



Recent Advances In Nano Drug Delivery Systems For Synergistic Antitumor Immunotherapy

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Abstract: Recent advances in nano drug delivery systems (NDDS) have demonstrated remarkable potential in enhancing synergistic antitumor immunotherapy. These innovative systems, including nanoparticles, liposomes, and micelles, enable precise drug delivery by encapsulating chemotherapeutic agents and immune modulators, leading to targeted tumor accumulation through the enhanced permeability and retention (EPR) effect while reducing systemic toxicity. NDDS improve drug pharmacokinetics and modulate the immunosuppressive tumor microenvironment, promoting immune cell infiltration and enhancing tumor immunogenicity. Emerging strategies combine NDDS with immunotherapies like checkpoint inhibitors, demonstrating enhanced immune efficacy and the potential to control tumor metastasis. Chemotherapy drugs encapsulated in nanoparticles can induce immunogenic cell death while minimizing toxic side effects. Furthermore, the ability to integrate multiple therapeutic approaches—such as chemotherapy, phototherapy, and immunomodulation—represents a significant breakthrough in personalized cancer treatment. These advancements signal a promising future for more effective, targeted cancer therapies that could lead to improved survival rates and reduced relapse in patients.

Index Terms - Synergistic, Immunomodulation, Nanoparticles, Targeted, Precision, Multimodal.

I. INTRODUCTION

Immunotherapy is a massive new development in cancer treatment that enhances the immune system to notice and obliterate cancerous cells. This method increases the ability of the body's immune system to fight diseases and is typically more effective and has longer lasting impacts than treatments like chemotherapy and radiation treatments. Wrapped within it are several approaches that include cell checkpoint inhibitors, CAR T cell therapy, and monoclonal therapy, approaches that are meant to enhance the immune system's ability to fight cancer cells. ^[1]

Ineffective control of cell division results in a group of diseases called cancer and cells can multiply abnormally and in other parts of the body. Depending on the presumed origin of the tumor cells sensitive to radiation therapy, cancers are grouped into carcinoma, sarcoma, lymphoma, leukemia, germ cell tumor, and blastoma. Carcinoma refers to tumors resulting from the uncontrolled growth of epithelial cells, and all breast, prostate, lung, pancreatic and colon malignancies are major types of carcinomas. Considering that several types of cancer are lethal, the common cancers around the world are skin and lung cancer. In addition, the commonest cancer type in women is breast cancer or BC. Shortly, the increasing trend in cancer remains the highest cause of death across the globe. more so that attention to research on the treatment of the disease is growing. The current treatments practices of cancers are immunotherapy, chemotherapy, radiation, and surgical; with the recommended combined therapy regimens. Immunotherapy is considered to be one of the most effective approaches to defeating the disease at the moment because it differs from traditional therapies with its focus not on the tumor itself but on the systemic immune system. ^[2]

Cancer immunotherapy has developed and shown clinical benefits since the US Food and Drug Administration (FDA) approved ipilimumab as the first immune checkpoint blockade in 2011. [5] Currently, the FDA has approved six additional immune checkpoint blockade drugs (Keytruda, Opdivo, Tecentriq, Imfzi, Bavencio, and Libtayo), and many other powerful immunotherapy drugs are in the pipeline for trials. The biggest threat to human health is cancer, a disease that causes death around the world every year. Since William B. Coley used bacterial toxins as an immunotherapy agent for the treatment of bone and soft-tissue sarcoma. [3]

OVERVIEW OF CANCER AS A LEADING CAUSE OF DEATH GLOBALLY

Throughout the world, including in the majority of low- and middle-income nations, cancer is the primary cause of death. As per the World Health Organization's (WHO) 2019 projections, cancer ranks first or second in 112 out of 183 nations and third or fourth in 23 other countries as the primary cause of death before the age of 70. Globally, the burden is predicted to rise due to aging and growing populations, changing risk profiles, and declining fertility rates in transitioning economies coupled with rising rates of obesity, physical inactivity, and smoking. Prior research has documented national patterns in cancer mortality; however, the majority of these investigations focused on specific cancer types. [4]

The main risk factors for cancer in western (host) countries have generally been found to be smoking, food habits, and reproductive practices; in economically developing countries, the main risk factors are infectious agents. These trends, though, are shifting quickly. Although smoking is becoming less common in economically developed nations, it is becoming more common in several developing nations in South America, Asia, and Africa. For instance, the prevalence of adult male smoking in the West, including the United States, is currently around 20%, but it is over 60% in China, Indonesia, Greece, and Jordan. Additionally, intake of

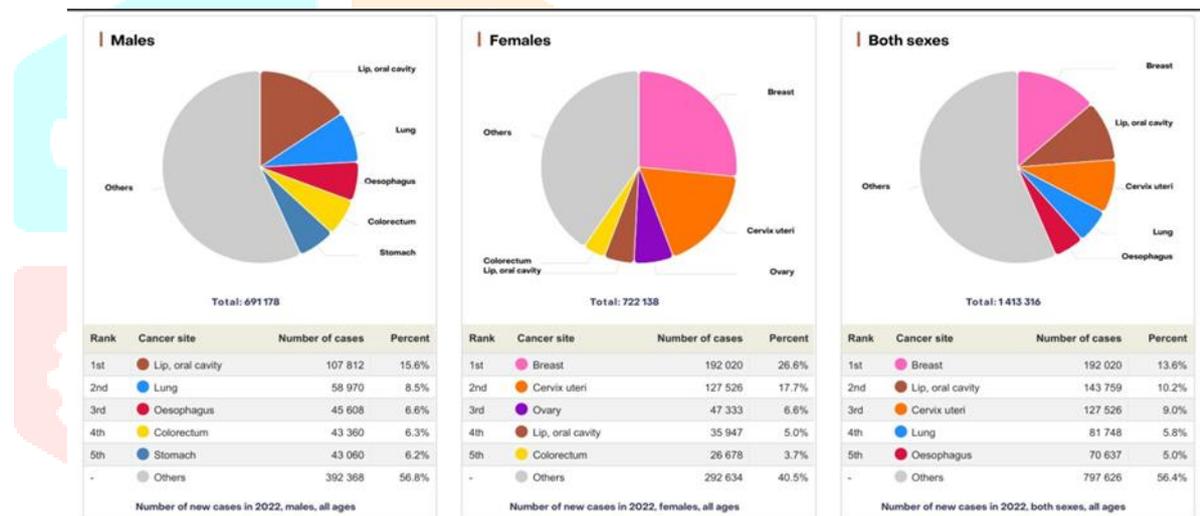


Figure 1: Top 5 most frequent cancers

foods high in calories and saturated fat, as well as physical inactivity, are on the rise, continuing earlier patterns in a number of western nations. [5]

CAUSES INTRODUCTION TO IMMUNOTHERAPY

Hepatitis B virus (HBV)

More than 2000 million people have been infected with HBV worldwide and 350 million people are chronically ill due to the virus. Chronic HBV infection is the most predominant in China Asia and Africa. The primary site of infection is the liver and the ability of the virus to be detected in the bloodstream of infected individuals makes HBsAg a useful marker of the current active HBV infection. HBV is actually most often transmitted from mother to child during childbirth, from parents to children in childhood, via sexual contact, blood transfusions and from sharing needles in adulthood. Altogether, HBsAg carriers were calculated to have a 13,7-fold increased relative risk of HCC compared with non-carriers. HBV has been identified as a definite cause of hepatocellular carcinoma in people depending on regional relations, cohort and case control studies. [6]

Hepatitis C virus (HCV)

Fortunately, Hepatitis C is the RNA virus belonging to the Flaviviridae family. With genome of 9.5 kilobases of single-stranded RNA it contains a number of structural and non-structural proteins such as C, E2/NS1, NS2, NS3, NS4 and NS5. Because of the lack of proof – reading ability, therefore, HCV reproduces with great speed meaning that there are many variants, which are immunologically distinct or quasi species. [7]

Human papilloma virus (HPV)

HPV is sexually transmitted. Numerous epidemiological findings support this: co- infection is rare; HPV is rare in people who have not been sexually active and nuns but increases with the number of sexual partners and age of having the first sexual intercourse; marital partners are highly comparable in terms of their infective status. This approximate with the poor nations in the range of 15% and with the industrialized nations 7%. [8]

INTRODUCTION TO IMMUNOTHERAPY

The use of cancer immunotherapy as a treatment modality has grown quickly. The process of cancer immunity, known as the "cancer-immunity cycle," involves multiple crucial stages, such as the release of antigens from cancer cells, the presentation of these antigens by antigen-presenting cells (APCs), the priming and activation of T cells, the transportation and infiltration of T cells into tumors, and finally the identification and elimination of tumor cells by cytotoxic T cells. In theory, it is likely that each of those steps may be a possible treatment target using a variety of techniques. Targeting these objectives, the primary strategies used in cancer immunotherapy today include cytokine therapy, cancer vaccines, adoptive cell therapy and therapeutic antibodies. [9]

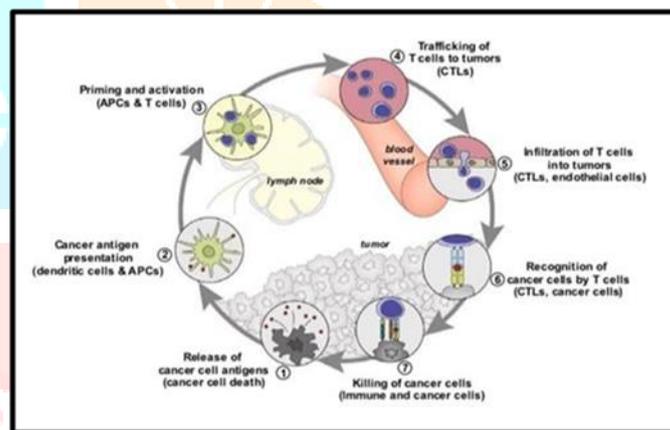


Figure 2: Cancer Immunity Cycle

Cancer Vaccine:

vaccination against cancer for more than hundred years, people try to find out whether vaccination can or cannot be used for prevention and treat cancer. A great progress has been accomplished in the creation of preventive vaccines—hepatitis B and human papilloma viruses (HPVs). HPV vaccines have yet unrealized potential to save millions of lives and halt cancer. Nevertheless, the process of creating therapeutic vaccinations turned out to be very arduous and was a long-time process. To date, the only therapeutic cancer vaccine that has been approved by the FDA for treatment of prostate cancer is Sipuleucel-T (Provenge). [10]

Cytokine Therapy:

Cytokine treatments Small, soluble signaling proteins called cytokines are short living and act immediately provoking the immune reaction after receiving stimuli from outside environment. Since they are involved in nearly all cellular activities including regulation of the immune cell kinetics and their differentiation, immune cells rely on them to eliminate tumor cells. IFN- α was the first cytokine medicine used in tumor immunotherapy which was approved by the FDA in the 1986. [11]

Immune Checkpoint Inhibitor:

Immunotherapy ‘T-cell exhaustion’ describes the state of effector T cells within the tumor that exhibit reduced cytokine secretion and effector functionality and cannot be restimulated. Several inhibitory surface markers including cytotoxic T Lymphocyte antigen 4(CTLA-4), programmed cell death protein 1(PD-1), lymphocyte

activation gene-3(LAG-3), T cell immunoglobulin and ITIM domain (TIGIT) are prominently expressed on exhausted T cells and have a strong tendency to restrain T cell activation. These restraining surface proteins are called immune checkpoints. ^[12]

NANO BASED DRUG DELIVERY SYSTEM (NDDS) IN CHEMOIMMUNOTHERAPY

However, most of the practical approaches aimed at achieving safety and improving the quality of life of cancer patients require further development in the context of early diagnosis and recognition of potentially curable precursors of malignant tumors, although significant progress has been made in the field of cancer treatment methods. The lack of treatments has heightened awareness of early detection as another possible pathway of managing cancer progression. Cancer or abnormal tissue are categorized under diseases that need early discovery because early discovery keeps treatment easy. To put it in other words, early detectability counts because treatment becomes easier if cancer or abnormal tissue is detected early. For instance, the recovery rates can go a notch higher when the disease is detected at an early stage. Possible cancer warning signs and more research help in early diagnosis of the illness. It may be highly advantageous for physicians, other healthcare workers, and the general public to increase awareness of possible early signs of cancer. First of all, one of the most significant initial actions in cancer treatment is cancer detection. The management of carcinomas resulting from viruses such as HPV have been made to reduce in recent years. ^[13]

Targeted drugs for targeted cancer therapy penetrate into cancer cells and affect specific molecules affecting cancer development and formation, so that non-cancerous cells cannot grow and spread. In order to overcome disadvantages of present cancer treatment processes, the scientific society used nanotechnology in creation of new and efficient drug carrier systems aimed at the safe deliver of anticancer medicines to the cancer cells. Research in nanomedicine and nanotechnology has given rise to new therapeutic strategies at the nanoscale because these agents are small in size, release medication slowly, and have very few side effects. Nanomedicine also involves identification, manufactures and development of Nano technology, tools, devices and drug delivery systems for diagnosis and treatment of disease conditions. Advanced imaging consequent of nanotechnology can increase probability of the detection of early tumor; this can enhance practices concerning the allocation of better improved new screening mechanisms. ^[14]

ADVANTAGES OF NANOCARRIERS FOR CANCER TREATMENT:

- Lower the concentration of the encapsulating chemotherapy drug in healthy body tissues and organs in an effort to decrease toxicity.
- Improve the dose of a drug that can be administered in an individual's body.
- Ensure maintenance of a variety of medications available.
- To deliver a large proportion of the drug to the tumor mass.
- Incorporates imaging contrast agents into nanoparticles for use in the diagnosis of cancer.
- Make the drug more specific to target and make it respond optically, magnetically, or by giving it hyperthermic abilities.

It can be supplied to the intracellular locale of action as far as possible by endocytosis or phagocytosis of the drug. ^[15]

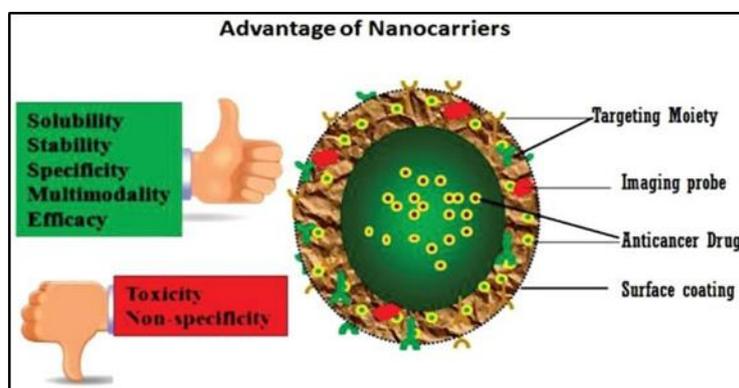


Figure 3: Advantages of Nanocarriers

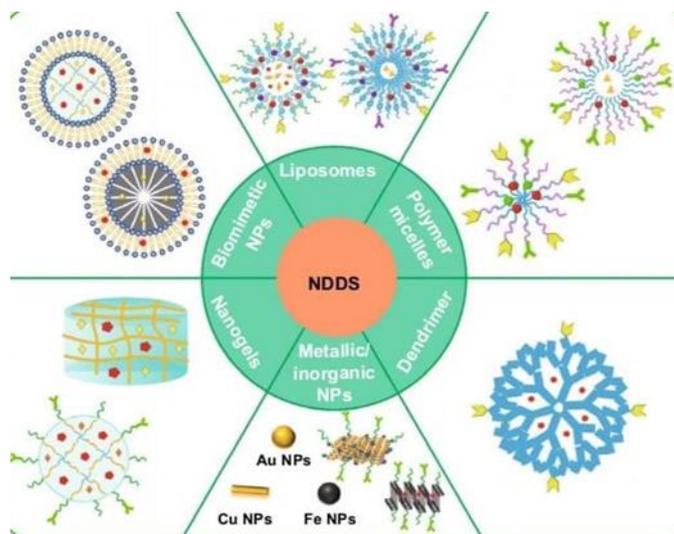
TYPES OF NANOCARRIERS:

Figure 4:Types of Nanocarriers

Liposomes:

Liposomes are bilayer vesicles containing cholesterol and phospholipids which possess high encapsulation efficiency, low toxicity and targeting properties. They also provide a lot of promise for commercial production. The immunotherapy agents may be surface adsorbed by interacting at the lipid charge level or through a chemical conjugate to the lipid bilayer or encapsulated at the hydrophobic core. Hydrophobic medicines can be encapsulated in the lipid- bilayers, whereas the solid hydrophilic small-molecule chemotherapeutic drugs may be lodged in the inner water channels. ^[16]

Hydrogels:

Hydrogels are formed by networks of water-soluble polymers having different structures of architecture. They can be divided into two groups: Solutions with a linear structure and solutions with a three dimensional polymeric structure with covalent crosslinking. The covalent bonding between the chains affect the properties of the hydrogel, how much it can swell, how much it can stretch, and how much drug it can load. This characteristic is due to the existence of hydrophilic groups in their structure that allow them to absorb from 10-20% (an added artificial lower bound) up to thousands of times their dry weight. Because of this, they are highly advantageous as possible drug carriers in micro- or nanoparticles form. In addition, some hydrogels allow the transport of fluid and may have stimulus responsive characteristics, which include light, pH, temperature and salinity. ^[17]

Polymeric micelles:

Polymeric micelles are formed by block copolymers which are made of chains with two or more polymer s having different hydrophilic properties. Depending on the conditions, especially in aqueous media these copolymers self-assemble into a core- shell paradigm. Hydrophobic materializations of any medication can be transported by the core blocks that are hydrophobic in nature and the outer shell is formed by the hydrophilic blocks. Due to the fact that a critical micelle concentration value is considerably lower for the amphiphilic copolymers commonly employed in the construction of polymeric micelles than for liposomes and many surfactant micelles, the latter structures are generally more stable in blood. Due to these properties, polymeric micelles have been used as efficient carriers for cancer treatment and image- based diagnose of tumor. secondly, it is now possible to create polymeric micelles with a pH sensitive property added to it and this improvement contributes to the mechanism of drug release in anticancer treatments. ^[18]

Dendrimers:

Dendrimers are synthetic polymers characterized by a high density of branching structures; they consist of an initiator core and several layers with terminal active groups. They are composed of repeated units and are called a generation (generation zero is the central core oneself). Dendrimers are ideal for the synthesis of smart nanocarrier for biomedical delivery due to flexibility provided by molecular construction and the possibility of introducing several brands to the molecule at predetermined locations. These have been applied for gene transfection therapy, tissue engineering scaffold, drug delivery system, and antibacterial/ antiviral drugs and

other uses. Another advantage is the applicability of the dendrimers to encapsulate bioactive chemicals or to provide such molecules in-situ for physical adsorption or covalent attachment to the dendrimer. [19]

Gold Nanoparticles:

Due to the fact that GNPs can be easily sized and shaped, the surface chemistry can be changed, and the cytotoxicity which is often associated with nanoparticles is low, GNPs are also used in immunotherapy. GNPs belongs to immunostimulatory NPs type that prove their response by activating the macrophages and leading them to differentiate into dendritic like cells that triggers proliferation of T cell and cytokine production. [20]

Silica Nanoparticles:

It was observed that, as compared to free CpG-ODNs, there is much higher cell uptake of the nanoconjugate by immune cells and enhanced immuno-stimulatory property. The finite results indicate that the stimulation of RAW264.7 cells with CpG hollow GNPs supplemented around 15 times higher TNF α release than CpG-ODNs alone. Most of the silica nanoparticles are non-toxic in nature and these are used in numerous biomedical applications such as drug/ vaccine delivery system, tumor therapy and bio imaging. [20]

Quantum dots:

Semiconductor particles with their diameter less than 10 nm are called quantum dots (QDs). Due to their size, they are often embedded in nanostructure scaffolds for diagnosis, treatment or they act as fluorescent markers in imaging. The ability to alter the size and composition of QDs gives the substance optic properties suitable for medical imagines especially in the context for the gastrointestinal tract. QDs is an active research subject in the theoretical quantum mechanics. [21]

MECHANISM OF IMMUNOSTIMULATORY NANOPARTICLES:

NPs are essential for cancer immunotherapy because they activate the host's immune system through three distinct strategies: There are three ways:

- (1) delivery of antigens or adjuvants
- (2) delivery of antigens with self-associating property as adjuvants, and
- (3) delivery or adjuvants together with antigen and induction of immunogenic cancer cell death.

However, effective from being a, delivery system, the following factors should be taken into consideration regarding NPs Whether as experimentalists or users. The nature of interaction between NPs and antigens is important to maintain efficiency of the delivery of the antigens since the core molecules have to be protected from degradation as well as early release within the blood stream. The methods such as chemical conjugation, encapsulation or physical adsorption have been applied for preconcentration of antigen and adjuvant molecules over the NPs. [20]

Targeting/Stimulation of T-Cells:

An another immunotherapeutic approach includes the direct stimulating or activation of T cells by NPs. There are generally two methods to promote T-cell activation: There are two strategies: (1) the ex vivo expansion of T-cells derived from a cancer patient's lymphocytes followed by reinfusion of the T-cells, which has been discussed earlier in this review by Broere and van Eden (2019); and (2) the design of nano vaccines to stimulate CD8+ T cells against a tumor according to Zhang et al. (2017). In both cases, artificial APCs also known as a APCs, must mimic the ability of natural APCs to present antigens to T-cells and activate them. Nevertheless, acellular or NP-based a APCs have many advantages over cell-based aAPCs that limit or can prevent the formation of the immune response.

To design a APCs capable for direct T-cell activation, multiple nano-formulation materials have been designed such as liposome, magnetic beads, paramagnetic nanoparticles and poly(ethylene glycol)-based biodegradable polymers. T-cells can be activated by aAPCs to provide co-stimulatory signals that include antibodies against CD3 or CD28 and peptide-MHC-I molecules in seconds. Furthermore, conjoining to immune-checkpoint antibodies and pro-inflammatory cytokines can enhance and extend T cell anti-tumor functions. The T-cell activation route by immunostimulatory NP for better cancer immunotherapy is depicted in figure 4(II) below. Zhang et al. (2017) have illustrated the method to activate T-cell response for cancer immunotherapy based on the magnetically recoverable nanoclusters that have been Surface modified with azide-modified leukocyte membrane fragments and coupled with MHC-I peptide and anti-CD28 antibodies.

Several immune-checkpoint molecules such as CTLA-4 and programmed death- 1/programmed death-ligand 1 (PD-1/PD-L1) are effective in regulating activator T-cell. To target and inhibit the immune checkpoint pathways, and amplify the signaling through T cells, immune-checkpoint antibodies that can either bind directly to CTLA- 4 or PD-1 are used, such as antiCTLA-4 or anti-PD-1. By blocking the inhibitory receptor

on the T-cells, conjugation of CTLA-4 antibody with PLHMGGA and PLGA, as described by Li S. et al. (2018) and enhanced anticancer immunotherapy. To optimise and dissect the effects of PLGA-derived aAPCs and CD8⁺ T cell activation and tumor growth suppression, Kosmides et al. (2017) incorporated an anti-PD1 monoclonal antibody. Ye et al. (2016) developed a microneedle-based transcutaneous delivery system for anti-PD-1 antibody conjugated self-assembled amphiphilic hyaluronic acid NPs encapsulated with 1MT and IDO inhibitor to enhance cell immunity and overcome immune suppression.

For improved cancer immunotherapy, NPs can also include plasmids expressing immunostimulatory cytokines. By inhibiting the phrase of immunosuppressive molecules, small interfering RNA also stimulates T cells. By downregulating CTLA-4 levels and boosting CD4⁺ and CD8⁺ T cell populations, for instance, PEG-PLA NPs [poly(ethylene glycol)-blockpoly(D,L-lactide)] loaded with CTLA-4 siRNA effectively restored

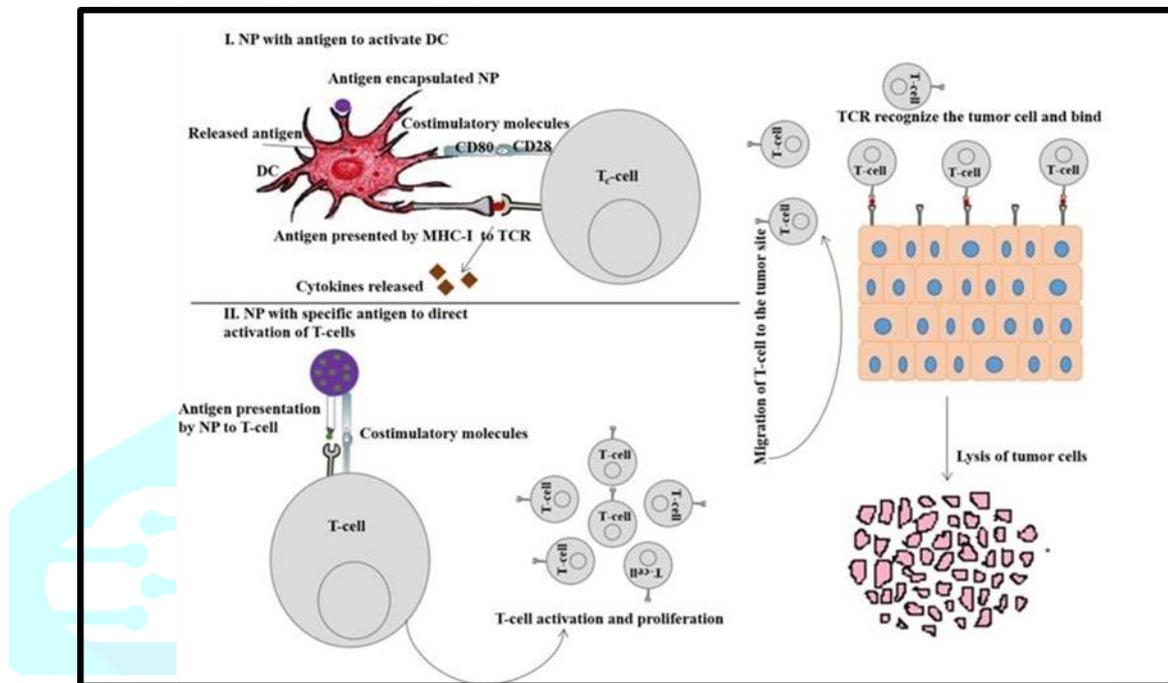


Figure 5: Targeting and Stimulation of T cells

T-cell functions and inhibited tumor growth in melanoma-affected mice. [20]

RECENT ADVANCES IN CANCER IMMUNOTHERAPY:

Gene Therapy:

According to ASGCT, gene therapy refers to the set of processes through which a patient's genetic material is either added, withdrawn or altered with the aim of eradicating a particular disease. As a technique in this therapeutic approach it involves the direct delivery of genetic material, most times DNA or RNA into cells in order to alter genetic details and biological effects. Some studies have also shown promising results in preclinical models and first-stage clinical trials have confirmed its efficacy but there are still many challenges include to ensure the therapeutic safety, to improve gene delivery efficiency and to avoid immunogenicity issues.

Photothermal and Photodynamic Therapy:

The complete essence of PTT and PDT is the ability to use the photosensitized materials together with the light radiation for the action on diseases and the attainment of the therapeutic objectives. The action mechanism of the photothermal and photodynamic agents is in the fact that when they get to the tumor lesion and interact with the radiation, they change the light energy into chemically or thermally active energy that causes the death of the tumor cells. Although the primary process involved in PDT is the generation of ros's subsequently releasing inflammatory mediators initiating immune response, PTT is used in regulating temperature changes by varying the light density to trigger cell death.

Cell Therapy:

Cell therapy which is also called cellular treatment is one of the modern techniques of treating cancer using healthy functional cells. The continued research and developments in cell therapy are making a way for other new medical inventions and provide hope to patients who need new and efficient treatments. The most common tumor cell therapies today are CAR T-cell therapy, TCR T-cells, Tumor infiltrating Lymphocytes, CAR NK cells, TCR modified T-cells, and CAR macrophages.

Anti-Angiogenesis Therapy:

Another characteristic of cancer include the ability to induce or gain access to vasculature through a process called angiogenesis. In contrast to angiogenesis under physiologic circumstances, such as development of new blood vessels during embryonic development, tumor angiogenesis is characterized by features such as random organization, increased permeability and paucity of pericytes or smooth muscle cells. The process of tumor angiogenesis is intricate and offers potential targets.

Tumor angiogenesis: molecular, route, and cellular network. The most popular chemical class investigated in the treatment decisions about cancer: tumor therapy strategies is the vascular endothelial growth factor (VEGF) family. VEGF family Human genome comprises five VEGF members out of which VEGF-A (previously referred to as VEGF) acts as the most relevant mediator in touching off migration landing, proliferation, and reprogramming of endothelial cells by binding to VEGF receptor 2 (VEGFR2) for tumor angiogenesis. When VEGFR2 binds, it autophosphorylates and activates signals like PI3K-AKT, ERK-MAPK, and RAS. [22]

CONCLUSION:

Recent advances in nano drug delivery systems for synergistic antitumor immunotherapy are revolutionizing cancer treatment by combining immunotherapy with nanotechnology. This innovative approach enhances the immune system's ability to fight cancer while improving drug delivery efficiency and specificity through nanoparticles. By targeting tumor sites directly, these systems aim to reduce side effects and enhance treatment efficacy, marking a significant shift from traditional therapies. Immunotherapy focuses on modulating the immune response rather than directly attacking tumors, potentially leading to longer-lasting effects compared to conventional methods like chemotherapy. The integration of diverse nanocarriers, such as liposomes and dendrimers, facilitates tailored therapeutic strategies for various cancer types. Additionally, the combination of chemotherapy and immunotherapy—chemo- immunotherapy—has shown promise in overcoming resistance and improving patient outcomes. With several nanoparticle-based therapies already approved by the FDA, ongoing research is exploring personalized therapies and innovative approaches like mRNA vaccines. These advancements aim to enhance the safety and effectiveness of cancer treatments, paving the way for more precise and effective therapeutic options in oncology.

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