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Perspective

Therapeutic Targeting of Epigenetic Writers, Readers, and Erasers in Hepatocellular Carcinoma

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DESCRIPTION

Hepatocellular carcinoma exhibits extensive epigenetic dysregulation involving writers, readers, and erasers of chromatin modifications, presenting multiple therapeutic opportunities for precision oncology approaches. Hepatocellular Carcinoma (HCC) is the most common primary liver cancer and the fourth leading cause of cancer-related deaths worldwide. The molecular pathogenesis of HCC involves complex interactions between genetic mutations, epigenetic alterations, and environmental factors. Recent advances in understanding epigenetic regulation have revealed that HCC exhibits extensive dysregulation of chromatin-modifying enzymes, creating multiple therapeutic vulnerabilities.

DNA Methyltransferases (DNMTs), the "writers" of DNA methylation, are frequently overexpressed in HCC. *DNMT1* and *DNMT3A* show increased expression in HCC tissues compared to normal liver, leading to hypermethylation of tumor suppressor genes such as *CDKN2A*, *GSTP1*, and *SOCS1*. The hypermethylation of these genes contributes to HCC initiation and progression by silencing critical growth control pathways.

The therapeutic targeting of DNMTs with inhibitors such as 5-azacytidine and decitabine has shown promise in HCC treatment. These agents can reactivate silenced tumor suppressor genes and restore normal growth control mechanisms. Clinical trials combining DNMT inhibitors with conventional chemotherapy or targeted therapies have demonstrated improved response rates and survival outcomes in HCC patients.

Histone Acetyltransferases (HATs) and Histone Deacetylases (HDACs) represent another important class of epigenetic regulators in HCC. The HAT p300 is frequently overexpressed in HCC and promotes oncogene expression through histone acetylation. Conversely, tumor suppressor genes are often silenced through the recruitment of HDACs and the removal of activating acetyl marks. HDAC inhibitors have shown significant activity in HCC treatment. Agents such as sorafenib, originally developed as a kinase inhibitor, also possess HDAC inhibitory activity, contributing to their therapeutic efficacy. Newer generation HDAC inhibitors, including panobinostat and belinostat, have demonstrated anti-tumor activity in HCC preclinical models and are being evaluated in clinical trials.

The Polycomb Repressive Complex 2 (PRC2) and its catalytic subunit EZH2 are frequently dysregulated in HCC. EZH2 overexpression leads to increased H3K27me3 deposition and silencing of tumor suppressor genes. EZH2 inhibitors such as tazemetostat have shown efficacy in HCC models, particularly in tumors with high EZH2 expression or specific genetic alterations.

Histone demethylases, the "erasers" of histone methylation, also play crucial roles in HCC. The Lysine-Specific Demethylase 1 (*LSD1*) is overexpressed in HCC and maintains stem cell characteristics in cancer cells. LSD1 inhibitors can promote differentiation and reduce tumor growth, making them attractive therapeutic targets. The combination of *LSD1* inhibitors with differentiation-inducing agents has shown synergistic effects in preclinical studies.

The Jumonji domain-containing histone demethylases are another important class of erasers in HCC. *JMJD3*, which removes the repressive H3K27me3 mark, can act as either a tumor suppressor or oncogene depending on the cellular context. In HCC, *JMJD3* is often downregulated, leading to increased H3K27me3 and silencing of tumor suppressor genes. Strategies to restore *JMJD3* activity are being investigated as potential therapeutic approaches. Chromatin readers, proteins that recognize and bind to specific histone modifications, represent emerging therapeutic targets in HCC. The Bromodomain and Extra-Terminal domain (BET) proteins, which recognize acetylated lysine residues, are frequently overexpressed in HCC. BET inhibitors such as JQ1 and OTX015 have demonstrated anti-tumor activity in HCC models by disrupting the transcription of oncogenes such as MYC and *FOSL1*.

The therapeutic potential of targeting chromatin readers extends beyond BET proteins. The Chromodomain Helicase DNA-binding protein 7 (CHD7) is overexpressed in HCC and promotes tumor growth through the regulation of stem cell genes. CHD7 inhibitors are being developed as potential

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therapeutic agents for HCC treatment. The tumor microenvironment significantly influences epigenetic regulation in HCC. Chronic inflammation, a key driver of HCC development, leads to extensive epigenetic changes in both cancer cells and stromal cells. The targeting of inflammation-induced epigenetic alterations represents a promising approach for HCC prevention and treatment. Combination therapies targeting multiple epigenetic pathways show enhanced efficacy in HCC. The simultaneous inhibition of DNMTs and HDACs has demonstrated synergistic effects in preclinical models. Similarly, combining epigenetic therapies with immune checkpoint inhibitors or targeted agents can overcome resistance mechanisms and improve treatment outcomes.

CONCLUSION

The development of predictive biomarkers for epigenetic therapies in HCC is an active area of research. Expression levels of target enzymes, methylation patterns of specific genes, and chromatin accessibility profiles are being evaluated as potential biomarkers for treatment selection. The integration of epigenetic profiling into clinical practice will be essential for personalizing HCC treatment approaches. Future research should focus on understanding the complex interactions between different epigenetic pathways and developing rational combination strategies. The identification of synthetic lethal interactions between epigenetic modifiers and other cellular pathways will create new therapeutic opportunities. As our understanding of epigenetic regulation in HCC continues to evolve, innovative treatment approaches will emerge to improve patient outcomes.