Proceedings of ICBioMed 2025 Symposium: AI for Healthcare: Advanced Medical Data Analytics and Smart Rehabilitation
DOI: 10.54254/2753-8818/2025.AU27104

Immunotherapy for Hepatocellular Carcinoma: Recent Progress and Future Prospects

Zixuan Zhang

College of Arts & Sciences, Georgia State University, Atlanta, USA
zzhang46@student.gsu.edu

Abstract. Hepatocellular carcinoma (HCC) is the leading cause of death from cancer, and current standard care is ineffective, particularly in advanced stages. In recent years, with the development of cancer immunotherapy, immunotherapy has provided promising approach for HCC, such as the ICIs, the CAR-T cell therapy and the oncolytic viruses. However, resistance and variability of biomarkers remain challenging aspects. For example, CAR-T cell therapies targeting glypican-3, AFP, and mesothelin in HCC are very encouraging, but the manufacturing of CAR-T cells faces hurdles due to the immunosuppressive liver microenvironment. In this regard, oncolytic viruses such as T-VEC and Oncorine, as well as ICIs, offer the potential to selectively destroy tumor cells while activating the immune system. However, consistent challenges such as resistance, adverse immune-related events and drug delivery mechanisms hinder the clinical translation of these drugs. Future studies should address core issues such as optimizing combination therapy, improving predictive biomarkers, and providing solutions to resistance and toxicity for HCC patients.

Keywords: HCC, ICIs, CAR-T cell therapy, Oncolytic viruses.

1. Introduction

Hepatocellular carcinoma (HCC) is a common and aggressive type of liver cancer and a major global health concern. The World Health Organization (WHO) indicates that HCC is responsible for 75–85% of all liver malignancies, with the number of new cases each year being approximately 800,000, and 700,000 annual deaths related to the disease. The HCC incidence statistics are notably high in areas where the population has a high prevalence of hepatitis B and C infections, which mainly comprise East Asia and sub-Saharan Africa. Taking into account the increasing rates of NAFLD and cirrhosis in Western countries, HCC cases are also rising. And due to the high infection rate of chronic hepatitis viruses, the incidence rate of HCC remains high in China,posing a threat to public health. HCC has a high mortality rate and causes severe complications, diminishing quality of life due to jaundice, abdominal discomfort and fatigue.

Treatment protocols for HCC include surgical resection, liver transplantation, locoregional interventions (such as transarterial chemoembolization), and chemotherapy. However, these approaches have limitations, such as high relapse rates, suboptimal overall survival and insufficient activity in advanced stages and side effects. The prognosis for unresectable or metastatic HCC is very poor. In recent years, with the development of cancer immunotherapy, immunotherapy has

© 2025 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2025.AU27104

provided new treatment options for HCC, such as Immune Checkpoint Inhibitors, CAR-T Therapy, Oncolytic Viruses and so on.

This article aims to elaborate on the immunopathogenesis of HCC and the advancements in novel immunotherapies for HCC, providing a theoretical foundation for clinical practice and research.

2. Immunological mechanisms in hepatocellular carcinoma

HCC belongs to the category of cancers for which inflammation is the main driver of development, and tumor microenvironment (TME) plays a central role in carcinogenesis and progression. Long-standing liver inflammation can lead to the accumulation of genetic mutations and the stimulation of malignancies, specifically HCC [1]. In such an inflammatory context, various immune cells are involved, including T lymphocytes, macrophages, and regulatory T cells. In addition, the impact on liver cancer occurs based on a series of immune escape reactions and tumor-promoting effects induced by the inflammatory microenvironment. By activating viral protein-related signaling pathways in the liver inflammatory environment, it further damages liver cells.

2.1. T lymphocytes

The most relevant T lymphocytes in antitumor immunity are CD8+ T cells, particularly the cytotoxic ones. While tumor-specific CD8+ T cells do not usually encounter such problems in other tumors, they often suffer a loss of diversifying features in HCC, CD8+ T cells took up exosomal circCCAR1, which caused dysfunction by stabilizing the PD-1 protein [2]. This exhaustion is characterized by a decrease in their cytotoxic functions, such as decreased cytokine production and reduced degrading efficiency, and increased expression of the immune checkpoint molecules, including PD-1 and TIM-3. Exhausted T cells become less capable of eliminating tumor cells, allowing the tumor to persist and contributing to a poor clinical outcome. Furthermore, the chronic presence of tumor antigens in an inflammatory microenvironment depletes the effectiveness of T cells, thereby impeding the body's ability to recognize and destroy the tumor.

2.2. Macrophages

Along with other immune system cells, macrophages are responsible for managing and controlling HCC. It has been found that tumor-associated macrophages (TAMs) mostly originate from blood-derived monocytes attracted to the tumor site. According to the TME, these macrophages become polarized towards the pro-tumorigenic phenotype once they are in the macrophages. They mainly achieve this by secreting cytokines such as IL-10, which disable T cell activity within the immune system. Specifically, TAMs encourage angiogenesis, tissue remodeling, and metastasis, thereby furthering HCC. Furthermore, these macrophages suppress anti-tumor immunity and guide the recruitment of regulatory T cells (Tregs). These cells are also known to produce TGF-β and IL-10, offering another mechanism for Treg immunosuppressive activity and stimulating tumor immune evasion [3].

2.3. Tregs

It plays a vital role in maintaining immune tolerance because they can prevent autoimmunity and promote recovery. In HCC, Tregs are predominantly found in the tumor microenvironment, where they play a pivotal role in shaping immune responses. Without sufficient Tregs, effector T cells become activated and produce more Th1 cells, which can cause the immune system to become

DOI: 10.54254/2753-8818/2025.AU27104

overactive. Furthermore, it has been demonstrated that Tregs produce immunosuppressive cytokines, such as the IL-10 and also the TGF-β, that have a detrimental effect on the immune system. Many studies have shown that Tregs in the tumor microenvironment are associated with late-stage liver cancer and resistance to immunotherapy treatment.

3. Immune Checkpoint Inhibitors (ICIs) in HCC

3.1. Introduction to ICIs

ICIs can regulate the upregulation of T cells and can also help release anti-tumor activity by inhibiting negative immune stimulatory molecules, which has revolutionized cancer therapy. These drugs act as immunostimulatory agents that activate the immune system to identify and kill malignant cells, which prevent immune checkpoint receptors, such as PD-1, PD-L1, and CTLA-4, from interacting with tumor cells, which are upregulated sites enabling tumor evasion of immune recognition. Once PD-1 and PD-L1 access each other, they turn off T cell function, allowing the tumor to evade immune surveillance. ICIs interrupt this connection during this process, enabling T cells to regain the ability to kill cancer cells.In 2017, the FDA approved nivolumab (Opdivo) as the first immunotherapy drug for HCC, the objective response rate (ORR) is 15% to 20% [4].

3.2. ICIs for hepatocellular carcinoma

The application of ICIs in HCC has proved to be very effective, particularly among patients with advanced or metastatic disease. Trials with PD-1 inhibitors, such as Camrelizumab, nivolumab and pembrolizumab, have shown increased survival rates among patients on these treatments compared to those on the first-line treatment, sorafenib, label, parallel-group, randomized Phase II clinical trial conducted by 13 research centers in China has been completed. One research evaluates the Camrelizumab efficacy for Chinese patients with advanced liver cancer. It showed that the ORR and the overall survival (OS) at 6 months is 14.7% and 74.4%, respectively, which indicates Camrelizumab has good antitumor efficacy and the adverse reactions can be managed [5].

Combining different treatment modalities has also emerged as the chief strategy in the management of HCC. It is a highly effective approach to overcoming the immunosuppressive TME of hepatocellular carcinoma. In a randomized clinical trial, the team documented the appreciably increased response rates and survival in patients who received the combination therapy of the nivolumab and ipilimumab (anti-CTLA-4 antibody) and sorafenib, whereas this was not the case with monotherapy [6].

On the other hand, ICI therapies appear not efficacious in various types of patients, and resistance to tumor also remains a grave concern, mainly due to immunosuppressive features of tumor microenvironment that might render the treatment unsuccessful. In particular, this situation occurs due to upregulation of other immune checkpoints such as the LAG-3 and TIM-3, or as a result of the presence of TGF-β. Eventually, this leads to the lack of effective T-cell response and the resistance to PD-1 inhibitors. Therefore, some do not benefit from treatment, which creates a need for improving the strategy for patient selection.

Discovering circulating biomarkers is one of the research subjects' scientists are looking at. Since recent ICIs seem to induce PD-L1 expression on the tumor cells, hyperaccretion of what is thought to be a biomarker of response, clinicians are attempting to establish its power of prediction, but the results are not guaranteed. And still, high tumor mutational burden (TMB) and low microsatellite

DOI: 10.54254/2753-8818/2025.AU27104

alterations (MSI) are possible pre-existing biomarkers currently, which scientists are seeking [7]. This would enable us to find the immunotherapy candidates who would likely benefit the therapy.

4. CAR-T therapy in hepatocellular carcinoma

4.1. Introduction to CAR-T therapy

This therapy is an innovative immunotherapy treatment for cancer. During this procedure, T lymphocytes are genetically modified using a viral vector, which allows the newly formed T cells to specifically destroy malignant cancer cells. The procedure begins with the extraction of CD8+ CTLs from the patient's blood. After isolation, these T cells are activated and expanded outside the body, where they are genetically manipulated to produce CARs that recognize a unique pattern of antigens found on the surface of tumor cells. thereby boosting the immune response against the tumor. Moreover, these cells persist in the patient's body and can continually multiply, enabling them to consistently attack and destroy the tumor and improve patient outcomes. As of August 2022, the FDA has approved six CAR-T products for marketing. Similarly, the National Medical Products Administration (NMPA) approved the marketing of two CAR-T products in 2021. This novel treatment has thus far proved to be highly effective in treating hematological malignancies, such as leukemia and lymphoma. CAR-T therapy could also greatly benefit patients with solid tumors.

4.2. Application in hepatocellular carcinoma

Glypican-3 (GPC3) is often overexpressed in HCC, while it is absent in healthy liver tissue, enabling the selective targeting of HCC cells and making it a promising target. Unlike the typical hepatocytes [8]. Clinical trials on GPC3 CAR-T cells chimeras have revealed the viability of the approach for HCC patients and have significantly reduced tumor size and prolonged survival, especially in patients with advanced HCC. Additionally, there is ongoing research and development of other potential targets with regard to HCC treatment options. Alpha-fetoprotein (AFP), the commonly known hepatocellular carcinoma (HCC) biomarker, is found to be elevated in a variety of liver cancer cases, which may lead it to become a target for therapy [9]. AFP-targeted treatment regimens intend to increase the effectiveness of therapy. Other approaches are directed against another target protein called mesothelin, which is featured in many cancers, particularly HCC. At the moment, the engaged mesothelin-specific CAR-T therapy is investigated as a possible cure.

However, the application also suffer from hepatic carcinoma may meet several challenging issues, like the impossibility of creating more T cells from the liver and finding a way of storing them. And the liver's immunosuppressive setting, which uses significantly high amounts of LOGIC-OF-PROCESSING Blog29 suppressive materials and cells, becomes a major detriment in the CAR-T cell's effectiveness. On the other hand, researchers are trying to shift the CAR T cells in such a way that they can adapt to the immunosuppressive environment and be more effective in combating hepatocellular carcinoma.

5. Oncolytic viruses in hepatocellular carcinoma

5.1. Introduction to oncolytic viruses

Oncolytic virus therapy is an emerging approach that uses natural or genetically modified viruses to selectively infect and kill cancer cells, while stimulating the human immune system to attack tumors. They invariably lead to destruction of abnormal cells with an insignificant loss of normal

DOI: 10.54254/2753-8818/2025.AU27104

cells. These hybrids (naturally or artificially) are chosen depending on their ability to target tumor cells highly effectively, considering the specific features of this disease's microenvironment, such as different cellular pathways, immune evasion mechanisms, and genetic mutations. Oncolytic viruses propose two distinct but complementary mechanisms of tumor elimination: either they are lethal to tumor cells by viral replication and then cell lysis or promote the anti-tumor immunity by mobilizing the immune system to destroy tumor cells.

The first type consists of naturally occurring viruses with a preference for killing tumor cells, such as HSV, whereas the second type includes genetically engineered viruses, such as adenoviruses, that have been altered to increase their oncolytic potential or harbor therapeutic genes that stimulate anti-tumor immunity. Due to their versatility and ability to provoke an immune response, oncolytic viruses appear efficacious in fighting different cancers, including liver cancer.

5.2. Application in hepatocellular carcinoma

T-VEC is a genetically modified herpes simplex virus that acts as an oncolytic virus, specifically infecting and killing tumor cells while activating antitumor immunity. Initially approved for melanoma, T-VEC treatment is now being studied for its potential use against HCC. T-VEC was found to be safe and well tolerated, with approximately 20-33% of HCC patients showing a partial response (with stable disease or tumor shrinkage being the endpoints) to the therapy in some clinical trials. Also, T-VEC has been shown to be safe in clinical trials and to decrease tumor sizes in some HCC patients who do not respond to conventional therapies. Prevailing hypothesis is that the virus replicates within the tumor cells, then cell lysis and tumor antigens release, activating the immune response and boost tumor destruction mediated by the immune system. Meanwhile, T-VEC's ability to significantly enhance the efficacy of other therapies, such as ICIs. T-VEC combined with pembrolizumab (a PD-1 inhibitor) was associated with the highest ORR in advanced liver cancer patients, with some achieving partial tumor regression outside of the liver.

Oncorine (also known as H101) is a genetically edited type 5 adenovirus. By deleting gene fragments in the E1B-55 kD and E3 regions, it not only enhances its safety but also enables selective replication in tumor cells. In 2024, ASCO announced a clinical study on the treatment of intrahepatic mass-forming cholangiocarcinoma using intertumoral injection of H101 combined with hepatic arterial infusion chemotherapy (HAIC). The results showed that the median OS period of the combined treatment reached 13.2 months, th ORR was 36.3%, and the disease control rate (DCR) was 90.9%.

In addition, virotherapy using engineered adenoviruses has demonstrated the potential for tumor shrinkage and improved survival in animal models of HCC. Early-phase clinical trials have shown that engineered oncolytic herpes simplex viruses can preferentially infect and eliminate HCC cells while simultaneously mounting a localized immune response that can further potentiate tumor destruction.

However, the application of oncolytic virotherapy in liver cancer is hindered by several complications, including the necessity of developing efficient delivery methods for the virus that enable it to reach the tumor site in the desired quantities and concentration. The immune system's pre-existing immunity to certain viruses may affect the response to viral therapies. Despite these challenges, scientists are working to overcome the difficulties by tailoring the viruses to evade immune detection, as well as exploring the possibility of using oncolytic virus therapy alongside other treatment modalities, such as ICIs, to enhance its effectiveness.

DOI: 10.54254/2753-8818/2025.AU27104

6. Challenges faced by current immunotherapy

Although cancer immunotherapy has been a trendsetter in oncology, numerous obstacles remain. The first critical issue is drug resistance. It can be divided into congenital (primary) resistance, acquired (secondary) resistance, and adaptive resistance. Primary resistance mechanisms are often associated with inherent genetic and epigenetic alterations in tumor cells, which may involve abnormalities in drug absorption, metabolism, target expression, and signaling pathways. Acquired resistance mechanisms typically occur after initial treatment is effective, when tumor cells resist treatment through a series of adaptive changes, such as secondary mutations in drug targets, overexpression of drug efflux pumps, and alterations in the apoptosis pathway. Adaptive resistance refers to the fact that tumor cells can be recognized by the immune system, but they can adapt to the attack of the body's immune system through certain mechanisms, thereby mediating immune resistance. Adopting a combination therapy strategy may help overcome the resistance issue in immunotherapy. In addition, dynamic changes such as mutations and copy number variations in the tumor genome can be monitored in real time, allowing for timely adjustments to the treatment plan to address the emergence of resistance.

The next challenge is immune-related adverse events (irAEs). The frequency and severity experienced by patients can differ greatly depending on the type of immunotherapy they receive and how their bodies react to it [10]. These inhibitors, for instance, might trigger symptoms of colitis, hepatitis, or pneumonitis in patients. Numerous investigations indicate that the frequency of these adverse events is not the same, and some clinical trials report that irAEs are present in more than 1/3 of the patient population. The mortality rate of irAEs can surge to 45% in extreme cases, involving cardiac toxicity and interstitial pneumonia. The irAEs clinical presentations are hidden, making it difficult to detect them early. Discovery of predictive biomarkers of irAEs is a key approach for increasing treatment effectiveness and reducing toxicity. Artificial intelligence can be utilized for this purpose by parsing clinical, imaging, and pathological information, which in turn will improve the early detection and differential diagnosis of irAEs. Another important question to consider is when should different immunotherapies and what different immunosuppressants be given.

7. Conclusion

HCC is one of the most complicated problems in modern oncology. Urgent attention needed due to its aggressive nature, the time it takes to diagnose it, and the limited therapies currently available. Conventional treatments often fail to achieve long-term survival goals due to the issues such as tumor recurrence and therapy-related resistance. The emergence of immune therapies offers a new perspective, with ICIs, CAR-T cell therapies and oncolytic viruses undergoing clinical trials and providing cause for optimism. However, despite these therapies proving effective in certain cases, the clinical application remains limited due to issues such as drug resistance and irAEs.

Future research endeavors should concentrate on fortifying combined therapeutic strategies and methodologies, transcending the constraints of monotherapy with immunotherapy. By integrating immunotherapy with epigenetic agents, targeted therapies, radiotherapy, focused ultrasound, and convective-enhanced delivery, remodel the immunosuppressive tumor microenvironment, augment the anti-tumor immune responses, and synergistically enhance overall therapeutic outcomes. Additionally, longer-term follow-up studies are needed to assess the prolonged efficacy and safety.

Also, future plans will need to focus on finding solutions to issues relating to immune resistance and effectively managing adverse events. Addressing the issue of drug resistance arising during treatment, future endeavors will delve deeper into dissecting the heterogeneity and the dynamic

DOI: 10.54254/2753-8818/2025.AU27104

evolution of tumor microenvironment. Leveraging technologies such as single-cell sequencing and liquid biopsy, we will monitor the onset of drug resistance in real-time and devise novel combination strategies. Regarding irAEs, the emphasis will shift towards predictive prevention and targeted management, with proactive interventions in high-risk populations. The development of engineered drugs to mitigate systemic toxicity will propel immunotherapy into a new era of enhanced safety and efficacy.

References

[1] Singh SP, Madke T, Chand P. Global Epidemiology of Hepatocellular Carcinoma. J Clin Exp Hepatol. 2025 Mar-Apr; 15(2): 102446.
[2] Hu Z, Chen G, Zhao Y, et al. Exosome-derived circCCAR1 promotes CD8 + T-cell dysfunction and anti-PD1 resistance in hepatocellular carcinoma. Mol Cancer. 2023; 22(1): 55. Published 2023 Mar 18.
[3] Arora M, Kundu A, Sinha S, Chosdol K. Immune factors and their role in tumor aggressiveness in glioblastoma: Atypical cadherin FAT1 as a promising target for combating immune evasion. Cell Mol Biol Lett. 2025 Jul 25; 30(1): 89.
[4] El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017; 389(10088): 2492-2502.
[5] Qin S, Ren Z, Meng Z, et al. Camrelizumab in patients with previously treated advanced hepatocellular carcinoma: a multicentre, open-label, parallel-group, randomised, phase 2 trial. Lancet Oncol. 2020; 21(4): 571-580.
[6] Yau T, Kang YK, Kim TY, et al. Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients With Advanced Hepatocellular Carcinoma Previously Treated With Sorafenib: The CheckMate 040 Randomized Clinical Trial [published correction appears in JAMA Oncol. 2021 Jan 1; 7(1): 140.
[7] Robinson HR, Lakritz S, Pavlick DC, Davis SL, Lieu CH, Eule CJ, Graham LS, Spiess PE, Li R, Kamat AM, Grivas P, Jacob JM, Bratslavsky G, Basnet A, Wong KA, Lin DI, Necchi A, Ross JS, Lam ET. Squamous cell carcinoma of unknown primary (SCCUP): a genomic landscape study. ESMO Open. 2025 Jun; 10(6): 105312.
[8] Zheng X, Liu X, Lei Y, Wang G, Liu M. Glypican-3: A Novel and Promising Target for the Treatment of Hepatocellular Carcinoma. Front Oncol. 2022; 12: 824208. Published 2022 Feb 16.
[9] Hanif H, Ali MJ, Susheela AT, et al. Update on the applications and limitations of alpha-fetoprotein for hepatocellular carcinoma. World J Gastroenterol. 2022; 28(2): 216-229.
[10] Princk MH, Pervan M, Riedl J. Nebenwirkungsmanagement unter Immuntherapie [Management of immune-related adverse events]. Urologie. 2025 Mar; 64(3): 281-287. German. doi: 10.1007/s00120-024-02517-x. PMID: 39932580.