Structure Modification and Metabolic Pathway Optimizations of Anticancer Drugs

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Abstract. Anti-cancer drugs have a critical position in modern medicine, and their structural modification and metabolic pathway optimization are key strategies to enhance efficacy and safety. Through the introduction of functional groups, changes in molecular ring structure, and covalent and non-covalent modifications, the pharmacokinetic properties of anticancer drugs can be optimized, which can significantly improve their stability, bioavailability, and targeting, as well as reduce toxic side effects. This paper reviews the main strategies for structural modification of anticancer drugs, including functional group addition, molecular ring modification, covalent and non-covalent modification, and analyses the case of metabolic pathway optimization of classical anticancer drugs such as paclitaxel and Adriamycin. These optimizations resulted in significant improvements in the metabolic stability and therapeutic efficacy of the drug. In addition, strategies for the generation and reduction of toxic metabolites, such as reduction of toxic metabolites through the combination of liposome encapsulation, nanoparticle modification, and metabolic inhibitors, are discussed in this paper. Despite significant advances in structure modification and metabolism optimization in anticancer drug development, drug metabolism prediction and individual variability are still challenges that need to be addressed. In the future, combining precision medicine, genomics, big data and artificial intelligence technologies, personalized design of anti-cancer drugs and optimization of metabolic pathways are expected to achieve more efficient and safer cancer treatment options.

Keywords: Anticancer drugs, Structural modification, Metabolic pathway optimization, Toxic metabolites, Personalized therapy.

1. Introduction

Anti-cancer drugs occupy an important position in modern medicine, with their development beginning in the early 20th century and rapidly evolving over the following decades to become the cornerstone of cancer treatment. Early anticancer drugs relied heavily on chemicals that inhibited the growth of cancer cells by interfering with cell division or metabolic processes [1].However, due to the non-selective nature of these drugs, they kill cancer cells while also causing damage to normal cells, leading to serious side effects [2]. With the advancement of molecular biology and biotechnology, targeted therapeutic drugs and biologics have been introduced one after another, significantly improving the selectivity and effectiveness of anticancer drugs [1].Currently, the mainstream categories of anti-cancer drugs include small molecule drugs, monoclonal antibody drugs and targeted therapy drugs. Small molecule drugs achieve their therapeutic effect by penetrating inside cancer cells and interfering with their key metabolic pathways; Monoclonal antibodies and targeted therapeutic drugs, on the other hand, precisely kill cancer cells by recognizing and binding to specific antigens or receptors on the surface of cancer cells [3].

The metabolic properties of drugs are crucial in their clinical application and directly affect the efficacy and safety of drugs. The metabolism of anticancer drugs in the body is usually accomplished through two major processes, i.e. phase I metabolism and phase II metabolism. Phase I metabolism promotes excretion by chemically modifying the drug molecules through oxidation, reduction, or hydrolysis reactions to increase their water solubility. Phase II metabolism, on the other hand, binds the drug molecule to an endogenous substance, such as a glucuronic acid or sulphate group, further increasing its polarity and accelerating drug clearance. However, the metabolism process of a drug is not just a process of removal; some metabolites may possess pharmacological activities different from

those of the original drug, or even produce toxicity [4].For example, Adriamycin (doxorubicin) is metabolized to produce cardiotoxic metabolites, which may lead to serious heart damage with prolonged use. The absorption, distribution, metabolism and excretion (ADME) characteristics of a drug in the body are key determinants of its efficacy in the body. Therefore, understanding and optimizing the metabolic process of anticancer drugs is important for improving drug efficacy and reducing side effects [5].

Despite the significant role of existing anticancer drugs in therapy, many challenges remain in their metabolism in the body. For example, certain anticancer drugs have low bioavailability or produce highly toxic by-products during metabolism, problems that limit their clinical application. To address these issues, scientists have adopted strategies of drug structure modification and metabolic pathway optimization. By introducing specific functional groups into a drug molecule or changing the molecular structure, the metabolic pathway of a drug can be significantly improved, and the generation of toxic metabolites can be reduced, thus improving the safety and efficacy of the drug. In addition, optimization of the metabolic pathway not only extends the half-life of the drug, but also reduces the toxic side-effects of the drug so that it can maintain an effective concentration in the body for a longer period of time, which is essential for enhancing the efficacy of the treatment [6].

The aim of this review is to summarize the current research progress in structure modification and metabolic pathway optimization of anticancer drugs. By analyzing the introduction of functional groups, changes in molecular ring structure and specific strategies for covalent and non-covalent modifications of drugs, this paper will explore the effects of different structural modifications on drug metabolism and analyze the effectiveness of metabolism optimization of anticancer drugs in the context of practical cases. It is hoped that this review will provide valuable references for the future research and development of anticancer drugs and promote the further development of highly effective and low toxicity drugs.

In the development of anticancer drugs, structural modification can effectively improve the stability, solubility and targeting of drugs by introducing different functional groups, changing the molecular ring structure, and covalent and non-covalent modifications.

2. Structural Modification Strategies for Anticancer drugs

Structural modification of anticancer drugs is an important drug design strategy aimed at optimizing the pharmacokinetic properties of drug molecules, improving their efficacy, and reducing toxic side effects by altering their chemical structures.

2.1. Addition of Functional Groups

Introduction of specific functional groups is one of the common strategies for structural modification of anticancer drugs. The addition of these functional groups can influence the metabolic pathway of the drug, improve its stability, and enhance its ability to bind to the target. For example, the introduction of groups such as hydroxyl (-OH), methyl (-CH3) or amino (-NH2) groups can often optimize the absorption and distribution properties of a drug by altering its polarity or water solubility [7].

A prime example is the development of lactate dehydrogenase A (LDHA) inhibitors. By introducing specific groups into the drug molecule, it can effectively inhibit the glycolytic pathway of tumor cells and reduce their energy supply, thus inhibiting tumor growth. In addition, the addition of polar groups can slow down the metabolism of the drug in the body by increasing its solubility in water, which in turn improves its bioavailability. For example, certain anticancer drugs enhance the stability of the drug in the tumor microenvironment by introducing hydroxyl or amino groups into the molecular structure [8].

In addition, the introduction of hydrophobic functional groups can alter the distribution properties of the drug in vivo. For example, the addition of maleimide groups (maleimide groups) can enhance the toxic effects of drugs on tumor cells by influencing intracellular energy metabolism through

interactions with tumor cell metabolites. This structural modification through the addition of functional groups can not only enhance the efficacy of drugs, but also significantly improve their stability and efficacy in clinical applications [9].

2.2. Alteration of Molecular Ring Structure

Alteration of molecular ring structure is also one of the important strategies for structural modification of anticancer drugs. The introduction or ring opening of an aromatic ring can reduce the degradation of a drug and increase its bioavailability in the body by affecting its interaction with metabolic enzymes. For example, in the structural modification of paclitaxel (paclitaxel), the metabolic stability of the drug was significantly improved by introducing specific aromatic ring structures. Paclitaxel is a classical anticancer drug that inhibits cancer cell division by interfering with microtubule function, but its original structure is metabolized at a rapid rate, resulting in low effective concentrations in the body. By optimizing its molecular ring structure, paclitaxel becomes more stable during metabolism, thus prolonging its half-life in vivo and improving its efficacy [10].

In addition, drug targeting can be further optimized by ring opening or changing the conformation of the molecular ring. For example, the introduction of polycyclic aromatic hydrocarbon (PAH) structures into the molecular structure of certain anticancer drugs not only improves their selectivity against cancer cells, but also reduces their degradation rate in the body. Such a change in the molecular ring structure can effectively reduce the non-specific metabolism of the drug and significantly reduce the toxicity of the drug to normal cells, resulting in better safety and efficacy in clinical applications [11].

2.3. Covalent and Non-covalent Modifications

Covalent or non-covalent modification of drug molecules is another effective strategy to prolong the residence time of the drug in the body and to improve its efficacy. For example, polyethylene glycation (PEGylation) technology is able to effectively prolong the blood circulation time and reduce the metabolism rate of a drug by covalently binding polyethylene glycol (PEG) to the drug molecule. This structural modification strategy has been widely used in the development of anticancer drugs, e.g., the PEGylation modification of paclitaxel and Adriamycin has greatly improved the clinical application of the drugs [12].

Non-covalent modifications, on the other hand, include the use of techniques such as nanoparticle or cyclodextrin encapsulation to alter the solubility and distribution properties of the drug by physically encapsulating the drug molecule. For example, cyclodextrins encapsulate anti-cancer drugs in their cores through non-covalent bonding, which not only improves the solubility of the drugs in water but also enhances their targeting at the tumor site. This non-covalent modification can effectively reduce the toxic side effects of drugs while enhancing their drug efficacy [13].

3. Case Studies on Metabolic Pathway Optimizations

Optimizations of metabolic pathways is essential to improve the efficacy and safety of anticancer drugs. Improvements in the metabolic pathway not only prolong the half-life of the drug in the body, but also reduce the production of toxic metabolites, thereby reducing the toxic response of the drug. Metabolic optimization strategies for paclitaxel, Adriamycin and other classical anticancer drugs will be explored in the following specific case studies.

3.1. Metabolic Optimizations of Paclitaxel

Paclitaxel is a widely used anticancer drug for the treatment of a variety of malignant tumors, including breast and lung cancer, and it prevents cancer cell division by promoting microtubule polymerization and inhibiting their depolymerization. However, the clinical use of paclitaxel is limited by its lower water solubility and faster rate of metabolism in vivo. To address this problem, researchers have used several metabolic optimizations strategies, the most representative of which is

polyethylene glycosylation (PEGylation).PEGylated paclitaxel effectively prolongs the half-life of the drug in vivo by covalently binding polyethylene glycol (PEG) to the drug molecule, increasing its blood circulation time and thus improving the bioavailability of the drug [12].

In addition, nanocarrier technology has been widely used in the metabolic optimization of paclitaxel. For example, by encapsulating paclitaxel in liposomes or nanoparticles, it is possible to significantly improve its in vivo distribution characteristics, reduce the accumulation of the drug in normal tissues, and reduce adverse effects. Paclitaxel nano formulations have improved targeting at the tumor site while reducing the toxicity of the drug in non-tumor tissues, thus further improving its therapeutic efficacy. These metabolic optimization strategies have enabled paclitaxel to show better efficacy and safety in clinical applications [14].

3.2. Improved Metabolic Pathway of Adriamycin

Adriamycin is an anthracycline antibiotic drug commonly used in the treatment of many cancers, which inhibits the proliferation of cancer cells by interfering with DNA replication and RNA synthesis. However, the clinical use of Adriamycin is limited by the toxic metabolites produced during its metabolism. When metabolized in vivo, Adriamycin generates cardiotoxic metabolites that can cause oxidative stress in cardiomyocytes, thereby triggering cardiotoxicity.

To reduce the toxicity of Adriamycin, the researchers used the liposome encapsulation technique. Liposome-encapsulated Adriamycin (Doxil) significantly reduces the cardiotoxicity of the drug by altering its in vivo distribution and reducing its accumulation in normal tissues. In addition, nanoparticle modification is also an effective metabolic pathway improvement strategy. By encapsulating Adriamycin in nanoparticles, it not only improves its accumulation at the tumor site, but also reduces the distribution of the drug in normal tissues, which further reduces its toxic side effects [15].

These structural modification and metabolism optimization strategies significantly improved the therapeutic efficacy of Adriamycin and reduced its toxic reactions in clinical applications, providing a new direction for the development of anticancer drugs.

3.3. Cases of Other Classical Anticancer Drugs

In addition to paclitaxel and Adriamycin, a number of other classical anticancer drugs have improved efficacy and reduced toxicity through structural modification and metabolic pathway optimization. Cyclophosphamide is a commonly used alkylating agent anticancer drug that inhibits the proliferation of cancer cells by cross-linking with DNA. However, the metabolic pathway of cyclophosphamide produces more toxic metabolites, such as acrolein, which may lead to serious side effects. By modifying the structure of cyclophosphamide, researchers were able to adjust its metabolic pathways and reduce the production of toxic metabolites, thereby improving the safety of the drug [16].

Cisplatin is an important metal anticancer drug that inhibits the division of cancer cells by forming adducts with DNA. However, the metabolic pathway of cisplatin in the body can burden the kidneys and lead to nephrotoxicity. To reduce this toxicity, the researchers modified the structure of cisplatin by introducing specific ligands to improve its water solubility and targeting properties. This optimization of the metabolic pathway significantly reduces the toxicity of cisplatin and improves the safety of its use in the clinic [17].

Optimizations of metabolic pathways not only enhances the efficacy of anticancer drugs, but also significantly reduces their toxicity. These optimizations strategies show great potential for practical clinical applications. For example, PEGylation, liposome encapsulation, and nanoparticle modification technologies have been widely used in the metabolic optimization of a wide range of anticancer drugs, significantly improving their clinical efficacy and safety. Through the optimization of these metabolic pathways, the biostability of anticancer drugs in vivo has been improved and their toxic reactions have been effectively controlled.

4. Toxicity of Metabolites and Drug Optimizations

During the metabolism of anticancer drugs in the body, a series of metabolites are often produced, some of which may have high toxicity and cause damage to normal tissues and organs. The production of such toxic metabolites often limits the dose and efficacy of the drug. Therefore, reducing the generation of toxic metabolites through drug structure modification and metabolic pathway optimization is one of the key strategies to improve drug safety and efficacy.

4.1. Generation and Problems of Toxic Metabolites

The metabolic process of anticancer drugs usually involves phase I and phase II metabolism, and the generation of metabolites is not only related to the structure of the drug, but also closely related to the characteristics of the individual's metabolic system. For example, Adriamycin (doxorubicin) is metabolized in the body to produce metabolites that are cardiotoxic. These metabolites cause damage to cardiomyocytes by triggering oxidative stress and ultimately cardiotoxicity. This toxicity problem significantly limits the long-term clinical use of Adriamycin, especially in high-dose regimens [18].

The generation of this toxic metabolite is a major source of adverse effects with long-term use of the drug, especially in high-dose chemotherapy regimens, and may trigger severe liver and bladder damage. Similarly, the metabolism of cyclophosphamide (cyclophosphamide) in the liver generates metabolites such as active phosphonamidite nitrogen mustard and acrolein, which is significantly toxic to the liver and urinary system [19].

For drugs such as cisplatin (cisplatin), its metabolites may cause nephrotoxicity, limiting its use in patients with renal insufficiency [17].

4.2. Strategies to Reduce Toxic Metabolites

Reducing the generation of toxic metabolites is one of the important strategies for drug optimization. The metabolic pathway of a drug can be altered by appropriate modification of the drug structure, thus reducing or eliminating the generation of toxic metabolites. For example, by liposomal encapsulation (Doxil) of Adriamycin, the distribution of the drug in the body can be altered so that it accumulates more at the tumor site and reduces its exposure to vital organs, such as the heart, thereby reducing its cardiotoxicity [15].

Liposome technology avoids the generation of toxic metabolites in large quantities by modulating the distribution characteristics of the drug. Nanoparticle technology also provides an effective solution to reduce the production of toxic metabolites. By encapsulating the drug in nanoparticles, not only can the metabolic pathway of the drug be altered, but also the enrichment of the drug at the tumor site can be improved, thus reducing the toxicity to normal tissues. In the case of cisplatin, its water solubility and targeting properties can be enhanced by modification of the drug's molecular structure, e.g., by the introduction of specific ligands, thereby reducing the production of nephrotoxic metabolites [17].

Another strategy to reduce toxic metabolites is the combination of drugs with metabolic inhibitors. Through the use of metabolic inhibitors, the production of certain toxic metabolites can be effectively reduced, thereby reducing the adverse effects of the drug. For example, the combination of cyclophosphamide with Mesna (sodium 2-mercapto ethane sulfonate) reduces the production of acrolein, thereby reducing the cytotoxicity of cyclophosphamide [19].

5. Future Challenges and Opportunities

At the same time, with the development of biotechnology and data science, the future holds great opportunities in the field of drug design and optimization. Structural modification and metabolic pathway optimization of anticancer drugs have provided many new ideas and technical means for drug discovery and development. However, despite significant research advances, the optimization of drug metabolism still faces many challenges, especially in the context of the growing need for precision medicine and personalized therapies.

5.1. Combination of Structural Modification and Precision Medicine

With the development of genomics and molecular biology, precision medicine has gradually become the core concept of anti-cancer treatment. Precision medicine aims to tailor the most appropriate treatment plan for a patient based on their genetics, tumor characteristics and metabolic status. In this context, structural modification strategies of anticancer drugs can be organically combined with precision medicine to achieve personalized optimization of drug metabolic pathways. By analyzing patient genomic data, key gene mutations or polymorphisms in metabolic enzymes that may affect drug metabolism can be identified, so that the structure of the drug can be adjusted accordingly and its metabolic pathway optimized.

For example, genetic testing can reveal significant reductions in the activity of certain metabolic enzymes in a patient's body, which can lead to increased drug accumulation and toxicity. In this case, structural modification of drugs can target these metabolic enzyme deficiencies and design drugs with more stable and safer metabolic pathways [20].

5.2. Technic Bottlenecks in Metabolic Optimizations

Although metabolic pathway optimization has shown promising applications in drug development, several bottlenecks still exist in the current technology. Firstly, the complexity and individual variability of the metabolic system in the human body makes accurate prediction of drug metabolic pathways extremely difficult. Metabolic pathways often involve multiple enzymes and cross-reactions, making it challenging to identify the major metabolic pathways of a given drug in different individuals.

In addition, the prediction of toxicity of drug metabolites is also a difficult issue in current research. Data obtained in external experimental models or animal experiments do not always fully reflect the metabolic situation in the human body, especially since the long-term cumulative effects of metabolites are difficult to be accurately assessed in short-term experiments. This requires drug developers to invest more resources in constructing more complex and representative metabolic models at the preclinical research stage to improve the success rate of drug metabolism optimization [21].

5.3. Prospects for Future Research and Clinical Applications

In the future, the metabolic optimization and structural modification of anticancer drugs will continue to develop in the direction of personalization and intelligence. First, predictive models based on big data and machine learning techniques will play an increasingly important role in the design of drug metabolic pathways. By integrating large amounts of drug metabolism data, machine learning models can predict the metabolic pathways, potential toxicity and their interactions with metabolic enzymes early in drug design, helping researchers to identify and optimize possible problems in advance.

Secondly, virtual screening and computational chemistry methods will also accelerate the process of developing new drugs. With the help of computer simulation, researchers can quickly screen drug candidate molecules with desirable metabolic properties among hundreds or even thousands of compounds, greatly improving the efficiency of new drug development. With the deeper application of AI, a fully automated drug design and optimization system may even be possible in the future, greatly facilitating the development of anti-cancer drugs.

In terms of clinical applications, personalized design of drugs and optimization of targeted metabolism will become the norm. Future anti-cancer drugs will not only have higher targeting but will also be customized according to the individual metabolic characteristics of the patient, ensuring that the drug achieves optimal efficacy in the body with minimal toxicity. For example, with the development of genomics, doctors can use a patient's genetic information to predict how a drug will be metabolized in his or her body and select the most appropriate drug or treatment plan accordingly. This trend will have a profound impact in terms of personalized treatment and improved anti-cancer efficacy [22].

6. Conclusion

Structural modification and metabolic pathway optimization of anticancer drugs provide important means to improve drug efficacy and safety. Through the introduction of functional groups, changes in molecular ring structure, and covalent and non-covalent modifications, scientists have been able to effectively improve the metabolic stability, bioavailability, and targeting of drugs, thereby reducing their toxic side effects. In specific drug optimization processes, metabolic pathway optimization and structural modification of classical anticancer drugs such as paclitaxel and Adriamycin have significantly improved the clinical application of these drugs.

However, although structural modification and metabolic optimization provide effective solutions for anticancer drug development, there are still many technical challenges that need to be addressed. For example, how to more accurately predict the toxicity of drug metabolites and how to overcome individual differences due to the diversity of metabolizing enzymes remains a challenge in drug development. In addition, the balance between the drug's longevity and safety needs to be achieved through more in-depth research.

In the future, with the rapid development of precision medicine, genomics, big data and artificial intelligence technologies, personalized design of anti-cancer drugs will become increasingly important. By combining the patient's genetic information, metabolic profile and the specificity of the tumor microenvironment, drug structure modification and metabolism optimization can more accurately enhance drug efficacy and reduce toxic side effects. This not only brings new opportunities for personalized treatment, but also points to the direction of anti-cancer drug development.

In summary, structural modification and metabolic pathway optimization of anticancer drugs will continue to play a key role in future cancer therapy. By continuously exploring new structural modification techniques and metabolic optimization strategies, researchers are expected to develop more anti-cancer drugs with high efficacy and low toxicity, providing cancer patients with safer and more effective treatment options.

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