International Journal on Science and Technology (IJSAT)
E-ISSN: 2229-7677 ● Website: www.ijsat.org ● Email: editor@ijsat.org

Advances in Dendritic Cell Targeted Delivery System

Dr. C.S. Parameswari[1], Ms. Manapati Manasa[2]

[1]M.pharm., phD, [2]B.pharmacy
Pharmaceutics
Dr.K.V. Subba Reddy Institute of Pharmacy
manapatimanasa055@gmail.com

Abstract

Dendritic cells (DCs) are highly effective antigen-presenting cells (APCs) that play a central role in coordinating both innate and adaptive immune responses. Their activity can be modulated in several ways to strengthen antitumor immunity. Within the tumor microenvironment (TME), DCs initiate antigen-specific T cell responses by processing and presenting tumor-associated antigens (TAAs), while tumor cells counteract this by releasing cytokines, metabolites, and other factors that suppress DC recruitment and function. Multiple DC subsets are present in tumor tissues, each with distinct roles, and understanding these subpopulations provides valuable insight into the potential effectiveness of tumor immunotherapies. Exosomes are nanosized vesicles, typically 30–120 nm in diameter, secreted by all cell types including dendritic cells. They serve key roles in cell-to-cell communication and tissue interaction within the body. Due to their functional properties, exosomes hold promise as biomarkers and therapeutic tools for disease diagnosis, monitoring treatment outcomes, and prognosis. For clinical application on a large scale, essential requirements include efficient, rapid, and low-cost methods that yield high-purity exosomes with reliable characterization, safety, and therapeutic potential. Depending on the sample type, stress conditions, and quantity needed, exosomes can be extracted from diverse sources such as body fluids, solid tissues, or cultured cells using multiple isolation techniques. This review examines current advances in exosome isolation and characterization, highlighting their respective strengths and limitations. Such insights support the selection of suitable separation approaches for different biological samples and promote the integration of exosomes into translational and clinical research, particularly in oncology.

Keywords: Dendritic cells (DCs), antigen presenting cells (APCs), tumor microenvironment (TME), tumor associated antigens (TAAs), tumor immunotherapy, innate immunity, adaptive immunity, cell-to-cell communication, exosomes, nanosized vesicles, biomarkers, therapeutic tools, disease diagnosis, prognosis, Oncology.

1. Introduction

The strategic landscape of modern medicine is shifting from broad, systemic therapies toward highly precise, cell-specific interventions. At the nexus of this revolution is the dendritic cell (DC), which stands as the most potent professional antigen-presenting cell (APC) within the mammalian immune system.

DCs are fundamentally the crucial bridge between the rapid, non-specific innate immune system and the precise, memory-forming adaptive immune system. Their indispensable role is to "sample" the

microenvironment—whether a healthy tissue, a site of infection, or a tumor—and, upon activation, migrate to secondary lymphoid organs. Once there, they present captured antigens to T cells, initiating a robust, antigen-specific immune response. This process determines the difference between an effective defence against pathogens and a damaging attack on one's own body.

Their historical naming comes from the Greek word Dendron (tree) due to their distinctive, long, branched membrane projections. This was first described by Paul Langerhans in 1886, who mistakenly identified the skin-resident DCs (Langerhans cells) as nerve cells. Decades later, the functional context of DCs was definitively established by the seminal work of Ralph M. Steinman and Zanvil A. Cohn in 1973, a discovery that earned Steinman the 2011 Nobel Prize.

The significance of DCs is rooted in their dual, opposing, and vital roles:

* Activating Immunity: Mounting a defensive response against threats like pathogens and cancer.
* Maintaining Immune Tolerance: Preventing autoimmunity, which involves recognizing and not attacking the body's own tissues.

This balancing act has cemented their status as the immune system's "gatekeepers," controlling the delicate equilibrium between defence and self-recognition. The therapeutic goal is to manipulate this balance through targeted delivery systems. This review focuses on two primary delivery modalities: Endogenous nanocarriers (Dendritic Cell-derived Exosomes) and Synthetic nanocarriers.

2. Dendritic Cell Biology, Subsets, and Maturation

DCs originate from pluripotent hematopoietic stem cells in the bone marrow and are strategically distributed throughout the body—in the skin, mucosal linings (lungs, gut), and circulating in the blood as immature forms. The functional complexity of the DC family is based on a constellation of subsets, each with a distinct origin, location, and specialized immunological role.

2.1. Major DC Subpopulations

Modern immunology classifies DCs into main groups based on function and specific molecular markers, moving past the historical categorization by location alone:

* Conventional DCs (cDCs): The most common and potent type, specialized for capturing and presenting antigens to T cells.
  * cDC1 : These cells are highly specialized in cross-presentation. This is the remarkable ability to take up antigens from the external environment (exogenous) and process them for presentation on MHC Class I molecules, a pathway typically reserved for intracellular (endogenous) antigens. This skill is indispensable for activating cytotoxic T lymphocytes (CTLs), making cDC1s critical for anti-viral and anti-tumor immunity.
  * cDC2 : Primarily present antigens via MHC Class II molecules to helper T cells . They are crucial for initiating inflammatory or T-helper-mediated responses, such as Th2 and Th17 responses.
* Plasmacytoid DCs (pDCs): Known as the "natural interferon-producing cells". While they are less effective at T-cell activation than cDCs, pDCs are exceptional at sensing viral infections via Toll-like receptors (specifically TLR7 and TLR9) and are capable of secreting massive amounts of Type I interferons.
* Langerhans Cells (LCs) and Dermal DCs (DDCs): LCs are the resident DCs in the epidermis of the skin. DDCs originate from non-native precursors and play a significant role in cutaneous immune responses, including antigen presentation and phagocytosis.

2.2. The Maturation Process: Immature vs. Mature DCs

DC function is directly tied to their maturation state, which represents a critical switch in their primary role:

* Immature DCs (iDCs): These cells reside in peripheral tissues and are specialized for antigen capture. They employ mechanisms like phagocytosis (eating debris) and pinocytosis (drinking fluid). They express high levels of Pattern Recognition Receptors (PRRs) for sensing threats, but possess low surface levels of MHC molecules and costimulatory molecules. Their default state is oriented toward tolerance induction.

* Mature DCs (mDCs): Maturation is a dramatic transition triggered by encountering pathogen- or danger-associated molecular patterns (PAMPs/DAMPs). Key changes during maturation include:

  * Loss of high-level endocytic capacity.

  * Significant upregulation of MHC molecules and costimulatory molecules CD80,CD86,CD40.

  * Migration to secondary lymphoid organs (lymph nodes).

The mDCs' primary function is T-cell priming and activation, leading to productive, adaptive immunity.

3. Role of Immune Tolerance

The greatest challenge for the immune system is the maintenance of immune tolerance—a state of non-responsiveness to self-antigens—while remaining aggressive toward foreign threats. A failure to maintain this state results in autoimmune diseases. Tolerance is achieved through a sequence of two interconnected mechanisms: central and peripheral tolerance.

3.1. Central Immune Tolerance

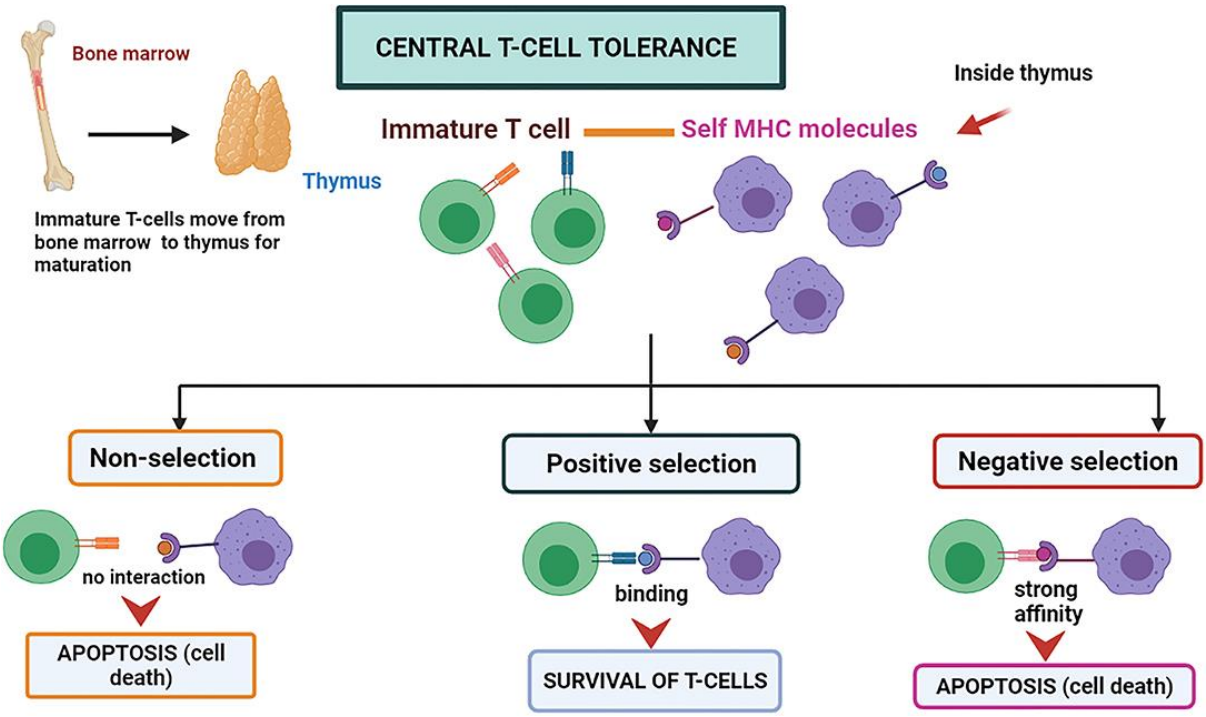
Central tolerance is the primary culling process, occurring in the primary lymphoid organs: the thymus (for T cells) and the bone marrow (for B cells). Immature lymphocytes are rigorously screened for self-reactivity during development.

* T-cell Selection in the Thymus: T cells undergo sequential positive and negative selection.

  * Positive selection ensures T cells can recognize self-MHC molecules; cells that fail this test are eliminated.

  * Negative selection eliminates T cells that bind too strongly to self-antigens presented by thymic epithelial cells. Cells that recognize self-antigens are either discarded or edited to prevent them from maturing into effector cells.

Figure 1 : Central T-Cell Tolerance



3.2. Peripheral Immune Tolerance and Tolerogenic DCs (tol-DCs)

Peripheral tolerance serves as a crucial fail-safe mechanism, operating in the peripheral tissues and lymph nodes to manage any self-reactive T cells that successfully escape the thymus.

This process relies on several key checkpoints:

* Anergy: Rendering self-reactive cells inactive and unresponsive.
* Clonal Deletion: Eliminating autoreactive T cells through activation-induced cell death.
* Suppression by Regulatory T cells (Tregs): Tregs, often identified by the transcription factor FOXP3, actively suppress the activation and proliferation of other effector T cells, representing an active brake on the immune system.

Tolerogenic Dendritic Cells (tol-DCs) are central players in this peripheral control mechanism. They differ from mature DCs in critical ways:

* They maintain an immature or semi-mature phenotype.
* They often display low levels of costimulatory molecules or express inhibitory ligands like PD-L1.

The interaction of a T cell with a tol-DC, in the absence of a strong co-stimulation or "danger" signal, leads to T-cell anergy, deletion, or, most importantly, the induction and expansion of Tregs.

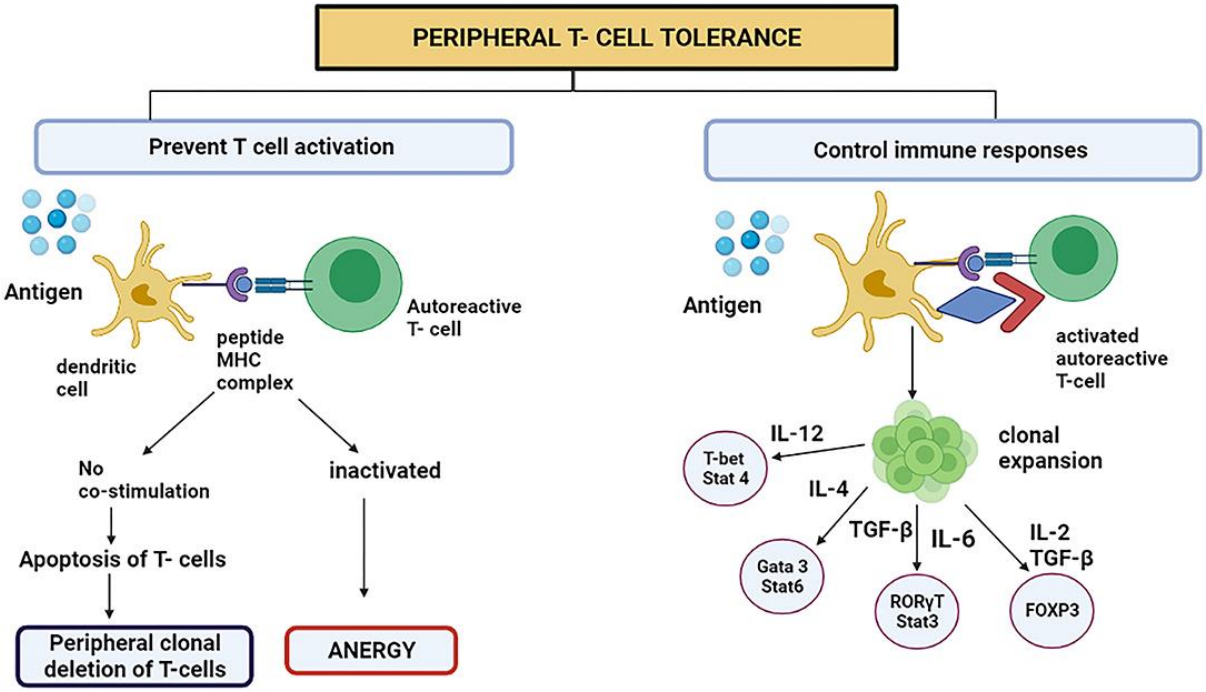


Figure 2: Peripheral T-Cell Tolerance

The strategic goal of DC-targeted therapies in autoimmunity is to precisely induce these tol-DCs in situ (in their natural environment). Nanotechnology-based drug delivery systems offer a potent pathway, enabling the precise and localized delivery of immunosuppressive or tolerogenic signals (like anti-inflammatory cytokines or specific autoantigens) directly to DCs, thereby regulating the antigen-specific immune response efficiently. This targeted approach, in contrast to traditional, broad immunosuppressants, promises to induce specific tolerance and potentially cure underlying diseases without systemic side effects.

4. Exosome Biology: Nature's Nanocarriers for DC Modulation

Understanding targeted delivery systems first requires an appreciation of the natural mechanisms for intercellular communication. Exosomes are nanosized, acellular vesicles, typically 30–150 nm in diameter, secreted by virtually all mammalian cells, including DCs. They are integral to intercellular communication, acting as mobile messengers that transfer a complex molecular cargo—including proteins, lipids, mRNA, and noncoding RNAs (like microRNA)—from a sender cell to a recipient cell.

4.1. Exosome Biogenesis and Composition

Exosomes are uniquely defined by their origin within the cell's endosomal system.

* Endocytosis and Early Endosomes: The process begins with the inward budding of the plasma membrane.

* Late Endosomes and Multivesicular Bodies (MVBs): Early endosomes mature into late endosomes, which then fold inward to form numerous small vesicles within their lumen, known as intraluminal vesicles (ILVs). The entire organelle containing these ILVs is termed a multivesicular body (MVB).

* Release: The final step involves the MVB fusing with the cell's plasma membrane, releasing the ILVs into the extracellular space. At this point, they are officially classified as exosomes. This is a key

distinction from other extracellular vesicles (EVs), such as microvesicles, which bud directly from the cell surface.

The cargo within an exosome acts as a molecular fingerprint of its parent cell and its current state (healthy or diseased). DC-derived exosomes (Dex) are particularly enriched with key immune molecules, including MHC I, MHC II, and costimulatory molecules CD86, CD40 which enables them to directly influence other immune cells. This powerful molecular transfer mechanism makes exosomes attractive as both diagnostic biomarkers and therapeutic tools.

4.2. Functional Role of DC-Derived Exosomes (DC-Exos)

DC-Exos are capable of modulating immunity with high precision, essentially representing a naturally pre-targeted delivery system:

* Immunostimulatory Exos: Exosomes released by mature DCs carry T-cell stimulating factors. They are capable of enhancing anti-tumor immunity by activating T cells and Natural Killer (NK) cells.

* Immunosuppressive/Tolerogenic Exos: Exosomes from tolerogenic or immature DCs can carry inhibitory molecules or specific microRNAs. They promote the development of Tregs or induce T-cell anergy in recipient cells, a mechanism that can be specifically leveraged to treat autoimmune conditions.

Due to their intrinsic functional properties and excellent biocompatibility, exosome-based therapies are a major focus in translational and clinical research, especially in oncology, evidenced by over 400 ongoing clinical trials globally.

5. Exosome Isolation and Purification Methodologies

The clinical translation of exosome research hinges critically on the ability to efficiently isolate highly pure, functional vesicles at a scalable capacity. The complexity of exosome isolation arises because they are nanosized and have a low buoyant density, making their separation from complex biological materials (proteins, lipoproteins, other EVs) a significant technical hurdle.

The choice of isolation technique depends on the source (body fluid, tissue, or culture supernatant), the required purity, and the final clinical or research application.

5.1. Sample Pre-processing: Biological Sources

Regardless of the final isolation method, initial pre-processing is essential to remove large debris and cells.

* Cell Culture Models: These offer a controlled environment, but the use of chemically defined media is crucial to prevent contamination from serum-derived vesicles. Cultures are typically subjected to low-speed centrifugation (e.g., 300\times g and 2,000\times g) to pellet cells and large debris.

* Blood (Plasma/Serum): Blood is frequently used, but pre-analytical variables are critical. Plasma is generally favored over serum because the clotting process used for serum collection can cause platelet aggregation and the massive release of platelet-derived vesicles, contaminating the exosome sample. Managing the choice of anticoagulant is also necessary to prevent unintended platelet activation. The primary challenge here is the immense ratio of lipoproteins and proteins to small EVs, which complicates purification immensely.

* Solid Tissue: Isolating EVs from solid tissues (e.g., tumors) requires gentle mechanical disruption and often enzymatic treatment (e.g., collagenase) to free the vesicles from the complex extracellular matrix, followed by sequential centrifugation to remove cellular components.

5.2. Detailed Isolation Techniques

Current methods are categorized based on the separation principle they employ: size, density, charge, or membrane affinity.

5.2.1. Ultracentrifugation Techniques (UC)

UC has historically been considered the gold standard and remains the most widely used technique, relying on the sedimentation rate of particles based on their size and density.

* Differential Ultracentrifugation (DUC): This involves a stepwise series of increasing centrifugal force. Initial low-speed spins sequentially pellet contaminants (cells, apoptotic bodies, large vesicles), followed by an extremely high-speed spin (100,000–150,000\times g) to pellet the exosomes.

* Pros: Inexpensive, scalable for large volumes 1–25ml, and chemical-free.

* Cons: Labor-intensive (up to 12 hours), prone to co-isolation of contaminating proteins, and the high shear forces can cause exosome aggregation and structural damage, leading to yield loss.

* Density Gradient Ultracentrifugation (DGUC): Also known as isopycnic ultracentrifugation, this method separates particles solely based on their buoyant density using layered media (like sucrose or iodixanol). Exosomes migrate until they reach a position matching their density typically 1.10–1.21 g/ml.

* Pros: Yields the highest purity of all UC methods, effectively resolving exosomes from protein complexes that share a similar size but have different densities.

* Cons: Extremely time-consuming (up to 24 hours), very labor-intensive due to complex gradient preparation, and generally results in lower yield, making it less suitable for large-scale clinical application.

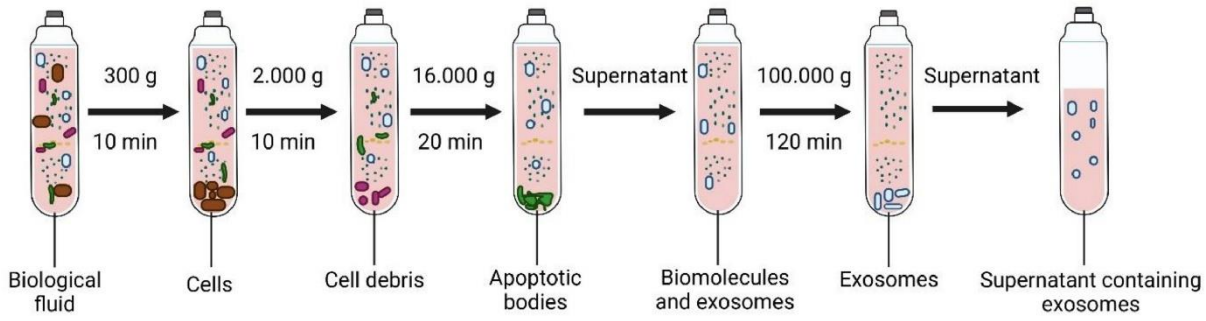


Figure 3: Ultracentrifugation Technique

5.2.2. Size-Based Techniques

These methods exploit the size difference between exosomes 50–150nm and other contaminants.

* Size Exclusion Chromatography (SEC): Considered the mildest technique, SEC (or gel filtration) separates particles by their hydrodynamic radius as they pass through a column packed with porous resin. Larger exosomes bypass the pores and elute quickly, while smaller molecules, like proteins, penetrate the pores and elute slowly.

* Pros: Preserves vesicle structure and biological activity well, is rapid (10–20 minutes), reproducible, and effective at removing protein contaminants.

* Cons: Cannot distinguish exosomes from other similarly sized EVs or protein aggregates (lower purity), often requires an additional concentration step (e.g., ultracentrifugation) post-separation, and columns can be expensive.

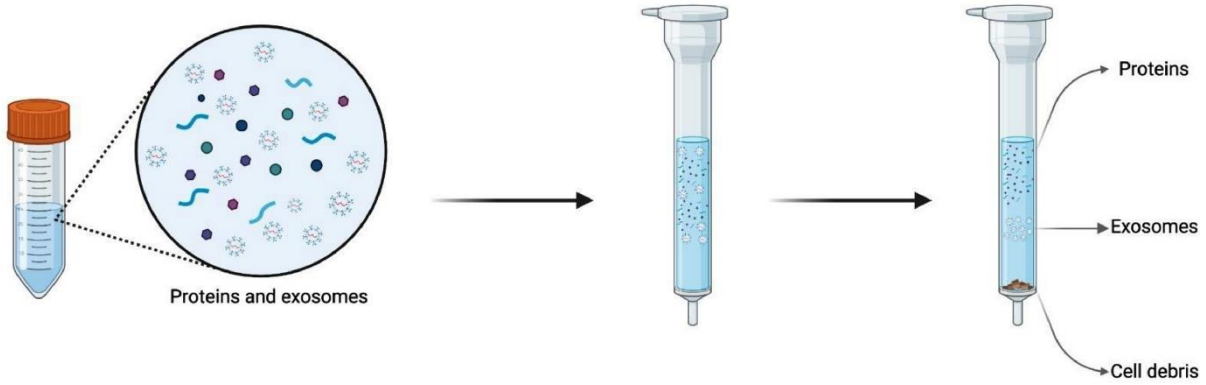


Figure 4: Size Exclusion Chromatography

* Ultrafiltration (UF) and Variants (TFF): UF uses membranes with defined molecular weight cutoffs (MWCO) to separate components by size and molecular weight.

* Pros: Simpler, quicker, and requires less specialized equipment than UC.

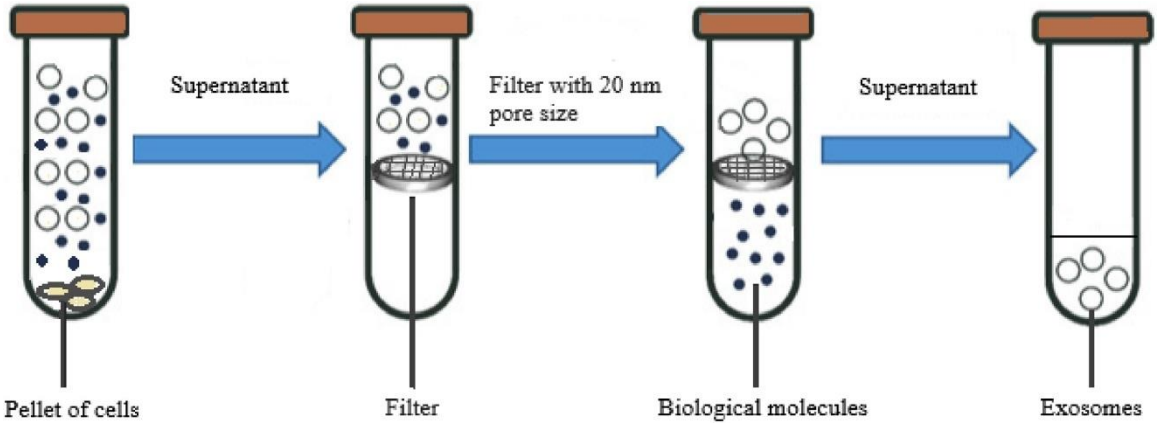
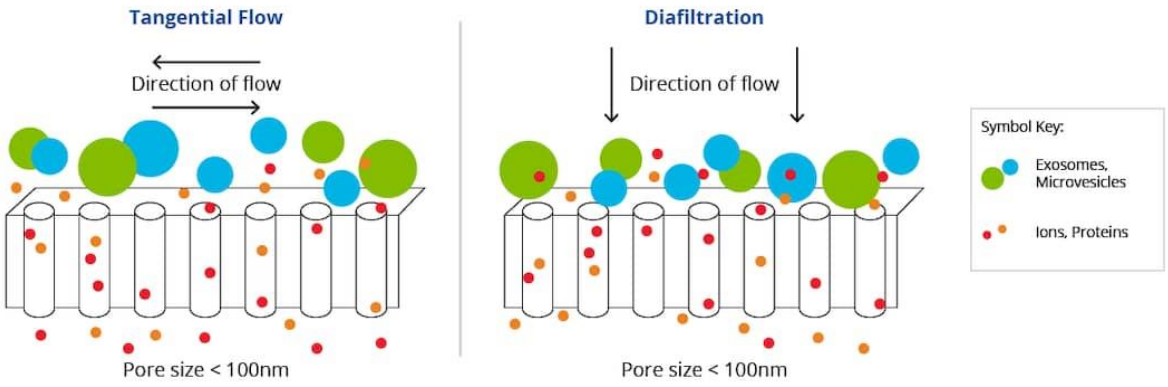


Figure 5 : Ultrafiltration Technique

* Tangential Flow Filtration (TFF): A superior variant where the flow is directed tangentially across the membrane. This minimizes membrane clogging and shear stress, making it gentler and more scalable than traditional dead-end filtration.

* Cons: Traditional UF risks exosome damage from shear stress and contamination with smaller molecules

Figure 6 : Tangential Flow Filtration



5.2.3. Immunoaffinity-Based Capture (IAC)

IAC uses antibodies or affinity ligands immobilized on magnetic beads to specifically bind to target proteins (e.g., CD9,CD63, CD81) found on the exosomal membrane.

* Pros: Offers the highest specificity, allowing for the selective isolation of defined exosome subpopulations (e.g., only tumor-derived or DC-derived exosomes expressing a specific marker).

* Cons: Very low overall yield, high cost due to the reliance on antibodies, time-intensive (requires extended incubation times), and can only capture the specific subpopulation carrying the targeted marker. Newer approaches using temperature or pH-responsive magnetic nanoparticles are being explored for faster capture.

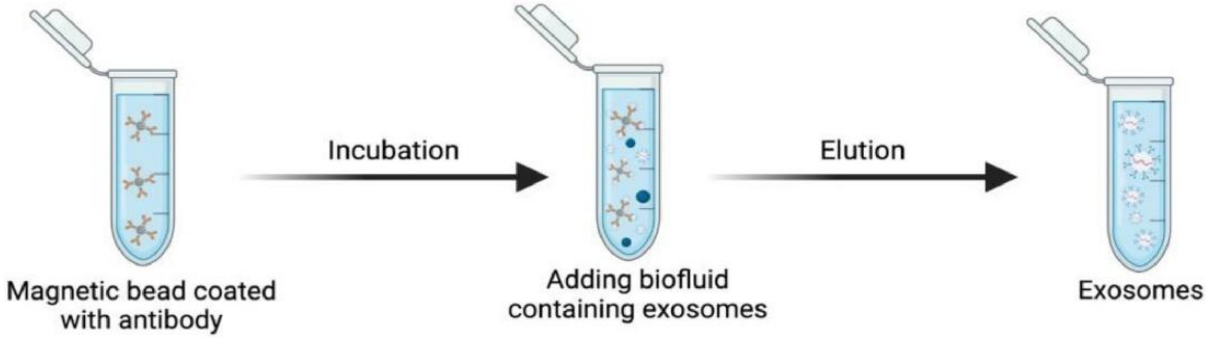


Figure 7 : Immunoaffinity Based Capture

5.2.4. Precipitation Techniques (PEG)

Polyethylene glycol (PEG) is the most common agent, utilizing its hydrophilic properties to sequester water. This reduces the solubility of vesicles, causing them to precipitate out of the solution.

* Pros: Simple, rapid, and requires no specialized equipment, making it highly attractive for commercial kits and clinical research. Offers significantly higher yields than centrifugation.

* Cons: Suffers from the lowest purity, as it co-precipitates massive amounts of non-exosomal proteins and polymer residues. This contamination can severely interfere with sensitive downstream analysis, such as proteomics.

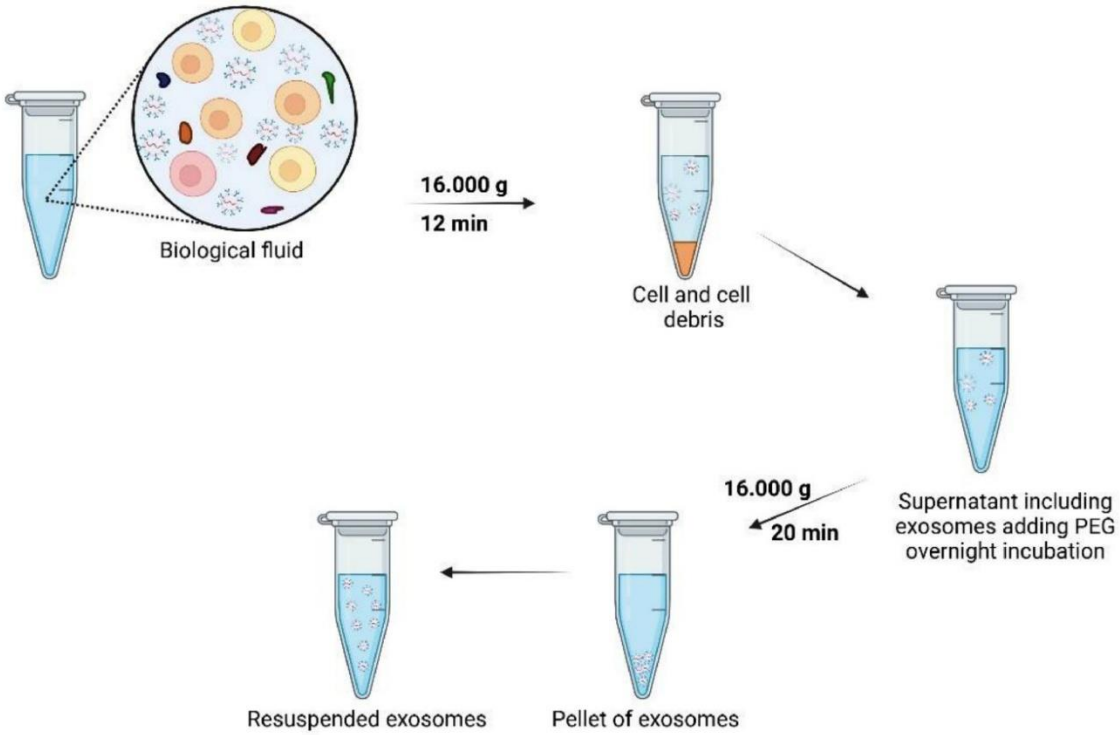


Figure 8 : Precipitation Technique

6. Advances in DC-Targeted Nanoparticles: Synthetic Delivery Systems

While DC-Exos are the immune system's intrinsic biological nanocarriers, synthetic nanoparticles (NPs) offer a fully tunable platform for delivering precise therapeutic payloads. The central goal of these systems is to engineer NPs that selectively and efficiently internalize into DCs over other cell types, leading to a predictable and robust immune outcome.

6.1. The Mechanism of Targeted Delivery

The strategy for synthetic targeting is to exploit the DCs' natural biology. DCs possess a rich surface repertoire of Pattern Recognition Receptors (PRRs) and C-type Lectin Receptors (CLRs) which they utilize to "sample" the environment, making these receptors ideal targets for nanotechnology-based functionalization.

6.2. Common Synthetic Nanocarriers

6.2.1. Liposomes and Lipid Nanoparticles (LNPs)

Liposomes are self-assembling spherical vesicles composed of a lipid bilayer. Lipid Nanoparticles (LNPs), including the revolutionary systems used in COVID-19 vaccines, are the gold standard for therapeutic delivery.

* DC Targeting: Liposomes can be functionalized by incorporating mannosylated lipids or attaching anti-DEC-205 antibodies to their surface. This functionalization dramatically increases their uptake by DCs via receptor-mediated endocytosis, successfully bypassing less efficient internalization mechanisms.

* Payloads: They are ideal for delivering hydrophobic drugs, antigens (proteins, peptides), and nucleic acids . The encapsulation protects the delicate payload from degradation and facilitates endosomal escape—a critical step for vaccines to access the cell’s protein synthesis machinery and be translated.

6.2.2. Polymeric Nanoparticles

These are constructed from biocompatible and biodegradable polymers, such as PLGA (Poly(lactic-co-glycolic acid)) and Chitosan. This material choice allows for precise control over the NP's size, surface charge, and degradation rate.

* Immune Modulation: Chitosan, being positively charged, can act as an adjuvant itself, actively stimulating DCs. Nano particles are commonly used to deliver tumor antigens, and their slow degradation provides sustained antigen release, leading to prolonged DC stimulation.

* Tolerogenic NPs: In the context of autoimmune therapy, polymeric NPs can be loaded with autoantigens and tolerogenic molecules and engineered to target tol-DCs. This active strategy promotes the formation of Tregs specific to the autoantigen, effectively reversing the autoimmune attack.

6.2.3. Metal and Inorganic Nanoparticles

NPs made from materials like gold, iron oxide, or silica offer unique physicochemical properties.

* Gold Nanoparticles (AuNPs): Their surface is easily functionalized with both antigens and adjuvants. AuNPs are readily internalized by DCs and can be designed to release their payload only under specific intracellular conditions (e.g., the low pH environment of the endosome).

* Iron Oxide Nanoparticles: Primarily used for imaging (Magnetic Resonance Imaging, MRI), they can also be functionalized to target DCs. This allows researchers to track the migration and destination of antigen-loaded DCs in vivo, providing vital mechanistic data for treatment optimization.

7. Clinical and Translational Applications

The ability to precisely target and modulate DCs opens up three major therapeutic frontiers in medicine: cancer immunotherapy, autoimmune disease treatment, and infectious disease vaccination.

7.1. DC-Targeted Systems in Cancer Immunotherapy

The tumor microenvironment (TME) is often highly immunosuppressive, actively hindering effective DC function and anti-tumor immunity. DC-targeted NPs and DC-Exos are specifically designed to overcome this suppression.

* Antigen Delivery for Vaccines: The most direct application is using DC-targeted NPs to deliver tumor-associated antigens (TAAs) and potent adjuvants directly to cDC1s. This ensures efficient cross-presentation and the priming of highly destructive cytotoxic T lymphocytes (CTLs) against the tumor.

* Exosome-Based Vaccines: Exosomes loaded with TAAs (either naturally expressed by tumor cells or engineered into the parent DC) have emerged as cell-free vaccines. They present the antigens in a highly immunogenic format, promoting anti-tumor immunity without the need for ex vivo cell handling, which significantly simplifies the manufacturing process.

7.2. Inducing Tolerance for Autoimmune Diseases and Transplant Rejection

For conditions like Type 1 Diabetes, Multiple Sclerosis, and Rheumatoid Arthritis, the therapeutic goal is to safely and specifically shut down the self-reactive immunity that is causing the disease.

* Engineering Tolerogenic DCs (tol-DCs): NPs are loaded with the specific autoantigen (the target of the autoimmune attack) and an immunosuppressive payload (e.g., {IL-10} or a specific microRNA). This payload is then specifically delivered to DCs, aiming to reprogram the DC into a tolerogenic phenotype(in situ). The ultimate outcome is the deletion or anergy of the self-reactive T cells and the expansion of protective Tregs. This approach is considered the most promising pathway toward a cure, as it targets only the problematic T-cell clone while preserving the integrity of the rest of the immune system’s function.

7.3. Next-Generation Infectious Disease Vaccines

The tremendous success of LNP-based mRNA vaccines has undeniably highlighted the power of targeted DC delivery.

* The LNP encapsulates the mRNA, protecting it from nucleases until it is endocytosed by DCs.
* Once inside, the mRNA is translated into the pathogen's antigen, which is then highly presented to T and B cells, generating a potent and lasting memory response.

Future vaccines are focused on further refining the LNP formulation or coating to specifically target high-potency subsets like cDC1s to generate superior T-cell immunity.

8. Exosome Characterization and Quality Control

Rigorous characterization of isolated extracellular vesicles (EVs) is essential for high-quality research and clinical translation. The International Society for Extracellular Vesicles (ISEV) has established the Minimum Information for Studies of Extracellular Vesicles (MISEV) guidelines to standardize reporting in the field.

8.1. Essential Characterization Techniques

A comprehensive characterization generally involves three key areas:

* Morphology and Size Distribution:
  * Nanoparticle Tracking Analysis (NTA): This technique determines the size distribution and concentration of the vesicles in the solution, confirming they fall within the exosome range (e.g., 50–150 nm).
  * Transmission Electron Microscopy (TEM) and Atomic Force Microscopy (AFM): These methods provide high-resolution visual confirmation of the exosomal morphology, typically a cup-shaped or spherical membrane structure.
* Biochemical Markers:
  * Western Blotting: This technique is used to confirm the presence of established exosomal protein markers.
    * Positive Markers: Include tetraspanins (CD9}, CD63, CD81) and cytosolic proteins (ALIX, TSG101).
    * Negative Markers: Confirmation of the absence of cellular contamination markers (e.g., Calnexin, a marker for the endoplasmic reticulum) is required to ensure sample purity.
* Functional Assays: The isolated EVs must ultimately be proven to retain the function of their parent cell. For example, a DC-Exo should be able to modulate T-cell proliferation or cytokine release in vitro.

9. Conclusion and Future Outlook

Dendritic cells are the undisputed decision-makers of the immune system. The rapid development of sophisticated delivery systems—both natural (exosomes) and synthetic (nanoparticles)—has brought the promise of cell-specific immune modulation into tangible clinical sight. DC-targeted delivery enables the precise engineering of immunity: provoking a potent anti-tumor response in oncology or safely re-establishing self-tolerance in autoimmune diseases.

Despite the significant strides made, key challenges remain, particularly in the clinical translation of exosomes:

* Manufacturing and Scale-Up: Isolating high-purity exosomes at the consistent scale required for clinical trials is demanding, largely due to the limitations of established methods like differential

ultracentrifugation. Advances in TFF and microfluidics are critical for achieving high-throughput, standardized isolation.

* Purity and Contamination: High-yield, simple methods like precipitation suffer from substantial co-precipitation of contaminating proteins that complicate regulatory approval and downstream analysis. Rigorous adherence to guidelines is non-negotiable for advancing the field.

* Targeting Specificity: For synthetic NPs, the next frontier is improving the specificity of ligands to target only the most potent DC subsets (e.g., only cDC1s for a cancer vaccine).

Despite these hurdles, the research landscape is robust, with DC-based therapies already showing encouraging results in clinical trials for conditions ranging from breast cancer to organ transplant rejection. As researchers continue to refine both the targeting mechanisms and the manufacturing of these next-generation delivery platforms, the therapeutic potential of harnessing the immune system's master regulator—the dendritic cell—is poised to reshape the landscape of clinical medicine.

References :

1. Steinman RM, Cohn ZA. Identification and functional studies of dendritic cells. Digital Commons @ RU; 1973.
2. Dendritic Cells- Definition, Structure, Immunity, Types, Functions [Internet]. Microbe Notes. 2022 Sep 16 [cited 2025 Oct 4].
3. Steinman RM, Cohn ZA. Identification of a novel cell type in peripheral lymphoid organs of mice. J Exp Med. 1973;137(5):1142-1162.
4. Steinman RM. The dendritic cell system and its role in immunogenicity. Annu Rev Immunol. 1991;9:271-296.
5. Langerhans P. [Original description of epidermal cells] (Translated). 1886.
6. Sprent J, Kishimoto H. The thymus and central tolerance. Immunol Rev. 2001 May;182:15-27. doi: 10.1034/j.1600-065x.2001.1820102.x.
7. Griesemer AD, Apostolou I, Thuille N, von Boehmer H. The role of the thymus in tolerance. J Immunol. 2010 Sep 14;185(6):3067-75.
8. Kowal J, Tkach M, Théry C. Biogenesis and secretion of exosomes. Curr Opin Cell Biol. 2014;29:116-125.
9. Théry C, Zitvogel L, Amigorena S. Exosomes: composition, biogenesis and function. Nat Rev Immunol. 2002;2(8):569-579.
10. Choi DS, Kim DK, Kim YK, Gho YS. Proteomics, transcriptomics and lipidomics of exosomes and ectosomes.Proteomics. 2013;13(10-11):1554-1571.
11. Helwa I, Cai J, Drewry MD, et al. A comparative study of serum exosome isolation using differential ultracentrifugation and three commercial reagents. PLoS One. 2017;12(1):e0170628.
12. Tai Y, Zhang X, Gao S, et al. Targeted dendritic cell delivery of PLK1-siRNA induces anti-tumor immunity and synergizes with checkpoint blockade immunotherapy in a mouse melanoma model. Nat Commun. 2020;11(1):4349.
13. Valadi H, Ekström K, Bossios A, Sjöstrand M, Lee JJ, Lötvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat Cell Biol. 2007;9(6):654-659.
14. Yang T, Martin P, Fogarty B, et al. Exosome delivered anticancer drugs across the blood-brain barrier for brain cancer therapy in Danio rerio. Pharm Res. 2015;32(6):2003-2014.

15. de Moura IA et al. Advances in vaccine delivery via exosome functionalization to target dendritic cells. 2025 .
16. Anguille S et al. Clinical use and challenges of dendritic cell vaccines for cancer therapy. Lancet Oncol. 2014.