



Review

Dendritic Cell-Derived Exosomes: Next Generation of Cancer Immunotherapy

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Abstract

Dendritic cells (DCs) are the most highlighted cell population for cancer immunotherapy development. Currently, DC-derived exosomes show promising anti-cancer activity. Exosomes are a subpopulation of extracellular vesicles (EVs) and originate from endosomes. It transports dynamic molecular cargos such as DNA, RNA, protein, and lipid. This cellular cargo exchange reprograms the recipient cell naturally. In cancer research, DC-derived exosomes (DEXs) are used as a therapeutic tool. There are some approaches followed in the application of DEX in cancer as a therapeutic tool. DEX-based drug delivery, tumor antigen-loaded DEX, and modified DEX are applicable approaches in cancer therapy. DEXs are biocompatible, nontoxic, and have ability-specific targeting. On the other hand, this method faces some challenges, such as large-scale production, isolation, and heterogeneity. A multidisciplinary approach (advanced nanotechnology, multi-omics, and single-exosome profiling) comes up with a solution to this issue. This review provides a comprehensive overview of the DEX approach, tracing its developmental journey and therapeutic application in cancer immunotherapy. It examines key findings from clinical trials and outlines the challenges and future research directions in this field, ultimately underscoring the potential of DC-derived exosomes as a research-backed, cell-free solution for the next generation of cancer immunotherapies.

Keywords: cancer; metastasis; DC exosomes; cancer immunotherapy



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1. Introduction

Cancer remains one of the major causes of mortality and represents a notable public health challenge globally, despite substantial advancements in conventional treatment modalities such as surgery, chemotherapy, and radiotherapy [1,2]. Over the past two decades, immunotherapy has emerged as a transformative approach in oncology, utilizing the body's innate and adaptive immune responses to recognize and destroy malignant cells by inhibiting oncogenic pathways [3,4]. Major approaches include immune checkpoint inhibitors (such as anti-PD-1, PD-L1, CTLA-4) that enhance T-cell responses, and adoptive cell therapy, like CAR T-cell therapy, monoclonal antibodies, and therapeutic vaccines [4].

Though the concept of cancer vaccines dates back to the 1970s, challenges such as immune escape and poor immunogenicity have hindered the progress of cancer vaccines in clinical translation [5,6]. Therapeutic cancer vaccines offer a wide range of approaches, including subunit vaccines (peptides, proteins, and tumor lysates), neoantigen-based personalized vaccines, dendritic cell-based vaccines, nanoparticle-assisted lymph node-targeting systems, mucosal and intratumoral delivery platforms, scaffold-based and injectable depot vaccines, and in situ tumor vaccines, all of which are designed to address tumor immune tolerance, enhance T cell priming, and improve tumor-specific immune responses [7–9]. Moreover, prophylactic vaccines such as the Human Papillomavirus (HPV)-based vaccines (available in bivalent, quadrivalent, and nonavalent forms) have shown significant success in preventing HPV-associated malignancies, particularly cervical cancer. However, these vaccines are preventive in nature and offer protection only against select HPV types, with limited therapeutic benefit once infection or malignant transformation has occurred [10]. This underlines the need for more effective broad-spectrum therapeutic strategies. Among the various immunotherapeutic strategies, dendritic cell (DC)-based vaccines have gained significant attention due to their pivotal role as professional antigen-presenting cells (APCs) that initiate and regulate tumor-specific immune responses. However, despite promising preclinical outcomes, the clinical efficacy of DC vaccines has been hindered by several limitations and challenges related to their ex vivo manipulation, limited in vivo migration, and immunosuppressive tumor microenvironment (TME) [11]. Addressing these challenges, recent research has shifted towards dendritic cell-derived exosomes (DEXs) as a promising alternative cell-free approach that could overcome many of the hurdles and push the boundaries associated with whole-cell DC therapies [6,12,13]. Exosomes are naturally secreted, nano-scale (30–200 nm) extracellular vesicles (EVs) of endosomal origin that are released by a wide variety of cells. They facilitate intercellular communication by transporting bioactive molecular cargoes like proteins, lipids, and nucleic acids (mRNAs, miRNAs, lncRNAs, and DNA fragments) [6,14,15]. Exosomes can be derived from a diversity of cells, including tumor cells [16], mesenchymal stem cells [17], and immune cells [18]. Recent scientific advances even suggest that plant-derived exosomes [19] and milk-derived exosomes [20] hold promising potential for cancer therapy and for minimizing drug resistance. Particularly, DC-derived exosomes (DEXs) preserve essential immunostimulatory properties of their parental dendritic cells. These properties include the presence of major histocompatibility complex (MHC) class I and class II molecules, costimulatory molecules (such as CD80, CD86), and adhesion molecules (e.g., ICAM-1), making them highly competent in antigen presentation. Most importantly, DEXs can be loaded with tumor-associated antigens (TAAs) and engineered to enhance their immunogenicity, thereby acting as cell-free nanocarriers that activate T cells and natural killer (NK) cells to initiate robust anti-tumor responses. On top of that, their miniature size, morphological stability, biocompatibility, low toxicity, and significant ability to circulate biomolecules systemically support their potential for therapeutic applications in cancer immunotherapy [13,21,22]. The immunomodulatory functions of DEXs have been extensively explored in preclinical cancer models, demonstrating their ability to stimulate CD8⁺ cytotoxic T lymphocytes (CTLs), polarize Th1 responses, and synergise with immune checkpoint inhibitors [13,23,24]. Several studies have also demonstrated that DEXs can modulate the tumor microenvironment by enhancing immune cell infiltration, reprogramming tumor-associated macrophages, and inhibiting regulatory T cells (Tregs), thus shifting the TME from an immunosuppressive to an immunostimulatory state [12,23]. Notably, early-phase (Phase I) clinical trials have provided encouraging evidence on the safety, tolerability, and partial immunogenic efficacy of DEXs in patients with non-small cell lung cancer (NSCLC) and melanoma. These findings support the potential of DEXs as scalable, off-the-shelf immunotherapeutics in personalized cancer

medicine [25,26]. Despite their tremendous promise, the clinical translation of DEXs still faces multiple hurdles. These include the need for standardized methods for isolation and purification, refined strategies for antigen loading, and scalable exosome production that meets general Good Manufacturing Practices (GMP) practices. Furthermore, improving in vivo targeting efficiency remains a key challenge [27,28]. Moreover, understanding the biodistribution, pharmacokinetics, and long-term immunological effects of exosome-based therapies is essential for advancing their clinical application. Advances in nanotechnology, molecular engineering, and systems immunology are expected to play a critical role in refining DEXs-based immunotherapies for enhanced specificity, durability, and efficacy [27,28]. As shown in Figure 1, the development of DEXs is described in detail in terms of application and clinical trials. DEXs represent a distinctive class of extracellular vesicles with several advantages over exosomes originating from tumor cells or mesenchymal stem cells (MSCs). Tumor-derived vesicles, while reflective of their cellular origin, often carry oncogenic proteins and nucleic acids that contribute to tumorigenesis and metastasis, thereby raising significant safety concerns for therapeutic application. By contrast, DEXs are enriched in immune-stimulatory molecules, including major histocompatibility complex (MHC) and co-stimulatory proteins, which collectively promote antigen-specific T-cell activation. This immunogenic profile positions DEXs as a safer and more effective option in immunotherapy [28]. MSC-derived exosomes have been extensively investigated for their regenerative and immunomodulatory properties, demonstrating utility in tissue repair and inflammatory disorders. However, their broad immunosuppressive effects may counteract the desired anti-tumor immune responses in cancer settings. From a translational perspective, MSC-derived exosomes benefit from scalability due to the robust expansion capacity of stem cells, which facilitates large-scale production [29–31]. Nevertheless, ongoing improvements in dendritic cell culture systems and standardized isolation methods are progressively addressing scalability challenges associated with DEXs [32]. Collectively, these comparisons underscore the unique positioning of DEXs as a therapeutic platform that integrates safety with potent immune activation, while maintaining growing feasibility for clinical translation. As research advances, DEXs are increasingly recognized as offering a balanced and clinically relevant alternative within the broader landscape of exosome-based therapies [32].

This review aims to provide a comprehensive overview of the current landscape of dendritic cell-derived exosomes in cancer immunotherapy, highlighting their biogenesis, functional mechanisms, engineering strategies, preclinical evidence, and translational potential. We also address the challenges and future directions that will shape the next generation of exosome-based cancer immunotherapies. By integrating the current knowledge and transformative insights, this review underscores the pivotal role of DEXs in reshaping the landscape of cancer immunotherapy and advancing toward clinically viable, cell-free immune therapeutics.

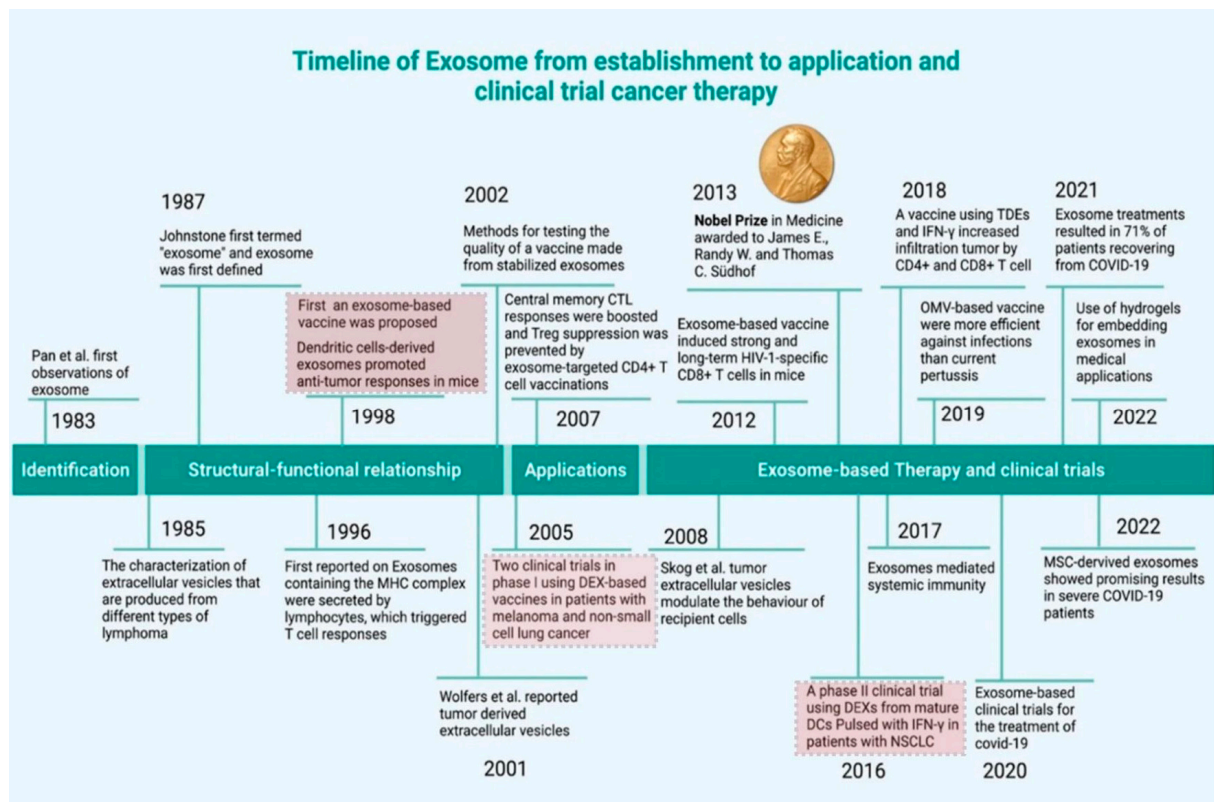


Figure 1. Exosome-based cancer therapy (reproduced with permission under Creative Commons CC BY 4.0 license from ref. [33] Copyright 2022, Springer Nature).

2. Biogenesis of Exosomes

Exosome biogenesis (Figure 2) in animal cells is a sophisticated and highly coordinated process, fundamental to how cells communicate and maintain their internal balance. This journey begins deep within the cell, specifically within the endocytic pathway, where tiny internal pockets, known as intraluminal vesicles (ILVs), form inside larger compartments called multivesicular bodies (MVBs) [34–36]. These MVBs, once docked and fused to the plasma membrane, the cell's outer membrane, release their ILV cargo as exosomes into the extracellular space to mediate cell-to-cell communication [34,35,37]. This biogenesis process is mainly regulated by two molecular mechanisms, the ESCRT-dependent and ESCRT-independent mechanisms [36–40]. The ESCRT-dependent mechanism is a highly regulated and orderly process that involves four protein complexes called the Endosomal Sorting Complexes Required for Transport (ESCRT), which function along with the VPS4 ATPase [34,41–43]. This process begins when ESCRT-0 recognizes and binds to ubiquitinated cargo proteins. ESCRT-I and ESCRT-II then aid in cargo recruitment and the initiation of MVB membrane inward budding. The final step of ILV budding is performed by ESCRT-III, while VPS4 disassembles and recycles the ESCRT complexes for reuse [34,36,37,39,41,42]. The process is also assisted by accessory proteins like TSG101 and ALIX that regulate cargo selection and vesicle formation. In particular, the syndecan-syntenin-ALIX complex is a major player that helps coordinate these factors by ensuring their proper recruitment to MVBs at the right time and location [34,37,43–46]. In certain immune cells like dendritic cells, where the specificity of exosome cargo is highly critical for immune signaling, this ESCRT machinery is well-regulated [32,47–51]. As professional antigen-presenting cells, these cells utilize these pathways to package and release specific sets of membrane and cytosolic proteins, as well as nucleic acids, in exosomes [32,47,51]. In this way, they create very specific and functionally distinct exosomes that can travel around the body and tune the immune response

by activating it, suppressing it, or inducing tolerance, depending on the state of the cell and the communication that it is trying to achieve [32,47–51]. In contrast, ESCRT-independent pathways offer alternative mechanisms for cargo sorting and ILV formation [34,39,52]. A key player in this alternative mechanism is ceramide, a lipid molecule that can induce a negative curvature in endosomal membranes, directly driving ILV budding, and thus determining the selective sorting of certain cargo, like proteolipid proteins [36,44,53]. Interestingly, more recent studies have also implicated ceramide-rich microdomains in a much more unconventional exosome biogenesis pathway that involves processes like nuclear envelope budding as well, suggesting a much wider scope for the mechanism in exosome formation [36,44,53,54]. Another contributor to ESCRT-independent biogenesis is a group of membrane proteins called tetraspanins. These proteins can organize specialized membrane domains and cluster specific cargoes to drive vesicle formation even without ubiquitination [34,39,45,52,55,56]. In addition, other lipid-driven processes like the production of phosphatidic acid by phospholipase D2 actively promote the recruitment of syntenin to drive exosome formation [36,57,58]. The final step of exosome release to the extracellular space is highly regulated by the Rab GTPases that mainly control MVB trafficking and docking at the plasma membrane, and SNARE proteins that mediate the membrane fusion events necessary for their secretion are the main orchestrators [59–61]. The sources of cargo that get selected for ILV incorporation are also extremely diverse: while ubiquitinated proteins are preferentially sorted through the ESCRT pathway, lipids and other RNA molecules can be incorporated via their interactions with RNA-binding proteins, or by direct recognition of specific sequence motifs [62,63]. In addition to these major players and mechanisms, there are other forms of regulation in place, like MVB acidification, precise calcium signaling, and even subtle changes in intracellular pH that all work together to fine-tune the efficiency and selectivity of the exosome biogenesis process [36,43,44]. In the context of cancer, exosome production is usually upregulated, and this is mainly driven by the phosphorylation of the various components of the syndecan-syntenin-ALIX complex, by aberrantly activated oncogenic signaling cascades [34,36,44]. In summary, a complex interplay of ESCRT complexes, lipid-driven mechanisms, accessory regulatory proteins, and more tightly controls exosome formation, cargo sorting and release, and subsequent secretion to allow exosomes to perform their diverse and often crucial functions in intercellular communication and overall physiological homeostasis.

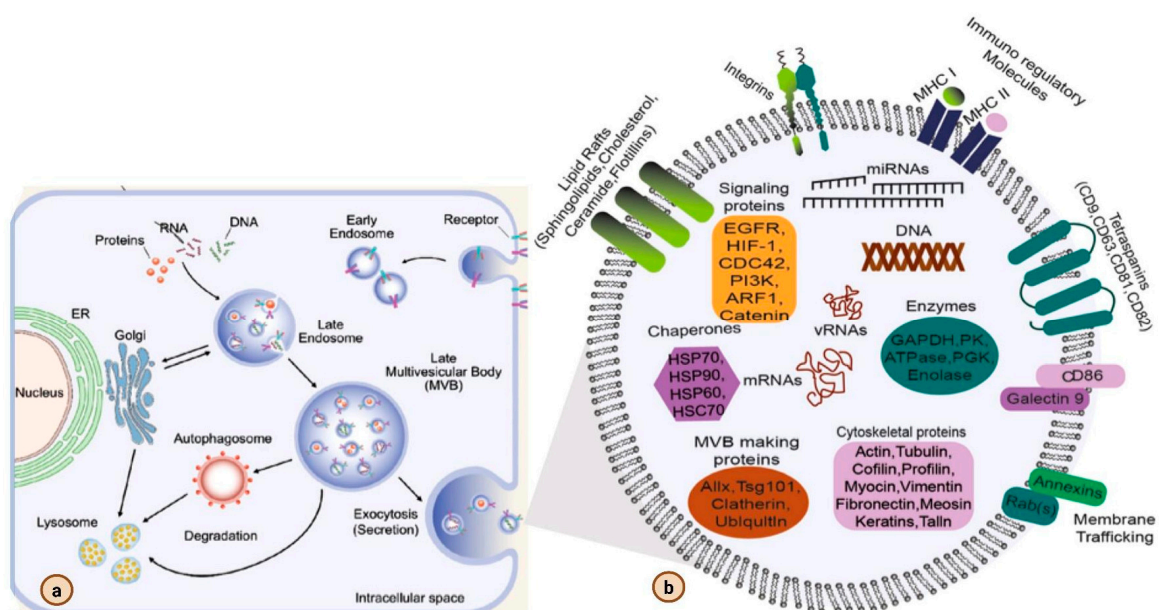


Figure 2. Exosome biogenesis and its components. (a) exosome biogenesis, and (b) exosome molecular cargo. (Adapted with permission from ref. [64] Copyright @ 2021 American Chemical Society.)

3. Exosome Isolation and Characterization

Exosomes, nanosized vesicles secreted by nearly all cell types, have garnered significant attention as mediators of intercellular communication and potential biomarkers for various diseases. When studying exosomes, a crucial step is collecting and isolating them from various sources. This section covers the common pre-processing techniques and methods for isolation and characterization. Exosomes can be isolated from a wide variety of sources, including biofluids and cell culture supernatants [65]. Here is a more detailed look at common sources (Table 1):

Table 1. Recent clinical advances of exosome-based theranostics.

Exosome for Liquid Biopsy for Cancer		
Exosome Source	Clinical Significance	References
Blood (Plasma/Serum)	Blood is a complex biofluid containing exosomes from various cell types. Plasma and serum are commonly used for exosome isolation due to their accessibility. However, they also contain abundant proteins like albumin and lipoproteins that can contaminate exosome preparations.	[65–67]
Urine	Exosomes are present in urine and can be valuable for studying kidney function and urological diseases.	[65]
Saliva	Saliva offers a non-invasive source of exosomes, useful for oral and systemic disease diagnostics.	[66]
Breast Milk	Breast milk is rich in exosomes, which play a role in infant immunity and development.	[65]
Amniotic Fluid	Exosomes in amniotic fluid can provide insights into fetal development and pregnancy-related complications.	[65]
Cerebrospinal Fluid	CSF-derived exosomes are valuable for studying neurological disorders.	[65]
Ascites Fluid	This fluid, found in the abdominal cavity of patients with certain cancers, contains exosomes that can provide information about the tumor microenvironment.	[65]
Sweat	Biomarker source	[68]
Tear	Biomarker source	[69]
Exosomes sources for therapeutic development		
Exosome source	Clinical significance	References
Plant cell	Use as a therapeutic tool	[70]
Immune cell	Use as a therapeutic tool	[71]
Stem cell	Use as a therapeutic tool	[72]
Tumor cell	Use as a therapeutic tool (not recommended due to its enrichment of oncogenic cargo)	[73]

Exosomes can be collected from the conditioned media of cultured cells. This allows researchers to study exosomes secreted by specific cell types in a controlled environment. As discussed earlier, many cell types from various biological kingdoms release exosomes, with the majority of research to date having focused on those derived from plants and animals [74]. The exosome yield can, however, vary significantly depending on the cellular source. For example, milk typically has a high exosome yield [75]. Thus, the choice of isolation method is critical for yield, purity, and processing costs and should be tailored to

the specific source [75], as contaminating components vary. For example, blood samples can be contaminated with lipoproteins and albumin [67]. Some unconventional sources of exosomes, such as plants and fungi, are also being explored [67]. Traditional Methods for exosome isolation, while foundational, each has specific characteristics and limitations that influence their application in research. These methods are based on the physical properties of exosomes, such as size and density. Ultracentrifugation is a widely used method that involves multiple rounds of centrifugation at increasing speeds to separate particles based on size and density [67]. It is relatively low-cost and can be used for large volumes. However, it can result in low purity [76]. Density Gradient Centrifugation is often used after ultracentrifugation for further purification; this method separates exosomes based on their buoyant density [77]. The purest exosomes are obtained this way. Size exclusion chromatography separates molecules based on their size as they pass through a porous matrix [78]. Immunoaffinity Capture uses antibodies to specifically bind to exosomal surface proteins [78].

The major challenge in exosome research is the lack of a simple, reliable, and standardized isolation method [76]. Traditional techniques can be labor-intensive and may result in co-purification of other molecules [79]. To address these limitations, researchers have developed integrated biosensor-based methods for exosome separation and detection [76]. Some other considerations may include that the choice of isolation method can impact the yield, purity, and integrity of the isolated exosomes [77]. Some methods may require specialized equipment, such as ultracentrifuges [80]. In summary, while ultracentrifugation is often considered the “gold standard” [77], researchers are exploring new methods to improve exosome isolation and analysis [76]. Among the modern methods is microfluidics-based isolation, where microfluidic devices offer precise control over fluid flow, enabling efficient and high-throughput exosome isolation [79]. These devices can integrate various separation principles, such as size-based separation, which utilizes microchannels with specific dimensions to trap larger particles while allowing exosomes to pass through. Affinity-based separation incorporates antibodies or aptamers within the microchannels to selectively capture exosomes based on their surface markers. Acoustic Separation uses sound waves to manipulate and separate exosomes based on their size and density. Acoustic separation is label-free and can be integrated into microfluidic devices for continuous exosome isolation. The DEX are isolated from blood, and the lipoproteins co-purify because they have similar physicochemical properties. This is a big issue as the lipoproteins have been shown to directly interfere with the desired immunomodulatory function of DEX. A new report [81] documents this, and a new strategy to effectively deplete the lipoproteins. They show that this greatly increases the purity of the exosome preparation while maintaining the important exosomal markers. Exosome Precipitation involves using polymers to reduce the solubility of exosomes, causing them to aggregate and precipitate out of solution. While simple, it may co-precipitate other proteins. Lab-on-a-chip biosensing now makes it possible to integrate the isolation and characterization processes into a single platform [79]. These newer methods aim to improve upon the limitations of traditional techniques by offering enhanced purity, yield, and ease of use [76]. However, it is worth noting that exosome research still faces a lack of standardized isolation methods [76]. Table 2 below is the summary of different methods for exosome isolation—principle, procedure, advantages, and disadvantages.

Exosome characterization (Table 3) using advanced techniques such as nanoparticle tracking analysis, transmission electron microscopy, and dynamic light scattering can provide valuable insights into their size distribution, morphology, and concentration.

Table 2. Comparison of different exosomes isolation methods.

Methods	Principle	Procedure	Advantages	Disadvantages	References
Differential Ultracentrifugation	This method involves multiple rounds of centrifugation at progressively higher speeds. Each step pellets particles of a certain size and density, allowing for the enrichment of exosomes.	<ol style="list-style-type: none"> 1. The sample is first centrifuged at low speeds (e.g., $300\times g$, then $2000\times g$) to remove cells, cell debris, and larger vesicles. 2. The supernatant is then centrifuged at a higher speed (e.g., $10,000\times g$) to separate exosomes from larger, non-exosomal vesicles. 3. Finally, the supernatant is ultracentrifuged at very high speed (e.g., $100,000\text{--}150,000\times g$) to pellet the exosomes. 4. The exosome pellet can be resuspended in a suitable buffer for downstream analysis 	Can be used for large volumes, relatively low cost, and with no need for additional chemical reagents	<p>Can be time-consuming and may result in low purity due to the co-purification of other molecules.</p> <p>Exosomes might be damaged during the process</p>	[67,82,83]
Density Gradient Ultracentrifugation	This method separates particles based on their buoyant density. The sample is layered on top of a density gradient medium (e.g., sucrose or iodixanol) and centrifuged until particles reach their equilibrium density.	<ol style="list-style-type: none"> 1. After differential ultracentrifugation, the exosome-containing pellet is resuspended and placed on top of a density gradient 2. Ultracentrifugation is performed until the exosomes migrate to their corresponding density within the gradient. 3. Fractions are collected from the gradient, and exosome-containing fractions are identified and pooled 	Higher purity compared to differential ultracentrifugation	More complex and time-consuming than differential ultracentrifugation, as well as low yields	[77,84,85]
Size Exclusion Chromatography (SEC)	SEC separates molecules based on their size as they pass through a porous matrix. A column is packed with a stationary phase consisting of porous beads. Smaller molecules enter the pores and take a longer, more tortuous path, eluting later. Larger particles, like exosomes, cannot enter the pores and elute earlier.	<ol style="list-style-type: none"> 1. The sample is loaded onto the SEC column. 2. A buffer is used to elute the sample through the column. 3. Fractions are collected as they elute from the column. 4. Exosome-containing fractions are identified based on their elution volume. 	SEC can separate exosomes based on their size Gentle method that preserves exosome integrity	A limited quantity of EVs recovered.	[78,86,87]
Filtration	Filtration methods use filters with defined pore sizes to separate particles based on size. Ultrafiltration membranes with specific molecular weight cut-offs are commonly used to enrich exosomes	<ol style="list-style-type: none"> 1. The sample is passed through a filter membrane with a specific pore size. 2. Particles larger than the pore size (including exosomes) are retained on the filter 3. Smaller molecules pass through the filter. 4. The retained exosomes can be recovered by back-flushing the filter or dissolving them in a suitable buffer. 	<p>Relatively simple and rapid.</p> <p>Can be used to concentrate exosome samples</p>	<p>Membrane clogging can be an issue.</p> <p>Exosomes may be damaged by shear forces during filtration.</p>	[77,80,88]
Precipitation with Polymers	This method involves using polymers to reduce the solubility of exosomes in solution. The polymers bind to water molecules, effectively forcing exosomes to aggregate and precipitate out of the solution	<ol style="list-style-type: none"> 1. The polymer solution is added to the sample containing exosomes. 2. The mixture is incubated for a specific time and temperature to allow for exosome precipitation. 3. The precipitated exosomes are then collected by centrifugation. 4. The exosome pellet is resuspended in a suitable buffer for downstream analysis. 	Simple and relatively inexpensive. Does not require specialized equipment like ultracentrifuges	<p>Co-precipitation of other non-exosomal contaminants, such as proteins and polymeric materials, is unavoidable.</p> <p>May be less pure compared to other methods like ultracentrifugation or size exclusion chromatography.</p> <p>The choice of polymer and precipitation conditions can affect exosome yield and purity.</p>	[89–91]

Table 2. Cont.

Methods	Principle	Procedure	Advantages	Disadvantages	References
Immunoaffinity Capture	This method uses the specific binding between an antibody and an exosomal surface protein to selectively capture exosomes. Antibodies against specific exosomal markers (e.g., CD9, CD63, CD81) are immobilized on a solid support (e.g., beads, columns, or microplates). When a sample containing exosomes is incubated with the antibody-conjugated support, exosomes expressing the target protein are captured.	<ol style="list-style-type: none"> 1. Antibodies against exosomal surface markers are immobilized on a solid support. 2. The sample containing exosomes is incubated with the antibody-conjugated support, allowing the exosomes to bind to the antibodies. 3. The solid support is washed to remove unbound material. 4. The captured exosomes are then eluted from the support, typically by changing the pH or ionic strength of the buffer 	<p>High specificity for exosomes expressing the target protein.</p> <p>Can be used to isolate specific subpopulations of exosomes.</p>	<p>Requires knowledge of exosomal surface markers.</p> <p>Antibody availability and cost can be limiting factors</p> <p>Elution steps can result in sample loss, making the method less suitable for downstream analysis.</p>	[78,91,92].
Microfluidic	Microfluidic exosome separation leverages the unique physical and chemical properties of exosomes in a controlled microenvironment. These properties include size, surface markers, deformability, and electrical characteristics.	<p>Size-based separation: This method separates exosomes based on their size using microchannels with precisely controlled dimensions.</p> <p>Dynamic methodologies: Separation based on other properties, such as electrical characteristics.</p>	<p>Enhanced purity: Microfluidic systems can achieve higher purity compared to ultracentrifugation.</p> <p>Cost-effectiveness: Microfluidic technologies offer a cost-effective solution for exosome isolation.</p>	<p>Technological immaturity: Exosome research using microfluidics is still in its early stages.</p> <p>Lack of standardization: The absence of standardized methods for exosome separation can lead to suboptimal inter-laboratory correlation and difficulty in comparing studies.</p> <p>Challenges in isolating exosomes: The inherent heterogeneity of exosomes and the complexity of biofluids pose significant challenges for their isolation.</p>	[93–95]

Table 3. Different exosome characterization techniques.

Characterization Types	Importance	Reference
Physical Characterization		
Nanoparticle Tracking Analysis	NTA is utilized for concentration measurements and size distribution curves of exosomes. NTA operates by tracking the Brownian motion of individual particles in a sample using light scattering. By measuring the rate of movement, the software calculates the hydrodynamic diameter of each particle using the Stokes-Einstein equation.	[96–98]
Dynamic Light Scattering	DLS, as well as NTA, fluorescence signals, and flow cytometry, are optical methods used to characterize vesicles.	[99]
Electron Microscopy (TEM/SEM):	Traditional detection techniques utilized to quantify the isolated exosomes include scanning electron microscopes and transmission electron microscopes.	[98]
NanoFCM	Nano-flow cytometry is a quantitative and qualitative measurement of single EVs, like exosomes (it is applicable for cell culture suspension and body fluid).	[100]
Super-Resolution Microscopy (SRM)	SRM works with Oxford Nano Imaging (ONI) and supports the decoding of exosomes' morphology, tracking of EV uptake, cargo composition, and heterogeneity.	[101,102]

Table 3. Cont.

Characterization Types	Importance	Reference
Characterization of Molecules		
Western Blotting	Western blotting can be performed using exosomal markers such as CD9, CD63, and CD81.	[98]
Flow Cytometry	It is one of the optical methods for characterizing vesicles. It can identify and characterize the cytoplasmic or surface proteins of EVs.	[99]
Exoview Chip	This is a microarray-based method where affinity-based antibodies are captured for exosomes' surface markers, such as CD9, CD63, and CD81. This capture visualization by the supporter of ExoViewR100	[103,104]
Analysis of Proteomes and Genomes	Mass Spectrometry, RNA-seq: These techniques are used for in-depth analysis of exosome contents.	[105,106]
Quantification and Evaluation of Purity	<p>Quantifying protein (BCA/Bradford test): These are standard methods for determining the overall protein concentration in the exosome sample.</p> <ul style="list-style-type: none">Finding contaminants (how well they remove albumin and lipoprotein): It is important to assess the presence of contaminating proteins like albumin and lipoproteins to determine the effectiveness of the isolation method.	[107]
Functional Analysis	<p>Studies on uptake (cell interaction tests and fluorescent labeling): These assays help to understand how exosomes interact with and are taken up by target cells.</p> <ul style="list-style-type: none">Functional assays in vitro and in vivo: These assays assess the biological effects of exosomes on cells or in living organisms.	[108]

In a nutshell, when evaluating exosome isolation procedures, it is crucial to consider both yield and purity, as these parameters significantly influence downstream applications such as diagnostics, therapeutics, and molecular characterization. However, a major challenge in the field is the absence of standardized isolation protocols, which complicates the comparison of results across different laboratories. Variability in techniques, equipment settings, and sample types can lead to inconsistent outcomes, limiting reproducibility and hindering the development of universally accepted benchmarks. This lack of standardization not only affects inter-laboratory correlation but also raises concerns about the reliability and clinical applicability of exosome-based analyses [76].

4. Role of Exosomes in Cancer

The tumor microenvironment (TME) is a highly complex, dynamic ecosystem. It is no longer perceived simply as a “bag of cancer cells” but is rather considered an intricate and active biological system consisting of a variety of supporting cells (stromal and immune), blood vessels, extracellular matrix, and a range of soluble factors [109–112]. Tumor growth and metastasis are also impacted by these heterogeneous cell–cell and cell–matrix networks. The most characteristic feature of TME, among various environmental stress factors, is hypoxia. Hypoxia is often caused by an imbalance between oxygen supply and consumption in TME [113–117]. The consumption of oxygen frequently exceeds the capacity for vascularization as a result of fast-growing tumors, leading to hypoxic (low oxygen) conditions in the tumor interstitium. When adapting to hypoxic stress, cancer cells utilize

a transcription factor known as hypoxia-inducible factors (HIFs), which regulates various sets of genetic and metabolic changes [113–117]. HIFs enable the cells to adapt to low oxygen levels, which may support aggressive proliferation, as well as reprogram metabolism, and eventually cause the cancer cells to invade adjacent normal tissue to obtain resources for unlimited proliferation [116,118,119]. As tumor cells adapt to the resulting hypoxic conditions, the TME becomes more permissive to malignancy and metastasis [113,120]. Tumor cells in hypoxic conditions have a greater release of exosomes, nano vesicles that are important mediators of intercellular communication [121,122]. Tumor-derived exosomes (TDXs) regulate multiple stages of cancer development and progression (Figure 3). For instance, melanoma cells are particularly adept at efficiently releasing exosomes under hypoxic conditions, which significantly contributes to the disease's aggressive nature [123–125]. TDXs are secreted more in hypoxic conditions and play a major role in remodeling the TME. TDXs contain a diverse range of cargoes, including proteins, lipids, and nucleic acids such as microRNAs, which can have a profound effect on the behavior of recipient cells [110,126,127]. A major role of TDXs is to promote angiogenesis, which is the formation of new blood vessels. This is crucial to provide the tumor with nutrients and oxygen. TDXs help in angiogenesis by delivering pro-angiogenic factors as well as exosomal microRNAs, including miR-210, which is enriched in exosomes derived from hypoxic tumor cells, to endothelial cells to stimulate their proliferation and migration [110,126–129]. This not only facilitates tumor growth and proliferation but also sets the stage for cancer cells to migrate through the bloodstream [128,129]. TDXs are also considered major players in reprogramming the immune landscape in the TME to suppress immune responses against the tumor. TDXs are able to reprogram immune cells within the TME to make the TME immunosuppressive [130–132]. For example, TEXs are able to reprogram macrophages in the TME from the antitumorigenic M1 state to the tumorigenic M2 state through exosomal miR-934, causing increased metastasis [133,134]. TDXs also promote the differentiation of monocytes into myeloid-derived suppressor cells (MDSCs), which suppress T cell responses through the secretion of various immunosuppressive factors such as PGE2 and TGF- β [29,135,136]. TDXs also inhibit T cell activation directly by carrying immunosuppressive molecules such as TGF- β and PD-L1, which inhibit T cell activation and promote regulatory T cell development [29,137–139]. Even the important antigen-presenting cells (APC), such as dendritic cells (DCs), can be tolerized by TDXs, resulting in a decreased ability of DCs to activate T cells, thus suppressing overall immune response [29,137–139]. Exosomes are also known to play a crucial role in metastasis [140]. They facilitate several critical processes involved in metastasis, such as epithelial to mesenchymal transition (EMT), which is a process by which epithelial cells lose their polarity and become mobile and invasive [140,141]. TDXs can deliver bioactive molecules that promote EMT, resulting in a significant increase in the metastatic potential of cancer cells [140,141]. For example, exosomal microRNA-106b-5p has been shown to promote colorectal cancer metastasis by modulating tumor-M2 macrophage crosstalk [142]. In addition, the surface proteins of exosomes, such as tetraspanins and integrins, have been shown to play important roles in organotropism and metastasis, and act as a homing signal that enables tumor cells in the circulation to home to specific organs and metastasize to those sites [56,143,144]. Resistance to therapy is one of the major roadblocks to cancer therapy. Recent evidence indicates that exosomes play a key role in this process by shuttling resistance genes and proteins between cells and, therefore, spreading resistance traits through the tumor [145–147]. For example, exosomes secreted from cisplatin-resistant lung cancer cells have been shown to transport miRNA-100-5p to drug-sensitive tumor cells, resulting in the activation of mTOR signaling and increased survival of drug-sensitive cells during chemotherapy [148,149]. In breast cancer, exosomes have also been shown to sequester HER2-targeted drugs or

even reprogram the gene expression of recipient tumor cells to decrease the effectiveness of anti-cancer drugs [150,151]. In conclusion, exosomes are not merely waste products of tumor growth but are active and versatile participants in almost every aspect of cancer biology [152,153], from supporting angiogenesis and immune evasion to facilitating metastasis and contributing to therapeutic resistance. Their diverse roles make them not just a significant challenge in cancer treatment but also a promising target for therapeutic intervention [152,154]. Ongoing research into the various roles of exosomes in the TME is not only broadening our understanding of cancer progression but also opening up new avenues for the development of effective and targeted therapies.

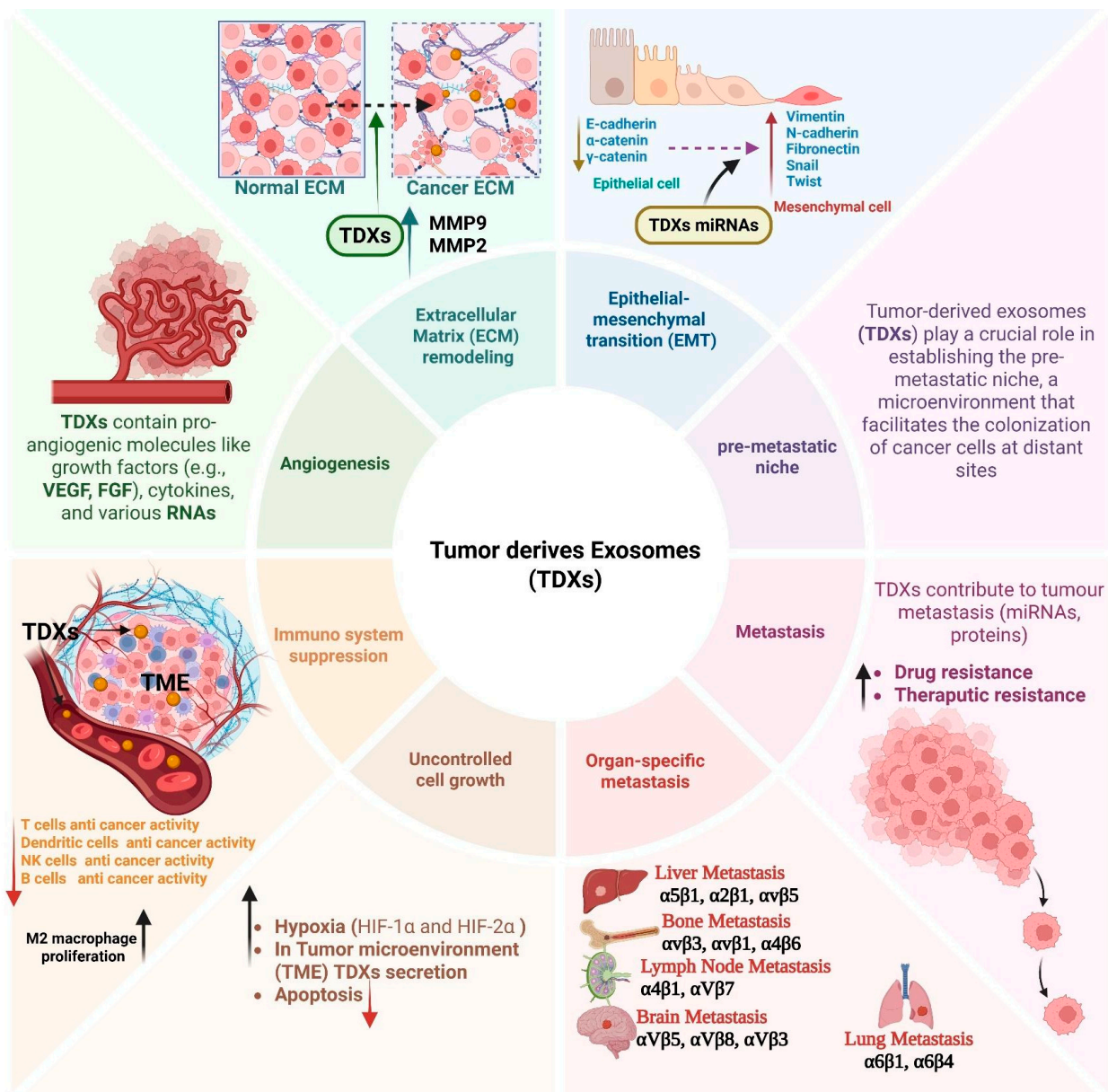


Figure 3. Tumor-derived exosomes (TDXs) role in cancer (created with biorender.com).

5. DC-Derived Exosomes in Therapeutic Application

Dendritic cell-derived exosomes (DEXs) are multifunctional nanocarriers with considerable promise in cancer immunotherapy [155–157]. Mature DEXs exhibit critical immune molecules like MHC-I and MHC-II, which are essential for tumor antigen presentation to T cells. Apart from MHC molecules, the activation of antigen-specific cytotoxic T lymphocytes

phocytes requires co-stimulatory proteins such as CD80 and CD86, which are carried abundantly by DEXs [158]. In comparison to whole dendritic cell therapy, DEXs perform better as candidates in cancer immunotherapy since they can resist the suppression in the tumor microenvironment (TME) [159]. Moreover, their application is widely being explored because reports have shown that exosomes secreted by dendritic cells have been regarded highly efficacious since they have been shown to possess good storage stability, safety with high biocompatibility, and content [160,161]. Dendritic cell-derived exosomes can also be engineered to express immunostimulatory molecules, antigens, or fusion proteins that enhance their therapeutic potential [6]. Exosome-mediated drug delivery is an innovative technology that presents distinct advantages compared to conventional drug delivery systems. One of the most commonly known advantages of using exosome-based drug delivery, like DEXs, is the fact that dendritic cells naturally originate from the human body, meaning that it is highly biocompatible with low immunogenicity [162]. DEX-based drug delivery also has a leverage over its proven barrier crossing [163]. Multiple studies have elucidated DEX's capability to travel through difficult biological barriers like the blood–brain barrier (BBB), which is known for its highly selective permeability from the bloodstream to the brain. Although its layers protect the brain from infections or toxins, it is also challenging to deliver drugs. DEXs are advantageous in the context of having recognizable molecules that allow them to pass and deliver their cargo. This characteristic makes them highly valuable in targeting malignancies beyond the brain [164]. Dendritic cell-derived exosomes rely on accomplished mechanisms, techniques, and strategies to fully leverage their therapeutic potential. Passive and active methods of drug loading are the two fundamental types that influence their release profiles, loading efficiency, and the distribution of the candidate drug. Incubation is a passive loading approach that involves mixing the DEXs with the drug and leaving it at an appropriate temperature to permit the drug to be infused or adsorbed into the bilayer of the exosome [165]. Sonication is an active loading method that requires temporary disruption of the exosome's membrane for drug entry. This can be achieved by exposing DEXs to ultrasonic waves with appropriate optimization via a sonicator [166]. One of the first utilizations of DEXs in cancer immunotherapy was to treat non-small cell lung cancer (NSCLC) [167]. Patients from phase I of the study received DEX-loaded MAGE tumor antigens. These peptides are small pieces of tumor antigens that stimulate CD8+ T cells, often known as cytotoxic T lymphocytes [168]. The study reported that there is an increase in NK cell activity, which is an indication of the tumor cells being exterminated by the patient's NK cells. The clinical investigation by Morse et al. 2005 was the first to demonstrate DEXs as a cell-free cancer immunotherapy in solid tumors and eventually became the foundation study in paving the way for more future advancements in the field [167]. Apart from NSCLC, DEXs were also used to treat hepatocellular carcinoma (HCC), a malignancy in the kidney. This time, DEXs were bioengineered to carry alpha-fetoprotein (AFP) as their cargo [169]. DEXs-based clinical trial phase I and II indicated that limitations promote anti-cancer activity [170]. Mature dendritic cell-derived exosomes are promising immune therapeutic tools for cancer [171]. In solid tumors, mature DEXs prime tumor antigen and activate Th1 and CD8+ T cells, which show a promising outcome against cancer [172]. DEXs also work as a potential immune response against cancer cells, and this is an effective cell-free immunotherapeutic approach [173]. Compared to the DC vaccine approach, DEXs are more effective due to their MHCI and MHCII capabilities, which promote a strong immune response [174]. Research evidence suggests that engineered DEX shows promising outcomes in an in vivo breast cancer model [175].

Research evidence for DEX-based cancer therapeutic applications is depicted in Figure 4.

Since AFP is abnormally overexpressed in adults with HCC, it is adopted as a biomarker for assessing the prognosis of liver cancer patients [176]. However, the immune

responses fail to recognize AFP as foreign, as it is an antigen that is produced during the development of the fetus, which leads to immune tolerance during adulthood [176]. The immune system is also actively being suppressed by HCC by creating an immunosuppressive tumor microenvironment (TME) through the upregulation of immune checkpoints like PD-L1, efficiently impeding T-cell functions [176,177]. These challenges were solved with AFP-loaded DEXs, genetically modified to present AFP in a more immunogenic way to re-activate the host's immune system [169,178]. By presenting AFP on MHC molecules coupled with necessary co-stimulatory signals, DEXs promote T-cell activation, break immune tolerance, and change the tumor microenvironment towards facilitating anti-tumor immunity. Therefore, DEX-based delivery has emerged as a promising approach to stimulate effective antigen-specific immune responses in HCC [179].

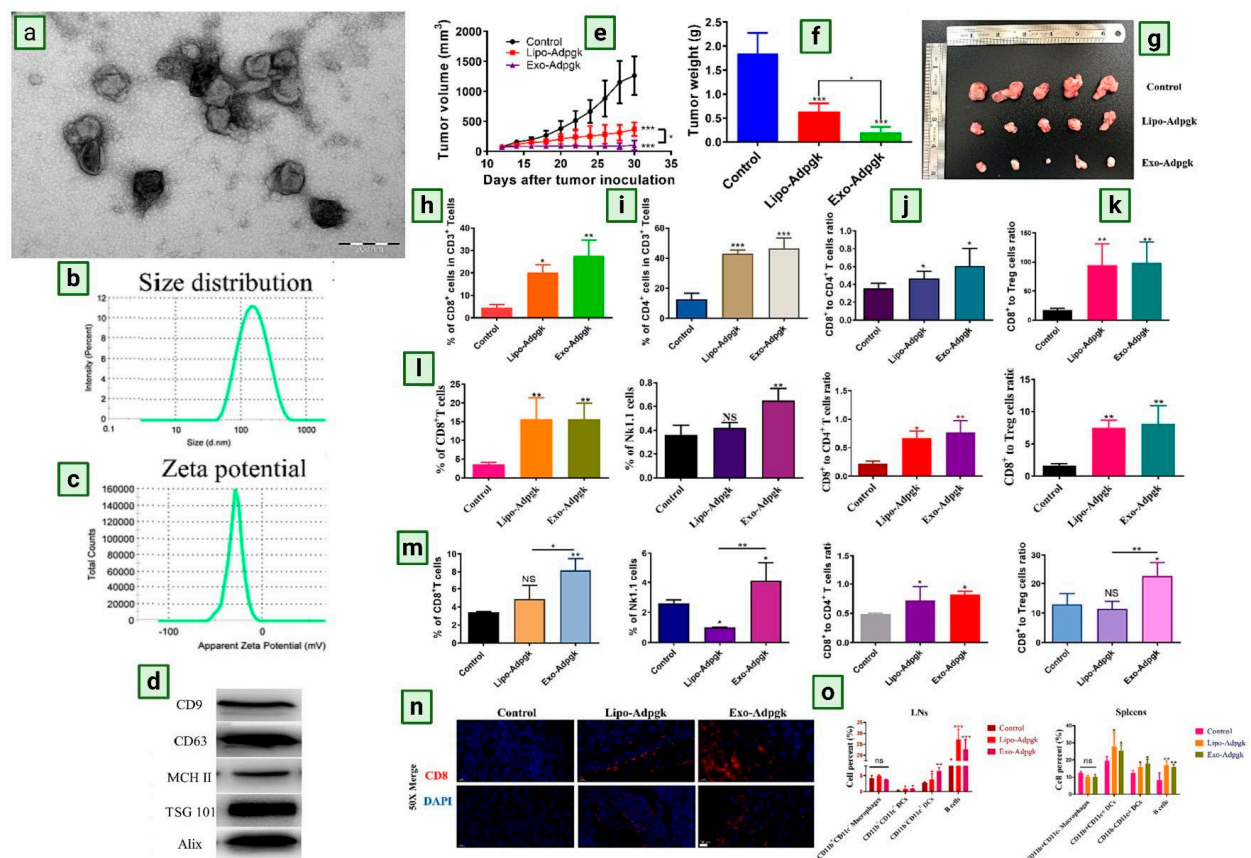


Figure 4. Dendritic cell-derived exosomes-based anti-cancer application. Dendritic cell-derived exosomes TEM images (a), size (b), and zeta potential (c) of exosomes measured by DLS. Scale bar: 200 nm. Marker proteins on exosomes by Western blot analysis (d). Antitumor response of Exo-Adpgk on MC-38 tumors of C57BL/6 mice. Tumor volume–time curve (e), tumor weight (f), and pictures of the tumors (g) isolated from mice on day 30 after the MC-38 inoculation. Proportions of CD8⁺ T cells (h), CD4⁺ T cells (i), CD8⁺ CTL to CD4⁺ ratios (j), and CD8⁺ CTL to Treg ratios (k). The frequency of CD8⁺ T cells, NK1.1 cells as well as CD8⁺ T/CD4⁺ T, CD8⁺ T/Treg ratios in LNs (l) and spleens (m) from mice of various treatments. (n) Representative immunofluorescence of CD8⁺ T cells (red) in B16F10 melanoma tumors (blue). Tumors' cryostat sections were stained with CD8 antibody (red), and tumor nuclei were stained with DAPI (blue). (o) Quantified APCs (including CD11b⁺CD11c⁻ Macrophage, CD11b⁺CD11c⁺ DCs, CD11b⁺CD11c⁻ DCs, and B cells) populations in LNs and spleens from vaccinated mice by flow cytometry analysis. (Reproduced with permission under Creative Commons CC BY-NC-ND 4.0 license from ref. [13] Copyright 2023, Elsevier publisher).

6. Clinical Trial of Dendritic Cell-Derived Exosomes

The clinical trial ID NCT01159288 (Table 4) examines a cell-free immunotherapy approach, where tumor antigen-loaded DEX is applied against non-small lung cancer (NSCLC). In this trial, DEXs are isolated from cancer patients. Gustave Roussy and Curie institutes have developed an immunotherapy involving metronomic cyclophosphamide (mCTX) followed by vaccinations with tumor antigen-loaded DEXs. mCTX inhibits Treg functions, restoring T and NK cell effector functions, and DEXs are able to activate the innate and adaptive immunity. Phase I trials showed the safety and feasibility of DEX vaccines, but no induction of T cells could be monitored in patients. Since 2007, a novel process has been developed and validated for the isolation of second-generation DEX, which demonstrated improved immunostimulatory capacities. A clinical trial was subsequently proposed to evaluate a maintenance immunotherapy regimen using this DEX-based treatment in 47 patients with advanced, unresectable non-small cell lung cancer (NSCLC). The primary objective of the study was to enhance the progression-free survival (PFS) rate at four months in patients who had shown a positive response or disease stabilization following induction chemotherapy. A phase I clinical trial of autologous exosomes in melanoma patients established the safety and large-scale manufacturing feasibility, with a partial clinical response in a single patient and stable disease in others, despite an absence of detectable peripheral MAGE3-specific T cell responses [174,180]. In addition to safety and manufacturability, a major obstacle to the advancement of DEX into Phase III trials has been its low immunogenicity and the technical challenge of eliciting robust, durable T-cell responses [174,180].

Table 4. Clinical trial of dendritic cell-derived exosomes.

Clinical Trials ID	Status	Cancer Types	Clinical Significant	Sponsor
NCT01159288	Completed	advanced non-small cell lung cancer (NSCLC)	Trial of a Vaccination With Tumor Antigen-loaded Dendritic Cell-derived Exosomes (CSET 1437)	Gustave Roussy, Cancer Campus, Grand Paris
Key insights from the clinical trial: Phase: Phase II Objective: To assess the efficacy of IFN-γ-DEXs as maintenance immunotherapy after platinum-based chemotherapy in advanced NSCLC.				
Patient Groups Number Enrolled/Treated: 26 enrolled/22 treated Diagnosis: Advanced (stage IIIB/IV) unresectable NSCLC Key Criteria: HLA-A2 positive, no progression after 4 cycles of platinum-based chemotherapy. Baseline: 64% had adenocarcinoma, 82% had stage IV disease.				
Interventions Treatment: IFN-γ-matured dendritic cell-derived exosomes (IFN-γ-DEXs) loaded with MAGE tumor antigens. Dosing: 0.13 μg MHC class II molecules per injection, administered intravenously. Schedule: Weekly for the first 4 vaccinations, followed by boosters administered every 2 weeks for 3 boosters, then monthly boosters. Adjunct Therapy: Oral metronomic cyclophosphamide (50 mg/day) to inhibit T-reg.				
Endpoint Primary: Progression-free survival (PFS) rate at 4 months. Secondary: Overall survival (OS), time to progression (TTP), safety, and immunological response.				

Table 4. *Cont.*

Clinical Trials ID	Status	Cancer Types	Clinical Significant	Sponsor
Key Findings				
Efficacy (Primary Endpoint): Not met. Only 32% (7/22) of patients were progression-free at 4 months (target was >50%). Median PFS was 2.2 months.				
Overall Survival (OS): Median OS was 15 months.				
Safety: Treatment was well-tolerated. One patient experienced a Grade 3 dose-limiting hepatotoxicity.				
Immunological Response: No MAGE-specific CD8+ T-cell responses were detected. An increase in NKp30-dependent Natural Killer (NK) cell function was observed and was correlated with longer PFS. Clinical benefit was associated with higher levels of the NK ligand BAG6 on the exosomes.				

Source: <https://clinicaltrials.gov/>. (accessed on 17 September 2025)

7. Challenges and Future Prospects

Exosomes research effectively transforms cancer theranostics research. There are still some domains that are developing support for the progression of exosome research. We need to develop a standard isolation procedure with high yield, high purity, and reproducibility. Exosome heterogeneity is one of the complications in exosome research. Multiple factors regulate it, such as exosome origin, size, and molecular diversity [181]. The single-exosome profiling approach (Figure 5) addresses this complexity, thereby facilitating the development of exosome-based biomarkers and advancing precision cancer therapeutics [181]. The multi-omics approach plays a significant role in revealing exosomes' molecular signature. Such high-throughput methods can reveal a global perspective of DEX heterogeneity and define specific subsets, and predict the functional outcome of each subset. This detailed information is critical for defining adequate quality control measures and avoiding the development of unpredictable off-target effects, such as immune activation/autoimmunity, for safe and predictable DEX therapies [106]. Large-scale production is a big challenge for exosome-based translational research and clinical trials. Exosome-based drug delivery overcomes several traditional issues in drug delivery, but in the case of the exosome loading approach, it is still under standardization [182]. Regulation and safety concern frameworks based on exosome-based theranostics are still evolving. Ensuring safety, minimizing immunogenicity, and establishing standard quality control measures are essential before clinical approval. DEX is not able to activate effective T cell-mediated anti-cancer activity; dendritic cell-like DEX cannot migrate to the tumor location; and heterogeneity and standardization challenge, large-scale production and storage, and several clinical trials indicate limited efficiency [183–185]. The development of advanced nanotechnologies for exosome isolation, such as microfluidic and affinity column-based techniques, has enabled the production of high-yield and high-purity preparations [186,187]. DEX-based cancer therapeutics' major limitation is that this approach does not induce sufficient T-mediated anti-cancer immune response [188]. Current research evidence reports that after modifications, DEX has become a promising therapeutic tool for cancer [189]. Exosome-based cancer translational research takes more time for proper clinical trial-based validation. Finally, after overcoming all challenges, exosomes may open a cutting-edge personalized medicine era for cancer.

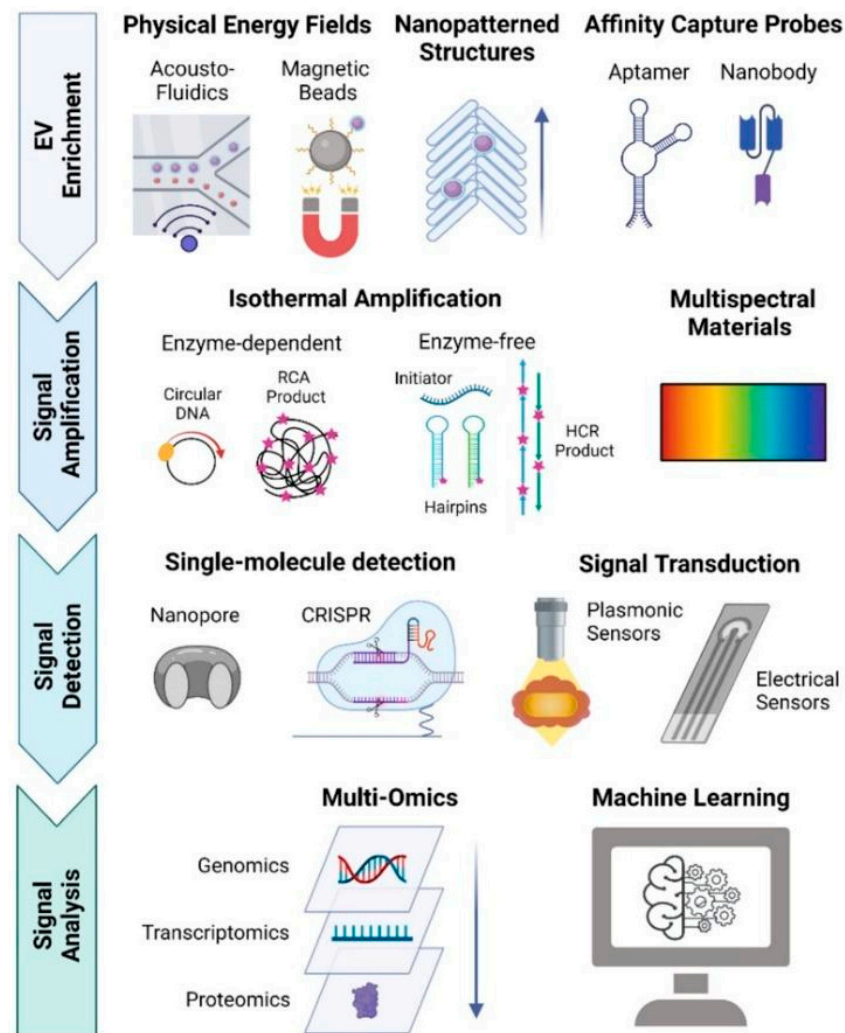


Figure 5. Single exosome profiling approach. (Adapted with permission from ref. [181] Copyright @ 2022 American Chemical Society.)

8. Conclusions

DEXs have emerged as a next-generation platform in cancer immunotherapy, offering a unique, cell-free approach that harnesses the immune-stimulating properties of dendritic cells while addressing the maximum limitations and challenges of conventional DC-based vaccines. With their inherent capacity to present tumor-associated antigens (TAAs), activate T lymphocytes, and modulate the immune microenvironment, DEXs have demonstrated considerable potential to initiate and amplify a robust anti-tumor immune response in both preclinical studies and early-phase clinical trials. Their nano-sized morphology, stability, high biocompatibility, low immunogenicity, and potential for systemic delivery of bio-active molecular cargoes make them an attractive therapeutic tool in the growing field of cancer nanomedicine and personalized immunotherapy. Despite their significant potential, several challenges still limit the clinical translation of DEX-based therapies. One of the major hurdles is the heterogeneity of exosomes themselves, not only among different DC subsets but also due to variations introduced during ex vivo culture and exosome isolation. This heterogeneity impacts therapeutic predictability, targeting specificity, and immune potency. Another major limitation is the lack of standardized, scalable, and reproducible isolation and purification methods. Ultracentrifugation, size-exclusion chromatography, and polymer-based precipitation often yield heterogeneous populations with variable purity, which may affect immunogenic outcomes and make

it difficult to obtain consistent results each time. In addition, antigen-loading strategies remain suboptimal, with limited efficiency in incorporating specific tumor antigens or immune modulators into exosomes without compromising vesicle integrity. On top of that, the pharmacokinetics, bio-distribution, and understanding of the mechanisms of DC-derived exosomes in vivo are not yet fully transparent, which complicates dose optimization and regulatory assessment in the clinical translation stage. Moreover, from an immunological perspective, the tumor microenvironment (TME) constitutes a major barrier by limiting the recruitment and functional activity of exosome-activated immune cells. Tumor-associated immunosuppression, such as the presence of regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and inhibitory cytokines, can blunt DEX-mediated responses. Overcoming these barriers will require synergistic strategies that incorporate DEXs modification with immune checkpoint inhibitors, adjuvants, or TME-modulating agents to design personalized cancer immunotherapy and move one step closer to precision oncology. Looking toward the future outlook, several perspectives are likely to shape the evolution of DC-derived exosome-based cancer immunotherapy. Advances in exosome engineering, including surface modification with targeting ligands, application of click chemistry, membrane fusion techniques, and synthetic biology approaches, may significantly improve antigen loading and immune activation profiles. Integration of CRISPR-based gene editing and nanotechnology could allow for the development of smart, programmable exosomes tailored for specific tumor types or patient immunoprofiles (personalized immunotherapy). Furthermore, multi-omics approaches, including proteomics, transcriptomics, and lipidomics, combined with artificial intelligence (AI) and advanced machine learning (ML) algorithms-based analytic tools, are expected to enhance exosome characterization and predict personalized therapeutic responses with higher precision and accuracy. Most importantly, efforts must also focus on developing Good Manufacturing Practice (GMP) and compliant protocols to ensure large-scale production, quality control, and regulatory acceptance of exosome-based therapies. In conclusion, dendritic cell-derived exosomes represent a promising and adaptable platform for cancer immunotherapy. Despite the existing challenges in scalability, targeting, and regulation, ongoing research and innovation could enable their successful clinical translation in the future. With continued support and collaboration, DEX may soon rise as a beacon of hope, reshaping the landscape of precision immune-oncology with sophistication and precision.

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