Research Status of Carrier-free Nano Antitumor Drugs: The Mechanism of Action and Future Trends of Four Carrier-free Nanomedicines

Dongjun Zuo[a]
Northwest University, Xi'an, Shanxi, China

Keywords: Anticancer Drugs, Nano Anticancer Drugs, Self-Assembled Systems.

Abstract: At present, there are four mainstream carrier-free nano anti-tumor drugs. The prodrug self-delivery system uses self-assembled targeted drugs constructed with small groups and anti-cancer drugs. A pure drug delivery system that uses two or more pure drugs to construct self-assembled drug-drug conjugates. Based on the self-delivery system of therapeutic carriers, a self-assembled anticancer drug is constructed using carriers with auxiliary therapeutic effects. Based on the self-delivery system of non-toxic agents, non-toxic groups are used to assist anticancer drugs to function. Carrier-free nano anticancer drugs solve the side effects of traditional nano anticancer drugs that nanocarriers cannot be metabolized by the body, and have broad research prospects.

1 INTRODUCTION

Cancer is the second most harmful disease to human health. The annual death toll from cancer is second only to cardiovascular and cerebrovascular diseases. There are more than 14 million new cancer cases worldwide each year. At present, humans have made very impressive research results in cancer. In fact, all cancers can be cured if they can be detected in time and treated correctly. The current mainstream treatment methods include: (1) surgical resection; (2) use of chemotherapy or other cancer-specific drugs; (3) use of radiotherapy; (4) immunotherapy; (5) gene therapy; (6) small molecule targets to medication (Roy 2016). Chemotherapy is currently a widely used treatment method. However, chemotherapy drugs act on the cells of the whole body and cause serious side effects. Therefore, precise and efficient drug delivery systems must be developed. The drug delivery system must solve the following problems: (1) PK parameters, especially half-life, biodistribution and maximum drug concentration; (2) toxic and side effects; (3) target fixation at the location of the lesion (Vargason 2021).

2 THE DEVELOPMENT OF NANO ANTI-TUMOR DRUGS

With the development of nanotechnology, huge innovations have taken place in drug delivery systems. Researchers have developed numerous nano-carrier drug delivery systems based on nanotechnology; liposomes; nanopolymers; dendrimers; micelles, etc. They have different molecular targets, sizes and surface properties. Nanomaterials as carriers have many advantages: (1) increase water solubility and increase the concentration of drugs in the blood; (2) accurately target organs, tissues or cells to prevent drug toxicity from accumulating in other organs such as the liver; (3) can Combine imaging technology to monitor drug effects in real time. The use of nanomaterials as drug carriers is undoubtedly an effective solution to the serious side effects of traditional chemotherapeutic macromolecular drugs (Li 2017).

[a] https://orcid.org/0000-0002-6094-8851

Zuo, D.
Research Status of Carrier-free Nano Antitumor Drugs: The Mechanism of Action and Future Trends of Four Carrier-free Nanomedicines.
DOI: 10.5220/0011214100003443
In *Proceedings of the 4th International Conference on Biomedical Engineering and Bioinformatics (ICBEB 2022)*, pages 434-439
ISBN: 978-989-758-595-1

3 ADVANTAGES AND CONSTRUCTION OF CARRIER-FREE NANO-ANTITUMOR DRUGS

However, the shortcomings of nano-carrier drugs are also obvious and inevitable. Their drug loading is low, and most of the carrier systems cannot be metabolized by the body, prone to inflammation at the lesion site, complex synthesis operations, and high cost. Therefore, some researchers have proposed the concept of carrier-free nano anti-tumor drugs. "Carrier-free nanomedicine" mainly refers to a system that does not use additional carriers during the administration process. Some researchers also named the carrier-free nanomedicine "carrier-free drug delivery system". According to the different construction methods, carrier-free nanomedicine is divided into several types: prodrug self-delivery, pure drug self-delivery, self-delivery based on therapeutic carrier, self-delivery system based on non-toxic agent (Zhang 2018). Carrier-free pure nanospheres (PND) composed of pure medicinal active molecules are currently considered to be the field with the most research potential. Nanoparticles are composed of two or more drugs, and the treatment efficiency can be doubled (Zhao 2015). This article summarizes, analyzes and summarizes several most significant carrier-free nano anti-tumor drugs in the research field of carrier-free nano anti-tumor drugs.

3.1 Prodrug Self-delivery System

The prodrug self-delivery system, that is, the active drug and the small group are connected through a cleavable bond that is responsive to the internal environment of the tumor, and self-assembled to form a nanostructure to achieve a self-delivery modality. Based on the assembly principle of carrier-free nanomedicine, that is, the use of amphiphilic hydrophobic drugs to assemble into drug-drug conjugates in water (Wang 2012). The construction principle of this drug-drug conjugate is generally to use the hydrophobicity or hydrophilicity of the precursor for synthesis, and the formed prodrug self-delivery system can protect the drug from rapid clearance and inhibit premature burst release. However, the conditions of prodrug design and self-assembly, such as pH, concentration, ionic strength, and kinetics, also affect the eventual spontaneous delivery. Small molecule activity modification drugs can be used to form amphiphilic self-assembled drugs and complete drug self-delivery. Because traditional nano-carrier drugs use high-molecular-weight nano-carriers, nano-carrier drugs usually have very low drug loading levels (Chen 2015). In the prodrug delivery system, the drug is added in a quantitative manner, so it has a higher drug loading. A key feature of nanomedicine is to release active drugs from the self-delivery system and induce apoptosis of cancer cells after intracellular delivery. Since cancer cells have physical and chemical environments different from normal cells, such as pH, redox potential, and special enzymes and proteins, building sensitive links such as acid, enzyme and redox sensitive bonds can effectively improve the success rate of drug release. Since many anti-cancer drugs are hydrophobic and do not have the amphipathic characteristics for self-assembly (Sun 2014). Therefore, the hydrophilic group is indispensable for the construction of amphiphilic prodrugs. Due to its excellent biodegradability, biological activity, adjustable amphiphilicity and sophisticated synthetic methods, short peptides have become ideal candidates for the preparation of amphiphilic prodrugs. It is worth noting that prodrugs composed of short peptides and active drugs have unique advantages in terms of self-assembly potential and drug-carrying ability. At present, some researchers have designed a method to bind β-sheet peptide to anti-cancer camptothecin (CPT), which is to self-assemble this amphiphilic prodrug into a nanostructure with a drug loading capacity of up to 38%. The formation of nanostructures can simultaneously protect the hydrolyzable CPT and the biodegradable linker from the external environment. After reaching the tumor-related sites, the nanomedicine breaks the reducible dithiobutyrate linkage by hydrolysis to release CPT and induce cancer cell apoptosis. Therefore, in vitro toxicity studies have found that reduction-sensitive nanomedicine exhibits greater cytotoxicity than insensitive maleimide-linked nanomedicine (Cheetham 2013).

3.2 Pure Drug Self-delivery System

The pure drug self-delivery system is composed of pure drug self-polymerizing nano-medicine and carries out intracellular transportation. The self-delivery system is established based on a single drug or multiple drugs, and is a true carrier-free system, which is finally prepared into a nano-level drug in an aqueous solution. According to the molecular self-assembly/co-precipitation process, drugs can

become nano-objects with specific sizes and shapes through self-aggregation. If all the inert excipients are removed, the pure drug can form a nanostructure through self-aggregation, which can reach the optimal drug loading of 100%, which enhances the anti-cancer activity of the drug and avoids the relative toxicity and immunogenicity of the carrier. In order to achieve this goal, a variety of free anti-cancer drugs have been used to construct pure nano-drugs, and great progress has been made in this field. Some researchers have connected water-soluble irinotecan (Ir) and water-insoluble chlorambucil (Cb) through ester bonds that are easily hydrolyzed and broken under acidic conditions, and designed an amphiphilic drug-drug Conjugate (Huang 2014). The study found that, compared with the free drug alone, the Ir-Cb nanoparticles formed by the self-assembly method of the Ir-Cb copolymer showed a longer blood circulation half-life and higher tumor accumulation. After self-delivery in cells, the ester bonds of Ir-Cb nanoparticles will be hydrolyzed and broken in the acidic environment of tumor cells, free Ir and Cb drugs are easily released from Ir-Cb nanoparticles, thus exerting a synergistic cell toxicity.

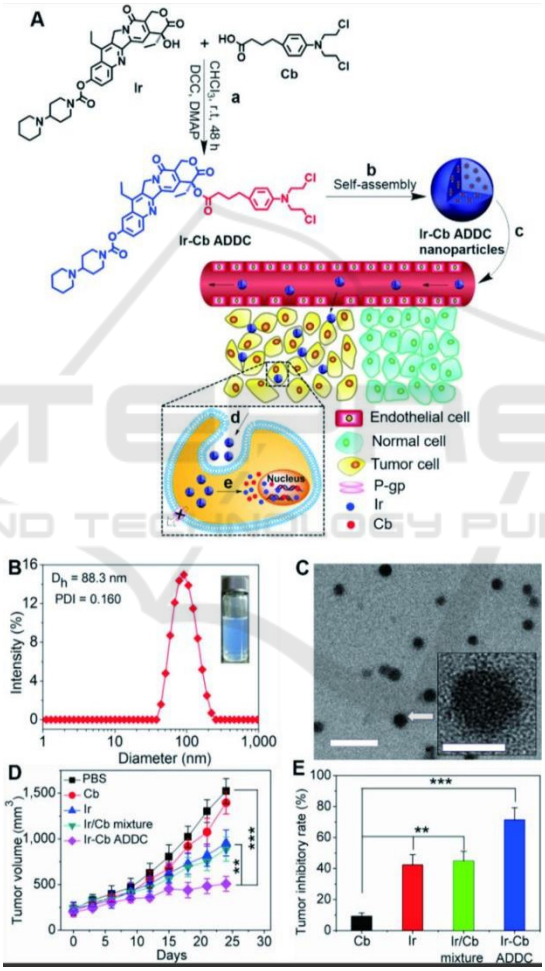

Figure 1: Based on amphiphilic drug-drug conjugated IR-CB nanoparticles and their antitumor activity (Huang 2014).

3.3 Self-delivery System based on Therapeutic Carrier

The self-delivery system based on the therapeutic carrier is that both the carrier and the loaded drug can be used as the therapeutic agent of the combination therapy. The use of carrier-free anticancer drugs is to obtain better therapeutic effects. The idea of the above-mentioned drugs is to improve the efficacy by reducing the ratio of the carrier to the drug. Or another way of thinking can be used, using a therapeutic vector. Such as the self-assembled micellar nanocomposite of epigallocatechin gallate (EGCG) derivatives and

protein drugs (Chung 2014). Among them, EGCG derivative carriers can also show anti-cancer effects. EGCG derivatives and anti-cancer proteins produce stable micellar nanocomplexes through sequential self-assembly, which show better anti-cancer effects than free protein drugs in in vitro and in vivo experiments, realizing the development of EGCG derivative carriers and drugs Combination therapy. DOX and EGCG can reach the tumor site at the same time for treatment of resistance to liver cancer (Liang 2010). Non-toxic doses of EGCG can increase the sensitivity of chemotherapy-resistant liver cancer cells to DOX by inhibiting the activity of the P-glycoprotein (P-gp) efflux pump, thereby enhancing the DOX-induced killing effect of liver cancer cells. In the past few decades, some compounds containing trace elements have been proposed as therapeutic agents and therapeutic nanocarriers, because they have a significant ability to enhance the immune response of cancer cells and produce anti-cancer metabolites, which can effectively Interfere with cell metabolism and induce cell apoptosis (Liu 2015). An example of this compound in cancer treatment is a selenium-containing reagent that regulates ROS in vivo to induce apoptosis. Self-assembled selenium-containing nanostructures can be used as self-delivery therapeutics (Liu 2013). A research team designed and synthesized an amphiphilic hyperbranched selenium-containing polymer that self-assembles into nanomicelles and is automatically delivered to tumor tissues through the EPR effect. After triggering the exclusive oxidizing microenvironment in cancer cells, the nanomicelles decompose, and the released selenium compounds can effectively induce cancer cell apoptosis. They further prepared a hyperbranched selenide macromolecular anticancer drug, which can not only achieve self-delivery based on its self-assembled nanomicelles, but also can be used as a carrier encapsulating hydrophobic DOX for combination therapy. In order to reduce the cytotoxicity of selenium-containing polymer anticancer drugs to normal cells, the researchers introduced PEGylated polymers to stabilize macromolecular anticancer drugs and prevent them from being attacked by proteins in the blood (Li 2015).

3.4 Self-delivery System based on Non-toxic Agent

There are also some multifunctional local delivery systems based on the participation of non-cytotoxic drugs, which can achieve controlled aggregation around tumors to induce cell apoptosis. This system is called a non-toxic agent-based self-delivery system. The anti-cancer effect of the self-delivery system based on non-toxic agents is dependent on non-toxic agents rather than conventional chemotherapeutic drugs. Conventional chemotherapeutic drugs, such as DOX and CPT, inhibit the growth of cancer cells by embedding in cell DNA and inducing cell death. The role of the non-toxic unit is to show anti-cancer active cells through self-aggregation and cause cytotoxicity. Recently, a research team reported a matrix metalloproteinase-7 (MMP-7) response precursor, which transforms into a gel before being taken up by cancer cells, and further enters the cells to form a hydrogel (Tanaka 2016). The formation of the hydrogel causes the pressure inside the cell to increase, thus initiating cell death. Some researchers have found that due to the dephosphorylation of D-peptide derivatives by alkaline phosphatase, the hydrogel/nanomesh will gather in the gaps of cancer cells to form a self-assembled structure, and block communication and mass exchange between cells (Zhou 2016). Way to remove cancer cells. In addition to low molecular weight precursors as therapeutic agents, the use of non-cytotoxic macromolecules has been extended to another paradigm for cancer treatment. The mechanism of macromolecular therapeutics in inducing cell apoptosis is the special biological recognition between cell surface receptors and natural or synthetic binding motifs. Based on this theoretical basis, a research team has developed a new therapeutic platform mediated by extracellular hybridization of two complementary nanoconjugates to induce apoptosis in B-cell lymphoma cells, which is further cross-linked B-cell lymphoma overexpresses the CD20 antigen (Chu 2014). In summary, these self-delivery systems show great advantages for cancer treatment, but have less toxic and side effects on healthy cells/tissues. In addition, since the efflux effect of the efflux pump in drug-resistant cells is one of the main mechanisms for the emergence of MDR, and self-assembled nanomedicine can bypass the efflux pump of cancer cells due to its size effect, so nanomedicine is the same for drug-resistant cancer cells. Can produce higher curative effect, Due to the unprecedented drug loading capacity, minimization of systemic toxicity, flexible preparation strategy and the nanometer size of passive targeted therapy, the scientific research of carrier-free nanomedicine has made great progress in recent years (Kunjachan 2013). However, we still know very little about

carrier-free nanomedicine. At present, many reports point out that the physical and chemical properties of nanomaterials, such as size, shape, surface properties, are crucial in regulating their cellular uptake and transport behavior in the body, and may affect the overall cancer treatment effect (Williford 2015).

4 PREPARATION OF DOX NANOPARTICLES

First dissolve DOX in DMSO, then add 1 mL of triethylamine to 10 mL of 1 mg/mL DOX.HCl/DMSO solution under moderate agitation at 25°C, and react for about 4 hours After stopping, the hydrophilic DOX.HCI is converted into hydrophobic DOX. Three preparation methods of DOX nanoparticles: (1) DOX 50 (particle size is about 50 nm): Drop a 3mg/mL DOX/DMSO solution into 5ml petroleum ether and stir for 5 minutes. (2) DOX100 (particle size about 100 nm): Drop the DOX/DMSO solution with a concentration of 3 mg/mL into 5 ml ultrapure water and stir for 5 minutes. (3) Dox 180 (particle size is about 180 nm): Drop 1 mg/mL DOX/DMSO solution into 5ml ultrapure water, and stir for five minutes.

5 CONCLUSION

Carrier-free nanomedicine solves the toxicity problem of nano-carrier drug carrier system. According to its construction principle, that is, to complete the self-assembly process through hydrophobic and hydrophilic groups, various construction ideas can be developed. It is worth mentioning that carrier-free nanomedicine provides different application ideas for some poorly water-soluble anticancer drugs. By constructing a carrier-free nanomedicine system, its water solubility can be greatly improved. The current frontier research on carrier-free nano-oncology drugs believes that pure drug carrier-free nano-oncology drugs have the most research potential and have very broad prospects.

REFERENCES

Cheetham, A. G.; Zhang, P.; Lin, Y. et al. (2013). Supramolecular nanostructures formed by anticancer drug assembly. Journal of the American Chemical Society, 135 (8), 2907-2910.

Chen, W.-H., Luo, G.-F., Lei, Q., et al. (2015). MMP-2 responsive polymeric micelles for cancer-targeted intracellular drug delivery. Chemical Communications, 51 (3), 465-468.

Chu, T.-W., Yang, J., Zhang, R., et al. (2014). Cell surface self-assembly of hybrid nanoconjugates via oligonucleotide hybridization induces apoptosis. ACS Nano, 8 (1), 719-730.

Chung, J. E., Tan, S., Gao, S. J., et al. (2014). Self-assembled micellar nanocomplexes comprising green tea catechin derivatives and protein drugs for cancer therapy. Nature Nanotechnology, 9 (11), 907-912.

Huang, P., Wang, D., Su, Y., et al. (2014). Combination of small molecule prodrug and nanodrug delivery: amphiphilic drug-drug conjugate for cancer therapy. Journal of the American Chemical Society , 136 (33), 11748-11756.

Huang P, Wang D, Su Y, et al. (2014). Combination of small molecule prodrug and nanodrug delivery: amphiphilic drug-drug conjugate for cancer therapy. J Am Chem Soc. ;136(33):11748-56. doi: 10.1021/ja505212y. Epub 2014 Aug 7. PMID: 25078892.

Kunjachan, S., Rychlik, B., Storm, G., et al. (2013). Multidrug resistance: physiological principles and nanomedical solutions. Advanced Drug Delivery Reviews, 65 (13-14), 1852-1865.

Li, C., Huang, W., Zhou, L., et al. (2015). PEGylated poly(diselenide-phosphate) nanogel as efficient self-delivery nanomedicine for cancer therapy. Polymer Chemistry, 6 (36), 6498-6508.

Li Z, Tan S, Li S, et al. (2017). Cancer drug delivery in the nano era: An overview and perspectives (Review). Oncol Rep. 38(2):611-624. doi:10.3892/or.2017.5718.

Liang, G., Tang, A., Lin, X., et al. (2010). Green tea catechins augment the antitumor activity of doxorubicin in an in vivomouse model for chemoresistant liver cancer. International Journal of Oncology, 37 (1), 111-123. Sredni, B., Immunomodulating tellurium compounds as anti-cancer agents. Seminars in Cancer Biology 2012, 22 (1), 60-69.

Liu, J., Pang, Y., Zhu, Z., et al. (2013). Therapeutic nanocarriers with hydrogen peroxide-triggered drug release for cancer treatment. Biomacromolecules, 14 (5), 1627-1636.

Liu, J., Huang, W., Pang, Y., et al. (2015). Hyperbranched polyphosphates: synthesis, functionalization and biomedical applications. Chemical Society Reviews, 44 (12), 3942-3953.

Roy PS, Saikia BJ. (2016). Cancer and cure: A critical analysis. Indian J Cancer. Jul-Sep;53(3):441-442. doi: 10.4103/0019-509X.200658. PMID: 28244479.

Sun, T., Zhang, Y. S., Pang, B., et al. (2014). Engineered nanoparticles for drug delivery in cancer therapy. Angewandte Chemie-International Edition, 53 (46), 12320-12364.

Tanaka, A., Fukuoka, Y., Morimoto, Y., et al. (2016) Cancer cell death induced by the intracellular self-

assembly of an enzyme-responsive supramolecular gelator. Journal of the American Chemical.

Vargason AM, Anselmo AC, Mitragotri S. (2021). The evolution of commercial drug delivery technologies. Nat Biomed Eng. doi: 10.1038/s41551-021-00698-w. Epub ahead of print. PMID: 33795852.

Wang, C., Wang, Z., Zhang, X., (2012). Amphiphilic building blocks for self-assembly: from amphiphiles to supra-amphiphiles. Accounts of Chemical Research, 45 (4), 608-618.

Williford, J.-M., Santos, J. L., Shyam, R., et al. (2015). Shape control in engineering of polymeric nanoparticles for therapeutic delivery. Biomaterials Science, 3 (7), 894-907.

Zhang, N., Li, M., Sun, X., et al. (2018). NIR-responsive cancer cytomembrane-cloaked carrier-free nanosystems for highly efficient and self-targeted tumor drug delivery. Biomaterials, 159, 25-36.

Zhao Y, Chen F, Pan Y, et al. (2015). Nanodrug Formed by Coassembly of Dual Anticancer Drugs to Inhibit Cancer Cell Drug Resistance. ACS Appl Mater Interfaces. 7(34):19295-305. doi: 10.1021/acsami.5b05347. Epub 2015 Aug 19. PMID: 26270258; PMCID: PMC4712650.

Zhou, J., Du, X., Yamagata, N., et al. (2016). Enzyme-instructed self-assembly of small D-peptides as a multiple-step process for selectively killing cancer cells. Journal of the American Chemical Society, 138 (11), 3813-3823.