

# Letter to the Editor

## The expression of PD-L1 APE1 and P53 in hepatocellular carcinoma and its relationship to clinical pathology

Dear Editor,

In this interesting article, Kan and Dong<sup>1</sup> describe for the first time the mutual relationships between PD-L1, APE-1 and p-53 expressions, and between their expression and clinico-pathological characteristics in hepatocellular carcinoma (HCC). HCC represents the fifth most common cancer worldwide and the second leading cause of cancer-related death<sup>2-4</sup>. Despite the high incidence, treatment options remain limited and unsuccessful for advanced HCC, resulting in a poor prognosis. Major risk factors for HCC include HBV, HCV, diabetes mellitus, obesity, excess alcohol consumption and metabolic diseases. All these factors contribute to a perpetual state of inflammation and fibrogenesis, leading to fibrosis and cirrhosis, preneoplastic conditions promoting the development of HCC<sup>5</sup>. In particular, many patients with chronic hepatitis will develop liver cirrhosis and eventually HCC in a progressive and dynamic process, thanks to an altered liver microenvironment characterized by the generation of highly reactive oxygen species and a constitutively active inflammatory milieu. Improving our knowledge about immunological mechanism during hepatocarcinogenesis could ultimately lead to novel and better treatment strategies for this deadly disease.

According to several studies, tumor-specific cellular and humoral immune responses occur in patients with HCC. However, these T cell responses fail to induce tumor regression and/or inhibit disease progression, due to the multiple immune-suppressive mechanisms that are regulated by the tumor itself. One of the most intriguing and promising mechanisms is represented by immune checkpoints, a group of co-inhibitory molecules with an inhibitory function on immune response, that is crucial for maintaining self-tolerance and modulating the duration and extent of physiological immune responses in peripheral tissues. Many immune checkpoint molecules, such as the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and PD-L1/PD-1, have been detected in the tumor microenvironment, and are often overexpressed as well<sup>6</sup>. Many human cancers express PD-L1, the ligand for the inhibitory receptor programmed cell death-1 (PD-1). Tumour-associated PD-L1 has been shown to induce apoptosis of effector T cells and is thought to contribute to immune evasion by cancers. In HCC, tumor infiltrating CD8+ T cells are characterized by an increase in PD-1 expression and intratumor Kupffer cells have been shown to upregulate PD-L1 and decrease the effector function of PD-1-expressing CD8+ T cells in HCC patients. These data suggest that the inhibition of PD-1/PD-L1 axis may be a potential strategy in the boosting of HCC-specific immunity<sup>7,8</sup>.

In this article, the authors have analyzed, in a total population of 128 patients with HCC, the expression of PD-L1, APE1 and P53 by immunohistochemistry. APE 1 has a dual function of the DNA damage repair and oxidative reduction, and is a multifunctional protein, which plays an important role in maintaining DNA stability and regulating the expression of cytokines (18K-D). The abnormal expression or distribution and function change of APE1 is closely related to tumorigenesis. The P53 gene encodes for a tumor suppressor that plays a negative regulatory

role in the cell cycle to regulate cell proliferation and differentiation. In this study, an increased expression of PD-L1, APE1, and P53 protein in HCC tissues was found in 82.03%, 92.19%, and 60.94% of the population, respectively. PD-L1 positive expression was significantly associated with clinical stage, resulting in higher expression in patients with I-II stage liver ( $p = 0.041$ ). Moreover, higher expression levels were found in HBV infection-positive cancer and non-portal vein thrombosis ( $p = 0.030$ ;  $p = 0.014$ ). It would be interesting to study also the relationship between PDL-1 expression and HCV-related infection, since chronic HCV infection, as well as HBV infection, is well known to induce a chronic proinflammatory hepatic and systemic state associated with immunosuppressive and immunomodulatory effects [BMR57, 78-85], with a negative regulation of both innate and adaptive arms of the immune system. Furthermore, PDL-1 resulted inversely correlated with P53 (correlation coefficient -0.227,  $p = 0.010$ ), and positively correlated with APE1 expression (correlation coefficient 0.189,  $p = 0.032$ ). The reason of this pattern of expression remains unclear and it would be useful to study the pathways which are responsible for the connections among these proteins. Probably, a higher expression of PD-L1 in cancer cells lead to the inhibition of tumor suppressor activity of p53.

Finally, the expression of PD-L1, unlike APE-1 and p53, is associated with a longer overall survival with a mOS of 10 months for patients with high expression of PD-L1 and 5 months for patients without high PD-L1 expression ( $p=0.001$ ). This result suggests a possible role of PDL-1 expression as a prognostic factor in HCC, since it is related to a longer overall survival. PD-L1 could be used not only as a prognostic factor, but also as a predictive factor of response to immunotherapy with anti-PD-L1 antibodies. In fact, different studies have shown greater response rate to immunotherapy in patients with higher expressions of target molecules.

One of the major challenges in the approach to HCC is an early diagnosis of the disease in a limited stage. It would be interesting to better understand the role of immune checkpoint in early phase of hepatocarcinogenesis to find a molecular marker able to predict the evolution from cirrhosis to HCC.

Since immunotherapy represents one of the most promising and biologically intriguing strategies today for the treatment of HCC, it is necessary to better define the patient population that will benefit from immunologic therapies through the identification of novel biomarkers to predict who may benefit from immunotherapy. Moreover, studies are needed to determine if combined strategies of immunotherapy and traditional treatment options are more effective in the treatment of HCC, considering also the multidisciplinary aspects of this disease<sup>9,10</sup>.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

### References

- 1) KAN G, DONG W. The expression of PD-L1 APE1 and P53 in hepatocellular carcinoma and its relationship to clinical pathology. *Eur Rev Med Pharmacol Sci* 2015; 19: 3063-3071.
- 2) NUNNARI G, BERRETTA M, PINZONE MR, DI ROSA M, BERRETTA S, CUNSOLO G, MALAGUARNERA M, COSENTINO S, DE PAOLI P, SCHNELL JM, CACOPARDO B. Hepatocellular carcinoma in HIV positive patients. *Eur Rev Med Pharmacol Sci* 2012; 16: 1257-1270.
- 3) URSINO S, GRECO C, CARTEI F, COLOSIMO C, STEFANELLI A, CACOPARDO B, BERRETTA M, FIORICA F. Radiotherapy and hepatocellular carcinoma: update and review of the literature. *Eur Rev Med Pharmacol Sci* 2012; 16: 1599-1604.
- 4) BERRETTA S, FISICHELLA R, SPARTÀ D, LLESHI A, NASTI G. Primary liver cancer: clinical aspects, prognostic factors and predictive response to therapy. *WCRJ* 2015; 2: e561.
- 5) DE RE V, CAGGIARI L, DE ZORZI M, REPETTO O, ZIGNEGO AL, IZZO F, TORNESELLO ML, BUONAGURO FM, MANGIA A, SANSONNO D, RACANELLI V, DE VITA S, PIOTELLI P, VACCHER E, BERRETTA M, MAZZARO C, LIBRA M, GINI A, ZUCCHETTO A,

- CANNIZZARO R, DE PAOLI P. Genetic diversity of the KIR/HLA system and susceptibility to hepatitis C virus-related diseases. PLoS One 2015; 10: e0117420.
- 6) GAO Q, WANG XY, QIU SJ, YAMATO I, SHO M, NAKAJIMA Y, ZHOU J, LI BZ, SHI YH, XIAO YS. Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in humanhepatocellular carcinoma. Clin Cancer Res 2009; 15: 971-979.
  - 7) CANZONIERI V, ALESSANDRINI L, CAGGIARI L, PERIN T, BERRETTA M, CANNIZZARO R, DE RE V. Hepatocellular carcinoma: an overview of clinico-pathological and molecular perspectives. WCRJ 2015; 2: e485.
  - 8) BERTINO G, DEMMA S, ARDIRI A, PROITI M, MANGIA A, GRUTTADAURIA S, TORO A, DI CARLO I, MALAGUARNERA G, BERTINO N, MALAGUARNERA M, MALAGUARNERA M. The immune system in hepatocellular carcinoma and potential new immunotherapeutic strategies. Biomed Res Int 2015; 2015: 731469.
  - 9) BERRETTA M, DI FRANCIA R, TIRELLI U. Editorial – The new oncologic challenges in the 3rd millennium. WCRJ 2014; 1: e133.
  - 10) BERRETTA M, DI FRANCIA R, DI BENEDETTO F, TIRELLI U. New entities in the treatment of epatocellular carcinoma: HIV-positive and elderly patients. WCRJ 2015; 2: e558.

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