Proceedings of the 2nd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/17/20240654

# An analysis of the application prospects of nano-targeted drug delivery systems in cancer therapy

**Yimeng Gao**

Shenyang Pharmaceutical University, Benxi City, Liaoning Province, China

satanssmile@tzc.edu.cn

**Abstract.** Cancer is an important cause of human death in the world today. Traditional cancer treatment methods have many defects, such as high damage to normal cells and the inability to efficiently remove tumor cells. In recent years, due to the EPR effect of nano-targeted drugs can stay in the tumor site for a long time, as well as their high specificity to cancer cells and better therapeutic ability than traditional drugs, more and more scholars believe that nano-targeted drug delivery system is a very promising research direction for cancer treatment. This article focuses on recent research in this field, focuses on targeting the tumor itself and various pathways by which T cells kill tumor cells, including promoting apoptosis, reversing polarization TAMs, Inducing iron death in cancer cells, Remodeling the tumor microenvironment and reprogramming metabolism. Through analysis of recent research, it was found that these methods have their own advantages and can be combined to improve the therapeutic effect of drugs. However, the more basic mechanism is still a blank, and more exploration is needed.

**Keywords:** Nanomedicine, Targeted Drug Delivery Systems, Cancer Therapy.

## 1. Introduction

Targeting drug delivery system (TDDS) is a system that can selectively concentrate drugs in target tissues, target organs, target cells or intracellular structures. Compared with many traditional drug delivery systems, targeting drug delivery system can make drugs have higher specificity, utilization rate and bioavailability, so targeting drug delivery technology is a hot spot in drug dosage form design in recent years. Among them, nano-targeted drug delivery system has attracted the attention of many scientific workers because of its unique properties. Compared with traditional drug carrier materials, nanomaterials have some special physical and chemical properties, such as surface effect, small size effect and macroscopic quantum tunneling effect [1], which makes nano-carriers have unique advantages, including better water solubility, targeting, protecting drug stability and facilitating combined medication. At present, nano-carrier targeted preparations have been used in many fields that need accurate delivery, including agronomy (mainly used to make highly targeted pesticides), neurology, medicine, and pharmacy, among which nano-targeted preparations have received extra attention in the treatment of cancer.

According to WHO statistics in 2019, cancer is the first or second leading cause of death in 112 countries and the third or fourth leading cause of death in 23 countries [2], which reveals that cancer has become a major factor endangering human health in today's world, Traditional treatments for cancer include surgical removal, chemotherapy and radiation therapy, although there are many measures to

DOI: 10.54254/2753-8818/17/20240654

fight against cancer, all of these treatments cannot effectively treat cancer. Thus, a complete treatment of cancer has always been a medical problem. There are many defects in traditional cancer treatment. Surgical resection is not only difficult to play an effective role in the early stage of cancer, but also likely to aggravate the condition of patients in the middle stage of cancer. Although chemotherapy and radiotherapy can kill most cancerous cells, these measures will also harm normal cells in the human body because of their lack of selectivity.

Under the action of "high permeability and long retention effect", nano drug-loaded targeting system is expected to become a cancer treatment method for accurately killing cancer cells. Its principle is that tumor cells that keep dividing rapidly need considerable blood and oxygen supply, so the tumor will secrete growth factors (mainly growth factors related to tumor angiogenesis). When the tumor grows continuously and reaches the size of 150-200 microns, In order to provide enough "nutrients" for tumor tissue, the newly generated tumor blood vessels undergo great changes in structure and morphology (the gap between endothelial cells is enlarged, the smooth muscle layer of the blood vessel wall is lacking, and the function of angiotensin receptor is lacking). These changes enable many macromolecules to pass through the blood vessel wall conveniently. In addition, because lymphoid tissue does not exist in tumor tissue, the blocked lymphatic reflux cannot take away these macromolecules, so those drug molecules are constantly enriched in the tumor. This phenomenon is called the "high permeability and long retention effect" (EPR) of solid tumors. The EPR effect is crucial for introducing liposomes and nanomedicine into tumor tissues [3].

Nowadays, the nano-drug-carrying system used for cancer treatment is mainly to make all kinds of anticancer drugs into various nano-preparations (including nanoparticles, nanoliposomes, nano micelles, nano-suspensions, etc.) in a special way, so as to achieve the purpose of eliminating cancer cells through various mechanisms such as blocking the pathway of cancer cell generation and division or inducing cancer cell death, and inducing T cells to have an immune response to kill cancer cells. Although nano-drug delivery system has many unique advantages, there are still some difficult problems to be solved because the current exploration in this field is still relatively shallow. For example, whether the fragments or remaining carriers generated after the decomposition of nanomedicine will affect the human blood circulation system, and how to metabolize the carriers safely and effectively. In this paper, the mechanisms of novel nano-targeted drug delivery systems for cancer treatment in the last four years are summarized, the advantages and disadvantages of these mechanisms are analyzed, and the development prospects of nano-targeted drug delivery systems are prospected. It is hoped that the information summarized in this paper can provide new ideas or references for follow-up research in this field.

## 2. Mechanism of treating tumor with nano drug delivery system

### *2.1. Promoting apoptosis*

Apoptosis means that, in order to keep the intracellular environment relatively stable, some specific genes will control the cells to die autonomously. So apoptosis is also called programmed cell death. This is very different from necrosis since it is closely related to the activation, expression and regulation of a series of genes, and it has become a very effective and promising target for designing cancer drugs.

At present, many chemical drugs for the treatment of cancer exert cytotoxic effects by promoting tumor cell apoptosis and finally eliminating tumors. Compared with other drug design methods, this mechanism is very direct. Finding a target in the reaction pathway of tumor cells' reproduction and growth metabolism can greatly reduce the threat of cancer cell proliferation to cancer treatment from the root. Some ubiquitous ways to promote apoptosis include: inducing the mutation of genes related to apoptosis by physical, chemical and biological means, directly modifying genes by gene editing means, hindering the synthesis pathway of DNA or RNA in cells, and promoting mitochondrion division and autophagy in cells as well. Take 5- fluorouracil as an example, this medicine can promote the death of tumor cells by inhibiting the synthesis of DNA and RNA in tumor cells, which belong to the mechanism of hindering DNA and RNA synthesis pathway. However, it is worth mentioning that the traditional

DOI: 10.54254/2753-8818/17/20240654

chemical drugs with the mechanism of promoting tumor cells are also very destructive to normal cells and will also cause great harm to liver cells [4]. Therefore, the advantages of high accuracy of nano-targeted drug delivery systems can be fully embodied in drugs using this mechanism.

Abscisic acid(ABA) is a drug that has been used to treat cancer in the last century. Liu and other people used hyaluronic acid (HA) and adipate diacyl (ADH) to synthesize HA-ADH, and then prepared HA-ABA nanoparticles with ABA by phase inversion and ultrasound [5]. After that, human esophageal cancer cell KYSE-30/70 was cultured in vitro for drug in vitro tests, and HA-ABA nanoparticles and ABA monomers were compared. After cycle detection, it was found that HA-ABA could stop the growth cycle of esophageal cancer cells in the G2 and M phases. western-blot experiments showed that HA-ABA nanoparticles could significantly down-regulate the expression level of P62 protein in tumor cells, increase the expression of Beclin1 and C3B, and increase the ratio of apoptotic proteins Bax/Bcl-2 and Bad/Bcl-2. After microscopic examination, the following results were obtained: HA has no effect on the growth of KYSE-30 and KYSE-70 cells, ABA monomer has the property of inhibiting the vitality of cancer cells, and HA-ABA nanoparticles can drastically reduce the survival number of experimental tumor cells, with the best effect among the three. Therefore, compared with the ABA monomer, the HA-ABA nano-drug-loaded targeted delivery system modified by using HA as nano-drug-loaded structure can greatly improve the probability of promoting apoptosis of cancer cells.

### *2.2. Reversing polarization TAMs*

Macrophages are white blood cells (WBC) derived from monocytes, which are induced to differentiate into tumor-associated macrophages (TAM) in the tumor microenvironment. TAMs are infiltrating cells in tumor tissues. It is not only the core hub of immunosuppression and cytokine cross-linking network but also plays an extremely important role in the process of tumor immune escape. According to the difference between functions and phenotypes, TAMs can be divided into two categories: classical-activated macrophages (M1 type) and alternative-activated macrophages (M2 type) [6]. Among them, M1 TAMs have anti-tumor functions, which can secrete tumor necrosis factor-α (INF-α), interleukin-12 (IL-12) and some other substances that inhibit tumor growth. On the contrary, M2-type TAMs can promote tumor growth by inhibiting the function of CD8+T cells. TAMs exist in every stage of tumor growth, so many new studies take TAM as the target of tumor treatment. According to the above basic principles, there are many kinds of treatments for TAMs, including inhibiting TAMs recruitment, depolarizing TAMs, and enhancing TAMs phagocytosis. By targeting nanotechnology to carry drugs to regulate these mechanisms related to TAMs, the adverse reactions caused by drugs can be greatly reduced and better clinical effects can be achieved [7].

Compared with the two methods of recruiting TAMs and promoting TAMs depletion, polarization affecting TAMs has greater advantages since it has fewer negative effects than the above two methods. Transforming M2-type TAMs that can promote tumor growth into M1-type TAMs that can inhibit tumor growth can not only reduce the growth rate of tumor cells but also effectively kill tumor cells and restore the original defense function of macrophages, which is a promising drug research and development direction. In recent years, there have been many studies on reverse-polarized M2 TAMs for the treatment of cancer. For example, MET (methionine) has been found to activate the protein kinase/NF-κB signal pathway through adenosine, thus effectively promoting the process of depolarization and inhibiting tumor growth and metastasis [8]. In this paper, three representative methods are analyzed, and the feasibility of these methods is discussed on the basis of existing studies.

*2.2.1. Selicrilumab.* One method that can stimulate the reverse polarization of M2-type TAMs to form M1-type TAMs, which have been put into phase I clinical trials of various solid tumors, is to use Selicrilumab, a monoclonal antibody of CD40. In addition, some small molecule inhibitors can also realize the transformation of macrophages from M2 type to M1 type by reprogramming. For example, the histone deacetylation inhibitor TMP195 is a small molecule inhibitor that can promote the reverse polarization process. This inhibitor can induce genetic characteristics that change their appearance, and

DOI: 10.54254/2753-8818/17/20240654

induce their accumulation in the microenvironment of breast tumors and improve their phagocytic activity [9].

*2.2.2. Fe-MOF.* Sun et al. used Fe-MOF ((Iron-based metal-organic framework, a nano-drug carrier with high drug loading and good biocompatibility) to couple this type of carrier (Fe-MOF) with M2pep by click chemistry, and carried Dic to synthesize Dic@M2pep-Fe-MOF [10]. After detecting the indexes from M2-type TAMs and M1-type TAMs by RT-PCR, Dic@M2pep-Fe-MOF was found. Through in vivo experiments, these researchers found that Dic@M2pep-Fe-MOF has a high targeting line for H22 tumor-bearing mice. After using this metal-organic framework to reverse polarize M2-type TAMs to form M1-type TAMs, it can obviously slow down the growth rate of tumor cells, prolong the survival time of mice, and has no obvious toxic and side effects on organisms, so it is a good nano-drug material.

*2.2.3. miR155.* Gao et al. used miR155 as a cross-linking agent to form nano-scale nucleic acid hydrogel with DNA, then wrapped the nano-hydrogel with a layer of red cell membrane, and finally modified M2pep peptide and HA2 peptide on the surface of red cell membrane [11]. This technology makes miR155 not easy to degrade by nuclease, and can effectively prolong its circulation time in the human body. When this hydrogel enters the cytoplasm, miR155 will be released from the nanogel under the action of ribonuclease H, and the M2-type TAMs will be remolded into M1-type TAMs. The experiments in mice show that the nano-scale water coagulation can remold the microenvironment of tumor cells and effectively inhibit the growth of tumor cells. This is a valuable research direction because the nano-gel technology used by Gao et al. not only reduces the growth rate of tumor cells through reverse polarization but also reprogrammes the microenvironment of tumor cells, which is closely related to drug resistance and immune evasion of tumor cells. Reprogramming the microenvironment of tumor cells can appropriately improve the drug-targeting ability as well as complement the reverse polarization.

The author believes that the use of Fe-MOF will have a better prospect in clinical practice, because this carrier also has the effect of inhibiting the iron efflux of cells and leading to ferroptosis of cancer cells (the mechanism will be described in the next subsection), so the use of this method should have a better effect on cancer treatment.

### *2.3. Inducing iron death in cancer cells*

Iron death refers to the inactivation of glutathione peroxide 4(GPX4), a lipid repair enzyme, under the direct or indirect action of some inducers, which eventually leads to the blocking of the antioxidant defense of cells. This phenomenon leads to the accumulation of lipid peroxide (LPO) produced by iron metabolism, which can not be consumed in cells. The accumulation of LPO damages the cell structure to a certain extent, and finally leads to cell iron death.

Tumor immunosuppression microenvironment is the main reason for the failure of many immune preparations in vivo. The micro-tumor environment of gastric cancer can even promote drug resistance [12,13]. Relieving immunosuppression can effectively improve the therapeutic results of immune preparations on tumors. Activating the iron death of cancer cells is helpful in promoting immunotherapy.

Among all kinds of nano-materials, inorganic nano-materials have unique advantages in regulating the intracellular iron death signal pathway to induce iron death in tumor cells because of their immunomodulatory characteristics and unique chemical catalysis. Therefore, there are many studies on the topic of inducing iron death in tumor cells using inorganic materials as nano-drug carriers. Fan et al. designed and manufactured a nano-drug: Tf-DHA-ASO-MnO2 based on MnO2-NSS. TF-DHA-ASO-MnO2 nano-drug can promote iron death in cells through the synergistic effect of GSH depletion, ROS production and GPX4 down-regulation, and it is a drug design with great development potential [14].

Additionally, GPX4 is an important antioxidant enzyme, and its existence can keep cells in a reduced state [15]. Studies have shown that reducing the level of GXP4 is helpful for iron death in gastric cancer cells [16]. Similarly: Li et al. developed a therapeutic strategy combining iron death with nano-immunotherapy and constructed a nano-reactor with Cu2-xSe coated with ZIF-8 loaded with iron death

DOI: 10.54254/2753-8818/17/20240654

activator [17]. Erastin, which generated oxygen and consumed GSH activity through the reaction between ions, thus achieving a better effect of inducing iron death in tumor cells. Li et al. also developed a kind of MOF nanosheets used to destroy GPX4/GSH and FSP1/CoQ10 signal pathways. Cu(II) and MESO- tetra (4- carboxyphenyl) porphine ferric chloride (TCPP(Fe)) were used to synthesize MOF nanosheets as the base material of this nano-drug-loading system, and then iron death inducer RSL3 was loaded through a series of synthetic reactions, and some targeting and other things were added to the nanosheets' surface modification.

In a word, in conclusion, the research on the influence of iron death on cancer cells has been a hot topic in recent years. There have been some kinds of literature about iron death participating in the regulation process of various tumors, which is a very good drug target. However, the relevant research is still in its infancy, and the exploration of the biological mechanism of iron death has never stopped, but the accurate mechanism still needs more in-depth experiments to prove. The author believes that this will be an important research object for designing nano-targeted drug delivery systems according to iron death.

### *2.4. Remodeling tumor microenvironment and reprogramming metabolism*

Due to the dense tissue structure of tumor matrix, high hydraulic pressure will be formed in this area, and the EPR effect will inhibit the penetration of nano-drugs from blood vessels to tumor tissue. Abundant tumor stromal cells form a dense physical barrier, which helps to maintain the microenvironment of tumor immunosuppression and inhibit the penetration of nano-drugs. In addition, the matrix outside tumor cells also have the function of blocking the infiltration of nano-drugs and immune cells in tumor sites. The main components of tumor matrix are some tumor-related fibroblasts, which can recruit immunosuppressive cells and secrete immunosuppressive factors, and have the function of inhibiting the activity of effector T cells. The factors mentioned above will lead to the lack of T cells in tumor sites, which greatly reduces the clinical therapeutic effect. Therefore, it is a promising cancer treatment method to use drugs to remove tumor matrix and reprogram tumor immune microenvironment.

The traditional treatments for tumor microenvironment remodeling and reprogramming include glycolysis, lipid metabolism, amino acid metabolism, and so on. For example, lactate dehydrogenase A(LDHA) is the key enzyme for glycolysis to produce China's lactic acid reaction pathway. Inhibition of LDHA activity can inhibit glycolysis of tumor cells, and then inhibit the development of tumor [18,19]. In addition to the traditional reprogramming control points such as grape sugar, lipid and glutamine, the researchers also found that other raw materials such as lactic acid, ketone body, acetic acid and branched-chain amino acids, BCAA) can also be the targets of reprogramming tumor immune microenvironment. A large number of research results can draw the following conclusions: reprogramming the key metabolic enzymes in the metabolic pathway or inhibiting the synthesis of various small molecular metabolites have shown remarkable cancer suppression effects for the treatment of tumors. Sang et al.found that the expression of CamK-A (long-chain noncoding RNA numbered NR_038131, full name LNC RNA for calcium-dependent kinase activitio) had a synergistic relationship with the activation of PNCK-NF-κB signal axis [20]. That is to say, CamK-A can significantly promote the growth of tumor cells, so San et al. proposed that targeted knockdown of CamK-A can promote tumor metabolic reprogramming and reshape tumor immune microenvironment, providing a new target for tumor clinical treatment.

## 3. Conclusion

The existence of EPR effect makes nano-targeted drugs have unique advantages in tumor treatment. This paper analyzes and compares the research progress of four nano-drug delivery systems and the mechanism of harm to tumor cells. Through the analysis, it is found that: First of all, drugs that promote cancer cell apoptosis mainly kill tumors by blocking the cell cycle of cancer cells and promoting the apoptosis of intracellular mitochondria. Under this mechanism, compared with the traditional drug delivery mode, the use of nano-targeted agents can greatly reduce the harm to the human body and has

DOI: 10.54254/2753-8818/17/20240654

shown initial success in the clinical treatment of esophageal cancer. Second, anti-polarization TAMs can significantly prolong the survival of patients. It can not only inhibit the growth of cancer cells, but also effectively kill tumor cells, with fewer side effects compared with other methods.

Nano-targeted drugs that trigger ferroptosis in cancer cells generally have strong inhibitory effects on tumor growth. They cause a series of chain reactions by inhibiting iron efflux and eventually destroy the cell structure to achieve the killing effect, but there is no clear research results on the detailed mechanism. Finally, reprogramming of tumor metabolism and remodeling of tumor microenvironment is often combined with the previous several mechanisms, because it is mainly to provide a suitable microenvironment for the better entry of nanomedicine into cells. It can be understood from some relevant experimental results and progress in the main text that the current use of nano-targeted agents for cancer treatment can combine the remodeling of the tumor microenvironment and reprogramming of tumor cell metabolism with other mechanisms to achieve better results.

In addition to the four mechanisms mentioned in this paper, there are some other starting points for drug design. For example, activating the anti-tumor immunity of T cells, using chemical reagents and biological methods to enhance the immune ability of T cells to achieve the purpose of treating cancer, this method is also of great significance for cancer treatment, because the immune escape of cancer cells has always been a problem in the treatment of cancer, and enhancing the immune response of T cells can effectively solve this problem. However, these studies are still lacking. At present, there are still some problems that need to be solved in nano-targeted drug delivery systems, such as: Due to the lack of in vivo experiments, the mechanism of action of nano-targeted drug preparations is not clear. The current technical means cannot guarantee that nano-targeted drugs have good controllability in vivo. It is not clear whether nano-carriers that cannot be disintegrated will harm health (block capillaries or cause microcirculation disorders in other ways) and the existence of blood-brain barrier. At present, the development of nanomedicine for brain tumors is less. In the future, there will be more experiments to explore the more detailed physiological mechanism of nanomedicine and solve the problem of residual nanocarrier in the body. Secondly, more in vivo experiments will be conducted to solve the difficult problems caused by the blood-brain barrier. It is hoped that this paper can provide ideas for subsequent experimentalists to choose their topics.

## References

[1] Mengzhen C, Jing S, Zhongyang W. 2019 Chinese Jour. of Lumi 42 01 61-72
[2] Wild C. World cancer report 2020. Imprimerie Faurite, France: World Health Organization 2020
[3] Fang J, Nakamura H, Maeda H. 2021 Advanced drug delivery reviews 63 3 136-151
[4] Choi J, Kim K, Mu J. 2022 J. Comm Jed Jour 20 19 1100-1106
[5] Liu W. 2021. Hen Univ 2020.002107.
[6] KOMOHARA Y, FUJIWARA Y, OHNISHIK, et al 2016 Adv Drug Deliv Rev 99 PtB 180-185
[7] Chaohan W, Ziqiaoqiao D, Xiaoqiong Z et al. Chinese Med Rev 222 41 11 1595-1604
[8] Li K. 2022.Chongqing Uni 001194
[9] S. F. Viehmann, A. M. C. Böhner, C. Kurts, et al. 2018, Cellular Immu, 330 97~104
[10] SUN K L. 2023 Huazhong Uni of sci and tech
[11] Gao, X., Li, S., Ding, F., Liu, X., Wu, Y., Li, J., Zhang, C. 2021. Adv Mate, 33 9 , 2006116.
[12] Yang L, Shi P, Zhao G, Xu J, Peng W, Zhang J, Zhang G, Wang X, Dong Z, Chen F, Cui H*. Sig Trans and Tard Ther. 2020, 5: p 8
[13] Tian Yu G, Yong F, Yuanfei G et al. The Influ of the Chem in life 1-14 2023-09-1
[14] FAN S H. 2023 Liaocheng University
[15] Zhi Z, Jin-quan L, Chun-yu W, et al. 2023, Shanxi Med Jour 52 09 1268-1271
[16] Stockwell, B R et al. 2017 Cell171 273–285
[17] LI K. 2022 Chongqing University
[18] Yufang Y Beiying D ang Yong Y. 2020, 26 18 216-223
[19] Ye Ling, Zhang Huafeng Shiting L. 2019 J. Tumor meta and Nutr ele magazine 6 (4) 401-408.
[20] SANG L J. 2023 Zhejiang University