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Research progress on the role of TGF-β in regulating the microenvironment of hepatocellular carcinoma and multidrug resistance

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Abstract: *Liver cancer is one of the malignant tumors of the digestive system with high incidence. The specificity of early clinical manifestations is not significant, and it is often difficult to detect. Most patients are diagnosed in the middle and late stage, at which time chemotherapy is the preferred treatment, and multi-drug resistance of patients to chemotherapy drugs is the main obstacle to poor chemotherapy effect. The microenvironment of liver cancer is closely related to the formation of multi-drug resistance of liver cancer. TGF-β, as a key regulatory factor in the microenvironment of liver cancer, plays an important regulatory role in the development, invasion, and metastasis of liver cancer cells, blood vessel production and epithelial-mesenchymal transformation in the microenvironment of liver cancer. At the same time, the regulatory effect of TGF-β on tumor microenvironment is closely related to multi-drug resistance of liver cancer. Studying the role and mechanism of TGF-β in regulating liver cancer microenvironment and multi-drug resistance, and finding the target of reversing multi-drug resistance of chemotherapy drugs has become an urgent problem for liver cancer treatment.*

Keywords: *liver cancer; Multidrug resistance; Tumor microenvironment; Liver cancer microenvironment; TGF - beta*

1. Introduction

Liver cancer is one of the most common gastrointestinal malignancies in the world [1-2] and the third leading cause of cancer-related death, with a 5-year survival rate of only 18% [3]. The main factor is that the onset of liver cancer is relatively hidden, and once it is found, most of it is in the middle and late stages, and the best treatment opportunity is lost. Therefore, there are still many challenges to improve the prognosis of middle and late liver cancer [4]. Early clinical diagnosis of liver cancer is not easy to find, most patients with poor surgical efficacy, chemotherapy has become the first choice of treatment for liver cancer patients. 5-fluorouracil, doxorubicin, cyclophosphamide, vincristine, and oxaliplatin are commonly used and effective chemotherapy drugs for patients with liver cancer. Although the mechanism of action of various chemotherapy drugs is different, after a certain course of clinical application, liver cancer patients have varying degrees of drug resistance to various chemotherapy drugs, which is called cancer multidrug resistance (MDR), which will indirectly affect the efficacy of chemotherapy drugs.

A large number of studies have shown that the complex composition of the liver cancer microenvironment and its interaction relationship network is one of the important reasons leading to multi-drug resistance [5]. The liver cancer microenvironment includes cellular and non-cellular components, and TGF-β(transformation growth factor-β) in non-cellular components is an important regulatory factor of the liver cancer microenvironment, secreted by a variety of tumor cells and stromal cells. Tumor growth and metastasis are regulated through immune escape, maintenance of tumor stem cell homeostasis, the influence of tumor-related micro angiogenesis, and induction of epithelial-mesenchymal transformation [6]. The effect of TGF-β on the microenvironment of liver cancer is closely

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related to the multi-drug resistance of tumors. Studying its mechanism of action will help us provide new ideas for the treatment of liver cancer. In this paper, the mechanism progress of TGF-β regulation of the liver cancer microenvironment involved in multi-drug resistance is summarized below.

2. Cancer multidrug resistance

In traditional chemotherapy, multidrug resistance is the main obstacle to the efficacy of chemotherapy and seriously affects the clinical efficacy. And the use of single-component chemotherapeutic drugs can lead to a variety of problems such as drug resistance, solubility, poor stability, non-targeting, uncontrolled drug release, use of high doses of drugs, and adverse reactions [7]. Drugs associated with reversing the multidrug resistance mechanism in tumors have significant advantages multiple chemotherapeutic drugs simultaneously increase sensitivity to cancer cells, reduce drug dosage, and prevent adverse reactions [8]. Therefore, starting from the multidrug resistance mechanism is the key to breaking through the dilemma of tumor treatment.

Tumor drug resistance is the reduction of the sensitivity of the cancer cells themselves to the drugs, which produces a tolerant response and can continue to proliferate and invade. It is mainly divided into two types: primary drug resistance and acquired drug resistance [9]. The former is a phenomenon in which the tumor cells' genes or specificity cause the cells to become resistant to drugs when they start using them. And acquired resistance is the tumor cells gradually developing tolerance manifestation to this type of drug after using the drug for a while. Among them, the phenomenon of tumor cells under the chemotherapeutic effect of one drug, while at the same time producing cross-tolerance to other drugs with diverse mechanisms of action and structural types, is called multidrug resistance [10]. The factors related to the occurrence of multidrug resistance in tumors are divided into two types: cellular and non-cellular mechanisms. The mechanisms of cellular resistance are as follows: ① membrane transporter protein-mediated resistance, the ABC transporter protein on the cell membrane will expel chemotherapeutic drugs to the outside of the cell, reducing the concentration of the drug and thus generating resistance[11]; ② enzyme system-mediated resistance, for example, the glutathione transferase in the drug-resistant cells catalyzes the combination of anticancer drugs and promotes the metabolism of the drug and conversion, and reduces the toxicity of the drug to the cell, thus generating Resistance[12-13];③ apoptosis gene-mediated resistance, some chemotherapeutic drugs induce apoptosis of tumor cells to fight against tumor cells, and the resistance of tumors to drug-resistant passages to increase the expression of relevant anti-apoptotic genes to produce resistance[14-15]; ④ DNA repair mechanism-mediated resistance, some chemotherapeutic drugs target the DNA of the tumor cells, and the damage indirectly inhibits the proliferation of cells to achieve the effect of killing the tumor. Some chemotherapeutic drugs target DNA in tumor cells, and their damage indirectly inhibits cell proliferation to kill the tumor. However, there is a DNA damage repair mechanism in cancer cells, and the cells interact with enzymes to improve DNA function and thus produce drug resistance [16]. Non-cellular mechanisms mainly include ① hypoxia and micro angiogenesis; hypoxia and micro angiogenesis are conducive to tumor proliferation and metastasis, and it has been found that the HIF-1α factor in hypoxia can regulate the MDR gene and thus produce drug resistance[17], in addition, hypoxia is often accompanied by abnormal vascular function, which can't spread the drug adequately and indirectly reduce the concentration of the drug, thus leading to drug resistance [18-19]; ② epithelial mesenchyme, epithelial-mesenchymal transition, cells with epithelial-mesenchymal transition characteristics are more invasive and migratory, affecting the sensitivity of the cells to the drug and resulting in drug resistance [20].

The various components mentioned above that influence the mechanism of multidrug resistance in tumors are also an important part of the liver cancer microenvironment, and the tumor cells themselves and the various substances in the microenvironment influence the growth and development of tumors through reciprocal effects, which is inextricably linked to tumor drug resistance [21]. Therefore, exploring the relationship between the microenvironment of hepatocellular carcinoma and multidrug resistance to hepatocellular carcinoma is of great clinical significance for the treatment of improving chemotherapy and reducing drug resistance in hepatocellular carcinoma.

3. Hepatocellular carcinoma microenvironment

3.1 Tumor microenvironment

It is well known that the tumor microenvironment provides cancer cells with the necessary growth

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nutrients and suitable environmental structure, and the system composition is complex. Dynamic interactions between cancer cells and their microenvironment affecting tumor therapy and related drug resistance mechanisms have become a hot topic in cancer research at this stage. The tumor microenvironment is mainly divided into cellular and non-cellular components. Cellular components include tumor cells themselves, endothelial cells, myofibroblasts or cancer-associated fibroblasts, adipocytes, and a variety of immune cells: neutrophils, tumor-associated macrophages, myeloid-derived suppressor cells, infiltrating lymphocytes, dendritic cells [22]. Non-cellular components mainly include inflammatory factors and chemokines secreted by various cells in the tumor microenvironment, e.g., interleukins and transforming growth factors; extracellular matrix: collagen, non-collagenous proteins, elastin, proteoglycan, amino glycans, etc. And tumor-associated microvascular system and microenvironment resulting in tumor-specific hypoxia, chronic inflammation, and hypotactic features [23-26].

3.2 Liver cancer microenvironment

As tumor microenvironment research continues to unfold, a large number of scholars have reported that the microenvironment plays a very important role in multidrug resistance in hepatocellular carcinoma. The liver cancer microenvironment is composed of cellular components and non-cellular components, which include hepatocellular carcinoma cells, a variety of immune cells, hepatic stellate cells, hepatocellular carcinoma-specific Kupffer cells, tumor-associated endothelial cells, fibroblasts, and non-cellular components of micro vessels, lymphatic vessels, cytokines, chemokines, and extracellular matrix (ECM), which provide liver cancer cells with a local microenvironment for their growth [27-29]. The development of hepatocellular carcinoma is inextricably linked to various substances in its microenvironment. When the microenvironment is disturbed by various factors, the development of liver cancer will be further aggravated.

3.2.1 Cellular Components in the Microenvironment of liver cancer

Hepatic stellate cells, kupffer cells, a variety of immune cells (regulatory T cells, cytotoxic T cells, tumor-associated macrophages), endothelial cells, fibroblasts, and other components specific to the liver are the basis for the liver to become an important immune organ in the body [27-28]. Its cells and cell secretion products interact with each other to maintain the health and stability of the microenvironment. Once tumor cells invade the microenvironment, the roles of the relevant cells are altered to form a unique tumor microenvironment. Hepatocytes provide an immunosuppressive environment for tumor cells by inducing myeloid-derived suppressor cells and regulating T cells; cancer-associated fibroblasts promote proliferation and metastasis of hepatocellular carcinoma cells by secreting multiple cytokines, growth factors, and chemokines; and hepatocyte-specific macrophages and kupffer cells secrete large amounts of osteoblasts, which play an important role in the signaling pathways related to inflammatory reactions, tumor development, and metastasis-related signaling pathways [30].

3.2.2 Non-cellular Components of the liver cancer microenvironment

Non-cellular components of the liver cancer microenvironment include cytokines, chemokines, micro vessels, lymphatic vessels, extracellular matrix (ECM), and microenvironment-specific features such as hypoxia, acidity, and chronic inflammation. It also plays an important role in the growth and development of hepatocellular carcinoma cells and the construction of the tumor microenvironment [21]. The interactions between cellular components and their non-cellular components in the microenvironment are further involved in regulating and influencing the hepatocellular carcinoma microenvironment, which further promotes tumor growth.

4. Liver cancer tumor microenvironment and multidrug resistance

The hepatocellular carcinoma microenvironment is a multilevel regulatory network composed of cellular and noncellular components, which is inextricably linked to its drug resistance. The mechanism of drug resistance is not only the endogenous variation of tumor cells but also the alteration of the microenvironment in which the cells are located. Tumor cells and their surrounding mesenchymal cells influence the biological behavior of tumors through reciprocal interactions, including epithelial-mesenchymal transformation, maintenance of tumor stem cell properties, tumor micro angiogenesis, and chemoresistance that contribute to the MDR phenomenon in hepatocellular carcinoma cells [31].

Among the endogenous transformations of tumor cells that affect drug resistance are closely related to a variety of components such as hepatic stellate cells, tumor stem cells, and immune cells, which play

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an important role in hepatocellular carcinoma growth, malignant progression, and drug tolerance. Among them, hepatic stellate cells can secrete certain related cytokines to increase the invasiveness of hepatocellular carcinoma cells, so that the cells have the characteristics of stem cells, which further induces the cells to produce drug resistance [31-32]; tumor stem cells and their progeny cells have the above natural resistance to chemotherapeutic drugs which enables them to survive in the patient's body and cause hepatocellular carcinoma recurrence [21]; hepatocellular carcinomas are enriched with immune cells, such as macrophages, Mast cells, T or B lymphocytes, etc. are not only able to promote tumor growth but also secrete cytokines that can produce tumor-promoting effects [33] and mediate the resistance of hepatocellular carcinoma cells to conventional chemotherapeutic drugs. Likewise, the extracellular matrix (ECM), tumor microvasculature, and pathological features such as hypoxia and acidity, which are unique to the microenvironment, in the non-cellular components of the liver cancer microenvironment, are also important factors triggering multidrug resistance in liver cancer. Among them, ECM contains a large number of proteoglycans, glycoproteins, polysaccharides, and other substances, for example, Ln-5, Fak, and other substances have an obvious role in promoting drug resistance in hepatocellular carcinoma, and at the same time, the production of ECM contributes to the invasion and metastasis of tumors and further promotes MDR [21]; the abnormalities of the tumor microenvironment can cause irregular changes in the intrinsic structure and overall distribution of tumor blood vessels, leading to interruption and narrowing of the blood vessel wall [34], change of blood flow direction, the elevation of mesenchymal pressure, and uneven blood distribution due to insufficient local blood supply [35], which can affect the entry of drugs into the tumor cells and lead to cellular hypoxia, thus indirectly affecting the drug resistance of tumors; hypoxia is a characteristic microenvironment of advanced tumors, and hypoxic environment can promote the generation of tumor micro vessels and the transformation of epithelial-mesenchymal stroma indirectly leading to the drug resistance of tumors [36]. can regulate MDR gene expression and participate in tumor drug resistance [37]. Therefore, an in-depth understanding of the characteristics of the microenvironment of hepatocellular carcinoma and its impact on multidrug resistance in hepatocellular carcinoma is of great significance in expanding new ideas for the clinical treatment of hepatocellular carcinoma and making up for the shortcomings of the existing diagnostic and therapeutic strategies.

5. The role of TGF-β in Regulating the tumor microenvironment in hepatocellular carcinoma with multidrug resistance

Transforming growth factor TGF-β, is a multifunctional cell growth factor. It is produced by cancer cells and several other cells present in the microenvironment of hepatocellular carcinoma, including Treg cells, fibroblasts, macrophages, etc. The TGF-β family mainly consists of three types, TGF-β1, TGF-β2, and TGF-β3), with TGF-β1 being the most relevant member involved in immune regulation. It mainly inhibits tumor growth in the early stage. However, in the middle and late stages with changes in the microenvironment, it can affect tumor development by participating in cellular immune evasion, hepatocellular carcinoma micro angiogenesis, inflammatory response, epithelial-mesenchymal transition, and related cellular signaling pathways, which can lead to drug resistance [38].

5.2 Role of TGF-β in Regulating the Microenvironment of hepatocellular carcinoma

5.2.1 TGF-β is involved in regulating multiple cellular functions in the liver cancer microenvironment

As a key regulator in the liver cancer microenvironment, TGF-β induces tumor immune escape and contributes to the formation of the tumor microenvironment. It is secreted by various cells such as hepatocellular carcinoma cells, TAMs, MDSCs, CAFs, etc. It prompts immune cell malfunction or apoptosis and even inhibits the proliferation and differentiation of immune cells, which ultimately leads to unlimited proliferation and growth of tumor cells. Specifically, it can inhibit the recognition and removal ability of TAMs on cancer cells, induce TAMs and TAN-like type 2 polarization, and produce tumor-promoting effects [39]; ② block the maturation of DCs, produce immune tolerance, and reduce their anti-tumor ability [40]; ③ recruit MDSCs aggregation, and inhibit the function of antitumor T cells [41]; ④ promoting regulatory T cell production, inhibiting multiple immune cell functions, and inducing and maintaining a tumor immune escape state [42].

5.2.2 TGF-β is involved in regulating the construction of the liver cancer microenvironment

TGF-β is closely related to the construction of the tumor microenvironment and can affect the cells in the microenvironment, signaling pathways, tumor micro angiogenesis and epithelial-mesenchymal transition [43-44]. TGF-β is an effective inducer of epithelial-mesenchymal transition, which can promote

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the recurrence and metastasis of hepatocellular carcinoma through the Smad signaling pathway and prompt tumor cells to undergo epithelial-mesenchymal transition. In addition, it can induce cancer cells to secrete a large number of pro-angiogenic factors, inflammatory factors and matrix proteins in the process of EMT, leading to invasion and metastasis, angiogenesis and immune evasion of hepatocellular carcinoma cells. ②Promote tumor micro angiogenesis: TGF-β can induce the expression of vascular endothelial growth factor VEGF, promote tumor neovascularization, and provide nutrients and a better survival environment for tumors. Some studies have demonstrated that TGF-β can recruit monocytes to release the pro-angiogenic cytokine VEGF, which provides conditions for the metastasis of endothelial cells and the formation of capillaries [45-46]. ③ It induces tumor immune escape, promotes tumor growth, and forms a tumor immune microenvironment [47-49].

5.3 TGF-β and multidrug resistance

5.3.1 TGF-β is involved in regulating ABC transporter protein expression

The main mechanism of multidrug resistance is through the ABC transporter proteins on the cell membrane, which release energy through ATP hydrolysis to transport chemotherapeutic drugs to the outside of the cell, thus reducing the concentration of intracellular drugs, and thus generating a drug-resistant response. Currently, transporter proteins have been found to include P-gp (ABCB1), MRP1 (ABCC1), BCRP (ABCG2), and so on. It has been found that TGF-β can generate tumor drug resistance by regulating the expression of transporter proteins. For example, in the study of TGF-β1 up-regulating P-gp and BCRP in hepatocellular carcinoma cells through the HOTAIR/miR-145 axis, TGF-β1 significantly promoted the expression of P-gp and BCRP proteins, which led to the enhancement of drug efflux transporter in hepatocellular carcinoma cells, and the decrease of intracellular drug concentration, indirectly leading to tumor drug resistance [50].

5.3.2 TGF-β is involved in the regulation of cell signaling pathways

There are multiple cell signaling pathways in the immune microenvironment of hepatocellular carcinoma, which are involved in regulating the relationship between cells and the microenvironment, and TGF-β can also interact with these pathways, leading to drug-resistant responses in tumors. For example, in valproic acid overcoming TGF-β-mediated sorafenib resistance experiments in hepatocellular carcinoma, it has been found that the antitumor effects of sorafenib were significantly inhibited in hepatocellular carcinoma cell line HepG2 and hepatocellular carcinoma cell line PLC/PRF/5 pretreated with TGF-β. The antitumor effects of sorafenib were markedly weakened in hepatocellular carcinoma cells sensitized by TGF-β, suggesting that TGF-β/ERK/ AKT signaling may play a key role in sorafenib resistance in hepatocellular carcinoma cells, and combination therapy with VPA can effectively counteract resistance [45].Activation of TGF-β and PI3K/AKT signaling pathways in HCC cells led to acquired resistance to sorafenib, whereas blockade of the activation of the TGF-β pathway overcame mir-216a/217-induced sorafenib resistance and prevented tumor metastasis ,and it was further found that overexpression of mir-216a/217 promoted hepatocarcinogenesis and tumor recurrence by targeting PTEN and Smad7 to activate the PI3K/AKT and TGF-β pathways [46].

5.3.3 TGF-β is involved in the regulation of epithelial-mesenchymal transition

TGF-β is an important inducer of epithelial-mesenchymal transition (EMT) and promotes tumor cell growth, invasion, and metastasis through EMT via Smad, PI3K, MAPK, and other signaling pathways. Combined inhibition of EMT and PD-L1 silencing induced by TGF-β1 sensitized the hepatocellular carcinoma to sorafenib treatment. In the study of the role of the PEG10 gene in TGF-β1-induced epithelial-mesenchymal transition in hepatocellular carcinoma, it was found that the PEG10 promotes migration, invasion, and endothelial cell transformation of hepatocellular carcinoma cells, and enhances TGF-β1-induced endothelial cell transformation, which contributes to chemoresistance of HepG2 cells; however, after stimulation of TGF-β1 by knockdown of TGF-β1 with the PEG10 gene, TGF-β1-induced endothelial cell transformation was significantly attenuated [51]. In addition, macrophages activate the stem cell properties of hepatocellular carcinoma through TGF-β1-induced epithelial cell transformation, which may lead to resistance to chemotherapy and targeted therapy [52-53]. These could confirm the involvement of TGF-β in tumor epithelial-mesenchymal causing tumor resistance.

6. Discussion

How to deal with tumor resistance to chemotherapeutic drugs has become an important challenge to be solved in the current stage of liver cancer treatment. Previous research on multidrug resistance in

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hepatocellular carcinoma has mostly focused on the tumor cells themselves, and the therapeutic effect is not satisfactory. In recent years, researchers and scholars have gradually discovered the role of tumor microenvironment in liver cancer multidrug resistance through a large number of experiments [21, 54].

A large number of studies have shown that in the liver cancer microenvironment, TGF-β, as one of the key regulators, participates in numerous tumor-associated immunoregulatory programs [43]. However, there are still many issues that still need to be further explored in depth. For example, what are the other mechanisms of transmission communication and action between TGF-β and other related cell signaling pathways in the liver cancer tumor microenvironment, and whether TGF-β interacts with other components of the microenvironment to produce cellular resistance; in addition, TGF-β targeted therapeutic agents have shown good efficacy in the treatment of tumor patients in clinical studies [6], and whether we can further explore the role of TGF-β inhibitors in liver cancer multidrug resistance in to address the problem of decreased sensitivity to chemotherapeutic agents. Therefore, an in-depth exploration of the relationship between the role of TGF-β in the microenvironment of hepatocellular carcinoma and its drug resistance provides new ideas for clinical hepatocellular carcinoma treatment.

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