Advances in the use of nanomaterials in tumour therapy

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Abstract. Cancer is one of the most common causes of death. It is indeed vital to develop advanced treatments against severe cancers. Traditional therapies like surgery may not clear the tumour cells completely, which will lead to cancer recurrence. The possibility of normal cells being killed cannot be excluded in chemotherapy, which is one of the most popular ways to treat cancer—using nanomaterials (NPs) as drug carriers can somewhat avoid these problems. And they are widely used in targeted therapies to treat cancer. The essay first introduces several types of biopolymeric NPs, such as liposomes, polymeric nanoparticles and inorganic particles. Mechanisms of treatments using NPs are included. For polymeric nanoparticles, dendrimers, polymeric micelles and gels are included. Reasons why inorganic NPs, including mesoporous silica NPs and metallic oxides, are used in treatment are then explained. Then, the functions of different NPs of the same type are compared. Finally, other studies about each specific NP are introduced. This article is significant for future studies on drug carriers for cancer treatment.

Keywords: Tumour, nanomaterials, therapy.

1. Introduction

Tumour development and progression is a multifactorial, multistep, and complex process that involves genetic variation, environmental exposure, immune response, and many other aspects. Traditional tumour treatments, such as surgery, chemotherapy and radiotherapy, have prolonged the survival of patients to a certain extent. Still, they also have many limitations, such as the difficulty of surgery in completely removing microscopic lesions, the poor selectivity of chemotherapeutic agents leading to systemic toxic side effects, and the damage to normal tissues caused by radiotherapy. Therefore, it is essential to explore more precise, efficient and low-toxicity tumour treatments [1].

Nanomaterials, due to their small particle size, large specific surface area, and accessible surface modification, can achieve targeted delivery and controlled release of drugs, thus improving therapeutic effects and reducing adverse reactions. In tumour therapy, nanomaterials can be used as drug carriers to increase the concentration of drugs in tumour tissues but also play a comprehensive therapeutic role by regulating the tumour microenvironment, enhancing the immune response and other mechanisms. Therefore, in-depth research on the application of nanomaterials in tumour therapy is of great significance in improving the effectiveness of tumour therapy and the quality of patients' survival [2].

In recent years, the application of nanomaterials in tumour therapy has made remarkable progress. Liposomes, as classical nano drug carriers, are widely used for targeted delivery of tumour drugs due to their excellent biocompatibility and cell affinity. Polymer nanomaterials, however, show broad application prospects in tissue engineering, drug-controlled release, and tumour therapy due to their biodegradability, low cytotoxicity, and ease of modification and processing. In addition, novel nanomaterials such as nanohydrogels also show unique advantages in tumour therapy, such as slow drug release and improved drug bioavailability. In immunotherapy, nanomaterials also play an essential role. Through rationally designed nanomaterials, specific tumour-killing effects can be triggered, antigen presentation can be optimized, and long-lasting immune responses can be induced. Compared with conventional immunotherapy, nano-immunomodulators have controlled pharmacokinetic behaviours that enhance the potential for immune activation through synergistic effects, overcoming barriers to effective immunotherapy of solid tumours. For example, nanoparticles loaded with immunomodulators directly target the tumour microenvironment to activate immune cells and inhibit tumour growth and metastasis [3].

Therefore, this paper discusses the application of several common nanomaterials in tumour therapy to provide valuable references for researchers in the field of tumour therapy.

2. Liposome

Liposomes can contain several phospholipid layers and more flexibly carry water-soluble and water-insoluble drugs to tumour sites. The solubility and availability of drugs are improved. And healthy cells can avoid being killed in targeted therapy.

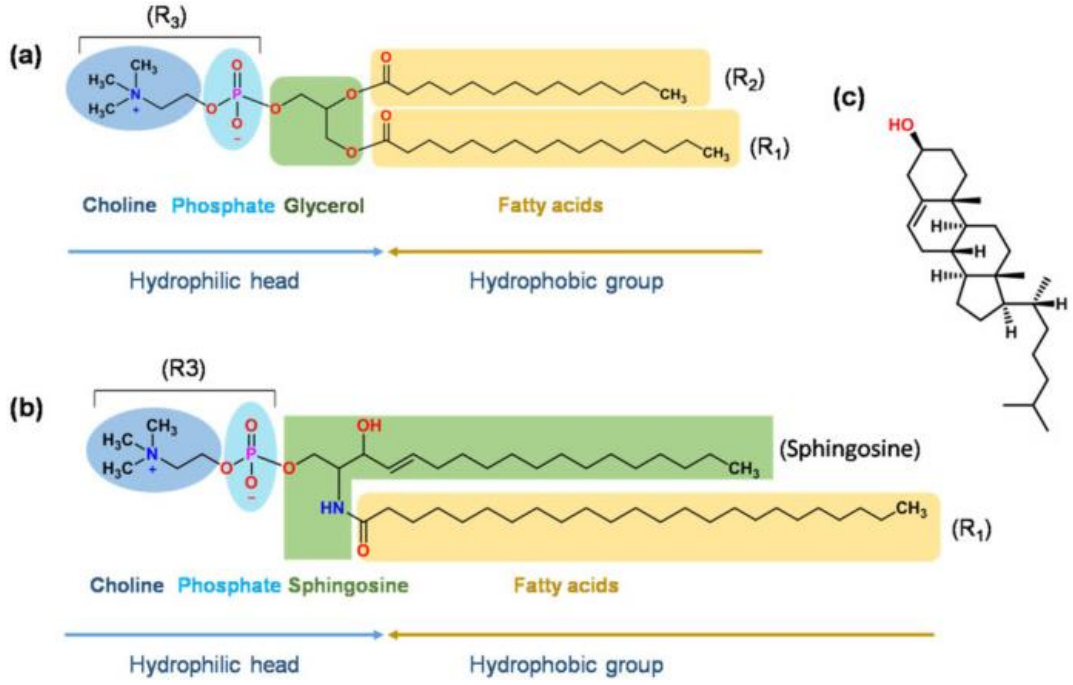


Figure 1. Structure of (a) GP, (b) SM, and (c) Chol [4]

Typical components used in profitable products include glycerolphospholipid (GP), sphingomyelin (SM), and cholesterol (Chol), as shown in Figure 1. In GP, one molecule of cholesterol is linked with two fatty acids and a hydrophilic head group. A series of hydrocarbon chain properties can determine the membrane's fluidity, phase transition temperature, rate of drug release and so on [4]. The structure of SM is similar to that of GP except for the glycerol replaced by sphingosine. Cholesterol is another primary material for the phospholipid bilayer. It is the precursor of the production of hormones and can produce bile, which is vital for digestion. It can regulate the rigidity of the membrane and release of the carried drug. Under moderate cholesterol concentrations, the membrane's fluidity drops significantly, and the release of the drug decreases. Micelles, nanoparticles, and copolymers are some cholesterol applications used as drug carriers. Small interfering RNA may be a potential cancer treatment. Muddineti et al. invented a chitosan-cholesterol micelle system loaded with curcumin, a hydrophobic cancer chemotherapy agent, to transport it to tumour sites as a potential siRNA carrier for cancer combination therapy [5]. In an acid environment, hydrolysis of lipids is inhibited significantly, so the stability of liposomes is increased. An acid environment is commonly used to provide a pH gradient that allows for the active transport of drugs. In other words, the circulation time of liposomes is increased, leading to enhanced drug transport to target cells. To bind overexpressed targeting biomarkers on tumour cells, non-covalent or covalent conjugation of target ligand and drug carrier allows for the active targeting of liposomes. Usually, the biomarkers are receptors that express more on tumour cells than on normal cells. So, the number of healthy cells killed decreases [6]. Figure 2 shows the mechanism for ligands to recognise and bind to the receptors on tumour cells.

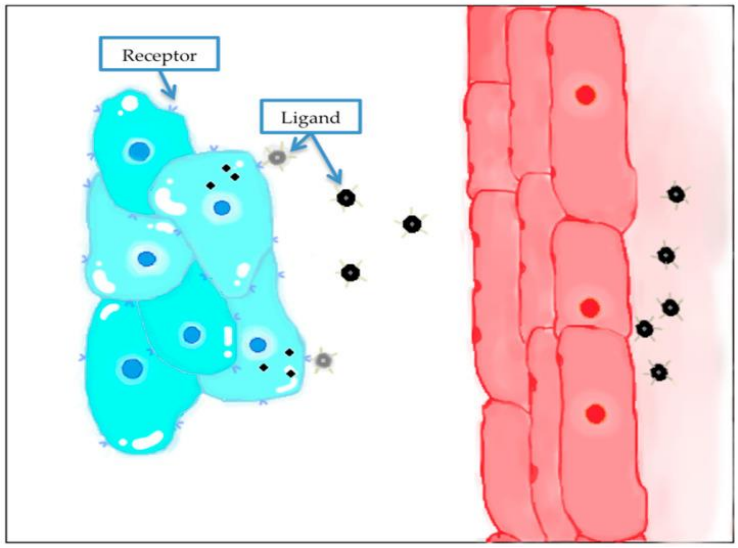


Figure 2. Mechanism for ligands to recognize and bind to the receptors on tumour cells [6]

3. Polymeric Nanoparticles

Polymeric nanoparticles can be generated naturally or artificially. Enhanced improvements are shown compared to intravenous and oral administration. Drugs can be controlled to be transported to specific tumour sites. Antibodies to cancer can be inserted in the surface of nanoparticles, encapsulated or distributed in the entire matrix. Polymeric nanoparticles include dendrimer, nanosphere, polymeric micelles and hydrogel.

3.1. Dendrimer

A dendrimer is composed of many highly branched monomers. It contains a core and multiple layers with active terminals, as Figure 3 shows. Drugs can be carried onto multivalent surfaces of dendrimers through covalent conjugation or electrostatic adsorption. Targeting therapies of dendrimers have been studied because dendrimers may deliver drugs to specific tumour sites without killing normal cells. Quintana et al. used a functionalized dendrimer, which is composed of a generation 5 polyamidoamine (PAMAM) dendrimer conjugated with folic acid, fluorescein isothiocyanate (FITC), and methotrexate (MTX) to target cells. It turns out that compared to free MTX, internalization and survival of cells are both enhanced [7]. Cavities in the dendrimer's core can carry drugs through hydrogen bonds, hydrophobic interactions and chemical linkage.

Peptide dendrimers can be targeted by modification through pegylation (PEG), which reduces dendrimers' toxicity. The volume of the dendrimer molecule increases to extend its half-life and cover its immune sites to improve macromolecules' biocompatibility. Excessive PEG will inhibit mutual interaction between dendrimers and targeted cells, which leads to a decreased uptake of drugs for cancer cells. Such ligands like saccharides, peptides, and antibodies are introduced to achieve active targeting and enhance the binding force between macromolecules and cells [8].

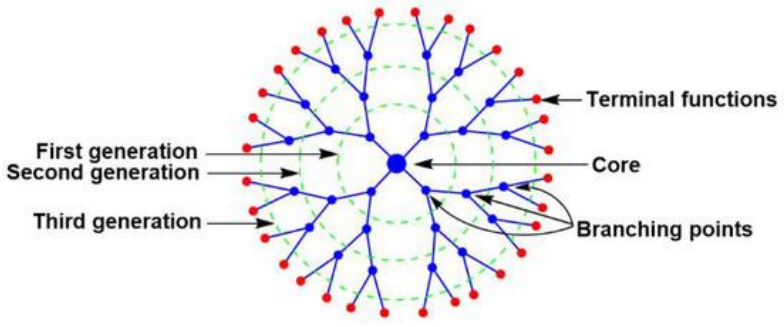


Figure 3. Structural features of a third-generation dendrimer

3.2. Polymeric micelles (PMs)

Due to the small size, reachable preparation and excellent solubilization properties of PMs, they can be drug carriers in different administration routes. They can improve the drug's uptaken or bioavailability and lead to a controlled and targeted release of the drug, which can reduce side effects significantly. Many problems still exist that will cause lower tumour inhibition ability than expected, like dilution of blood, clearance of organs and hydrolysis of different enzymes. A series of research studies have been conducted about how to improve the stability of PMs. The first way is to undergo crosslinking when preparing. The second is to develop a prodrug delivery system, and the last is to produce stable PMs with low critical micelle concentration (CMC) values. Unimolecular micelles are also preferred. Wu et al. synthesized two amphiphilic block copolymers (mPEG-b-P(LA-co-MPA) and mPEG-b-P(LA-co-MPT)), one with adenine (MPA) and another with thymine (MPT). Studies indicated that PMs with stable cross-linked core layers are formed through hydrogen bonds between MPA and MPT [9].

3.3. Hydrogel

Gels perform good hydrophily, fluidity and deformability, leading to carriers with controllable size, accessible building of multivalent interface and functionalization modification. They are usually produced by cross-linked form through covalent force, hydrogen bonds or physical entanglement and chemical induction. They are expanded in water to package the drug and then injected into the body. Hydrogel can respond to external and internal stimulations like light, pH, redox potential and magnetism. Anti-cancer substances can be controlled remotely and released when needed. Stanford engineers developed a gel composed of two ingredients: polymer from cellulose and biodegradable nanoparticles. This gel can temporarily hold cytokine and chimeric antigen receptor (CAR) T cells. Exposure to high concentrations of specialized cytokine signaling proteins, CAR-T cells are strongly activated to replicate rapidly and destroy tumours. Intravenous infusions are avoided to prevent cytokine toxicity to other body parts.

4. Inorganic Particles

4.1. Mesoporous Silica Nanoparticles (MSNs)

In nano-delivery systems, MSNs are extensively used, especially in multi-function systems, such as targeting, treatment, and imaging. The advantages of MSNs include large surface area, low toxicity, adjustable pore size, good biocompatibility compared to other metallic oxides, etc. Also, MSNs can easily undergo functionalization modification. And they have a high drug-loading capacity. Due to the strong Si-O bond, MSNs are more stable to external responses like degradation and stress than liposomes and dendrimers. MSNs delivery system mainly includes passive targeted carriers and active targeted carriers. Passive targeted carriers rely on the Enhanced permeability and retention (EPR) with specific physical properties of MSNs [10].

MSNs with TiO_2 coated are first generated to be used as carriers of the drugs for the expansion of vessels. According to the study, MSNs sphere has better safety. Not only does it have no side effects on vessel function, but it also significantly increases the biocompatibility and drug uptaken by the aorta. Another study is about the modification of MSNs using transferring ferroproteins, which allows MSNs to specifically recognize receptors of transferring ferroproteins on tumour cells. Targeting delivery of drug DOX is achieved, and drug uptake by tumour cells is increased, too.

4.2. Metallic Oxide

Metal, metallic oxides and other biological compounds comprise most antimicrobial nanoparticles. Due to their small size, metal nanoparticles can easily interact with the bacterium membrane. They can form conjugates with polymers to conduct anticancer and antitumor properties [11]. Some metallic particles can perform magnetic properties called magnetic nanoparticles (MNPs).

MNPs can be used in hyperthermia for cancer therapy. Common MNPs contain nickel (Ni), iron (Fe) and cobalt (Co). MNPs' disadvantages include low chemical stability and biocompatibility, easy oxidization, and pyrophoricity at room temperature. When polymers, organic materials, or ceramics are added to MNPs, they can avoid being oxidised to some extent. For hyperthermia, e.g. Fe-Au, Fe-Al, and Fe-Cu alloys are considered to reach the needs of therapies. The potential instability and toxicity of Co and Ni restrict them.

5. Conclusion

Nanoparticles used as drug carriers have more developments compared to conventional treatments. First, the solubility and stability of the drug are enhanced so that patients can take in more drugs. Due to its small size, the specific surface area is big enough to achieve targeted therapy. Finally, the circulation time of the drug in the body is prolonged, which will cause a more extended period of validity for tumour cells. Besides having fewer side effects, nanoparticle therapies can have a better curative effect against tumours. In targeted therapies, many different types of nanoparticles are commonly used. Liposomes, polymeric nanoparticles (e.g. dendrimers, gel) and inorganic particles are introduced in this essay. For liposomes, the solubility of the drug is improved. Liposomes can also package both signalling molecules and drugs into tumour sites. Polymeric nanoparticles can undergo surface modification and carry antibodies. Ligands like peptides are used to enhance the binding with receptors. And gel has a promising future in tumour treatment. Mesoporous silica nanoparticles are easily functionalized. They also have stable physical properties that prevent deformation. Metallic oxides can form conjugates, and some magnetic metallic particles can be used in hyperthermia to destroy cancer cells.

However, there are still disadvantages to nanoparticles used for cancer treatment. Some nanoparticles have unknown toxicity to the body, which may be accumulated if metabolism is delayed. Too much harmful substance may lead to death. Some tumour cells will secrete extracellular vesicles, which will block the delivery of nanoparticles to cells. The preparation and surface modification of nanoparticles is still tricky. And the way of decomposition and metabolism of nanoparticles is still unclear. To improve the effects, research about the path of nanoparticles in the body should be studied, such as marking the materials using isotopes or magnetic particles when preparing and imaging them. The nanoparticle delivery system should also be improved for better delivery.

References

[1] Alqahtani AA, Aslam H, Shukrullah S, et al. Nanocarriers for innovative therapeutic strategies to treat drug-resistant tumors: A Review. Assay and drug development technologies, 2022, 20 (5): 191 - 210.

[2] Zhang P, Ye G, Xie G, et al. Research progress of nanomaterial drug delivery in tumour targeted therapy. Frontiers in Bioengineering and Biotechnology, 2023.

[3] Zhou Q, Zhang L, Wu H. Nanomaterials for cancer therapies. Nanotechnology Reviews, 2024, 6.

[4] Hamad I, Harb AA, Bustanji Y. Liposome-based drug delivery systems in cancer research: an analysis of global landscape efforts and achievements. Pharmaceutics, 2024, 16 (3): 400.

[5] Ruwizhi N, Aderibigbe BA. The efficacy of cholesterol-based carriers in drug delivery. Molecules, 2020, 25 (18): 4330.

[6] Nsairat H, Khater D, Sayed U, et al. Liposomes: structure, composition, types, and Clinical Applications. Heliyon, 8 (5): e09394.

[7] Cruz A, Barbosa J, Antunes P, et al. A glimpse into dendrimers integration in cancer imaging and theragnostic. International journal of molecular sciences, 2023, 24 (6): 5430 - 5430.

[8] Wang P, Xu S, Wei J, et al. Functionalizing peptide dendrimers and its application in tumour treatment and diagnosis: a review. Materials Reports, 2022, 36 (11): 20080149 - 20080148.

[9] Li Y, Tian R, Wang X, et al. Research progress of polymeric micelle nanomedicine. Polymer Materials Science & Engineering, 2020, 36 (1): 8.

[10] Han K, Ren T, Li D, et al. Research Progress in the Application of mesoporous silica nanoparticles in tumour therapy. Chemical Reagents, 2023, 45 (9): 1 - 10.

[11] Saha S, Ali, et al. Metal oxide nanocarrier for targeted drug delivery towards the treatment of global infectious diseases: a review. Journal of Drug Delivery Science and Technology, 2023, 86: 104728.