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New Directions for Target Therapy of Hepato-alveolar Echinococcosis

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Abstract: *Hepatoalveolar echinococcosis is a chronic zoonotic parasitic disease caused by the larvae of the tapeworm Echinococcus multilocularis. Because its biological characteristics are similar to liver malignant tumors and have a certain degree of invasiveness, radical surgical treatment is difficult. Currently, the mainstream treatment plan for hepatoalveolar echinococcosis is surgical resection, supplemented by oral antiparasitic drugs, but the postoperative recurrence rate is still high. With the continuous development of targeted and immunotherapy, the development of new targeted drugs for hepatic alveolar echinococcosis has also become a trend. This article will review the current treatment status of hepatic alveolar echinococcosis and its potential therapeutic targets, and provide a new theoretical basis for the development of new targeted drugs.*

Keywords: *Hepatic alveolar echinococcosis; target; immunotherapy; targeted*

1. Current treatment status of alveolar echinococcosis

Hepatoalveolar echinococcosis (HAE), also known as "worm cancer", grows infiltratively like malignant tumors and is a chronic disease between benign and malignant liver lesions. Clinical treatment of alveolar echinococcosis is mainly surgical, including radical liver resection, palliative resection, and liver transplantation (allogeneic liver transplantation and autologous liver transplantation) [1]. Among them, radical hepatectomy has become the current mainstream surgical procedure due to its relatively low postoperative complication rate and postoperative recurrence rate. However, it is difficult to control the distance between the lesion resection margin and normal liver tissue, and the resection margin is too narrow. It will increase the recurrence rate of HAE. If the resection margin is too wide, it will lead to insufficient compensation of liver function and cause the occurrence of small liver syndrome. Therefore, oral albendazole and other antiparasitic drugs will be used to control it after surgery [2]. Secondly, due to its invasive nature and lack of obvious symptoms in the early stages, HAE often reaches the end stage when it is diagnosed. It has invaded surrounding important blood vessels and bile ducts, and the lesions are large in scope, making it impossible to undergo radical surgery. At present, liver transplantation is often chosen for end-stage treatment. Traditional allogeneic liver transplantation has a relatively wide range of indications, but insufficient donor livers and self-rejection are its main challenges. Long-term immunosuppressive drugs are also required after surgery, which increases the risk of patient financial burden [3]. On the basis of traditional liver transplantation, Wen Hao et al. [4] used ex vivo liver resection + contralateral liver transplantation for the first time in 2001 to treat patients with end-stage alveolar echinococcosis. In the process, they also used low-temperature mechanical perfusion and Technologies such as venous bypass can effectively prevent hypoxic damage to the liver and avoid the economic pressure caused by insufficient liver donors. Subsequently, autologous liver transplantation has also been carried out in various institutions, which has made up for the shortcomings of insufficient donors for allogeneic liver transplantation. However, the applicable conditions for autologous liver transplantation are relatively stringent, requiring no cirrhosis and normal liver tissue exceeding 40% of the total weight of the liver, and the Child classification of liver function is generally A level, the technology is still in its infancy and is still immature [5]. At present, compared with liver transplantation, after comprehensive consideration of all aspects, palliative liver resection is often the first choice for patients with end-stage HAE. Postoperative oral medications can improve the patient's survival as much as possible, but it cannot be denied that Palliative liver resection has many problems such as low survival rate, high recurrence rate, postoperative bile leakage, long-term catheterization, and high postoperative infection rate [6]. Therefore, drug treatment is still the main method for asymptomatic end-stage HAE.

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With the continuous development of minimally invasive techniques, various minimally invasive techniques are also used in the treatment of HAE. At present, the minimally invasive surgical treatment of HAE includes percutaneous interventional therapy, image-guided thermal ablation therapy, high-intensity focused ultrasound and laparoscopic surgery [7]. Although minimally invasive technology has solved some shortcomings of traditional surgical treatment, and the curable range of hepatic alveolar echinococcosis has been expanded, it is still in the initial exploration stage, and a complete treatment system has not been formed, and some of its limitations need to be solved. As far as the current status of HAE treatment is concerned, it is not difficult to see that the current treatment of HAE is facing the dilemma of initial recurrence and end-stage refractory. No matter what kind of treatment, oral drug therapy plays a vital role. The combination of surgery and drugs can further improve the survival of patients. At present, the drugs for HAE are mainly benzimidazoles, and have good therapeutic effects. However, long-term oral administration of benzimidazoles and their derivatives can lead to adverse reactions such as liver and kidney function damage, bone marrow suppression, dizziness, nausea, gastrointestinal discomfort, skin allergy and hair loss, and they are water-soluble drugs. Therefore, the bioavailability, plasma concentration and liver distribution concentration are low, and the drug effect cannot be fully exerted [8]. Therefore, there is an urgent need for new drugs to be applied to the treatment system of HAE at this stage. With the rapid development of molecular biology, targeting and immunotherapy have gradually entered people 's field of vision. These two emerging treatments have brought good news to HAE patients. Researchers are also constantly exploring potential therapeutic targets for HAE to further improve the survival rate and quality of life of HAE patients.

2. Potential therapeutic targets of HAE

2.1. Immunotherapy - the discovery of HAE immune checkpoints

In recent years, with the in-depth understanding of the human immune system, immunotherapy has become one of the targeted therapies against tumors. The so-called immunotherapy is to artificially enhance or inhibit the immune function of the body through some drugs that regulate the immune function of the body to achieve the purpose of treating diseases. However, if we want to complete targeted immunotherapy, we must understand the immune escape and tolerance mechanism of the disease, and then find the corresponding immune target to complete the desired therapeutic effect. One of the main mechanisms of human infection with alveolar echinococcosis is immune escape and tolerance, by manipulating and guiding the body 's various immune responses to exhaustion. Recent studies have revealed that this process of guiding the body 's immune exhaustion is related to the activity of macrophages and dendritic cells, as well as T cells [9]. According to the similar biological characteristics of HAE with malignant tumors, researchers have found many immune examination sites such as PD-1, CTLA-4, and TIGIT. Application of corresponding blocking agents for these sites can block the immune escape process of HAE patients, thereby achieving the results of targeted therapy for HAE. (Figure 1)

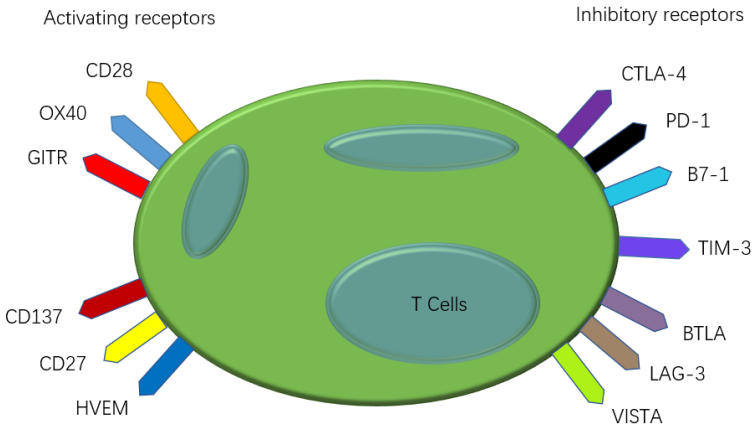

Figure 1: Activation and inhibitory signaling of T cells

PD-1 is a crucial target in tumor immunotherapy. PD-1 binds to its ligand, inhibits the activation and proliferation of T cells, the killing ability of NK cells, and ultimately leads to T cells in an immune-depleted state [10]. Taking advantage of the role of PD-1, the new anti-PD-1 antibody can inhibit the role of PD-1, thereby activating the immune ability and playing a role in the treatment of diseases. Parvez A,

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Singh V and many other experts [11] have applied this emerging immunotherapy method to the treatment of various diseases such as tumors and autoimmune diseases. Whether it is equally applicable to use PD-1 as a therapeutic target for HAE has attracted wide attention and research in the industry. HAE lesions induce Th2 shift and increase of Treg cells by inducing Th1 / Th2 balance, and secrete factors such as IL-10 and TGF-β through PD-1 pathway to inhibit human immunity, so as to achieve immune tolerance and immune escape [12]. It can be seen that PD-1 provides a basis for the living environment of the worm by inhibiting T cells, and IL-10 inhibits Th1 cells, so that Th2 cells play a leading role in the middle and late stages, which is conducive to the long-term survival of the worm. Li et al. [13] found that soluble PD-1 and soluble PD-L1 were significantly increased by measuring the expression of PD-1 in HAE serum. Both of them participated in the immune regulation of the body through dynamic balance and promoted the immune escape of echinococcosis. Study found that in mice infected with Echinococcus multilocularis, the expression of PD-1 and CTLA-4 in the liver was higher than that in normal liver tissue, and a small amount of expression in the early stage, significantly increased in the middle and late stages, and maintained at a certain level, suggesting that the increased expression of PD-1 and CTLA-4 may promote the progression of alveolar echinococcosis, participate in immune evasion and facilitate the long-term parasitism of alveolar echinococcosis [14]. It can be seen that the expression of anti-CTLA-4 can also prevent the immune escape of HAE, and anti-CTLA-4 therapy can kill parasite by reversing T cell exhaustion and reactivating immune function in vivo [15]. The above studies have shown that many immune factors such as PD-1, PD-L1 and CTLA-4 are involved in the process of immune tolerance and escape of HAE, which is likely to provide a theoretical basis for the application of PD-1 antibody and CTLA-4 antibody in the treatment of HAE. By blocking the expression of PD-1, PD-L1, CTLA-4, IL-10 and other related cytokines, it can delay the development of HAE and play a good therapeutic effect. These immune checkpoints may become potential target sites for HAE immunotherapy. (Table 1)

Table 1: PD-1/PD-L1 inhibitor products currently on the market

Target	*Common name*
PD-1	Nivolumab
	Perbrolizumab
	Cemiplimab
	Jemperli
	Toripalimab
	Sintilimab
	Camrelizumab
	Tislelizumab
	Penpulimab
	Candonilimab
	Zimberelimab
	Serplulimab
	Pucotenlimab
PD-L1	Atezolizumab
	Avelumab
	Durvalumab
	Envafolimab
	Sugemalimab
	Adebrelimab

In addition, CD155 / T cell immune receptor with Ig and ITIM domains (TIGIT) is a novel immune checkpoint discovered so far. CD155 is up-regulated during tumor progression and promotes the proliferation and migration of tumor cells through various pathways. TIGIT is an inhibitory receptor, mainly expressed on natural killer (NK), CD8 + T, CD4 + T and T regulatory (Treg) cells. CD155 interacts with TIGIT to transmit immune signals, thereby inhibiting the function of T cells and NK cells. At present, some preclinical studies have used TIGIT blockers as monotherapy or in combination with other immune checkpoint inhibitors for the treatment of advanced solid malignancies [16]. Zhang C et al. , in the study of the mechanism of TIGIT in alveolar echinococcosis infection, found that the expression of immunoglobulin-containing liver T cell immune receptors and immune receptor tyrosine-based inhibitory motif domain (TIGIT) was significantly enhanced, and was positively correlated with the lesion activity of HAE patients. The high expression of TIGIT in liver infiltrating T cells and blood T cells is related to its functional failure, and its ligand CD155 is highly expressed in hepatocytes around infiltrating lymphocytes. In the co-culture experiment using human blood T cells and liver cell line HL-7702, CD155 induced functional impairment of TIGIT T cells, and blocking with TIGIT antibody in

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vitro restored the function of T cells in patients with HAE. Similar TIGIT-related functional exhaustion of liver T cells and abundant CD155 expression in hepatocytes were observed in a mouse model of alveolar echinococcosis infection. Importantly, blocking TIGIT in vivo prevents T cell exhaustion and inhibits disease progression [17]. On the basis of this, Zhang C 's team also found that NK cells from the blood and closed liver tissue (CLT) of HAE patients expressed a high level of inhibitory receptor TIGIT and were functionally depleted, with low expression of granzyme B, perforin, interferon-γ (IFN-γ) and TNF-α. The addition of anti-TIGIT monoclonal antibody to the peripheral blood mononuclear cell culture of HAE patients significantly enhanced the synthesis of IFN-γ and TNF-α by NK cells, indicating that TIGIT blockade can reverse depleted NK cells. In addition, TIGIT deficiency or in vivo blockade inhibited the growth of retrohepatic tapeworms, reduced liver injury, and increased the level of IFN-γ produced by liver NK cells. Interestingly, NK cells from persistent chronically infected mice expressed higher levels of TIGIT than self-healing mice in the infected mouse model experiment. The results of this study on TIGIT in HAE infection and development provide a new theoretical basis for the application of TIGIT immune checkpoint [18].

2.2. Targeting angiogenesis of HAE lesions

With the deepening of HAE genomics research, many studies have found that the lesion and its peripheral infiltration zone have the formation of new blood vessels, and it has been proved by experiments that HIF1α, VEGFA, VEGFR signaling pathway may be involved in the formation of its blood vessels, and participate in the occurrence and development of HAE. Zhang et al. [19] found that MVD and VEGF were highly expressed in the lesion tissues of gerbils infected with alveolar echinococcosis and were higher than those in the surrounding liver tissues by measuring the microvessel density and vascular endothelial growth factor in the liver alveolar echinococcosis tissues of gerbils. At the same time, it was found that the expression levels of MVD and VEGF in the liver tissues around the lesions increased progressively with the prolongation of the onset time. The animal model test proved that there was new angiogenesis in the liver alveolar echinococcosis lesions and surrounding liver tissues, which was likely to be related to VEGF and other related signal factors. Jiang Huijiao et al. [20] further studied the role of VEGFA / VEGFR2 in the angiogenesis of hepatic alveolar echinococcosis in mice. The results showed that VEGFA and VEGFR2 were mainly expressed in the fibrous-endothelial cell infiltration area between the outer cyst wall and the liver cell and the inner cyst wall of the multilocular echinococcosis, which also proved that there may be neovascularization in these two areas. A large number of studies have confirmed that the feeding vessels of HAE lesions are related to the expression of HIF1α / VEGF / VEGFR signal. On the basis of this theory, Sang Zejie et al. [21] found that bevacizumab could inhibit the effect of VEGF and thus inhibit angiogenesis when treating hepatic alveolar echinococcosis in rats with hepatic artery infusion of bevacizumab. The application of targeted drugs in the treatment of hepatocellular carcinoma in the treatment of HAE patients has become a new direction of future treatment strategies. (Figure 2 and Figure 3)

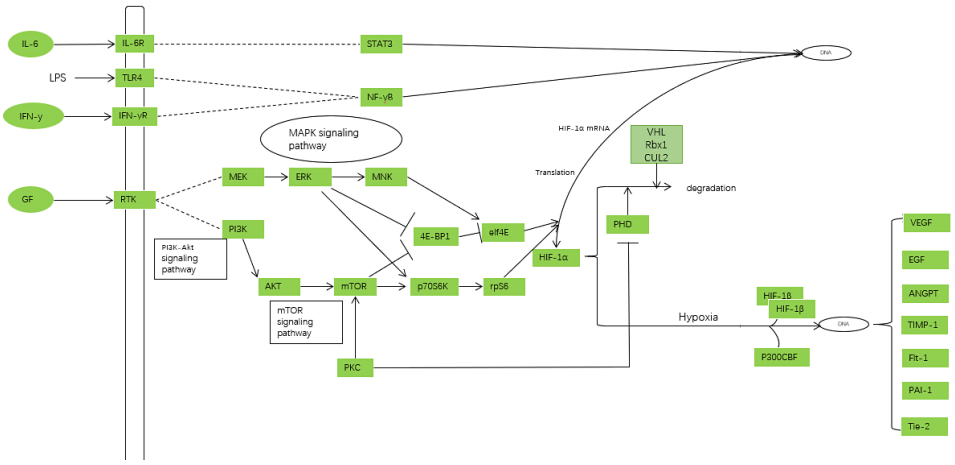

Figure 2: HIF-1α SIGNALING PATHWAY

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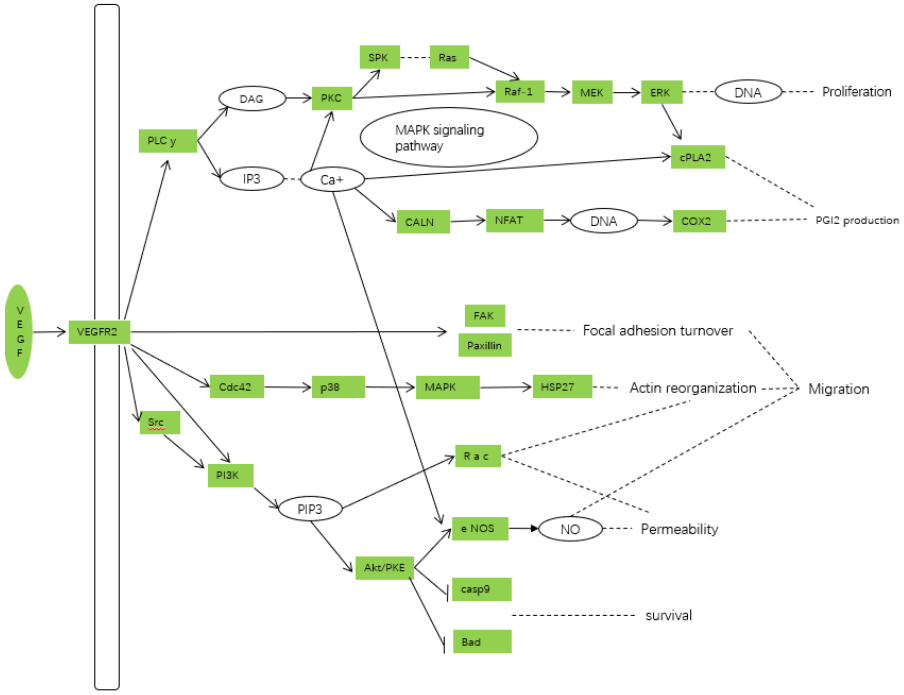

Figure 3: VEGF SIGNALING PATHWAY

2.3. Anti-parasitic drug targeting carrier

At present, the clinically recognized effective oral drugs for the treatment of HAE are benzimidazoles. For example, albendazole has a good anti-parasitic effect, but its extensive drug toxicity greatly reduces its anti-parasitic effect. For this reason, scholars have studied a variety of derivative preparations and composite preparations. For example, albendazole-hydroxyethyl sulfonate (ABZ-HES) / hydroxypropyl methylcellulose succinate (HPMC-AS) composite tablets (TABZ-HES-H) have higher solubility and bioavailability in mice infected with Echinococcus granulosus compared to the albendazole control group [22]. In addition, the researchers also extracted carbazole alkaloids from anti-parasitic traditional Chinese medicine. Based on this, carbazole amino alcohol derivatives were synthesized and designed. They have broad-spectrum insecticidal activity against parasites such as echinococcus, trypanosomes and schistosomes [23-25]. Although good results have been achieved in the field of new drug research and development against parasites, they all have a common problem, which cannot fully exert the fixed-point anti-parasitic effect, which greatly reduces the drug utilization, and the large-dose use of these anti-parasitic drugs also has certain toxic and side effects on the body itself. With the deepening of the concept of fixed-point targeted therapy, researchers have combined anti-parasitic drugs with newly developed high-precision biological materials to install navigation radars for drugs, so as to achieve targeted therapy and improve the efficacy of drug treatment. Abulaihaiti M [26] and other groups combined albendazole with chitosan microspheres (CS-MPs) to produce albendazole-chitosan microspheres (ABZ-CS-MPs) particles. They compared the efficacy of ABZ-CS-MPs, liposome-albendazole (L-ABZ) and albendazole tablets (ABZ-T) in an experimental mouse model. They found that ABZ-CS-MPs induced a shift from Th2-dominant immunity to Th1-dominant immunity in mice. They concluded that CS-MPs act as a carrier of albendazole. In the treatment of alveolar echinococcosis infection in mice, the absorption and bioavailability of albendazole were improved. Similarly, Jun Li et al [27]. designed an oral antiparasitic agent loaded PLGA nanoparticles using polymer nanomaterials to encapsulate the carbazole amino alcohol derivative (H1402) in the nanoagent (PLGA-PEG-PLGA). They found that this can effectively deliver the mother drug to the liver as accurately as the ' eye ' and promote the extensive accumulation of the drug in the lesion. Compared with free H1402, H1402-NPs significantly improved the results of anti-vesicular echinococcosis treatment, while reducing systemic toxicity. These in-depth studies on liver targeted therapy are the representatives of new treatment strategies for HAE in the future, and need further exploration and research.

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3. Summarized and prospected

With the continuous development of science and technology, the research on targeted therapy of hepatic alveolar echinococcosis has achieved remarkable results. Through various experiments, it has been found that immunotherapy, signal pathway blocking, biomaterial physical guidance and other means can become new treatment strategies for the treatment of hepatic alveolar echinococcosis. However, the current targeted therapy for hepatic alveolar echinococcosis still faces many challenges, such as drug side effects, evaluation of therapeutic effects, individualized treatment, etc. In the future, the research on the following aspects may become a new breakthrough : the research and development of new drugs to improve the therapeutic effect and reduce side effects ; the study of multi-target combined treatment strategies to achieve an all-round strike against hepatic alveolar echinococcosis; the study of individualized treatment plan to meet the treatment needs of different patients; the comprehensive treatment of targeted therapy combined with immunotherapy and interventional therapy is studied to improve the therapeutic effect. In conclusion, the research progress of targeted therapy for hepatic alveolar echinococcosis provides new ideas and methods for clinical treatment. With the deepening of research, it is believed that in the near future, the treatment of hepatic alveolar echinococcosis will achieve greater breakthroughs.

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