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Research progress of nanomedicine for tumor immunotherapy

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ABSTRACT

Cancer, a pervasive threat to human health, presents formidable challenges to traditional treatment approaches. Tumor immunotherapy has emerged as a promising strategy for combating malignancies by bolstering the body's immune response to thwart tumor metastasis and recurrence. Nonetheless, the intricacies of tumors, patient heterogeneity, and the presence of tumor-immunosuppressive microenvironments have limited the overall efficacy of immunotherapy, achieving only approximately a 20% success rate. In recent years, nanomaterials have garnered increasing attention in the realm of tumor immunotherapy due to their inherent advantages, such as excellent biocompatibility, precise targeting, and controlled drug release. Nanomaterials empower immunostimulatory molecules and therapeutic agents with the ability to specifically target tumors, amplify drug accumulation at tumor sites, facilitate local immune modulation, alleviate immunosuppressive microenvironments, and thereby enhance the effectiveness of tumor immunotherapy. This review provides an overview of the current state of immunotherapy and offers insights into the ongoing research progress surrounding various nanomaterials aimed at augmenting the efficacy of immunotherapy.

KEYWORDS

Nanomaterials; Tumor; Immune microenvironment; Immunotherapy; Nanomedicine

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1. Introduction

The International Agency for Research on Cancer (IARC) reported that in 2020 there were 19.29 million new cancer cases wrldwide, with China alone accounting for 4.57 million, constituting 23.7% of the global total [1-2]. This escalating burden of malignant tumors in China imposes significant pressure on both society and patients. Effectively preventing, diagnosing, and treating cancer has become an urgent concern in medical research. Fortunately, the cancer survival rate has progressively improved through the collaborative efforts of scientific researchers and healthcare professionals. Data from the National Cancer Institute indicates that the overall survival for cancer patients has been increasing, with a 5-year relative survival rate of 69.3% (it's an average across all cancers), owing to advancements in early screening and improved medical care. This improvement underscores the pivotal role of healthcare in extending lives. Traditional cancer treatment methods encompass surgery, chemotherapy, and radiation therapy, each with its own limitations. Surgical intervention entails the removal of tumor tissue at its source [3-4]. It is the most effective approach for patients with early-stage tumors. However, in cases of advanced tumor stages, complete eradication of cancer cells through surgery is often impeded due to their infiltration, exposing patients to surgical risks, infections, and the peril of postoperative recurrence. Chemotherapy, which involves the administration of chemotherapy drugs that interact with DNA to combat tumors, lacks the ability to exclusively target cancer cells, leading to significant collateral damage to normal tissues. This can result in severe side effects such as vomiting and pain in patients, along with the development of drug resistance, diminishing treatment effectiveness. Radiation therapy, a method of treating malignant tumors and certain benign lesions using ionizing radiation, inflicts damage on normal tissues while aiming to cause tumor cell death by damaging tumor cell DNA directly or indirectly inducing cell death by stimulating the production of reactive oxygen species (ROS) from water molecules, which then inflict oxidative damage on DNA, cell membranes, and other components.

Immunotherapy has emerged as an effective treatment for various primary and metastatic cancers, offering new avenues for cancer treatment by boosting the patient's innate immune response, fortifying the anti-tumor response, or mitigating immunosuppressive effects. This approach has achieved remarkable success. However, owing to the intricate nature of tumors, patient heterogeneity, and the limited specificity of these methods, there are inherent challenges, such as tumor immune evasion and systemic immune toxicity, leading to an overall efficacy rate of only approximately 20%. These limitations restrict the clinical applicability of these treatment strategies, rendering them unsuitable for all cancer patients. One of the primary challenges in the evolution of cancer immunotherapy lies in safely and effectively stimulating immune responses [5-6]. Encouragingly, the rapid development of nanomedicine, particularly the advent of functional nanomaterials with distinctive physical and chemical properties, such as large specific surface area, adjustable structure, and photomagnetic responsivity, has attracted significant attention in the realm of cancer treatment. This advancement has introduced new prospects for developing efficient tumor treatment modalities. Nanomaterials exhibit responsiveness to specific tumor microenvironments, such as hypoxia, low pH, overexpression of H2O2, and glutathione, as well as to external stimuli like light, heat, magnetism, electricity, and ultrasound. They enable effective and precise treatments while minimizing harm to normal tissues.

Leveraging nanomaterials as carriers not only enhances the solubility and bioavailability of hydrophobic drugs but also improves their biocompatibility, extends drug circulation time in the body, mitigates immune system recognition and clearance, and optimizes drug distribution within the body. This approach facilitates precise drug release, minimizing toxic side effects. Additionally, nanomaterials can passively target tumors through enhanced permeability and retention (EPR) and actively target tumors through surface modification with targeting molecules, thus efficiently delivering one or more drugs, antibodies, immune modulators, or functional molecules to the tumor site. This approach results in drug enrichment, local immune modulation, and improved immunosuppressive microenvironments, thereby enhancing the effectiveness of tumor immunotherapy. Currently, various

nanomaterials have been employed in tumor immunotherapy, including inorganic nanomaterials, organic nanomaterials, and biomimetic nanomaterials. This article predominantly reviews the research progress concerning these types of nanomaterials in augmenting the efficacy of tumor immunotherapy.

2. Tumor Immune Microenvironment

Tumor cells can manipulate the microenvironment of normal tissues, rendering it conducive to tumor growth by orchestrating immune cells and releasing immunosuppressive factors. The tumor immune microenvironment encompasses lymph node clusters, immune cells, cytokines, and more [7-8]. Notably, immune cells with pivotal roles include CD8+ T cells, tumor-associated macrophages, myeloid-derived suppressor cells, and regulatory T cells. CD8+ T cells execute their mission of eliminating tumor cells by binding to the human leukocyte antigen I (HLA-I) and β2 microglobulin (β2m) complexes expressed on the surface of tumor cells through the surface T cell antigen receptor (TCR). They release cytotoxic mediators such as perforin, interferon, tumor necrosis factor, and serine ester alcohol to eliminate target cells [9-10]. A critical factor in tumor development is the inhibition or even complete loss of cytotoxic T cell function. In various tumor infiltrations like melanoma, colorectal cancer, breast cancer, lung cancer, ovarian cancer, CD8+ T cells frequently exhibit a distinctive phenotype with high expression of inhibitory receptors like programmed cell death 1 (PD-1), LAG-3, TIM-3, and CTLA-4. Tumor-associated macrophages (TAMs) represent a unique class of macrophages within tumor tissue, predominantly displaying an M2 macrophage-like functional phenotype. TAMs exhibit low expression of human leukocyte antigen DR (HLA-DR), high levels of B7 homolog 1 (B7-H1), and interleukin-10 (IL-10). These cells secrete essential fibroblast growth factors and vascular endothelial growth factors, thereby promoting angiogenesis, breaking down the extracellular matrix, supplying nutrients for tumor growth, and fostering tumor development and metastasis.

Myeloid-derived suppressor cells (MDSCs) belong to a group of bone marrow-derived cells that exert immunosuppressive effects on T cells. Human MDSCs can be categorized into Mo-MDSCs and PMH-MDSCs. As tumors progress, human MDSCs can further differentiate into dendritic cells, TAMs, or granulocytes. They express inducible nitric oxide synthase, inducible nitric oxide inducthase, and indole-2, 3-dioxygenase, promoting angiogenesis and inhibiting immune responses. Regulatory T cells (Tregs) represent a typical class of inhibitory cells. Tumor-infiltrating Tregs secrete immunosuppressive factors, directly suppress or inhibit the proliferation of effector cells, and dampen T-cell activation (see Figure 1). Beyond these cell types, various other immune cells have also been observed to experience inhibition in the tumor microenvironment, including dendritic cells (DCs), macrophages, natural killer cells (NKs), and natural killer T cells (NKTs). Each of these cells contributes to the complex processes involved in tumor initiation and development. While consensus is still lacking on the precise roles immune cells play in the tumor microenvironment, and differences exist in the degree of infiltration and immunosuppression among various tumors and individuals, research on the tumor immunosuppressive microenvironment offers novel insights for tumor treatment.

3. Research on Inorganic Nanomaterials in Tumor Immunotherapy

Inorganic nanomaterials offer distinct chemical properties, controllable shapes and sizes, ease of design, and unique optical, electrical, and magnetic characteristics. These attributes render them advantageous for applications in cancer immunotherapy, vaccine development, and autoimmune therapy. Inorganic nanomaterials can be categorized into metallic and non-metallic nanomaterials, serving as novel carriers that bridge the gap between therapeutic drugs and their intended targets (refer to Figure 2). It is important to note that while inorganic nanomaterials demonstrate superior optical, thermal, and magnetic properties, along with effective targeted drug delivery and controlled release capabilities, some issues are encountered in practical biomedical applications. Some

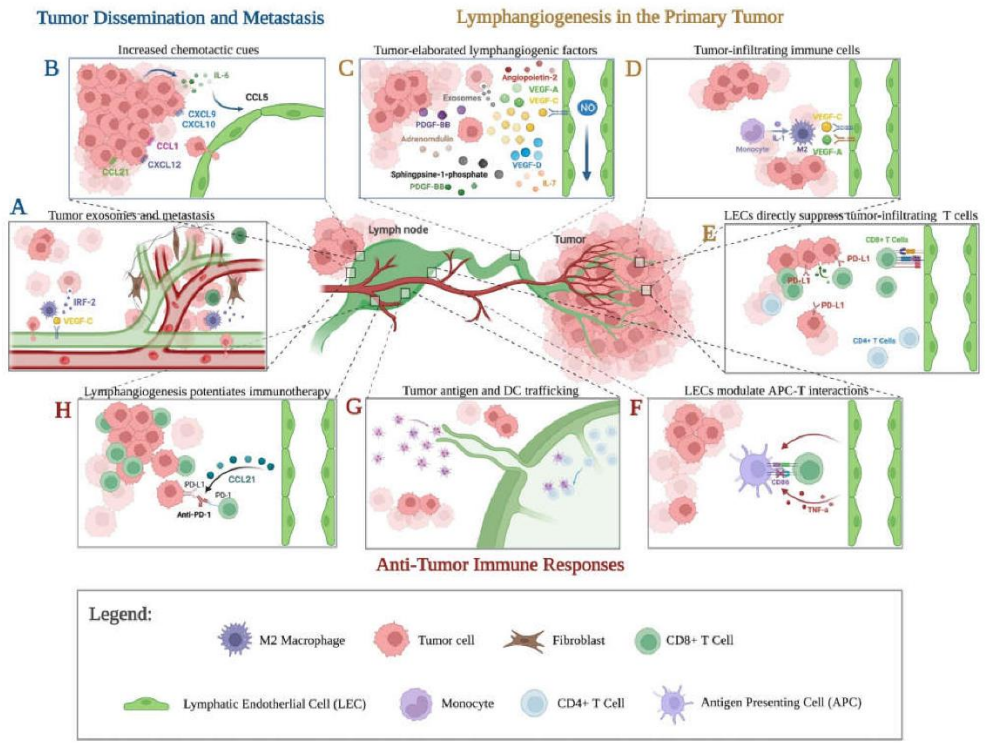

Figure 1. The role of lymphatics in tumor progression and immunomodulation.

inorganic nanomaterials may not readily biodegrade within the body, resulting in prolonged residence times and potential adverse reactions.

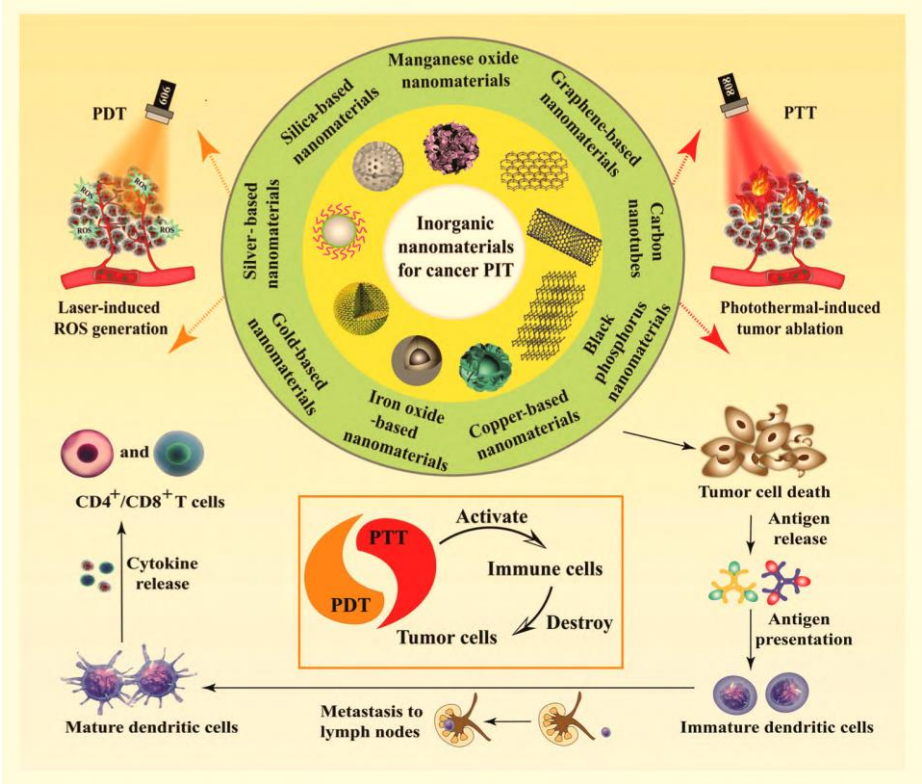

Figure 2. Schematic diagram of inorganic nanomaterials and their mechanism of action in tumor therapy. Reproduced/Adapted with permission.

3.1. Silicon-Based Nanomaterials

Silicon-based nanomaterials are widely employed due to their biodegradability and biocompatibility, making them suitable carriers for various biomedical applications. Among them, mesoporous silica particles (MSNs) have garnered significant research attention. MSNs are characterized by their honeycomb-structured pores and exceptional adsorption capacities for various bioactive molecules. Their adjustable size, biocompatibility, surface customization, and chemical and thermal stability make them valuable in cancer diagnostics and immunotherapy [11-12]. Recent studies have emphasized the potential of MSNs in immunotherapy. Their impact on monocyte-derived DCs is dependent on particle size and concentration, with larger particles and higher concentrations exhibiting greater effectiveness. MSNs can be tailored to carry tumor-associated antigens (TAAs) or adjuvants, producing immune-modulating effects. Additionally, MSNs, owing to their small size, can be designed to carry vaccines and internalized into antigen-presenting cells (APCs) for antigen delivery [13].

Yang et al. [15] achieved promising outcomes in hepatocellular carcinoma treatment using mesoporous silica co-loaded with the photothermal therapy (PTT) agent indocyanine Green (ICG) and the multi-kinase inhibitor sorafenib. Under near-infrared light (NIR) excitation, the nanocomposite exhibited significant PTT-mediated tumor destruction in a mouse model bearing H22 tumors. This study found that the synergistic drug delivery system triggered a robust immune response, leading to increased interferon-γ secretion and vital relapse prevention. Thus, photothermal/immune-enhancing combined therapy proved effective in in vivo tumor eradication. Xu et al. [16] developed biodegradable MSNs loaded with the CpG adjuvant, the photosensitizer chlorine e6 (Ce6), and neoantigen peptides. These complexes, based on PET imaging and PDT technology, facilitated personalized cancer vaccination using neoantigens. In vivo, results demonstrated PDT's synergy with biodegradable silica nanoparticles (bMSN)-mediated vaccination, inducing dendritic cell recruitment and generating a robust response from neoantigen-specific CD8α+ cytotoxic T lymphocytes (CTLs). This bMSN-mediated drug delivery system holds promise for personalized tumor immunotherapy (refer to Figure 3). Yang et al. [17] developed an intelligent nanocarrier employing pH-responsive polymer-modified HMS, targeting mitochondria and carrying therapeutic molecules for cancer treatment. This system significantly enhanced photodynamic therapy (PDT) efficacy against solid tumors through the breakdown of endogenous hydrogen peroxide at the tumor site and alleviating hypoxia. Furthermore, the combination of PDT nanocarriers with anti-PD-L1 checkpoint blockade immunotherapy displayed a remarkable synergistic effect, increasing CTL infiltration into distant tumors and effectively inhibiting tumor metastasis.

3.2. Carbon-Based Nanomaterials

Carbon-based nanomaterials, which encompass graphene and carbon nanotubes, efficiently transport drugs. Research indicates that binding graphene oxide to tumor-selective molecules such as peptides, ligands, and antibodies enhances in vivo targeting. For instance, YU et al. [18] improved the targeting of pegylated graphene oxide by linking it with the integrin αvβ6-specific targeting peptide (HK). Functionalized graphene oxide was then loaded with the photosensitizer HPPH for effective photodynamic therapy, ablation of the primary tumor, and destruction of residual tumor cells. This process activated the host's anti-tumor immune response, preventing distant tumor metastasis and stimulating immune memory to prevent tumor recurrence. Recent studies demonstrate that graphene-based nanomaterials can effectively activate macrophages, leading to the production of immune factors and improved immune responses. CpG, a widely used therapeutic nucleic acid with potent immunostimulatory activity, specifically targets mammalian toll-like receptors, inducing the secretion of various pro-inflammatory cytokines. Functionalizing with polyethylene glycol (PEG) ensures that nanomaterials maintain stealth properties, protecting drugs from macrophage interference and reducing adverse immune reactions. Tao et

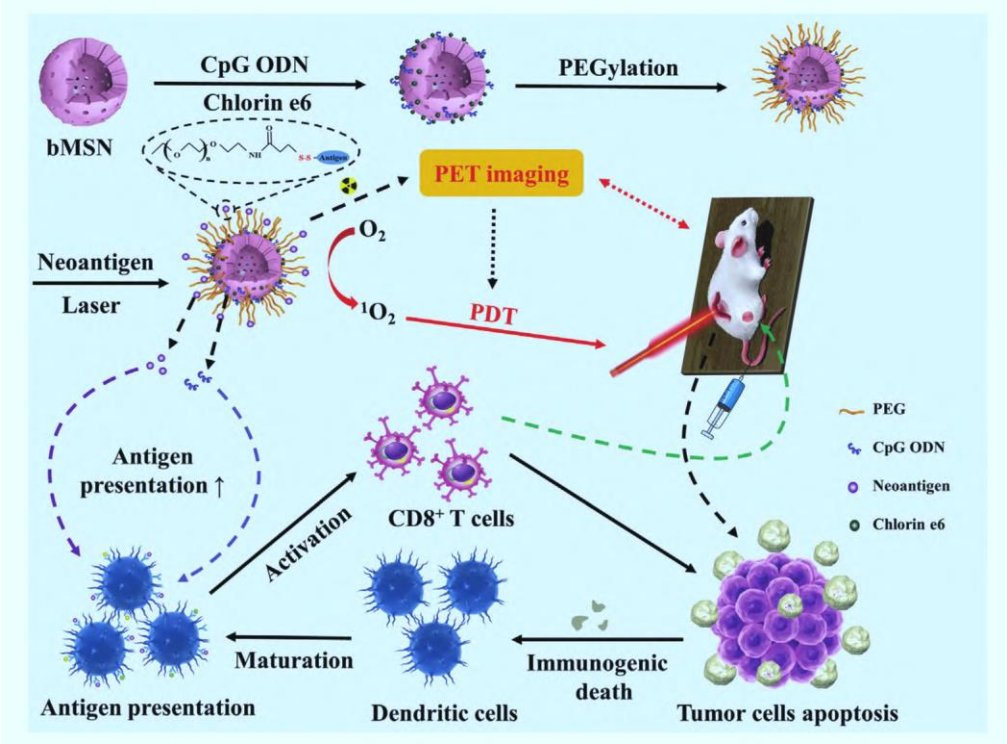

Figure 3. Application of the bMSN mediated drug delivery system in personalized immunotherapy of tumors. Reproduced/Adapted with permission.

al. [21] designed a graphene oxide-based nanocarrier (GO-PEG-PEI) functionalized with PEG and PEI copolymers for efficient CpG transport. Thanks to the photothermal properties of GO, this carrier can facilitate intracellular CpG transport under laser irradiation, effectively modulating the immune response.

In vivo results revealed that CT26 colon tumors in the treatment group exhibited the smallest volume compared to other control groups, indicating the broad potential of GO as a photothermal immunotherapy nanomaterial for cancer treatment. Furthermore, GO can function as an immune stimulator by activating the host's immune system, reducing intracellular ROS production, and modifying macrophage repolarization [22]. Early M1 macrophage therapy transformation and regulation of inflammation-induced ROS production play critical roles in M1 macrophage therapy [23]. Wu et al. [24] developed a graphene-based nanocomposite material with mitochondrial targeting and NIR activation capabilities. This material, modified with triphenylphosphine and the photosensitizer IR820, specifically targeted mitochondria. Under NIR activation, the nanocomposite generated abundant ROS and high temperatures, causing mitochondrial collapse and cancer cell damage, resulting in irreversible apoptosis. Furthermore, the nanocomposite significantly enhanced tumor immunogenicity by loading CpG immune adjuvants. In vivo experiments demonstrated that the graphene nanocomposites effectively inhibited tumor growth in mice with EMT6 tumors, exerting minimal toxicity.

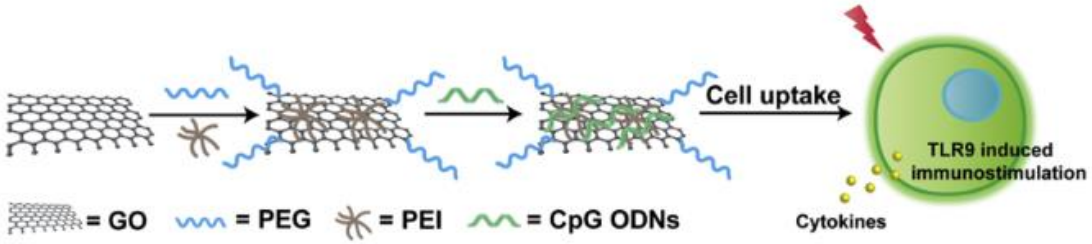

Figure 4. Schematic showing the synthesis of GGIC and its immunostimulatory effect. Reproduced/Adapted with permission.

3.3. Metallic Nanomaterials

Ferric oxide (Fe3O4), a magnetic metal nanomaterial, boasts excellent protein capture efficiency and lymph node targeting capabilities, enhancing the efficacy of cancer immunotherapy. For instance, WANG et al. [25] designed a core-shell nanostructure (Ce6/Fe3O4-L) with a solid Fe3O4 core and a lipid bilayer shell loaded with the photosensitizer porphin E6 (Ce6). ROS produced by the material post-ultrasonic treatment could destroy tumor cells and enhance the immunogenicity of tumor cells by releasing endogenous tumor antigens (ETAs). Fe3O4, when released, could capture ETAs and enhance immunotherapy through lymph node targeting. The study found that the Ce6/Fe3O4-L group, treated with ultrasound, effectively eliminated the primary tumor and inhibited the growth of distal tumors compared to the non-ultrasonic group. Gold nanoparticles (AuNPs), a classic inorganic nanomaterial, offer controllable shape and particle size, a large specific surface area, good biocompatibility, adjustable surface functionality, and unique optical, electrical, and magnetic properties. They find wide applications in biomedicine, particularly in recent years, exhibiting potential in tumor therapy and imaging. Tumor-derived vesicles can transport tumor antigens to dendritic cells (DCs) for processing and presentation to T cells, inducing immune responses. Zhang et al. [26] developed a novel immune AuNP that leveraged intracellular generation and exocytosis in cells for combined tumor photothermal and immunotherapy. The DC-derived AuNPs were further internalized into DCs via in situ generation in mouse melanoma cells (B16F10) and exocytosis-secreted AuNPs containing tumor antigen vesicles (AuNP@B16F10). This approach improved biocompatibility and enhanced immune responses. AuNPs, acting as a photothermal agent, generated high temperatures under light conditions, stimulating anti-tumor immune responses. The study found that irradiation of AuNP@DCB16F10 with near-infrared light effectively inhibited melanoma growth in mice, achieving tumor elimination and a substantial reduction in volume. The results highlight the potential of AuNPs, with their high photothermal conversion efficiency and photostability, in enhancing the efficacy of tumor photothermal therapy when combined with immunotherapy. Furthermore, surface modification endows AuNPs with immune properties, facilitating the amalgamation of photothermal tumor therapy and immunotherapy, ultimately enhancing therapeutic outcomes.

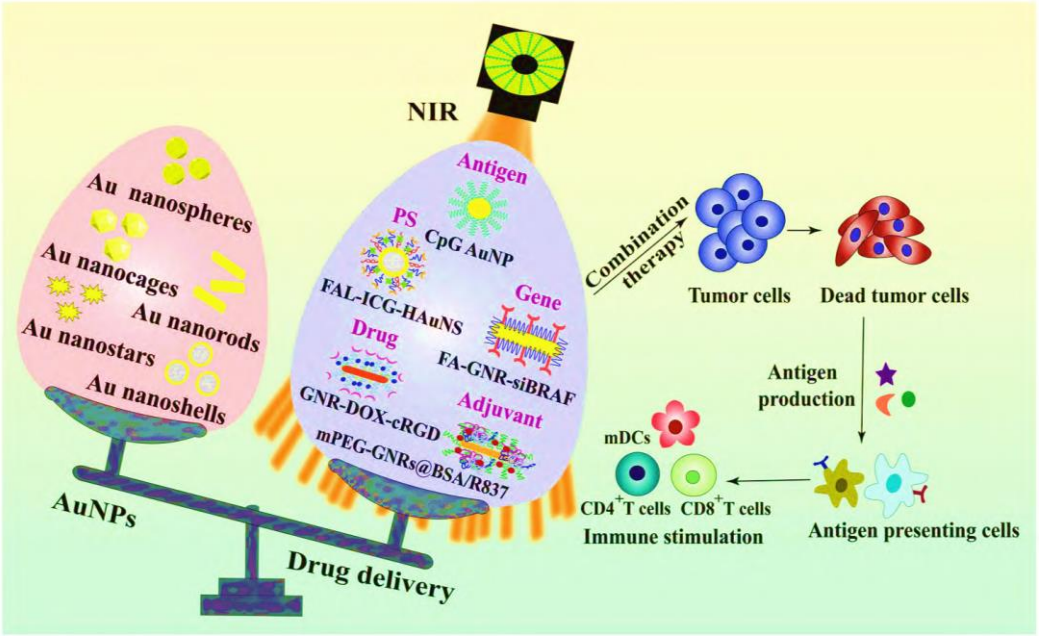

Figure 5. Schematic diagram of different types of AuNPs used in drug delivery. Reproduced/Adapted with permission.

4. Research on Organic Nanomaterials in Tumor Immunotherapy

4.1. Liposomes

Liposomes are hollow bilayer vesicles formed by the hydrophobic binding of phospholipid biomolecules. Their structure resembles cell membranes, exhibiting low cytotoxicity and excellent biocompatibility. Liposomes also possess strong cellular affinity and can target the reticuloendothelial system, making them effective drug carriers. The encapsulation of drugs within bilayer structures enhances drug targeting, stability, and circulation time in the body, thereby improving therapeutic efficacy. Several liposomal nanoformulations have gained approval from the United States Food and Drug Administration (FDA), such as daunorubicin liposomes, adriamycin liposomes, and irinotecan liposomes. In tumor immunotherapy, liposomes are employed to efficiently encapsulate immune agents or therapeutic drugs, promoting cancer immunotherapy by activating humoral or cellular immune responses. Recently, studies have highlighted the potential of oligodeoxynucleotides containing unmethylated cytosine guanine phosphate (CpG) motifs to bind to Toll-like receptor 9 (TLR9) on antigen-presenting cells. This interaction promotes the expression of co-stimulatory molecules and the secretion of inflammatory cytokines, making CpG a valuable immune adjuvant. CpG has also demonstrated the ability to inhibit the immunosuppressive function of bone marrow-derived suppressor cells (MDSCs) and guide their differentiation into anti-tumor macrophages. For example, Li et al. designed a nanoparticle liposome composite (IR-7-Lipo/HA-CpG) coated with a multivalent immune adjuvant (HA-CpG) and containing internally a photosensitizer for combined photothermal and immunotherapy of tumors. Their study showed that HA-CpG, through covalent interaction, stimulated TLR9 more effectively than simple CpG adjuvant. After near-infrared irradiation (NIR), the treatment group exhibited reduced MDSC levels and increased tumor-infiltrating dendritic cells (DCs) and CD8+ T cells, resulting in effective tumor suppression. Additionally, liposomes can efficiently deliver drugs or cytokines with diverse physicochemical properties, enhancing the immunosuppressive features of the tumor microenvironment. For instance, Park et al. developed a biodegradable liposome-polymeric gel system (nLG) with a shell-nuclear structure. It contained hydrophobic TGF-β blocker (SB) and hydrophilic cytokine IL-2 inside the liposome, enclosed by a biodegradable polymeric polylactic acid-glycolic acid copolymer (PLGA) shell. This approach demonstrated significant tumor growth inhibition and complete tumor regression, indicating the ability to induce local therapeutic immune responses and alleviate the immunosuppressive tumor microenvironment.

B7-H1 is a member of the B7 immunoglobulin superfamily, expressed on the surface of various immune cells such as lymphocytes, as well as on the surface of various tumor cells, weakening the immune response of the body against tumor cells in various ways IL-10 is an important negative immunoregulatory cytokine. Overexpression of IL-10 has been found in many tumor tissues, including pancreatic cancer. It can inhibit the expression of Th1, make the balance of Th1/Th2 shift to Th2, and play an important role in the process of tumor escaping from immune attack.

4.2. Polymer Nanomaterials

Synthetic medical polymer nanomaterials like PLGA, polycaprolactone, and polyglycolic acid have found extensive use in tissue engineering, controlled drug release, and tumor therapy due to their biodegradability, low cytotoxicity, and versatility for modification and processing.

For instance, Zhou et al. prepared a polymer nanoparticle (RPTDH) with chelating capabilities for copper ions and pH-responsive behavior. This material efficiently loaded and released requinomide R848 (TLR8 agonist) in response to the acidic tumor environment. This approach improved immune stimulation, inhibited tumor growth, and extended the survival of tumor-bearing mice. Combining radiation therapy and immunotherapy with

nanotechnology to enhance tumor therapy efficacy has also gained attention. For example, PLGA nanoparticles with antigen-trapping functions can enhance the immune response after radiotherapy. Chen et al. developed PLGA-R837@Cat nanoparticles that delivered hydrophobic imiquimod R837 (TLR7 agonist) in response to radiotherapy. This treatment significantly slowed secondary tumor growth in mice, and combining αCTLA4 administration resulted in the complete elimination of the secondary tumor, demonstrating effective tumor inhibition and immune memory formation. Polymer micelles with high drug-loading capacity, stability, and controlled drug release have great potential in drug delivery. Su et al. created a pH- and matrix metalloproteinase (MMP)-responsive polymer nano micellar carrier (sAMcP) for the controlled release of anti-PD-1 antibody (αPD-1) and paclitaxel (PTX) in solid tumors. This system combined chemotherapy and immunotherapy to effectively inhibit tumor growth.

Polymer vesicles, which share similarities with liposomes, are biomaterials with a hollow inner cavity structure assembled by amphiphilic polymers. They have demonstrated significant advantages in drug delivery systems. For example, the STING-NPS material was designed to activate STING signaling efficiently, enhancing immune stimulation and effectively inhibiting tumor growth.

4.3. Nano-Hydrogel

Hydrogels, three-dimensional biomaterials with porous structures, are widely used in biomedicine, particularly in tumor treatment and tissue engineering. As drug delivery systems, Nano-hydrogels can deliver small molecule immunotherapeutic drugs, promoting anti-tumor immune responses and reducing potential side effects. These systems often combine anti-tumor and immune stimulation functions. Jin et al. synthesized a melittin RADA32 doxorubicin (MRD) hydrogel. This system effectively delayed melanoma growth, killed tumor cells, activated dendritic cells, and initiated an anti-tumor immune response. Vaccines for chronic infections, like cancer, often require a robust CD8+ T cell response. Small molecular peptide hydrogels have emerged as vaccine adjuvants that promote immune responses, including L- and D-configuration peptide hydrogels that enhance IgG production. These hydrogels stimulate DC maturation and germinal center formation, indicating their potential for vaccine adjuvant applications.

4.4. Nanoemulsion

Nanoemulsions are multi-component drug delivery systems composed of mixed immiscible liquids with 1 to 100 nm diameters, stabilized by surfactants. They offer several advantages, such as small particle size, stability, high bioavailability, and adjustable properties. Nanoemulsions have shown promise in cancer immunotherapy. Jia et al. developed a Pickering nanoemulsion (D/HY@PNE) with a multi-response nanogel (SNG) as an oil/water interface stabilizer. This system effectively inhibited tumor growth by releasing both HY19991 (HY) and DOX in response to the tumor's acidic environment. The released HY blocked the PD-1/PD-L1 signaling pathway, promoting T cell activation. Simultaneously, DOX released by the nanogel penetrated the tumor interior and induced immunogenic cell death, achieving the synergistic effect of chemotherapy and immunotherapy.

5. Research on Biomimetic Nanomaterials in Tumor Immunotherapy

In recent years, the field of biomimetic nanomaterials, inspired by nature, has garnered significant attention for its innovative modification strategies using nanocarriers. A pivotal milestone in this domain was the groundbreaking work of Hu's research team in 2011 [42], which introduced the concept of cell membrane-based camouflage modifications for nanomaterials. This approach involves encapsulating nanoparticles with various cell membranes, including erythrocyte, bacterial, exosome, macrophage, or tumor membranes, to create what can be aptly described as "invisible" synthetic nanomaterials. These cell membranes are rich in sugars, lipids, and proteins,

playing critical roles in exchanging biological information. Nanomaterials camouflaged with cell membranes can retain their inherent functionality while acquiring the natural properties of the membrane they're derived from. Among these, erythrocyte membranes were the first to be used for nanomaterial modification. Nanomaterials modified with erythrocyte membranes exhibit remarkable biocompatibility and effectively evade immune recognition by the body, allowing for prolonged circulation in the bloodstream. The use of immune cells or tumor-derived cell membranes for modification empowers nanomaterials to selectively target tumors, thereby enhancing their safety and tumor-specific homing, ultimately resulting in improved therapeutic outcomes. For instance, Kroll et al. [43] coated PLGA nanoparticles, loaded with the immune adjuvant CpG, with B16F10 mouse melanoma cell membranes. They harnessed the principles of biomimetic nanotechnology to develop an immune nano anticancer vaccine (CPG-CCNP) with the capability to activate multiple antigens. CPG-CCNP was shown to significantly inhibit melanoma growth in mice ($P<0.001$), achieving an impressive tumor inhibition rate of 86%. Studies have demonstrated that nanoscale membrane delivery in combination with immune adjuvants not only enables homing to tumor sites but also promotes antigen-presenting cell maturation, the activation of tumor-specific T cell responses, and the generation of robust in vivo anti-tumor effects.

Natural Killer (NK) cells are innate immune cells and serve as the body's first line of defense against infections and cancers. Deng's team [44] engineered NK cell membrane-camouflaged nanoparticles (NK-NPS) loaded with the photosensitizer tetraphene (4-carboxyphenyl) porphin (TCPP). The integration of photodynamic therapy (PDT) with immunotherapy not only eliminated primary tumors but also effectively suppressed the growth of distant tumors. NK cell membrane coating enhanced nanoparticle targeting to tumors, and stimulated macrophage polarization toward the M1 phenotype, thereby initiating tumor immune responses. Furthermore, TCPP played a dual role by directly inducing tumor cell death via PDT and promoting immunogenic tumor cell death while activating antigen-presenting cells, thus enhancing the material's anti-tumor immune response efficiency.

Macrophages, which are abundant within the tumor microenvironment, play pivotal roles in tumor development and metastasis. During the lung metastasis of breast cancer, macrophages interact with the vascular cell adhesion molecule-1 (VCAM-1) on cancer cells through α-4 integrins on their surface. This interaction promotes the binding of metastatic cancer cells, enhancing their survival and growth, ultimately leading to metastasis. Cao et al. [45] developed drug-loaded liposomes modified with macrophage cell membranes (MEL), which enabled specific targeting of lung metastasis sites in breast cancer. This innovative approach significantly increased material uptake by metastatic 4T1 breast cancer cells and effectively inhibited the vitality of these metastatic cells.

6. The Impact of Nano-Drugs on the Tumor Immune Microenvironment

Nanomaterials were initially introduced into the biomedical field as delivery vehicles for a wide range of chemotherapy drugs, with the primary goal of achieving a slow and controlled release of medications. This approach aimed to reduce the toxic side effects of chemotherapy, enhance biosafety, and serve various other functions. Nanomedicine has garnered increasing attention due to its exceptional stability, solubility, and specific in vivo pharmacokinetics and has experienced rapid development over the past few decades. Notably, more and more nanomaterials are being designed to diagnose and treat tumors based on their unique ability to modulate the tumor microenvironment and regulate the immune response. Examples such as albumin-bound paclitaxel, utilized in treating metastatic and recurrent breast cancer, and doxorubicin liposomes, a frontline option for ovarian cancer, have demonstrated significant success. The regulatory effects of nanomaterials on the tumor immune microenvironment are multifaceted, encompassing the enhancement of tumor immunogenicity, targeted activation of antigen-presenting cells (APCs), activation and expansion of tumor-infiltrating T cells, regulation of tumor-associated macrophages, inhibition, or even elimination of myeloid-derived suppressor cells (MDSCs), and targeted activation of tumor-infiltrating natural killer (NK) cells.

6.1. Enhancement of Tumor Immunogenicity

Immunogenic cell death (ICD), characterized by the induction of immunostimulatory damage-associated molecular patterns (DAMPs), such as calreticulin exposure on the cell membrane, plays a vital role in promoting antigen presentation and initiating an autoimmune response. Li et al. [46] devised a dual endoplasmic reticulum (ER)-targeting nanosystem consisting of ER-targeted paratoxin peptides (FAL), hollow gold nanospheres (Fal-ICG-Hauns) loaded with modified indocyanine green (ICG), and oxygen-transfused hemoglobin liposomes (FAL-Hb lipids). When precisely targeted to the ER, these nanosystems induce potent ER stress and calreticulin exposure in response to near-infrared light. This serves as a signal for ICD, which stimulates antigen presentation by dendritic cells. This, in turn, leads to the activation of CD8+ T cells and the secretion of cytotoxic cytokines, fostering a range of immune responses. Furthermore, ER-targeted photodynamic and photothermal therapy (PDT-PTT) facilitate ICD-related immunotherapy, yielding enhanced anti-tumor efficacy.

6.2. Targeting and Activating Antigen-Presenting Cells (APCs)

Tumor-specific antigens are captured by APCs after exposure and are subsequently presented to T cells to activate cytotoxic T lymphocytes (CTLs). Wu et al. [47] developed a novel nanomedicine, PC@CpGD, comprised of polydopamine-stabilized graphene quantum dots and an immunostimulant cationic polymer with CpG oligodeoxyribonucleic acid adjuvant, designed to activate dendritic cells (DCs). This nanomedicine possesses effective photothermal and photochemical therapeutic capabilities, specifically targeting CpG adjuvant to DCs. Activated DCs promote the secretion of pro-inflammatory factors, facilitating DC maturation. In mouse models of breast cancer (EMT6 mouse model), this approach substantially suppressed tumor growth by increasing CD8+ T cell infiltration. Additionally, Barillet et al. [48] used PLGA nanoparticles to assess the impact of nanoparticle surface characteristics on DC activation and maturation. Their study examined the effects of nanoparticle uptake on DC viability, phenotype, and secretory activity. Results revealed that both human and mouse immature DCs efficiently phagocytosed PLGA nanoparticles and subsequently exhibited characteristics associated with mature DCs. This was attributed to the transient activation of mitogen-activated protein kinases in response to nanoparticle phagocytosis.

6.3. Targeted Activation and Expansion of Tumor-Infiltrating T Cells

Tumor immunity revolves around specialized APCs presenting MHC-antigen complexes and immunogenic signals to activate T cells, which, in turn, differentiate into CD8+ cytotoxic T lymphocytes (CTLs). Steenblock et al. [49] designed a system for antigen presentation and T-cell expansion. This system employed biodegradable PLGA polymer shells to encapsulate interleukin-2 (IL-2), conjugated avidin palmitate via emulsification to promote avidin presentation on the nanoparticle surface. The nanoparticles were then linked to anti-CD3, anti-CD28 antibodies, and polypeptide-MHC complexes through biotinylated ligands, enabling them to recognize, co-stimulate, and signal cytokines efficiently. Consequently, this nanosystem demonstrated its capability to efficiently stimulate and amplify antigen-specific T cells. In cancer, tumors have evolved various mechanisms to evade the body's immune response. One such mechanism is through the immune checkpoint receptor PD-1, which suppresses T cell proliferation and vitality when highly expressed due to the presence of PD-L1 ligands. Blocking immune checkpoints offers hope for cancer treatment. Gu et al. employed nanotechnology to create a nanomedicine by binding anti-PD-L1 antibodies to platelet surfaces using a bifunctional linking agent. The results demonstrated increased infiltration of CD8+ and CD4+ T cells into tumors, effectively inhibiting lung metastasis and extending the survival of mice with incomplete tumor resection. This approach significantly prolonged the recurrence-free period in the case of triple-negative breast cancer.

6.4. Targeting and Regulating Tumor-Associated Macrophages

Tumor-associated macrophages (TAMs) are the most abundant immune cells in the tumor microenvironment. Depending on environmental cues, macrophages can differentiate into M1 or M2 types, with distinct biomarker profiles. M1 macrophages are pro-inflammatory and contribute to anti-tumor responses by releasing gamma-interferon (IFN-γ) and activating the Notch signaling pathway. In contrast, the hypoxic tumor microenvironment promotes the differentiation of macrophages into the immunosuppressive M2 type, which releases anti-inflammatory cytokines like TGF-β and IL-10. The interaction between M2 macrophages and tumor cells activates the STAT3 signaling pathway, leading to the secretion of cytokines that recruit more myeloid-derived suppressor cells (MDSCs) and enhance the immunosuppressive tumor microenvironment, enabling tumor cells to evade immune surveillance. This process results in tumor escape from immune detection and clearance. When nanomedicine enters the bloodstream, it binds to plasma proteins, forming a protein corona. The formation of protein coronas on the surface of nanomaterials is influenced by particle size, surface charge, hydrophobicity, and surface chemical properties. Once within the tumor, these surface proteins can specifically bind to M1 macrophage surface receptors, leading to their internalization and clearance. This physiological barrier affects the passive targeting of nanomedicine based on the enhanced permeability and retention (EPR) effect, as well as active targeting using ligands. The formation of protein coronas on the surface of nanomedicine reduces the exposure of target groups or ligands, diminishing specificity distribution.

6.5. Inhibition and Elimination of Myeloid-Derived Suppressor Cells (MDSCs)

MDSCs are a diverse group of immunosuppressive cells capable of inhibiting T cell and NK cell function and proliferation through the secretion of immunosuppressive factors such as nitric oxide, arginase, and reactive oxygen species (ROS). Burkert et al. [52] designed enzymatically degradable nanocups loaded with paclitaxel and sealed with nano-gold. These nanocups effectively targeted and inhibited MDSCs, leading to an increase in CTL infiltration at the tumor site and displaying a synergistic anti-tumor effect in a B16 melanoma mouse model. Furthermore, Ledo et al. [53] introduced an advanced strategy for reversing MDSC-mediated immunosuppression by targeting the CCAAT/enhancer binding protein β (C/EBP-β) pathway. Multilayer nanocapsules incorporated chemokine CCL2, immunomodulatory drugs polyarginine and hyaluronic acid, RNA sequence shC/EBPβ, and miR-142-3p. In the MCA203 fibrosarcoma mouse model, this approach effectively down-regulated C/EBP-β mRNA levels in MDSCs, reduced monocyte polarization towards TAM, and, to some extent, changed the immunosuppressive tumor microenvironment, thereby achieving an anti-tumor effect.

6.6. Targeted Activation of Tumor-Infiltrating NK Cells

NK cells are innate immune effector lymphocytes and serve as the first line of defense against tumor growth and metastasis. NK cells also act as important immune regulators, influencing T cells, DCs, macrophages, and endothelial cells by secreting various cytokines, including IFN-γ. In solid tumors, NK cells are exposed to a prolonged acidic environment, leading to reduced cell activity and compromised recognition and killing abilities. As a result, tumor cells evade NK cell surveillance. The antibody-dependent cell-mediated cytotoxicity (ADCC) mechanism is a significant approach for clinical tumor treatment involving monoclonal antibodies. In ADCC, the Fab segment of antibodies binds to tumor cell epitopes, while the Fc segment binds to the NK cell membrane protein CD16, facilitating NK cells' direct killing of target cells. Activated NK cells release perforin and granzyme B to kill target cells and secrete inflammatory cytokines and chemokines, which indirectly contribute to anti-tumor effects. Ji et al. [55] developed a polypeptide-antibody immunoconjugate nanodrug to address the challenge of tumor heterogeneity. By covalently linking antibodies or their Fc and polypeptide chains to the pHLIP polypeptide at the

N-terminus through a water-soluble amino-sulfur cross-linking agent (Sulfo-SMCC), this system leverages the pHLIP polypeptide's ability to induce specific changes in the secondary structure in the slightly acidic tumor environment. This results in the efficient assembly of Fc or antibody molecules on the surface of tumor cells. This strategy combines passive and active targeting, which activates the NK cell-mediated ADCC effect and effectively kills a variety of tumor cells, including triple-negative breast cancer cells. In in vivo experiments, this approach demonstrated a significant impact on early tumors and metastases. The efficient binding of effector molecules mediated by polypeptide assembly in the slightly acidic tumor environment shows promise for addressing tumor heterogeneity, as it is independent of the efficiency and specificity of antibody-antigen interactions.

7. Summary and Future Prospects

In summary, nanomaterials, with their unique physical and chemical properties, hold great promise in revolutionizing cancer treatment when compared to traditional methods. They offer specific tumor-targeting capabilities, prolonged circulation times in the body, and the potential to ameliorate the immunosuppressive tumor microenvironment while activating killer T cells. This multifaceted approach enhances the overall efficacy of cancer treatment while simultaneously reducing the therapeutic dosage of drugs and minimizing toxic side effects on healthy organs. Current research is particularly focused on inorganic nanomaterials as a prominent field of study in tumor therapy. Notably, nanomaterials based on iron oxide have already gained approval in Europe to treat glioblastoma. Biomimetic nanoparticles, characterized by their unique transport kinetics, immune-stimulating properties, and precise targeting abilities, have paved the way for developing effective vaccine formulations, such as OMV-derived meningococcal vaccines. In the clinical realm, liposomes, including liposomal doxorubicin (DOX), stand as the first class of nanomedicine to receive FDA approval for cancer treatment. Presently, nanoparticles continue to dominate the market, with advancements such as clopidogrel nanemulsion injection, based on oil-in-water technology, obtaining patents in the United States, European Union, and Japan for myocardial infarction treatment. The regulatory influence of nanomaterials on various cell types within the immunosuppressive microenvironment enables the potential application of nanomaterials in tumor immunotherapy. This holds the promise of eliminating primary tumors or distant metastases and establishing long-term adaptive immune memory. However, the amalgamation of nanomedicine and immunotherapy continues to encounter challenges and barriers throughout the translation into clinical applications. Firstly, the targeted anti-tumor ability of nanomedicine primarily relies on the enhanced permeability and retention (EPR) effect. Although the EPR effect has been validated in rodents, the amount of nanomedicine passively accumulating in tumors through the EPR effect remains limited, and its efficacy in humans remains uncertain. Secondly, the tumor microenvironment is highly complex and characterized by substantial heterogeneity. Most nanomedicine studies are confined to animal experiments, focusing on improving the anti-tumor effect against a single cell line, while the broader impact of nanomedicine on the regulation of the tumor immune microenvironment and its mechanisms within the human immune system require further extensive research and clarification. Mouse tumor models lack the complexity of human tumors, and treatments that prove effective in mice may not necessarily translate to human treatment. Therefore, the design of combined nanomedical drugs and immunotherapy should consider the diverse immune responses during drug transport and account for the distinct characteristics of different tumors. This approach will help enhance tumor targeting, introduce innovative therapeutic methods, and promote the normalization of the tumor immune microenvironment. As pertinent theories, engineering technologies, and methods continue to break new ground and regulatory norms and standards are established, the clinical transformation and application of nanomedicine hold great potential for significant advancements and breakthroughs in the near future.

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Conflict of interest

All the authors claim that the manuscript is completely original. The authors also declare no conflict of interest.

References

1. Topalian S L, Weiner G J, Pardoll D M. (2011). Cancer immunotherapy comes of age. *J Clin Oncol* 29(36), 4828-4836. https://doi.org/10.1200/JCO.2011.38.0899
2. Galluzzi L, Vacchelli E, Bravo-san Pedro J M, et al. (2014). Classification of current anticancer immunotherapies. *Oncotarget* 5(24), 12472-12508. https://doi.org/10.18632/oncotarget.2998
3. Rosenberg S A, Restifo N P. (2015). Adoptive cell transfer as personalized immunotherapy for human cancer. *Science* 348(6230), 62-68. https://doi.org/10.1126/science.aaa4967
4. Parker B S, Rautela J, Hertzog P J. (2016). Antitumour actions of interferons: implications for cancer therapy. *Nat Rev Cancer* 16(3), 131-144. https://doi.org/10.1038/nrc.2016.14
5. Rosenberg S A. (2014). IL-2: the first effective immunotherapy for human cancer. *J Immunol* 192(12), 5451-5458. https://doi.org/10.4049/jimmunol.1490019
6. Asmana Ningrum R. (2014). Human interferon alpha-2b: a therapeutic protein for cancer treatment. *Scientifica (Cairo)* 2014, 970315. https://doi.org/10.1155/2014/970315
7. Robert C, Schachter J, Long G V, et al. (2015). Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med* 372(26), 2521-2532. https://doi.org/10.1056/nejmoa1503093
8. Borghaei H, Paz-ares L, Horn L, et al. (2015). Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 373(17), 1627-1639. https://doi.org/10.1056/NEJMoa1507643
9. Ma W J, Gilligan B M, Yuan J D, et al. (2016). Current status and perspectives in translational biomarker research for PD-1/PD-L1 immune checkpoint blockade therapy. *J Hematol Oncol* 9(1), 47. https://doi.org/10.1186/s13045-016-0277-y
10. Ledford H. (2013). Immunotherapy's cancer remit widens. Nature 497(7451), 544. https://doi.org/10.1038/497544a
11. Cheung AS, Zhang DKY, Koshy ST, Mooney DJ. (2018). Scaffolds that mimic antigen-presenting cells enable ex vivo expansion of primary T cells. *Nat Biotechnol* 36(2), 160-9. https://doi.org/10.1038/nbt.4047
12. Lee JY, Kim MK, Nguyen TL, Kim J. (2020). Hollow Mesoporous Silica Nanoparticles with Extra-Large Mesopores for Enhanced Cancer Vaccine. *ACS Appl Mater Interfaces* 12(31), 34658-66. https://doi.org/10.1021/acsami.0c09484
13. Vallhov H, Gabrielsson S, Strùmme M, Scheynius A, Garcia Bennett AE. (2007). Mesoporous silica particles induce size dependent effects on human dendritic cells. *Nano Lett* 7(12), 3576-82. https://doi.org/10.1021/nl0714785
14. Nguyen TL, Choi Y, Kim J. (2019). Mesoporous Silica as a Versatile Platform for Cancer Immunotherapy. *Adv Mater* 31(34), 1803953. https://doi.org/10.3390/bios12020109
15. Yang H, Liu HS, Hou W, Gao JX, Duan Y, Wei D, et al. (2020). An NIR-responsive mesoporous silica nanosystem for synergetic photothermal-immunoenhancement therapy of hepatocellular carcinoma. *J Mater Chem B* 8(2), 251-9. https://doi.org/10.1039/d0tb90040k
16. Xu C, Nam J, Hong H, Xu Y, Moon JJ. (2019). Positron Emission Tomography-Guided Photodynamic Therapy with Biodegradable Mesoporous Silica Nanoparticles for Personalized Cancer Immunotherapy. *ACS Nano* 13(10), 12148-61. https://doi.org/10.1021/acsnano.9b06691
17. Yang G, Xu L, Xu J, Zhang R, Song G, Chao Y, et al. (2018). Smart Nanoreactors for pH-Responsive Tumor Homing, Mitochondria-Targeting, and Enhanced Photodynamic Immunotherapy of Cancer. *Nano Letter* 18(4), 2475-84. https://doi.org/10.1021/acs.nanolett.8b00040

18. Yu X, Gao D, Gao L, et al. (2017). Inhibiting metastasis and preventing tumor relapse by triggering host immunity with tumor-targeted photodynamic therapy using photosensitizer-loaded functional nanographenes. *ACS Nano* 11(10), 10147-10158. https://doi.org/10.1021/acsnano.7b04736
19. Lebre F, Boland JB, Gouveia P, Gorman AL, Lundahl MLE, R IL, et al. (2020). Pristine graphene induces innate immune training. *Nanoscale* 12(20), 11192-200. https://doi.org/10.1039/c9nr09661b
20. Ding Z, Luo N, Yue H, Gao Y, Ma G, Wei W. (2020). In vivo immunological response of exposure to PEGylated graphene oxide via intraperitoneal injection. *J Mater Chem B* 8(31), 6845-56. https://doi.org/10.1039/d0tb00499e
21. Tao Y, Ju E, Ren J, Qu X. (2014). Immunostimulatory oligonucleotides loaded cationic graphene oxide with photothermally enhanced immunogenicity for photothermal/immune cancer therapy. *Biomaterials* 35(37), 9963-71. https://doi.org/10.1016/j.biomaterials.2014.08.036
22. Hulsmans M, Sam F, Nahrendorf M. (2016). Monocyte and macrophage contributions to cardiac remodeling. *J Mol Cell Cardiol* 93, 149-55. https://doi.org/10.1016/j.yjmcc.2015.11.015
23. Gombozhapova A, Rogovskaya Y, Shurupov V, Rebenkova M, Kzhyshkowska J, Popov SV, et al. (2017). Macrophage activation and polarization in post-infarction cardiac remodeling. *J Biomed Sci* 24(1), 13. https://doi.org/10.1186/s12929-017-0322-3
24. Wu C, Wang L, Tian Y, Guan X, Liu Q, Li S, et al. (2018). "Triple Punch" Anticancer Strategy Mediated by Near-Infrared Photosensitizer/CpG Oligonucleotides Dual-Dressed and Mitochondria-Targeted Nanographene. *ACS Appl Mater Interfaces* 10(8), 6942-55. https://doi.org/10.1021/acsami.7b18896
25. Wang BH, AN JY, Zhang H F, et al. (2018). Personalized cancer immunotherapy via transporting endogenous tumor antigens to lymph nodes mediated by nano Fe_3O_4 Small. 14(38), e1801372. https://doi.org/10.1002/smll.201801372
26. Zhang D, Wu TT, Qin XY, et al. (2019). Intracellularly generated immunological gold nanoparticles for combinatorial photothermal therapy and immunotherapy against tumor. *Nano Lett* 19(9), 6635-6646. https://doi.org/10.1021/acs.nanolett.9b02903
27. ZOGLMEIER C, BAUER H, NOERENBERG D, et al. (2011). CpG blocks immunosuppression by myeloid-derived suppressor cells in tumorbearing mice. *Clin Cancer Res* 17(7), 1765-1775. https://doi.org/10.1158/1078-0432.CCR-10-2672
28. Li L, Yang S, Song L, et al. (2018). An endogenous vaccine based on fluorophores and multivalent immunoadjuvants regulates tumor microenvironment for synergistic photothermal and immunotherapy. *Theranostics* 8(3), 860-873. https://doi.org/10.7150/thno.19826
29. Park J, Wrzesinski S H, Stern E, et al. 2012). Combination delivery of TGF- β inhibitor and IL-2 by nanoscale liposomal polymeric gels enhances tumour immunotherapy. *Nat Mater* 11(10), 895-905. https://doi.org/10.1038/nmat3355
30. Zhou P, Qin J Q, Zhou C, et al. (2019). Multifunctional nanoparticles based on a polymeric copper Chelator for combination treatment of metastatic breast cancer. *Biomaterials* 195, 86-99. https://doi.org/10.1016/j.biomaterials.2019.01.007
31. Chen Q, Chen J, Yang Z, et al. (2019). Nanoparticle-enhanced radiotherapy to trigger robust cancer immunotherapy. Adv Mater 31(10), e1802228. https://doi.org/10.1002/adma.201802228
32. Su Z W, Xiao Z C, Wang Y, et al. (2020). Codelivery of anti-PD-1 antibody and paclitaxel with matrix metalloproteinase and pH dualsensitive micelles for enhanced tumor chemoimmunotherapy. *Small* 16(7), e1906832. https://doi.org/10.1002/smll.201906832
33. Shae D, Becker K W, Christov P, et al. (2019). Endosomolytic polymersomes increase the activity of cyclic dinucleotide STING agonists to enhance cancer immunotherapy. *Nat Nanotechnol* 14(3), 269-278. https://doi.org/10.1038/s41565-018- 0342-5
34. Chao Y, Chen Q, Liu Z, et al. (2020). Smart injectable hydrogels for cancer immunotherapy. *Adv Funct Mate*r 30(2), 1902785. https://doi.org/10.1002/adfm.201902785
35. Jin H L, Wan C, Zou Z W, et al. (2018). Tumor ablation and therapeutic immunity induction by an injectable peptide hydrogel. *ACS Nano* 12(4), 3295-3310. https://doi.org/10.1021/acsnano.7b08148
36. Bencherif S A, Warren Sands R, ALI O A, et al. (2015). Injectable cryogel-based whole-cell cancer vaccines. *Nat Commun* 6, 7556. https://doi.org/10.1038/ncomms8556
37. Wang H M, Luo Z C, Wang Y Z, et al. (2016). Enzyme-catalyzed formation of supramolecular hydrogels as promising vaccine adjuvants. *Adv Funct Mater* 26(11), 1822-1829. https://doi.org/10.1002/adfm.201505188
38. Luo Z C, Wu Q J, Yang C B, et al. (2017). A powerful CD8+ T-cell stimulating D-Tetra-peptide hydrogel as a very promising vaccine adjuvant. *Adv Mater* 29(5), 1601776. https://doi.org/10.1002/adma. 201601776

39. Wang Z Y, Shang Y N, Tan Z Q, et al. (2020). A supramolecular protein chaperone for vaccine delivery. *Theranostics* 10(2), 657-670. https://doi.org/10.7150/thno.39132
40. Sheth T, Seshadri S, Prileszky T, et al. (2020). Multiple nanoemulsions. *Nat Rev Mater* 5(3), 214-228. https://doi.org/10.1038/s41578-019-0161-9
41. Jia L, Pang M H, Fan M, et al. (2020). A pH-responsive Pickering Nanoemulsion for specified spatial delivery of Immune Checkpoint Inhibitor and Chemotherapy agent to Tumors. *Theranostics* 10(22), 9956-9969. https://doi.org/10.7150/thno.46089
42. Hu C M, Zhang L, ARYAL S, et al. (2011). Erythrocyte membranecamouflaged polymeric nanoparticles as a biomimetic delivery platform. *Proc Natl Acad Sci U S* 108(27), 10980-10985. https://doi.org/10.1073/pnas.1106634108
43. Kroll A V, Fang R H, JIANG Y, et al. (2017). Nanoparticulate delivery of cancer cell membrane elicits multiantigenic antitumor immunity. *Adv Mater* 29(47), 1703969. https://doi.org/10.1002/adma.201703969
44. Deng G J, Sun Z H, Li S P, et al. (2018). Cell-membrane immunotherapy based on natural killer cell membrane coated nanoparticles for the effective inhibition of primary and abscopal tumor growth. *ACS Nano* 12(12), 12096-12108. https://doi.org/10.1021/acsnano.8b05292
45. Cao H Q, Dan Z L, He X Y, et al. (2016). Liposomes coated with isolated macrophage membrane can target lung metastasis of breast cancer. *ACS Nano* 10(8), 7738-7748. https://doi.org/10.1021/acsnano.6b03148
46. Li W, Yang J, Luo L, et al. (2019). Targeting photodynamic and photothermal therapy to the endoplasmic reticulum enhances immunogenic cancer cell death. *Nat Commun* 10(1), 3349. https://doi.org/10.1038/s41467-019-11269-8
47. Wu C, Guan X, Xu J, et al. (2019). Highly efficient cascading synergy of cancer photo-immunotherapy enabled by engineered graphene quantum dots/photosensitizer/CpG oligonucleotides hybrid nanotheranostics. *Biomaterials* 205, 106-119. https://doi.org/10.1016/j.biomaterials.2019.03.020
48. Barillet S, Fattal E, Mura S, et al. (2019). Immunotoxicity of poly (lactic-co-glycolic acid) nanoparticles: influence of surface properties on dendritic cell activation. *Nanotoxicology* 13(5), 606-622. https://doi.org/10.1080/17435390.2018.1564078
49. Steenblock E R, Fahmy T M. (2008). A comprehensive platform for Ex Vivo T-cell expansion based on biodegradable polymeric artificial antigen-presenting cells. *Mol Ther* 16(4), 765-772. https://doi.org/10.1038/mt.2008.11
50. Freeman G J, Sharpe A H, Keir M E, et al. (2008). PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol* 26(1), 677-704. https://doi.org/10.1146/annurev.immunol.26.021607.090331
51. Wang J C, Sun X, Ma Q, et al. (2018). Metformin's antitumour and anti-angiogenic activities are mediated by skewing macrophage polarization. *J Cell Mol Med* 22(8), 3825-3836. https://doi.org/10.1111%2Fjcmm.13655
52. Ledo A M, Sasso M S, Bronte V, et al. (2019). Co-delivery of RNAi and chemokine by polyarginine nanocapsules enables the modulation of myeloid-derived suppressor cells. *J Controlled Release* 295, 60-73. https://doi.org/10.1016/j.jconrel.2018.12.041
53. Burkert S C, Shurin G V, White D L, et al. (2018). Targeting myeloid regulators by paclitaxel-loaded enzymatically degradable nanocups. *Nanoscale* 10(37), 17990-18000. https://doi.org/10.1039/C8NR04437F
54. Lpez-Soto, Alejandro, Gonzalez S, Smyth M J, et al. (2017). Control of metastasis by NK Cells. *Cancer Cell* 32(2), 135-154. https://doi.org/10.1016/j.ccell.2017.06.009
55. Ji T, Lang J, Ning B, et al. (2019). Enhanced natural killer cell immunotherapy by rationally assembling Fc fragments of antibodies onto tumor membranes. *Adv Mater* 31(6), e1804395. https://doi.org/10.1002/adma.201804395