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Strategies of designing lymph nodes-targeting nanoparticles for cancer immunotherapy

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ABSTRACT

Lymph nodes (LNs), as specialized secondary lymphoid organs with highly organized micro-architecture containing various immune cells, play a pivotal role in antigen presentation and immune cell activation. Compared to traditional immunotherapy delivery methods, LN-targeted delivery demonstrates greater effectiveness in modulating the immunosuppressive environment within tumor-draining lymph nodes (TDLNs), thereby activating anti-cancer immunity, and reducing potential systemic side effects. This review summarizes various types of LN-targeted nanoparticles (NPs) and factors influencing targeting efficiency as well as outlining recent advances in LN-targeted immunotherapeutic agents. It is expected that this review will provide a comprehensive understanding of the current research landscape and emerging trends in this field, offering guidance for future studies.

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1. Introduction

Cancer remains a significant threat to human health, posing challenges to effective treatment [1]. While conventional approaches like chemotherapy and radiotherapy can kill cancer cells, they frequently harm healthy cells, leading to severe side effects [2–4]. Immunotherapy, on the other hand, harnesses the body's own immune system to target and eliminate cancer cells, offering a more precise and durable treatment option [5,6]. Despite its promise, the overall success rate of immunotherapy remains modest, with response rates below 30 % for most cancers [7,8]. For instance, while it has shown remarkable outcomes in treating melanoma, its effectiveness in combating solid tumors like pancreatic and prostate cancers is limited [9]. Furthermore, the complexity of the immune system introduces the risk of immune-related adverse events (irAEs), affecting approximately 40 % of patients [10–14]. These adverse effects, often caused by overactive T cells and loss of immune tolerance, pose a critical barrier to the success of immunotherapy [14,15]. As noted by Keam *et al.*, improving the specificity of immune checkpoInt. inhibitors (ICIs) is essential to reducing these adverse effects and optimizing therapeutic outcomes [15].

Cancer immunotherapy represents a paradigm shift from traditional cancer treatments by leveraging the immune system to target and eliminate cancer cells (Fig. 1) [16,17]. In recent decades, it has gained prominence as an alternative that addresses the limitations of conventional therapies, such as high cytotoxicity, poor control over metastatic cells, and high recurrence rates [5,6]. Immunotherapy methods, including ICIs, chimeric antigen receptor (CAR)-T cell therapy, and tumor vaccines, have demonstrated considerable promise [17,18]. ICIs are monoclonal antibodies that block inhibitory checkpoInt. molecules on tumor or T cells, reactivating anti-tumor immunity by enhancing immune surveillance (Fig. 1E) [19]. The key target receptors, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed cell death ligand 1 (PD-L1), normally regulate T cell activity to maintain immune homeostasis [20]. CAR-T cell therapy involves the genetic engineering of T cells to recognize and specifically target tumor cells (Fig. 1F) [10,21]. Cancer vaccines introduce antigens or immunostimulatory agents to train the immune system

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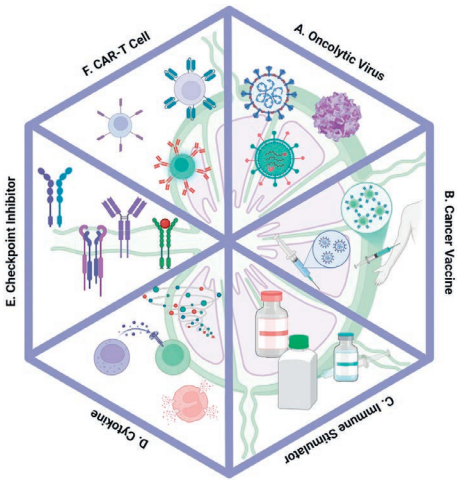


Fig. 1. Strategies in cancer immunotherapy.

to identify and eliminate cancer cells (Fig. 1B) [22,23]. Other immunotherapy approaches include oncolytic viruses, immune stimulators and cytokines (Figs. 1A, C and D). While immunotherapy has shown efficacy in treating some tumor types, challenges such as therapeutic resistance and immune-related side effects persist [3,4].

A key mechanism of immunotherapy involves reactivating exhausted T cells to boost anti-cancer responses and counteract tumor induced immunosuppression [24]. However, the tumor microenvironment (TME) is highly immunosuppressive, characterized by abundant immunosuppressive cells, hypoxia, and checkpoInt. molecules (*e.g.*, PD-L1), all of which collectively impair T cell function. Consequently, attempts to reactivate exhausted T cells within this context often yield sub-optimal results, which can lead to reduced therapeutic efficacy [24]. Given the challenges of reinvigorating exhausted T cells within the immunosuppressive TME, recent sights have shifted toward targeting lymph nodes (LNs)-key sites for early immune activation-where naïve T cells can be primed before encountering the tumor. Strategies can be divided into intranodal injection, antibody-mediated cell targeting, albumin-mediated targeting, *etc.* [25]. As key secondary lymphoid organs, LNs are essential for priming, proliferating and differentiating T cells, making them critical for mounting an effective anti-cancer immune response [26,27]. Within the LNs, antigen-presenting cells uptake and present tumor antigens to naïve T cells, which are subsequently activated and migrate to the tumor site to exert their effects [27]. Compared to reactivating exhausted T cells within the TME, modulating naïve or early-differentiated T cells within the LNs allows for the initiation of anti-tumor responses at an earlier stage [24]. Qu and his team use hydrogel-based electroporation system (hydro-EP) for *in vivo* gene editing, thereby constructing PD1-deficient T cells within LNs [28]. The engineered T-cells, which are deficient in PD1, infiltrate the tumors and contribute to tumor growth suppression, metastasis prevention, and improved survival in animal models. Overall, targeting LNs not only enhances therapeutic outcomes but also may reduce systemic side effects.

The rapid advancement of nanotechnology has introduced novel strategies for targeting tumor-draining lymph nodes (TDLNs) in cancer immunotherapy [8,29]. Nanocarriers have been widely explored as delivery platforms, with recent advances significantly improving their ability to target TDLNs [30,31]. Nanoparticles (NPs) have several advantages over traditional drug delivery methods (such as solutions), including high payload capacity, good biocompatibility, and customizable surface properties [30]. With surface modification and functionalization, NPs can be engineered to specifically target immune cells in TDLNs [29,32]. Moreover, targeted delivery by NPs is also promising for ensuring a higher concentration at the target site while minimizing systemic distribution [33], thereby reducing immune-related adverse effects, such as cytokines release syndrome and irAEs [13].

This review aims to systematically illustrate the characteristics and advantages of NPs on current targeted LN-delivery studies, while categorizing the present progress on NPs modulating immune cells in TDLNs. By comprehensively analyzing experimental studies focused on LN-targeted immune cell modulation, we aim to provide a reference framework for future research on NPs in targeted cancer immunotherapy.

2. Anatomical structure and physiology of LNs

LNs are oval or kidney-shaped secondary lymphoid organs [26]. The human body contains approximately 500–600 LNs, many of which are found in concentrated clusters at specific anatomical sites [34,35]. LNs initiate and regulate antitumor immunity by gathering diverse immune cell types [36]. Their intricate structure is designed to coordinate immune responses, ensuring that B and T lymphocytes are compartmentalized appropriately while facilitating interaction between effector and other immune cells [26,37].

LNs are encapsulated in connective tissue made mainly of collagen fibers, with elastic fibers and occasional smooth muscle cells [38]. Connective tissue projections radiate from the outer layer capsule into the node to form trabeculae [26]. The trabecular sinuses divide various sections within the LNs which correspond to the entry poInt. of an afferent lymphatic vessel or its terminal branches into the subcapsular sinus (Fig. 2A) [39,40].

LNs consists of the cortex and medulla. The cortex is mainly composed of the superficial cortex, paracortex, and the cortical lymphatic sinuses [36,41]. The superficial cortex contains lymphatic follicles and diffuse lymphoid tissue between the follicles, which composes much B cells. Paracortex consists of larger areas of diffuse lymphoid tissue, enriched with T cells and high endothelial venules, and is thus referred to as the thymus dependent zone [42]. The cortical lymphatic sinuses can be further divided into the subcapsular sinus and the peri-trabecular sinuses, which communicate with the medullary sinuses. The lining of the lymphatic sinuses are lined with flattened endothelial cells, supported by stellate endothelial cells that maintain the sinus lumen [39]. The parenchyma of LNs is divided into medullary cords and medullary sinuses. The medullary cords primarily consist of lymphocytes, with macrophages and plasma cells also present.

In LNs, lymph fluid enters the subcapsular sinus *via* the afferent lymphatic vessels. Some lymph infiltrates the cortical lymphoid tissue and subsequently enters the medullary sinuses, while others flows directly into the medullary sinuses *via* the peritrabecular sinuses, eventually draining through the efferent lymphatic vessels.

Each LN contains a network of lymphatic sinuses connected to a parenchyma composed of reticular fibers, fibroblastic reticular cells (FRCs), specialized vasculature, and various immune cells [42]. Specific phenotypes of macrophages within the sinuses are responsible for eliminating microbes and their by-products [43,44]. Lymphatic endothelial cells (LECs) line each sinus, forming a barrier between lymph and parenchymal compartment [42].

A portion of the NPs enter the subcapsular sinus through the afferent lymphatic vessels, which in turn infiltrate the cortex [42]. Another portion of NPs enters the paracortex zone through the postcapillary venule. When NPs enters the medullary cords, where plasma cells, B cells, and macrophages homes, NPs localize depending on their surface characteristics [45,46]. These distribution patterns are critical for the success of targeted drug delivery and diagnostic applications. Intratympanic or local adminis-

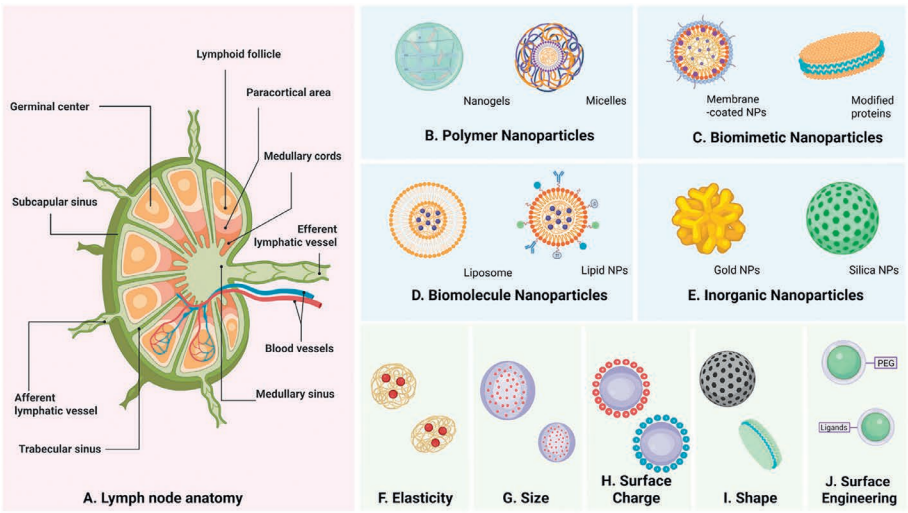


Fig. 2. Anatomical structure of LNs and classification of nanocarriers.

trated nanocarriers specifically accumulate in LNs *via* the phagocytosis uptake mechanism. In contrast, nanocarriers without specific surface modifications do not exhibit lymphotropism and rely on tissue penetration and lymphatic drainage for transportation to LNs [47]. Studies have identified several factors influencing lymphotropism, including small size, modified surfaces (*e.g.*, lipid bilayers), and negative surface charge [47].

LNs are pivotal in initiating and sustaining anticancer immune responses, serving as central organs in the immune system [48–50]. Effective immune responses against tumors are orchestrated through the cancer-immunity cycle, which proceeds iteratively through several key stages [16,20,51]. Initially, tumor antigens are released and subsequently processed and presented by antigen-presenting cells (APCs). Dendritic cells (DCs) transport antigens from peripheral tissues to the LNs, where they present these antigens to T cells [52,53]. This antigen presentation primes and activates immune effector cells, leading to the generation of memory cells. Secondary lymphoid organs, particularly LNs, are critical sites for lymphocyte priming [27]. B cells in the sentinel LNs can process and present tumor antigens to activate effector T-cell responses [54]. Subsequently, T cells migrate and infiltrate tumor tissues, where they recognize and destroy cancer cells. The destruction of cancer cells releases more tumor-associated antigens, initiating another round of immune activation and amplifying the scope and intensity of subsequent immune responses [16].

3. Significance of LNs in tumor immunotherapy

In the mammalian immune system, TDLNs serve as critical hubs for immune coordination, where they facilitate the proliferation of antigen-activated T cells and orchestrate immune cell interactions [18,32,36]. While traditionally regarded as centers for antitumor immune responses, emerging evidence suggests TDLNs may also play paradoxical roles in tumor immunity. On one hand, they are essential for initiating anti-tumor immunity and modulating responses to immunotherapy [19,55,56]. Notably, studies in head and neck squamous cell carcinoma mouse models demonstrate that conventional type I DCs and type I interferon (IFN) signaling upregulation in TDLNs are crucial for ICIs effectiveness [57]. On the other hand, some studies propose that TDLNs may simultaneously foster tumor-immune tolerance, possibly through mechanisms that remain to be fully elucidated [58]. This functional duality positions TDLNs as both launchpads for antitumor responses and potential barriers to complete tumor eradication. The therapeutic implications are significant: ICIs exert their effects by reactivating T cells that originate in TDLNs before infiltrating the TME, suggesting that targeted modulation of TDLNs function could enhance immunotherapy outcomes [59].

4. Characteristics and classifications of nanocarriers for LN delivery

4.1. Factors affecting the efficiency of NPs delivery to LNs

The efficacy of drug delivery is significantly influenced by the administration route. Research demonstrates that NPs can achieve LNs targeting through strategic selection of injection sites (*e.g.*, subcutaneous, intramuscular, or intramuscular) [60].

While intranodal injection represents the most direct approach for achieving optimal drug accumulation in LNs, the deep-seated location of most LNs necessitates sophisticated guidance systems (*e.g.*, ultrasound imaging or dye tracing) for accurate administration [29,61]. Furthermore, the limited volumetric capacity of LNs imposes strict constraints on injectable doses [62]. Despite these limitations, the unparalleled targeting precision of intranodal delivery maintains its relevance in cancer immunotherapy. A representative example includes Josi *et al.*'s work, where post-surgical administration of virus-like particles (VLPs) into LNs triggered potent immune activation in murine models, effectively suppressing tumor recurrence [63].

The subcutaneous (s.c.) and intramuscular (i.m.) routes are widely used for LN-targeted drug delivery due to their high vascular and lymphatic capillary density, which facilitates efficient uptake by APCs [64,65]. These administration methods are preferred for their ease of injection and well-developed lymphatic drainage, making them suitable for NP-based drug delivery. However, NPs delivered *via* s.c. or i.m. routes primarily rely on passive lymphatic drainage, which lacks TDLN-specific targeting [66]. Additionally, physiological factors such as age, disease state, and lymphatic function can significantly influence drainage efficiency, leading to variable drug delivery outcomes.

Intravenous administration enables LNs targeting through two distinct mechanisms [67]. The conventional pathway requires NPs to traverse multiple biological barriers: After entering systemic circulation, particles must extravasate across vascular endothelium into interstitial spaces before being drained by lymphatic vessels, a process with inherently low efficiency due to sequential barrier penetration [68]. Alternatively, specialized high endothelial venules

(HEVs) in LNs provide direct access [69]. 100-nm NPs functionalized with MECA-79 antibodies can achieve efficient LNs homing by specifically binding to 6-sulfo sialyl Lewis X glycans expressed on HEV surfaces. Current clinical applications of intravenous LNs targeting are limited, primarily focused on managing LNs metastases, reflecting the technical challenges of systemic delivery [70].

Oral administration remains the preferred clinical route due to its unparalleled convenience, patient compliance, and dosing flexibility [68]. Current strategies for oral lymphatic targeting primarily exploit two physiological pathways: Chylomicron-mediated transport: Lipid-based formulations (*e.g.* nano-emulsions, solid lipid NPs (LNPs)), M-cell targeting: Specialized microfold cells (M-cells) in Peyer's patches actively transport particulate antigens to gut-associated lymphoid tissue (GALT), initiating immune responses [71–73].

This mechanism has been extensively explored for oral tumor vaccines, with attenuated bacterial vectors (*e.g.*, salmonella) showing particular promise for GALT delivery [74]. Hu *et al.* developed an oral DNA vaccine system using attenuated Salmonella coated with DNA-loaded polymeric NPs [75]. The bacterial vector's natural tropism for Peyer's patches facilitated targeted delivery. However, quantitative analyses revealed that less than 1% of administered NPs reach lymphatic tissues, underscoring the critical need for specialized delivery vehicles.

4.1.1. Size

The particle size represents a critical determinant for lymphatic drug delivery efficiency (Fig. 2G). For intravenous injection NPs smaller than 10 nm are typically cleared by the kidneys, whereas those larger than 100 nm may activate the reticuloendothelial system and are rapidly cleared by the liver and spleen [76–78]. Following extravascular administration, NPs within the 10–200 nm range demonstrate superior lymphatic targeting, whereas smaller particles (<5 nm) preferentially enter systemic circulation rather than lymphatic vessels. Conversely, larger particles (>500 nm) may become sequestered at the injection site [79,80].

4.1.2. Charge

Surface charge characteristics profoundly influence NPs biodistribution patterns (Fig. 2H). Comparative studies con-sistently demonstrate the superior performance of anionic NPs, attributable to reduced entrapment in negatively charged extracellular matrix components and attenuated cellular toxicity profiles compared to cationic counterparts [81]. Nakamura *et al.* provided compelling evidence through their microfluidic-engineered 30 nm liposome system, where anionic variants exhibited: (i) 2.7-fold greater LNs accumulation than cationic liposomes, (ii) enhanced penetration depth into LNs parenchyma, and (iii) preferential splenic targeting following intravenous administration [82].

4.1.3. Shape

NP morphology plays a significant role in determining their biological interactions during lymphatic transport (Fig. 2I). While spherical NPs follow conventional flow patterns in lymphatic vessels, non-spherical geometries such as discoidal particles exhibit distinct transport behaviors [82]. The asymmetric shape induces rotational movements and tumbling effects during circulation, which promotes more frequent interactions with endothelium. This enhanced contact, combined with the increased surface area available for adhesion, facilitates more efficient extravasation from lymphatic vessels compared to spherical counterparts [83].

4.1.4. Elasticity

The elasticity modulus of NPs represents another critical parameter influencing their biological fate (Fig. 2F). Stiffer NPs demonstrate substantially higher uptake efficiency by phagocytic cells such as macrophages compared to softer variants [84]. This phenomenon can be attributed to fundamental differences in cellular internalization mechanisms. Rigid particles more effectively induce actin filament recruitment at the particle-cell interface, while their deformable counterparts require additional energy expenditure for complete cellular engulfment [85]. Computational models estimate this energy differential to be approximately 30% for ellipsoidal versus spherical particles, explaining the observed preference for rigid nanomaterials in phagocyte-rich environments like LNs [86].

4.1.5. Surface engineering

Surface characteristics represent a pivotal determinant of NP biodistribution and therapeutic efficacy (Fig. 2J). Strategic surface modifications can simultaneously enhance stability, prolong circulation half-life, and improve target specificity while minimizing adverse effects [87].

Polyethylene glycol (PEG) conjugation remains the most widely employed approach, where PEG chains create steric hindrance to prevent NP aggregation. However, this steric stabilization may concurrently reduce macrophage-mediated clearance [76]. The drainage and retention characteristics of PEGylated liposomes in LNs can be altered by regulating the length and density of PEG chains. Comparative studies in rat models demonstrate that liposomes incorporating 15 mol% PEG350-1,2-distearoyl-*sn*-glycero-3-phospho-ethanolamine (DSPE) display slower subcutaneous drainage but superior LNs retention relative to those containing 6.7 mol% PEG2000-DSPE [87]. This phenomenon arises from differential macrophage recognition of surface architectures: The brush-like conformation of longer PEG2000 chains proves more susceptible to phagocytic uptake than the mushroom configuration of shorter PEG350 chains [87]. 1,2-Dioleoyl-3-trimethylammoninum propane (DOTAP) liposomes showing two-fold greater LNs accumulation at 1 mol% PEG2000-lipid compared to 5 mol% formulations [88]. However, excessive PEGylation may inadvertently promote hepatic sequestration, compromising lymphatic targeting efficiency.

Alternative targeting strategies employ cell-specific ligands to achieve precise LN delivery. Antibody conjugation against CD markers enables selective cellular targeting, while carbohydrate moieties (*e.g.*, mannose) can engage C-type lectin receptors on antigen-presenting cells [76,89]. Cai *et al.* engineered mannose-functionalized self-assembling glycopeptides that exhibit selective binding affinity for mannose receptors, enabling targeted lymphatic delivery [90].

4.2. Commonly used NPs

NPs for target delivery are mainly divided as following sections: LNPs, polymer NPs (PNPs), inorganic NPs, and biomimetic NPs [29,45,46,91]. Ideal LNs targeted NPs should meet the following criteria: High density in LNs, low toxicity, and enhanced immunity [92].

4.2.1. Lipid-based NPs

Lipid-based NPs are extensively used in tumor immunotherapy, such as liposomes and LNPs (Fig. 2D) [91,93]. These lipid-based NPs deliver antigens, immunomodulators, or nucleic acids (*e.g.*, mRNA) to antigen-presenting cells or T cells within TDLNs, thereby promoting immune activation and the expansion of effector cells.

Liposomes represent the largest subgroup of lipid-based NPs. They are typically made of phospholipids and form vesicular structures that can carry hydrophilic, hydrophobic, and lipophilic drugs [94,95]. Liposome stability is influenced by factors such as size, surface charge, and lipid composition [96]. However, surface modifications are often necessary to extend circulation time and im-

prove delivery efficiency, as liposomes are rapidly cleared by the reticuloendothelial system [97–99].

In contrast, LNPs contain an outer phospholipid layer that forms a micellar core [100]. LNPs use cationic lipids to encapsulate negatively charged nucleic acids under acidic conditions. As pH increases, LNPs become neutral, thereby reducing toxicity and protecting the encapsulated nucleic acids [46,93,94]. In tumor immunotherapy, LNPs enhance immunogenicity by simultaneously delivering adjuvants and antigens [101–103]. Recent studies indicate that surface modification with PEG or targeting ligands enhances delivery precision [46,104]. This modification enhances the capacity of antigen-presenting cells to recognize and process antigens, thereby increasing T-cell activation. LNPs are considered the most efficient method for delivering therapeutic agents to LNs [105]. However, LNPs still face challenges, including limited drug loading capacity and suboptimal biodistribution, which result in high uptake by the liver and spleen.

4.2.2. PNPs

PNPs are composed of natural or synthetic polymer monomers or units, which can be divided to polymersomes, micelles and dendrimers (Fig. 2B) [46,106].

PNPs possess a high capacity for surface modification [107]. Surface modification with ligands, antibodies, or peptides enables precise delivery of drugs to LNs and TME, achieving targeted drug release [29,107–109]. Additionally, PNPs can encapsulate various types of cargo, including small molecules, protein antigens, and nucleic acid, thereby supporting co-delivery and synergistic therapy [46,110].

However, PNPs still face technical challenges. Aggregation and stability issues of PNPs may impact their efficacy and safety *in vivo* [46,111]. Particle aggregation during storage and use may result in uneven drug release or reduced bioavailability. Further improvements in batch consistency, stability, and sterilization are necessary to enable broader clinical application [29,111].

4.2.3. Inorganic NPs

Inorganic NPs include silica NPs, gold NPs, iron oxide NP, quantum dots, *etc.* (Fig. 2E) [29,112]. Significantly, many inorganic NPs exhibit intrinsic immunogenicity that can be precisely tuned through control of their size, shape, and surface chemistry, making them ideal platforms for targeted drug delivery [29,113]. Their large surface areas can be easily modified to facilitate co-delivery and effective exposure of immune-related molecules [91,114,115]. Additionally, inorganic NPs exhibit resistance to general chemical degradation [113,116]. This property prevents the denaturation of biomacromolecules, such as antigens, that are attached or encapsulated, thereby extending their half-life *in vivo* [113]. Inorganic NPs possess distinctive physical and chemical properties that differentiate them from other types of NPs, such as selective adsorption and enhanced conductivity [112,117,118]. These properties, along with their thermal and magnetic characteristics, facilitate their integration into applications such as photothermal therapy and magnetic resonance imaging, thereby enhancing both diagnostic and therapeutic effectiveness [118,119]. Some Inorganic NPs can absorb specific wavelengths of light and convert them into thermal energy, generating localized heat to destroy tumor cells. Recent studies in photothermal therapy have explored the use of these NPs to modulate immunosuppressive cells [120–122]. Key advantages of combining immunotherapy with photothermal therapy include precise targeting, low toxicity, and versatility.

Inorganic NPs application *in vivo* is limited by their slow biodegradation rate [29]. Furthermore, potential metal toxicity remains a concern [123,124]. Fei *et al.* found that intravenous injection of NPs can accelerate the infiltration and metastasis of breast cancer cells [125].

4.2.4. Biomimetic NPs

Biomimetic NPs are nanomaterials designed to mimic cell membranes or biomolecules, including albumin-bound NPs and membrane-coated NPs (Fig. 2C). Membrane-coated NPs exhibit enhanced immune evasion by emulating cell membrane properties, allowing them to evade detection by the reticuloendothelial system [126]. This property prolongs their circulation time in the bloodstream, thereby facilitating effective delivery. Membrane-coated NPs are also capable of carrying multiple antigens or immune modulators, thereby improving targeted delivery efficiency. When modified with tumor cell membranes, Membrane-coated NPs can specifically direct immunomodulators to TDLNs, thereby initiating tumor-specific immune responses. Gan's team developed aluminum phosphate NPs (APMC) coated with B16F10 tumor cell membranes [127]. Upon subcutaneous administration, APMC accumulates effectively in LNs and stimulates antitumor immune responses by releasing membranes and CpG. Additionally, membrane-coated NPs mimicking DCs membranes enhance antigen presentation efficiency, thereby strengthening T-cell activation. Yang *et al.* developed a biomimetic nanovaccine, dendritic cell membrane(DCM)/histidine-modified stearic acid-grafted chitosan(HCtSA)/ovalbumin (OVA) micelle, designed with DC membrane coating and pH-responsive antigen release [128]. The DCM/HCtSA/OVA micelles demonstrated strong targeting and accumulation in LNs, thereby enhancing antigen uptake and DCs maturation within the LNs. *In vivo* tests in mice showed that the micelles inhibited tumor growth and caused swelling in LNs, indicating activation of antitumor immunity.

Protein NPs commonly derive from natural proteins, such as bovine and human serum albumin, or from modified and de novo designed proteins [107,129,130]. Similar to membrane-coated NPs, it has characteristics suitable for *in vivo* application such as biocompatibility, adjustability and multifunctionality [131]. However, Protein NPs are sensitive to pH and temperature, and may face insufficient stability due to the influence of blood components *in vivo*. Additionally, the size, shape, and surface properties of protein NPs may trigger an immune response, affecting their immunogenicity [130,131]. Amphiphilic molecules, such as amph-peptides and amph-CpG, constructed by Liu *et al.* combine with albumin to facilitate efficient LNs delivery, ensuring effective CpG transport in LNs [132]. Researchers have proposed an *albumin hitchhiking* strategy that leverages amphiphilic structures to enhance targeted delivery to LNs, providing new insights into drug delivery.

5. Immunomodulation in tumor-draining TDLNs *via* cell-targeted NPs

Before tumor metastasis occurs in LNs, TDLNs undergo microenvironmental remodeling, which results in an immunosuppressive state [133,134]. Influenced by tumor-secreted cytokines, exosomes, and other regulatory factors, immune cells within TDLNs are gradually reprogrammed to acquire tumor-supportive phenotypes [135]. In TDLNs, DCs remain immature and express elevated levels of inhibitory molecules, such as indoleamine 2,3-dioxygenase (IDO), thereby hindering the effective activation of effector T cells [136]. Additionally, large amount of regulatory T cells (Tregs) accumulates and become activated within TDLNs [133,134]. Tregs release suppressive cytokines, such as transforming growth factor-β (TGF-β) and interleukin-10 (IL-10), which inhibit the antitumor activity of $CD8^+$ T cells [135,137]. Myeloid-derived suppressor cells (MDSCs) impair effector T cell functionality by releasing immunosuppressive factors, such as nitric oxide (NO) [138]. Collectively, these cell populations constitute a robust immunosuppressive network, positioning TDLNs as critical sites for tumor immune evasion [135]. Surface-modified NPs can deliver immune modulators to minimize undesired distribution and activate the immune

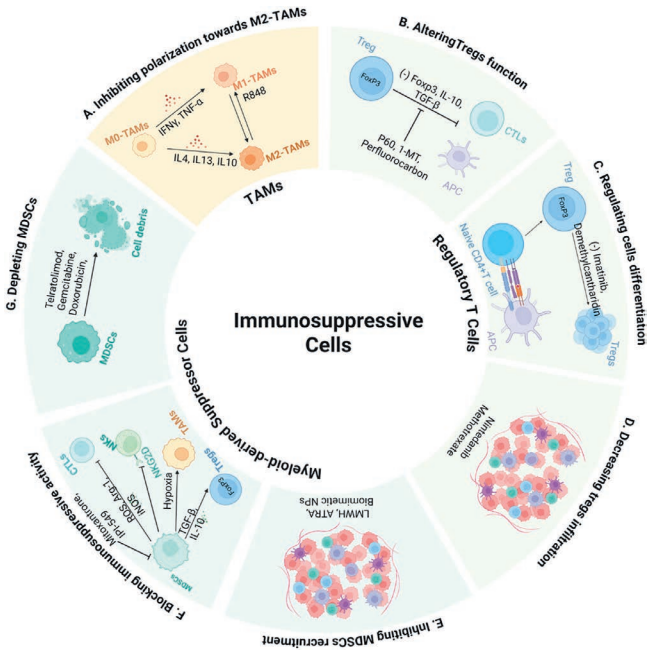


Fig. 3. Mechanisms of immune suppressive cell regulation in TDLNs to enhance anti-tumor immune responses.

system [46]. The mechanism relies on interactions with molecules on the target cell surface, including those mediated by ligands and receptors [139]. This section discusses the immunological effects within the TDLNs enhanced by NPs.

5.1. Immunosuppressive cells

5.1.1. TAMs

Tumor-associated macrophages (TAMs) primarily originate from peripheral blood monocytes and are categorized into classically activated M1 phenotype and alternatively activated M2 phenotype [140]. The M1 phenotype exhibits anti-tumor activity and produces pro-inflammatory cytokines to enhance immune responses [140]. M2-TAMs promote tumor growth, metastasis, and immune cell suppression [141]. Their roles include the secretion of growth factors (*e.g.*, C-X-C motif chemokine ligand 8 (CXCL-8) and IL-6) to stimulate tumor cell proliferation, the release of matrix metalloproteinases to promote extracellular matrix degradation and endothelial cell migration, thereby aiding angiogenesis, and the production of IL-10 and TGF-β to inhibit the adaptive immune response and enhance regulatory T cell production [142–144]. Hypoxia and lactate can drive TAMs towards immunosuppressive phenotype, resulting in the predominance of M2-TAMs in TDLNs [145]. Experiments have demonstrated that TAMs can be reprogrammed into M1-TAMs under pharmaceutical inducement, such as with SGLT1 inhibitors or MIF-CD74 blockade [145–147]. Regulating TAM polarization to enhance the immune microenvironment represents a promising therapeutic strategy (Fig. 3A) [144,148]. The content of this section is summarized in Table S1 (Supporting information).

To combat TAMs, a key strategy involves inhibiting their polarization toward the immunosuppressive M2 phenotype, which is often accomplished through specific cytokines or immunomodulators [149,150]. Kubara *et al.* developed an LNP-based mRNA vaccine (L17-F05) encapsulating mRNA encoding the tumor antigens Gp100 and Trp2 [151]. The L17-F05 NPs employ ionizable lipids with a pH-responsive design to enhance LNs targeting, enabling efficient delivery to LN-resident macrophages and DCs. In TDLNs, these LNPs activate macrophages *via* the stimulator of interferon genes (STING) type-I interferon (IFN1) pathway, inducing the production of IFN-I and the upregulation of co-stimulatory molecules (CD40, CD80, CD86) in DCs. This immune activation enhances the maturation and antigen-presentation capacity of DCs, culminating in a robust $CD8^+$ T cell-mediated anti-tumor response that significantly inhibits tumor growth in melanoma models. The Toll like receptors (TLR)7/8 agonist R848 is among the most effective molecules for inducing macrophage polarization toward the M1 phenotype *in vitro* [152]. Beta-cyclodextrin NPs (CDNP-R848) loaded with R848 effectively accumulate within macrophages in tumors and TDLNs due to their physicochemical properties [152]. *In vivo* experiments demonstrated that CDNP-R848 specifically targets TAMs within tumors, promoting their phenotypic transformation and inducing the expression of IL-12. This transformation subsequently activates the immune response of Th1 cells. Solely applied CDNP-R848 demonstrates efficacy in regulating tumor growth and improving the survival rate of tumor-bearing mice. However, when combined with anti-PD-1, CDNP-R848 exhibits a pronounced synergistic effect, achieving superior control over tumor growth and further enhancing the survival probability of tumor-bearing mice. Tong *et al.* developed pH-sensitive, size-switchable nanoclusters (SPN-R848) by conjugating the TLR7/8 agonist R848 with polyamidoamine (PAMAM) derivatives [153]. These nanoclusters target TAMs and TDLNs, and their size reduces under acidic conditions, facilitating their penetration and the repolarization of M2-TAMs to an antitumor M1 phenotype. Silva *et al.* employed biodegradable NPs (pR848M-NPs) to co-deliver poly(I:C), R848, and MIP3α, reprogramming the immune TME within tumors and TDLNs [154]. R848 significantly facilitated the transition of TAMs from an M2-like immunosuppressive phenotype (Ly6Cmed) to an acute inflammatory phenotype associated with M1-TAMs (Ly6Chi). poly(I:C) and R848 activate TLR3 and TLR7/8, markedly augmenting the expression of CD40, CD80, and CD86 on the surface of DCs and stimulating the secretion of IL-12. This subsequently modulates Th1 cell differentiation and the cytotoxic activity of cytotoxic T lymphocytes (CTLs). MIP3α recruits immune cells expressing CCR6/CD196, including immature DCs, T cells, and natural killer (NK) cells, to the tumor site, significantly enhancing immune cell diversity and quantity within the TME. Xu *et al.* engineered an oral NP system (MTG/siSIRPα/pMUC1) with surface modifications of glycocholic acid and mannose, encapsulating the immune checkpoInt. inhibitor signal regulatory protein α (SIRPα) small interfering RNA (siRNA) and the mucin-1 (MUC1) pDNA vaccine [155]. Glycocholic acid facilitates the transepithelial passage of NPs through the intestinal epithelium into the lymphatic system, enhancing their accumulation in TDLNs. Mannose modification further enhances NPs binding to macrophages. Xu *et al.* engineered mannose and glycocholic acid-modified trimethyl chitosan (MTG) nanoparticles. The SIRPα siRNA payload in MTG/siSIRPα/pMUC1 NPs downregulates SIRPα expression in macrophages, promoting their phenotypic shift from the tumor-promoting M2 to the anti-tumor M1 phenotype. Simultaneously, the MUC1 pDNA vaccine stimulates T-cell immunity against the MUC1 antigen, amplifying the systemic anti-tumor response. Nano-PI is an albumin-based NP encapsulating the phosphatidylinositol 3-kinase (PI3Kγ) inhibitor (IPI-549) and the chemotherapy drug paclitaxel (PTX) [156]. Leveraging the natural circulation properties of albumin, Nano-PI specifically targets and accumulates in macrophages within TDLNs and tumors. Nano-PI delivers IPI-549, inhibiting the PI3Kγ signaling pathway and promoting the polarization of immunosuppressive M2-TAMs into tumor-fighting M1-TAMs. Additionally, Nano-PI activates M1-TAMs and DCs, boosting antigen presentation in TDLNs. This increases the number of active $CD4^+$ and $CD8^+$ T cells, reduces exhausted T cells and Tregs, and strengthens the local anti-tumor immune response.

5.1.2. Tregs

Tregs are a subset of negative regulatory $CD4^+$ T cells which participate in the formation of the immunosuppressive environment in TDLNs [157,158]. On one hand, Tregs inhibit the functions of $CD8^+$ T cells and DCs by secreting inhibitory cytokines such as Foxp3, IL-10 and TGF-β [159,160]. On the other hand, Tregs block effector T cells and induce monocytes to differentiate into M2 subtypes to induce immune tolerance [161]. The immunosuppression in TDLNs microenvironment is often due to the high expression of Tregs, which may limit the migration of activated T cells drainage [162,163]. Current methods on enhancing efficacy of immunotherapy by NPs can be divided to three charter, namely regulating Tregs differentiation (Fig. 3C), decreasing Tregs infiltration (Fig. 3D) and altering Tregs function (Fig. 3B) [158]. The content of this section is summarized in Table S2 (Supporting information).

The differentiation of naïve $CD4^+$ T cells into Tregs can be influenced by specific signaling pathways and environmental factors. Fu *et al.* designed the NP P@HP-tLyp1 to target Tregs and deliver imatinib (IMT) through the surface-modified tLyp1 peptide [164]. IMT suppresses the expression of the key transcription factor Foxp3 in Tregs, there by inhibiting Tregs activation. Ou and colleagues have constructed tLyp1 peptide decorated NPs (tLyp1-hNPs) for targeting Tregs [165]. When combined with CTLA4 inhibitors treatment, IMT loaded tLyp1-hNPs are capable of downregulating Tregs and increasing the infiltration of CTLs in tumors. He *et al.* designed an acid-activated charge-reversal polymer NPs (SPDMCN) [166]. Within acid microenvironment, SPDMCN releases demethylcantharidin (DMC) and generates singlet oxygen to induce tumor cell death. DMC inhibits protein phosphatase 2A activity, downregulating FOXP3 expression in Tregs and thereby reducing their differentiation and overall numbers.

Reducing the infiltration of Tregs into the TME is a key strategy to mitigate immune suppression. Nintedanib is a multi-tyrosine kinase inhibitor which clinically applied in idiopathic pulmonary fibrosis and lung cancer [167]. In a KRAS-driven pancreatic cancer model, treatment with nintedanib-loaded lipid-coated mesoporous silica NPs (Si-Ninte NPs) reshapes the immune landscape by increasing the ratio of $CD8^+$ to $FoxP3^+$ T cells and enhances PD-L1 expression [168]. Si-Ninte NPs significantly reduce Tregs infiltration and increased CTLs recruitment. In 4T1 breast cancer model, PeiPLGA-MTX NPs effectively down-regulate signal transducer and activator of transcription 3 (STAT3) and nuclear factor kappa-B (NF-κB) and reduce the recruitment of Tregs [169].

Targeting Tregs function can help relieve immune suppression and restore effective immune responses against tumors. Lozano *et al.* designed a NP called CD28Apt-P60 that targets T lymphocytes through CD28 [170]. This NP carries the Foxp3 inhibitor peptide P60, which reduces the immunosuppressive function of Tregs and lessens their suppression of effector T cells. The hypoxic TME increases the infiltration of Tregs. Hypoxia-inducible factor-1α induced by hypoxia promotes the expression of Foxp3 and the proliferation of Tregs, resulting in immune suppression [171]. To counter this, oxygen-storing perfluorocarbon (PFC) in FEM@PFC NPs can alleviate tumor hypoxia and suppress Tregs levels [172]. Under laser irradiation, the prodrug carried by FEM@PFC can effectively consume TSH and reduce the expression of Foxp3 in Tregs. IDO1 is an enzyme that plays a role in tryptophan metabolism and highly expressed in TME, which supports the functionality of Tregs and the suppression of the immune response [173]. Fu *et al.* designed a liposome-based inducer (NIL-IM-Lip) that targets TDLNs and TME through pH-sensitive Asn-Gly-Arg (NGR) peptide and matrix metalloproteinase 2 (MMP2)-sensitive ligand IL-15 [120]. This liposome also carries the photothermal agent IR780 and IDO1 inhibitor 1-MT. NIL-IM-Lip prevents IDO1 from breaking down tryptophan, thus maintaining the tryptophan level and changing the metabolic balance. Overall, NIL-IM-Lip limits the survival and functional role of Tregs *in vivo*, thus alleviating the suppressive effect of Tregs on the immune response.

5.1.3. MDSCs

MDSCs are immature myeloid cells with immunosuppressive effects [174]. By producing significant amounts of immunosuppressive factors, such as reactive oxygen species (ROS), NO, and IL-1, MDSCs contribute to the establishment of an immunosuppressive microenvironment and inhibit effector T cell activity [175,176]. Current nano-immunotherapeutic approaches to regulate MDSCs include hindering recruitment (Fig. 3E), blocking immunosuppressive activity (Fig. 3F), and inducing direct depletion (Fig. 3G). The content of this section is summarized in Table S3 (Supporting information).

One primary approach involves hindering the recruitment and proliferation of MDSCs. The innate receptors of neutrophil membranes can neutralize pro-inflammatory cytokines, thereby reducing the recruitment of MDSCs [177]. By encapsulating neutrophil membrane vesicles with neutrophil plasma membranes to create pseudoneutrophil cytokine sponges (pCSs), Li *et al.* mimicked the phenotype and morphology of MDSCs [178]. pCSs absorb cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and CXCL2, which drive MDSCs migration and activation, thereby disrupting their recruitment into TDLNs.

Another strategy is to alleviate the immunosuppressive environment and inhibit MDSCs activity. PI3Kγ signaling plays a pivotal role in the activation and migration of myeloid cells [174]. Ding and his team co-encapsulated the PI3Kγ inhibitor IPI-549 and the photosensitizer Ce6 into liposomes to construct the nanomedicine LIC [179]. LIC alleviates the inhibitory effects on $CD8^+$ T cells by inhibiting the PI3Kγ-AKT signaling pathway, reducing Arg-1 and ROS levels, and promoting the apoptosis of MDSCs and Tregs. Under laser irradiation, Ce6 in LIC generates ROS and induces immunogenic cell death (ICD) of tumor cells. During this process, damage-associated molecular patterns (DAMPs), such as calreticulin, stimulate DCs maturation and activate specific effector T cells and NK cells. Lin synthesized IPI549@UPS-IGS-PDMAEMA@CXCL9 cDNA (IUIPC) following a similar principle [180]. This liposome consists of Janus silica NPs, featuring one part encapsulating the PI3Kγ inhibitor IPI549 and another part grafted with polycations that adsorb CXCL9 cDNA. IPI549 delivered by IUIPC inhibits PI3Kγ, reduces Tregs recruitment, and diminishes the immunosuppressive effects of MDSCs. CXCL9 chemokine expression induced by embedded CXCL9 cDNA in IUIPC promotes $CD8^+$ T cells and NK cells infiltration, thereby enhancing anti-tumor efficacy. ROS play a dual role in the immune response, mediating MDSC-induced immunosuppression and inducing M2-TAM differentiation and polarization [181]. MRC NPs are composed of a pH-responsive carrier MPEG-PPDA, the immune agonist RGX-104, and the photosensitizer Ce6 [182]. Upon irradiation with a 660 nm laser, Ce6 generates ROS that damage organelles. RGX-104 activates ApoE *via* the LXR/ApoE axis, reduces MDSC activity, remodels TME, and indirectly enhances ROS generation. Together, they synergistically enhance ROS levels, induce pyroptosis, release DAMPs, promote DCs maturation and T cell infiltration, and strengthen the anti-tumor immune response.

The third approach focuses on depleting MDSCs by inducing apoptosis. Guo *et al.* developed integrin-targeted micelles (ATN-mG/P) containing gemcitabine and paclitaxel, combined with polymer vesicles loaded with CpG (NanoCpG), for the treatment of postoperative triple-negative breast cancer [183]. Gemcitabine in ATN-mG/P induces ICD by disrupting the cell cycle, prompting the release of DAMPs, and selectively eliminating MDSCs [184]. Paclitaxel promotes transformation of MDSCs into mature $CD80^+CD86^+$ mDCs by regulating the TLR4 pathway, which facilitates APC proliferation and polarization, increasing the proportions of mature

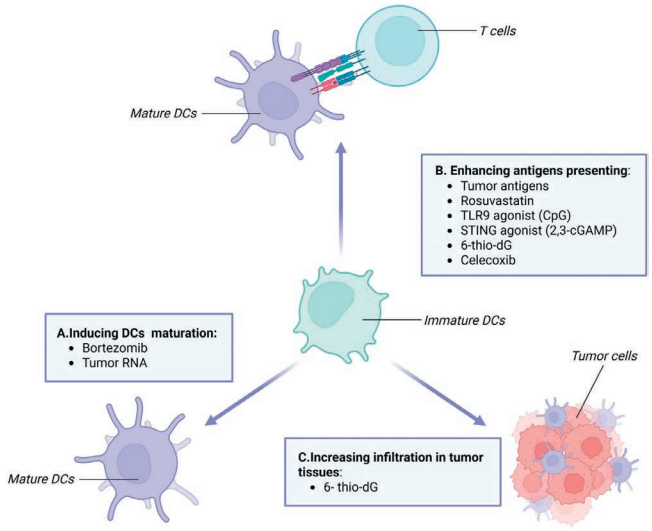


Fig. 4. Mechanisms of DCs modulation for enhanced anti-tumor immune responses in TDLNs.

DCs and $CD8^+$ T cells. Telratolimod, the TLR7/8 agonist with immuno-stimulatory properties, can achieve controlled release *in vivo* [185,186]. Liu *et al.* designed an injectable phase-change gel (PGE) for loading telratolimod, synthesizing Tel@PGE, which undergoes *in situ* phase change *in vivo* to enable sustained release [186]. Tel@PGE significantly reduces the number of MDSCs by modulating the TME, promotes the recruitment of effector $CD8^+$ T lymphocytes, and reshapes the immunosuppressive microenvironment.

5.2. DCs

DCs are responsible for presenting antigens to TDLNs to activate T cell-mediated immune responses. TDLNs contain two subpopulations of DCs: Conventional DCs (cDCs) and plasmacytoid DCs (pDCs) [187]. cDCs are primarily classified into cDC1 and cDC2 subgroups, which are responsible for activating $CD8^+$ T cells and $CD4^+$ T cells, respectively [188]. pDCs synthesize type-1 IFN, which plays a pivotal role in activating innate immunity and regulating adaptive immunity. The maturation of DCs can be inhibited by the TME, leading to dysfunction and silencing of related immune cells [189,190]. In recent years, the strategies for regulating DCs functions can be divided into two types: Regulating the maturation of DCs (Fig. 4A) and the antigen presentation function of DCs (Fig. 4B). The content of this section is summarized in Table S4 (Supporting information).

Researchers have developed a novel type of polymer NP (PAG/BTZ) by conjugating aminoguanidine (AG) to the surface of pH-responsive polymer NPs loaded with bortezomib (BTZ) [191]. BTZ release induces ICD in cancer cells, characterized by increased exposure of calreticulin (CRT) and release of high-mobility group box 1 (HMGB1). AG stimulates the TLR4 signaling pathway in a dose-dependent manner, enhancing DCs uptake and maturation in response to tumor antigens. *In vivo* experiments on 4T1 breast cancer cells show that PAG/BTZ administration significantly inhibits 4T1 tumor growth and enhances the efficacy of αPD-L1 therapy. RNA vaccines have entered clinical trials, but their response rates and stability require further improvement. Su and colleagues hypothesize that RNA from chemotherapy-treated tumor cells carries antigens capable of inducing immune responses [192]. Based on this, they extracted RNA from tumor cells and combined it with protamine to construct C-RNA NPs. Following injection into mice, C-RNA NPs rapidly reach LNs *via* lymphatic drainage and are subsequently internalized by DCs. By activating the TLR3 signaling pathway, C-RNA NPs induce DC maturation and promote high-level expression of co-stimulatory molecules, including CD80 and CD86. *In vivo* experiments demonstrated that C-RNA NPs increased the ratio of $CD8^+$ T cells in tumors and enhanced $CD4^+$ and $CD8^+$ T cell infiltration. Kaplan-Meier survival analysis revealed that mice treated with C-RNA NPs exhibited prolonged survival, particularly when combined with the PD-1 antibody, which significantly inhibited tumor growth and further extended survival.

Cholesterol and glycolysis metabolism influence DCs immune responses [190]. The downstream product GGPP of the mevalonic acid (MVA) pathway activates GTPases, accelerating antigen transport to lysosomes and downregulating antigen processing and presentation [193]. Yang *et al.* developed a mannose-modified hydrogel delivery system (Gel@NPs) encapsulating the MVA pathway inhibitor rosuvastatin (RSV) [194]. Gel@NPs target DCs *via* mannose modification and activate antigen cross-presentation by inhibiting the MVA pathway through embedded RSV. Lu *et al.* synthesized a delivery platform (GDMON-P) using polyethyleneimine (PEI)-modified silica particles (GDMON) to co-deliver tumor antigens and TLR9 agonists into APCs [195]. Once phagocytosed by DCs, PEI induces endosome escape, allowing the antigen and agonist to enter the cytoplasm. The nanoplatform consumes GSH and disintegrates to regulate antigen release, upregulating CD80 and CD86 to enhance antigen presentation. The immune response initiated by DCs involves multiple steps including ICD, recruitment of DCs, and cross-presentation by DCs [196]. To regulate these steps simultaneously, Qin *et al.* synthesized a photodynamic nanosystem (CC-6td NPs) encapsulating Ce6, celecoxib, and 6-thio-dG (Fig. 4C) [197]. Encapsulated celecoxib recruits DCs by inhibiting cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2), while inducing chemokine CCL5 production. 6-thio-dG induces DNA damage in tumor cells, activates the STING/IFN-I pathway, and enhances DC cross-presentation capability. Ce6 is responsible for stimulating ICD. The synergistic effect of these three drugs enables CC-6td NPs to significantly inhibit colon cancer development and recurrence both *in vitro* and *in vivo*. CRT, expressed on the surface of cancer cells undergoing ICD, enhances DCs ability to capture and process tumor antigens [198]. To enhance chemotherapy efficacy against fibrosarcoma, Wang *et al.* synthesized the biomimetic nanovaccine cGAMP@PLGA@CRTM (GP@CRTM), encapsulated with fibrosarcoma cell membranes and loaded with the STING agonist 2,3-cGAMP [199]. CRT-enriched cell membranes were derived from low-dose doxorubicin-induced ICD in fibrosarcoma cells. CRT on the outer layer of GP@CRTM mimics an *eat-me* signal, significantly enhancing DCs uptake and processing of tumor-associated antigens, thus promoting T cell recruitment and activation. Once internalized by DCs, GP@CRTM gradually releases 2,3-cGAMP to activate the STING signaling pathway. This activation upregulates costimulatory molecules (*e.g.*, CD80, CD86, and major histocompatibility complex class II (MHC-II)) and stimulates the secretion of immune-related cytokines, such as IFN-β, TNF-α, and IL-6. The expression of costimulatory molecules enhances the interaction between DCs and T cells, while the cytokines recruit additional CTLs and NK cells, thus strengthening the anti-tumor immune response. Trp2/CpG-NPs employ poly(L-histidine)-poly(ethylene glycol) as a skeleton to load the immunomodulators Trp2 and CpG [200]. CpG promotes antigen-presenting cell maturation by interacting with TLR9 [201]. Trp2, a melanoma-related antigen epitope peptide, is used as a tumor vaccine antigen. Following subcutaneous injection, accumulation efficiency in TDLNs is significantly increased [200]. The immunomodulators in Trp2/CpG-NPs synergistically promote BMDCs maturation, increasing the expression of costimulatory factors CD80 and CD86. Additionally, the structural features of Trp2/CpG-NPs facilitate NPs entry and cargo delivery into the DC cytoplasm, reducing antigen retention time and enhancing cross-presentation.

5.3. Effector immune cells

The applications of NPs in tumor immunotherapy have been extensively studied. By combining tumor-associated antigens (TAAs) with NPs, they can function as anticancer vaccines. These engineered NPs can deliver TAAs to TDLNs through lymphatic drainage, where they activate DCs and T cells while modulating the immunosuppressive TME. Kim *et al.* demonstrated that poly(lactic-*co*-glycolic acid) (PLGA) NPs loaded with TLR7/8 agonists efficiently migrated to TDLNs, triggering DC expansion and activation. The total number of DCs and $CD8^+$ T cells increased 3- and 4.5-fold, respectively, after treatment. This potent and specific immune activation demonstrated preventive and therapeutic efficacy in a lung cancer metastasis model and a subcutaneous tumor model, inducing a strong protective immune response and inhibiting tumor growth [202]. Kang *et al.* concluded that NP size is a critical factor influencing immune response induction and delivery efficacy in NP-based vaccines. The results indicated that the size threshold for inducing potent cellular responses and T-cell poly-functionality by GNPs ranges between 10 nm and 22 nm [203]. The content of this section is summarized in Table S5 (Supporting information).

5.3.1. NK cells

NK cells are cytotoxic innate immune cells of lymphoid origin, currently classified as effector cells similar to CTLs [204]. They inhibit the proliferation, migration, and colonization of tumor cells in distant tissues. NK cells play a crucial role in tumor immunity, exhibiting more flexible recognition and killing mechanisms than $CD8^+$ T cells, as they do not require antigen sensitization or depend on MHC-I molecules [205,206]. NK cells directly recognize and kill tumor cells, inducing apoptosis through the release of cytotoxic granules, expression of death receptor ligands, and antibody-dependent cell-mediated cytotoxicity (ADCC) [204,207]. NK cells secrete cytokines, including IFN-γ and TNF-α, which influence other immune cells and regulate the immune microenvironment to enhance antitumor responses [208,209]. The acidic and hypoxic TME, enriched with immunosuppressive factors such as IL-6, IL-10, TGF-β, and PGE2, suppresses NK cell function and facilitates immune evasion [209]. Current therapies for modulating NK cell function in TDLNs focus on upregulating activating factors (Fig. 5A) and downregulating inhibitory molecules to enhance NK cell activation (Fig. 5B).

Various strategies have been constructed to upregulate activating factors for NK cells. Jiang *et al.* prepared micelles (IL-15-NPs) using poly(L-histidine)-poly(ethylene glycol) as a scaffold, linking IL-15 to the surface *via* disulfide bonds [200]. Despite lacking specific targeting molecules, the particles effectively delivered and accumulated in TDLNs due to their optimal size. IL-15 on the particle surface binds to IL-15R on NK cells, activating the Janus kinase (JAK)-STAT pathway. This activates phosphorylated STAT5 dimers, which translocate to the nucleus to regulate gene expression, promoting NK cell proliferation and enhancing IFN-γ secretion. IFN-γ enhances NK cell cytotoxicity, activates macrophages, and modulates the TME. Similarly, NIL-IM-Lip carries IL-15 conjugated through an MMP2-sensitive peptide [120]. *In vitro* experiments demonstrated that NIL-IM-Lip treatment significantly increased NK cell cytotoxic activity. *In vivo* experiments showed that NIL-IM-Lip reshaped the TME, relieving the inhibitory effects of Tregs on NK cells. Furthermore, MMP2 triggers NIL-IM-Lip to release IL-15, activating NK cells. Sun *et al.* [210] modified poly(γ-glutamic acid) to conjugate the TLR3 agonist poly(I:C) onto the nanovaccine SVNP-IC for TDLNs targeting (Fig. 6A). *In vivo* fluorescence imaging demonstrated that SVNP-IC effectively migrated to and targeted TDLNs, achieving long-term retention (Fig. 6B). Immunofluorescence imaging showed that SVNP-IC delivered OVA and poly(I:C) to TDLNs, where they colocalized and were taken up by subcapsular sinus macrophages ($CD169^+$), medullary macrophages ($F4/80^+$), and DCs ($CD205^+$), demonstrating efficient targeting (Figs. 6C and D). SVNP-IC administration significantly increased the expression of pro-inflammatory cytokines, including TNF-α, IL-6, and IFN-β, in TDLNs (Fig. 6E). Subcutaneous injection of SVNP-IC and monitoring of CD69 expression in mouse NK cells revealed that SVNP-IC significantly promoted NK cell expansion and activation compared to soluble poly(I:C) (Fig. 6E). The TLR3 agonist poly(I:C) encapsulated within SVNP-IC initiates MyD88-dependent and TRIF-dependent signaling pathways, leading to the activation of transcription factors such as NF-κB. This process stimulates the secretion of IFN-I by immune cells, thereby enhancing NK cell proliferation and activation. Additionally, SVNP-IC-mediated immune activation resulted in significant tumor suppression in EG7-OVA tumor-bearing mice and improved survival outcomes. Research on renal tumor lung metastasis found that LNPs (STING-LNPs) loaded with STING pathway agonists are internalized by liver macrophages, producing IFN-I to activate NK cells [211]. Activated NK cells proliferate and migrate to tumor sites for direct cytotoxic effects. Additionally, NK cells secrete C-C motif chemokine ligand 5 (Ccl5) to recruit cDC1, further regulating the immune response in TME.

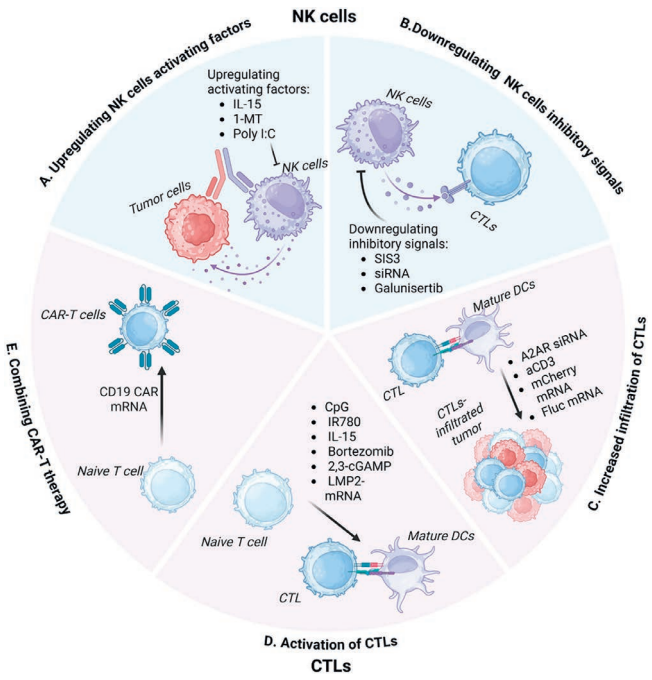


Fig. 5. Mechanisms of effector immune cells modulation for enhanced anti-tumor immune responses in TDLNs.

Another emerging strategy involves silencing or downregulating inhibitory molecules associated with NK cells. The immunosuppressive molecule TGF-β suppresses NK cell cytotoxicity. However, anti-TGF-β therapies may result in cardiotoxicity, skin toxicity, and autoimmune diseases [212]. SIS3 acts as an inhibitor of Smad3, a downstream protein in the TGF-β signaling pathway. Lian *et al.* synthesized a nanomedicine carrying SIS3 (SCND-SIS3) that enhances NK cell cytotoxicity by inhibiting Smad3-mediated Ndrg1 transcription [213]. This enhanced cytotoxicity correlates with increased expression of the activating receptor NKp46 and reduced levels of Trib3 and TSP1. Biber *et al.* developed a lipid-based nanocarrier (SHP-Cbl-NP) that encapsulates siRNA and is coated with an anti-NKp46 antibody to target NK cells [214]. The siRNA it carries silences genes associated with inhibitory NK cell molecules, including SHP-1, Cbl-b, and c-Cbl [215,216]. Experimental results demonstrate that siRNA targeting inhibitory genes, delivered by

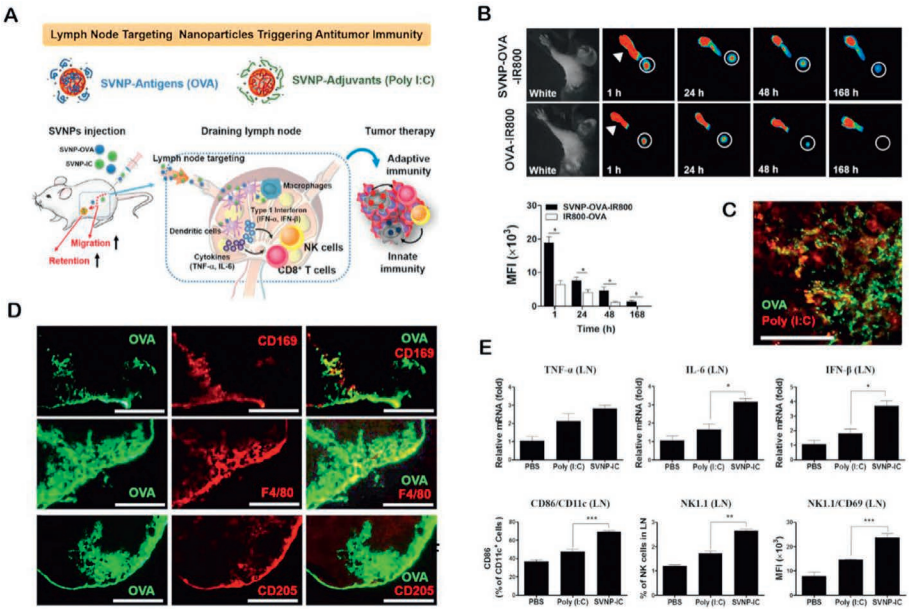


Fig. 6. LNs-targeting synthetic vaccine NPs (SVNPs) for enhanced innate and adaptive antitumor immunity. (A) Schematic illustration of NPs (SVNP-OVA and SVNP-IC) designed for delivering antigens and immune adjuvants to TDLNs. (B) Near-infrared fluorescence imaging showing the migration and retention of SVNP-OVA-IR800 and IR800-OVA in TDLNs. (C) Immunofluorescence image of TDLNs showing the colocalization of OVA (green) and poly(I) (red) delivered by SVNP-IC. (D) Immunofluorescence images showing the uptake of OVA delivered by SVNP-IC in subcapsular sinus macrophages (CD169+), medullary macrophages (F4/80+), and DCs (CD205+) in TDLNs. (E) Expression of pro-inflammatory cytokines (TNF-α, IL-6, and IFN-β), DC activation markers (CD86), and NK cell activation markers (CD69) in TDLNs after SVNP-IC treatment. Reproduced with permission [210]. Copyright 2024, Elsevier Ltd.

SHP-Cbl-NPs, downregulates inhibitory factors affecting NK cell activity, thereby enhancing their tumor cell killing ability [214].

Gal/IL-15@CaLN is an NP capable of simultaneously delivering both galunisertib and IL-15 [217]. Galunisertib can block the TGF-β/SMAD signaling pathway, thereby relieving its suppressive effects on NK cells. IL-15 activates the JAK/STAT and PI3K/mTOR pathways in NK cells, promoting proliferation, activation, and secreting cytotoxic factors. Overall, current research on regulating the activity of NK cells in tumor LNs primarily focuses on modulating immune factors to enhance NK cell activity.

5.3.2. CTLs

In tumor immunity, CTLs recognize MHCI molecules on tumor cells, releasing perforin and granzymes to induce apoptosis, while secreting IFN-γ to enhance immune responses. However, in TME, T cell activity is often suppressed by immunosuppressive molecules such as PD-L1 and TGF-β, as well as cells like Tregs and MDSCs. These factors inhibit CTL activation, proliferation, and effector functions, reducing their infiltration and cytotoxic capacity [218]. Nanotechnology strategies aim to overcome these barriers by using nanocarriers to deliver antigens or immune modulators that enhance T cell cytotoxicity and regulate their migration and infiltration, thereby improving their functionality within tumors and increasing the efficacy of antitumor immunotherapies. The content of this section is summarized in Table S6 (Supporting information).

In experiments involving the modulation of DCs by nanomedicines, a significant enhancement in T cell activity after the completion of antigen presentation by these cells is observed (Fig. 5D) [120,191,192,195,199,200]. As described in the part of antigen-presenting cells, Trp2/CpG-NPs promote the presentation of Trp2 in the cytoplasm of DCs and then activate CTLs through the process of antigen cross-presentation [200]. GDMONPs co-deliver antigens and TLR9 agonists to DCs to enhance their antigen presentation ability, thereby indirectly activating CTLs to exert anti-tumor effects [195]. Albumin can circulate within the blood and lymphatic system and is taken up and processed by cells within the LNs during its passage. As mentioned before, the amphiphilic molecules constructed by Liu *et al.* achieve the efficient delivery of NP vaccines to LNs through the *albumin hitchhiking* strategy [132]. Among them, Amph-CpG triggers signal transduction by binding to TLR-9, prompting immune cells to secrete cytokines and activate T cells. DCs process Amph-peptide and activate T cells, which then differentiate into effector and memory T cell populations. Combination delivery can effectively stimulate a higher systemic $CD8^+$ T cell response and improve anti-tumor efficacy. Xiang *et al.* developed an LMP2-mRNA vaccine (C2@mLMP2) based on ionizable LNPs for the treatment of Epstein-Barr virus (EBV)-related tumors [219]. These NPs encapsulate mRNA encoding latent membrane protein 2 (LMP2) and achieve efficient delivery to the tumor-draining LNs. The LMP2 protein activates $CD8^+$ T cells and promotes their proliferation into CTLs, initiating an immune response against tumor cells. In a mouse model, C2@mLMP2 significantly increased the proportion of $CD8^+$ memory T cells and effector memory T cells in the spleen, demonstrating enhanced immune memory. When combined with PD-1 inhibitors, C2@mLMP2 effectively reversed $CD8^+$ T cell exhaustion in the TME and improved anti-tumor efficacy.

Another method is to increase the infiltration of CTLs (Fig. 5C). In TME, CD39 and CD73 on cancer cells convert ATP to adenosine, fostering an immunosuppressive environment *via* A2AR [220]. Masjedi *et al.* developed A2AR-targeting siRNA-loaded NPs (A2AR/PEG-PCL NPs) that efficiently deliver siRNA molecules to T cells, reducing intracellular A2AR levels [221]. The NPs suppress A2AR expression in T cells, thereby dampening the downstream signaling, which results in reduced protein kinase A (PKA) and cAMP response element-binding protein (CREB) activity. Consequently, this intervention mitigates the suppression of T cell proliferation and apoptosis, boosts IFN-γ secretion, and lowers IL-10 levels within the microenvironment.

Under glucose deprivation, CTLs preserve their anti-tumor efficacy by enhancing peroxisome proliferator activated receptor alpha (PPAR-α) and fatty acid oxidation [218]. Kim *et al.* developed NPs

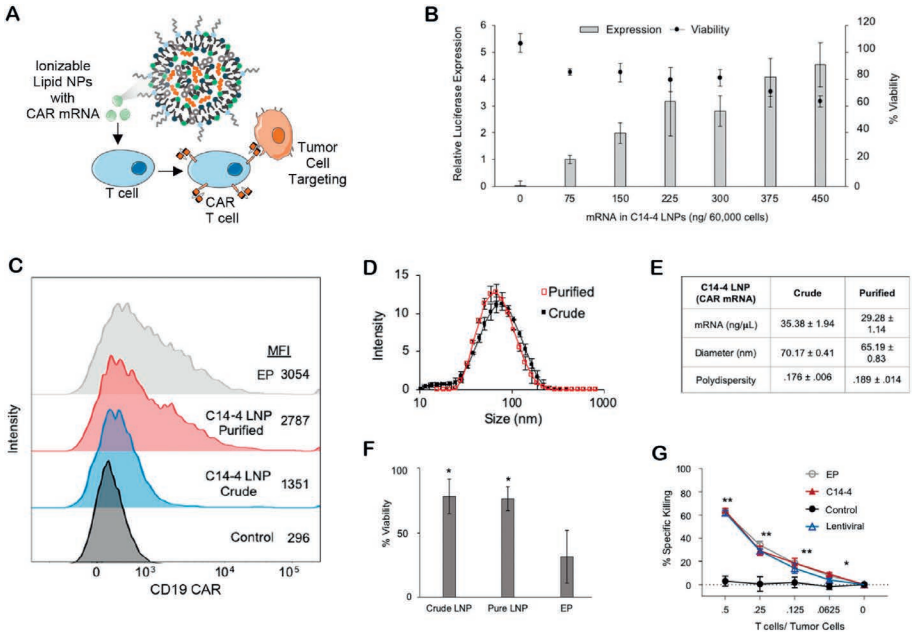


Fig. 7. Ionizable LNP-mediated mRNA delivery for CAR T cell engineering. (A) Schematic illustration of C14-4 LNPs encapsulating CAR mRNA for delivery to T cells, inducing CAR expression and tumor targeting. (B) Dose-dependent mRNA delivery by C14-4 LNPs to primary human T cells with minimal cytotoxicity. (C) Flow cytometry analysis of CAR expression levels in T cells treated with purified and crude LNPs compared to electroporation. (D) Size distribution of purified and crude C14-4 LNPs measured by dynamic light scattering (DLS). (E) Characteristics of crude and purified C14-4 LNPs, including mRNA encapsulation efficiency, diameter, and polydispersity. (F) Viability of T cells treated with C14-4 LNPs compared to electroporation. (G) Tumor cell killing efficiency of CAR-T cells generated with C14-4 LNPs, electroporation, and lentiviral transduction. Reproduced with permission [226]. Copyright 2024, American Chemical Society.

(aCD3/f/Ans) loaded with the PPAR-α agonist fenofibrate for the selective targeting of T cells [222]. The anti-CD3 antibody on the surface of aCD3/F/ANs targets and binds specifically to the CD3 receptor on T cell surfaces, thereby enabling targeted delivery. Upon internalization, fenofibrate activates the PPAR-α pathway and upregulates intracellular fatty acid metabolism. This leads to a significant increase in the cytotoxic activity of T cells, evidenced by elevated secretion of cytotoxic cytokines such as granzyme B and IFN-γ, thereby enhancing their efficacy against B16F10 cells. Similarly, Kheirolomoom *et al.* developed anti-CD3 antibody-conjugated LNPs (aCD3-LNPs) for the targeted delivery of mRNA to T cells and their subsequent activation [223]. Following injection, aCD3-LNPs accumulate in the spleen and LNs, enhancing $CD8^+$ T cell function and migration while increasing the expression of activation markers such as CD69, CD25, and OX40. In tumor models, transfected T cells effectively localize to tumors and LNs, demonstrating the potential to boost anti-tumor immune responses.

CAR-T cell therapy has advanced cancer treatment but depends on *ex vivo* viral transduction, leading to complex production, high costs, and risks of side effects like cytokine release syndrome and B cell aplasia [224,225]. Billingsley *et al.* focused on enhancing T cell antitumor efficacy by integrating nanotechnology with CAR-T therapy (Fig. 5E) [226]. C14-4 LNPs encapsulate CAR mRNA and efficiently deliver it to T cells, inducing CAR expression on their surface to enable tumor targeting and killing activities (Fig. 7A). C14-4 LNPs efficiently deliver mRNA to primary human T cells in a dose-dependent manner while maintaining minimal cytotoxicity, demonstrating their high delivery efficiency and safety profile (Figs. 7B and G). CAR expression induced by C14-4 LNPs is comparable to traditional electroporation, achieving functional CAR-T cells capable of specific tumor killing activities (Fig. 7F). By enabling mRNA delivery for CAR expression, this method bypasses the complex *ex vivo* procedures associated with traditional CAR-T engineering, offering a more streamlined process for T cell modification (Figs. 7C–G).

6. Perspectives

Despite promising laboratory results, LN-targeted NPs faces challenges in clinical application. More studies in animal models are needed to confirm the bio-compatibility and predict *in vivo* safety, particularly for inorganic NPs. Enhanced clinical trial designs and diverse patient inclusion criteria would accelerate practical use. Tumor heterogeneity also complicates the choice of antigens for each patient, thereby making personalized treatment more difficult.

Currently more than 15 NPs have been approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA) for cancer therapy, which are liposomes, followed by protein-based NPs and polymeric micelles. Meanwhile, ClinicalTrials.gov lists over 100 ongoing clinical trials of oncology therapeutic nanomedicines. Emerging trends in oncology immunotherapy include active targeting and multi-component delivery strategies.

Looking forward, research should refine NP design for better LNs targeting. Combination therapies with existing treatments, like ICIs and CAR-T cells, may also enhance the therapeutic outcomes. A multidisciplinary approach will help close the gap between lab successes and practical applications, advancing LNs-targeted NPs in cancer immunotherapy.

Future research can focus on refining the characteristics of NPs to improve the targeting efficiency for LNs. Moreover, LNs-targeted NPs can incorporate multiple immunomodulatory approaches to activate the immune system on multiple levels, thereby enhancing overall cancer immunotherapy and reducing tumor recurrence.

CRediT authorship contribution statement

Zhiyuan Huang: Writing – original draft. **Fangqiu Fu:** Writing – original draft. **Chaoqiang Deng:** Writing – original draft. **Shiyang Wu:** Writing – original draft. **Mingxuan Huang:** Writing – original draft. **Xianyi Sha:** Conceptualization. **Ming Q Wei:** Conceptualiza-

tion. **Zhiwen Zhang:** Conceptualization. **Yang Zhang:** Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2025.111993.

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