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The Application Progress of Tumor Microenvironment-Responsive Drug Carriers in Precision Chemotherapy

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Abstract:

Drug therapy is a necessary means of treating malignant tumors. By taking or injecting drugs, it effectively inhibits or reduces the number of tumor cells in the body and controls the metastasis of tumor cells. However, drug therapy may resultin a series of side effects during the treatment process, such as hair loss and liver function damage, which aggravates the treatment pain of patients. In recent years, researchers have proposed a type of responsive drug carrier based on the tumor microenvironment (TME) cells in response to the differences between the extracellular environment of tumor cells and that of normal cells, in order to improve therapeutic targeting and reduce therapeutic side effects. This article focuses on the differences in pH value, REDOX substance concentration and enzyme expression between tumor cells and normal somatic cells in the TME, explores the differences among different indicators and the mechanism of designing responsive carriers. Meanwhile, taking an experimental model of delivering curcumin based on a pH-temperature combined responsive polymer carrier as an example, the feasibility of targeted release is analyzed. Meanwhile, due to the high heterogeneity of human cancer cells, the possible errors and limitations of the experimental model are evaluated. In addition, the prospects of artificial intelligence-assisted personalized drug carriers are discussed in a multivariate manner based on the TME.

Keywords: Drug therapy, tumor microenvironment, responsive carriers.

1. Introduction

Cancer is the second most common disease after cardiovascular and cerebrovascular diseases and has posed a significant threat to human life since the 20th century. However, most patients are diagnosed with

cancer at the middle or advanced stage. According to data from the International Agency for Research on Cancer (IARC), there were nearly 20 million new cancer cases worldwide in 2022, among which lung cancer and breast cancer were the most common types among men and women, respectively.

The necessary means for treating cancer include chemotherapy, hormone therapy, radiotherapy, targeted therapy and surgery. Among them, drug therapy is a relatively common method, including intravenous injection (cisplatin, paclitaxel), oral administration (capecitabine, Tegafur), etc. [1] However, during the treatment process, the drugs will be delivered to cancer cells and healthy cells in the body in a non-targeted manner, causing side effects such as hair loss and liver and kidney function damage to a certain extent, and causing harm to healthy cells. Studies have shown that the tumor microenvironment (TME) of tumor cells has many differences from that of normal cells, including the concentrations of immune cells and stromal cells, the pH differences caused by metabolites, the concentration differences of REDOX substances, and the expression of enzymes, all of which are potential areas to break through the insufficiency of targeting drug delivery.

Considering that these differences can be utilized as different response mechanisms, the sensitivity of drug release and the level of drug absorption by cells can be enhanced. Therefore, this article focuses on the design and mechanism of action of TME-sensitive drug carriers in tumor cells, explores the potential to improve the targeting of drug release, and reduces the damage to normal cells during chemotherapy.

2. Characteristics and Response Mechanism of TME

Due to metabolic requirements, tumor cells take in more glucose, generating more lactic acid and carbon dioxide. Excessive protons accumulated intracellularly can be transferred to the extracellular space by tumor cells, creating an acidic microenvironment with a pH ranging from 6.0 to 7.0. The pH of normal human tissue cells is weakly alkaline, ranging from 7.35 to 7.45. Meanwhile, tumor cells are in a REDOX metabolic environment, and the concentrations of both oxidants and antioxidants are relatively high. [2] Glutathione is a thiol with a relatively high content in human cells. Its intracellular concentration is 100 to 1,000 times that of the extracellular matrix, while its concentration in the extracellular matrix or blood is only 2 to 20 μM. The proliferation rate of tumor cells is much higher than that of normal cells, and the concentration of glutathione can reach 0.5-10 mM, which is much higher than the content in normal tissues. In addition, the abnormal expression of certain enzymes is also a key indicator for diagnosing tumors [3].

2.1 pH Response

The pH response is based on the breaking of acidic unstable chemical bonds under pH sudden changes or the sudden change in solubility of polymers with ionizable groups in nanomaterials when pH changes. The advantages of the chemical bond drug loading method include the connection of drugs with the hydrophobic ends of polymer carriers, a relatively high loading capacity, and stable properties in the human body environment. Chemical bonds sensitive to acids include hydrazone bonds, imine bonds, acetals, orthoformates, etc. Among them, the synthesis of hydrazone bonds includes three pathways (Figure 1), namely the condensation reaction of the shin and aldehydes and ketones, the Jap-Klingemann reaction, and the coupling of aryl halides with hydrazones [4]. For example, in the preparation of keratin-doxorubicin, the combination of doxorubicin and keratin is achieved through hydrazone bonds. The hydrazone bonds of the material break in the acidic TME of the tumor, completing the drug release. Prabaharan et al. prepared a carrier for delivering the therapeutic tumor drug doxorubicin (DOX), which was based on folic acid-conjugated monomeric micelles [H40-P(LA-DOX)-b PEG-OH/FA] of amphiphilic lipid hyperbranched block copolymers. In this system, DOX reacts with the arylhydrazine group in the hydrophobic fragment of the amphiphilic lipid hyperbranched block copolymer through its own ketone carbonyl group to form pH-sensitive hydrazone bonds in the form of covalent bonds, achieving targeted drug release in the tumor part [5].

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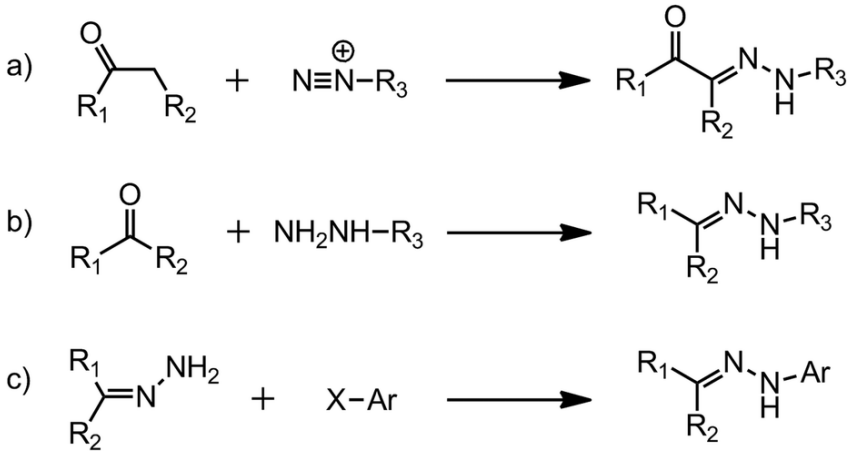

Fig. 1 Three main pathways for hydrazone bond synthesis [6].

2.2 REDOX Response

Reactive oxygen species and glutathione at higher concentrations in tumor cells than in normal cells can act as responses. Reactive oxygen species (ROS) can undergo REDOX reactions with dimethyl sulfide. The hydrophobicity of dimethyl sulfide suddenly changes to hydrophilicity, releasing drugs. Glutathione is prone to react with disulfide bonds, and the former becomes a thiol group after the reaction [7]. Doping glutathione in silicon dioxide is beneficial for the targeted release of drugs. For PEG-SS-CA-DOX micelles, doxorubicin and polyethylene glycol were linked through disulfide bonds, and doxorubicin was efficiently released under the dual response of pH and glutathione. A ROS-responsive carrier (Figure 2) encapsulates drugs with polyethylene glycol (PEG). When exposed to high concentrations of ROS, the thioketone bond breaks, releasing the drug [8].

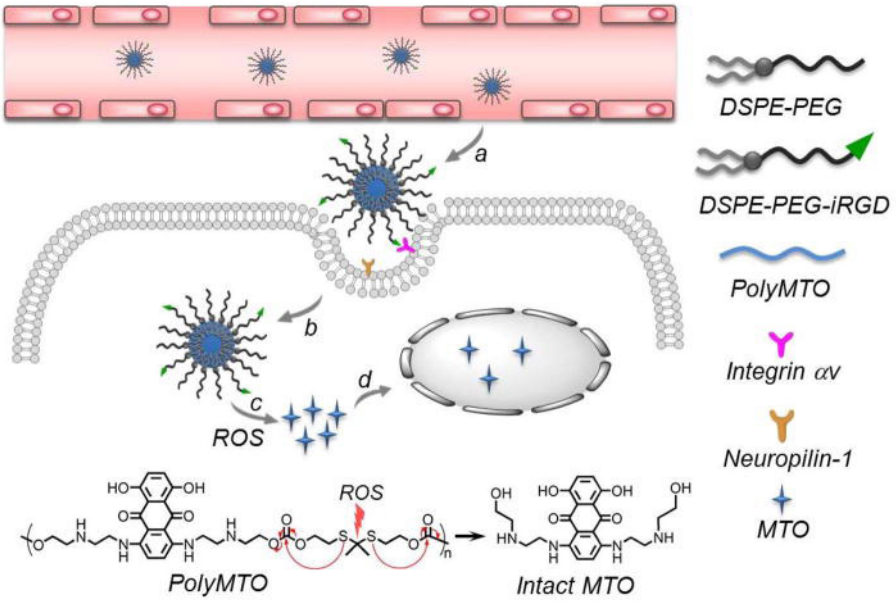

Fig. 2 Schematic diagram of the structure of ROS-responsive multidrug prodrug nanoparticles [9].

2.3 Enzyme Response

Enzymes are catalysts for the normal operation of many biological functions in the human body, and their abnormal expression may lead to the occurrence of diseases. The abnormal expression of enzymes such as α -amylase and hyaluronidase is often used as a criterion for judging the production of tumor cells in the human body. For example, MMP2/9 is overexpressed in most tumor cells compared with normal cells. Using enzymes as response signals can stimulate the carrier to specifically release

drugs at the lesion site. Unlike REDOX responsive vectors, enzyme-responsive vectors do not take intracellular delivery as the stimulus but use the extracellular environment as the active site. Research has found that liposomes bound to PEG through the cleavage bonds of MMP-like enzymes can enable PEG to be recognized and cleaved extracellular, achieving endocytosis [10].

3. Experiment and Application of TME Response Materials

3.1 pH-Temperature Dual-responsive Drug Carrier Model in Digestive Tract Cancers

Curcumin, as a typical drug for the treatment of rectal cancer, researchers have designed a chitosan carrier material modified by deoxycholic acid and hydroxybutyl for the delivery of curcumin. This chitosan contains amino groups and can be protonated in an environment with a pH lower than 7. Meanwhile, at temperatures above the critical dissolution temperature, the covalent bond force and hydrophobicity of nanoparticles increase, causing the material to shrink. Since the drug passes through the highly acidic gastric juice of the TME after oral administration, to ensure that the carrier is not prematurely responded and released by the excessively low pH of the gastric juice, this drug combines the pH response with the thermal response, ensuring that the pH response is expansion and the thermal response is contraction. In the simulation experiment, when passing through the simulated stomach (with a pH of approximately 1.2), pH and the thermal effect responded together. The dimensions of temperature-sensitive contraction and expansion caused by the lowest critical dissolution temperature offset each other, keeping the carrier stable. When reaching the simulated intestine (with a pH of approximately 7.0), the pH was unresponsive while the thermal response caused the carrier to contract, and curcumin was released explosively [11] (Figure 3).

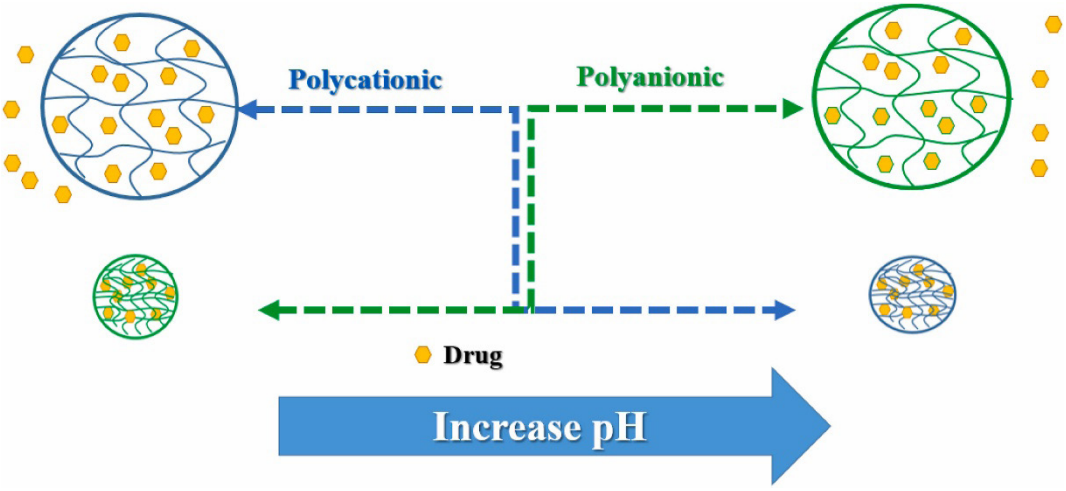

Fig. 3 Schematic diagram of the size change of drug-loaded pH-sensitive hydrogel in response to pH stimulation [10].

Wang et al. designed a set of experiments to explore the delivery effect of this chitosan in a simulated human body environment. The experimental results were measured by the amount of drug leakage, the amount of drug absorption, the median inhibitory concentration (IC50 value), etc. Within 2 hours, the leakage of curcumin encapsulated by DAHBC27 nanoparticles (NPs) in the gastric environment in all three groups was less than -10%, while that in the free curcumin group was as high as 95%. DAHBC27 NPs can increase the absorption of curcumin through paracellular cells by about 10 times. By comparing free curcumin and curcumin encapsulated in DAHBC27 NPs, the IC50 value under the action of free curcumin was approximately (35.6±3.2) μM, while the IC50 under the action of curcumin encapsulated in DAHBC27 NPs was (10.2±1.5) μM. Under fluorescence labeling, it was determined that curcumin in the DAHBC27 NPs group was absorbed by paracellular cells by approximately 10 times compared with the free group [12] (Figure 4).

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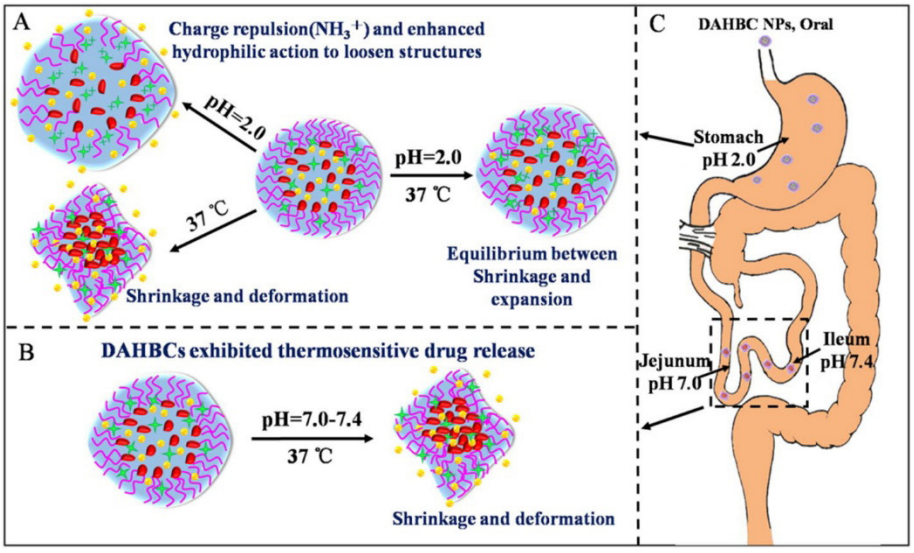

Fig. 4 The principle of thermal and pH dual-response morphological transformation of oral delivery of DAHBC NPs. (A) The pH responsive expansion and thermal responsive contraction are balanced, and the DAHBC NPs remains stable. (B) DAHBC NPs exhibit drug release activity due to thermal reaction shrinkage. (C) The DAHBC NPs pathway in the gastric and intestinal environments after oral administration [12].

Although experiments have shown that DAHBC27 NPs are an effective drug delivery material, due to the combined effect of pH and temperature responses, there may be limitations in treating the types of cancer. The critical dissolution temperature of general shell polysaccharide carriers is 30-50°, and the thermal response may fail in some human tissues with lower temperatures. Meanwhile, the stability and sensitivity of the response also need to be improved.

3.2 Carrier models in Other Cancer Treatments

Luo et al. inoculated 4T1 cells into the subcutaneous tissue of the mammary glands or backs of mice to simulate human breast cancer and construct a mouse breast model. In addition, control mice were set up to preserve their complete immune systems for evaluating the immune microenvironment immune effect. In the experiment, the carrier SYN@MnO_2-PEG degrades in an acidic environment, releasing the small molecule combination drug (SYN); Meanwhile, macrophages undergo intensified regulation and polarization from M2 to M1, that is, from tumor-promoting macrophages (M2) to tumor-inhibiting macrophages (M1), generating reactive oxygen species to induce apoptosis of tumor cells and releasing antigens to activate the systemic immune response. In the experimental results, it was detected that compared with the control group mice, the tumor volume inhibition rate of the experimental group mice could reach 65%, and the number of apoptotic cells in the tumors increased. Meanwhile, the increase in the M1/M2 ratio proves the increase in antigen presentation capacity; The pH also rose from 6.5 to 7.0. These results all support the efficacy of SYN@MnO_2-PEG in mouse mimicking human breast cancer TME-targeted therapy [13].

However, experiments have not yet been able to determine the compatibility and toxicity of this material in the human body. Meanwhile, the mouse model cannot precisely reproduce the human environment. Therefore, further research is needed before it is used for clinical treatment.

Furthermore, considering the individual differences in treatment, there may be minor differences in the digestive tract pH of patients, resulting in deviations in the carrier response. In future clinical applications, personalized targeted therapy can be considered, such as setting the most suitable pH response threshold for patients to maximize precise targeted therapy.

4. Limitations and Future Prospects of TME-responsive Drug Carriers

TME-responsive carrier drugs make full use of the pH, REDOX substances, enzymes and even genes of tumor cells in tumor treatment. While treating tumors, they can be combined with other disease treatments such as immunotherapy to improve treatment efficiency and reduce harm to the human body.

However, TME-responsive nanocarriers also have problems to be improved in terms of stability, biosafety, degradability and production cost. At present, this type of drug carrier has not been put into use in clinical medicine.

However, human tumor cells are highly heterogeneous, and the conclusions obtained by using other biological models or simulating the human body environment in experiments may differ from the real human body environment. Secondly, the stability of the preparation process and the product need to be improved. For example, in the case of hydrazone bond-type responsive carriers, since the synthesis of hydrazone bonds relies on the aldehyde-ketone structure, and the chemical properties of the aldehyde-ketone structure are unstable, it may be impossible to connect the carrier. Meanwhile, the manufacturing of TME responsive carriers is rather complex and has not yet been put into large-scale industrial production. In addition, for some metal nanomaterials, their safety for the human body and degradability also need to be taken into consideration.

The previous text proposed that TME-responsive drug carriers achieve precise drug release by sensing the unique physicochemical characteristics of the TME (such as acidic pH, highly expressed enzymes, etc.), thereby enhancing therapeutic specificity. However, there are still many bottlenecks and challenges in this aspect at present. For example, the TME characteristics (such as enzyme activity and pH gradient) in different patients or even within the same tumor vary significantly, while the traditional carrier design relies on fixed threshold trigger release, which is difficult to adapt to individual differences. Meanwhile, the precise response of TME relies on a multi-response mechanism. When constructing multiple response carriers, the number of parameter combinations is too large and cannot be achieved merely by manual means. The solution to these problems may rely on machine algorithms and artificial intelligence for assistance.

For example, in the future, in the diagnosis and personalized treatment of tumors, AI can be utilized to construct pH gradient images of tumor tissue imaging data, and machine simulation can be used to analyze the correlation between pH and tumor density in pathological sections to predict the optimal trigger threshold for carrier release. Meanwhile, AI can also simulate and predict personalized drug carriers. Through machine algorithms, it traverses the carrier response values, and the pH fit of individual tumors to select suitable drug carriers for different patients [14]. At present, the use of artificial intelligence to assist in cancer diagnosis and treatment is still in the theoretical and experimental stage and has not yet been universally applicable. In the future diagnosis and treatment of cancer, efforts should be made to develop in the direction of low side effects, environmental friendliness and early intervention. By skillfully using technological assistance, the mortality rate of cancer can be reduced, and the early diagnosis rate can be improved.

5. Conclusion

This article explores the response mechanisms of different components and properties of the TME. In the specific model analysis, the Ph-temperature combined responsive polymer carrier loaded with curcumin in the simulated intestine has a high rate of carrier protection for drug unrelease when passing through gastric juice and a high drug release efficiency when reaching the digestive tract and has good targeting. In the mouse model, the ratio of tumor suppressor type to tumor promoter type of macrophages increased, confirming the effectiveness of vector targeted release. The results show that the existing experimental models of TME-responsive vectors have practical reference value and provide a theoretical basis for the clinical application of this type of vector in the future. This article has not yet combined the comprehensive analysis of the immune system. In future research, the composition of the tumor TME should be comprehensively analyzed to improve accuracy. Meanwhile, the high heterogeneity of human tumor cells mentioned in the text leads to deviations between the animal model and the actual situation. In future studies, this issue should be deeply explored and studied. Future cancer treatment is expected to alleviate the pain and side effects of patients during the treatment process, while achieving personalized treatment.

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