

## Progress in the study of anti-tumor drugs targeting mitochondria

Yi Hu<sup>1</sup>, Ruocheng Pei<sup>2</sup>, Tao Tao<sup>3</sup>, Shuping Wang<sup>4,\*</sup>

<sup>1</sup>School of Pharmacy, China Pharmaceutical University, Nanjing, China, 211198

<sup>2</sup>School of Life Sciences & Biotechnology, Shanghai Jiao Tong University, Shanghai, China, 200240

<sup>3</sup>College of Biological Sciences, China Agricultural University, Beijing, China, 100193

<sup>4</sup>Institute of Medical Biochemistry and Molecular Biology, School of Basic Medical Sciences, Lanzhou University, Lanzhou, China, 730000

\* Corresponding Author Email: wangsp16@126.com

**Abstract.** Cancer poses a significant yet concealed threat to human health, necessitating the prompt pursuit of efficacious anti-tumor tactics. Mitochondria, functioning as an intracellular energy generator, participate in numerous vital physiological processes and serve as pivotal determinants in the proliferation and metabolism of tumor cells. Consequently, targeting of mitochondria is deemed a burgeoning and auspicious anti-tumor strategy that can leverage the highly negative electrical characteristics of the mitochondrial inner membrane to selectively aim at tumor cells via specific targets. Moreover, targeting of mitochondria has the potential to decrease the emergence of tumor drug resistance and partially surmount the multidrug resistance (MDR) of tumors that arise from conventional chemotherapy, thereby augmenting the effectiveness of conventional drugs. The aim of this manuscript is to examine the design principles and mechanisms of action of targeted mitochondrial antitumor drugs, and to introduce innovative and efficacious mitochondria-targeted adjuvant combination therapy strategies in cancer chemotherapy, with the intention of furnishing a point of reference for the advancement of mitochondria-targeted drugs.

**Keywords:** Targeting Mitochondria; Cancer Therapy; Drug Design; Cancer Chemotherapy

### 1. Introduction

Cancer is a high-risk and difficult-to-treat malignant tumor, and according to the World Health Organization (WHO), the number of global cancer deaths will be about 10 million in 2020, accounting for nearly one-sixth of global deaths [1]. In order to effectively treat cancer, the development of antitumor drugs targeting mitochondria is a promising strategy. Mitochondria are important organs for energy metabolism and signaling in cells, and are involved in the regulation of various physiological processes such as cell growth, differentiation, and apoptosis [2]. In recent years, more and more studies have shown that mitochondria play a key role in tumorigenesis, development and drug resistance formation [3]. Current studies have concluded that tumor cell mitochondria have multiple specific targets that can be exploited [4]; therefore, developing drugs against these targets can improve drug targeting efficacy, reduce toxic side effects, and overcome multidrug resistance of tumor cells to conventional chemotherapeutic agents or targeted therapeutic agents.

This paper reviews the research progress of Mitochondria-Targeted Anticancer Drugs (MTADs) in recent years, focuses on the molecular mechanisms and drug strategies for targeting mitochondria against tumors, and summarizes the advantages of the drug combination strategy to fight against tumors and overcome tumor cell resistance. It is hoped that this article will provide useful reference and inspiration for in-depth research and innovation in this field.

Cancer treatment mainly includes five modalities: surgery, immunotherapy, radiotherapy, chemotherapy and targeted therapy. Surgical treatment is the most traditional and effective method, but the effect of surgical treatment on tumors that have already spread needs to be improved, and it is difficult to completely remove cancer cells [5]. Immunotherapy has the advantages of strong targeting, low side effects, and good durability, but also encounters technical challenges such as tumor

immune escape and microenvironment interference [6]. Radiotherapy is characterized by the use of ionizing radiation effects of radiation to kill cancer cells, with the limitation that it may damage normal tissues surrounding the tumor, leading to different degrees of side effects [7]. Nowadays, researchers have developed various types and mechanisms of action of chemotherapy antitumor drugs based on different mechanisms [8], which can inhibit rapidly dividing tumor cells, but also damage normal cells and bring a series of adverse reactions [9]. In addition, chemotherapy also suffers from the problem of tumor multidrug resistance (MDR), which reduces the effective concentration of chemical drug molecules in tumor cells or increases the rate of their efflux, thus weakening their killing effect [10]. In order to improve the efficiency of chemotherapy, some scholars have proposed the strategy of combining drugs targeting mitochondria to break through the MDR barrier and enhance the toxic effects of other drugs on tumor cells [11]. The chemotherapeutic treatment modality targeting mitochondria can directly inhibit the pathways of cancer cells to obtain energy and escape death, thus leading to the death of cancer cells; at the same time, chemotherapeutic drugs targeting mitochondria have a stronger killing effect on cancer cells than non-targeted drugs, so the drugs are used in low doses and have fewer side effects on normal tissues. Analyzing from the aspect of targeted therapy, the mitochondria-targeting drugs have the following advantages over other targeted drugs and chemotherapeutic drugs in anticancer: firstly, they can directly inhibit the process of mitochondria providing energy for cancer cells, so as to cause apoptosis, autophagy, or necrosis of the cancer cells; secondly, due to the fact that mitochondria in normal tissues are more intact in their function, they can avoid causing excessive damage to the normal tissues; thirdly, they can overcome the drug resistance problem faced by some traditional chemotherapeutic drugs. Therefore, targeting mitochondria for cancer treatment has great potential and prospect.

## 2. Targeting the mitochondrial anti-tumor pathway

Mitochondria are important cellular organelles and can be used as a precise target for anti-tumor cells because tumor cell mitochondrial metabolism is quite different from normal cells, such as aerobic glycolysis, altered redox state, and reorganization of energy metabolism [12].

There are three main pathways to target mitochondria: targeting mitochondrial metabolism, targeting reactive oxygen species (ROS) and targeting mitochondrial DNA (mtDNA) [13]. Among them, targeting mitochondrial metabolism is to cut off the energy supply and synthesize metabolites of cancer cells by inhibiting glycolysis or oxidative phosphorylation (OXPHOS), thus inducing apoptosis or autophagy in cancer cells [14]. Studies have confirmed the inhibitory effect of metformin and other biguanides on mitochondrial respiratory chain complex I [15], and clinically good efficacy has been achieved in non-small-cell lung cancer using metformin for monotherapy and in combination with other anticancer therapies [16]; targeting ROS is a way to eliminate ROS through the use of antioxidants or to increase ROS through the use of pro-oxidants, and to change the level of ROS to induce DNA damage and affect the DNA-damage response (DDR), which leads to apoptosis or survival of cancer cells [17]. The conventional strategy for this pathway is to artificially modulate ROS levels in mitochondria, i.e., using ROS-eliminating compounds such as N-acetylcysteine, lipoic acid, and vitamin C or ROS-producing compounds such as transition metal complexes, quaternary ammonium salts, and organophosphine/sulfur salts [18,19], but also designing drugs using aberrant ROS levels as a target, as in the case of a new type of responsive nanoparticles that can carry both a chemical (camptothecin) and a photosensitizer (zinc phthalocyanine) and release them into mitochondria at high ROS levels to induce lung cancer cell death [20]. Since mtDNA mutations lead to the transformation of normal cells into tumor cells, targeting mtDNA, i.e., by repairing mutations or deletions in mtDNA, restores normal mitochondrial function and signaling pathways, thereby inhibiting tumorigenesis and progression [21]. For example, researchers have utilized a nanoparticle, MITO-Porter, that can effectively transport drugs or DNA into the interior of mitochondria. MITO-Porter can alter the mtDNA structure and mitochondrial RNA (mitochondrial RNA (mtRNA)) levels, which thereby affecting mitochondrial function [22]. In addition, mitochondrial autophagy and

interactions with lysosomes can also serve as targets. Enhanced mitochondrial autophagy in cancer cells removes damaged mitochondria, enhances metabolism, and promotes cancer cell proliferation, possibly by regulating the PINK1 /Parkin and Nix/BNIP3 signaling pathways in order to inhibit mitochondrial autophagy in cancer cells in order to control cancer cell division [23]. Lysosomal stress induced by high intensity metabolism in cancer cells induces mitochondrial morphological and functional damage and apoptosis through ROS signaling or lysosomal release of histone proteases can also alter mitochondrial membrane permeability to activate cysteine-dependent cell death, while mitochondrial membrane permeability can also cause lysosomal damage, resulting in ever-increasing positive feedback that ultimately leads to tumor cell death [24]. Targeted mitochondrial gene therapy, on the other hand, is a therapeutic method that uses specific gene expression vectors to introduce exogenous genes into the mitochondria of tumor cells, thereby altering mitochondrial function and metabolism, and inducing apoptosis or inhibiting drug resistance in tumor cells [25]. This method has the advantages of high efficiency, safety and specificity, and can be used to treat many types of tumors. A variety of targeted mitochondrial gene expression vectors have been developed, such as liposomes, nanoparticles, and peptides containing mitochondria targeting sequence (MTS) [26].

Several studies have demonstrated the effectiveness of targeted mitochondrial gene therapy in suppressing drug resistance in tumor cells. For example, Yu Shicang et al [27] attempted to construct a eukaryotic expression vector containing the human N-Methylpurine DNA Glycosylase (MPG) gene and MTS, and transfected it into human non-small cell lung cancer multidrug-resistant cells A549/DDP to screen for stable transfection progeny. They used RT-PCR and Western Blot to detect that MPG was successfully guided by MTS into the mitochondria of A549/DDP cells, and detected by flow cytometry that MPG was able to increase the level of free radicals in the mitochondria, which led to a decrease in their proliferative capacity and some cell death. In addition, targeted mitochondrial gene therapy can also affect the growth and differentiation of tumor cells by altering gene expression within the mitochondria. Some studies have shown that the introduction of Bcl-2 gene into the mitochondria of tumor cells can inhibit the decrease of mitochondrial membrane potential, thus inhibiting tumor cell apoptosis [28]. In conclusion, targeted mitochondrial gene therapy is a novel, efficient and safe therapeutic approach with great potential in inhibiting drug resistance and promoting apoptosis in tumor cells. At present, this field is still in the rapid development stage, and further in-depth investigation of its mechanism and clinical application prospect is still needed in the future.

### **3. Targeted mitochondrial antitumor drugs**

#### **3.1. Direct targeting of mitochondrial small molecule drugs**

Direct targeting of mitochondrial small molecule drugs is a novel anti-tumor strategy, they can interfere with mitochondrial function of tumor cells through different mechanisms, thus inducing apoptosis or autophagy. As early as 1987, Weiss discovered that Dequalinium (DQA) is both mitochondria-targeting and cytotoxic.

#### **3.2. Triphenylphosphine (TPP)-mediated targeted drugs**

TPP-mediated targeting is one of the more well-established classes of drugs for targeting mitochondria. TPP is a lipophilic cation with a three-benzene ring structure that forms a dispersed positive charge and a large molecular surface area. The mechanism by which TPP penetrates membranes and enters the mitochondria by hydrophobic interactions was described by Liberman, E. A., et al. as early as 1969.

#### **3.3. Peptide-targeted drugs**

Peptides are widely used in the biological field due to their excellent selectivity, high activity and proven solid phase peptide synthesis techniques [29]. For targeting mitochondrial peptides, a variety

of short peptides and polypeptides have been identified, which have been proposed as alternatives to lipophilic cations for targeting mitochondrial molecules.

## **4. Strategies for targeting mitochondrial drugs in combination with chemotherapeutic agents**

### **4.1. Novel metalloplatinum-based drugs**

Platinum-based drugs, such as cisplatin, carboplatin, and oxaliplatin, are important tools for cancer chemotherapy, but their high cytotoxicity and tumor resistance limit their clinical effectiveness [30]. In order to overcome platinum drug resistance, there are two main strategies: one is to improve existing platinum drug structures or carriers (e.g., designing platinum-based nanomedicine platinum nanoclusters) in order to enhance their targeting and stability; and the other is to combine with other drugs or therapeutic agents in order to interfere with the metabolism or repair mechanisms of platinum drugs by tumor cells. In the second strategy, targeting mitochondria to direct the action of platinum drugs to overcome drug resistance has achieved better results. Su et al [31] designed and synthesized a cyclometallic iridium (III) complex (Ir-Rhein) based on rhuibarbic acid, a natural product, and proposed a new strategy: the complex was used to inhibit mitochondrial energy metabolism, induce mitochondrial autophagy, and regulate the metabolism of cisplatin drugs so as to overcome the cisplatin resistance. In tumor cells, over-activated autophagy may protect tumor cells from killing by chemotherapeutic drugs. Therefore, the toxicity of chemotherapeutic drugs such as cisplatin on tumor cells can be enhanced by inhibiting autophagy. In addition to utilizing Ir-Rhein to intervene in mitochondrial energy metabolism and autophagy, there are several other approaches to overcome cisplatin resistance by targeting mitochondria. For example, Kelly et al [32] achieved the goal of target-specific breakage of mtDNA in tumor cells by connecting platinum drugs with peptides targeting mitochondria; Mao et al [33] designed Ru-Pt complexes based on the fact that Ru complexes have the targeting ability, and generated ROS through photochemotherapy, which had the effect of breaking mtDNA; Wang Kun et al [34] designed a series of pyridine platinum complexes, which targeted the mtDNA; Wang Kun et al [34] designed a series of pyridine platinum complexes, which targeted the mtDNA, which had the effect of breaking mtDNA; and Wang Kun et al [34] designed a series of pyridine platinum complexes, which targeted the mtDNA. Wang Kun et al [34] designed a series of pyridine-platinum complexes to target mtDNA, thus overcoming the resistance of cancer cells to platinum drugs. All of these methods use mitochondria to play an important role in the mechanism of cisplatin action to achieve the killing of tumor cells.

### **4.2. Anti-tumor antibiotic DOX innovation**

DOX is a broad-spectrum antitumor drug, which belongs to anthracycline antibiotics, and its mechanism of action is mainly by embedding in the DNA of tumor cells, thus inhibiting the synthesis of DNA and RNA, and disrupting cell division and proliferation [8]. DOX is commonly used in the treatment of malignant tumors including solid tumors, leukemias, and lymphomas, but has a strong adverse effect and is prone to lead to drug resistance in tumor cells [35]. To overcome DOX-induced tumor resistance, some novel DOX modifiers have been developed. For example, Yang Jianmiao et al. verified that TPP-DOX and combined with chloroquine (CQ) could enhance the killing effect on K562/DOX cells [36]. They found that the combination of TPP-DOX and CQ was significantly more effective than that of DOX and CQ at low concentrations, and hypothesized that this was due to the ability of TPP-DOX to target mitochondria and release free radicals to cause cell death, and the ability of CQ to inhibit autophagy and block transcription of drug-resistant genes. Columbus Zhang et al. constructed mitochondria-targeted calcium arsenite/doxorubicin lipid nanoparticles (TPP-LPs-CaAs/DOX), which were able to target mitochondria and trigger localized overloading of calcium ions after aggregation in mitochondria. glycoprotein, P-gp) expression level, which is the most critical

for triggering multidrug resistance, in drug-resistant cells [37]. These results suggest that targeting mitochondria is an effective strategy to inhibit tumor resistance to chemotherapeutic drugs.

## 5. Conclusions

Targeted mitochondrial antitumor drugs are a novel anticancer strategy that can effectively induce tumor cell death or inhibit their drug resistance by exploiting the specific targets and specific functions of tumor cell mitochondria. This article describes the research progress of targeted mitochondrial antitumor drugs, including the molecular mechanism, design principle, mechanism of action and clinical application of targeted mitochondrial drugs. However, targeted mitochondrial antitumor drugs are still facing some problems and challenges [38], such as: the selectivity and stability of targeted mitochondrial drugs need to be further improved in order to reduce the toxicity to normal cells and improve the bioavailability of the drugs in vivo [39]; there are still fewer clinical trials of targeted mitochondrial drugs, and more evidences are needed to support the safety and efficacy of them [40]. Based on these problems, the outlook of the development direction of this class of targeted drugs is as follows [41], using nanotechnology, peptide technology and other new delivery systems to improve the specificity and penetration of targeted mitochondrial drugs; combined with other therapeutic means to achieve the combination therapy or synergistic therapy of targeted mitochondrial drugs. From the development trend in recent years, targeted mitochondrial antitumor drugs are a promising anticancer strategy, which can effectively induce tumor cell death or inhibit its drug resistance by targeting the key links of tumor cells such as energy metabolism, oxidative stress, and DNA damage. It is believed that with the advancement of science and technology and the advancement of clinical trials, targeted mitochondrial antitumor drugs will bring new hopes and breakthroughs in cancer treatment.

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