TOPICAL REVIEW

PLGA-based drug delivery system for combined therapy of cancer: research progress

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Abstract

In recent years, PLGA micro/nano particle drug delivery systems has been widely used in cancer treatment. According to the unique properties of PLGA, carriers of various structures are designed to keep the function of drugs or bioactive substances, ensure the effective load of molecules and improve the bioavailability of drugs in diseased parts. PLGA is one of the earliest and most commonly used biodegradable materials. It is often used for functional modification with other polymers (such as polyethylene glycol and chitosan) or other molecules (such as aptamers and ligands) to deliver various small molecule drugs (such as DOX and DTX) and bioactive macromolecules (such as proteins and nucleic acids) to improve targeting, controlled release and therapeutic properties. In this paper, the preparation methods, physical and chemical properties and medical applications of PLGA micro/nano particles are discussed. We focused on the recent research progress of the PLGA-based drug carrier system in tumor combination therapy.

Abbreviations

PLGA Poly(lactic-co-glycolic acid)
FDA Food and Drug Administration
PRINT Non-wetting templates
LA:GA Lactide: Glycolide
O/W/O Oil in water in oil
W/O/W Water in oil in water
MCF-7 Michigan Cancer Foundation – 7
MCF-7/ADR Michigan Cancer Foundation -7/ adriamycin
TAM Tumor-associated macrophages
DC Dendritic cells
4T1 Breast cancer cells
IFN-γ Interferon-gamma
Th-1 Helper T cells
TC-1 Cytotoxic T cell
IL-10 Interleukin-10
IL-12 Interleukin-12
NK Natural killer

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1. Introduction

Cancer is still one of the main causes of threats to human health and death. At present, many therapies have been developed to improve the anti-tumor effect. Including immunotherapy, chemotherapy, combination therapy, etc. Common immunotherapies include immune checkpoint therapy and immune cell therapy. The former uses antibodies or other molecules to block receptors on the surface of tumor cells to promote the phagocytosis of immune cells or other cells [1, 2], and the latter uses direct stimulation immune cell activation further kill tumor cells [3–5]. Chemotherapy can kill tumors by directly using cytotoxicity [6]. Photodynamic therapy increases the production of reactive oxygen species in tumor cells under light, which leads to protein degeneration and DNA damage, and achieves the purpose of inhibiting the growth of tumor cell, such as small molecule photosensitizers such as R837 and CE6 [7]. Although a variety of highly active and specific drug molecules have been used for anti-tumor therapy and achieved good results. However, single therapy usually faced the problems of high dose and low bioavailability [8, 9]. In addition, frequent drug administration is more likely to lead to systemic cytotoxicity and increase the pain of patient [10]. Therefore, researchers usually combine one or more treatment methods to enhance anti-tumor effects.

Developing an efficient drug delivery system for cancer has become a research hotspot in the biomedical field [11]. Researchers have prepared various micro/nanoparticle as delivery vehicle [12], breaking through the restriction of free drug applications [13]. Usually, in the design of drug delivery systems, in order to obtain higher drug loading rate, suitable release rate and maintain drug activity, the selection of materials is a key factor [14]. Among all kinds of materials, synthetic or natural polymer materials have received widespread attention, among which synthetic materials are divided into non-degradable and degradable polymers [15]. PLGA is a degradable aliphatic polyester, which has been approved for clinical use by the Food and Drug Administration (FDA) [16]. PLGA micro/nanoparticle have excellent biocompatibility, degradability, non-immunogenicity, micro-cytotoxicity, adjustable structure, and controllable slow-release according with degradation kinetics, which has become a widely used material in drug delivery systems [17–20]. In addition, because its molecular weight and composition ratio will affect the release and degradation rate of drugs, PLGA micro/nanoparticle are a good barrier to protect the premature release and degradation of drugs [21]. In addition, polymerization with other polymers or modification of specific molecules on the particle surface can guide targeted drug delivery and reduce systemic side effects [22–24]. For lipophilic molecules, simple single emulsification technique is used for encapsulation while for biological macromolecules such as protein double emulsification technique is mainly used [25, 26]. More flexible routes of administration include oral administration, inhalation, intravenous injection, subcutaneous injection, intramuscular injection or in situ humoral injection, so as to deliver drug-loaded particles to target lesions, thus improving the treatment and prognosis [27–31]. PLGA microspheres increase the drug load and avoid phagocytosis by macrophages, thus achieving a longer-lasting drug release effect [32]. PLGA nanoparticles have smaller size and targeting characteristics, and they are easier to accumulate in tumor cells through the EPR effect [33]. However, it cannot be ignored that PLGA micro/nanoparticle inevitably have problems such as residual organic solvents, poor tumor tissue penetration and cancer uptake, incomplete drug release, and instability of encapsulated active molecules [34–37].

As a biosafety material, PLGA is a drug delivery vehicle with great potential and has been successfully applied to improve tumor treatment, and it still has greater application prospects in the future. Therefore, this article reviews how PLGA micro/nanoparticle as an anti-tumor agent can activate anti-tumor immunity and enhance anti-tumor efficiency through combination therapy in different tumor models in vivo and in vitro in recent years, hoping to provide future development and design based on PLGA micro/nanoparticle combined treatment to improve anti-tumor research has brought inspiration (figure 1). It is mainly divided into four parts, including the preparation methods of various new and traditional PLGA micro/nanoparticle, and the physical and chemical properties and characteristics of PLGA micro/nanoparticle. How to successfully encapsulate various drug molecules into PLGA micro/nanoparticle to improve the pharmacokinetics, and how PLGA
micro/nanoparticle improve the stimulation of various cells in the tumor microenvironment to trigger effective combined anti-tumor therapy.

2. Preparation methods of PLGA micro/nanoparticle

PLGA micro/nanoparticle can be prepared by various methods, including traditional emulsification technology, spray drying, nano-precipitation method and so on. At present, the widely used preparation methods include modified emulsification, microfluidic and membrane emulsification. According to the characteristics of polymer, PLGA micro/nanoparticle were prepared by emulsion solvent evaporation method. The preparation process is simple, and it has been widely studied, including single emulsion method and double emulsion method [38]. The particle size, morphology, encapsulation rate and drug release behavior are affected by many factors, such as the types and components of polymers and surfactants. However, the drug encapsulation efficiency is low, and the residual organic solvents is still an urgent problem to be solved [39].

Phase separation technology and nano-precipitation method are also methods to obtain PLGA micro/nanoparticle with controllable release ability by simple preparation process [40, 41]. In addition, the nano-precipitation method can complete the preparation of particles in one step, and it is simpler and more effective than emulsification method to encapsulate drugs [42]. The salting-out method is an improved emulsification technique, which is suitable for high-concentration polymer solutions and is beneficial to the encapsulation of heat-sensitive drugs [43]. Another spray drying method is also suitable for packaging heat-sensitive substances, and it is the preferred method for removing organic solvents [44–46]. Membrane emulsification technology is a new technology that uses a combination of emulsification methods and porous membranes. The particle size is more uniform, the drug encapsulation rate is high, and the activity is well maintained, which overcomes the shortcomings of the emulsification solvent evaporation technology [47]. Gas shearing technology is a reliable method.
method to accurately control the preparation of symmetric or anisotropic particles with different numbers and different characteristic compartments, and it can also be used for cell culture [48–50]. In addition, in-situ formation technology has also been developed to prepare microparticles directly at the site of the disease [51]. Although there is an initial outbreak of drug release, this method overcomes the high manufacturing cost and potential toxicity [52]. As a method which can be used to accurately control the shape and size of particles to obtain monodisperse micro/nanoparticle, it mainly includes particle replication in non-wetting templates (PRINT) and microfluidic technology [53, 54]. The former is a soft lithography-based molding technology that is more suitable for mass production of particles [55]. Microfluidic technology, especially at the micro level, has been widely used in bioengineering research, drug carriers and other fields [34, 35, 56, 57]. By selecting different methods to prepare particles with specific characteristics, the release kinetics, entrapment efficiency, stability and degradation rate of drug molecules can achieve more effective therapeutic effects. The advantages and disadvantages of several commonly used PLGA micro/nanoparticle preparation methods were discussed (figure 2).

3. Types of PLGA micro/nanoparticle

PLGA micro/nanoparticle have a variety of morphological structures, including solid, porous, core-shell structure and multi-compartment particles. Porous particles and core-shell particles are the most widely used types at present, and they can realize the co-delivery of multiple drugs [11, 58]. Single-layer polymer carriers prepared based on PLGA are widely used to deliver hydrophilic or hydrophobic drugs [59]. However, the single-layer particles are dense and nonporous, which may cause difficulty in drug release, slow degradation, and difficulty in achieving satisfactory drug molecular release kinetics [60–62]. This defect can be improved by reducing the polymer concentration, selecting the PLGA with the appropriate composition ratio (Lactide (LA): Glycolide(GA)), changing the proportion of additives, and adjusting the conditions of different preparation methods (such as the stirring speed of the emulsion method, the voltage of the electrospray microfluidics, and the pressure of the supercritical method) to make smaller particles [63–65]. PLGA is one of the most widely used materials in macroporous microspheres, which has good aerodynamic and slow release characteristics [66]. In recent years, PLGA-based porous microspheres have been widely used as long-term reservoirs in the delivery of drugs and bioactive molecules [67]. Compared with the traditional PLGA micro/nanoparticle monolayer structure, two or more layers have superior multi-drug delivery capacity [68, 69]. Loading multiple drugs (such as chemotherapy drugs, antibodies or nucleic acids) in the core layer and shell layers at the same time allows different molecules to be stably and continuously released from the polymer particles, which makes it easier to maximize the therapeutic effect and is unlikely to generate drug resistance [70, 71]. In addition to the controlled and sustained release of drugs, it can also meet the need of the timed release of drugs [72]. However, it is still a challenge to solve the problem of drug loading rate of hydrophilic drugs and adverse reactions caused by sudden release. Multi-compartment particles allow multiple materials to be used in different separation phases, thus
creating two or more compartments, allowing individual particle to have different characteristics, such as independent release when encapsulating drugs, and also encapsulate magnetic beads, photosensitizers and nucleic acids [73–76]. At present, due to the limitation of the preparation process, the preparation of double compartments is relatively easy to realize, but it is not so easy to obtain more stable multi-compartment micro/nanoparticle. Therefore, the flexibility to choose the appropriate type of PLGA micro/nanoparticle is very important to improve the effect of disease treatment.

4. Physical and chemical properties of PLGA micro/nanoparticle

PLGA is a kind of amorphous polymer composed of lactic acid and glycolic acid. This feature enables the loaded drug to be more evenly dispersed in the polymer (figure 3). PLGA degrades slowly in the physiological environment or tumor sites, and decomposes into the original monomer components (LA:GA) [77, 78], both of which are physiological metabolites of the citric acid cycle [79]. Therefore, the decomposition products of PLGA can be completely eliminated from the human body in the form of carbon dioxide and water [80], but the increase in acidic products may also lead to toxicity and inflammation [81]. The properties of PLGA polymer depend on the composition ratio and molecular weight of the polymer, hydrophilicity and hydrophobicity, concentration, terminal group (ester or carboxyl) functionality, supported drugs, and the type or concentration of surfactant [82]. LA and GA have different hydrophilic groups, and the different ratios determine the amphipathic property [83], degradation rate [84], mechanical strength [85], glass transition temperature [86], solubility and structure of PLGA. In addition, the lower the molecular weight, the higher the carboxyl content at the end of PLGA, and the faster the degradation speed, mainly because the hydrophobicity of low molecular weight is smaller, and carboxyl can increase hydrophilicity [87]. The results showed that PLGA with the ratio of (LA:GA) 50:50 was more hydrophilic and had the fastest degradation rate, and it had advantages over other ratios in drug encapsulation and release [44]. The multi-phase degradation mechanism of PLGA provides a theoretical basis for better design of the release of loaded drugs. The release of the drug is through the disintegration of the polymer network structure and the erosion of the water environment, so it is widely used in slow control agents. Some researchers have studied the biodegradation of PLGA and found that both extracellular enzymes and intra-encapsulated enzymes can affect degradation, including trypsin or bromelain [88, 89]. However, this statement is still controversial, and the related mechanism is not particularly clear. In addition, the desired surface pore size and particle size of the carrier can be prepared by selecting a suitable pore-forming agent, surfactant, polymer concentration and production process [12, 90–92].
5. Method of encapsulating/loading drugs into PLGA micro/nanoparticle

PLGA micro/nanoparticle prepared by the above-mentioned various traditional and latest technologies are widely used for drug delivery. Most small-molecule fat-soluble drugs can be prepared by directly mixing with polymer solutions [93], but water-soluble drugs need to be converted into a hydrophobic form first, or after mixing with surfactants, through oil in water in oil (O/W/O) or water in oil in water (W/O/W) double emulsion method [37, 94]. Drug molecules are delivered to the diseased parts in the form of encapsulation inside the particles, and are polymerized and bound or adsorbed on the surface [95–98]. According to the nature of the drug contained, different methods are chosen to achieve the purpose of treating diseases. For example, small molecule drugs and proteins can be wrapped inside the particles, and most nucleic acids are adsorbed on the surface of the particles through electrostatic action or crosslinking agents [12]. Especially for biologically active molecular therapy, it is still the focus of research to efficiently encapsulate and maintain long-term biological activity [99]. In addition, it is often combined with other polymers, such as polyethylene glycol, polyethyleneimine, alginate and chitosan, to construct PLGA hybrid particles, including modified copolymer particles, core-shell composite particles and polymer micelles, which are commonly used methods to load drugs and bioactive molecules [20, 100, 101].

6. Combined treatment of tumor based on PLGA micro/nanoparticle drug delivery system

The limitations of monotherapy can easily lead to poor curative effects of tumor. Combined therapy can deliver a variety of anti-cancer drugs at the same time, which has been widely used in the treatment of tumors and has shown good prospects in clinical applications [102–104]. Therefore, the rational design of PLGA micro/nanoparticle drug delivery system and delivery of various molecules to the tumor site can not only reduce the drug resistance of tumor cells and improve the therapeutic effect, but also provide a new approach for the treatment of various tumors. As shown in table 1.

6.1. Delivery to cancer cells

Loading drugs into PLGA micro/nanoparticle directly into tumor cells is a conventional method to increase the bioavailability of drugs to tumor cells and reduce damage to normal tissues [109, 126, 127]. For killing tumor cells, PLGA micro/nanoparticle usually deliver chemotherapeutics, photothermal preparations or radioactive preparations, and the drug-loaded particles are delivered to the tumor site by in-situ injection or transvascular transport [128]. The use of drugs released in the body to directly kill tumor cells at the same time or add light and heat, magnetic field conditions or combined with immune molecules to activate the immune response to achieve tumor suppression [108, 112]. In addition, many studies have further improved the penetration and absorption of drug tumor cells by modifying tumor cell targeting molecules on the surface of PLGA micro/nanoparticle [113]. It is a promising strategy to prepare a multifunctional PLGA carrier drug delivery system combined with chemotherapy, photothermal therapy or radiotherapy and other therapeutic modes to produce synergistic or combined therapeutic effects for tumors [110, 129]. In recent years, PLGA micro/nanoparticle delivery systems have been widely used as drug delivery systems in combination with tumor treatment due to their increased specific surface area, drug loading capacity, and adjustable structure. It has shown potential clinical application potential in various tumor models such as liver cancer and lung cancer [105–107]. In order to overcome the limitations of monotherapy, GUO et al. designed a drug delivery system that integrates chemotherapy and photothermal. By using the biomimetic coating of the tumor cell membrane to target and PH-sensitive drug release, compared with free DOX, the successful delivery of the drug to the tumor cell nucleus has a more powerful cytotoxic effect. The study found that the tumor cell MCF-7/ADR efflux rate of free drugs was 100%, while the nanosystem group significantly decreased, and the efflux rate is an indicator of overcoming cell resistance. In vitro studies on cytotoxicity found that the survival rates of MCF-7 and MCF-7/ADR cells in the chemotherapy-photothermal treatment group were reduced to more than 95% and 75%, respectively. The co-treatment group also showed excellent anti-tumor effects in the breast cancer model of drug-resistant mice [111]. Another study also found that inhalable PLGA porous microspheres loaded with dual drugs significantly inhibited tumor growth and metastasis in tumor-bearing mice with lung cancer in situ [130].

6.2. Delivery to immune cells

In addition to tumor cells and tumor stem cells, the tumor microenvironment also includes various immune cells, such as tumor infiltrating lymphocytes, tumor-associated macrophages (TAM) and dendritic cells (DC) [131]. Compared with directly targeting tumor cells, recent studies have also found that the PLGA micro/nanoparticle delivery system is a good carrier for improving immunotherapy. In preclinical studies, it was also
| Drug@ Formulation | Fabrication techniques | Application         | Functions                                                                                          | Results                                                                                                                                                                                                 | References |
|-------------------|------------------------|---------------------|---------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| REGO@/PLGA MPs + Miriplatin | Emulsion-solvent evaporation/extraction | Hepatocellular carcinoma | Limit the proangiogenic response after TACE; Local and sustained drug release; The average tumor weight of the Miriplatin plus REGO microsphere group was 0.48g, which was significantly lower than the other groups.; Tumor angiogenesis is reduced, which antagonizes drug resistance; | In liver cancer tumor models, tumor growth inhibition and treatment response are the most significant; Tumor angiogenesis is reduced, which antagonizes drug resistance; | [105] |
| Re/DOX@PVSA/PLGA MPs | Double emulsification | Hepatocellular carcinoma | Chemotherapy and radiotherapy; Local embolization; | In liver cancer tumor models, tumor growth inhibition and treatment response are the most significant; | [106] |
| ultrasound + DOX@PLGA MPs | Double emulsion solvent evaporation technology | Melanoma | US physical damage; DOX chemical damage | The average survival time of mice in the US plus DOX/PLGA microsphere group was more than doubled than that of the control group.; | [107] |
| ANG/DTX@GS/PLGA NPs | Emulsion solvent evaporation method | Glioma | Chemotherapy; hyperthermia; X-ray imaging; active targeting | ANG/GS/PLGA/DTX/808nm laser nanoparticles show significant tumor suppression efficiency; Increased expression of MHC i molecules; slowed tumor progression and improved median survival | [108] |
| ICG/NextA@PLGA NPs | Nano emulsion synthesis scheme | Melanoma | PTT; epigenetic therapy; | Increased expression of MHC i molecules; slowed tumor progression and improved median survival | [109] |
| NIR700@PLGA/PEG NPs | Emulsion and solvent evaporation-extraction method | Colon cancer | Photodynamic therapy; immunotherapy; enhanced EPR effect | Induce anti-tumor immune response; induce vascular rupture and ensure the accumulation of NP in the tumor area; reduce tumor volume; | [110] |
| PIO/Dox/Mcl-1siRNA@PLGA-CSNPs | Emulsion solvent evaporation method | Breast cancer | MCF-7 cancer cell membrane coating; chemical-photothermal therapy; magnetic targeting; | Inhibits almost 80% of tumor growth in MCF-7/ADR tumor model | [111] |
| A12@PLGA MPs + PTX@HA-SS-TOS | Solvent evaporation method | Colon cancer | Precision chemotherapy; Immunotherapy; Redox sensitivity; Activate host immune response; | Significantly improve the efficacy of a variety of tumor models; reduce immunosuppression caused by chemotherapy; Distal tumor suppression effect is remarkable | [112] |
| Rutin/Benzamide@PLGA MPs | Emulsion method | Breast cancer | Active targeting; inhibition of multidrug resistance; sustained release of drugs; | Potential cancer treatment effect; low genotoxicity in zebrafish model; | [113] |
| ART/ALA@HA-PLGA NPs | Self-assembly | Hepatocellular carcinoma | Dual administration; new core-shell structure; PH sensitivity; sonodynamically active; | The minimum tumor volume (V/V0) in the HA-PLGA@ART/ALA group was 0.77 ± 0.19; the tumor cell apoptosis rate was the highest when combined with US; | [103] |
| T cell | | | | | |
| Dox/CpG@ PLGA MPs | Emulsion method | B lymphoma; B16 melanoma | Chemotherapy; immunotherapy; In situ immunization; Break tumor tolerance; activate T cells | Dox/CpG MPS group suppresses tumors in situ and distant; mice are tumor-free; combined anti-CTLA-4 and anti-OX40 therapy significantly reduces B16 tumor growth; | [114] |
| Drug @ Formulation | Fabrication techniques | Application | Functions | Results | References |
|--------------------|------------------------|-------------|-----------|---------|------------|
| CCMP/R837@PLGA NPs | Oil-in-water (o/w) emulsion method | Breast cancer | Bionic cell membrane; enhance long-term anti-tumor immunity; Stimulates DC maturation and IL-2 secretion | Inhibition of tumor growth and prolonged survival (75% of mice survived more than 30 days after tumor formation). In the treatment group, CD8+ T cells and memory T cells increased, and regulatory T cells decreased; | [115] |
| TA/Met@PLGA MPs   | Emulsion method         | Breast cancer; melanoma | Photothermal effect; immunotherapy; regulating immune memory CD8+ T cells; changing cell metabolic behavior; | In 4T1 tumor model and B16F10 tumor model, the number of CD8+ TCM increased, and tumor metastasis and inhibition were significantly reduced; after combined anti-PD-1 peptide therapy, the number of CD8+ TCM increased significantly; | [116] |
| OVA/Rib@PLGA MPs  | Double emulsification solvent evaporation method | Melanoma | Increase of specific CD8+ T cells; DC activation; immune checkpoint block; Tumor ablation | Mice in the MP-OVA/rib PLGA treatment group showed more significant peptide-specific killing; combined with anti-CTLA-4/anti-PD-1, it significantly increased the tumor suppression effect and the reconstruction of anti-tumor immunity; | [4] |
| TAM BODIPY/TM R@PLGANPs | Nano-precipitation | Breast cancer; lung cancer; | Chemothrapy; Radiotherapy; TAM quantitative Macrin imaging; EPR; | In vivo Macrin imaging found that Macrin was selectively taken up by macrophages >90%; in addition, in tumor models, TAMs increased by 180%–650% after treatment, and the aggregation of TAM-rich tumor nanoparticles increased by more than 700%; | [117] |
| Ec-R848@PLGA + DOX@PLGA NP | Emulsion solvent-evaporation method; | Breast cancer; | Induces ICD; stimulates severe polarization of TAM; antagonizes immunosuppression; | In the 4T1 tumor model, the M1/M2 ratio was increased to 3.79 times that of PBS, and the number of CD4+ and CD8+ T cells increased; after 18 days, the tumor volume was significantly suppressed; | [118] |
| PLGA-ION-R837 @ M | Solvent evaporation | Breast cancer; | Bionic carrier; magnetic targeting; polarized TAM enhanced immunotherapy; | In the in vivo model, after treatment, the M1/M2 ratio increased to 2.88, CD4+ T lymphocyte infiltration increased, and the tumor suppression rate reached 72.5%; | [119] |
| DC ATP/E7@PLGA NPs. | Two-stage emulsification method. | Papilloma virus-associated tumor | ATP new vaccine adjuvant; | After adding ATP adjuvant treatment, DC maturation and nanoparticle uptake increased, tumor volume was completely eliminated and durable immunity was established; | [120] |
| Drug@Formulation Cancer cell | Fabrication techniques | Application | Functions | Results | References |
|-----------------------------|------------------------|-------------|-----------|---------|------------|
| 522@PLGA NPs               | Double-emulsion solvent evaporation technique | Melanoma | The load of 522 is increased by 33 times; Gas (CO2)-producing nanoparticles; | In the melanoma model, the drug is released in response to acid, CD8 T cells and natural killer (NK) cells increase, antigen presentation increases, and tumor volume is suppressed; | [121] |
| Man-RBC/PLGA NPhgp         | Nanoprecipitation method | Melanoma | Active targeting; redox sensitive release; antigen reservoir; | The secretion of costimulatory factors increased by about 2 times to induce DC maturation, tumor growth and metastasis inhibition; | [122] |
| NK cell                    | Emulsion method         | Prostate cancer | Nano-reservoir; controlled release; co-localized nano-immunotherapy; | In the in vitro model, the natural killer cell-mediated J-Lat cell killing activity is enhanced; | [95] |
| Circulating tumor cell     | Emulsion solvent evaporation method | Breast cancer | Cancer membrane coating; induce calcium ion accumulation and EMT; | Effectively inhibit the generation and circulation of tumor CTC clusters, thereby inhibiting tumor metastasis, and synergistically promoting tumor apoptosis; | [123] |
| Cancer stem cell           | Modified double emulsion method | Triple negative breast cancer, | Dual response nanoparticles; reduce drug resistance; active targeting; EPR; | In breast cancer models, it effectively destroys cancer stem cells, which is 500 times more effective than other groups; | [124] |
| Cur/Sal@PEG-PLGA NPs       | Double emulsion method  | Malignant tumor | Complementary drug function; targeted co-delivery; limit EMT; | In vitro experiments proved that basic fibroblast growth factor, cell migration and EMT inhibition, and the cumulative toxicity of drugs to cells; | [93] |
| SAL/DTX@PLGA/TPGS NPs      | Nanoprecipitation method | Breast cancer | Optimal drug synergy ratio; longer drug circulation time; active targeting; | Compared with other control groups, the SAL/DTX-PLGA/TPGS NPs experimental group showed the best anti-tumor and anti-CSCs activity; | [125] |
found that delivered antigens, adjuvants, and immune drugs can cause effective immune stimulating responses, which has attracted the interest of more researchers [132].

6.2.1. T cells

T cells play a key role in activating the body’s immune response in immunotherapy and combination therapy [115]. At the tumor site, T cells are subject to signal regulation from tumor cells or aggregation of immunosuppressive cells, leading to failure or exhaustion of T cells to recognize abnormal cells [133]. Generally speaking, molecules delivered by PLGA micro/nanoparticle [such as antibodies, antigens, immune adjuvants] can directly recruit T cells to the tumor site or block related protein molecules on the surface of tumor cells or increase the exposure of tumor-related antigens to activate T cells. Initiates a stable and systemic T cell immune response [116]. It has also been found in various preclinical mouse tumors models that PLGA drug-loaded particles alone or in combination with antibody therapy can continue to inhibit tumor growth. Attributable to the drug release in vitro and the pharmacokinetics in the body, it shows longer drug release and the continuous stimulation of immune cells ensures the quantity and quality of T cells [4, 134]. In addition, PLGA micro/nanoparticle are faster in stimulating and enhancing immune responses than other delivery systems [135]. In particular, PLGA microspheres mediate the delivery of antigens and other molecules to T cells, resulting in a rapid increase in the infiltration of CD8+ T cells, reducing regulatory suppression of T cells and the establishment of immune memory [102, 116, 136]. Various types of immune adjuvants have been shown to cause an enhanced immune response [114, 137]. Therefore, PLGA micro/nanoparticle as a cancer vaccine are expected to solve the problems of limited immune response and systemic inflammatory response. Encapsulation and delivery of biologically active substances such as antigens and proteins in PLGA micro/nanoparticle can not only avoid rapid degradation, but also activate the immune response. Combined with other antibodies, chemotherapeutics or photosensitizers to further kill the tumor [115]. Recently, a combination therapy that delivers drug molecules and adjuvants has achieved rapid establishment of anti-tumor immunity in tumors [138]. For example, it induces the infiltration of circulating cancer-specific T cells, stimulates the maturation of cytotoxic T cells, down-regulates regulatory T cells and promotes the secretion of inflammatory factors [139, 140]. Therapies based on immune checkpoints have also made progress in relieving T cell suppression and changing the tumor microenvironment [112, 141]. The functionalized PLGA nanoparticle encapsulating the therapeutic agent achieve the up-regulation of early and late CD8+ T cell function in the mouse 4T1 tumor model. The drug has not been completely metabolized within 48 h of injection into mice, and the half-life is about 13 h [142]. Studies have shown that photothermal treatment can further increase the sensitivity of tumors to immunotherapy. This may be due to the destruction of tumor cells, exposure to more antigens, and inflammation to stimulate the production of cytokines, which in turn stimulates the infiltration and activation of T cells at the tumor site [134, 143, 144]. There are also studies to enhance the immune response by directly stimulating the activation of T cells. The author proved that the agonist of Invariant natural killer cells successfully induced IFN-γ release, T cell toxicity and Th-1 antibody response. In vivo drug distribution kinetics study found that after 30 min of intravenous injection, antigens can appear in the lymph nodes. In addition, the combination of anti-PD-1 antibody and anti-4-1BB agonistic antibody further inhibited tumor growth in the TC-1 mouse tumor model [145].

6.2.2. Tumor associated macrophages

Tumor-associated macrophages (TAM) are immunosuppressive cells that infiltrate the tumor microenvironment [146]. A large number of TAMs play a vital role in tumor metastasis and malignant proliferation. M1-types macrophages are the main cells that inhibit tumor metastasis and malignant proliferation. The use of cytokines or bacteria can stimulate the transformation of TAM into M1-types, and can also down-regulate related pathways to inhibit the polarization of TAM to M2-types [147, 148]. In addition to the immune checkpoint pathway between T cells and tumor cells, the tumor microenvironment also exists between tumor-associated macrophages and tumor cells [149]. There have been many reports on the use of PLGA micro/nanoparticle to directly present drugs to TAM at the tumor site, hoping to activate and reverse the phenotype of TAM [150]. Or delivery of immunosuppressive molecules to block the immunosuppression of TAM by tumor cells and increase the infiltration of M1-type macrophages to improve the tumor microenvironment [94, 151]. The use of PLGA micro/nanoparticle to wrap cytokines, antigens, adjuvants, photosensitizers or antibodies can improve the accumulation of drugs in the tumor site [117]. It has also been proven to successfully reverse the TAM phenotype, and further promote the increase in the secretion of inflammatory factors such as tumor necrosis factor-α and interleukin-6, and the activation of the anti-tumor immunity of T cells after exposure to tumor-associated antigens [118, 119, 152]. Some researchers wrap antigen peptides, chemotherapeutics and immune adjuvants together in PLGA nanoparticles, and coat the surface of the particles with galactose-embedded erythrocyte membranes to achieve TAM targeting. The detection of increased levels of IL-12 and decreased levels of IL-10 proved that TAM was successfully polarized into M1-type.
The author also found that the significant activation of T cells and CTL response at the tumor site enhanced the anti-tumor effect [153]. Recently, this research group has constructed another targeted PLGA nanoparticle. In the melanoma mouse model, it was found that the particles first reached the tumor site after entering the mouse body, and were still mainly distributed in the tumor site after 72 h. The large secretion of inflammatory factors once again proves the successful polarization of TAM. In addition, it was found that TAM further presents antigens to T cells. After T cells secrete a large amount of cytokines, they stimulate the cascade of NK cells to kill tumors, and the tumor inhibition rate reaches more than 80% [154].

6.2.3. Dendritic cells

Dendritic cells (DC) are the most critical cells in the tumor microenvironment to regulate the immune response [155]. The absorption of antigens can be through receptor-mediated endocytosis, macropinocytosis, and macrophage-dependent phagocytosis [29]. In addition, DC, as the most powerful antigen-presenting cell, also has a good absorption capacity for micro-/nanoparticles. Presenting antigens by direct or crossover methods promotes the activation of T lymphocytes and produces a cellular immune response dominated by CD8+ T cell infiltration, which is the basis of DC as an immunotherapy method [126, 140]. However, the immunosuppression in the tumor microenvironment leads to a decrease in the number of DCs and their function is inhibited [156]. Combining the controlled release of PLGA micro/nanoparticle and effective drug molecular load to deliver antigens, adjuvants or low-dose chemotherapeutics to DC. By directly stimulating and recruiting DCs to migrate to tumor sites or regulating tumor cells to expose tumor-associated antigens, the maturity and number of DCs can be increased [120, 121, 157]. In addition, PLGA itself also has the effect of an immune adjuvant, inducing the activation of the inflammasome of DC, thereby enhancing the immune response [114, 158]. Studies have shown that the activation of the immune response is highly dependent on the antigen presentation of DCs, which is a prerequisite for initiating the anti-tumor T cell response [29, 122]. Therefore, in order to improve the effect of tumor combination therapy, some researchers have developed a double particle combination method. On the one hand, alginate-encapsulated lymphocyte chemokine (XCL-1) is injected into the tumor site to attract DC migration. On the other hand, PLGA-DOX NPs was injected intravenously into model mice, a large number of tumor-associated antigens were exposed and then stimulated the maturation of DCs, and then presented antigens to T cells. After T cells were activated, various cytokines were secreted to maintain anti-tumor immunity [159].

6.2.4. NK cells

Due to the rapid lysis of tumor cells by NK cells, they have gradually become a hot spot in tumor therapy in recent years [160]. Encapsulate antibodies, antigens or NK cell agonists and other molecules (antibodies, drugs, etc) into PLGA micro/nanoparticle to improve the tumor microenvironment or present it to NK cells [160]. By enhancing NK cell-mediated cytolysis or down-regulating tumor cell surface signals or stimulating the secretion of cytokines, stimulating activation and inducing immune response to kill tumors [95, 161]. In order to relieve the tumor microenvironment’s immunosuppression of NK cells and enhance the anti-tumor effect. Recently, a study has constructed a kind of PLGA nanoparticles encapsulating manganese dioxide nanoparticles. The results of permeation in the tumor sphere show that by generating a large amount of oxygen, the hypoxic state of the tumor microenvironment is effectively alleviated, and the immunosuppression of hypoxia on NK cells is relieved and the toxic effect of NK cells is enhanced [162].

6.3. Delivery to other cells

Circulating tumor cells (CTC) have great potential to induce tumor metastasis [163, 164]. Compared with tumor cells with limited proliferation, cancer stem cells (CSC) which are prone to multidrug resistance (MDR) and can promote the development of tumor have the potential to cure tumor as targets [93, 165]. Therefore, the development of a targetable multifunctional PLGA micro/nanoparticle to deliver a variety of drug molecules and synergistically inhibit the proliferation of circulating tumor cells or cancer stem cells is essential in inhibiting tumor metastasis and malignant proliferation [125]. Recently, studies have constructed cancer cell membrane-coated PLGA nanoparticles. Cancer cell membranes have the ability to mediate homologous targeting of tumor cells and CTCs, and can also produce immune escape to avoid premature clearance of nanoparticles. In vitro experiments, the released digoxin promotes the decomposition of CTC and inhibits the occurrence of EMT (epithelial-mesenchymal transition) by causing an increase in the concentration of CA ions. At the same time, in orthotopic tumors and lymphatic and CTC clusters metastasis tumor models, it cooperates with DOX to inhibit tumor metastasis [123]. Hyaluronic acid is a good ligand for the CD44 receptor on the surface of cancer stem cells. It is often used to modify the surface of PLGA micro/nanoparticle to target cancer stem cells to deliver drugs [124, 166, 167]. GANT61, as a small molecule antagonist that induces cancer stem cell death, was co-encapsulated with curcumin in PLGA nanoparticles for the first time. The results showed that it successfully
down-regulated GLI1, EGFR protein and PI3K protein, and inhibited the growth of CSCs and bulk tumor cells. The results of dual drug delivery encapsulated by PLGA nanoparticles showed a significant prolongation of plasma half-life time, indicating that it is expected to effectively improve the killing effect on cancer stem cells. In the mouse MCF-7 tumor model, it showed a tumor growth inhibition rate of about 80% [168].

7. The prospect of PLGA micro/nanoparticle drug delivery system combined therapy for tumor

As a biodegradable polymer material, PLGA has special physical and chemical properties, especially the ability to adjust the structure and controllable drug release, which has surprising clinical application prospects as a drug delivery system for combined treatment of tumors [68][169–172]. For example, targeted therapy can effectively avoid systemic cytotoxicity and increase drug accumulation in tumor site [173]. In order to further increase the therapeutic effect, besides targeting cancer cells, we should also consider xenogenic cells, such as tumor stem cells or circulating tumor cells [174]. These cells play an important role in metastasis and recurrence of tumor. At present, in the process of cancer treatment, tumor recurrence is still the main reason leading to poor prognosis. In addition to eliminating existing tumors, combined therapy can also eradicate tumors, such as activating DC and stimulating T cells, so as to mediate an enhanced systemic immune response or inhibit the survival of tumor stem cells [141, 167]. It is worth noting that it is necessary for researchers to further explore ways to avoid the antagonism between the combination of drugs and the adverse reactions, such as the abnormal cellular immune response in combination of antigen and adjuvant or the compensatory reaction in targeting a certain route [175]. In addition, it is still a challenge to prepare PLGA micro/nanoparticle of more suitable size to deliver antigens, adjuvants or cytokines and other drug molecules to stimulate immune cells, and the acidic products of degradation may further lead to molecular degradation and dysfunction [26, 132, 176]. Therefore, by adjusting the proportion of encapsulated drug molecules, we can achieve a more optimized synergistic anti-tumor effect, regulate the drug release in vivo, fully integrate the characteristics of the tumor microenvironment and mobilize more immune cells [115, 121]. It is still a problem worthy of deep consideration and exploration to develop multi-functional preparations for personalized therapy to improve the efficiency of tumor treatment.

8. Summary

In this paper, the preparation methods, physical and chemical properties of PLGA micro/nanoparticle and their application in combined anti-tumor therapy are reviewed. At present, the PLGA micro/nanoparticle have high drug loading, adjustable morphology and controllable release behavior, so as to improve the bioavailability. And can be easily combined with other polymer materials or molecules, so that a single drug and two drugs with different properties (hydrophilic and lipophilic) or the same properties can be simultaneously loaded, or hybrid particles targeting specific cells can be modified on the surface of the hybrid particles. Especially in recent years, it has shown great application prospects in the field of comprehensive anti-tumor treatment. Whether it is the encapsulation and anti-tumor effect of small molecule drugs, or bioactive molecules, it shows unique advantages. However, many current studies are only based on some tumor models, and there are still many difficulties in achieving clinical applications, such as how to overcome the cytotoxicity of materials, prepare smaller particles to increase the uptake of cells, overcome the heterogeneity and multiplicity of tumors and reduce off-target effects during targeted therapy. Therefore, we should pay more attention to the development of preparation technology, universality of clinical applications and commercial mass production in the future.

Data availability statement

No new data were created or analysed in this study.

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