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Review Article

Unfavorable Tumor Responses to Immunotherapy in the Liver: Lessons Learned from Clinical and Preclinical Studies

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Abstract

Objective: Immunotherapy with immune checkpoint inhibitors (ICIs) has become a standard of care for many malignancies. The tumor microenvironment (TME) varies across different organs and affects tumor initiation, progression, and treatment outcomes. Organ-specific differential responses to ICIs have been observed in various cancers. The underlying mechanisms warrant further investigation. **Data Sources and Study Selection:** We enrolled relevant clinical and preclinical studies conducted by our groups and others. Current evidence and data were reviewed and future implication was discussed. **Results:** In patients with advanced hepatocellular carcinoma or esophageal cancer, non-small cell lung cancer, or melanoma with liver metastases, the efficacy of ICI-based therapy was generally lower in the liver than in other organs. The mouse liver cancer study showed that myeloid-derived suppressor cells (MDSCs) might play a role in immunosuppressive TME in the liver as compared to subcutaneous tissues; targeting MDSCs enhanced anti-tumor efficacy in the liver. The metastatic colon cancer models showed that monotherapy with anti-programmed death ligand-1 (PD-L1) antibody was less effective in suppressing tumor growth in the liver than in subcutaneous tissues. Mechanistically, modulation of hepatic innate immune cells was associated with the improved response of anti-PD-L1 antibody in the liver. **Conclusion:** The relatively unfavorable tumor response to immunotherapy in the liver of various cancers may be attributable to the immunosuppressive hepatic TME. Future comprehensive immune profiling is required to identify key factors and mechanisms in specific organs to overcome immunosuppressive TME, particularly in the liver.

Keywords: Cancer, immunosuppression, liver, tumor microenvironment; immune checkpoint inhibitor

Introduction

Immunotherapy with immune checkpoint inhibitors (ICIs), such as anti-programmed cell death protein 1 (PD-1) and anti-programmed death ligand-1 (PD-L1) antibodies, has become a new paradigm for the treatment of many malignancies. However, only a small portion of patients could get benefit from the treatment. The antitumor effects of ICIs have been associated with $CD8^+$ T-cell infiltration, PD-L1 expression, tumor mutational burden, and the inflammatory

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signatures of the tumor microenvironment (TME).[1] Unlike chemotherapy and molecular-targeted therapy, which directly attack cancer cells, ICIs enhance antitumor immunity by reinvigorating tumor-specific T cells. It is conceivable that other immune and nonimmune cells in the TME may affect T-cell functions and ICI efficacy.

Different organs or tissues harbor distinct TME, such as different immune cell compositions and various levels of soluble mediators.[2] Once a tumor metastasizes to a specific organ, the immune contexture in that organ may affect the growth of the tumor and its response to immunotherapy. Previously, heterogeneous tumor responses (i.e., the enlargement of metastatic tumors in one organ and their amelioration or stability in another organ after treatment) have been reported in patients with solid tumors receiving chemotherapy or molecular-targeted therapy.[3-5] The mixed responses might be due to the clonal evolution of tumor cells. In the era of immunotherapy, more and more clinical observations showed organ-specific differential responses in various cancers. In general, the response of tumors to ICIs was poorer in the liver than in other organs. Preclinical studies also have started to address the potential underlying mechanisms. In this article, we review recent relevant studies and discuss implications for future directions.

Clinical Observations of Organ-Specific Differential Tumor Responses to Immune Checkpoint Inhibitors

The objective response rates (ORRs) of advanced hepatocellular carcinoma (HCC) to anti-PD-1 or anti-PD-L1 monotherapy have been modest and generally lower than other cancers such as melanoma or non-small cell lung cancer (NSCLC). In our previous study, which included a total of 75 patients with advanced HCC who received anti-PD1/PD-L1, anti-cytotoxic T-lymphocyte–associated antigen 4, or a combination of both, the overall ORR, according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, was 28.0%. At baseline, a total of 58, 34, 19, and 18 patients had measurable hepatic tumors and lung, lymph node, and intra-abdominal metastases, respectively; the corresponding organ-specific ORRs were 22.4%, 41.2%, 26.3%, and 38.9%, respectively. Intrahepatic HCC tumors were less responsive to ICIs than extrahepatic lesions.[6] Similar findings have been reported in other studies based on real-world cohorts of patients with advanced HCC who received nivolumab, an anti-PD-1 antibody.[7,8]

Recently, ICIs have also become a key treatment modality for unresectable esophageal cancer (EC). We previously evaluated 37 patients with unresectable EC who received ICIs. Metastatic tumors were detected in the liver, lungs, and lymph nodes of 13, 17, and 26 patients, respectively. The overall ORR, according to the RECIST 1.1, was 13.5%. The organ-specific ORRs were 15.4%, 26.9%, and 29.4% for hepatic tumors and lymph node and lung metastases, respectively, also showing liver metastases were less likely to respond to ICIs as compared to other metastatic lesions in patients with unresectable EC.[9]

Mixed responses to immunotherapy have been reported in patients with melanoma, for which immunotherapies other than ICIs were used.[10-13] In the KEYNOTE-001 phase I clinical trial, patients with metastatic melanoma were treated with pembrolizumab, an anti-PD-1 antibody. Individual lesions were analyzed and lung lesions exhibited the highest rate of complete response (42.3%), followed by peritoneal (37.3%), and liver (24.4%) metastatic lesions.[14] Another study, including patients with melanoma or NSCLC who received pembrolizumab in several clinical trials reported decreased response rates and shortened progression-free survival in patients with liver metastases than in those without liver metastases.[15] Nivolumab was used in a large retrospective study on 214 patients with metastatic NSCLC of totally 761 lesions. Although the response patterns were similar among different organs, the rate of disease progression varied across organs; this rate was considerably higher in the liver (50%) than in other organs (lymph nodes, 16%; lungs, 26%; and adrenal glands, 28%).[16]

Taken together, these clinical observations reveal that liver tumors, both primary and metastatic, exhibit the poorest response to ICIs. The phenomenon has been shown in various cancers. However, the underlying mechanisms are still under investigations.

Preclinical Studies Addressing the Impact of Hepatic Tumor Microenvironment

Prior preclinical studies have explored the impact of different organs on the TME and effect of treatment.[17-19] We developed preclinical mouse models through the orthotopic and subcutaneous implantations of the syngeneic liver cancer cells BNL to investigate tumor-related inflammatory and immunosuppressive mechanisms in various organs. Using these models, the effects of different TMEs on the efficacy of sorafenib, a multikinase inhibitor for HCC, was explored. We found that orthotopic liver tumors were less responsive to sorafenib than subcutaneous tumors. Mechanistically, after sorafenib treatment, interleukin-6 (IL-6) and the proportion of $Ly6G^+$ myeloid-derived suppressor cells (MDSCs) were increased in the TME of orthotopic liver tumors but not in that of subcutaneous tumors. In mice with orthotopic liver tumors, targeting IL-6 or Ly6G in addition to sorafenib resulted in decreased proportion of $Ly6G^+$ MDSCs; however, the proliferation of T cells increased, and the antitumor efficacy of sorafenib was enhanced [Figure 1a]. The results demonstrated that the proinflammatory and immunosuppressive TME of the liver differs from that of subcutaneous tissues; targeting the $Ly6G^+$ MDSCs may be a potential strategy to improve the antitumor efficacy in the liver.[20]

In our recent study of mouse models with metastatic colon cancer, MC38 cells were used to develop liver metastases

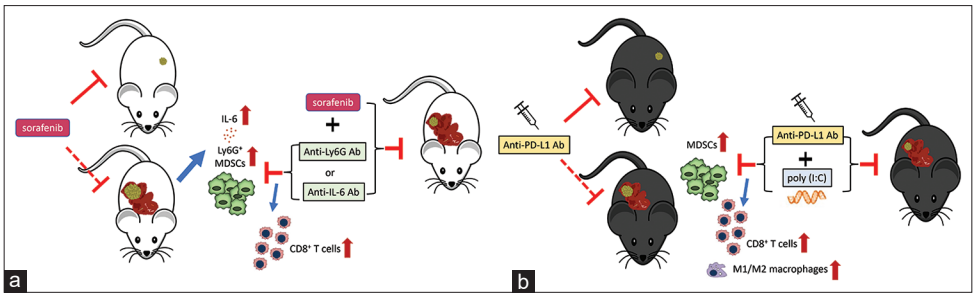

Figure 1: Preclinical models showing poorer treatment responses of liver tumors than subcutaneous tumors and the combination therapies overcome the immunosuppressive TME in the liver. (a) In BNL models, after sorafenib treatment, IL-6 and the proportion of Ly6G$^+$ MDSCs increased in the TME of orthotopic liver tumors. Targeting IL-6 or Ly6G in addition to sorafenib decreased proportion of Ly6G$^+$ MDSCs, increased the proliferation of T cells, and enhanced the antitumor efficacy in the liver. (b) In MC38 models, the pretreatment immunoprofiles of the liver revealed that the proportion of MDSCs was higher. The addition of poly (I: C) to anti-PD-L1 decreased tumor-infiltrated MDSCs, increased the ratios of M1 to M2 macrophages and CD8$^+$ to CD4$^+$ T cells, and markedly suppressed the metastatic liver tumors. IL-6: interleukin-6, MDSC: myeloid-derived suppressor cell, TME: tumor microenvironment

and subcutaneous tumors through portal vein or splenic vein injection and skin inoculation, respectively. Similarly, anti-PD-L1 monotherapy suppressed tumor growth in the skin; however, the therapy was ineffective in the liver. The addition of polyinosinic: polycytidylic acid (poly [I: C]) – a synthetic double-stranded RNA that stimulates the production of interferons (IFNs) and other cytokines – to anti-PD-L1 markedly suppressed the metastatic liver tumors. The pretreatment immunoprofiles of the liver and subcutaneous tumors revealed that the proportion of MDSCs was considerably higher in liver tumors than in subcutaneous tumors, whereas the proportion of macrophages was lower in liver tumors than in subcutaneous tumors. The combination therapy with anti-PD-L1 and poly (I: C) decreased tumor-infiltrated MDSCs but increased the ratios of M1 to M2 macrophages, CD8$^+$ to CD4$^+$ T cells, and CD8$^+$ T cells to regulatory T cells (Tregs) in liver tumors [Figure 1b]. Depletion of macrophages and blocking type I IFN signaling abrogated the synergistic effect of the combination therapy.[21] Poly (I: C) could engage Toll-like receptor 3, thus activating antigen-presenting cells and natural killer cells (NKs) and inducing the priming and proliferation of CD8$^+$ T cells.[22] These findings suggest that the unique hepatic TME decreases the efficacy of anti-PD-L1 monotherapy; modulating hepatic innate and adaptive immunity by poly (I: C) may improve tumor responses to immunotherapy in the liver.

In a study conducted using a KPC model of pancreatic cancer, multiomics methods, including mass cytometry, immunohistochemistry, and RNA sequencing, were used to analyze the TME of lung and liver metastases, which were established through tail vein and portal vein injections, respectively. Elevated infiltration and activation of tumor-associated immune cells, particularly T cells, and strong proimmune and immune-recruiting signaling (e.g., CXCL9, CXCL10, CXCL11, and CXCL14) were observed in the lung TME, whereas an immunosuppressive TME with high levels of protumor cytokines (e.g., CCL5, CCL22, CCL28, and CXCL12) was noted in the liver TME. The findings were partially validated using paired lung and liver metastatic samples obtained from patients with pancreatic cancer. Lung and liver primary cancer samples obtained from TCGA datasets were also compared, and many of the site-specific expressions of immunomodulatory genes were recapitulated, suggesting the liver exhibited a more immunosuppressive and protumor TME.[23]

The Liver: An Organ with Immunosuppressive Tumor Microenvironment

The liver is constantly exposed to self and foreign antigens, such as nutrients and microorganisms released from the gastrointestinal tract. The unique immunotolerant feature of the liver helps maintain homeostasis and prevents detrimental inflammation and autoimmune diseases. Multiple innate and adaptive immune cells and nonhematopoietic cells in the liver contribute to the physiological balance between tolerance and immunity.[24]

Kupffer cells, the resident macrophages located in the liver sinusoid, capture foreign antigens, and pathogens released into the bloodstream from the gastrointestinal tract, thus preventing excessive immune stimulation and maintaining tolerance in the liver. Kupffer cells generally exert immunosuppressive effects by expressing high PD-L1, secreting IL-10, and presenting antigens to CD4$^+$ T cells to induce tolerance.[25] Dendritic cells (DCs) are heterogeneous in the liver. Unlike those found in other organs with antigen-presenting functions, hepatic DCs produce IL-10 and anti-inflammatory molecules such as indoleamine 2, 3-dioxygenase to reduce the responses of T cells. Hepatic DCs also express PD-L1, further limiting adaptive immune responses.[26,27] Hepatic NKs also differ from those found in the blood and lymphoid tissues. Hepatic NKs are regarded as hepatic innate lymphoid cells, which play a role in maintaining immune homeostasis in the liver. Recent studies found that these NKs suppress the antiviral functions of T cells through PD-1/PD-L1 signaling.[27,28]

Parenchymal cells and other nonhematopoietic cells found in the liver also contribute to hepatic immune hyporesponsiveness

by suppressing adaptive immunity. For example, liver sinusoidal endothelial cells (LSECs), which also serve as antigen-presenting cells in the liver, express PD-L1 but not costimulatory molecules. The interaction between LSECs and T cells does not lead to the effective activation of T cells; in fact, their interaction induces anergy in T cells.[29,30] Hepatic stella cells, which are located in the space of Disse, can also present antigen to T cells and promote the differentiation of Tregs.[31] Finally, hepatocytes, which account for 90% of all cells in the liver, are crucial for metabolism, protein synthesis, and toxin neutralization. Under specific conditions, hepatocytes can present antigens to T cells. However, they cannot induce T-cell proliferation; instead, they induce T-cell apoptosis.[32,33]

In the hepatic TME, other immunosuppressive cells facilitate tumor growth and reduce the efficacy of antitumor treatment. For example, MDSCs support tumor growth by suppressing T cells and NKs, inducing Tregs, and promoting angiogenesis. In patients with HCC, higher proportions of PD-L1$^+$ MDSCs were found in tumor-infiltrating leukocytes than in liver-infiltrating leukocytes and peripheral blood mononuclear cells.[34] Many preclinical models confirmed the roles of MDSCs in the development and progression of HCC and demonstrated that targeting MDSCs may increase the efficacy of systemic therapy.[35] Tumor-associated macrophages (TAMs), which are derived from monocytes circulating in the bloodstream, were demonstrated to be skewed in the hepatic TME. Under the influence of different cytokines, monocytes are differentiated into M1 macrophages, which are more proinflammatory, or M2 macrophages, which are more immunosuppressive. TAMs are immunosuppressive and can promote tumor initiation and progression. Previous clinical studies showed that TAMs suppress effector T-cell functions and induce Tregs, and are associated with poor prognosis in patients with HCC.[36] In addition, other immune cells, such as tumor-associated neutrophils and B cells, also interplay with TAMs in the hepatic TME.[37,38]

In summary, the liver is a unique organ with immune tolerance. The immunosuppressive hepatic TME is maintained by several physiological and pathological mechanisms, which lead to poor tumor responses to immunotherapy.

Future Directions

Precision medicine in oncology has been focused on the features of tumor cells according to their anatomic origins, such as EGFR mutations in NSCLC. Recently, tissue-agnostic drugs have been approved for various cancers with common genetic alterations, such as mismatch repair deficiency and NTRK gene fusions.[39] In the future, personalized immunotherapy should be designed with consideration for the different TMEs of each organ, such as different types of cancer with metastases into the same organ and a single type of cancer with metastases into different organs. Before that, however, organ-specific immune contexture requires comprehensive investigation using both preclinical and clinical samples. Organ-specific niches need to be identified using various preclinical models. Human tumor samples should be explored not only by disease type but also by the affected organs. State-of-the-art technologies, such as quantitative and spatial multiomic analysis with single-cell resolution, may be used to explore the specific immune contextures of different organs in both normal and disease conditions. Once a thorough understanding of each organ-specific immune contexture has been achieved, we may possibly anticipate a new paradigm shift toward precision medicine using immunotherapy; such knowledge may help improve the overall therapeutic benefits for patients with different metastatic cancers.

Conclusion

Organ-specific differential responses of tumors to ICIs have been observed in retrospective clinical studies and also preclinical models of various cancers. The immunosuppressive hepatic TME may be responsible for the poor efficacy of immunotherapy in the liver. The sophisticated design of preclinical experiments and vigorous collection and characterization of human samples are warranted to discover the key mechanisms underlying immunosuppression in different organs. Knowledge in this regard may help overcome immunosuppressive TME in patients receiving immunotherapy for cancer.

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Conflicts of interest

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