Z., Chen, J., Xiao, J., Liu, D., and Hou, Y. (2025). New insights into extracellular vesicles in metastatic cancer: From mechanisms to diagnostics and targeted therapies. Molecular Therapy, 33(10), 4731–4747. https: //doi.org/10.1016/j.ymthe.2025.07.016

[5] Mahamed, R., Monchusi, B., Penny, C., and Mirza, S. (2025). Cancer-derived exosomes: mediators of immune crosstalk and emerging targets for immunotherapy. Frontiers in Immunology, 16, 1679934. https: //doi.org/10.3389/fimmu.2025.1679934

[6] Dong, X., Li, C., Deng, C., Liu, J., Li, D., Zhou, T., Yang, X., Liu, Y., Guo, Q., Feng, Y., Yu, Y., Wang, Z., Guo, W., Zhang, S., Cui, H., Jiang, C., Wang, X., Song, X., Sun, X., and Cao, L. (2024). Regulated secretion of mutant p53 negatively affects T lymphocytes in the tumor microenvironment. Oncogene, 43(2), 92–105. https: //doi.org/10.1038/s41388-023-02886-1

[7] He, Q., Xiang, L., Luo, Y., Wang, R., Zheng, C., Gao, Y., and Yao, H. (2025). Tumor-associated macrophages in colon cancer immunotherapy: mechanisms, natural product interventions, and microenvironment remodeling. Frontiers in Immunology, 16, 1642091. https: //doi.org/10.3389/fimmu.2025.1642091

[8] Wang, Q., Sun, Z., Guo, J., Li, H., Zhang, J., Zhang, B., Zhou, B., and Feng, Y. (2025). Tumor-derived exosomal LINC01812 induces M2 macrophage polarization to promote perineural invasion in cholangiocarcinoma. Cancer Letters, 617, 217596. https: //doi.org/10.1016/j.canlet.2025.217596

[9] Li, Y., Chen, Z.-K., Duan, X., Zhang, H.-J., Xiao, B.-L., Wang, K.-M., and Chen, G. (2022). Targeted inhibition of tumor-derived exosomes as a novel therapeutic option for cancer. Experimental & Molecular Medicine, 54(9), 1379–1389. https: //doi.org/10.1038/s12276-022-00856-3

[10] Zhang, Y., Li, B., Gu, W., Fan, L., Wang, X., Xu, M., Zhu, M., and Jin, C. (2025). Hepatoma cell-derived exosomal SNORD52 mediates M2 macrophage polarization by activating the JAK2/STAT6 pathway. Discover Oncology, 16(1), 36. https: //doi.org/10.1007/s12672-024-01700-y

[11] Hosseini, R., Asef-Kabiri, L., Yousefi, H., Sarvnaz, H., Salehi, M., Akbari, M. E., and Eskandari, N. (2021). The roles of tumor-derived exosomes in altered differentiation, maturation and function of dendritic cells. Molecular Cancer, 20(1), 83. https: //doi.org/10.1186/s12943-021-01376-w

[12] Maus, R. L. G., Jakub, J. W., Hieken, T. J., Nevala, W. K., Christensen, T. A., Sutor, S. L., Flotte, T. J., and Markovic, S. N. (2019). Identification of novel, immune-mediating extracellular vesicles in human lymphatic effluent draining primary cutaneous melanoma. OncoImmunology, 8(12), e1667742. https: //doi.org/10.1080/2162402X.2019.1667742

[13] Ludwig, N., Yerneni, S. S., Azambuja, J. H., Gillespie, D. G., Menshikova, E. V., Jackson, E. K., and Whiteside, T. L. (2020). Tumor-derived exosomes promote angiogenesis via adenosine A2B receptor signaling. Angiogenesis, 23(4), 599–610. https: //doi.org/10.1007/s10456-020-09728-8

[14] Jia, X., Xi, J., Tian, B., Zhang, Y., Wang, Z., Wang, F., Li, Z., Long, J., Wang, J., Fan, G.-H., and Li, Q. (2024). The tautomerase activity of tumor exosomal MIF promotes pancreatic cancer progression by modulating MDSC differentiation. Cancer Immunology Research, 12(1), 72–90. https: //doi.org/10.1158/2326-6066.CIR-23-0205

[15] Xi, Y., Zhao, Z., Wang, F., Zhang, D., and Guo, Y. (2024). IRTIDP: A simple integrated real-time isolation and detection platform for small extracellular vesicles Glypican-1 in pancreatic cancer patients. Talanta, 280, 126766. https: //doi.org/10.1016/j.talanta.2024.126766