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Research Progress of Resveratrol in the Prevention and Treatment of Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in clinic. Although there are various treatment methods, the overall curative effect is not effective. Resveratrol is an antitoxin secreted by plants when stimulated. It is a non-flavonoid polyphenol organic compound, which has many biological functions, such as antiplatelet aggregation, regulating lipid metabolism, anti-inflammatory, and antioxidant and so on. In recent 20 years, resveratrol has been found to have preventive and therapeutic effects on a variety of cancers. This paper reviews the prevention and treatment of hepatocellular carcinoma by resveratrol from the aspects of tumor prevention, tumor microenvironment, tumor metabolism, invasion and metastasis.

Keywords: Hepatocellular Carcinoma; Resveratrol; Research Progress

Abbreviations: HCC: Hepatocellular Carcinoma; HBx: Hepatitis B Virus X; MMPs: Matrix Metalloproteinases; PA: Plasminogen Activators; VEGF: Vascular Endothelial Growth Factor.

Introduction

According to Global Cancer Statistics 2020, liver cancer is the sixth most common tumor and the third most common cause of cancer-related deaths in the world. China's new cases and related deaths account for 45% and 47% of the global total respectively [1]. The main pathological type is hepatocellular carcinoma, accounting for 75% [2]. Resveratrol was originally isolated from resveratrol by Japanese scientist Takaoka in 1939, and was later found to be widely present in the plant kingdom, such as common grapes, peanuts, mulberry, blueberries, and so on [3]. As a plant antitoxin, resveratrol didn't attract much attention from the medical community until 1990, when it came to prominence because of the "French paradox" [4]. Subsequently, more and more studies found that resveratrol has a variety of pharmacological activities, among which it has preventive and therapeutic effects on many tumors, such as breast cancer [5], lung cancer [6], hepatocellular carcinoma [7], gastric cancer [8], and so on. For hepatocellular carcinoma, resveratrol exhibits diverse anticancer mechanisms, which are summarized as follows:

Prevention of Hepatocellular Carcinoma

The main predisposing factors for hepatocellular carcinoma include viral hepatitis, obesity, alcohol, and aflatoxin exposure [9,10]. Research has found that hepatitis B virus X (HBx) can promote the occurrence of HCC through

multiple pathways [11]. Lin, et al. [12] used resveratrol to treat HBx transgenic mice and found that it not only delayed the occurrence of HCC, but also reduced the incidence of HCC. This may be related to inhibiting fat formation, temporarily stimulating liver regeneration, and enhancing antioxidant capacity.

Regulating the Microenvironment of Hepatocellular Carcinoma

The tumor microenvironment consists of cancer-related fibroblasts, endothelial cells, immune cells, and various cytokines. Its importance in solid tumors has been widely recognized [13,14]. M2 type macrophages and $CD8+CD122^+$ regulatory T cells can inhibit anti-tumor immune responses [15,16]. Zhang, et al. [17] used resveratrol to act on the subcutaneous transplanted tumor model of mouse liver cancer and the orthotopic transplanted tumor model of mouse liver cancer, and found that it can effectively inhibit the development of cancer, mainly manifested in inhibiting cell proliferation, tumor angiogenesis, and inducing cell apoptosis. The mechanism may be that resveratrol inhibits the production of $CD8+CD122^+$ regulatory T cells and the polarization of M2 macrophages. A main characteristic of HCC is hyper vascularity, which is predictive of a poor prognosis [18]. Yan, et al. [19] found that hepatic stellate cells can promote the expression of vascular endothelial growth factor (VEGF) by up-regulating the expression level of Gli-1 protein on HepG2 cells, thus mediating the angiogenesis of human umbilical vein endothelial cells, while resveratrol can inhibit this process by down-regulating the expression of Gli-1 protein. Yu, et al. [20] used resveratrol on BALB/c nude mouse model of liver cancer, and also found that resveratrol can reduce VEGF expression and inhibit tumor angiogenesis, which may be related to the inhibition of NF-κB activity.

Regulation of Hepatocellular Carcinoma Metabolism

Reactive oxygen species produced during metabolic stress play an important role in the occurrence and development of liver cancer. Divya, et al. [21] used alcohol-aflatoxin B1 to induce male albino rats to establish an animal model of liver cancer, and found that resveratrol could negatively regulate the activation of NF-κB, restore the normal levels of catalase and glutathione peroxidase, and thus inhibit the occurrence and development of tumor.

Regulation of Invasion and Metastasis of Hepatocellular Carcinoma Cells

Breaking through the extracellular matrix and basement membrane is the key to the successful invasion of tissues by cancer cells. Matrix metalloproteinases (MMPs), plasminogen activators (PA), serine proteinase and cathepsins play an important role in this process [22]. Yu, et al. [23] found that resveratrol can down regulate TNFα-mediated MMP9 transcription and expression by inhibiting the activation of NF-κB, thereby preventing invasion and migration of HepG2 hepatoma cell. Pan, et al. [24] found that red sandalwood Astragalus (a natural dimethylated analogue of resveratrol) can also down-regulate the transcription and expression of MMP9 and reduce the invasiveness of hepatoma cells. The molecular mechanism is that red sandalwood Astragalus inhibits PKCs/MAPK/AP-1 and PI3K/AKT/NF-κB signaling pathways. Chao, et al. [25] used resveratrol to act on Huh-7 hepatoma cells and found that it can significantly inhibit the migration and invasion of hepatoma cell migration. The underlying molecular mechanism may be that resveratrol down regulates SP-1 by inhibiting JNK1/2 phosphorylation, ultimately reducing u-PA expression. c-Met is a tyrosine kinase receptor whose natural ligand is hepatocyte growth factor (HGF) [26]. When c-Met is activated, it can activate multiple downstream signaling pathways through GRB2 and GAB1 to regulate cell cycle, survival, proliferation, invasion, and metastasis [27]. Gao, et al. [28] used resveratrol to act on liver cancer cell lines and xenotransplantation nude mice models, and found that resveratrol can significantly reduce the invasive ability of liver cancer cells. The molecular mechanism is that resveratrol can not only inhibit HGF-induced c-Met activation, but also down regulate the expression of c-Met on the cell membrane. De, et al. [29] found that resveratrol can directly inhibit the secretion of HGF.

Regulate Regulatory Cell Death in Tumor Cells

In 2018, the naming committee of cell death divided cell death into accidental cell death and regulatory cell death. Regulatory cell death can occur under physiological or pathological conditions, including apoptosis, autophagy, Pyroptosis and iron death [30]. Zhang, et al. [31] used resveratrol to act on the MHCC97-H hepatoma cell line and found that resveratrol promoted the expression of the autophagic marker Beclin1, up regulated the LC3 II/I ratio, and significantly down regulated the expression of p62 in a dose dependent manner. The mechanism may be that resveratrol completed by regulating the p53 and PI3K/Akt pathways. Chai, et al. [32] used resveratrol to act on liver cancer cell lines and found that the apoptosis rate in the resveratrol group was significantly increased. The mechanism was that resveratrol could significantly up regulate the Bax/Bcl-2 ratio, activate caspase-3 and caspase-7, and induce the cleavage of PARP. This is consistent with the conclusion found by Devaraja, et al. [33] in the N-nitrosodiethylamine induced male Wistar rat liver cancer model. In addition, Devaraja, et al. [33] also discovered two phenomena:

- Medication in the late stage of cancer has therapeutic effects, although it is not as effective as medication in the

early stage.

- Resveratrol has no or minimal effect on the normal group of rats, indicating that resveratrol itself may be a good targeted drug.

Regulation of Liver Cancer Cells by Modified Resveratrol

Resveratrol is a natural non-flavonoid drug with a variety of anticancer activities. However, the bioavailability of free resveratrol is low (oral activity < 1%), and its biological half-life is low (30 min - 45 min), limiting its clinical application [34]. Nano carriers can effectively solve these problems. Due to the activation of the scramblase enzyme or oxidative stress in the tumor microenvironment, the symmetry of plasma membrane is lost, resulting in the exposure of negatively charged phosphatidylserine on the surface, which is a unique feature of cancerous cells. Satveer, et al. [35] prepared resveratrol cationic liposomes based on this property, and conducted pharmacokinetic and pharmacokinetic studies on rat liver cancer induced by N-nitrosodiethylamine. It was found that compared to free resveratrol, the localization of resveratrol cationic liposomes in liver cancer tissue increased by 3.2 times, AUC and Cmax increased by 2.2 times, and the number of liver cell nodules in animals treated with resveratrol cationic liposomes significantly decreased, which is consistent with Rahman's research conclusion [36]. Zheng, et al. [37] modified nanoparticles containing resveratrol and curcumin with SP94, which has high affinity with various liver cancer cells, and achieved the same effect in animal experiments. Similarly, Doaa, et al. [38] obtained a similar conclusion by conjugating resveratrol with sulfasalazine using dual targeted micelles. Iris, et al. [39] treated six resveratrol oligomers on HepG2, Hep3B liver cancer cell lines, and HH4 normal human liver cell lines. Compared with resveratrol monomer, resveratrol tetramer has the strongest cytotoxicity and exhibits low toxicity to HH4 cells, suggesting that resveratrol oligomer has stronger anticancer effect.

Effect of Resveratrol Combined with Other Drugs on Hepatocellular Carcinoma

Sorafenib is the only approved targeted drug for patients with advanced liver cancer that can improve overall survival [40,41]. However, high prices, low tumor response, and significant drug side effects limit the use of sorafenib [42]. Gao, et al. [7] used resveratrol in combination with sorafenib in HepG2, Huh-7 hepatoma cell lines, and BALB/c nude mouse tumor xenograft models. He found that the combined treatment group was more able to induce S phase arrest and apoptosis in hepatoma cell lines than the single treatment group, which may be related to down regulating the expression of CDC25A and CDK2, inhibiting the PKA/AMPK/eEF2K signaling pathway, and blocking the activation of Caspase-3/8/9. Resveratrol combined with 5-FU43 and paclitaxel [43,44] also obtained good anticancer effects. TXNIP may appear a potential novel therapeutic target. Certain anti-diabetic agents like metformin, GLP-1 agonists and CRMs like resveratrol have been shown to inhibit TXNIP expression [45].

Conclusion

In summary, the mechanisms of action of resveratrol in preventing and treating hepatocellular carcinoma are diverse, covering multiple stages of the occurrence and development of hepatocellular carcinoma. Unfortunately, the above experiments are limited to the cellular and animal levels and have not been further confirmed by corresponding clinical studies.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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