

Research Progress of Tumor Microenvironment-responsive Anti-tumor Nano-drug Carriers

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Abstract. Cancer is the most serious disease threatening human health at present, and the incidence and mortality of cancer in China ranks first in the world. Chemotherapy is an important means to treat cancer in clinic. However, many traditional small molecule chemotherapy drugs have some defects such as poor solubility, low bioavailability and great toxic and side effects. Small molecule drugs have the disadvantages of low bioavailability, such as rapid metabolism in vivo, short half-life and rapid decrease of in vivo concentration, which affects the therapeutic effect. Therefore, repeated administration is needed to improve the drug concentration. (NDS) can deliver drugs to cancer sites to improve distribution specificity, increase internalization and intracellular drug delivery, minimize adverse side effects and improve drug efficacy. In this paper, the concept, types and drug release of nano-drug carriers are expounded, and the application of nano-drug carriers in cancer treatment is analyzed by taking polymer micelle drug carriers as an example.

Key words: Tumor microenvironment; Nano drug carrier; Nano-delivery systems.

1. Introduction

At present, the main methods used for cancer treatment are surgery, radiotherapy, chemotherapy or their combination therapy. Although these traditional tumor treatment methods can hinder the development of tumors, prolong the survival time of patients and improve the quality of life of patients to a certain extent, there are still defects that cannot be ignored [1]. Cancer is a big killer threatening human health, and it is the main reason leading to the increase of global mortality. Cell proliferation is uncontrolled, and the cells produced will not die. Except hematological cancer, it will produce abnormal cell clusters or tumors [2]. The rising prevalence of malignant tumor has become a serious social problem. At present, the treatment of cancer mainly depends on surgical resection, radiotherapy and chemotherapy [3]. Among them, chemotherapy still occupies an important position. Small-molecule drugs have the disadvantages of low bioavailability, such as fast metabolism, short half-life and rapid decrease of in-vivo concentration, which affects the therapeutic effect. Therefore, repeated administration is needed to improve the drug concentration, but too high drug concentration will increase the toxic and side effects of drugs on human body [4]. There are some shortcomings in the treatment of cancer, such as difficult to cure, easy to relapse and large side effects, so it is urgent to develop strategies with high efficiency and low side effects to treat tumors [5].

With the development of nanotechnology and the in-depth study of tumor microenvironment, stimulus-responsive

intelligent nano-drug carriers designed based on tumor microenvironment have attracted wide attention in anti-tumor drug delivery systems. As a common local treatment method of tumor, surgical treatment mainly hopes to completely remove tumor tissue in order to achieve the success of surgery and cure cancer [6]. However, in the complicated surgical procedure, only the in-situ tumor tissue with obvious boundaries can be removed, and the lesion sites that have spread and metastasized but have not formed obvious tissue blocks cannot be completely removed. NDS is generally constructed by using nanoparticles as drug carriers and integrating strategies such as stimulus-responsive release mechanism and targeting molecules through multifunctional modification [7]. NDS can deliver drugs to cancer sites, improve distribution specificity, increase internalization and intracellular drug delivery, minimize adverse side effects and improve drug efficacy [8]. Nanoparticle drug carriers play an important role in improving the bioavailability, enhancing the curative effect and reducing the toxic and side effects of anti-tumor drugs because of their unique enhanced permeability and retention (EPR) effects. In this paper, the concept, types and drug release of nano-drug carriers are expounded, and the application of nano-drug carriers in cancer treatment is analyzed by taking polymer micelle drug carriers as an example.

2. Advantages and disadvantages of nano-drugs in clinical trials

Nano-drug carriers are colloidal nano-systems that can transport anticancer drugs. Cancer has become the main cause of death for people all over the world. Therefore, on the basis of traditional small molecular drugs in the treatment of tumors, the introduction of polymer nano-drug-carrying system can give priority to maximizing the cell killing effect and minimizing the systemic side effects. The carrier system and ultrasonic technology have made great progress in improving several drugs, and drugs can selectively interact with tumors. The development of nanotechnology has laid the foundation for the clinical transformation of nano-drugs [9]. siRNA is easy to degrade *in vivo*, which makes drug molecules escape from inclusion bodies and reduces the therapeutic effect. The combination of nucleotide drug siRNA and liposome to prepare nano drug ATU027 targeting PKN3 can reduce the degradation of siRNA *in vivo*, inhibit the expression of protein kinase N3 in vascular endothelium, and then inhibit the spread of metastatic tumor cells [10].

Colloidal nano-system is an indirect targeted therapy for cancer, which requires these anticancer drugs to avoid damaging normal tissues and accumulating in tumors. Compared with free drugs, the cytotoxic concentration of anticancer drugs in tumors is several times higher than that in other parts of the body, so as to get better therapeutic effects [11]. Nanoparticles have special advantages in targeting tumor cells. First, they can interact with tumor cells by using different strategies. Secondly, due to their nano-size, these colloidal systems penetrate into rapidly growing tumor masses and concentrate preferentially, which can serve as drug reservoirs for long-term control of the supply of encapsulated therapeutic compounds to tumors [12]. Nano-drug carriers can effectively increase the half-life of drugs, reduce the side effects of drugs, and alleviate the pain of patients taking drugs for a long time to some extent. Although nano-drugs prepared from chemotherapy drugs, nucleic acid drugs and nano-carriers can be used in clinical tumor treatment, which can reduce the *in-vivo* degradation of drugs and promote the enrichment of drugs in tumor tissues, only about 0.7% of the injection dose enters the tumor focus, and 90% of nano-drugs eventually enter the liver or spleen, which is easy to cause systemic adverse reactions and lead to poor treatment effect [13].

Compared with conventional preparations, nano-size also makes them suitable for intravenous injection, intramuscular and subcutaneous applications, and has lower irritation at the injection site [14]. Targeting includes modifying or designing the molecular weight and size of the system, changing the surface hydrophobicity and surface charge of the system, so as to make it circulate in the blood for a long time and target it to the desired site. Nano-drugs combined with other components in the body can reduce the therapeutic effect of drugs. After nano-drugs enter the body, they will still produce side effects such as skin toxicity [15]. At present, the nano-drugs in transformation still can't achieve the safe and efficient treatment effect of malignant tumors, and it is still urgent

to research and develop new anti-tumor nano-drugs. Nanocarriers can also increase the local drug concentration by wrapping drugs, and achieve the effect of controlled release when combined with target tumor cells.

Chemotherapy has been widely used in tumor treatment, and a large number of anticancer drugs have been used in clinic. These drugs have shown certain curative effects on different tumors and patients bear less trauma and risk [16]. However, because most chemotherapy drugs are administered systemically, the specificity of drugs to tumor tissues is small, and an ultra-high drug dosage is needed when they are administered, so that they can kill cancer cells and inhibit tumor growth, but also have strong toxicity to normal organs in the body, and long-term use will also cause drug resistance [17]. Polymers chemically bound to drugs are usually considered as new chemical entities (NCEs) because of their different pharmacokinetic characteristics [18]. Some small-molecule chemotherapy drugs are easy to be removed in the process of blood circulation, which makes the accumulation of drugs in tumor sites less, leading to poor anticancer effect [19]. The problems of incomplete treatment, great toxic and side effects, lack of tumor specificity, easy recurrence and metastasis are still the main barriers to tumor treatment at present, and it is urgent to explore new treatment strategies to overcome these problems.

3. Application of nano-drug delivery system in tumor treatment

At present, although nano-drug carriers preferentially accumulate in tumor sites due to targeting or receptor-mediated active targeting, the inefficient release of drugs in tumor cells may be an obstacle to reducing drug efficacy. Among different types of environmental stimuli, pH-responsive nanosystems have a wide range of practical application values in drug delivery for cancer treatment. Over the years, people have made some in-depth research on the drug release system stimulated by pH. The drug delivery system is made by using polymers as carriers to connect with drugs or encapsulate anticancer drugs. Because these polymers are generally responsive, the drug release can be controlled, thus treating diseases [20]. At present, the deficiency of available treatment methods stimulates the demand for improvement of treatment technology. Tumor diseases seriously endanger human life and health, and its morbidity and mortality are second only to cardiovascular and cerebrovascular diseases and infectious diseases. Chemotherapy is one of the main methods to treat tumor diseases at present [21]. However, many anticancer drugs used in clinic usually have strong cytotoxicity and lack of specificity, which can kill normal tissue cells as well as tumor cells, so they have great toxic and side effects. Due to the rapid metabolism of cancer cells, insufficient utilization of oxygen and nutrients, and excessive lactic acid produced by ATP hydrolysis, the pH value of tumor sites is always lower than that of normal tissues, ranging from 5.7 to 7.8.

It is difficult for drugs to cross the physiological barrier to reach the tumor site in blood circulation, thus reducing the bioavailability of drugs. The efficiency and side effects of chemotherapy are mainly related to the dosage form, distribution in vivo, toxicity to normal cells and drug resistance of tumor cells [22]. The gradient of pH value has a very important influence on the internalization of drugs and carriers, and the pH of inclusions or lysosomes is about 4.5-6.0 [23]. Therefore, for the controlled release of some hydrophobic anticancer drugs, pH-sensitive drug delivery system has a good application prospect. The surface of nanocarriers can be modified by related ligands, and the specific binding between ligands and high-expression receptors in tumor tissues gives nanocarriers active targeting ability [24]. However, under the passive and active two-stage targeting, nanocarriers can further increase the drug concentration in tumor sites, improve the uptake of tumor cells and improve the anti-tumor effect [25].

Nanodrug based on polymer nanocarriers is a new kind of drug dosage form, which can change the distribution and metabolism of drugs in the body and improve the bioavailability of drugs, so it shows great advantages in the field of tumor treatment. In practical application, temperature and pH change are two important factors, and they are also the most easily available polymers for designing and synthesizing responsive drug carriers [26]. Temperature-responsive segments can carry drugs in the extended state, and form a core-shell-crown structure when they collapse. The stability of the carrier is improved, and the release of drugs in normal tissues is inhibited. The pH-sensitive connection between core and shell can realize the intelligent release of drugs. The ideal polymer nano-drug carrier should have the advantages of low toxicity and good stability, which can protect the biological activity of drugs, change the distribution of drugs in the body, and deliver drugs in the boot direction. The application of nanotechnology in drug delivery is a rapidly developing field, which can not only realize the controlled release of drugs, but also reduce the side effects of drugs and increase the stability of drugs. Now more and more research focuses on developing a drug delivery system with good structural stability, high biological applicability and little toxic and side effects to realize the controlled release of certain drug molecules [27]. Understanding the characteristics of human tumor tissue is very necessary for designing ideal drug carriers. Therefore, it is necessary to introduce the characteristics of tumor tissue properly and make full use of the differences between tumor tissue and normal tissue in order to design and synthesize polymer nano-drug carriers that meet the requirements. Among different types of nanoparticles, magnetic nanoparticles are famous for their great potential in drug delivery. Magnetic liposomes can accumulate in target tumors by applying magnetic orientation, and have been used as drug carriers [28]. In the field of biological applications, such as gene or drug delivery, Fe₃O₄ is considered as an ideal magnetic nanoparticle with promising application prospects due to its unique magnetic properties. At present, magnetic nanoparticles have also been successfully used in the treatment of cancer by magnetic hyperthermia.

4. Conclusion

Tumor is one of the main diseases that endanger human health and threaten human life, and chemotherapy is one of the main methods to treat tumor diseases at present. However, small molecule anti-tumor drugs have great toxic and side effects, which can kill normal tissue cells as well as tumor cells. Nanocarriers can protect drugs from degradation, reduce the renal clearance rate and prolong their half-life in blood, increase the effective concentration of cellular drugs, control the release kinetics of anticancer drugs, and improve the solubility of drugs. Polymer micelle drug carrier assembles drugs and micelles by chemical bonding and physical embedding, which can obtain high drug loading rate and target tumor cells, and achieve better results than drugs themselves. These polymer nano-drug carriers have good biocompatibility, can effectively load anti-tumor drugs and control the release of drugs, and do not release or release a small amount of drugs in normal physiological environment, but release drug molecules quickly and in large quantities when they reach the tumor cell environment, effectively killing tumor cells. Studying the intracellular mechanism of nano-drugs and clarifying the release and killing mechanism of nano-drugs in vivo will help to design and develop nano-drugs better.

References

1. Chen Xi, Zhu Xingyu, Ma Bole, et al. Research progress of nano-targeted carriers based on tumor microenvironment [J]. *China Pharmacy*, 2017, 28(13):6.
2. Yu Zhang, Yin Shaoping, Xu Jianan, et al. Research progress of polymer nano-drug delivery system in tumor microenvironment [J]. *Pharmaceutical Progress*, 2018, 42(5):9.
3. Wan Dong, Xi Yujing, Li Sunfan, et al. Research progress of responsive nano-drug carriers based on tumor microenvironment [J]. *Chemical Industry and Engineering*, 2021, 38(5):8.
4. Wu Qing, Tang Yiyuan, Yu Miao, et al. DNA nanostructure drug delivery system based on tumor microenvironment response [J]. *Progress in Chemistry*, 2020, 32(7):8.
5. Ke S. Targeting tumor microenvironment with nano-drug delivery system [J]. *Journal of China Pharmaceutical University*, 2018, 49(4):392-400.
6. Huang Linzhuo, Cai Pei'e, Yin Dong, Xu Xiaoding. Research progress of tumor microenvironment-responsive nanocarriers for siRNA delivery in vivo [J]. *China Science*, 2020, 050(010):P.1082-1102.
7. Li Chen, Qi Yingqiu, Wang Yazhou, et al. Research progress of polypeptide nano-drug system based on targeted regulation of tumor microenvironment [J]. *Journal of functional polymers*, 2019, 32(5):15.
8. Gu Wenxian. Construction of anti-tumor drugs based on heteroatom-doped mesoporous carbon ball

- nanoenzyme [J]. *Contemporary Chemical Research*, 2021, 000(015):P.35-36.
9. Lv Chengliang, Zhang Fan, Wei Wei, Xie Haiyan. Research progress in constructing nano-drugs based on tumor microenvironment [J]. *Bioprocessing*, 2020, 18(6):7.
 10. Gong Jiazhu, Li Fengyun, Pei Zerong, et al. Design and application of nano-drug delivery system based on tumor microenvironment to enhance anti-tumor therapeutic effect [J]. *China Pharmaceutical Journal*, 2022, 57(20):12.
 11. Tian Ye, Zhang Yang, Wang Xiaoyong, et al. Progress in the application of biomembrane nano-drug delivery system in tumor immunotherapy [J]. *China Pharmacy*, 2020, 031(005):636-640.
 12. Fang Yuxiao, Zhang Na, Liu Yongjun. Research progress of tumor microenvironment responsive nano-drug delivery system in tumor treatment [J]. *Chemistry of Life*, 2020, 40(10):7.
 13. Xu Xiaoyi, Qi Xiaole, Wu Zhenghong. Research progress of tumor microenvironment responsive nanogel drug delivery system [J]. *Pharmaceutical Progress*, 2020, 44(1):8.
 14. He Xinyu, Du Xiaojiao, Wang Jun. Nanodrug research based on tumor microenvironment regulation [J]. *China Basic Science*, 2019, 21(6):6.
 15. Xu Xiuli, Ma Jinzhu. Chemical resistance of breast cancer stem cells and application of nanocarriers [J]. *Practical Medicine and Clinical*, 2019, 22(2):7.
 16. Wu Suying, Nie Guangjun, Li Suping. Research progress of intelligent nano-drugs for regulating tumor vascular microenvironment [J]. *China Materials Progress*, 2022, 41(11):921-929.
 17. Zeng Chenxing, Li Rong, Zhang Pei, et al. Study on tumor microenvironment sensitive nano drug delivery system [J]. *Materials Science*, 2019, 9(3):7.
 18. Tang Zhaomin, Zhao Jianqing, Fan Lixia, et al. Constructing nanoparticle strategy to overcome the limitations of tumor microenvironment delivery [J]. *Chinese Sci-tech Journal Database (full-text version) Medicine and Health*, 2021(5):3.
 19. Lu An, Wang Xiangyu, Yan Yi, et al. Research progress of tumor microenvironment responsive RNA drug delivery system [J]. *Journal of Pharmacy*, 2022, 57(1):14.
 20. Wu Shiyang, Chang Shuang, Chen Qing, et al. Research progress of targeted drug delivery system for tumor microenvironment [J]. *Acta Pharmacy*, 2022(006):057.
 21. Jing Xiaodong, Sun Ying, Yu Bing, et al. Design of tumor microenvironment response drug delivery system [J]. *Progress in Chemistry*, 2021, 33(6):16.
 22. Dai Xianhua, Zhang Tingying, Huang Yong, et al. Research progress of anticancer drugs based on nanocarriers [J]. *Oncology*, 2019, 9(6):5.
 23. Lu Chengliang, Zhang Fan, Wei Wei, et al. Research progress in constructing nano-drugs based on tumor microenvironment [J]. *Bioprocessing*, 2020(006):018.
 24. Yang Jianmiao, Xu Donghang, Li Fanzhu. Design and new research direction of drug co-delivery nanocarriers to overcome multidrug resistance in tumors [J]. *chinese journal of modern applied pharmacy*, 2020, 37(6):5.
 25. Liu Yanhong, Chen Liqing, Zhang Xintong, et al. Research progress of tumor immune regulation strategies based on nano-drug delivery carriers [J]. *Journal of China Pharmaceutical University*, 2023, 54(1):10.
 26. Yang L, Jlab C, Zeb E, et al. Tumor microenvironment-activated self-recognizing nanodrug through directly tailored assembly of small-molecules for targeted synergistic chemotherapy[J]. *Journal of Controlled Release*, 2020, 321:222-235.
 27. Yang G, Xu L, Chao Y, et al. Hollow MnO₂ as a tumor-microenvironment-responsive biodegradable nano-platform for combination therapy favoring antitumor immune responses[J]. *Nature Communications*, 2017, 8(1):902.
 28. Zhang P, Wang J, Chen H, et al. Tumor Microenvironment-Responsive Ultrasmall Nanodrug Generators with Enhanced Tumor Delivery and Penetration[J]. *Journal of the American Chemical Society*, 2018, 140(44):14980-14989.
 29. Zhang, ZhiqiangYu, MiaoAn, TongYang, JunZou, MeijuanZhai, YingleiSun, WeiCheng, Gang. Tumor Microenvironment Stimuli-Responsive Polymeric Prodrug Micelles for Improved Cancer Therapy[J]. *Pharmaceutical research*, 2020, 37(1).