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The Role of MerTK in Immune Checkpoint Inhibitor Resistance in Hepatocellular Carcinoma

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Abstract. Immune checkpoint inhibitors, PD-1 / PD-L1 inhibitors, have been approved for the treatment of unresectable hepatocellular carcinoma, which actually represents a significant advancement in treatment options for this aggressive type of cancer. However, their effectiveness is often hindered by primary or acquired tumor resistance. It is necessary to study the molecular mechanisms involved and create targeted strategies. Recent findings indicate that the proto-oncogene tyrosine kinase MerTK (MER) is overexpressed in HCC tissues and is significantly associated with poor responses to these inhibitors.This review the various roles of MerTK in the progression of HCC, including its supportive effects on tumor cell survival, migration, and immune evasion. This review also discusses how MerTK promotes immunotherapy resistance by altering the tumor microenvironment, such as reducing the function of anti-tumor immune cells. Additionally, the review considers MerTK's potential as both a therapeutic target and a predictive biomarker, proposing new opportunities to improve the effectiveness of current HCC immunotherapies.

Keywords: MerTK, ICIs, HCC, Therapy Resistance

1. Introduction

Hepatocellular carcinoma (HCC), is a primary malignant tumor of the liver with an extremely high mortality rate. The pathogenesis of this cancer is very complex, which poses a great challenge to its treatment. In recent years, immune checkpoint inhibitor (ICIs) antibodies, such as PD-1 / PD-L1 antibodies, have shown a good impact in the treatment of advanced HCC. It has given many patients the hope of living longer. However, clinical analyses have shown that many HCC patients develop primary or acquired resistance to ICIs, which limits the therapeutic effect of ICIs. Studying the molecular mechanisms of resistance to tumor immunosuppressants and effective ways to overcome resistance is an extremely urgent task for liver cancer immunotherapy at present.

The tumor immune microenvironment (TME) has a very prominent impact on the anti-tumor immune response and treatment resistance, with myeloid cells, notably tumor-associated macrophages (TAMs) and dendritic cells (DCs), playing a critical role in T cell activity and the effectiveness of immune checkpoint inhibitors (ICIs). The MerTK proto-oncogene mainly exists in myeloid cells. It promotes tumor development by creating an immunosuppressive environment. In solid tumors like hepatocellular carcinoma, its high expression is associated with a poor prognosis. Despite this, the mechanism by which MerTK promotes ICI resistance in HCC and the potential

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benefits of targeting MerTK to enhance ICI effectiveness remain uncertain. This clearly indicates a significant gap in knowledge in this area.

Against this background, in this paper, we will systematically unveil the important role of MerTK in the immune checkpoint inhibition resistance of HCC. We will first describe the biological nature of MerTK and expression for HCC. Subsequently, it will analyze the current application of ICIs in HCC treatment and the associated challenges of resistance. The focus will then shift to exploring the core mechanisms by which MerTK mediates ICI resistance through reshaping the tumor microenvironment (e.g., regulating macrophage polarization, upregulating PD-L1 expression, etc.). Finally, it will review targeted therapeutic strategies against MerTK, particularly the potential and preclinical evidence for combining MerTK inhibition with existing ICIs. This aims to provide novel insights and potential solutions for overcoming clinical immunotherapy resistance in HCC and improving patient prognosis.

2. The role of MerTK in HCC

2.1. Basic biological characteristics of MerTK

Mer tyrosine kinase (MerTK) is a member of the TAM receptor tyrosine kinase family (Tyro3, Axl, and MerTK). It is expressed in various tissues and cell types, including various cancer cells, encompassing multiple cancer cell lineages, macrophages, monocytes, microglia, dendritic cells, natural killer (NK) cells, as well as epithelial cells in the retina, lung, testis, ovary, prostate, and kidney [1]. Current research confirms that MERTK promotes the infiltration of tumor-associated macrophages in the tumor microenvironment and helps cell immune escape. Unnormal activation is a major driving driver of immunotherapy resistance in hepatocellular carcinoma [2]. As a key receptor involved in endocytosis, MerTK recognizes phosphatidylserine (PtdSer) on the apoptotic cell surface which increases ligand binding affinity and TAM receptor mediated signaling. This text discusses the role of Gas6/PROS1-mediated trimeric complexes in the immunologically silent clearance of apoptotic cells by macrophages. It emphasizes the pathological effects of abnormal expression in tumor microenvironments, focusing on the distinct roles of M1 and M2 macrophages. M1 macrophages are associated with antitumor functions through the production of reactive species and pro-inflammatory cytokines, while M2 macrophages support tumor progression by secreting cytokines that accelerate disease. The MerTK receptor is highlighted as a significant factor in macrophage polarization, inhibiting the M1 phenotype and promoting a shift toward the pro-tumor M2 phenotype [3,4].

2.2. Expression patterns and associations of MerTK in HCC

Mer tyrosine kinase (MerTK) exerts distinct oncogenic functions through its ectopic and aberrant expression across multiple human cancers. Multi-omics analyses have confirmed its pan-cancer expression pattern, in which MerTK is aberrantly activated in numerous malignancies, including leukemias, lymphomas, and solid tumors such as colorectal, lung, gastric, breast, and prostate cancer. In tumor microenvironments rich in cellular renewal, abundant ligands, and apoptotic cells, this overexpression drives malignant progression and invasiveness, particularly in HCC [5-7]. Homologous proteins Growth Arrest-Specific Protein 6 (Gas6) and Protein S (Pros1) serve as primary ligands for MerTK activation. These ligands induce MerTK homodimerization and autophosphorylation, activating downstream pathways that promote tumor cell proliferation, inhibit apoptosis, and suppress anti-tumor immunity [8,9] . Clinical data indicate that MerTK expression in

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cancer tissues reached 62.71% (74/118), significantly higher than the 6.78% (8/118) observed in adjacent non-cancerous tissues, with this difference being statistically significant (χ^2=69.945, 81.408, both P<0.001) [6]. Other studies have shown that while MerTK protein expression is significantly elevated, its mRNA levels do not differ significantly between tumor and adjacent normal liver tissues [10].

Concurrently, MerTK drives tumor progression through dual mechanisms of ligand-dependent activation and immune evasion. Specifically, phosphatidylserine (PtdSer) released from apoptotic cells binds to PROS1/Gas6, triggering MerTK dimerization and phosphorylation of the downstream PI3K-AKT pathway, which promotes tumor cell proliferation. By regulating Akt and GSK3β, it confers proliferative and migratory advantages to HCC cells [10].

3. Role of immune checkpoint inhibitors in HCC treatment

3.1. Mechanisms and applications of immune checkpoint inhibitors in HCC

In hepatocellular carcinoma (HCC), the immune system's tolerance and chronic inflammation lead to dysfunction in various immune cells, maintaining an immunosuppressive state through checkpoint molecules like CTLA-4 and PD-1. These molecules inhibit T cell activation and lead to T cell exhaustion. Immune checkpoint inhibitors (ICIs) act on these pathways to suppress antitumor responses, causing many of these procedures to become critical for HCC therapy. Current treatment techniques include ICI monotherapy, treatment with tyrosine kinase inhibitors (TKIs), treatment with dual ICIs, and treatment with chemotherapy or local therapies. The main ICIs are nivolumab, pembrolizumab and atezolizumib, some of which are first line of treatments.Additionally, classic therapies like sorafenib have shown improved overall survival in trials, though response rates remain low [11,12].

3.2. Resistance to immune checkpoint inhibitors

Despite the breakthrough progress of immune checkpoint inhibitors (ICIs) in treating various cancers, the majority of patients eventually develop resistance to ICIs. This resistance may be primary or secondary. In hepatocellular carcinoma (HCC), the development of ICI resistance is a complex process driven by multiple factors and intertwined signaling pathways. Resistance to immune checkpoint inhibitors is due to three factors: intrinsic tumor cell characteristics, regulation by tumor microenvironment (TME), and dynamical evolution under therapeutic conditions. In terms of the tumor cells themselves, on the one hand, they may lose their immunogenicity (e., more gene mutations), and weaken the antigen presentation machinery (e,g., making them difficult to recognize) on the other hand, activate intrinsic signaling pathways that block immune signaling and actively prevent key immune cells (e: dendritic cells) from entering the tumor tissue, thereby creating a defense barrier prior to a diagnosis. On the other side, the immunosperceptory nature of surrounding tumor micro environment (TME) is another critical factor. Tumors recruit diverse immunospressive cells and create an environment with inhibitory signaling molecules and metabolic waste products. This combination of factors leads to functional exhaustion, depletion or even reprogramming of aggressive T cells into suppressive cells. Moreover, the remodeling of tumor tissue (e;g., abnormal vascularization and dense stroma) leads to T cell infiltration and survival. On a final side, under drug pressure, tumour cells evolve dynamic to develop acquired resistance by eliminating cell clones that are immune-targeted and activate novel immunosparceptors. In summary, HCC resistance to ICIs stems from the combined shaping of intrinsic tumor cell

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adaptations and extrinsic immunosuppressive microenvironments, which continuously evolve throughout treatment to establish a multi-layered defensive system [13].

4. The relationship between MerTK and immune checkpoint inhibitor resistance

In hepatocellular carcinoma (HCC) treatment, patients receiving immune checkpoint inhibitors (ICIs) that block PD-L1+VEGF/PD-L 1+CTLA-4 pathways still show high resistance and low response. New strategies (e.g., blocking other immunosuppressive molecules) need to be introduced to overcome ICI resistance. Recent studies show that vaccination is associated with upregulation of the immunoregulatory molecule MERTK in DCs. Blockade of MERTK enhances vaccine efficacy, resulting in improved therapeutic outcomes. Furthermore,combining MERTK blockade with ICIs further potentiates treatment effects. In hepatocellular carcinoma (HCC),MerTK inhibits the immune checkpoint inhibitor (ICI) by transforming the tumor immune microenvironment. Recent studies indicate that as orthotopic HCC tumors grow the population of MerTK myeloid cells (dendritic cells and tumor-associated macrophages (TAMs) becomes larger in the tumor. MerMK myecells are also highly expressed to the co-stimulatory molecule CD86, and they also express an extremely high expression of the immune immune checkpoint molecule PD-1. Moreover, MerTK expression levels demonstrate a positive correlation with PD-L1, suggesting MerTK may directly regulate PD-L1 expression [14]. Further mechanistic studies have confirmed that MerTK deficiency significantly reduces PD-L1 expression in dendritic cells, establishing its pivotal role in upregulating this key immunosuppressive molecule [15]. Meanwhile, an infiltration of MerPMF myeloids in tumors contributes positively to the levels of antigen-sensitive T cells (PD-1-expressing CD4+ and CD8+ T cells), though their function decreases with growth in tumors. MerTK thus establish an inhibitory tumor microenvironment by upregulatory of immunosipressive molecules, such as PD-L1 and interacting with PD-1-positive T cells, potentially representing a primary mechanism of ICI resistance in HCC.

5. Targeted therapeutic strategies against MerTK

Although immune checkpoint inhibitors (ICIs) have represented a major breakthrough in cancer treatment over the past decade and have demonstrated remarkable therapeutic effects in the treatment of many malignant tumors, in addition to the problem of drug resistance, they are also associated with a series of immune-related adverse events(IRAEs) that can affect multiple organ systems. These adverse events include autoimmune endocrine disorders, colitis, hypophysitis, hepatitis and pneumonia. These events can be life-threatening in severe cases [16]. Different ICI regimens also have significant differences in safety. Take anti-PD-1 /PD-L1 monotherapy as an example, it is generally safer than anti-CTLA-4 monotherapy. And the combination therapy approach, such as nivolumab plus ipilimumab, It will cause a higher incidence of adverse reactions, and the degree of adverse reactions will also be more severe. These combinations also increase the risk of recurrence of specific IRAEs, such as colitis, which is particularly related to hepatocellular carcinoma. Severe hepatic injury and hepatotoxicity are major contributors to treatment-related mortality with PD-1/PD-L1 inhibitors, regardless of whether used alone or in combination [17,18]. In the tumor microenvironment of hepatocellular carcinoma, the MerTK receptor on myeloid cells can mediate immunosuppression and also lead to resistance to immune checkpoint inhibitors. If the MerTK or PD-1/PD-L1 pathways are targeted alone, the therapeutic effect is relatively limited due to the existence of compensatory immunosuppressive pathways. However, when MerTK inhibitors are used in combination with anti-PD-1 antibodies, they can produce a very prominent anti-tumor

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effect, promoting T cell activation and improving antigen presentation. This combination can also reprogram tumor-associated macrophages to the anti-tumor M1 phenotype. When MerTK inhibitors are used in combination with established HCC immunotherapy regimens, they enhance the infiltration of lymphocytes into tumors [19,20]. These findings suggest that MerTK blockade can effectively potentiate the therapeutic efficacy of existing ICIs, particularly in myeloid cell-enriched HCC, providing a new approach to overcome clinical drug resistance and also offers a theoretical basis for the development of more refined combined immunotherapy regimens.

6. Conclusion

This review systematically explores the mechanism by which MerTK mediates resistance to immune checkpoint inhibitors in hepatocellular carcinoma and its potential therapeutic significance. By reviewing and analyzing the existing literature, the following key conclusions can be drawn: : First, MerTK is aberrantly highly expressed on myeloid cells within the HCC tumor microenvironment (TME), most notably on tumor-associated macrophages (TAMs). This over-expression acts as a key driver of immune suppression and ICI resistance. Its mechanisms operate through two primary ways:The first pathway is that the activation of the Gas6/PROS1 ligand of MerTK triggers downstream signaling pathways, which promotes the polarization of macrophages towards the pro-tumor M2 phenotype and also inhibits the anti-tumor M1 phenotype. This situation dynamically reshapes the immune environment favorable for tumor growth. The second pathway is that the expression of mertk shows a very prominent positive correlation with the level of PD-L1. Functional studies have also confirmed that MerTK can up-regulate the expression of PD-L1, which gives MERTK-positive bone marrow cells their inherent immunosuppressive characteristics. It will also rely on amplifying the typical PD-1 / PD-L1 immunosuppressive axis to aggravate T-cell exhaustion, thereby reducing the efficacy of ICIs. Second, in terms of therapeutic strategies, the efficacy of monotherapy targeting the MerTK or PD-1 / PD-L1 pathways in preclinical models is limited, which also highlights the complexity of the immune resistance mechanism of HCC. However, combination therapy has great potential. The combined use of MerTK inhibitors and anti-PD-1 antibodies can produce a synergistic anti-tumor effect and effectively reprogram the tumor immune microenvironment. This includes promoting the activation and infiltration of cytotoxic T cells, enhancing the efficiency of antigen presentation, and inducing Tams to repolarize towards the anti-tumor M1 phenotype. More notably, the synergistic effect of MerTK inhibitors is not limited to PD-1 blocking. When combined with the currently approved first-line combination regimens for the treatment of advanced HCC, For instance, when "atezolizumab + bevacizumab" or "durvalumab + tremelimumab" are used in combination, they can enhance the therapeutic effect and offer a promising new strategy to overcome clinical drug resistance. Overall, MerTK is a key regulatory molecule in the immunosuppressive microenvironment of HCC and a major mediator of ICI resistance. Targeting MerTK and combining it with existing ICIs provides a new therapeutic approach for HCC treatment.

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