Proceedings of ICMMGH 2026 Symposium: Biomedical Imaging and AI Applications in Neurorehabilitation
DOI: 10.54254/2753-8818/2026.AU29885

PLGA Nanoparticle in Tumor Immunotherapy: Advances in Research and Application

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Abstract. Immunotherapy holds significant promise in the cancer treatment, but its clinical application is hindered by challenges such as systemic toxicity and limited targeting efficiency. In recent years, biodegradable PLGA nanoparticle have emerged as a promising tool to address the safety and efficacy challenges of immunotherapy, owing to their high biocompatibility and capabilities for drug delivery. This article provides a comprehensive review of the research and application of PLGA nanoparticle in tumor immunotherapy, emphasizing their mechanisms and advantages as multifunctional drug carriers for co-delivering antigens and adjuvants, remodeling the tumor microenvironment, and enhancing immune responses. This review offers new insights for the development of low-toxicity, high-efficiency personalized immunotherapy strategies and holds significant potential for future clinical translation through advanced material design and technological integration.

Keywords: PLGA nanoparticle, Tumor, Immunotherapy, Drug delivery

1. Introduction

As the second leading cause of death globally after cardiovascular diseases, malignant tumors have long posed a major threat to human health [1-3]. While conventional treatments, including surgical resection, radiotherapy, and chemotherapy, have achieved remarkable success and remain indispensable in therapeutic regimens, they are still accompanied by substantial limitations, such as severe side effects, the development of drug resistance, and insufficient effectiveness against metastatic lesions, all of which significantly impact patient survival and prognosis.

Immunotherapy, which activates or enhances the immune system to recognize, attack, and eliminate cancer cells, has emerged as a central focus of research in both scientific and clinical communities [4,5]. It holds significant clinical translational potential and has achieved impressive therapeutic outcomes. Numerous studies and clinical cases have established tumor immunotherapy as a highly effective treatment strategy. However, monotherapeutic approaches still encounter several critical challenges, critical significant systemic toxicity (such as cytokine release syndrome and immune-related adverse events), low drug concentration at tumor sites, short half-life and limited response rates [2,3]. These issues necessitate urgent attention for further optimization.

PLGA nanoparticles have emerged as a prominent research focus in targeted drug delivery in recent years, owing to their efficient drug loading capacity, controllable drug release properties, and excellent biocompatibility. These characteristics also enable PLGA-based

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DOI: 10.54254/2753-8818/2026.AU29885

microparticles/nanoparticles to effectively address current limitations in tumor immunotherapy. On one hand, PLGA nanoparticles facilitate precise targeted drug release to the tumor site, which minimizes systemic toxicity caused by blood exposure of the loaded drugs while increasing drug concentration within tumor tissue. This approach ensures treatment efficacy and reduces side effects. On the other hand, the ability to load diverse therapeutic agents allows composite PLGA nanoparticles to exert synergistic effects in tumor immunotherapy, such as inhibiting immune escape, remodeling the tumor microenvironment, and enhancing immunogenicity [6-8].

Based on this context, we present a comprehensive review on the applications of PLGA nanoparticle in tumor immunotherapy. We summary the properties, preparation methods, and targeted delivery characteristics of PLGA nanoparticle. Furthermore, we delve into the underlying mechanisms, application strategies, administration routes, and key advantages associated with the use of PLGA nanoparticle in immunotherapy. This study provides insights into future directions for the development of PLGA-based delivery platforms aimed at enhancing the efficacy of immunotherapy in oncology [9,10].

2. PLGA nanoparticle

2.1. Definition and properties

PLGA nanoparticle serve as an intelligent drug delivery vehicle, with diameters typically ranging from 1 to 100 nanometers. Composed of the biodegradable polymer poly(lactic-co-glycolic acid), they exhibit excellent biocompatibility. Upon administration, PLGA undergoes hydrolytic degradation into non-toxic metabolites—lactic acid and glycolic acid—subsequently eliminated through natural metabolic pathways [11-13]. A key feature of these nanoparticles is their capacity to encapsulate various therapeutic agents, including antigens, adjuvants, cytokines, or small molecule inhibitors, within their polymeric matrix or to adsorb them onto the surface. This encapsulation significantly enhances the stability of the payload by shielding it from premature metabolism and degradation, thereby facilitating targeted and controlled delivery to specific sites [14,15]. PLGA nanoparticle are constructed from a matrix of poly(lactic-co-glycolic acid) a linear polyester formed by random copolymerization of two α-hydroxy acids: lactic acid (LA) and glycolic acid (GA). By modulating the LA:GA ratio and the molecular weight of the copolymer, the degradation kinetics and drug release profile of the nanoparticle can be precisely engineered. In vivo, PLGA undergoes hydrolysis into its constituent monomers, lactic acid and glycolic acid, which are endogenous metabolites that can be efficiently cleared via natural respiratory and renal pathways. This favorable metabolic fate underscores the exceptional biocompatibility and biodegradability of PLGA, which has led to its approval by major regulatory agencies—including the FDA and EMA—for use in a wide range of biomedical applications [16].

2.2. Preparation of PLGA nanoparticle

Common techniques for fabricating PLGA nanoparticle include emulsion-solvent evaporation, phase separation, and spray drying [17,18]. Among these, the emulsion-solvent evaporation method stands as the most classical and extensively adopted approach. This method involves dissolving both the drug and PLGA in an organic solvent to form an oil phase, which is then dispersed into an aqueous phase, which is then emulsified into an aqueous phase containing a stabilizer (e.g., polyvinyl alcohol) under controlled stirring. Subsequently, the solvent is evaporated, leading to the solidification of PLGA into nanoparticle. Based on the formulation design, the technique can be

DOI: 10.54254/2753-8818/2026.AU29885

subdivided into single emulsion (oil-in-water, O/W) and double emulsion (water-in-oil-in-water, W/O/W) systems, the latter being particularly suitable for encapsulating hydrophilic compounds [19-21]. The phase separation method facilitates polymer precipitation and nanoparticle formation through the addition of a non-solvent to the polymer solution. Spray drying, on the other hand, employs atomization of a drug–PLGA solution through a nozzle to generate fine droplets, which are rapidly dried by hot gas to solidify into nanoparticle [22]. This technique is especially advantageous for large-scale manufacturing owing to its operational efficiency and excellent scalability [23,24]. In addition to the conventional approaches, alternative techniques—including solvent displacement, microfluidics, electrospinning, and Particle Replication in Non-wetting Templates (PRINT)—have also been developed for the production of PLGA nanoparticle. Current research efforts continue to drive innovation in fabrication strategies, enabling more precise control over particle properties and expanding the potential applications of PLGA-based systems [25-27].

2.3. Key characteristics of PLGA nanoparticle

PLGA nanoparticles are fundamentally used for drug loading, protecting drugs during systemic circulation, and enabling controlled drug release. This makes them particularly suitable for delivering sensitive biomolecules—such as peptides, proteins, and nucleic acids—that are prone to enzymatic and hydrolytic degradation. By encapsulating these bioactive agents within the biodegradable PLGA polymer matrix, the nanoparticles can significantly reduce metabolic losses encountered in various administration routes (e.g., enzymatic degradation, pH fluctuations, protein binding), thereby enhancing both bioavailability and absorption efficiency [28].

Controlled release is the most prominent characteristic of PLGA nanoparticle [29]. Controlled release from PLGA nanoparticles is primarily governed by two mechanisms: diffusion and degradation. In diffusion-driven release, drug molecules migrate through aqueous pores and the polymer matrix into the surrounding tissue. In contrast, degradation involves the hydrolysis of the PLGA shell, leading to the erosion and disintegration of the nanoparticle structure and the subsequent release of the drug. By adjusting the material properties and microstructural characteristics during PLGA nanoparticle synthesis, the release profile can be precisely modulated to achieve controlled release over periods ranging from several days to months. This tunable temporal control allows the release kinetics to be aligned with diverse clinical needs, enabling personalized adaptation to the patient's immune response cycle and improved synergy with other treatments such as surgery and radiotherapy.

The targeting strategies of PLGA nanoparticles can be broadly categorized into passive and active mechanisms. Passive targeting primarily relies on the enhanced permeability and retention (EPR) effect, which exploits the pathophysiological characteristics of tumor tissues [30,31]. Unlike normal tissues with regular structure, tumor tissues typically exhibit defective vascular architecture with enlarged endothelial gaps and impaired lymphatic drainage. By optimizing PLGA nanoparticle size and administering intravenously, these nanoparticles extravasate through the leaky vasculature into tumor interstitium while being poorly cleared due to insufficient lymphatic drainage. This process leads to prolonged accumulation and retention of PLGA nanoparticles at the tumor site, thereby achieving passive targeting [32,33]. It is important to note that the EPR effect remains a subject of debate and has certain limitations. Although it has been extensively validated in animal models of various tumors, direct evidence supporting its broad applicability in human tumors is still insufficient. This discrepancy may be attributed to factors such as individual patient variations, tumor type, and anatomical location. Consequently, active targeting strategies demonstrate higher efficiency and greater potential for clinical translation compared to passive approaches.

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Active targeting is achieved by surface-functionalizing PLGA nanoparticles with specific targeting ligands such as antibodies, peptides, or aptamers. These molecules can specifically recognize and bind to receptors or antigens overexpressed on tumor cells, thereby enhancing accumulation at the tumor site and promoting intracellular delivery via endocytosis. Although this approach considerably increases the cost of drug delivery, it significantly improves targeting accuracy and reduces off-target effects compared to passive strategies [34,35].

3. Formatting your paperapplication of PLGA nanoparticle

3.1. Mechanisms of PLGA nanoparticle application

The fundamental rationale for utilizing PLGA nanoparticle in tumor immunotherapy stems from the inherent biodegradability and tunable release kinetics, which together enable the design of an integrated immune signal delivery platform. This system mimics pathogenic infection, efficiently and persistently activating antigen-presenting cells (APCs) to initiate a robust and specific anti-tumor immune response [36,37].

Specifically, PLGA nanoparticles can be applied in tumor immunotherapy by incorporating immunogenic components such as tumor-associated antigens, antigen-presenting adjuvants, and cytokines. For instance, common immune-related adjuvants like TLR agonists or STING agonists, when delivered via PLGA-based targeting systems, can specifically enhance dendritic cell maturation and antigen presentation—effects often unattainable with conventional administration—thereby facilitating effective antitumor immunity [38]. On the other hand, the encapsulation and targeted release of cytokines (such as IL-2, IFN-γ and IL-12) by PLGA nanoparticles within tumor tissues can remodel the tumor immune microenvironment, enhance local immunostimulatory signals, and avoid the side effects associated with systemic cytokine exposure [39,40]. Furthermore, strategies targeting immune checkpoint molecules such as PD-1/PD-L1 represent another significant direction for PLGA nanoparticle-based immunotherapy. Additionally, PLGA nanoparticles serve as effective carriers for nucleic acid therapeutics—including mRNA, siRNA, and plasmid DNA—enabling precise regulation of specific genes in immune cells or tumor cells within the tumor tissue, and thus advancing tumor immunotherapy through a precision medicine approach [41].

3.2. Administration strategies of PLGA nanoparticle

Administration strategies primarily include local injection, systemic delivery, and mucosal administration. Local injection represents the most widely utilized strategy, enabling precise deposition of nanoparticle directly into the tumor or target tissue. This approach facilitates high local drug concentrations and sustained release kinetics, which promote in situ activation of anti-tumor immune responses—such as enhanced antigen presentation and T-cell infiltration—while actively remodeling the immunosuppressive tumor microenvironment. This approach also significantly reduces systemic side effects of highly toxic agents (chemotherapeutics or cytokines) and can elicit a systemic immune response capable of targeting metastatic lesions through the abscopal effect [42].

Systemic delivery, most commonly achieved through intravenous injection, offers theoretical whole-body coverage. However, unmodified nanoparticle are rapidly cleared by the mononuclear phagocyte system (MPS), resulting in predominant accumulation in the liver and spleen. Surface engineering strategies, such as PEGylation (for stealth effects) or conjugation with specific targeting ligands (e.g., antibodies or peptides) are often employed to improve enhance pharmacokinetic profiles, extend half-life, and improve tumor-specific accumulation. Despite these advances, the

DOI: 10.54254/2753-8818/2026.AU29885

technical and regulatory complexities associated with functionalized nanoparticle have hindered their widespread adoption in immunotherapy [43].

Mucosal administration, often via the oral route, presents considerable challenges due to harsh physiological conditions—including acidic gastric pH, digestive enzymes, and the mucosal barrier—that can degrade therapeutic payloads and impede absorption. Current research aims to overcome these obstacles through material-based strategies (e.g., enteric coatings), mucoadhesive agents, or nano-sized formulations. While promising for patient compliance and non-invasive vaccination, mucosal delivery of PLGA nanoparticle remains in early developmental stages and requires further refinement to achieve clinical relevance [44,45].

4. Therapeutic strategies of PLGA nanoparticle in tumor immunotherapy

4.1. Targeting immune checkpoints

Conventional immune checkpoint inhibitors, such as anti-PD-1/PD-L1 antibodies, are typically administered systemically, which often leads to immune-related adverse events due to their widespread distribution [46,47]. Encapsulating PD-1/PD-L1 inhibitors within PLGA nanoparticle offers a promising strategy to overcome this limitation. This formulation allows for enhanced accumulation at the tumor site through either passive or active targeting mechanisms, facilitating localized and sustained drug release. As a result, therapeutic efficacy is markedly improved, while the risk of systemic side effects is reduced.

Significant advances have been made in the development of PD-1/PD-L1-targeted strategies, leading to a paradigm shift in tumor treatment. Evidence from a study employing anti-PD-L1 F(ab) fragment-conjugated PEGylated PLGA particles demonstrated that this targeted delivery system markedly increased intratumoral drug concentration, enhanced infiltration of cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells, and potently suppressed tumor growth in an MC38 colon cancer mouse model. This PLGA particles-formulation yielded efficacy on par with free antibodies while mitigating systemic toxicity risks. Further extending this approach, a multifunctional PLGA-based nanoparticle was engineered for the co-delivery of an anti-PD-1 antibody and ferroferric oxide, with its surface functionalized by the targeting peptide GRGDS. In a B16/F10 melanoma model, the combination of photothermal therapy and checkpoint blockade produced a potent synergistic effect, leading to significantly prolonged survival. Alternatively, another strategy focuses on using PLGA nanoparticles to directly deliver siRNA into the tumor microenvironment to silence checkpoint genes. For instance, nanoparticles co-loaded with siPD-1 and siPD-L1 have been shown to effectively reduce the expression of these immune checkpoints on both T cells and tumor cells. When integrated with a PLGA-based cancer vaccine, this siRNA delivery strategy resulted in complete tumor eradication in models of thymoma and myeloma [48-50].

4.2. Remodeling tumor microenvironment

“Cold” tumors are typically characterized by a scarcity of T-cell infiltration and a profoundly immunosuppressive tumor microenvironment (TME), which collectively contribute to their resistance to conventional immunotherapies [51,52]. To counteract this, PLGA particles can be engineered to deliver various immunomodulatory agents to reprogram the TME. For instance, PLGA nanoparticle loaded with TLR agonists can activate antigen-presenting cells, whereas those

DOI: 10.54254/2753-8818/2026.AU29885

encapsulating chemotherapeutic drugs can induce immunogenic cell death (ICD) to stimulate tumor antigen release.

In a representative study, PLGA nanoparticles co-encapsulating the TLR7/8 agonist R848 were functionalized with an M2 macrophage-targeting peptide and coated with tumor cell membranes. This sophisticated design effectively reprogrammed tumor-associated macrophages (TAMs) from an immunosuppressive M2 to an immunostimulatory M1 phenotype. This shift in polarization successfully activated a robust T-cell-mediated antitumor response, leading to significant tumor regression in a B16/F10 melanoma model. In a complementary approach, encapsulating oxaliplatin into PEG-PLGA nanoparticles was shown to enhance the induction of ICD in a pancreatic cancer model more effectively than the free drug. This process triggered the release of damage-associated molecular patterns, promoted the activation of dendritic cells and T cells, and elicited a superior antitumor effect in immunocompetent versus immunodeficient mice, thereby validating an immune-dependent mechanism of action [53-55].

4.3. Developing cancer vaccines

Cancer vaccines represent a pivotal immunotherapeutic strategy designed to prime the host's adaptive immune system for the precise recognition and eradication of malignant cells [56,57]. Poly(lactic-co-glycolic acid) (PLGA) particles have emerged as a highly versatile and promising platform for vaccine delivery, owing to their exceptional capacity for the co-encapsulation of diverse tumor-associated antigens—including neoantigen peptides, proteins, or mRNA—and potent immune adjuvants, such as Toll-like receptor (TLR) agonists (e.g., CpG ODN, poly(I:C)). This co-delivery system ensures the synchronized trafficking of payloads to antigen-presenting cells (APCs), particularly dendritic cells (DCs), within lymphoid tissues, thereby facilitating robust antigen presentation and the subsequent initiation of a potent, cytotoxic T lymphocyte (CTL)-dominated antitumor response.

Based on this strategy, Creemers, J. and colleagues developed PLGA-based immunomodulatory nanoparticles by conjugating the cancer-testis antigen NY-ESO-1 peptide with the natural killer T cell stimulant IMM60 [58]. In mouse models, they demonstrated that these PLGA nanoparticles induce NY-ESO-1-specific $CD8^+$ T cell responses and significant antibody production, effectively activating both cellular and humoral immune responses for tumor immunotherapy. Furthermore, these nanoparticles have advanced to a Phase I clinical trial for patients with NY-ESO-1-positive malignant tumors, underscoring the considerable clinical translation potential of PLGA-based cancer vaccine strategies.

Beyond subunit vaccines, PLGA particles also serve as an excellent scaffold for constructing in situ vaccines, which aim to convert the established tumor microenvironment into an immunogenic site. In a innovative approach, researchers co-loaded the photothermal agent indocyanine green (ICG) and the TLR7 agonist imiquimod into PLGA nanoparticles. Upon administration and subsequent near-infrared (NIR) laser irradiation in a 4T1 murine breast cancer model, this combination effectively mediated photothermal ablation of the primary tumor. This process triggered immunogenic cell death (ICD), resulting in the release of tumor-native antigens in situ. The simultaneous release of the adjuvant then created a potent in situ vaccination effect, which not only activated systemic antitumor immunity but also significantly inhibited the growth of untreated distal metastases [59-61].

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5. Conclusion

PLGA nanoparticle, with their outstanding biocompatibility, biodegradability, and tunable release kinetics, are rapidly emerging as a highly attractive multi-functional delivery platform in the field of tumor immunotherapy. Their potential is increasingly recognized, and future advancements are expected to transform them from passive carriers into active immunomodulator. By co-encapsulating a variety of therapeutic agents—such as tumor antigens, immune adjuvants, and immune checkpoint inhibitors—PLGA nanoparticle are poised to enable one-step, synergistic delivery. This approach has the potential to spatiotemporally mimic and optimize the natural immune response, thereby effectively inducing and sustaining a robust anti-tumor immune reaction.

PLGA nanoparticles offer a platform for developing personalized cancer vaccines and reprogramming the tumor microenvironment. By enabling localized delivery, they can transform immunologically "cold" tumors into "hot" ones, which enhances immune-mediated tumor killing while minimizing systemic exposure and off-target toxicity. Furthermore, their potential extends to synergizing with other modalities. For instance, in solid tumors—where immunosuppressive microenvironments often limit efficacy—PLGA nanoparticles could deliver sustained pro-survival signals to augment CAR-T cell therapy [62,63].

However, translating these promising systems into clinical practice faces several hurdles. Key technical challenges include optimizing drug encapsulation and maintaining the stability of large biomolecules. Scalable manufacturing also remains complex and lacks standardization, complicating efforts to ensure consistent product quality and batch-to-batch reproducibility [64]. Additional concerns involve initial burst release and potential local inflammation triggered by polymer degradation by-products, which can undermine the predictability of therapeutic safety and efficacy. Finally, as combination products with complex mechanisms of action, PLGA-based therapeutics must navigate lengthy clinical pathways and rigorous regulatory scrutiny, creating significant development risks and uncertainty.

In conclusion, while PLGA nanoparticles represent a promising oncotherapy strategy with substantial potential to advance cancer immunotherapy, fulfilling this target will require deeper collaboration across materials science, immunology, and oncology. Successfully bridging the gap from rational design to robust clinical validation is now the critical next step toward offering patients new and effective treatment options.

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