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Research Progress on the Mechanism of Dihydroartemisinin Against Colorectal Cancer

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Abstract

Research shows that colorectal cancer has become one of the most common malignancies in the world. Its incidence rate ranks third in the world among all kinds of tumors, and its mortality rate ranks second in the world. In China, the incidence of colorectal cancer is also increasing year by year. In recent years, a large number of studies have shown that dihydroartemisinin, an antimalarial component of traditional Chinese medicine, has a certain anti-colorectal cancer effect, which has attracted widespread attention. This paper summarizes and analyzes the effect of dihydroartemisinin in anti-colorectal cancer and the possible mechanisms involved in recent years. Meanwhile, it provides a reference for the clinical application and pharmacological research of dihydroartemisinin.

Keywords

Dihydroartemisinin; Colorectal Cancer; Mechanism.

1. Introduction

In recent years, the incidence of colorectal cancer(CRC) in the world has shown an obvious upward trend. The number of new cases is about 1.2 million and the number of deaths exceeds 600,000 each year. The incidence rate ranks third and the mortality rate ranks second [1]. CRC is excepted to reach more than 2.2 million new cases and 1.1 million deaths by 2030 [2]. Artemisinin is a sesquiterpenoids extracted from the traditional Chinese medicine Artemisia annua. It has a special peroxide bridge and it is currently the most effective treatment against malaria [3]. Nowadays, DHA is considered as a potential anti-colorectal cancer drug that promotes apoptosis of cancer cell, induces cell cycle arrest, and inhibits the invasion and migration of cancer cells.

In the paper, the anti-tumor mechanism, drug effect and drug toxicity of DHA against colorectal cancer are described.

2. Anti-tumour Mechanism

Colorectal cancer is a complex multi-gene and multi-step process, which generally includes normal epithelium - abnormal epithelium - tumour - cancer - cancer metastasis. The pathogenesis mainly includes three molecular mechanisms[4], namely, Chromosomal Instability (CIN), Microsatellite Instability (MSI) and CpG Island Methylisation (CIMP).

2.1. Promote Apoptosis of Tumour Cells

Apoptosis refers to the death mode in which the cell disappears itself according to its own procedures under certain physiological or pathological conditions. Through apoptosis, it is of great significance to remove damaged or mutant cells in the body to maintain the stability of the environment in the body and prevent tumours. Studies such as Li[5] et al. show that DHA can promote tumour cell apoptosis by up-promoting genes (Bax), downgrading or blocking

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anti-apoptosis genes (Survivin, Bcl-2), and coordinating bidirectional regulatory genes (Bid, Bim), thus playing an anti-cancer role. Some studies have further confirmed that DHA can block the expression of survivalin gene, increase the expression of caspase (caspase-3, caspase-8, caspase-9) gene, and promote colorectal cancer cells. Apoptosis[6]. Lu[7]et al. further confirm that DHA can cause apoptosis of colorectal cancer cell lines by promoting mitochondria-dependent pathways.

2.2. Promotes the Expression of Oncogene and Inhibit the Expression of Prooncogene

Proto-oncogenes are usually in a state of low expression or no expression. Their mutation activation can cause malignant proliferation and metastasis of cells and promote tumour occurrence. If the oncogenes that can inhibit cell growth in normal cell tissue are missing or muted, they can also cause cell malignant transformation and lead to tumours. Research[8] shows that protooncogenes closely related to colorectal cancer include Her-2, Braf, C-myc, PEK3CA, K-ras, etc., while oncogenes include SLC5A8, APC, DCC, p53, PTEN, etc.

2.3. Induction of Endoplasmic Reticulum Stress formation

Endoplasmic reticulum stress (ERS) usually forms when cells are confronted with extrinsic or intrinsic stimuli. Individuals with low ERS expression have rapid tumor cell proliferation, early lymph node metastasis, and high tumor metastatic invasion capacity, which directly affect their prognosis. Through proteomic studies, Lu [9]et al. suggested that redox imbalance may assist DHA to induce ERS, therefore improves DHA anticancer activity and helps it to exert anticancer effects.

2.4. Promotes Free Radical and Oxidative Stress Formation in Tumor Cells

The instability of free radicals determines their effect of causing cellular loss of function, gene mutation and death. Oxidative stress is a negative intracellular effect of free radicals, whose formation leads to a decrease in the tolerance of tumor cells to hypoxia or drugs, increasing the efficiency of treatment. Studies on the cytotoxic mechanisms of DHA and its related drugs have shown a correlation between the antitumor activity of DHA and free radical formation[10].

2.5. Other

Under normal conditions, the body's immune system can recognize and destroy pathogens (such as cancer cells). However, the massive proliferation of cancer cells and the secretion of related factors can antagonize, block or inhibit the immune response, making it difficult to exert anti-cancer effects. In recent years, some studies have shown that DHA can also exert anti-cancer effects through other mechanisms. Wang [11] et al. found that DHA could exert anti-cancer effects by inhibiting the tumor metastasis-associated factor uPA protein and reducing the number of positive units in colorectal cancer cells. It has also been reported that DHA and other artemisinin derivatives have inhibited tumor vascular endothelial cell proliferation, migration and tube formation, which provides a theoretical basis for the conjecture of inhibiting colorectal tumor angiogenesis[12] .

3. Drug Effects

As mentioned above, the anti-cancer mechanism of dihydroartemisinin, a TCM, is still unclear, but its adjuvant effects on the development and treatment outcome of colorectal cancer and other diseases should not be underestimated. In this paper, we analyze the following aspects of DHA to control the development of colorectal cancer and improve the treatment outcome of patients.

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3.1. Control the Development of the Occurrence

Inflammatory bowel disease, as a high-risk factor for colorectal carcinogenesis, plays an important role in the development of colorectal cancer, and controlling the extent and degree of its lesions can promote mucosal healing and help reduce the possibility of carcinogenesis. Bai [13] et al. established a colorectal cancer colitis (CAC) model and confirmed that the administration of DHA at different stages could inhibit the inflammatory effect and thus control the development of colorectal cancer, and no related side effects were observed.

3.2. Improved Treatment Outcomes

In the treatment of colorectal cancer, drug resistance is a major challenge that is difficult to overcome and is of great significance to patient outcomes.

Tumor hypoxia is one of the main biological factors leading to resistance to chemotherapy and radiotherapy, and it is no exception in the treatment of colorectal cancer. Some studies have shown that DHA exerts significant cytotoxic activity under both normoxic and severely hypoxic conditions [14]. It is suggested that the use of DHA therapy may provide new ideas to improve the outcome of colorectal cancer patients with tumor hypoxia. It is well known that acquired drug resistance is a major cause of treatment failure in colorectal cancer, and YAO Z[15] et al. demonstrated that DHA could improve patients' drug resistance, enhance treatment efficiency and improve treatment outcome by mediating apoptosis and increasing cell sensitivity to 5 - fluorouracil (5-FU). Currently, DHA has been widely accepted as a sensitizer for cancer therapy (specifically colorectal cancer). According to Li Q et al., who summarized the anti-cancer studies of artemisinin-based drugs, DHA was found to enhance the sensitivity of colorectal cancer cells to chemotherapy and improve treatment outcomes by acting on four proteins or pathways to wield anti-cancer effects.

4. Drug Toxicity

A large number of studies have shown that artemisinin drugs have the advantages of safety, high efficiency and few adverse reactions. At present, the drug toxicity studies of dihydroartemisinin mainly focus on the comparison and combination of dihydroartemisinin with common clinical drugs for colorectal cancer. Details are as follows:

4.1. Comparison with Commonly Used Clinical Drugs

At present, the treatment of colorectal cancer mainly adopts local surgical resection and drug combination therapy, and clinically commonly used chemotherapy drugs mainly include 5-FU and its derivatives, platinum and Topoisomerase Ⅰ inhibitors, etc. [16]. Slezakova and Ruda-Kucerova[17]through relevant studies on the safe dose range of DHA and related drugs, found that DHA, as an anticancer drug, did not produce significant toxicity, and on the basis of inhibiting Solid Tumors and playing the role of Chemical Sensitization in vivo, had the advantage of low incidence of adverse reactions compared with commonly used clinical chemotherapy drugs.

4.2. Effect of Drug Combination

Drug combination is a common strategy and method in the treatment of tumor. Some studies have shown that the combination of DHA and Sodium Salicylate (SS) can significantly inhibit the proliferation of colorectal cancer cells at low concentrations, but the synergistic mechanism between the two has not been clarified [18]. At present, DHA's advantages over traditional anticancer drugs are mainly reflected in fewer adverse reactions and lower doses required to exert cytotoxicity. Therefore, the research on DHA combination against colorectal cancer needs to be further deepened and expanded.

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5. Conclusions and Recommendations

In conclusion, as an anti-colorectal cancer drug, DHA, its anti-tumor mechanism is still lack of perfection, its therapeutic effect remains to be investigated, and further research is needed to confirm it. However, it is currently believed that DHA can promote tumor cell apoptosis, regulate the expression of tumor suppressor and tumor-promoting genes, and induce the formation of endoplasmic reticulum stress. At the same time, DHA can also control inflammation and improve hypoxia environment. We found that there is a lack of clinical data, so more clinical trials are needed to further confirm the direct impact of DHA on the disease outcome of colorectal cancer patients. In terms of drug toxicity, DHA has the characteristics of safety and low toxicity, but its toxicity to tumor cells remains to be investigated.

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