Proceedings of the 4th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/58/20241337

Research progress of paclitaxel in the field of antitumor

Qingyue Bu

Heilongjiang University Of Chinese Medicine

1203846808@qq.com

Abstract. Cancer is the second leading cause of human death globally, and its incidence is still increasing year by year. How to prevent and treat cancer is currently the focus of attention. Paclitaxel is a natural anti-tumor drug that has multiple important applications in tumor diseases due to its interactions with various cells and molecules. Although paclitaxel has shown high utility value and significant advantages in tumor treatment, it has limitations such as low solubility, fast metabolism, and poor targeting. This article focuses on the mechanism of action and drug resistance of paclitaxel in anti-tumor applications, as well as the research progress in the treatment of various tumor diseases.

Keywords: paclitaxel, drug resistance mechanism, anti-tumor.

1. Introduction to paclitaxel

Paclitaxel (PTX) is an effective ingredient extracted from the bark of Taxus chinensis, with the chemical formula C47H51NO14. It is a diterpenoid alkaloid compound. It is used in the clinical treatment of various cancers, dealing with various malignant tumors, especially in breast cancer. Its mechanism of action is mainly to stabilize and enhance the polymerization of microtubule proteins, prevent microtubule depolymerization, inhibit cell mitosis, and thus fight cancer. In treatment, the combination of albumin and paclitaxel is often used to improve the stability of paclitaxel.

2. The anti-tumor mechanism of paclitaxel

Firstly, paclitaxel can directly act on tumor cells, achieving a tumor-killing effect. Paclitaxel can inhibit microtubule depolymerization, leading to mitotic arrest and ultimately causing cancer cell death. Paclitaxel treatment prevents cell mitosis due to the presence of a small number of independent centromeres. BethA Weaver et al. found that paclitaxel did not inhibit cell mitosis, but rather induced the formation of multipolar spindles [1].

In addition, paclitaxel can stimulate the body's immune response and indirectly kill tumor cells. Research has shown that paclitaxel has a significant impact on different immune cells [2]. Teff cells can recognize and kill tumor cells. Studies have shown that the addition of effector T cells increases the number of Teff cells, indicating that effector T cells can enhance anti-tumor effects. For cytotoxic T cells, studies have shown that compared to monotherapy with cisplatin, the therapeutic effect of cisplatin combined with paclitaxel is stronger in enhancing the ability of cytotoxic T cells to recognize tumor antigens and perform specific killing on tumor cells. For regulatory T cells, studies have shown that the treatment with paclitaxel leads to regulatory T cell failure, breaking tumor immune tolerance and enhancing anti-tumor immune response. For macrophages, they can kill tumor cells through various

DOI: 10.54254/2753-8818/58/20241337

mechanisms, such as releasing nitric oxide. Paclitaxel can induce macrophages to release nitric oxide, enhancing anti-tumor effects. For dendritic cells (DCs), low and medium concentrations of paclitaxel have a promoting effect on DC maturation, enhancing self-antigen presentation. High concentrations of paclitaxel can kill DCs, weakening their immune activity. Meanwhile, the combination therapy of paclitaxel and DC can effectively inhibit tumor growth. For natural killer cells (NK), NK cells belong to the innate lymphocyte family and play an important role in natural immunity. They can kill both virus infected cells and cancer cells. Paclitaxel can activate NK cells without affecting their activity.

Table 1. Mechanisms of action of paclitaxel on different cells

Cell type	**Cellular action**	**Effect of paclitaxel**
Effector T cells	A very important immune effector cell can promote the occurrence and development of various inflammatory diseases. TEFF cells could recognize and kill tumor cells.	Enhanced immune function
Cytotoxic T cells	Identify tumor antigens and apply specific killing to tumor cells	Plays a regulatory role on toxic T cells
Regulatory T cells	Has significant ability to inhibit adaptive and innate immune responses	Directly acting on regulatory T cells, it not only affects the number and percentage of cells, but is also related to the inhibitory function of surviving cells
Macrophage	Kill tumor cells through various mechanisms, such as releasing lysosomal enzymes and nitric oxide.	Inducing macrophages to release nitric oxide and enhancing anti-tumor effects
Dendritic cells	The mechanism of action of this cell in stimulating antigen-specific immune response is to obtain and process tumor antigens, while presenting them to lymphocytes	Low to medium concentrations of paclitaxel have a promoting effect on dendritic cell maturation and enhance self-antigen presentation
NK cells	It can kill both virus infected cells and cancer cells	Activate NK cells without affecting their activity

3. Mechanism of paclitaxel resistance

3.1. Expression of drug efflux proteins

Upregulation of multidrug transporter protein expression can increase the efflux of PTX in cells, thereby reducing the concentration of drugs in tumor cells. FOXM1 is a transcription factor and proliferation-specific gene in the FOX family; It's expression and transcriptional activity are crucial in G1/S and G2/M cell cycle regulation, cell division, chromosome stability, and apoptosis. The expression of FOXM1 is closely related to ATP binding cassette (ABC) drug transporters, and its upregulation in the cell membrane leads to increased drug efflux and decreased drug influx, which may be an important mechanism of paclitaxel resistance [3]. Meanwhile, ABCC5 is a member of the ATP binding cassette (ABC) drug transporter protein, involved in pumping PTX out of cancer cells. In addition, studies have found rapid efflux of paclitaxel in certain drug-resistant tumor cells overexpressing 170-kD transmembrane proteins [4]. The ABC superfamily of drug efflux proteins includes P-glycoprotein (P-gp), also known as multidrug-resistant protein-1 (MDR-1). This protein is an effective ATP-dependent drug efflux pump that reduces the net intracellular concentration of natural product drugs, including paclitaxel, leading to paclitaxel resistance.

DOI: 10.54254/2753-8818/58/20241337

3.2. Changes in Microtubule Systems

The factors that lead to resistance to anti-mitotic drugs include intracellular accumulation of drugs, genetic or functional alternation of microtubule proteins, and alternation of MAP kinase cascade reactions [5]. Microtubulin is a group of proteins encoded by a highly conserved multi-gene family, participating in various cellular functions, and playing important roles in maintaining cell morphology, cell division, signal transduction, and material transport. β Type III microtubule protein isoforms are typically expressed in neurons of the central and peripheral nervous systems and can develop resistance to paclitaxel by inhibiting its microtubule stabilization ability. Experiments have shown that during chemotherapy β The expression of 3-tubulin showed an obvious upward trend. With the increase in the number of chemotherapy courses, the probability of resistance of breast cancer to taxanes was also increasing. That is to say β The expression of 3-tubulin is not only related to the primary drug resistance of breast cancer but also an important factor in the occurrence of secondary drug resistance of taxus [7]. For microtubule-associated proteins (MAP), studies have shown that paclitaxel inhibits the catalytic activity of MAP kinase in lung cancer cell lines. This biological effect may be the reason for the increased affinity between MAP2 and microtubule proteins, thereby promoting microtubule assembly. It is also one of the important mechanisms of drug resistance, as it is resistant to the action of paclitaxel drugs.

3.3. Cell apoptosis

The efficacy of chemotherapy drugs may be determined by many different factors, including the genotype of tumor cells. P53 tumor suppressor gene often mutates in human tumors, which can block cells in G2/M phase of the cell cycle as a survival factor of breast cancer cells treated with paclitaxel [8], which may lead to chemotherapy resistance [9]. In addition, previous studies have shown that the mitogen-activated protein kinase (MAPK) ERK and p38MAP kinase cascade are essential for paclitaxel induced cell death and are independent of p53 activity. It can also indirectly lead to cell resistance to paclitaxel.

4. The application of paclitaxel in the field of anti-tumor therapy

4.1. breast cancer

Breast cancer is still a global public health problem and is currently the most common tumor in the world. Among all malignant diseases, breast cancer is one of the main causes of postmenopausal women's death, accounting for 23% of all cancer deaths. Currently, there are three ways to treat breast cancer with paclitaxel: single drug therapy, combination therapy and targeted therapy.

1. Single drug treatment: Taxol has been widely recognized as a single drug for the treatment of advanced breast cancer. Clinical studies have shown that paclitaxel can effectively slow down the development of breast cancer and prolong the survival time of patients. During the treatment of breast cancer, paclitaxel can cause hypersensitivity and peripheral neuropathy. The combination of nanoparticle albumin and paclitaxel can minimize this toxicity and avoid prophylactic antihistamine and steroid treatments. Compared with paclitaxel, the average maximum concentration of free paclitaxel bound to albumin paclitaxel is 10 times higher. In addition, albumin bound paclitaxel is transported faster in the endothelial cell layer and exhibits greater tissue penetration and slower paclitaxel elimination [10].

2. Combination chemotherapy: Paclitaxel combined with other chemotherapy drugs can effectively control the condition and improve the quality of life of patients. Such as anthracycline drugs, platinum drugs, etc., to enhance therapeutic effects, improve patient survival rates, achieve more effective inhibition of tumor cell proliferation, induce cell apoptosis, and reduce the risk of tumor recurrence.

3. Targeted therapy: Paclitaxel often has limited efficacy due to delivery difficulties. Cationic antimicrobial peptides have been shown to enhance the absorption of chemotherapy drugs by tumor cells through membrane breaking. A thermosensitive gel has been designed and developed to co load Dermaseptin PP and paclitaxel liposomes to increase local chemotherapy. In vitro and in vivo anti-tumor

DOI: 10.54254/2753-8818/58/20241337

studies have shown that Dermaseptin PP/paclitaxel liposome gel can significantly inhibit tumor growth and has good biological safety for local chemotherapy [11].

4.2. Lung cancer

According to the World Health Organization, there are 6 million cases of cancer worldwide. Lung cancer accounts for one million, accounting for one sixth of it, and is the most common cancer worldwide [12]. In the treatment of lung cancer, paclitaxel mainly helps to control the spread of cancer by interfering with the growth and division of cancer cells. It can also trigger apoptosis signals inside cancer cells, inducing self-destruction of cancer cells. Paclitaxel plays an important role in various stages of lung cancer. For early-stage lung cancer patients, paclitaxel can be used as an adjuvant treatment after surgery to reduce the risk of tumor recurrence; For advanced lung cancer patients, the combination of paclitaxel and other chemotherapy drugs can effectively control the condition and improve the patient's quality of life. Research has shown that compared to monotherapy for lung cancer, the solvent-free albumin bound nanoparticle formulation of paclitaxel (albumin bound paclitaxel) aims to limit side effects and improve clinical efficacy, with higher concentrations within the tumor. The combination of paclitaxel and docetaxel in the treatment of non-small cell lung cancer has shown a response rate of nearly 25% for monotherapy, while the response rate after combination therapy ranges from 35% to 50% [13].

4.3. Ovarian cancer

According to reports, ovarian cancer causes more deaths than any other type of female reproductive tract cancer. Although less than 20% of ovarian cancer is diagnosed as limited to the ovaries, women with localized tumors have a five-year survival rate of over 90%. Approximately 90% of primary malignant ovarian tumors are epithelial (cancer), and most researchers believe that they originate from the surface epithelium of the ovary (OSE) or are more likely to originate from surface epithelial inclusion cysts [13]. According to reports, there is a water-soluble formula for a biopolymer that combines paclitaxel with synthetic polyamino acid poly (l-glutamic acid), called paclitaxel poly (grape ketone) (PPX), which can improve its delivery performance. Once PPX enters the tumor, it will accumulate within phagocytic cells (such as fixed tissue macrophages). In macrophages, glutamic acid residues are specifically cleaved by tissue protease B, producing active paclitaxel, thereby minimizing exposure to non-target tissues [14], reducing hypersensitivity reactions, and prioritizing their targeting of tumors. The treatment effect will also be better [15], and a combination of paclitaxel and docetaxel can also be used to treat ovarian cancer [16].

5. Summary and Outlook

Due to the effectiveness and safety of natural products, they have attracted the attention of researchers as potential chemotherapy agents. Paclitaxel is a natural anti-tumor drug that has shown important roles in cancer treatment. The significant challenges brought by cancer, as well as the adverse reactions and drug resistance caused by long-term treatment with a single drug, force us to shift our focus from a single target to regulating the in vivo network. The emergence of nanotechnology has further opened vast opportunities for exploring and expanding the use of paclitaxel in the medical field. The nano delivery system using paclitaxel and its derivatives has better bioavailability and solubility, and has obvious advantages in anti-tumor therapy, and can provide drugs for different targets or action sites. As reported in this review, the research on paclitaxel nanocarrier systems has received much attention, which will become a new method for cancer treatment. It is believed that paclitaxel will have more extensive and important applications in the field of anti-tumor in the future.

References

[1] Weaver B A. How tax/paclitaxel kills cancer cells [J] Molecular Biology of the Cell, 2014, 25 (18): 2677-2681

[2] Liu N, Zheng Y, Zhu Y, etc Selective introduction of CD4+CD25+foxp3+regulatory T cells by paclitaxel is explained by bcl2/bax mediated apoptosis [J] International Immunopharmacology, 2011, 11 (2): 212-219
[3] Hou Y, Dong Z, Zhong W, et al. FOXM1 promotes drug resistance in clinical cancer cells by regulating ABCC5 gene transfer [J] BioMed Research International, 2022, 2022: e3032590
[4] Covelli A. [SDZ PSC 833: a novel modulator of MDR] [J] Tumori, 1997, 83 (5 Supply): S21-24
[5] Fukuoka K, Saijo N. [antagonistic agents] [J] Gan to Kagaku Ryoho Cancer&Chemotherapy, 1997, 24 (11): 1519-1525
[6] Cui H, Arnst K, Miller D D, et al Recent advantages in elucidating paclitaxel resistance mechanisms in non-small cell lung cancer and strategies to overcome drug resistance [J] Current Medical Chemistry, 2020, 27 (39): 6573-6595
[7] Yang C P H, Horwitz S B. Taxol ®: The first microtubule stabilization agent [J] International Journal of Molecular Sciences, 2017, 18 (8): 1733
[8] Bacus S, Gudkov A V, Lowe M, et al. Taxol induced apoptosis depends on MAP kinase pathways (ERK and p38) and is independent of p53 [J] Oncogene, 2001, 20 (2): 147-155
[9] Sangrajrang S, Fellow A. Taxol resistance [J] Chemotherapy, 2000, 46 (5): 327-334
[10] Ueno N T, Mamounas E P. Neoadjuvant nab paclitaxel in the treatment of breast cancer [J] Break Cancer Research and Treatment, 2016, 156 (3): 427-440
[11] Combined thermosensitive gel co loaded with dermasteptin PP and PTX poses for effective local chemotherapy - PubMed [EB/OL] [2024-05-10] https://pubmed.ncbi.nlm.nih.gov/36711004/.
[12] Maghfoor I, Perry M C. Lung Cancer [J] Annals of Saudi Medicine, 2005, 25 (1): 1-12
[13] Cho K R, Shih I M. OVARIAN CANCER [J] Annual review of pathology, 2009, 4:287-313
[14] Galic V L, Wright J D, Lewin S N, etc Paclitaxel polarumex for ovarian cancer [J] Expert Opinion on Investigational Drugs, 2011, 20 (6): 813-821
[15] Galic V L, Wright J D, Lewin S N, etc Paclitaxel polarumex for ovarian cancer [J] Expert Opinion on Investigational Drugs, 2011, 20 (6): 813-821
[16] Paclitaxel and docetaxel in bread and ovarian cancer [J] Drug and Therapeutics Bulletin, 1997, 35 (6): 43-46