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Hyperbaric oxygen facilitates teniposide-induced cGAS-STING activation to enhance the antitumor efficacy of PD-1 antibody in HCC

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Recently, we followed the report by Yang *et al* that hyperbaric oxygen facilitates teniposide-induced The cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway(cGAS-STING) activation to enhance the antitumor efficacy of an anti-PD-1 antibody in Hepatocellular carcinoma (HCC) with interest.[1] The authors provided new insight into hyperbaric oxygen and teniposide chemotherapy, showing that this combination could synergistically trigger efficient tumor STING activation and eventually stimulate a robust adaptive antitumor immune response in hepatocellular carcinoma. Researchers can use these findings to try to improve the response rates of patients with HCC to anti-PD-1 therapy and broaden therapeutic strategies for advanced HCC. We appreciate the authors' work on Tumor Immune Microenvironment (TIME) remodeling and proposing new treatments for the future. However, after reading this article, we want to highlight some key issues in this study.

For their TME survey experiments, the authors used orthotopic models established with Hepa1-6 cells that replicate the vessels, stroma, and lymphatic system of the Tumor Microenvironment (TME), but Won Jin *et al* reported that Hepa1-6 tumors are infiltrated with more immunologically active cells, such as cytotoxic T cells, helper T cells, B cells, and dendritic cells, than immunosuppressive cells, which contrasted with the results for the immune microenvironment of human HCC.[2] They used the TIBx cell line to mimic the HCC tumor microenvironment, a model containing large numbers of 'M2-like' tumor-associated macrophages and relatively few PD-1$^+$ T cells that more closely resembles the immunosuppressive microenvironment of human HCC. This may suggest that using this cell model to reassess the HCC antitumor response before and after treatment with HBO+teniposide would be more accurate.

For anti-PD-1 sensitization experiments, it is important to note that subcutaneous models are not the best choice for researching microenvironmental aspects of liver cancer, as the microenvironment of the tumor is greatly impacted by the organ in which it develops.[3] The complex etiology of the underlying liver disease, the resulting high heterogeneity of HCC, and the vastly varying immunotherapy responses in HCC patients are extremely important constraints in the field of liver cancer. Recent research has shown that patients with HBV infection develop specific mechanisms of resistance to anti-PD-1 therapy,[4] highlighting the importance of animal models that accurately reflect the various facets and heterogeneity of the disease under study. Therefore, it is important to combine multiple mouse models of liver cancer rather than models of different cancer types to overcome HCC-related limitations and improve the relevance of findings.

Collaborators -

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