Molecular Therapy
Nucleic Acids
Commentary

Deciphering the shield: Lnc-CCNH-8's pivotal role in crafting PD-L1-mediated immune camouflage in hepatocellular carcinoma

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https://doi.org/10.1016/j.omtn.2024.102151

Hepatocellular carcinoma stands as a formidable challenge in oncology, with its intricate molecular landscape dictating the urgent need for novel therapeutic targets and prognostic biomarkers.[1] Dr. Xiaolong Liu's study revealing that Lnc-CCNH-8 is significantly upregulated in hepatocellular carcinoma (HCC) tissues not only highlights its potential as a biomarker for disease progression but also illuminates its complex role in modulating the immune response.[2] This long non-coding RNA emerges as a key player in the complex interplay between tumor cells and the immune system, particularly through its interaction with PD-L1, a critical immune checkpoint molecule. By upregulating PD-L1 expression, Lnc-CCNH-8 facilitates an immunosuppressive tumor microenvironment, allowing cancer cells to evade immune surveillance. This mechanism highlights the sophisticated strategies employed by HCC cells to sustain their growth and spread, emphasizing the necessity for innovative approaches to disrupt these pathways and restore immune competence. Dr. Liu et al.'s study does more than just elucidate a novel mechanism of immune escape; it paves the way for the development of targeted therapies that could inhibit the function of Lnc-CCNH-8, thereby enhancing the efficacy of immunotherapies in HCC. The identification of Lnc-CCNH-8 as a potential therapeutic target opens exciting possibilities for the creation of RNA-based treatments or small-molecule inhibitors that can prevent Lnc-CCNH-8 from facilitating PD-L1 expression. Furthermore, the discovery that exosomal Lnc-CCNH-8 levels could serve as a predictive marker for immunotherapy response offers a valuable tool for personalizing treatment approaches. By determining which patients are most likely to benefit from anti-PD-L1 therapies based on Lnc-CCNH-8 expression, clinicians can tailor treatments more effectively, maximizing therapeutic success while minimizing unnecessary exposure to potentially ineffective therapies.

The discovery of Lnc-CCNH-8's involvement in immune escape mechanisms offers a promising pathway for enhancing the efficacy of existing immune therapies. By targeting Lnc-CCNH-8, it may be possible to disrupt its regulatory effect on PD-L1, thereby restoring the immune system's ability to detect and eliminate HCC cells. This strategy could potentially amplify the therapeutic impact of PD-L1 inhibitors, which are already used in treating various cancers but often exhibit limited efficacy in HCC due to the tumor's adeptness at evading immune detection. The study by Dr. Liu et al. suggests that combining PD-L1 inhibitors with agents that target Lnc-CCNH-8 could synergize to overcome immune resistance, offering a novel approach to immunotherapy that is specifically tailored to exploit the vulnerabilities of HCC. Furthermore, the study underscores the critical role of microRNAs (miRNAs) in cancer progression and their potential as therapeutic targets. miR-217 and miR-3173, by being sponged by Lnc-CCNH-8, highlight how the dysregulation of miRNA activity can contribute to tumor growth and immune evasion. The ability of Lnc-CCNH-8 to intercept these miRNAs and alter PD-L1 expression exemplifies the complex regulatory networks that govern cancer cell survival and proliferation. Investigating other miRNAs that may similarly be involved in HCC pathogenesis could reveal additional targets for intervention, potentially leading to the development of miRNA-mimic therapies or miRNA inhibitors that could be used in conjunction with Lnc-CCNH-8-targeting strategies to provide a more comprehensive treatment approach.

The utilization of exosomal Lnc-CCNH-8 as a biomarker for predicting the efficacy of immunotherapies ushers in a new era of personalized medicine in the treatment of HCC. This approach not only promises to refine patient selection, enhancing the success rates of immunotherapies, but also opens the door to non-invasive monitoring of treatment response and disease progression. Exosomes, as carriers of Lnc-CCNH-8, provide a window into the tumor's molecular makeup, allowing clinicians to tailor therapy based on dynamic changes in biomarker levels. This capability could significantly improve the management of HCC, enabling adjustments to treatment plans in real time, thereby optimizing outcomes and minimizing the risk of adverse effects. The elucidation of the relationship between hepatitis B virus (HBV) infection and Lnc-CCNH-8 expression through the interferon γ/STAT1 signaling pathway adds a critical dimension to our understanding of HCC pathogenesis, particularly in HBV-endemic regions. This insight not only

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underscores the viral contribution to cancer development but also highlights potential targets for interrupting this process. Targeting the pathways that regulate Lnc-CCNH-8 expression in the context of HBV infection could yield novel therapeutic strategies that address the root causes of viral-related HCC. Moreover, the study's findings suggest that antiviral therapies and interventions aimed at modulating the immune response might be combined with Lnc-CCNH-8-targeted therapies to achieve a more comprehensive approach to treating HCC, especially in patients with chronic HBV infections.

While the study's contributions are substantial, it acknowledges inherent limitations that pave the path for future inquiries. The translational leap from murine models to human clinical application necessitates caution, as differences in immune system intricacies can impact therapeutic outcomes.[3] Additionally, the study raises questions regarding Lnc-CCNH-8's role in HCC's heterogeneity and resistance mechanisms to current therapies. Further research is essential to explore these aspects, potentially broadening the therapeutic landscape for HCC.

In conclusion, the research conducted by Liu et al. signifies a breakthrough in our understanding of HCC's molecular underpinnings, with Lnc-CCNH-8 emerging as a focal point for future therapeutic and diagnostic developments. By bridging fundamental science with translational potential, this study not only advances our comprehension of HCC but also illuminates the path toward more effective and personalized treatment strategies, underscoring the dynamic interplay between cancer biology and immune modulation.

ACKNOWLEDGMENTS

This study was sponsored by the National Science Foundation of China (81802504 and 82302855), grants from the Sichuan Science and Technology Bureau (2023YFH0010, 2022YFS0111, and 2021YFS0380), and a grant from the Heath Commission of Sichuan Province (21PJ078).

AUTHOR CONTRIBUTIONS

Y.W., S.-Y.S., and Y.L. meticulously reviewed and edited the manuscript to ensure its precision and coherence. Y.W. extensively revised the final version of this manuscript. All authors have thoroughly read and given their approval for the final version of the manuscript, confirming their collective endorsement of the work presented.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Pan, A., Truong, T.N., Su, Y.H., and Dao, D.Y. (2023). Circulating Biomarkers for the Early Diagnosis and Management of Hepatocellular Carcinoma with Potential Application in Resource-Limited Settings. Diagnostics *13*, 676.
2. Zhao, B., Zheng, X., Wang, Y., Cheng, N., Zhong, Y., Zhou, Y., Huang, J., Wang, F., Qi, X., Zhuang, Q., et al. (2024). Lnc-CCNH-8 promotes immune escape by up-regulating PD-L1 in hepatocellular carcinoma. Mol. Ther. Nucleic Acids *35*, 102125.
3. Qiu, Z., Li, H., Zhang, Z., Zhu, Z., He, S., Wang, X., Wang, P., Qin, J., Zhuang, L., Wang, W., et al. (2019). A Pharmacogenomic Landscape in Human Liver Cancers. Cancer Cell *36*, 179–193.e11.