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Research Progress on the Regulation of Ferroptosis by Traditional Chinese Medicine in the Intervention of Hepatocellular Carcinoma

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Abstract: Hepatocellular Carcinoma is a common malignant tumour in China, with high morbidity and mortality rates, seriously threatening people's lives and health. Traditional treatments for liver cancer have poor efficacy, high toxicity and side effects, drug resistance and easy recurrence. Traditional Chinese medicine, however, has the advantages of multiple pathways and low side effects because it is derived from natural products. Ferroptosis, as a new type of cell death, can effectively inhibit the proliferation and metastasis of hepatocellular carcinoma cells, and significantly improve the resistance of hepatocellular carcinoma patients to chemotherapeutic drugs and their sensitivity to radiotherapy. Numerous studies have shown that the active ingredients in traditional Chinese medicine can induce the occurrence of ferroptosis and inhibit the progression of hepatocellular carcinoma through lipid peroxidation, iron metabolism, and Xc--GSH-GPX4 system in order to exert anti-hepatocellular carcinoma efficacy. This paper summarises the relationship between the occurrence of ferroptosis and hepatocellular carcinoma, and discusses the mechanism of targeting and regulating the ferroptosis of TCM extracts against hepatocellular carcinoma, with a view to providing research ideas and theoretical basis for the treatment of hepatocellular carcinoma by traditional Chinese medicine.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumours [1], and is the fourth most common malignant tumour and the second most lethal cause of malignant tumours in China [2], with approximately 110,000 deaths per year, making it a major challenge for global healthcare. Primary hepatocellular carcinoma has an insidious onset, with no obvious symptoms in the early stage, and the disease progresses more rapidly, and most patients are already in the middle or late stage when they are detected, and the choices of chemotherapy and targeted therapy for advanced hepatocellular carcinoma are still limited and have a poor prognosis [3]. Chemotherapy

resistance is a major constraint in the clinical treatment of hepatocellular carcinoma patients in advanced stages. Most chemotherapeutic drugs, as well as immunosuppressants and targeted drugs, have a series of drawbacks such as intolerance and high toxicity and side effects for most patients. However, traditional Chinese medicine is mainly based on natural ingredients, and has shown multiple advantages in clinical treatment, such as multiple pathways, high efficiency, and low adverse effects [4], so traditional Chinese medicine is getting more and more attention in the field of anti-hepatocellular carcinoma.

Ferroptosis is a new form of cell death [5], which plays an important role in the development of hepatocellular carcinoma. Some studies have shown that sorafenib resistance in hepatocellular carcinoma is associated with ferroptosis [6], and the proliferation, invasion and metastasis of hepatocellular carcinoma cells can be inhibited by regulating ferroptosis, thus improving the resistance of hepatocellular carcinoma patients to chemotherapy and the sensitivity of radiotherapy. Therefore, further research on the mechanism of action of targeting to induce ferroptosis in tumour cells is a new way to treat liver cancer and has potential significance for future clinical applications. Therefore, this paper takes the ferroptosis mechanism as an entry point to explore the molecular mechanism and action target of TCM to regulate ferroptosis in the development of hepatocellular carcinoma, so as to enrich the theory of TCM and provide a theoretical basis for the research of clinical prevention and treatment of hepatocellular carcinoma.

2. Ferroptosis mechanisms and their relationship to hepatocellular carcinoma

2.1 Ferroptosis

Ferroptosis is a cell death process driven by iron-dependent phospholipid peroxidation [7], which involves a variety of cellular metabolic pathways including redox homeostasis, iron metabolism, and lipid metabolism [8], and occurs by exogenous pathways through inhibition of cystathionine/glutamate transport proteins or activation of iron-transporting proteins and endogenous pathways through the inhibition of antioxidant enzymes such as glutathione peroxidase 4, GPX4. The main mechanism driving ferroptosis is the accumulation of lipid peroxides in the cell [9]. ferroptosis is triggered when drivers such as polyunsaturated fatty acid-phospholipid peroxidation, iron and mitochondrial metabolism exceed the detoxification capacity of the defence systems. In this regard, the regulatory role of the antioxidant reduction defence system Xc - GSH - GPX4 inferroptosis is that Xc - provides raw material for the synthesis of GSH by uptake of cystine and its reduction to cysteine.GSH acts as a cofactor for GPX4 to help GPX4 to reduce lipid peroxides and maintain intracellular redox homeostasis to prevent ferroptosis [10]. Key features of ferroptosis include lipid peroxidation mediated by an imbalance in iron ion homeostasis and diminished cellular reducing power [11]. Iron ions generate hydroxyl radicals via the Fenton reaction, which react with polyunsaturated fatty acids (PUFAs) in the cell membrane and plasma membrane, triggering a chain reaction that generates large amounts of lipid ROS, leading to cell death [12].

2.2 Ferroptosis regulates an important signalling pathway in HCC

2.2.1 NRF2

NRF2 (Nuclear factor erythroid 2-related factor 2) is a key transcription factor that regulates cellular antioxidant and metabolic stability. Under normal conditions, NRF2 binds to Keap1 and is ubiquitinated and degraded. Under oxidative stress, NRF2 dissociates from Keap1 and initiates transcription of downstream genes. It has been shown that NRF2 protects cells from ferroptosis by regulating the activity of glutathione peroxidase 4 (GPX4) and system Xc- (SLC7A11) [13]. In HCC, activation of NRF2 increases resistance to sorafenib by hindering lipid metabolism through

upregulation of metallothionein-1G (MT-1G).

2.2.2 ACSL4

ACSL4 (long chain fatty acid coenzyme A synthase 4) is one of the key regulators of ferroptosis. ACSL4 expression levels were higher in liver tissues that responded favourably to sorafenib, whereas the opposite was true in patients with poor therapeutic efficacy.ACSL4 enhances cellular sensitivity to ferroptosis by promoting the synthesis of polyunsaturated fatty acids (PUFAs) and increasing the amount of PUFAs in cellular membranes [14]. Therefore, ACSL4 could be a potential biomarker for predicting the efficacy of sorafenib.

2.2.3 P53

p53 plays an important role in the development and progression of hepatocellular carcinoma. Studies have shown that p53 silencing does not exacerbate the progression of HCC, but instead enhances the efficacy of sorafenib by contributing to ferroptosis. The mechanism mainly involves the disturbance of iron metabolism, which leads to the accumulation of lipid ROS, thus enhancing the therapeutic effect of sorafenib [15]. In addition, activation of the p53 signalling pathway induces the expression of ACSL4 and increases the sensitivity of cells to ferroptosis.

3. Modulation of ferroptosis by herbal extracts in anti-HCC studies

3.1 Dioscorea opposita

The history of Dioscorea spp. in China can be traced back to thousands of years ago, and it is one of the earliest plants with the same origin of medicine and food. Traditional medicine believes that it can enter the meridians of the spleen, lungs, and kidneys, and it has the ability to tonify the triple jiao qi and yin and tonify the astringency, which can both tonify the middle and benefit the qi, and prolong the longevity of the body [16]. Diosgenin is a class of natural compounds mainly extracted from the rhizomes of Dioscorea spp and belongs to the class of phytosteroid compounds, which is widely used as a basic raw material in the field of synthesising steroidal drugs [17]. Due to the advantage of lower side effects of its natural constituents and various pharmacological effects such as anticancer, hepatoprotective, antioxidant, etc., it has received wide attention and application in various fields of medicine [18].

Studies have shown that Diosgenin reduces the formation of hepatic lipid vacuoles and prevents cellular damage, oxidative stress, lipid accumulation and mild inflammation by inhibiting the expression of two adipogenic genes, namely sterol regulatory element-binding protein 1c (SREBP-1c) and fatty acid synthase (FAS), and thus exerts hepatoprotective effects [19]. Stearoyl coenzyme a desaturase 1 (SCD1), regulated by SREBP1, is a key regulator of fatty acid metabolism.SCD1 desaturates palmitoyl coenzyme a or stearoyl coenzyme a to form palmitoleic acid and oleic acid, respectively[20]. Down-regulation of SCD1 inhibits the synthesis of monounsaturated fatty acids (MUFAs) and increases the sensitivity of cancer cells to ferroptosis, which in turn inhibits tumour progression [21]. In addition, SCD1 was reported to be significantly upregulated in hepatocellular carcinoma cells and its expression was associated with poor prognosis [22]. It was found that SCD1-catalysed MUFAs effectively inhibitedferroptosis by replacing polyunsaturated fatty acids in lipid membranes, thereby reducing lipid ROS accumulation [23].

3.2 Rhizoma Paridis

As a traditional medicinal herb, Chonglou has the effect of clearing heat and detoxification,

reducing swelling and cooling the liver. Modern studies have shown that Chonglou contains a variety of active ingredients and pharmacological effects with significant antitumour activity, especially in hepatocellular carcinoma. Among them, Chonglou saponin 1 showed dose-dependent inhibition of hepatocellular carcinoma cells, increasing the levels of reactive oxygen species and MDA in hepatocellular carcinoma cells through the Nrf2/HO-1/GPX4 axis, depleting GSH, inhibiting the redox defence system Xc--GSH-GPX4, and contributing to the accumulation of Fe2+ inducing the ferroptosis of hepatocellular carcinoma cells thereby inhibiting hepatocellular carcinoma cell proliferation, invasion, and the cycle progression [24].

3.3 Scutellariae Radix

Scutellaria baicalensis, as a commonly used traditional Chinese medicine, has the effects of clearing heat and removing toxins, cooling blood and stopping bleeding. Modern pharmacological studies have shown that a variety of active components in Scutellaria baicalensis have anti-inflammatory, antioxidant and antitumour effects as well as immunomodulatory effects. Among them, baicalin, as an extract of Scutellaria baicalensis, can inhibit the progression of hepatocellular carcinoma by inhibiting the expression of GPX4 and xCT in hepatocellular carcinoma cells, inhibiting the production of GSH, destroying the cellular antioxidant system, contributing to the accumulation of ROS, and inducing cellular ferroptosis, and baicalein is not only limited to the treatment of hepatocellular carcinoma, but also can be applied to iron metabolism disorders, immunomodulatory diseases and other disorders [25].

4. Conclusion

Ferroptosis is a novel mode of cell death involving multiple pathways, mainly including lipid peroxidation, iron ion accumulation, and System Xc-/GSH/GPX4. ferroptosis plays an important role in hepatocellular carcinoma occurrence, development and treatment. Especially, it is related to drug resistance in hepatocellular carcinoma patients, and the inhibition of ferroptosis can alleviate the drug resistance of patients, which is of great clinical significance in the treatment of hepatocellular carcinoma. And compared with traditional chemotherapeutic drugs, traditional Chinese medicine has significant advantages such as multi-targeting and low side toxicity. In conclusion, Chinese traditional medicine has shown a broad application prospect in intervening hepatocellular carcinoma by regulating ferroptosis, and future studies need to further clarify the key nodes of ferroptosis regulation in the process of hepatocellular carcinoma development, so as to provide a more solid and scientific theoretical basis for the regulation of ferroptosis by Chinese traditional medicine in the treatment of hepatocellular carcinoma.

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