Proceedings of the 4th International Conference on Materials Chemistry and Environmental Engineering
DOI: 10.54254/2755-2721/61/20240913

Applications of nanomaterials in medicine against cancer

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Abstract. Nowadays, all walks of life are developing with innovation at their core, and the subject of materials is no exception, while nanomaterials occupy an important position in the emerging field due to their unique properties and wide coverage. In addition, the incidence of cancer, a difficult disease with a very high mortality rate, is increasing day by day. Therefore, research on cancer has received extensive attention from society. Therefore, this paper explores how cancer can be treated by means of nanomaterials through the organization of current research and papers in the field. Research at this stage suggests that nanomaterials play a major auxiliary role in anti-cancer technology, as follows: enhancing the ability of other substances to disrupt cell membranes, assisting in the delivery of anti-tumor drugs, improving imaging capabilities, and enhancing the ability of some substances to inhibit tumor growth through specific mechanisms. In future research, the focus will be on minimizing the side effects of the treatment and improving its safety.

Keywords: Iron Tetraoxide Nanoparticles, Ultrasound, Fullerene Derivatives, GNPS, Bacteria

1. Introduction

Chemotherapy and radiotherapy are currently the primary methods of treating tumors, but drug resistance and strong side effects make these two techniques inadequate for treating tumors [1]. Due to the complex immunosuppressive mechanisms and the process of screening and identification of antigens, therapeutic vaccines are not able to meet the immediate needs of treating tumor [2]. Therefore, the medical community is in urgent need of a therapeutic approach that can be quickly applied in the clinic with few side effects. Nanomaterials, by virtue of their size advantage and certain electromagnetic properties, can be combined with drugs to achieve in vivo therapeutic effects. Nanomaterials in medicine mainly appear in the form of carriers so as to fulfil the role of targeting and delivery of drugs, but because of poor stability, a poor long-term cycling effect, and a penetration effect that is not enough, the release of drugs is not accurate enough, and the nano-delivery system has not shown good enough efficacy [3]. However, researchers have designed nanomedicine carriers based on the multi-spectrum, high-temperature-resistant, high-strength, radiation-resistant and electromagnetic-wave-absorbing properties of a variety of nanomaterials, which have been used in clinical trials [4]. This paper will summarize how the multiple properties of nanomaterials can be harnessed so that they can play a key supporting role. Through this paper, people can have a clearer understanding of the current progress and application of nanomaterials in the field of anti-tumor, and at the same time, improving people's knowledge can also promote the development of this field.

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2. Destruction of cell membranes

This part will summarize the pathways by which nanomaterials are involved in the process of direct killing of tumor cells and their role in the therapeutic process. Currently, there are two main ways to kill cells directly, which are the use of the mechanical properties of ultrasound in Li's study and the use of the photothermal effect to generate high temperature in Wang's study, and nanomaterials play an important role in both processes [5,6].

Ultrasound is divided into two types: high-intensity focused ultrasound (HIFU) and low-intensity ultrasound (LUS). The former has a shorter wavelength and higher energy, which can make better use of the mechanical and thermal effects to destroy tumor cells, while the latter has the advantage of weakening the impact on the surrounding tissues and reducing the damage to the healthy organism. However, the use of high-intensity sound waves will cause irreversible effects on the healthy organism, which means that normal organs can become dysfunctional or even necrotic as a result of the intense energy of the ultrasound, and the use of low-intensity sound waves will greatly reduce the therapeutic effect as the depth increases, so the use of ultrasound technology alone cannot meet the requirements of killing tumor cells. Based on this, researchers have developed several special nanomaterials to reduce the intensity of sound waves, first of all a material called MAPP, which has the effect of sensitizing HIFU to produce thermal effects at 120 watts. In addition, the researchers used nanomaterials to catalyze the conversion of hydrogen peroxide in the tumor environment into hydrogen peroxide, which promotes the cavitation effect and kills tumor cells at 80 watts of HIFU irradiation [5].

The relaxation process is a gradual recovery of matter from an excited state to an equilibrium state, and a nanocarrier called GNPs, whose resonance generates energy that can cause lattice vibrations during relaxation, which in turn produces a photothermal effect. By modifying some substances on the surface, GNPs can be accurately attached to the surface of tumor cells, and can kill the tumor cells under laser irradiation with a photothermal effect. Another advantage of GNPs is that its surface can be modified with a lot of targeting molecules, which enables GNPs to bind to tumor cells in a targeted manner, thus reducing harm to other organisms [6].

3. Delivering drugs

Nanomaterials often have the ability to alter the permeability of cell membranes, which makes access to drugs much easier. The drug's ability to work depends largely on its ability to cross the cell membrane and thus be delivered inside the cell, so that's helpful in terms of efficacy.

3.1. Ultrasound

The cell membrane temporarily forms reversible holes under ultrasonic radiation. This provides a novel solution for the intracellular entry of drug molecules. Microbubbles have been widely used as a transport medium, but their use has been limited by their large size, inability to penetrate the interstitial space between vascular endothelial cells with pore sizes of less than 700 nm, short residence time in the target area, poor stability, short half-life, and unavoidable retention in the lungs. For example, the residence time of microbubbles in a fixed region of the body may range from a few minutes to a few hours, and their half-life may be as little as 10 minutes. With the help of nanomaterials, the current shortcomings of microbubbles can be overcome and the tumor EPR (enhanced permeability and retention effect) effect can be utilized to enable the rapid accumulation of microbubbles in tumor cells to achieve targeted therapy [5].

3.2. Bacteria and charge

Although nanomaterials are good carriers of drugs by virtue of their size advantage and quantum-limited domain effects, they have transport deficiencies in the complex tumor environment. Some anaerobic bacteria have strong localization abilities for anaerobic tumour environments, so bacteria and nanomaterials can be combined through amino groups and finally play a complementary role. In addition, some bacteria exhibit negative potentials, so adding a positive charge to the nanoparticles can also allow the two to bind tightly, such as PEI and protonation treatments, which can allow nanoparticles

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to carry a positive charge. Finally, drugs such as ICG and DOX carried in the nanoparticles can enter the tumour environment more smoothly through the dual targeting of nanomaterials and acteria [7]. There is another example of an application that utilizes the charged nature of nanoparticles. γ-glutamyltranspeptidase (GGT) is highly expressed in tumor cells and on the surface of TVEC membranes in hepatocellular carcinoma and pancreatic carcinoma tissues. The researchers developed an actively transported liposomal nanocarrier GCSDL, which mainly consists of DOPE-GSH, HSPC, and CHOL. DOPE-GSH can undergo glutamyl transfer catalyzed by GGT, which transforms GCSDL from anionic to cationic type. When GCSDL is transported to the vicinity of tumor tissues, a charge flip occurs under the catalytic action of GGT, and the positively charged GCSDL is actively transported across the TVEC into the tumor periphery through activation of follicle-mediated endocytosis and vesicle-mediated transcytosis to increase the tumor aggregation [8]; subsequently, positively charged GCSDL is actively transported to the tumor parenchyma via consecutive vesicle-mediated transcytosis to achieve deep penetration drug delivery.

3.3. PDL1

Programmed cell death protein-1/programmed cell death ligand 1 (PD-1/PD-L1) antagonistic therapy has shown favorable efficacy in patients with advanced cancer, and has therefore received attention from various researchers in recent years. The lack of targeting results in the possibility that the PDL1 antibody may appear outside of the tumor locality and may cause inflammation to occur in healthy tissue. The team investigated a nanoliposome that can be modified with a protective shell, PEG, that is shed under certain circumstances, only in the specific acidic environment of the tumor site, which ensures that the antibody binds and is enriched only specifically to the tumor site [9]. This approach has been shown to be feasible in mouse models of breast cancer. In the mouse contrast experiments, the experimenters found that the injection of nanoliposomes significantly reduced the frequency of binding of PD-L1 antibodies to normal organs in the mice.It can be extended to the application of radiotherapy, which also plays a facilitating role.

3.4. PLGA

PLGA is a polymer composed of lactic acid and hydroxyacetic acid that possesses good biodegradability, and the time and rate of degradation of PLGA in organic environments can be controlled by adjusting the molecular weight ratios and temperatures of the two components of the polymer. Although paclitaxel and curcumin are good anticancer drugs, their low water solubility, fast release rate and poor absorption have resulted in poor therapeutic efficacy, whereas PLGA can greatly improve the efficacy of the drugs by accurately releasing the drugs and even increasing the cellular uptake rate [10]. In addition to passive targeting, PLGA can also be used in active targeting and receptor mediation with the addition of surface modifications, which has a wide range of applications.

3.5. Mesoporous silica nanoparticles (MSNs)

The EPR effect means that after tumor cell occurrence or the formation of metastases, cancer cells continue to proliferate into clusters, and the supply of nutrients from the primary tissue environment alone can no longer meet the needs of growth. When the diameter of the solid tumor tissue mass reaches about 2 mm, it will release angiogenic factors to induce microangiogenesis and form a new blood supply system to meet the tumor. The growing nutritional and oxygen demands of the tumor tissue can be met by the formation of a new blood supply system [11]. Mesoporous materials with high biocompatibility and adjustable pore size give them an inherent advantage in drug delivery. The passive targeting of MSNs drug-carrying system to tumors can take advantage of the EPR effect, which can be achieved by changing the size of MSNs so that the MSNs drug-carrying system is easy to seep out of the highly permeable and incomplete tumor gross vascular network into the interstitial space of tumor tissues and difficult to pass through the normal vasculature to achieve the accurate delivery of the drug and to allow the toxicity of the drug to accumulate in the tumor tissue and increase the retention time. Therefore, by adjusting the diameter and size of MSNs particles and utilizing the

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EPR effect, the MSNs drug delivery system can achieve the purpose of passively targeting tumor tissues to release drugs [6].

4. Imaging capability

When the light beams into the tiny structure, its wavelength is smaller than the structure, and the direction of light emission is limited by the structure, so the structure surface produces a strong surface plasmon resonance (SPR). This effect can cause local aggregation of surface charges on the sample to cause local amplification of the optical signal. By using highly sensitive detectors, the intensity and distribution of the optical signal at the nanoscale can be directly detected, thus achieving high-resolution imaging of the sample.

Most cancer cells are covered with epidermal growth factor receptors. Epidermal growth factor receptor (EGFR) is a specialized protein whose expression is significantly higher than in other normal cells, thus providing a new diagnostic target for cancer. The ability to detect the epidermal growth factor receptor is key to determining the presence of cancer cells in the body. Several researchers have now used epidermal growth factor receptor antibody-modified GNPs for the early diagnosis of tumors. The researchers took advantage of the good light absorption and scattering ability of GNPs and combined them with active molecules, thus using the scattering ability of GNPs for the early diagnosis of tumors. Jain et al. showed that GNPs bind to cancer cells 600 times more than normal cells. Combining EFGR antibody with GNPs can be used to detect tumor cells by their scattering properties. EFGR antibody binds to GNPs, causing GNPs to attach to cancer cells, and the strong absorptive properties of GNPs make it possible to detect tumor cells [6].

A researcher has designed phase change nanoparticles containing the phase change material PFH in a shell of the superparamagnetic material Fe_3O_4 so that it can utilize the magnetic-thermal properties of Fe_3O_4 and also promote the liquid-gas phase change of PFH when it is heated up to facilitate ultrasonography. Although the boiling point of free PFH is about 56 ℃, previous studies have shown that the nanoparticles prepared with PFH can cause the phase transition of PFH to produce gas bubbles once heated at 60 ℃+. In the present study, a temperature of 80 ℃ was reached within 3 min after local injection of PFH-HIONS, which was sufficient to cause tumor cell necrosis and phase transition of PFH, but the control group failed to observe the phenomena of warming and phase transition, which also verified the therapeutic and developmental properties of PFHHIONS nanoparticles [12].

5. Special mechanism

Nanomaterials can have the effect of inhibiting or even killing tumors through some of their own properties, in addition to playing a complementary role in some conventional treatments. They may interact with some macromolecules in the human body, or they may cause a series of reactions or special mechanisms in the body.

5.1. Fullerene derivatives

Fullerene is a spherical dodecahedron consisting of 12 five-membered rings and 20 six-membered rings, which resembles a soccer ball and has a diameter of 0.71 nm. Each carbon atom of the six-membered ring is bound to other carbon atoms by a double bond to form a structure similar to that of the benzene ring. Fullerenes, metal-embedded fullerenes and their derivatives have a wide range of applications in the biomedical field due to their unique structure and physicochemical properties. Fullerene derivatives can accomplish tumor cell inhibition by two mechanisms. One is to remove the reactive oxygen species inside and outside the cell to inhibit cell activity. The reactive oxygen radicals it scavenges include superoxide anion, monoclinic oxygen, and hydroxyl radicals. The other is to promote the secretion of immune factors by T cells to activate the body's immune function and improve the immune response ability, which in turn inhibits the growth of tumor cells. The researchers verified these two ideas in mice.

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5.2. Nitrogen Carbide and E. coli

In mammals, arginine is reduced to NO by NO synthase, and NO is spontaneously oxidized to NO3- under physiological conditions. E. coli MG1665 can reduce NO3- to NO and release it again by NO synthase. MG1665 can reduce NO3- to NO again by NO-generating enzymes in the body and release it. A certain concentration of NO gas molecules can kill tumor cells. However, due to the weak metabolic strength of the bacteria in the normal state, the NO produced is insufficient to produce a significant therapeutic effect. The researchers chose carbon quantum dot-doped nitrogen carbide (CCN), a material with photovoltaic conversion effects, to enhance NO production. They connected CCN to E. coli through electrostatic interactions to construct a bacterial/nanomaterial complex. When the bacteria carried CCN to the tumor site due to anaerobic targeting, the CCN generated photoelectrons under light and transferred them to E. coli, which promoted the production of NO-generating enzyme NADH in E. coli, and then promoted the reduction of endogenous NO3- to NO, and the large amount of NO rapidly generated at the tumor site induced oxidative stress and DNA damage in tumor cells, which ultimately led to the death of cancer cells [7].

6. Discussion

Currently, the clinical research of nanomaterials for the anti-cancer effect has made considerable progress. A considerable number of technologies have been applied in the actual treatment, but there are still many ideas in the conceptual stage. The conversion of clinical materials still needs a large number of tests to prove their safety and stability, and there are still a lot of deficiencies in technology waiting to be resolved.

1. Potential safety issues. Long-term circulation and metabolism of inorganic nanomaterials in living organisms, especially non-degradable inorganic nanomaterials. With the use of nanomaterials in pharmaceutical applications, since nanomaterials need to bind to the cell membrane or even enter the cell in order to function, this results in a large amount of material that will be enriched in the body, which may have an impact on cellular function when a certain amount is reached.

2. Drugs made from nanomaterials have efficiency and cost issues in large-scale mass production, and there is a need to find appropriate development methods. Because the design of nanomaterials is a micro-level technology, it requires very strict technical requirements, and in the early stages of experimentation, the cost of drug manufacturing can be significantly higher due to the immaturity of the technology and the low success rate. Therefore, it is not yet possible to meet the requirements for large-scale mass production of drugs.

3. At present, many of the experiments are conducted in mice, and the real application to humans still needs many safety experiments to ensure consistent efficacy. Although both rats and humans are mammals, the complexity of their body structures is not of the same order of magnitude. There are countless structures or physiological mechanisms in the human body that mice do not possess. Therefore, the success of the experiment in mice only shows that the drug has the potential to be used in living organisms, but the real application to the clinic still needs a lot of safety tests.

7. Conclusion

This article summarizes the role of nanomaterials in four fields: auxiliary killing of tumor cells, auxiliary drug delivery, auxiliary imaging, and inhibition of tumor cells through special mechanisms. Among them, nanomaterials have improved their performance in ultrasound-related technologies, liposome construction technology and drug carrier design. The research perspective of this article focuses on the healing process of tumors. The treatment process for tumours is far beyond this stage. The process of preventing recurrence after a cure is also critical. Whether nanomaterials can also play a role in this process has not been studied in this article, which is the missing part. In future research, the focus will be on the process of preventing recurrence after cure and exploring whether nanomaterials can effectively inhibit tumour recurrence by combining some drugs or special mechanisms.

DOI: 10.54254/2755-2721/61/20240913

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