

Commentary

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Comment on “APOBEC3B interaction with PRC2 modulates microenvironment to promote HCC progression”

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Accounting for 75%-85% of all primary liver cancer cases, hepatocellular carcinoma (HCC) is nowadays one leading cause of cancer-related mortality worldwide^[1]. More than half of HCC patients are diagnosed at the advanced stage, for which limited treatment options are available and no curative ones exist so far, leading to poor prognosis^[2]. The main risk factors for HCC, such as infection with HBV and HCV, excessive alcohol consumption, obesity, and diabetes, all contribute to chronic liver inflammation, which leads to the formation of an altered liver microenvironment. In turn, an altered liver microenvironment can reciprocally reprogram the immune cells and hepatocytes involved in inflammation, together setting the stage for progression to cirrhosis and eventually to HCC^[2-4].

It has been demonstrated that tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) are the most abundant immune cell populations infiltrated in the tumor microenvironment of HCC. As pivotal players in cancer-related inflammation, TAMs and MDSCs promote hepatocarcinogenesis by stimulating angiogenesis and inducing immunosuppression and correlate with inferior prognosis^[5-7]. Thus, it is of crucial importance to gain an in-depth look at the interplay between hepatocytes and immune cells, especially TAMs and MDSCs, during the development of HCC.

Recently Wang *et al.*^[8] presented a remarkable study unraveling the functional significance of hepatocyte-intrinsic apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3B [APOBEC3B (A3B)] in



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promoting HCC progression by recruiting TAMs and MDSCs to the tumor microenvironment, thus inhibiting CD8⁺ T cell function and further facilitating immune escape.

In this issue, the authors first demonstrated elevated abundance of A3B in HCC patients due to overactivation of the non-classical NF- κ B pathway and direct transcriptional regulation by RelB. Taking advantage of both immunocompetent and immune-deficient mouse HCC models, they revealed that A3B activated HCC initiation through modulation of the immune system as A3B exerted its carcinogenic function only in mice with complete immune system, which was accompanied by increased secretion of CCL2, IL-34 and BMP7 and the subsequent accumulation of TAMs, MDSCs and Programmed cell death 1(PD1)⁺ CD8 T cells.

After establishing the impact of hepatocyte-intrinsic A3B on immunological environment in HCC development, Wang and his colleagues performed a series of analyses to investigate the molecular basis of this phenomenon. They found out that A3B inhibited PRC2 activity through both interference of its binding affinity and attenuating its enzymatic activity, while PRC2 has been reported to be indispensable in the methylation of H3K27 and regulate chemokine expression^[9,10]. Bioinformatic analyses showed a highly overlapping cohort of target genes, whose expression levels altered in inverse correlation upon exogenous A3B expression and H3K27me3. Experiments further demonstrated H3K27me3 sites at the promoter regions of CCL2, IL-34 and BMP7. Taken together, upregulated A3B suppressed occupancy of H3K27me3 on the promoter of chemokines CCL2, IL-34 and BMP7 by inhibiting PRC2 activity.

In last decade, immunotherapy dramatically revolutionized the therapeutic landscape in oncology and was announced as Breakthroughs of the Year by Science in 2013. However, the progress of introducing either chimeric antigen receptor (CAR)-modified T cells or checkpoint inhibitors into HCC therapy is rather slow. In 2017, Nivolumab was approved as the only anti-PD-1/L1 antibody for the treatment of HCC patients^[11]. However, the response rate reached only about 20%^[12]. One major cause of such low effectiveness lies in the immunosuppressive tumor microenvironment and immune escape. In addition to immunotherapy, epigenetic therapy has drawn much attention in recent years as well. However, outcome of pre-clinical and clinical trials of epigenetic drugs in HCC was rather disappointing, indicating other molecular mechanisms involved in epigenetic modulation^[13]. This work by Wang and his colleagues discovered a crucial role of A3B in promoting HCC initiation by modulating immunological microenvironment via inhibition of H3K27 methylation, revealing A3B as a novel therapeutic target in immunotherapy of HCC, explaining partially the current failure of epigenetic drugs, and demonstrating the significance of combined therapy targeting both innate and acquired immune systems in future HCC treatment.

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

Availability of data and materials

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Conflicts of interest

The author declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

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