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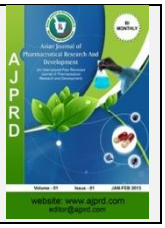

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Review Article

A Review on Recent Success in Cancer Nanomedicine

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A B S T R A C T

Cancer continues to be one of the most difficult global healthcare problems. Although there is a large library of drugs that can be used in cancer treatment, the problem is selectively killing all the cancer cells while reducing collateral toxicity to healthy cells. There are several biological barriers to effective drug delivery in cancer such as renal, hepatic, or immune clearance. Nanoparticles loaded with drugs can be designed to overcome these biological barriers to improve efficacy while reducing morbidity. The pathological processes of cancer are complex. Current methods used for chemotherapy have various limitations, such as cytotoxicity, multi-drug resistance, stem-like cells growth, and lack of specificity. Nanomedicine plays an important role in these evolving tumor treatment modalities. We discuss how nanomedicine can be combined with these treatment modalities, provide typical examples, and summarize the advantages brought by the application of nanomedicine. This highlights the progress, challenges and opportunities in cancer nanomedicine and discusses novel engineering approaches that capitalize on our growing understanding of tumour biology and nano–bio interactions to develop more effective nanotherapeutics for cancer patients. This review discusses the current use of clinically approved nanomedicines, the investigation of nanomedicines in clinical trials, and the challenges that may hinder development of the nanomedicinesfor cancer treatment.

Keywords:-Nanoparticles, Bioavailability, Chemotherapy, Nanodrug, Immunotherapy, Cancer.

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INTRODUCTION:

Cancer is currently among one of the leading causes of deaths worldwide, with 1,688,780 new cases and 600,920 cancer deaths projected for 2017. Over the next 20 years, the number of new cases is projected to increase by about 70% [1].Cancer is a common, complex, and heterogeneous disease. As the population ages, cancer is becoming a leading cause of morbidity and mortality worldwide, with approximately 9.5 million cancer-related deaths annually[2].

Therefore, studies aimed at developing treatments for cancer are urgently needed. Surgery, chemotherapy, and radiotherapy are the three main treatments for cancer but often lead to unsatisfactory outcomes and side effects [3,4]. Current treatments may include chemotherapy, radiation, and surgery, but the effects of these procedures may damage not only the tumor tissue but also normal tissue of their DNA and thus allow them to replicate infinitely. The formation of new blood vessels, or angiogenesis, is a method for cancer cells to obtain nutrients and remove waste. Cancer cells can also migrate to new sites and form new; secondary tumors. Nanomedicine can be defined as nanotechnology, or the use of materials between 1 and 100 nm, applied to health and medicine[5]. Nanomedicine is an emerging method for treating cancer. Current problems in treating cancer include low specificity, rapid drug clearance and biodegradation, and limited targeting [6].The properties of nanocarriers, including their nanoscale sizes, high surface-to-volume ratios, favorable drug release profiles, and targeting modifications, can allow them to better reach target tumor tissue and release drugs in a stable, controlled manner[7].Nanocarriers can accumulate in leaky vasculature, which is a characteristic of tumor tissue, in an effect known as the enhanced permeability and retention effect (EPR) effect[8].Nanoparticulate delivery systems (NDSs)is an important way to optimize drug delivery, which can effectively improve the accumulation, penetration and target cell uptake of drugs in tumor tissue and achieve controllable drug release. The poor solubility of small molecule drugs

often restricts their delivery to the tumor, and therefore encapsulating the drugs in nanocarriers may facilitate travel through the bloodstream, thus preventing rapid clearance and improving bioavailability. The potential of nanomedicines can be further extended to early detection of cancers as well as combination therapies that can start treating tumors earlier and more effectively.

Currently, a wide variety of platforms are being investigated as nanocarriers for cancer treatment, including lipid-based, polymer-based, inorganic, viral, and drug conjugated nanoparticles.(Fig.1).

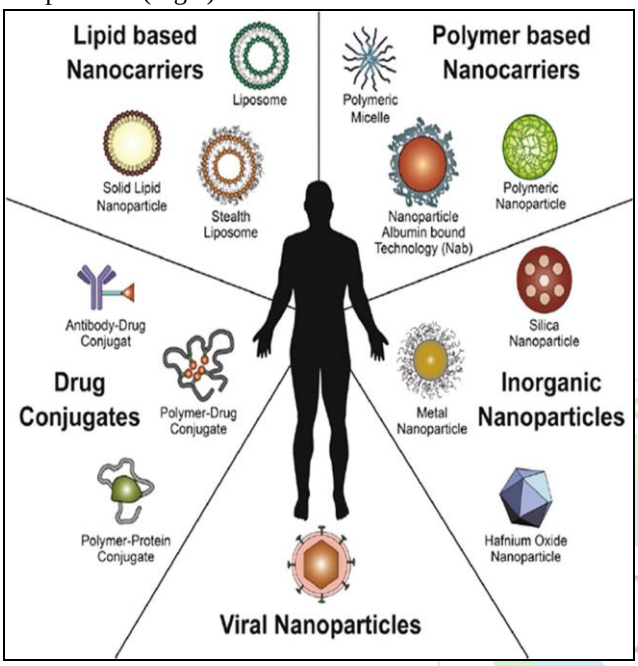

Figure 1: Overview of established nanomedicines in the clinic. This diagram shows an overview of the nanomedicines currently being investigated in the clinic for cancer treatment. Lipid-based, polymer-based, inorganic, viral, and drug-conjugated nanoparticles are examples of platforms that have been established in clinical research[5].

This review will discuss the current use of clinically approved nanomedicines, the investigation of nanomedicines in clinical trials, and the challenges that may hinder development of the nanomedicines for cancer treatment. Several properties of nanocarriers make them suitable for delivering chemotherapeutic drugs to the target tumor tissue. Small molecule drugs like most chemotherapies have very short circulation half lives inside the body and nanoparticles can be made long-circulating thereby improving the bioavailability of these drugs and thus improving efficacy without the need for higher doses[9].Nanoparticles also offer the opportunity to control the release of the encapsulated payload such that a high percentage of the trapped drug is released after the particles have reached their target tissue. This property of controlled release from nanoparticles can improve efficacy of the drugs while reducing off-target toxic effects[9].

In this review, we will review the progress of NDSs and the application of nanomedicine in cancer therapy, focusing on the new progress in the application of nanomedicine in chemotherapy, gene therapy and immunotherapy.

ADVANCES IN NANOTECHNOLOGY FOR TARGETED DELIVERY

Cancer treatment based on nanomaterials shows advantages over using free drugs, particularly for targeted delivery. Compared to free drugs, targeted delivery exhibits reduced toxicity, decreased degradation, increased half-life, and enhanced capacity [10,11] . Recent advances have been made in nanomaterial-based targeted drug delivery systems, including in active or passive targeting. Active targeting is achieved using antibodies or small molecule conjugated nanoparticles, whereas passive targeting occurs through enhanced permeability and retention effects. Active targeting displays great potential and acted as an alternative strategy to passive targeting and the ability of tumor localization in active targeting was improved by increased efficiency and retention [12]. Compared with traditional chemical therapies, nanomaterial-based drugs display increased specificity, improved bioavailability, lower cytotoxicity, better loading capacity, and a longer half-life. To date, many nanomaterials for cancer treatment have been developed based on remarkable advances in nanoscience, technology, and cancer pathology. However, few nanomaterial-based drugs have been intensively studied and utilized in clinical practice.

NANOCARRIER PROPERTIES

Physico-chemical properties:

The nanomaterials available for cancer research can bemodifiedin size, shape, and surface characteristics for customization to treat specific tumors. Size is important for travel through the bloodstream and subsequent delivery of the nanocarriers to tumor tissue. While smaller nanoparticles can accumulate more easily in the leaky blood vessels of tumors than those that are larger, they can also extravasate into normal tissue. On the other hand, larger nanoparticles cannot extravasate as easily and thus their distribution in the bloodstream is highlyvariable[6]. The optimization of nanoparticle size may help improve specific uptake into tumor tissue. The shape of the nanocarriers may impact fluid dynamics and thus influence uptake. Currently, the use of spherical nanocarriersappears to be more common than that of then on spherical variety due to challenges in synthesis andtesting[13].The charge of nanocarriers may also affect their stability and distribution in the blood. Positively charged nanoparticles were previously shown to most effectively target tumor vessels, but a switch to a neutral charge after extravasations allowed quicker diffusion of the nanoparticles to the tumor tissue[14]. The surface of the nanocarriers can also be modified with ligands that may prolong blood circulation and promote specific types of endocytosis and cellular uptake into tumor tissue.

Solubility, degradation, and clearance:

Drugs with poor water solubility may be eliminated from the bloodstream before reaching tumor tissue. The useof hydrophilic nanoparticles to encapsulate these drugsmay improve their solubility, in turn improving their bioavailability in vivo and thus allow more effective delivery[5]. Coating nanoparticles with polyethylene glycol (PEG), a hydrophilic and non-ionic polymer, was shown to increase solubility and stability of nanoparticles [9].Since PEG is uncharged, it does not disrupt the function of charged molecules, such as DNA[15].

The reticulo-endothelial system (RES) recognize shydrophobic materials as foreign and eliminates themfrom the bloodstream, taking them up in the liver orthe spleen. Foreign materials coated with opsonin proteinsare more easilyrecognized by monocytes and macrophages[16]. Opsonization of hydrophobic moleculescan reduce their ability to reach the tumor tissue andtrigger inflammation following the secretion of cytokinesfrom the phagocytic cells[16,17]. PEGylated nanoparticlesmask their hydrophobicity and therefore can prolongtheir circulation in the blood to allow adequate time toreach tumor tissue[15]. This reduction in clearance notonly increases the half-life of the nanoparticle but alsoimproves its bioavailability[15,16]. Controlled release mechanisms may also prevent non-specific delivery of the toxic drug to normaltissue.

Targeting:

Nanocarriers may be modified to utilize passive and active targeting mechanisms to reach tumor tissue (Fig. 2). The enhanced permeability and retention (EPR) effect allows nanoparticles to passively accumulate in the leaky blood vasculature exhibited by tumors without anysurface modifications[5,8,9]. Passive targeting, however, cannot eliminate the potential of nanocarriers building up in tissues that normally have fenestrated blood vessels, such as the liver or the spleen [5]. Furthermore, themicroenvironments of specific tumors vary and may pose as barriers for nanomedicine development. Active targeting utilizes the attachment of ligands to surface of the nanocarriers [18]. These ligands have high specificity to receptors and other cancer-specific targets that are overexpressed on the surface of tumor cells, such as glycans[18]. Conjugation of these ligands may eliminate non-specific of nanocarriers to tissue other than tumor tissue. Such ligands may include transferrin, folic acid, enzymes, engineered antibodies, and macromolecules like proteins and carbohydrates [5,9]. The density of these ligands should be optimized to allow nanoparticles to avoid recognition by the RES and interaction with serum proteins, thus prolonging their blood circulation time[5].

Stimuli-responsive and triggered release systems:

The use of stimuli-responsive systems may reduce nonspecific exposure to chemotherapeutic drugs (Fig. 2). Both internal and external stimuli can trigger the release of drugs by evoking a change in the nanocarriers. in pH, redox, ionic strength, and stress in target tissues are examples of internal stimuli[5]. The differences in the pH of blood and intracellular organelles may allow nanocarriers to release drugs specifically when they reach tumor tissue [19]. pH responsive sodium alginate and hydroxyapatite bi-coated iron oxide nanoparticles were shown to exhibit a controlled drug release profile for the hydrophobic drugs curcumin and 6-gingerol and mayoffer a potential platform for cancer therapy [18]. Tumors typically have a hypoxic microenvironment with low oxygen and nutrient levels and thus high levels of reductive agents, such as glutathione [19,21]. Nanocarriers with disulfide bonds may be used to target these types of tissue. Nanocarriers with disulfide bonds can help carry out the redox reaction that oxidizes glutathione, which maycellular apoptosis [20].

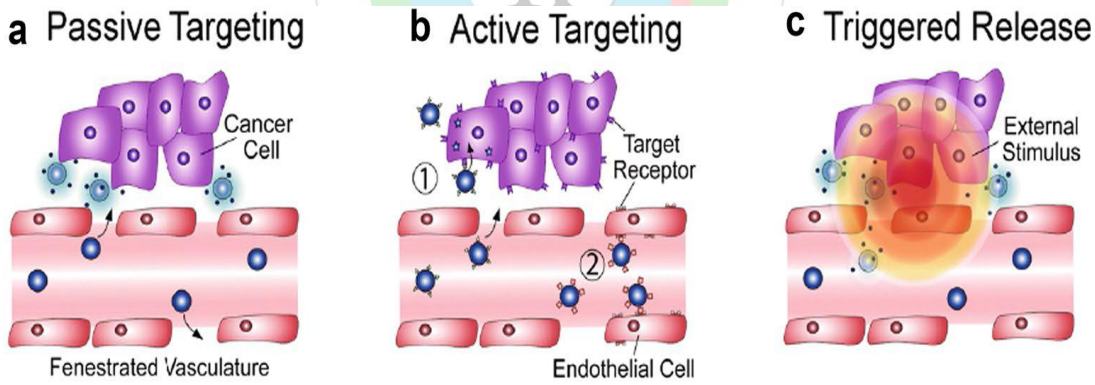

Figure: 2 Types of targeting for nanoparticle delivery to tumor tissue. a Passive targeting relies on the leaky vasculature that is exhibited by tumors,allowing nanoparticles to travel through the fenestrations and reach tumors. b Active targeting can be used when nanoparticles have ligands ontheir surface that can recognize and bind receptors that are overexpressed on tumor cells. c Triggered release allows nanoparticles to congregate ifexposed to an externalstimulus such as a magnetic field or light (Reproduced with permission from[5]).

Combination therapy and theranostics:

The ability of nanomedicines to carry multiple therapeutic agents may increase their ability to improve treatment. Co-loaded nanoparticles with bortezomib and doxorubicin were found to exhibit an antitumor synergistic effect on ovarian cancer [22]. Loading multiple siRNAs alone or together with other drugs may increase sensitivity of the tumor to the treatment [23]. The use of stimuli-responsive systems with targeting ligands has also been investigated. An emerging method is the use of theranostics, which combines both the ability to diagnose and treat cancers. In theranostics, not only can drug release be monitored, but the effects of the drugs in the tumor tissue can also be visualized[24]. These abilities may open their potential to be used for personalized treatment [25]. Successful delivery of chemotherapeutic drugs is often dependent on the properties of the biological barriers involved (Fig. 3) in cancer. Next, we will discuss multiple biological barriers to effective drug delivery.

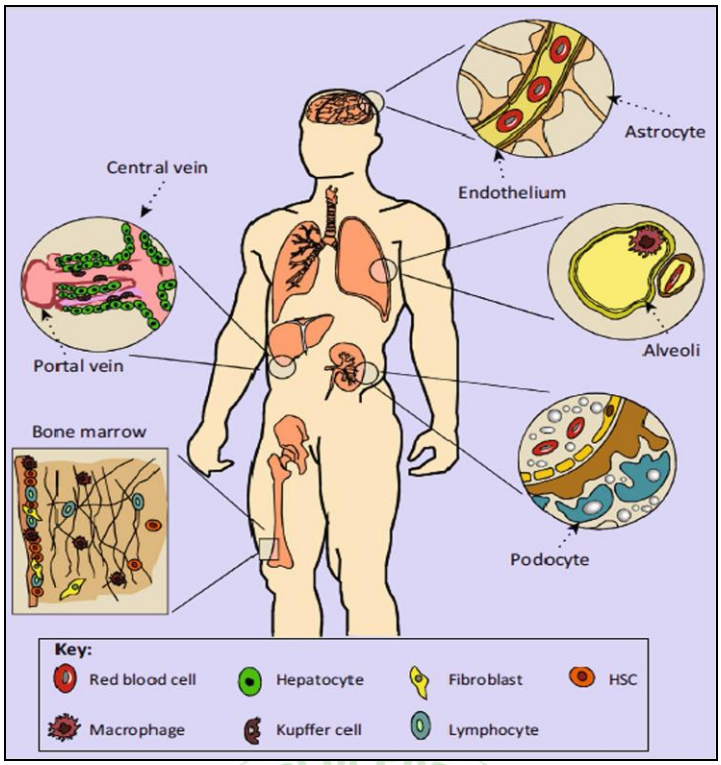

Figure: 3 Organ systems that affect nanoparticle delivery. The method of entry affects circulation time, organ processing, and overall efficacy. Intravenouslyinjected nanoparticles can extravasate from the bloodstream and enter organs such as the liver, spleen, bonemarrow, and central nervoussystem. Nanomedicines that are administered orally can enter the gut and pass through the liver via the hepatic portal system. Inhaled nanomedicinesmay contact macrophages in pulmonary alveoli. Following circulation in organs, nanoparticles may encounter renal clearance in the kidneys (Reproduced with permission from [17]).

TYPES OF NANOPARTICLES

Protein-drug conjugated nanoparticles:

Protein-drug conjugated nanoparticles consist of proteins conjugated to drug molecules. The link between the protein and the drug is typically biodegradable upon arrival in the cell. This can lead to premature release of the drug, as the biodegradable linker is readily destroyed by proteases and redox-altering agents foundin blood. Protein drug conjugated nanoparticles are typically very small (10 nm), allowing the nanoparticle to have a long halflife in vivo and thus facilitating its delivery to the target tumor site[26].Therefore, certain drugs may not be suitablefor this nanoparticle delivery system. The linkers used inthese systems may also be rapidly degraded by enzymesand agents commonly found in blood plasma, leading topremature activation of the drug and a decrease in circulationtime, while increasing the drugs bioavailability[27].

Liposomal nanoparticles:

Liposome-based nanoparticles are spherical nanoparticles created via the use of lipid bilayers. These nanoparticles are created immediately when an amphiphilic lipid is added to water or other hydrophilic liquids, yielding spheres roughly between 50 and 500 nm. This procedure allows for the encapsulation of hydrophilic drug molecules by simply dissolving the drug in the liquid used for formation of the nanoparticles. Hydrophobic and amphiphilic drugs can be encapsulated by direct addition to the lipid solution before formation of the nanoparticles, leading to a layer of drug molecules between the lipid bilayer. Common lab methods used to create liposomal nanoparticles include sonication, extrusion, reverse phase evaporation, and solvent injection [28].Depending on the polymer used, the ability of the nanoparticle to easily fuse withthe target cell can be hindered, and in such cases, an additional mechanism must be incorporated to release the drug payload. The use of polymeric coatings can also lead to other key benefits, such as increasing circulation time, improving bioavailability of encapsulated drug, increasing targeting efficiency, and altering surface charge of the liposomes.

Polymeric nanoparticles:

Polymeric nanoparticles are comprised of synthetic polymers, allowing customization of many key properties, such as molecular weight, biodegradability, and hydrophobicity. The synthesis of polymeric nanoparticles has also been well studied. A variety of methods have been designed to efficiently encapsulate drug molecules. Some examples of these methods include nanoprecipitation, electrospray, and emulsification. Polymeric nanoparticles are typically comprised of dense matrices with well known degradation curves, making the drug release of these nanoparticles easier to manipulate in comparison to many other nanoparticle drug delivery systems. This, the aesthetic properties of the nanoparticles, as well as the amount, rate, and pathway used for cellular uptake of the encapsulated drug molecule, may be tailored[29].

Dendrimeric nanoparticles:

Dendrimeric nanoparticles are comprised of dendrimers, which are spherical macromolecules with many branches originating from a central point. These nanoparticles are created layer by layer. The initial core of the dendrimeris

incorporated onto the previous layer before branchesare allowed forming. By using specific initiator cores, the size and degree of branching of the dendrimer can be easily manipulated, allowing for the polydispersity of the nanoparticle to be minimized. By carefully planning the scheme of cores and branching units, the molecular weight, size, branch density, flexibility, and water solubility can be specified.

Hydrogels:

Hydrogels are three-dimensional networks of crosslinked water soluble polymers that are able to retain fluid in large quantities. Most synthetic hydrogels are notbiodegradable, but enzymatic, hydrolytic, and stimuli responsive components can be added into the hydrogel matrix in order to create nanoparticles that are degradable under certain conditions. The uniqueness of hydrogels is in their fluid retainment—the high water content is very similar to biological tissues, reducing tension when introduced to tissue and making this nanoparticle biocompatible [30]. By controlling the amount of cross linking in the hydrogel matrix, the porosity of the hydrogel can be adjusted to control drug loading and release rates. Hydrogels also naturally have a positive surfacecharge and thus may strongly interact with the negatively charged cell membranes, increasing cellular uptake of drug payload. Since serum proteins alsoare negatively charged, however, hydrogels may aggregate to serum proteins, decreasing the circulation time of the nanoparticles.

GENE THERAPY NANOMEDICINE

In recent years, with the increasing maturity of gene manipulation technologies such as gene silencing and gene editing, scientists have begun to treat various diseases by site-specific up-regulation or down-regulation of target genes, and have achieved certain progress and widespread attention, especially in cancer therapy. The drugs used in gene therapy are nucleic acid therapeutics with lower cytotoxicity, which show significantly fewer adverse reactions and better therapeutic effects compared with conventional treatments such as chemotherapy[31]. Commonly used gene therapy strategies include gene enhancement therapy and gene suppression therapy, in which the application value of nanomedicine will be described here [32].

Gene Enhancement Therapy:

Gene enhancement therapy generally refers to “expressing a certain gene” or “expressing a certain protein” by introducing a plasmid or mRNA. Tumor suppressor genes can inhibit cell proliferation when activated or over expressed. Over expression of one or more tumor suppressor genes can effectively inhibit the growth and progression of tumors, among which protein 53 (p53) gene and phosphatase and tensin homolog (PTEN) gene are the most classical and the most deeply studied[33,34,35]. In addition, the suicide gene therapy systems are also commonly used for gene enhancement, such as herpes simplex virus thymidine kinase (HSV-TK), of which TK gene is a drug susceptibility gene. After tumor cells were transfected with this gene, they were sensitized and killed by the nontoxic prodrugs glycoxyguanosine or acyclovir[36]. A study reported that in vivo delivery of the TK-p53- nitroreductase triple therapeutic gene by poly (D,L-lactic-co-glycolic acid)-poly (ethylene glycol)-Polyethylenimine NPs functionalized with SP94 peptide (a peptide that targets hepatocytes) restored p53 function and enhanced cancer cells’ response to the prodrug ganximation glycoxyguanosine and CB 1954[37]. Due to the negative charge of mRNA, most of the NPscurrently used to deliver mRNA drugs contain a cationic gradient, which can form stable complexes with mRNA to achieve high loading rates, such as ionizable lipid NPs[38], polymer-lipid hybrids NPs, and biological nanostructures with higher biocompatibility [39,40].

Gene Suppression Therapy:

Gene suppression can also treat cancer by silencing specific genes that produce abnormal or harmful proteins, such as small interfering RNA (siRNA) therapy. Several in vitro and in vivo studies have confirmed that siRNA-mediated silencing can significantly inhibit abnormal cancer cell proliferation[41,42,43]. In addition, siRNA can sensitize drug-resistant cancer cells, showing great promise in enhancing chemotherapy[44]. Currently developed CRISPR/Cas9 NDSs include cationic liposomes[45], lipid NPs cationic polymers, vesicles, and gold NPs. In order to better reduce the off-target effects, researchers have developed a stimulus-based intelligent NDSs. Intelligent NPs can be based on endogenous signals (including pH, redox and ATP) and exogenous signals (including radiation, magnetic ultrasound), to control or regulate the delivery of CRISPR/Cas9 to specific cells. For example, designed a multifunctional NPs modified with pH-sensitive epidermal growth factor receptor targeting and nuclear guide peptides to efficiently deliver CRISPR/Cas9 and epirubicin to the human tongue squamous cell carcinoma SAS cells and SAS tumor mice, providing a pH-responsive co-delivery platform for chemotherapy and CRISPR/Cas[46]. It could significantly improve genome editing efficiency and make it possible to control the expression of endogenous genes in a cell type-specific manner through specific endogenous or exogenous miRNAs.

CANCER VACCINES

Cancer vaccines kill tumor cells without damaging healthy cells by activating the body’s immune system, and they can trigger immune memory to provide long-term protection against tumor recurrence. As a potential drug development concept, cancer vaccines are extremely valuable whether they are used alone or in combination with other immunotherapies[47,48]. With the deepening of research, the advantages of applying nanomedicine in cancer vaccines have gradually emerged[49]. Cancer vaccines are typically combinations of immunogenic components (eg, neoantigens and adjuvants) that are delivered to antigenpresenting cells in peripheral lymphoid tissue. First, encapsulating immunogenic components in nanocarriers can prevent antigen degradation and effectively improve antigen stability. Second, nanovaccines coencapsulate and co-deliver antigens and adjuvants, which can effectively enhance the immunogenicity and therapeutic efficacy of vaccines[50].

In particular, nanovaccines further modified by targeting ligands can also be actively targeted and delivered to specific sub regions of immune cells. For example, a click

chemistry-based active lymphatic accumulation system was developed to enhance the delivery of antigens and adjuvants to the lymphatic sub capsular sinus. Ultimately, NPs can enhance immune responses through sustained or controlled release capabilities. For example, showed that a single injection of clay NPs sustained the release of immunogenic agents, which significantly enhanced the immune response in regional lymph nodes for up to 35 days. Disease associated antigens. Another important advantage of nanomedicine in this field is the safe and effective enhancement of T cell therapy. It designed a T cell receptors signaling-responsive protein nanogel to co-deposit immune stimulatory cytokines, such as interleukin-15 agonists, onto the surface of CAR-T cells, which significantly extended the therapeutic window and improved tumor clearance in CAR-T cell therapy against solid tumors.

PERSPECTIVES AND FUTURE DIRECTIONS

In recent years, the concept, method and pattern of tumor treatment are constantly changing, which provides a broad space and prospect for the application of nanomedicine. It is the application of intelligent NDSs for tumor chemotherapy, gene therapy and immunotherapy to solve the problem of drug (chemotherapy, biological drug) delivery, optimize its delivery efficiency, and achieve targeted, precise and controllable delivery to a certain degree. However, how to translate preclinically studied antitumor nanomedicines into clinically feasible therapeutics still faces several key challenges. For example: 1) how to optimize patient population stratification in clinical trials; 2) how to optimize the dosing regimen of nanomedicines in combination therapy; 3) how to ensure high quality and reproducibility for industrialized production of nanomedicines, etc. Expectantly, with the deepening of nanotechnology research, the combination of molecular-level scientific design and precise control of process engineering is expected to overcome the core technology of NDSs research and development, thereby opening a new situation for NDSs.

CONCLUSIONS

The advent of nanomedicines represents significant advances in the field of drug delivery. The options for nanoparticle design and function are extremely varied and the list of potential applications continues to grow,to the point where the drug delivery system can be tailormadeto best suit the selected drug. However, it is importantto remember that nanoparticle-based treatments arenot miracle cures. While many cancers over express surface proteins common in normal cells, overabundance of a specific surface protein is not enough to guarantee selectivity using targeted treatment.

There is also a reproducibility issue with nanoparticle production. Reproducible, large-scale synthesis of nanomedicines is still a challenge for the distribution of a homogeneous batch of nanomedicines, especially when considering that these nano-platforms often require specific conditions for production via self-assembly. Thorough characterization of these nanomedicines, at every stage of the production process must be enforced to ensure both reproducibility of synthesis and efficacy. Ideal nanomedicines will have a modular design that can be easily scaled up for cGMP manufacturing and stored for a long time prior to use in patients. Cross collaborations between theoretical and experimental scientists across academia, with the pharmaceutical industry, medical doctors and the regulatory agencies will help translate more findings from the lab to the clinic and usher in the next era of clinical cancer nanomedicines.

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