Front. Chem. Sci. Eng. 2025, 19(7): 60
https://doi.org/10.1007/s11705-025-2565-y

REVIEW ARTICLE

Exploring the immunological impact of particles across dimensions in antigen and drug delivery systems

Hua Yue (✉)[1,2*], **Shaoyu Guan**[3*]

1 State Key Laboratory of Biopharmaceutical Preparation and Delivery, Institute of Process Engineering, Chinese Academy of Sciences, Beijing 100190, China
2 University of Chinese Academy of Sciences, Beijing 100049, China
3 Pharmaceutical Sciences Research Division, Department of Pharmacy, Medical Supplies Centre of PLA General Hospital/ Medical School of Chinese PLA, Beijing 100853, China

Abstract Particle formulation engineering stands as a focal point of research and a critical trajectory within the chemical industry. In response to the challenges associated with antigen/drug delivery, our research group has proposed a suite of strategies centered on micro/nanoparticle platforms. This review integrates our investigations into the applications of particles across various dimensions in biomedical delivery systems. Specifically, it delineates the mechanisms by which particles augment vaccine-induced immune responses, notably through antigen cross-presentation, and the pivotal roles they play in facilitating drug-mediated targeting of cancer cells via confined mass transfer. This review also encompasses recent advancements in particle formulations, offering prospective insights into the utilization of chemical engineering principles in the design of next-generation biomedical delivery systems.

Keywords micro/nanoparticles, graphene oxide, precise drug delivery, vaccine adjuvant

1 Introduction

Owing to their similar size and dimensions to pathogenic bacteria and viruses in nature, micro/nanoparticles are oftentimes recognized by the body as foreign agents and can activate the immune response [1,2]. The specific immune response is required by different subunit vaccines [3]. Based on clarifying the biological effects of micro/nano particles, the rational design of adjuvants with favorable physicochemical properties is an important strategy for the development of new particle adjuvant vaccines [4,5].

Particle formulations have now become a significant breakthrough in the development of vaccines for infectious diseases and innovative drugs. The efficacy is noticeably enhanced whether the approach involves the encapsulation of antigens or drugs in three-dimensional (3D) particles [6,7] or drug loading on two-dimensional (2D) sheets [8]. Each discovery made during exploration serves as essential support for novel technological formulations [9]. Notable international research groups, including the R&D team from Robert S. Langer and GlaxoSmithKline plc., have developed successful vaccine adjuvant systems, such as lipid nanoparticles (NPs) for the SARS-CoV-2 vaccine [10,11] and AS01 [12,13] for Shingrix (herpes zoster vaccine). These works are distinguished by a deep focus on NP immunology. Our institute has pioneered the field of particuology and mesoscience [14], which inspired us to leverage these fundamental rules and concentrate on the study of particulate vaccine/drug carriers. To begin with the fine-tuning of the physicochemical properties of micro/nanoparticles, we investigated their relationships with immune mechanisms to enhance vaccination, offering a promising avenue for vaccine research and development. In the context of drug delivery, there has been a long-standing expectation for particle formulations that enable the precise administration of anticancer agents [15−17]. Therefore, the advancement of efficient and safe innovative particle formulations represents a critical opportunity to overcome existing challenges and meet national health care needs.

Particle formulations have focused primarily on increasing the circulation time of drugs or enrichment within focal lesions [18]. It is essential to develop designs

Received December 26, 2024; accepted April 8, 2025; online June 16, 2025

E-mail: hyue@ipe.ac.cn

* These authors contributed equally to this work.

that facilitate efficient loading and precise delivery for ample bioavailability and exertion of biological effects [19−22]. Moreover, vaccines differ significantly from drugs in terms of metabolism, cellular targeting, and response pathways in the body [23,24]. These distinctions render the continued application of the traditional trial research paradigm for screening new particle adjuvants impractical. Consequently, the foremost challenge that current research must address is to bridge the long-standing gap in comprehending the structure-efficacy relationships in particle immunology, and develop enhancement mechanisms to achieve rational design of advanced particle carriers.

In response to these challenges, Yue et al. [24] integrated various disciplines regarding chemical engineering, immunology, and pharmaceutics, supported by specialized expertise from the team of Academician Ma in particulate fabrication techniques. 2D and 3D particles with uniform and tuned properties have been constructed to reveal the structure-efficacy relationships and immune response mechanisms during delivery (Table 1). The sequential processes include "interfacial recognition, cellular internalization, and mass transfer processing," during which "efficacy, quantity, and category" are analyzed (Fig. 1). Building upon this knowledge, immune activation strategies and modalities for precise delivery have been developed to meet the requirements for the prevention and treatment of infectious diseases and cancers.

2 Profile of the immune response to 3D particles

Micro/nanoparticles with sizes and morphologies comparable to those of pathogens (e.g., bacteria and viruses) are easily recognized by antigen-presenting cells (APCs) as exogenous substances that trigger innate immune defense responses [25,26]. Owing to the complexity and unpredictability of the immune response, the preparation of highly uniform 3D particles with controllable sizes presents significant challenges [27]. To address these issues, Ma et al. [28] utilized a microporous membrane emulsification technique to produce uniform-sized particles [29] with narrow size distributions. They established a library of polymeric particles characterized by fine-tuned physicochemical properties, including size, structure, shape, charge, hardness, hydrophobicity, etc [30,31]. In addition, particles with advanced biomimetic merits, such as environmental (pH-, thermo-, or photo-) sensitivity, membrane infusion, and deformability, were developed to increase the immune efficacy of prophylactic or therapeutic vaccines [31].

Macrophages, which are APCs, are widely explored in the context of pathological changes and vaccination to examine their immune effects [32−34]. Soluble antigens are usually difficult for cells to internalize. With the assistance of micro/nanoparticles, the amount of antigen can be significantly elevated by improving cellular filopodia sensing [35], augmenting cellular uptake [36], as well as regulating the immunoactivity microenvironment (Fig. 2) [35−38]. During the internalization process, a complicated network and strong interactions occur between target particles and extended stress macrophage filaments. The number of concentrated filopodia augmented with increasing particle size, implying that larger particles demand more time for macrophages to detect, encapsulate, and internalize [35]. Additionally, macrophages have an unquenchable appetite for cell-sized microparticles (MPs), which surpass NPs in terms of the maximum volume. This volume burden of MPs, which is 2.64 times greater than the cell volume, is highly correlated with a 19-fold reduction in membrane loss (the ratio of total particle surface area to the cell membrane surface area) and more noticeable deformation of the cell membrane/nucleus compared to NPs [36]. For further delineation of the particles functioning as an immune activator, cytokine secretion was measured, which revealed that the NPs promoted the secretion of Th1-

Table 1 Comparisons of different characteristics of 2D and 3D particles from research findings

Comparison categories	3D particles	2D particles
Definition	Particles characterized by the volume, shape in three-dimensional space like spheres or cubes.	Particles with planar or sheet-like structures and a flexible backbone for wrapping and folding.
Typical materials	Polylactic acid (PLA)/poly(lactic-co-glycolic acid) (PLGA) NPs/MPs, liposomes, Pickering emulsions, and exosomes.	Graphene oxide (GO), PEGylated poly(L-lactide acid) sheets (PLLA-P-sheets).
Physical properties	Tunable properties such as size, structure, shape, charge, hardness, hydrophobicity, etc., and biomimetic merits such as pH-, thermo-, or photo-sensitivity, etc.	Large surface area in contact with the cell surface, ultrahigh drug/antigen loading capacity.
Bio-interfacial effects	Recognition by cellular filopodia.	Membrane lipid fluidity, sandwiched superstructure, plane-to-plane interactions, and partial insertion into the membrane surface.
Cellular uptake/response	Internalized by various pathways (e.g., clathrin, caveolins, micropinocytosis, phagocytosis, etc.), escape from lysosome and induce antigen cross-presentation.	Selective internalization only by phagocytes, a cytokine self-producer, and antigen cross-presentation via autophagy.
Drug/antigen loading	Different types with efficient loading through material polymerization, pathogen mimicry, or structural modulation.	Ultra-high loading efficiency through π-π stacking, electrostatic, hydrophobic, and hydrogen bonding.
Applications	Infectious disease prevention, chronic infectious disease treatment, and anticancer drug delivery.	Antitumor immunotherapy, neuronal protection, and vascular disease treatment.

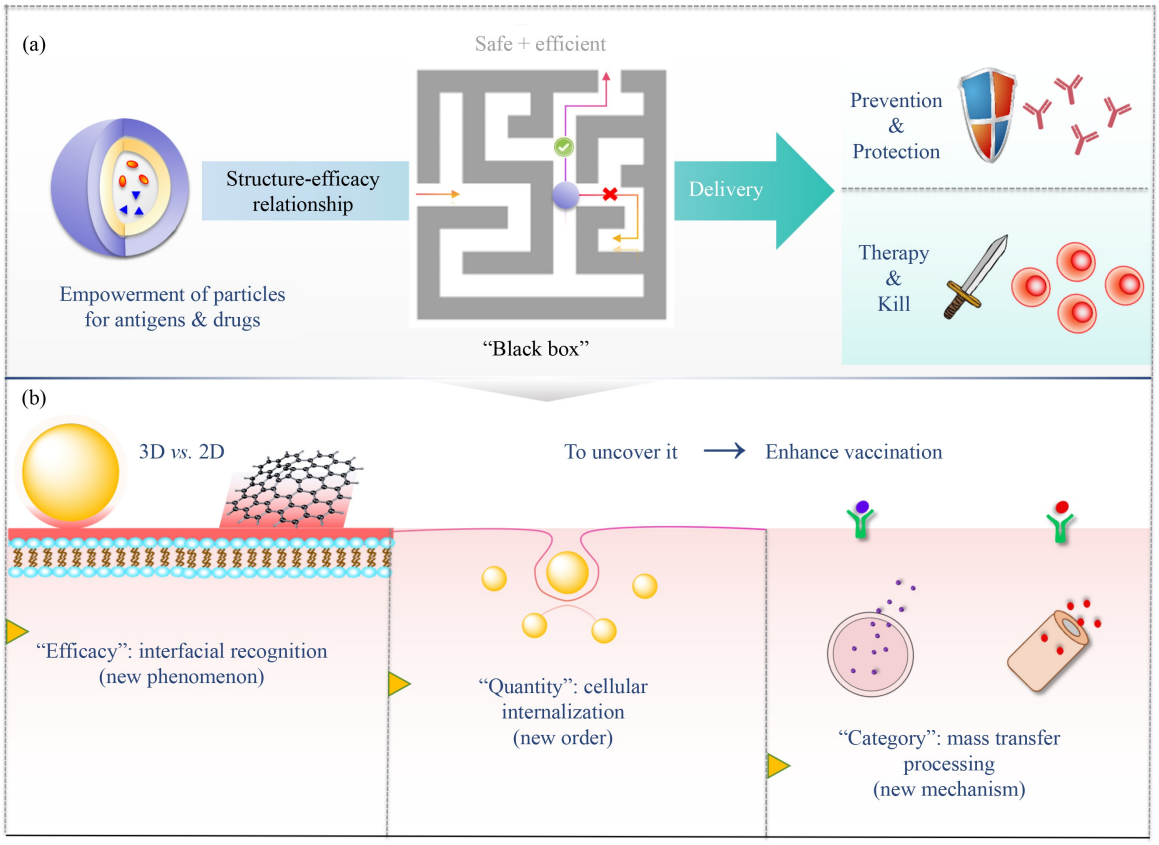

Fig. 1 Obstacles and strategies in the study of structure-efficacy relationship and mechanism of particle formulations. Rational construction of safe and efficient particles requires uncovering the "black box" of structure-efficacy relationships and delivery mechanisms (a) during a sequential process includes interfacial recognition, cellular internalization, and mass transfer processing, to sum up, "efficacy, quantity, and category". By and large, this new phenomenon, order and mechanism (b) in particology and mesoscience hold significant importance in guiding prophylactic and therapeutic applications.

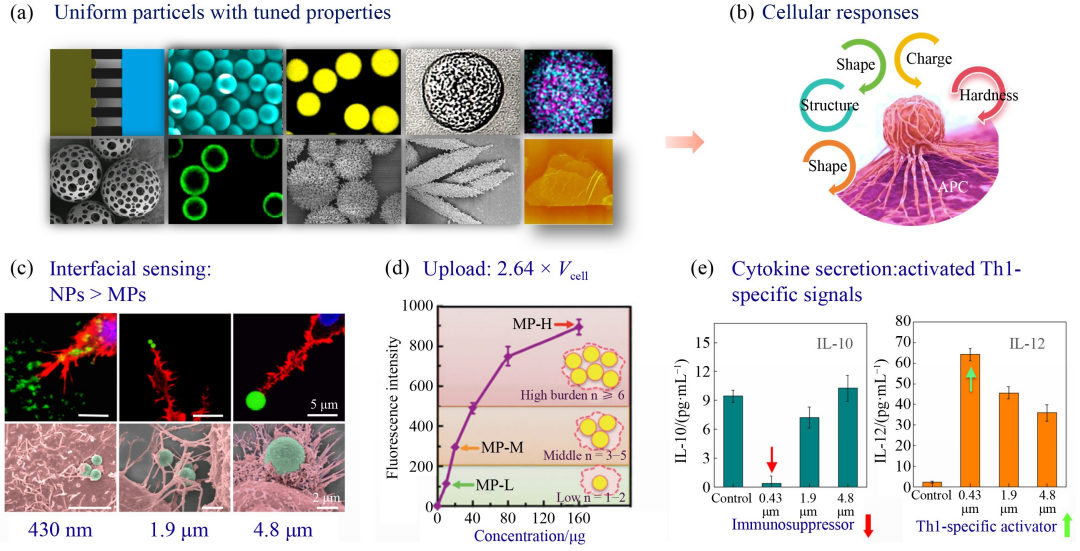

Fig. 2 Structure-efficacy relationship of 3D micro/nanoparticles and its assessment system based on APC. The realization of preparing uniform-sized 3D particles (a) with fine-tuned physicochemical properties, like size, structure, shape, charge, hardness, etc. (b). The rational structure design of 3D particles enables potent immune responses to antigens. Confocal laser scanning microscope (CLSM) images (c) showing the interaction of macrophage filopodia with 430 nm, 1.9, and 4.8 μm particles after 6 h incubation [35]. The corresponding scanning electron microscope images are displayed below. Cellular internalization of MPs (d) at different particle concentrations after 24 h incubation [36]. The particle burden levels were defined according to the fluorescence intensity of the internalized particles. The concentration (e) of IL-10 and IL-12 for macrophages after stimulation with three different sized particles [35].

specific molecules (e.g., IFN-γ, IL-12) and suppressed the secretion of the danger signal IL-10 [35,37]. These findings offer quantitative and standardized insights into the structure-efficacy relationships of 3D particles in the immune system, thereby serving as a crucial setting point for the design of particle vaccines.

With respect to the theoretical mechanisms involved in these outcomes, Yue et al. [39−43] identified distinctive mechanisms by which particles enhance intracellular transport pathways and activate specific immune responses. These nanosized [39], positively charged [37,40,41], pH-responsive [42], and autophagic particles [43] are not confined to the conventional lysosomal pathway and MHC II presentation in the cytoplasm. Instead, the antigens are promoted to mimic endogenous proteins and have access to cross-presentation through the MHC I pathway, thereby activating $CD8^+$ T cells (cytotoxic T lymphocytes, CTLs). By and large, the conventional immunological theory posits that external antigens exclusively elicit the humoral immune response. However, the finding of the "cross-presentation" mechanism via lysosomal escape challenges previous understanding, enabling the delivery of antigens for the orchestration of humoral and cellular responses via various strategies (Fig. 3).

Based on current knowledge, researchers have developed strategies (e.g., material polymerization, pathogen mimicry, and structural modulation) to expand particle types to Pickering emulsions [44−48], poly(lactic acid) (PLA) NPs [39], liposomes [42], etc. [43]. A series of antigen cross-presentation strategies have been established to augment cellular responses. For example, Xia et al. [49] developed a poly(lactic-co-glycolic acid) (PLGA) NP-stabilized Pickering emulsion adjuvant system and exploited its pliability and lateral mobility to augment the contact area, triggering the internalization and subsequent cross-presentation of antigens. This mechanism has emerged as a divergent method of cytosolic antigen trafficking with the assistance of particles for the activation of $CD8^+$ T cells in the application of cancer vaccine designs [50,51].

3 The unique interfacial bioeffects of 2D particles

Spherical particles have traditionally served as the primary functionalized carriers in delivery, whereas research on particles of other dimensions, particularly 2D particles, is relatively underexplored [8,52,53]. Using graphene oxide (GO), researchers reported that particles with flat or sheet-like structures presented distinctive physical, chemical, and electronic attributes [54−60]. In addition to these properties, the interaction between 2D graphene and the biological interface was also strengthened, and distinct cellular responses were induced (Fig. 4) [54]. For example, an ultrahigh drug/antigen loading capacity (500%) was achieved for 2D GO [54], in which the mechanism was revealed to involve a combination of π-π stacking, electrostatic, hydrophobic, and hydrogen bonding through molecular dynamics

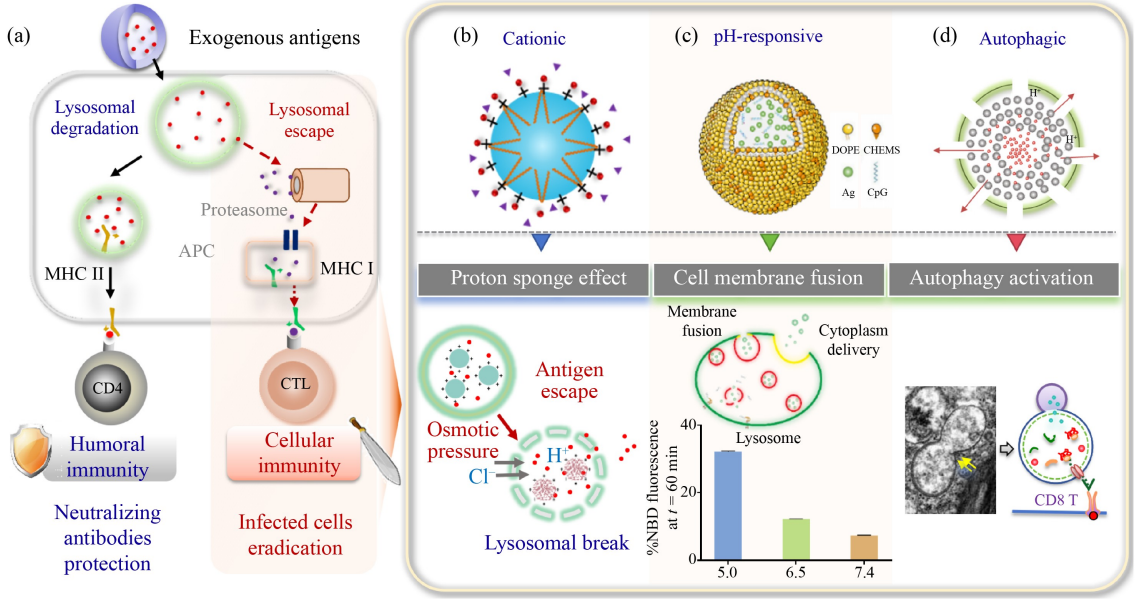

Fig. 3 (a) Enhancement of cellular immune responses by virtue of the "lysosomal escape-cross-presentation" mechanism in particles. Once exogenous antigens delivered by particulate carriers enter an APC, they can be presented via the MHC II pathway or escape lysosomes for proteasome processing, activating CTLs through the MHC I pathway. (b) Positively charged MPs trigger a proton sponge effect, in which osmotic pressure causes the lysosome to break, releasing antigens into the cytoplasm [37]. (c) A pH-responsive nanocarrier induces cytosolic delivery of antigens through membrane fusion [42]. (d) A cellular autophagy response shows preferred lysosomal escape advantage and antigen cross-presentation to CTLs [43].

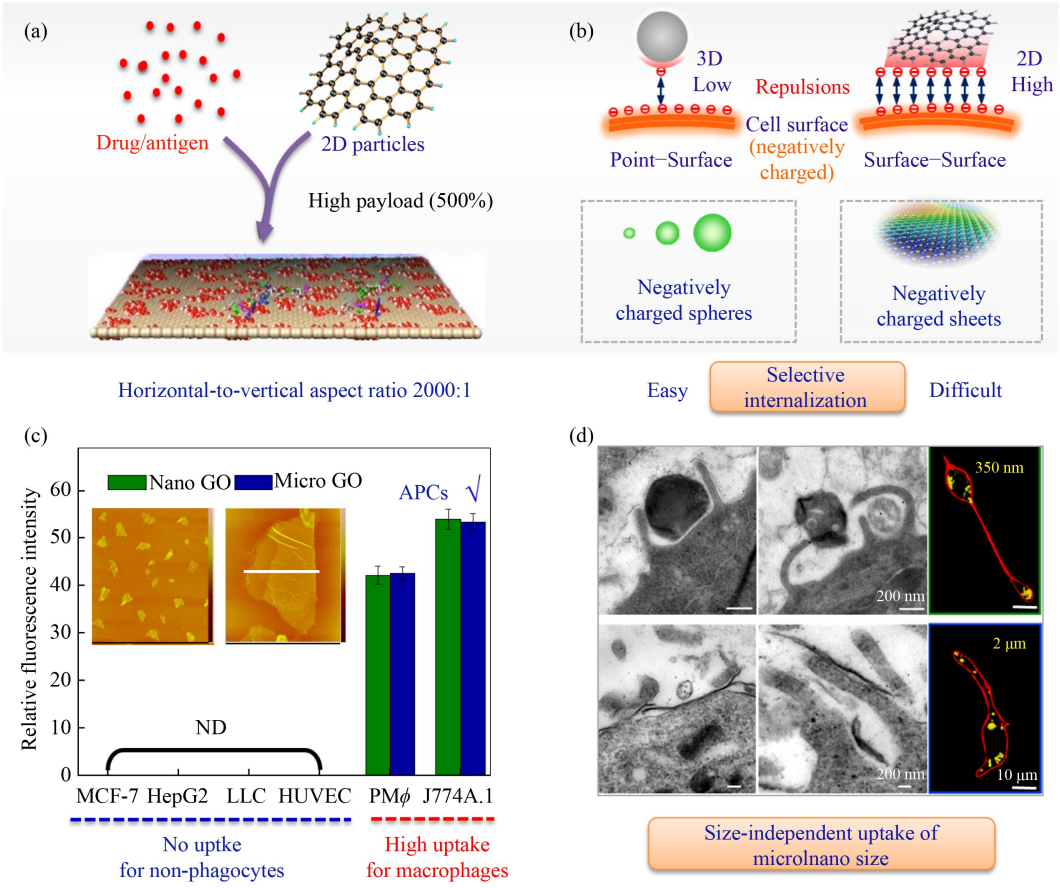

Fig. 4 Unique biointerfacial effects of 2D particles. (a) Illustration of an ultrahigh drug/antigen loading capacity for 2D GO. (b) Dissimilar to negatively charged 3D particles, 2D GO sheets internalization is selective on account of strong electrostatic repulsions between GO and negatively charged cell surface. (c) Data revealing the GO uptake capability of different cells [54]. (d) Transmission electron microscopy (TEM) images of different GO interacting with cell membrane during initial cellular uptake. CLSM images depicting morphology changes when phagocytes come across different GO sheets [54].

simulations [61,62]. Unlike conventional 3D particles, 2D GO selectively internalized different types of cells, with only phagocytes capable of overcoming transmembrane barriers to actively internalize GO sheets. In addition, a size-independent uptake event was revealed for GO with the tested lateral sizes (2 μm and 350 nm), which was attributed to the parallel surface area of GO for antibody opsonization and the subsequent entry pathway (IgG-Fcγ receptor-mediated phagocytosis). Microsized GO elicited a much stronger cellular response and immune activation cytokines (IL-12 and chemoattractant protein), subsequently inducing the accumulation of monocytes at the injection sites [63]. After these intriguing experimental results were obtained, researchers conducted specialized simulation calculations to elucidate the mechanism of phagocytosis mediated by membrane receptor density and membrane tension, extending the Canham-Helfrich theory [64].

Moreover, the "folding" effect upon the confined intracellular space was further discovered for 2D particles, which are characterized by a "zigzag" morphology in the cells (Fig. 5(a)). These particles have larger surface areas and undergo "folding" due to steric hindrance, forming a cytokine self-producer and reservoir to regulate antigen release [65]. Through particle wrapping and folding, these crumpled sheet-like structures and flexible 2D backbones are endowed with unique cargo loading merits [66]. This effect additionally induces the cellular "autophagy" response, which efficiently promotes the activation of APCs and antigen cross-presentation to CTLs following processing [67], suggesting a novel concept for designing high-performance therapeutic particles. In further investigations, Yan et al. [68] conducted extensive simulations and analyses of the mass transfer diffusion and molecular dynamics of sandwiched 2D GO superstructures (Fig. 5(b)). In experiments, super-resolution cryogenic-TEM was used to visualize the interactions between 2D particles and the interface within an aqueous environment close to the native state. This approach provides robust evidence supporting sandwiched graphene-cell membrane superstructures in different cells. The combination of simulations and analysis revealed a GO-induced pore within the cell membrane leaflets, which transitioned

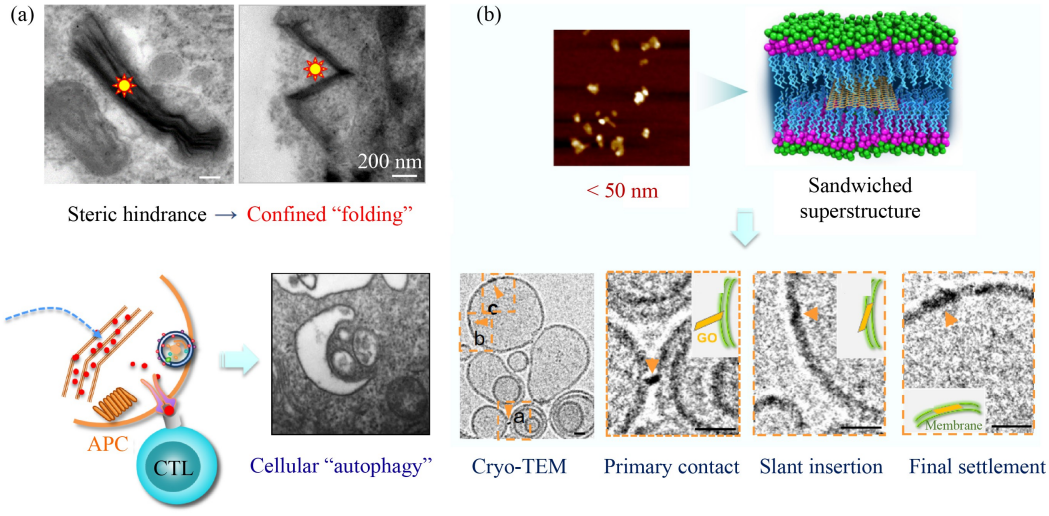

Fig. 5 Confined mass transfer of GO and visualization of sandwiched GO superstructure. (a) TEM Images showing the behavior of 200 nm GO after being internalized and the autophagy procedure undergone by the GO-pulsed dendritic cells (DCs) [63]. (b) The cartoon illustration of the superstructure of GO (< 50 nm) inside the cell membrane, and cryogenic-TEM images of the lipid vesicles in the presence of GO. The sandwiched graphene-membrane superstructure was formed via three possible processes [68].

through unstable, metastable, and stable phases. The analytical model, which quantitatively matches simulations, explained the different states of the membrane pores and offered a mechanistic interpretation of the emergence of Lévy and directional dynamics. Research on the transport of graphene nanosheets has revealed that such a structure alters membrane rigidity and fluidity, indicating promising compelling advantages for drug delivery in the biomedical field.

4 Potential immunoadjuvanticity via 3D particles

Conventional adjuvants, such as aluminum-based adjuvants, primarily elicit a humoral immune response and are ineffective at inducing a cellular response [69]; thus, they fall short of the evolving requirements for vaccine development. Building on the aforementioned immunoactivation mechanisms of cross-presentation via particulate carriers, Researchers engineered liposomes [42], exosomes [70], polymeric NPs [39], and MPs [37] with lysosomal escape capabilities for disease immunotherapy (e.g., against chronic hepatitis B (CHB)). Moreover, a variety of antigen delivery modes considering various antigen types or administration routes have also been investigated.

Vesicles such as cell liposomes or exosomes are typical NPs involved in potent antigen-delivery systems. For example, a pH-responsive liposome was constructed to mimic natural biological behavior by cytosolic delivery of the antigen through membrane fusion and the subsequent process of CTLs. The results revealed that the cross-presentation activity induced by liposomes was 1/2000 of the concentration of the soluble antigen. This nanocarrier also augmented the strong CTL response, the number of IFN-γ-secreting splenocytes, and the secretion of Granzyme B, which verified the design of membrane fusion *in vivo* [42]. In addition, a two-pronged strategy utilizing exosomes extracted from stimulated APCs was proposed to combat CHB. After both the spleen and liver are targeted, exosome formulations can effectively activate APCs and reverse the immunosuppressive microenvironment of the liver, thereby triggering the proliferation of CTLs (Fig. 6) [70].

In addition to natural or synthetic vesicles, polymeric particles display good biocompatibility and have been investigated for their adequate immune efficacy. For example, compared with free antigen, PLA NPs not only induced greater antigen internalization of HBsAg in APCs by 270% but also increased CD80/86, MHC II, and MHC I expression in APCs. $CD8^+$ T cells are activated to release perforin/granzyme and create pores in the target cell membrane, leading to the lysis of infected cells. The NPs subsequently enhanced CTL cytotoxicity (HBsAg specific lysis) and IFN-γ production more efficiently than the commercial aluminum-based adjuvant did [39]. This preferred efficacy was indispensable for the facilitation of particle adjuvants, especially for extended antigen trafficking in the cytoplasm. Specifically, Lu et al. [37] integrated an immunopotentiator into PLA MPs, triggering a proton sponge effect due to its cationic properties, which further aided in lysosomal escape to the cytoplasm. In the CHB mouse model, MP-based vaccines achieved a 50% seroconversion rate for HBsAg, along with an HBcAg reduction in the liver. Moreover, the MPs produced more memory T/B cells to overcome infection in a sustained manner.

Particle-induced cellular immune responses not only

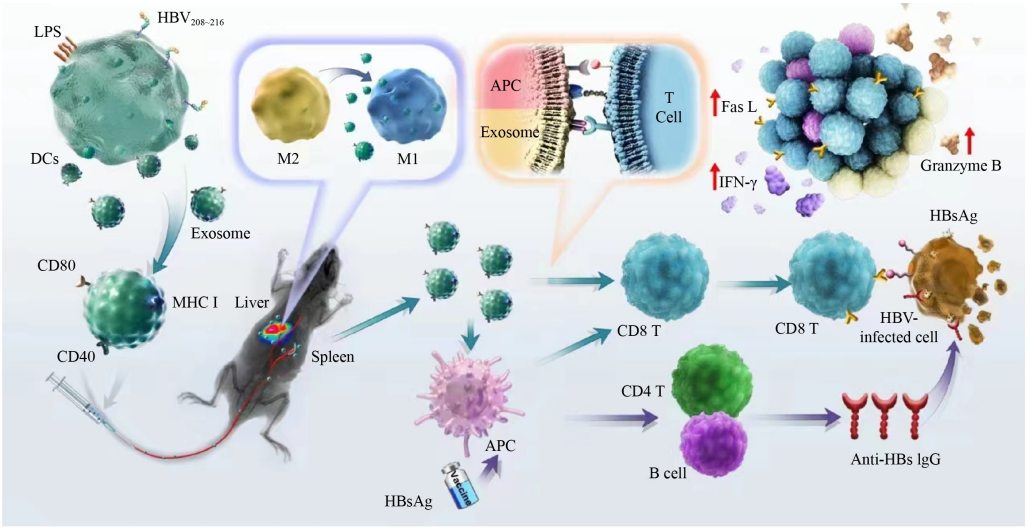

Fig. 6 The schematic diagram of the generation of DCs-derived exosomes (DC-exo) and *in vivo* immunological effects. DC-exo were isolated from the culture supernatant of bone marrow-derived dendritic cells stimulated with lipopolysaccharides and hepatitis B virus 208-216. Upon intravenous injection, DC-exo targeted both the liver and spleen after i.v. injection in mice, in which they exerted their immune effects [70]. LPS: lipopolysaccharides; M2: M2 macrophages; M1: M1 macrophages; Fas L: Fas ligand; HBV: hepatitis B virus.

increase the efficacy of immunotherapy but also hold significant importance for the prevention of infectious diseases, especially those associated with cross-protection. By tuning the particle structure, Ye et al. [71] developed an aerosol SARS-CoV-2 vaccine, which encapsulated NP chassis comprising proteinaceous cholera toxin B subunits, displaying the RBD antigen within porous PLGA MPs. By ingeniously constructing and transforming into dry powder formulations, a single inhalation with high delivery efficiency prolonged sustained systemic and mucosal immune responses in mice, hamsters, and nonhuman primates. Within 14 d after immunization, antibody levels increased and were sustained for up to one year, reducing the viral load by six orders of magnitude and offering cross-protection against different virus variants. In this context, MPs offer new insights into the efficient prevention and control of emerging respiratory infectious diseases. Given that polylactide derivates have high biocompatibility, the scale-up preparation of these particle adjuvants has already been completed, with active steps being taken to move them toward clinical application.

5 Therapeutic enhancements via 2D particles

Currently, particulate carriers improve the efficacy of eradicating tumor cells, primarily through the modifications of ligands or the chemical grafting of regulatory molecules [72,73]. Based on prior research concerning intriguing structure-efficacy relationships of 2D particles, Yue et al. [65] incorporated 2D particles into tumor immunotherapy formulations, developing an innovative GO-based “one but all”. The prepared GO imparted numerous immune activation tactics, including an ultrahigh antigen payload for release, acting as a cytokine self-producer for APC recruitment, and a particular autophagy inducer for antigen cross-presentation. Without extra modification of any bio/chemical ligand or stimulant, such an unadorned but intelligent vaccine platform produces cytotoxic lysis activity against antigen-specific tumor cells, causing further tumor rejection programmatically. Significant suppression of tumor growth (80% decrease) and an obvious increase in survival time were observed in mouse models, and multiple therapeutic effects were achieved with a single dose.

Coupled with their advantages in delivery, novel drug delivery strategies have also been developed with the assistance of 2D materials. Notably, 90% of anticancer drugs are insoluble and rely on organic solvents for dispersion, leading to adverse effects [74]. Additionally, most drug targets (e.g., epidermal growth factor receptors) are located on the cell surface, posing obstacles for traditional carriers that must be internalized first, thereby limiting their efficacy [75]. Researchers have developed a sandwiched graphene-cell membrane superstructure based on nano-bio interfacial effects and mass transfer mechanisms in 2D particles (Fig. 7) [68]. In this study, the insoluble anticancer drug vandetanib (VTB) was loaded on GO with high absorption efficiency via π-π hydrophobic effects, and encapsulated VTB liposomes (lipo-VTB) were used as a control. In contrast to initial cellular internalization followed by slow diffusion of the liposome, the sandwiched structure allows the drug to accumulate or diffuse within the

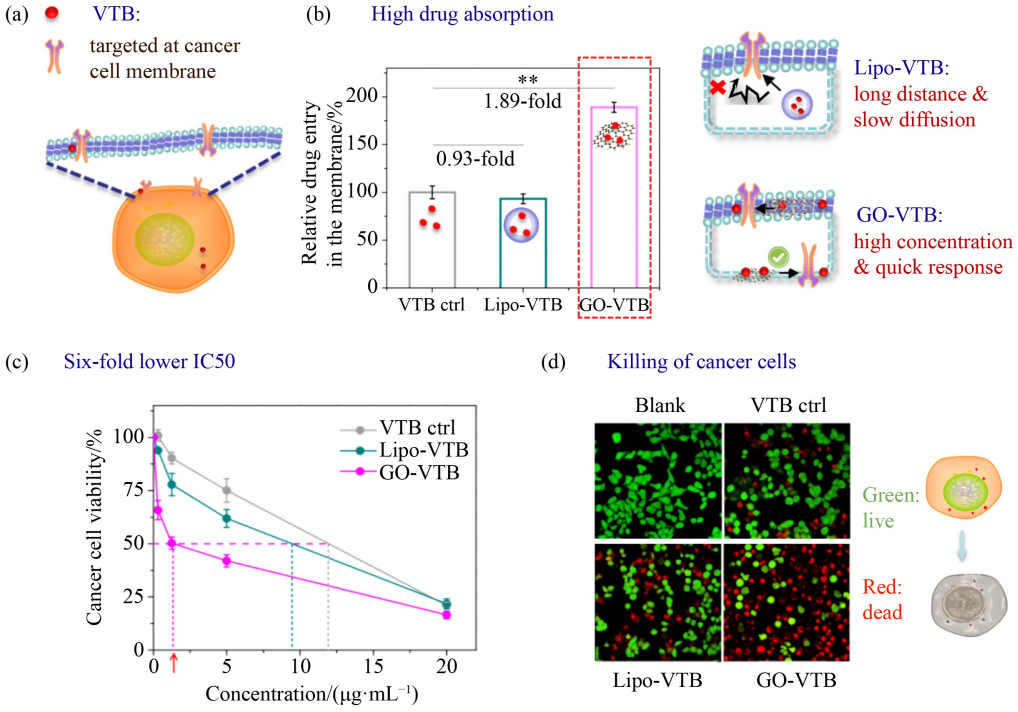

Fig. 7 GO's efficient/precise drug delivery to cell membrane. (a) Illustration of VTB targeting at cancer cell membrane. (b) Analysis of relative drug distribution in the cell membrane shows easy cellular internalization of GO-VTB. (c) Relative cell viability of VTB with the assistance of GO or liposomes in breast cancer cells MCF-7. (d) Corresponding live (green)/dead (red) images at a dose of 5 mg·mL^{-1} [68].

constrained cell phospholipid layers and then rapidly respond to the membrane targets. This formulation markedly improved drug bioavailability, substantially lowered the maximum inhibitory concentration of tumor cells by 9- and 6-fold compared with those of free VTB and lipo-VTB, respectively, and introduced an innovative modality for precise drug delivery to the cell membrane.

To broaden the applications of 2D particles in different disease models, Huang et al. [76] devised biodegradable PEGylated poly (L-lactide acid) sheets (PLLA-P-sheets) with a safer preparation for treating neuronal damage. This research showed that PLLA-P-sheets could induce a flip-flop orientation change in phosphatidylinositol lipids in the membrane, thereby limiting the ability of the hydrolysis site to block cleavage-mediated inositol 1,4,5-trisphosphate. This effect at the nanobiointerface diminished Ca^{2+}-related stress in the endoplasmic reticulum, providing protection to neurons in mice with Parkinson's disease. After investigating the immunological response of vascular endothelial cells (VECs) following i.p. exposure to PEGylated GOs in mice [77], Ding et al. [78] found that VECs could be strongly activated by PEGylated GOs, inducing inflammatory cytokines in VECs without being internalized. These findings shed light on the general utility of derivative 2D particles in selectively modulating membrane-lipid dysregulation related to neurodegenerative disorders and vascular diseases. Owing to the aforementioned 2D structure-efficacy profile and biointerfacial interaction mechanism, the utilization of these materials has also been extended to a wide range of biomedical application scenarios, such as other biomedical carriers or regenerative engineering [79].

The nanosize and high specific surface area of 2D materials make it possible to trigger cytotoxic or inflammatory responses upon interaction with biological tissues and cells. For example, graphene and its derivatives may induce apoptosis or inflammatory responses (activation of macrophages and neutrophils) through oxidative stress, damage to cell membranes, etc. Moreover, the prolonged presence of 2D materials within biological organisms can potentially disrupt immune system homeostasis. For example, long-term exposure to graphene has been associated with tissue fibrosis and immune tolerance, which negatively impact the body's immune defenses. Hence, it is imperative to develop appropriate methods and suitable strategies (e.g., functionalization of materials [80,81]) to mitigate concerns about the therapeutic application and clinical translation of 2D materials.

6 Conclusions and perspectives

In the pursuit of rationally designing particles for vaccines and antitumor treatments, the structure-efficacy

relationships of particles with different dimensions have been investigated in recent years. The empowering behavior and the underlying mechanisms toward the efficacy, quantity, and type of cellular uptake/processing were delineated for uniform 3D particles. Moreover, unique interfacial adsorption, selective cellular internalization, and confined delivery were revealed for 2D particles, further bridging the knowledge gap dominated by conventional particles. These demonstrated bioparticle interactions offer design concepts to overcome the bottlenecks of antigen/drug loading and immune/therapy inefficiency, by tuning the physicochemical properties of the particles. However, some characteristics of these bioparticles including their limitations, need to be acknowledged. In one respect, 2D particles exhibit cytoplasmic delivery in APCs, which enhances cellular immunity, making them more suitable for eliciting antitumor responses via effective cytotoxicity. However, relatively weak humoral immune responses render it suboptimal against infectious diseases. Furthermore, owing to its inert surface (lack of glycosylation or protein modifications), its capacity to interact with immune cell receptors is restricted. In another respect, 3D particles with structures engineered to encapsulate antigens and incorporate adjuvants can eliminate infected cells and neutralize viruses, thereby preventing infection. Nonetheless, a unique and rational design is needed to boost relatively weak cellular immunity.

In addition, the clinical translation of novel dimensional particles is awaited, thereby broadening the range of applicable delivery modes and disease models. There remains significant potential for further exploration of novel 2D particles, such as those associated with stimulus-responsive release; in contrast, research related to 3D particles has undergone abundant development. Several clinical studies on tumor-specific antigenic peptide (also known as neoantigen) vaccines have been conducted both domestically and internationally [82−85]. These studies consistently demonstrate the immunogenicity and safety of these vaccines, but obstacles remain, including the need for multiple injections and a weakened immune response. To this end, based on previous studies, we utilized an FDA-approved PLA as the preparation material to develop a macroporous sustained-release adjuvant for antitumor immunotherapy. Its vaccination has been shown to substantially augment cellular immune responses and improve tumoricidal efficacy. In addition, the vaccination frequency can be reduced from the original 4–5 times per month to once per month, thereby significantly increasing both the convenience of administration and patient adherence. At present, the project has been approved by the Ethics Committee and has now entered the Investigator-initiated Trial phase.

By virtue of the analysis of targeting mechanisms, immune efficacy kinetics, and the mechanisms of aging/dysfunction, natural and synthetic particles are being utilized to address the requirements for long-term/wide-spectrum protection or therapeutic efficacy. Combined with novel mechanisms and strategies, prior knowledge of particle adjuvants has been integrated to construct dynamic data sets detailing the antigen release and degradation behaviors of multistructured microspheres, as well as derivative adjuvant databases based on immune enhancement mechanisms. These data sets are interconnected through simulation calculations, and with the help of artificial intelligence (AI) and machine learning, a rational design for particle delivery and immune activation is achieved. For example, AI-designed pulse release of antigens is employed to precisely modulate immunodynamics, thereby increasing the levels of mucosal-specific antibodies and tissue-resident cellular immunity. This paradigm facilitated the establishment of a tripartite collaboration encompassing model development, experimental validation, and mechanistic understanding, in turn revolutionizing the conventional trial-and-error paradigm in adjuvant research. Consequently, innovative dosage forms for antigen delivery with potential for clinical translation have been developed. In conclusion, by making full use of multidisciplinary experiences and collaborations with experts in chemistry, immunology, and AI, the challenges associated with the development and realization of intelligent particles are poised for resolution.

Competing interests The authors declare that they have no competing interests.

Acknowledgement This work was supported by the National Natural Science Foundation of China (Grant Nos. 82341405, 32030062, and U20A20361), the National Key Research and Development Program of China (Grant Nos. 2021YFC2302603 and 2023YFC2307700), the CAS Project for Young Scientists in Basic Research (Grant No. YSBR-083), the IPE Project for Frontier Basic Research (Grant No. QYJC-2022-012).

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