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NANOMEDICINE AND MACROSCALE MATERIALS IN IMMUNO-ONCOLOGY

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ABSTRACT

Immunotherapy is revolutionizing in the treatment of cancer. In advanced stage patients it can achieve remarkable responses, including complete recovery and long-term survival. However, immunotherapy also has limitations, such as its relatively low response rate and the development of serious side effects. These deficiencies are gradually overcomed by improving our understanding of the immune system and establishing a combination of immunotherapy and other treatment modalities. Additionally, in recent years, advances in materials science, chemistry, nanotechnology have begun to affect immuno-oncology, resulting in more efficacious and reduced toxic immunotherapy interventions. The extensive relationship between the immune system and cancer is opening up a new exploration hallmark for nanomedicine. Here, all the commonalities and synergies between these two fields are reviewed and described, as well as recent methods that show the advancement of biomarkers developed by banks in nanomedicine and tumor immunotherapy. In this regard, it has been shown that a variety of different nanomedicine formulations and macroscopic materials can stimulate immunity against cancer and the efficacy of immunomodulatory drugs.

Keywords: Nanoparticles, Nanodiagnostics, Macroscale materials, Antigen Presenting cells

INTRODUCTION

The extensive relationship between the immune system and cancer has opened up new treatments for tumors, such as monoclonal antibodies, adoptive T cell transfer, vaccination, immune checkpoint inhibitors, and oncolytic virus therapy.

These innovative immunotherapies mainly rely on the self-defense system of the body to riot and conquer cancer. Current research focuses on reactivating the immune system to attack cancer cells with powerful cytokines, vaccines, antibodies, and immune-stimulatory adjuvants. However, these immunotherapies may have various disadvantages, side effects (due to systemic treatment), low efficacy, and drug resistance.

Therefore, nanomedicine is a novel arena with strong application potential in immuno-oncology, which can overcome the bottleneck and improves the currently available immunotherapies. Nanotechnology is a new field that has a significant impact on medical and biomedical research, because it allows carrying out highly specific targeted delivery to tumors or immune cells, obtain better clinical effects, and reduces adverse reactions, which helps for the administration of vaccines and immunomodulatory agents. This is achieved by nanoparticles (NP), which can be highly variable in structure and function. Considering all these, it seems very interesting to explore all these fields (nanotechnology, immuno-oncology, immunotherapy, nanomedicine, etc.) to find and discover synergistic effects and new opportunities. Therefore, here is a brief review of the main areas of these fields characteristics and achievements.

Nanomedicine and Macroscale materials

Nanomedicine targets tumors through passive mechanisms (also known as enhanced penetration and retention effect, EPR effect) and / or active mechanisms **[1]**. Several important directions are being studied to improve the clinical performance of nanomedicine, including the improvement of the efficacy of targeting of tumors **[2]** and tissue penetration **[3]** and the application of more basic design principles clinical trials, such as patient stratification **[4]**.

The macroscale system is generally used for local administration to regulate the release of the payload that diffuses into the surrounding tissues. The macroscale system is designed to accommodate payloads ranging from small molecules to macro molecules and cellular therapeutics **[5, 6]**.

Nanotechnology

In the last 20 years, nanotechnology has made its mark in the field of science and technology. When works on this scale, the physical and chemical properties of the substance will undergo fundamental changes.

Nanomedicine

Nanomedicine is expected to lead to develop better equipment, drugs and other

applications for the early diagnosis or treatment of a wide range of diseases, with high specificity, effectiveness and actualization, with the aim of upgrading the patient's life quality. Three main areas are being covered by nanomedicine: Nanodiagnosis, nanotherapy (controlled drug delivery) and regenerative medicine **[7]**.

Nanodiagnostics

Nanomaterials can be used for *in vivo* diagnostics, as a contrast agent to visualize the structure of internal tissues of the human body and distinguish healthy tissues from pathological tissues. For this reason NPs are designed to have different contrast characteristics for different modes such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission computed tomography (SPECT) or fluorescence imaging. Some of the examples include Quantum dots, Liposomes, AuNP, Silica NPs, Diamond polymer, Exosomes, Polymer NPs etc **[8]**.

Controlled drug release

For nanomedicine to have a high therapeutic effect in the administration of anticancer drugs, it must comply with the five steps of the CAPIR cascade in the most effective way: blood circulation, accumulation and penetration into tumors, cell internalization and intracellular release of the drug (CAPIR) **[9]**. Polymer NP, gold NP or liposomes have also been used as tumor peptide vaccine carriers that play a crucial role in tumor immunotherapy **[10, 11, 12]**. Chemotherapy based on platinum (II), ruthenium, and gold (III) compounds kills tumor cells **[13, 14]**. Combination therapy targeting multiple tumor targets may enhance the effect of treatment **[15]**.

Regenerative medicine

Regenerative medicine aims to use nanotechnology tools to repair or replace damaged tissues and organs **[7]**. Bioimplants, such as cell-based therapies, are also very important in regenerative medicine. An example is the use of stem cells to regenerate defective tissues **[16]**.

Nanomaterials in Medicine

One of the most promising nanoparticles is biodegradable nanoparticles, which often use poly (lactic acid glycolic acid) (PLGA), which also has the advantage of protecting against antigens **[17]**. These NPs are the same size as the pathogen, so they are more easily absorbed by antigen-presenting cells (APC). AuNPs show great promise due to their safety and adjustability, increasing potency through better permeability and retention and reducing the toxicity of immunotherapeutic drugs **[18]**. The binding of AuNPs bound to tumor peptides to CD13 (cluster of differentiation) in tumor endothelium has been shown to transport

and release TNFα (tumor necrosis factor) more effectively in the body **[19]**.

Immuno-Oncology

Coley developed the first cancer immunotherapy drug based on a mixture of bacteria (the so-called Coley toxin). This field has a long history in the shadow and cancer treatment is mainly based on surgery, radiotherapy, chemotherapy and later targeted therapies in different ways.

Cancer Hallmarks

Cancer cells have defects in the signaling pathways that regulate homeostasis and normal cell proliferation. However, cancer cells from different tumors have a wide variety of genotypes. Based on this complexity, Hanahan and Weinberg proposed that these genotypes are the result of six important basic changes: self-sufficiency in growth signals, insensitive to growth inhibitory signals, avoids apoptosis (programmed cell death), metastasis, tissue invasion, unlimited replication potential and continuous angiogenesis. Each of these physiological changes is an ability acquired during tumor development to evade cancer defense mechanisms related to cells and tissues. These six capabilities are shared by most human tumor types. These capabilities are called "cancer hallmarks" **[20]**.

Cancer Immune Cycle

For the immune response against cancer to effectively destroy / kill cancer cells, specific events must occur in a staggered and continuous manner. These eventualities are the steps in the "Cancer Immune Cycle". The release of neoantigen (formed by oncogenesis) is then captured by dendritic cells (DC) for processing (Step 1). To generate an anticancer T lymphocyte response, it must be accompanied by a specific immune signal, to avoid inducing peripheral tolerance to the tumor antigen. These signals can be pro-inflammatory cytokines and factors released by damaged tumor cells. The DC then presents the new antigens on the MHCI and MHCII molecules to the T cells (Step 2). Antigen presentation on MHC (major histocompatibility complex) molecules activates effector T cells to target cancer-specific antigen (Step 3). It is at this step that the nature of the immune response is determined and a balance is established between effector T cells and regulatory T cells. The effector T cells then migrate to the tumor site (Step 4) and infiltrate the bed of the tumor (Step 5). After arriving here, the T cells specifically recognize cancer cells and bind to them through the interaction between the T cell receptor (TCR) and its associated antigen that binds to MHCI (Step 6). Eventually, the T cells kill the target cancer cells (Step 7). Killing the cancer cell will release the tumor associated antigen (TAA), causing the cycle to restart. This increases the breadth and depth of the consequent response **[21]**.

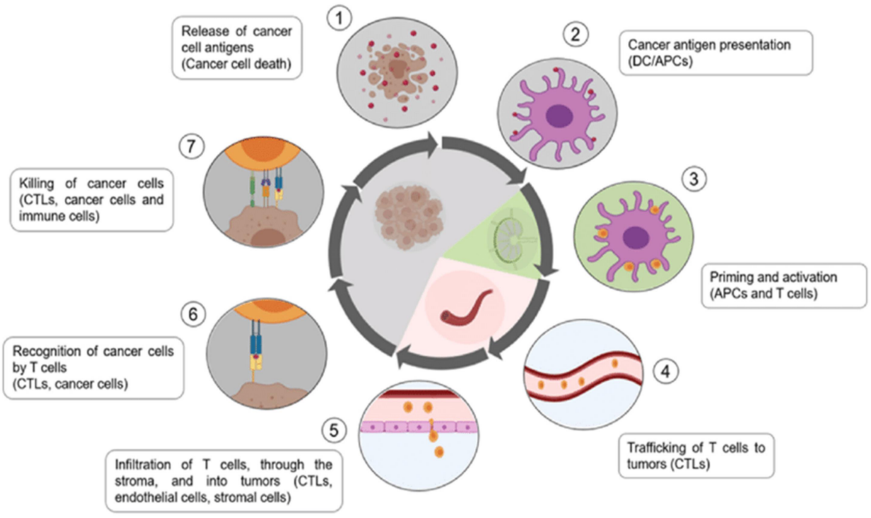

Figure 1: Schematic diagram of the cancer immune cycle

Cancer Immunotherapy

Once the characteristics of the immune cycle and cancer are described, different immunotherapies will work, and new immunotherapies can also be designed based on them.

Cytokines

Cytokines are polypeptides or glycoproteins that produce growth, differentiation, and inflammatory or anti-inflammatory signals for different types of cells. They are released in response to specific stimuli at a specific time in, and have a limited half-life in the cycle **[22]**. Therefore, the administration of cytokines allows manipulation of the immune system in autoimmune diseases, infectious diseases, improved vaccine efficacy (due to inherent auxiliary diseases) and cancer treatment **[23]**.

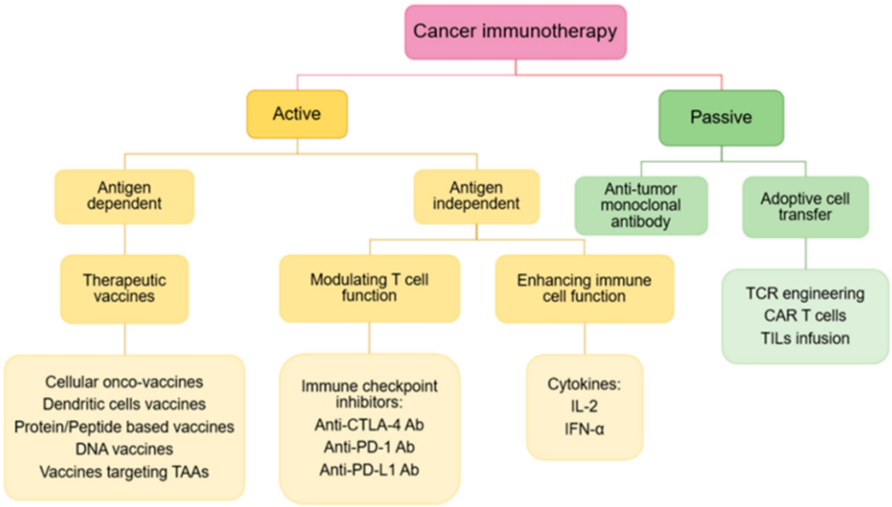

Figure 2: Schematic classification of immunotherapies designed for cancer

Monoclonal Antibodies

The first monoclonal antibodies (mAbs) used in clinical trials for cancer treatment were murine mABs, but their delivery problems in humans limited their clinical applications **[24]**. The success of mAb therapy is accompanied by the development of technologies that allow genetic modification of murine mAbs to produce chimeric mouse-human mAbs or humanized mAbs that behave similarly to human IgG.

CAR-T Cells

There was development of techniques to introduce the antitumor T cell receptor (TCR) into autologous lymphocytes for their treatment. Ordinary αβ TCR and chimeric antigen receptor (CAR) which has antitumor specificity can be introduced into normal lymphocytes to deliver them with antitumor activity.

Endogenous Vaccination Initiation:

The cancer vaccine is designed to encourage the immune system to fight tumors. The clinical strategy for cancer vaccination uses endogenous TAA produced in the body and is designated "endogenous vaccination" **[25]**. In practice, the treatment of cancer with chemotherapy and radiation therapy sometimes stimulates the immune system. In this sense, it is also a endogenous vaccination **[26]**. For example, cytotoxic chemotherapy drugs, including anthracyclines, oxaliplatin, and cyclophosphamide, induce apoptosis in cancer cells, which usually shows significant immunogenicity. This so-called immunogenic cell death (ICD) sensitizes and matures APC, and subsequently leads to the production of CTL (cytotoxic T lymphocytes).

Nanomedicine mediated immunogenic cell death

Generally, pharmaceutical therapies, such as the ICD promoters which are utilized for endogenous vaccination, are administered in their free forms either locally or systemically. Recently, several nanoparticles (NP) have used to deliver ICD promoters to induce antitumor immunity **[27]**, and ICD promoters delivered by NP after intravenous administration have showed better effects than the free form of the same drug. ICB therapy is a promising cancer treatment for patients, but is associated with a low response rate (approx < 30%) of cancer patients **[28, 29]**. This is largely because non-responsive tumors (so-called ''cold tumors'') **[30]**.

Macroscale materials to induce local immunity

Recently, in local chemotherapy for endogenous vaccination there was an implementation of a more advanced polymer-based injectable hydrogel. The hydrogel which was designed by Gu and colleagues was based on crosslinking polyvinyl alcohol with a ROS-labile crosslinking agent, and

reacting its phenylboronic acid with the diol in polymer. The gemcitabine dose has been shown to be the key for the effect of vaccination. Local administration of low doses (5 mg / kg gemcitabine) in conjunction with hydrogel can significantly increase tumor infiltration of lymphocytes and reduce myeloid-derived suppressor cells, M2-polarized macrophages, and local ROS concentrations. However, the highest dose (25 mg / kg) caused lymphocyte depletion in the tumor.

Exogenous Vaccination Enhancement:

Compared to endogenous vaccination strategies that rely on to release TAA from tumors to activate T cells, most of the cancer vaccine is achieved by administering of such TAAs together with adjuvants, generally defined as "exogenous vaccination." **[31]**.

Adjuvants delivery to lymphoid organs

TLR (toll-like receptor) agonists are one of the most effective immune adjuvants. However, due to its working mechanism and high toxicity, their exposure in the body must be limited to dLN (draining lymph node), and it is the site where APC presents the antigen. To facilitate the targeted administration of dLN, Irvine and colleagues designed an "albumin hitchhiking" approach. Dyes with certain hydrophobic portions are known to bind effectively to endogenous albumin, and then these albumin / dye complexes are transferred to LN (lymph node).

NPs are also used to provide TLR agonists to LNs. De Geest and colleagues developed a nanoparticle adjuvant based on a pH-sensitive nanogel combined with the TLR7/8 agonist imidazoquinoline.

Whole tumor vaccine

Since the costimulatory signal is essential for the APC to begin processing and presenting the whole tumor vaccine, several strategies have been developed to combine adjuvants with the whole tumor antigen. De Geest and colleagues have designed a microparticle-based whole cell vaccine combining the TLR7/8 agonist. Without the need to recognize and produce specific antigens, whole tumor antigens can be readily obtained.

Recruitment of antigen-presenting cells

In the context of cancer vaccination, APC plays a central role in the immune cascade, mediating communication between antigens and effector T cells. The role of APC is that is highly effected by cytokines and chemokines in the immune microenvironment. GM-CSF (granulocyte-macrophage colony-stimulating factor) is one of the most effective cytokines that promotes DC recruitment and activation. Mooney and his colleagues used GM-CSF in vaccines that are characterized by effective recruitment of DCs.

The dose of GM-CSF in the vaccine was found to be critical to the efficacy of the vaccine with respect to the recruitment of cells and the production of pro-inflammatory cytokines. By optimizing the GM-CSF dose,

the APC recruitment vaccine has shown very promising results in the preclinical setting.

CONCLUSIONS AND PERSPECTIVES

Nanomedicines and macroscale materials research used in cancer treatment mainly focused on direct killing of tumor cells by chemotherapy, radiotherapy, surgery, immunotherapy and targeted therepy. Immunotherapy is based on identification of tumor cells as foreign by the immune system. To be successful, immunotherapy must activate and expand tumor-specific T cells. It uses several methods for this purpose: direct activation of antitumor immunity by means of cancer vaccines (tumor antigen), recombinant cytokines, or by infusion of tumor-specific cells.

One of the most promising strategies is to use the ICD concept to derive a source of highly immunogenic antigens for to develop a "next generation" DC-based vaccine. Inducers of ICD can be used to generate immunogenicity in dying tumor cells and load DCs, enhance their ability to stimulate effector cells, and enhance the response of T cells to cancer in the body. This can improve overall immunity or create a tumor microenvironment that is favorable to the immune system **[34]**.

However, the arising and developing strategy of using nano- and macroscale materials to modulate the immune system has caused a sensation in immuno-oncology. The limitations of large-scale production of nano- and macroscale materials hinder the full utilization of their potential in immunotherapy. Considering their scalability, GMP (Good Manufacturing Practice) production and quality control of pharmaceutical products, the complexity of the design of most materials at the nano- and macroscale materials is a major obstacle.

Although current nano and macroscale materials still have limitations, it is exciting that a variety of emerging trends will bring prosperity to this rapidly developing field. Firstly, nano and macroscale materials have been widely combined with immunotherapy, or a more effective combined immunotherapy. Secondly, administration in combination chemo-immunotherapy is very important. In the context of combination therapy, the combination of chemotherapy and immunotherapy has considerable clinical potential and relevance, especially for chemotherapy that has the effect of stimulating the immune system (eg via ICD). Thirdly, nanopharmaceutical-based drug delivery has shifted from targeting tumor cells to cells and organs that control the immune response. Interestingly, non-tumor targeting methods take advantage of the inherent characteristics of nanomedicine, which are generally considered the shortcomings of targeted nanomedicine. Therefore, considering that

immune cells and organs are very interesting and easily accessible targets, a different way of thinking must be adopted when designing the drug delivery system for immunotherapy.

Through the exponential expansion of efforts in this multidisciplinary research field, through the advancement of nano/macro material design, and through our growing understanding of cancer immunity, the use of custom-built immunomodulatory materials and its successful clinical implementation will have a major impact on cancer therapies and patients in the next 5 to 10 years.

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