Editorial

Exploring HMGB2 in hepatocellular carcinoma: charting new paths for diagnostic and therapeutic innovations

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Hepatocellular carcinoma (HCC) remains a critical concern in oncology, holding its status as the most prevalent liver cancer and a significant contributor to global cancer-related morbidity and mortality (1-3). Its widespread occurrence, especially in areas with high hepatitis B and C infection rates (4,5), coupled with the distressingly high mortality due to delayed diagnosis and insufficient late-stage treatment options, highlights the critical need for novel biomarkers and advanced therapeutic approaches to enhance early detection and treatment efficacy (6).

In the study by Lu *et al.* (7), published in *Journal of Gastrointestinal Oncology*, the important role of high mobility group box 2 (HMGB2) in the progression of HCC is highlighted, offering new insights into its significance as a critical factor in the disease's development. The team enrolled 62 HCC patients, employing quantitative real-time polymerase chain reaction (qRT-PCR) and immunohistochemical methods to conduct a comprehensive analysis of HMGB2 expression. The study's use of the cell counting kit-8 (CCK-8) and cell migration & invasion assays offers a comprehensive evaluation of the proliferative potential and motility of HCC cells. This analysis is further enhanced by the innovative use of recombinant human vimentin protein to partially restore vimentin expression. This methodological approach is crucial in understanding the interaction between HMGB2 and vimentin, elucidating the HMGB2-Zinc finger E-box-binding homeobox 1 (ZEB1)-vimentin axis, and assessing the functional consequences of HMGB2 upregulation on HCC cells. Particularly, it allows for a controlled examination of vimentin's role in the observed cellular behaviors, such as proliferation and invasion, and provides insight into potential therapeutic targets by elucidating the molecular mechanisms underlying HCC progression.

The study's revelation that HMGB2 is markedly overexpressed in HCC, and its downregulation substantially diminishes malignant characteristics, particularly influencing cellular growth and movement, is of significant importance. This discovery provides clarity on the HMGB2-ZEB1-vimentin axis's role in promoting aggressive tumor behavior in HCC. Furthermore, the established link between elevated HMGB2 expression and the postoperative survival of HCC patients is particularly noteworthy. This connection highlights HMGB2's promising role as a prognostic marker,

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emphasizing the complex layers of cancer progression and the exploitation of molecular pathways by cancer cells, such as the HMGB2-ZEB1-vimentin axis, in augmenting their malignancy.

Distinctly, the upregulation of HMGB2 in HCC sets it apart as a more precise prognostic factor compared to traditional markers such as alpha-fetoprotein (AFP). HMGB2's specific correlation with cancerous cell behaviors, including proliferation and metastasis (8), surpasses the general markers like AFP, which may increase in various liver conditions and lack cancer specificity (9,10). This characteristic of HMGB2 not only emphasizes its utility in predicting tumor aggressiveness and metastatic potential but also hints at its role in guiding more focused and personalized treatment strategies. The molecular characteristics of HMGB2 afford deeper insights into the biological state of the tumor, potentially offering advantages over conventional, nonspecific markers. Furthermore, its involvement in cellular processes central to cancer progression, such as DNA repair and transcription (8), amplifies its significance in both diagnostic and therapeutic contexts.

The research by Lu *et al.* opens a gateway to extensive future investigations, highlighting the far-reaching implications of their findings. The possibility of utilizing HMGB2 for therapeutic applications in HCC presents an exciting and promising area for exploration. Investigating the efficacy of drugs that can modulate HMGB2 expression or disrupt the HMGB2-ZEB1-vimentin axis could lead to significant advancements in HCC treatment. Crucially, the expansion of patient cohorts in subsequent studies is imperative to guarantee a more comprehensive applicability and validation of these findings. This is an important step in transitioning these laboratory insights into viable clinical practices. The conduct of thorough *in vivo* studies and clinical trials is essential and warrants strong emphasis, given their pivotal role in assessing the real-world efficacy and safety of targeting the HMGB2 pathway. Implementing these comprehensive research methodologies, which blend extensive patient data with practical clinical applications, is crucial for establishing a solid foundation for the integration of these novel findings into effective, patient-centered cancer treatment. This approach holds the promise to dramatically reshape the management of HCC, signifying a transformative shift in the field of cancer therapy.

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