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Cancer Nanomedicine: A New Era Of Successful Targeted Therpy

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ABSTRACT:

Cancer is still a deadly disease around the world. Right now, conventional cancer treatments and modern immunotherapies are not specifically designed to target tumors. They struggle to tell the difference between cancer cells and healthy cells, which results in many unwanted side effects. Recent developments in nanotechnology, along with our improved understanding of cancer biology and Nano-bio interactions, have led to the creation of various Nano carriers. These Nano carriers aim to boost the effectiveness of cancer drugs while lowering the side effects by targeting tumor tissue, cells, or organelles specifically. However, most Nano carriers lack hierarchical targeting ability. Their effectiveness is often reduced due to poor tumor accumulation, ineffective cellular uptake, or incorrect subcellular localization. This review discusses current and future strategies for designing cancer Nano medicines that target tumor tissue, cells, and organelles. It also highlights recent progress in hierarchical targeting technologies that can combine these three targeting stages to improve treatment results. Finally, we touch on the challenges and future possibilities for bringing cancer Nano medicines into clinical use. The major modalities of antitumor drug resistance may be grouped into at least five categories: decreased drug influx, increased drug efflux predominantly via ATP-driven extrusion pumps frequently of the ATP-binding cassette (ABC) superfamily, activation of DNA repair, metabolic modification and detoxification as well as inactivation of apoptosis pathways with parallel activation of anti-apoptotic cellular defense modalities (2009). Members of the ABC superfamily including P-glycoprotein (P-gp/ABCB1), multidrug resistance proteins (MRPs/ABCC) and breast cancer resistance protein (BCRP/ABCG2) function as ATP- driven drug efflux transporters, which form a unique defense against chemotherapeutics and numerous endo- and exotoxins. These pumps significantly decrease the intracellular concentration of a multitude of endogenous and exogenous cytotoxic agents which are structurally and mechanistically distinct, thereby result-ing in MDR.

KEYWORDS:

1. Cancer therpy
2. Nanomedicine
3. Immuno-therpy
4. Nanomaterial
5. Nanocarrier
6. Therapeutics

INTRODUCTION:

There are several methods to treat tumors and their surrounding environments. One of these methods is chemotherapy. This was first tested in 1942 when Louis Goodman and his team used nitrogen mustard to treat non-Hodgkin's lymphoma. Since then, many chemotherapy drugs have been used to stop cancer from progressing. Today, there are many examples of chemotherapy agents used in clinics to manage various cancers, including doxorubicin, paclitaxel, gemcitabine, and cisplastin. However, while chemotherapy has improved cancer treatment for some patients, more advanced stages of cancer often arise. In many cases, multidrug resistance occurs.

Researchers have also explored targeting the tumor's surrounding environment. Cancer cells rely mainly on oxygen and new blood vessel growth for survival and spread Radiotherapy is another method to destroy cancer cells since these cells are more vulnerable to damage than normal cells. Gene therapy and immunotherapy have also been used in cancer treatment. However, many of these approaches have side effects, resistance, or recurrence after initial treatment.

Chemotherapy often fails in clinics mainly due to varying levels of multidrug resistance (MDR), which leads to about 90% of cancer patients dying. MDR happens when tumor cells resist different classes of chemotherapy drugs, either by inactivating the drugs or by pumping them out of the cells, making treatment difficult. Several hypotheses exist about the molecular mechanisms of MDR. These include increased efflux of membrane transport proteins, detoxification through reduced drug activation and boosted drug metabolism, changes in drug targeting due to enhanced DNA repair, blockage of cell death, and alterations in cell cycle regulation.

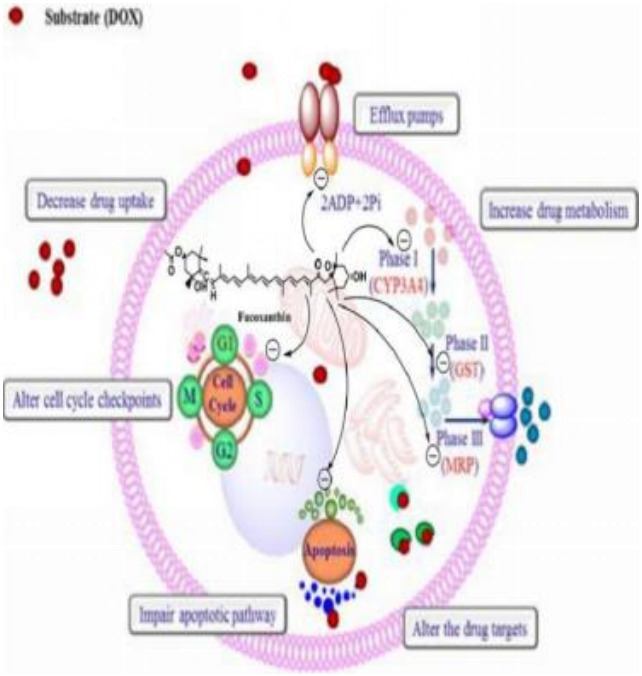

Figure 1: Molecular mechanisms of multidrug resistance in cancer.

Nanomedicine as Immune-Modulating Agents.

Most research on nanomaterial-immune cell interactions has focused on studying the toxic effects of nanoparticles. However, harnessing the immunomodulating properties of nanomaterials to treat patients with cancer or autoimmune diseases is a growing area of interest. Liposomal or polymeric nanoparticles can be designed to mimic the biological interactions between antigen-presenting cells and T cells or to function as specific subcellular granules that promote antitumor immunity. Additionally, nanomedicine can be tailored to use immune cells to target and attack different types of tumors.

For instance, nanoparticles loaded with chemotherapeutic agents are delivered into neutrophils, which are then recruited to the resection site of brain tumors by postsurgical inflammatory cytokines. These neutrophils release the drugs, which help reduce local recurrences. This immune-cell-based tumor targeting strategy also works for other innate immune cell types. For example, directly attaching anti-PD-L1 antibodies to the plasma membrane of platelets, which gather in the resection cavity after tumor surgery, can

significantly improve the delivery of the antibody to the surgical site. This approach leads to lower risks of local and distant recurrences and extends survival in tumor-bearing mice.

Nano- and microparticles can also be designed to imitate the functions of immune cell subsets. For example, polydimethylsiloxane (PDMS) particles modified with activating antibodies to CD3 and CD28 promoted greater expansion of CD4+ and CD8+ T cells in vitro. Similarly, multivalent synthetic dendritic cells made of polymeric nanoparticles greatly improved T cell activation efficiency. While still in early development, these studies stress the importance of nanoparticle size, shape, rigidity, and surface features, especially around major histocompatibility complex (MHC) and co-stimulatory molecules, for generating T cell responses. A recent study further emphasized that the size of nanoparticles used as substrates for artificial antigen-presenting cells is crucial for T cell activation. If a nanoparticle or nanoparticle cluster falls below a certain threshold size, even a higher ligand density may not adequately stimulate a T cell response.

Another emerging area in immune cancer nanomedicine involves identifying or engineering nanostructures that can adjust specific steps in the immune activation cascade. For example, ferumoxytol, an iron oxide nanoparticle formulation approved by the United States Food and Drug Administration for treating anemia, has recently been shown to polarize tumor-associated macrophages toward the pro-inflammatory M1-like phenotype and promote reactive oxygen species (ROS)-mediated tumor cell killing. Systemic injection of ferumoxytol significantly reduced tumor growth in orthotopically implanted MMTV-PyMT breast tumors and notably inhibited the formation of metastatic lesions in the liver and lungs. However, it remains unclear what molecular mechanisms are behind the changes in phenotypes and functions of macrophages caused by ferumoxytol.

Nanoparticles can also be engineered to enhance tumor delivery and boost antitumor immune responses. Magnetic nanoparticles made with therapeutic fucoidan-dextran were modified with PD-L1 inhibitors and T cell activators (anti-CD3 and anti-CD28) to create a multifunctional complex. The magnetic core of this nanocomplex facilitates in vivo magnetic navigation to improve tumor targeting and reduce off-target effects. At the same time, combining the PD-L1 inhibitor and T cell activator further enhances antitumor immune response.

This special issue on Nanomedicine and Cancer Immunotherapy came together to mark the 40th anniversary of Acta Pharmacologica Sinica from 1980 to 2020. The main goal with this collection is to share high-impact reviews and research articles. These pieces reach out to a broad international audience. They focus on the latest advances in nano-immunotherapy. They also cover methods to improve the effectiveness of cancer immunotherapy.

Doctors typically handle primary tumors through surgery, chemotherapy, and radiotherapy. Tumor relapse and eventual treatment failures still pose a major hurdle in clinical settings. The innate and adaptive parts of the immune system play a key role in how well standard cancer treatments work. Studies in preclinical models provide evidence that immunotherapy drives the long-term wins in cancer care. Cancer immunotherapy stands out as a reliable option for clearing primary tumors and metastases. It helps build lasting immune memory too.

Nanomedicines allow for delivering multiple immune agents all at once. The real potential of nanomedicine lies in reshaping or adjusting immune responses. This happens through targeted hits on specific biological pathways.

We put this special issue together to strengthen cancer immunotherapies overall. It digs into the ways tumors and immune cells avoid detection by the immune system. Nanomedicines offer tools to

rework the tumor microenvironment. They interact directly with immune components in precise ways. Still, immunotherapy faces real obstacles and key limits that slow down clinical rollout.

The issue features one research article along with ten reviews. Short overviews of each topic follow below.

1.Immunotherapy has shifted the landscape in cancer treatment pretty dramatically. Monoclonal antibodies and T-cell therapies serve as the leading options right now. Small molecule immunotherapeutics could bring benefits compared to biologics though. They tend to have less complexity and better tissue access. Manufacturing costs come down, and stability plus shelf life improve as well.

2.Small molecule drugs spread quickly through the whole system. That rapid distribution often leads to serious side effects in unintended areas. Nanotechnology steps in to help formulate these molecules more effectively. It enhances delivery straight to targeted immune cell groups.

3.The review by De Geest and colleagues outlines recent work on altering the pharmacokinetics of small molecule immunotherapeutics. They put heavy emphasis on Toll-like receptor agonists in particular.

4.Li and Nie's review describes approaches using nanoscale smart drug delivery systems. These systems amplify cancer immunotherapy outcomes by guiding drugs to tumors more reliably. The article offers insights into expanding nanoparticle use for stronger anti-tumor immunotherapy in the future.

5.Approvals for immune checkpoint inhibitors like Ipilimumab and Pembrolizumab moved forward quickly. A small group of patients showed striking long-term survival boosts over traditional chemotherapy. Most treated cancer patients do not gain from these checkpoint blockade methods . Challenges arise from weak T-cell responses and low tumor immunogenicity. The suppressive tumor environment adds to the difficulties in current cancer immunotherapy. Nanotechnology packs various functions into defined sizes and shapes. It opens up new paths for advancing cancer immunotherapy.

6.The review by Luo and team explores nanoengineered vaccines in depth. These vaccines trigger strong T-cell attacks on tumors. Nanomedicine also reshapes the immunosuppressive tumor microenvironment. This boosts overall anti-tumor immune activity.

Immune checkpoint in cancer therapy.

People keep developing drugs for cancer treatment. Many of these have gone through clinical trials already. Some even earned approval from the FDA. Still, plenty of tough challenges linger when it comes to truly curing cancers. The immunosuppressive tumor microenvironment stands out as one of the hardest hurdles. It creates a real roadblock for the bodys cancer immunity response.

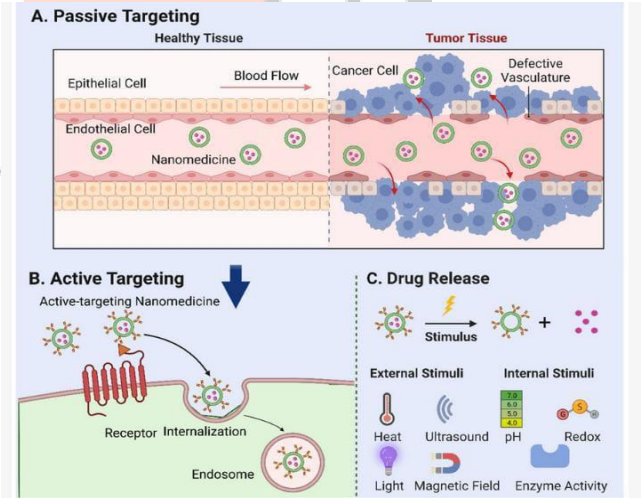

Figure 1. Mechanisms of nanoparticle-mediated drug delivery. (A) Passive targeting: the accumulation of nanomedicine in tumor tissues based on their specific physical and chemical properties—a phenomenon known as the "enhanced permeation and retention (EPR) effect". (B) Active targeting: the use of ligands or antibodies to target tumor cell surface ultrasound,

light, magnetic fields, and internal factors, including pH, redox reactions, and enzyme activation, that can be employed to trigger the release of drugs loaded in nanoparticle.

nanomedicine approach could stand as an alternative treatment option to induce the autophagy in cancer therapy. Several investigators developed a variety of nanomaterials which themselves act as autophagy inducers or inhibitors. Considering this, the present review article will focus on the recent developments of nanomedicine in the area of autophagy that have been focused on the treatment of cancers. We also summarised the detailed mechanisms of nanoparticles mediated autophagy which could be helpful for developing new strategies to fight against cancer. Also, the present review article covers the current clinical status of nanomedicine and future challenges.

Clinically approved nanomedicines

The FDA gave its first-ever green light to a nanoformulated medicine, Doxil [Doxorubicin hydrochloride in PEG coated liposomes (stealth liposomes)], to be used in 1995 for treating Kaposi's sarcoma in HIV patients [Table 2]. This decision was primarily taken because the drug had much less toxicity than the conventional one, while cardiotoxicity was the most affected aspect of toxicity[55]. Presently, the medicine is still quite popular for the same indication and also for treating breast and ovarian cancer as well as multiple myeloma[52]. Furthermore, Abraxane, which is a formulation of paclitaxel (PTX) complexed with albumin bound nanoparticle, got FDA approval in 2005 for treating the condition of metastatic breast cancer after showing a considerable decrease in toxicity[56]. Due to its very high hydrophobic nature, PTX required dilution in polyethoxylated castor oil (Kolliphor EL, formerly known as Cremophor EL), which led to intense systemic and neurological toxicity[57]. With the usage of Abraxane which is Cremophor-free, higher tolerance is suggested, thus, better safety profile is provided allowing higher doses of PTX to be administered which in turn yields greater efficacy.

In general, a pharmaceutical agent will be dispersed uniformly in the entire body. Nevertheless, the perfect chemotherapeutics demand that a high local concentration of the drug exists at the disease site(s) and that the concentration in other non-target organs and tissues is below a certain level, which is the minimal level of Tconcentration humans can tolerate, to avoid any negative side effects. The idea of drug targeting, which is also referred to as the "magic bullet", has its roots in the early 20th century when the German chemist Paul Ehrlich selectively stained bacteria for histological examination. The "magic bullet" as an entity comprises two components: one must identify and attach to the target, while the other must impart a therapeutic effect in this target. In the clinical context, the delivery of anticancer payloads, such as radionucleotides, toxins and chemotherapeutic agents to tumors through monoclonal antibodies, has been practiced.

CONCLUSION:

Nanomedicine-mediated cancer starvation therapy is a method that could, in a very selective manner, cut the supply of nutrients and oxygen through different antiangiogenesis treatment methods like tumor vascular disrupting or blockade, and others. Also, along with the mentioned methods, the process of directly depleting intratumoral glucose and oxygen could be used for combined chemotherapeutic drugs,. Moreover, by combining the right nanocarriers, such as metal nanoparticles (NPs), hypoxia-activated prodrugs, inorganic NPs, Fenton-reaction catalysts, photosensitizers, or photothermal agents, two or more therapeutic agents could be integrated into one single formulation, which will lead to better treatment outcomes. The success of the nanomedicine-based therapy primarily hinges on the early detection of cancer. Conventional diagnostic and imaging techniques, however, may not help in spotting cancer in its initial phases due to their restricted capacity of distinguishing between malignant and benign cells. On the other hand, nanoparticles have a remarkable advantage in the sense that they are more sensitive and smarter in detecting tumor cells.

This characteristic makes them ideal candidates for transporting anticancer drugs with minimal harm to the healthy tissues.

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