



Targeting Immune Checkpoint Proteins as Novel Strategy for Treatment of Hepatocellular Carcinoma

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Editorial

In recent years, cancer immunotherapy has been a recent hot topic among scientists over the world. So far, the discovered checkpoint protein molecules include cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1), lymphocyte activation gene-3 (LAG-3) and several others. The overexpression of the checkpoint proteins could lead the decreased T-cell cytotoxicity, proliferation and cytokine production. It is believed that inhibition of the immune checkpoint proteins by specific antibodies, the suppressed immunity can be restored and the tumor cells are targeted by the T cells. CTLA-4 is the first immune checkpoint molecule to be clinically targeted for treatment of melanoma. Following the success of CTLA-4 as potential cancer therapy, PD-1 becomes the recent crucial immune checkpoint currently being investigated for cancer treatment. PD-L1 (CD274) and PD-L2 (CD273) are the two ligands of PD-1. PD-L1 was found to express in a wide range of cells, including antigen presenting cells, myeloid cells, epithelial cells and cancer cells while PD-L2 is majorly expressed on antigen presenting cells after the exposure to IFN- γ . However, recent studies reported that PD-L2 is also expressed on cancer cells [1,2]. Since hepatocellular carcinoma (HCC) is developed in an immune-suppressive environment, the role of these immune checkpoints in this disease has been recently studied.

Hepatitis B virus (HBV) chronic infection has been linked to the development of hepatocellular carcinoma (HCC) for decades of years. The association of the PD-1 immune checkpoint protein to HBV was verified by the positive correlation of PD-1 expression on CD4+ and CD8+ T cells to the serum HBV [3]. In addition, Cheng et al. [4] found that PD-1 expression could be reduced by anti-HBV therapy, and the elevated plasma soluble PD-1 was correlated to the maintaining of high viral load. The overall survival (OS) of patients with HBV-related HCC was associated with PD-1 single-nucleotide polymorphisms (SNPs) [5]. The PD-1 polymorphism rs10404525 with allele G was significantly associated to longer OS of the patients. The polymorphisms of PD-1 may lead to differential expression of the checkpoint proteins, so the rs10404525 with allele G may cause lower PD-1 expression. Therefore, the patients without the rs10404525 may have higher PD-1 expression, which results in poorer patient's survival

through inhibition of the T-cell mediated antiviral and antitumor immunity. Apart from the SNP, which is correlated to the survival of patients, microRNA (miRNA) was also found to alter the expression of the checkpoint protein. miRNAs are small non-coding RNA molecules that regulate gene expression at post-transcriptional level. Zhang et al. [6] found that miRNA differentially interacts with the polymorphisms of PD-1. miR-4717 miRNA significantly suppressed the luciferase activities of pMIR bearing segments from PD-1 polymorphism rs10204525 with G allele. However, it is also found that patients with chronic HBV infection and HBV-related cirrhosis had significantly lower miR-4717 levels. However, it remains unknown whether miR-4717 differentially regulates the PD-1 expression in a positive or negative manner. miR-4717 could possibly inhibit the PD-1 expression so the patients with chronic HBV are prone to the enrichment of PD-1 due to the lower expression of miR-4717.

Sorafenib is the first line drugs approved by FDA for treating advanced HCC. It was reported that sorafenib treatment significantly enriched PD-1 expressing CD8+ T cells in HCC patients with low pErk expression [7]. These patients also have poorer overall and disease-free survivals. Besides, the prolonged sorafenib therapy could cause tissue hypoxia that creates an immunosuppressive microenvironment. It is found that the sorafenib treatment increased PD-L1 expression in HCC tumor cells [8]. Based on this finding, co-treatment of sorafenib with anti-PD-L1 antibody may exert enhanced therapeutic efficacy. However, such combination only exerted enhanced efficacy when CXCR4 is inhibited. Apart from sorafenib, paclitaxel and etoposide increased PD-L1 expression on breast cancer cell lines [9]. The treatment of trastuzumab significantly upregulated the PD-1 on HER2-enriched subtype of breast cancer tissue [10]. Peng et al. [11] studied the tumor from patients with ovarian cancer, and found that after 4 days of paclitaxel plus carboplatin chemotherapy, the cancer cells showed 5-fold higher PD-L1 expression. The *in vitro* treatment of gemcitabine or paclitaxel also significantly induced the NF- κ B signaling pathway in the ovarian cancer cells. It is deduced that NF- κ B signaling is the pathway that induces overexpression of PD-L1 on cancer cells after chemotherapy.

The therapeutic efficacy of targeting immune checkpoint proteins for treatment of HCC is currently tested in various clinical trials. Tremelimumab, a monoclonal antibody blocking CTLA-4, has been evaluated in a Phase II study for HCC treatment [12]. This therapeutic antibody was demonstrated to exert favorable antitumor activity with tolerable side effects. Another immune checkpoint being targeted for HCC cancer therapy is the PD-1. Nivolumab, a fully human IgG4 monoclonal antibody that specifically targets PD-1, was recently approved by FDA for the treatment of non-small cell lung carcinoma and melanoma [13,14]. A phase I/II clinical trial has been performed to evaluate its tolerance and anti-tumor activity in sorafenib-refractory HCC patients with or without infection of HBV/HCV viruses. The results showed that this antibody was well tolerated, and exerted favorable responses across all drug doses and different patient cohorts. A phase III trial has just started to compare its efficacy with sorafenib as first-line treatment in patients with advanced HCC (NCT02576509). Although it remains a question of whether these antibodies would provide better survival benefits to patients as monotherapy or in combination with other drugs over sorafenib, targeting immune checkpoints by antibody approach may be a novel therapeutic strategy against HCC.

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