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EDITORIAL

ZEB1 Fuels Serine Metabolism to Promote HCC Metastasis

Primary liver cancer, specifically hepatocellular carcinoma (HCC), is a highly metastatic malignancy that poses significant challenges in the medical field. A large proportion of HCC patients are diagnosed at an advanced stage when the cancer already has metastasized to intrahepatic or extrahepatic sites. Furthermore, even if the HCC is resectable, the postsurgical cancer recurrence remains a significant concern. Therefore, it is crucial to explore the molecular mechanisms driving HCC metastasis to facilitate the discovery of new therapeutic interventions.

One of the critical factors involved in cancer metastasis is Zinc finger E-box binding homeobox 1 (ZEB1), a transcription factor that plays a pivotal role in the epithelial–mesenchymal transition process. ZEB1 has been implicated in various types of human cancers, including HCC, primarily owing to its ability to bind to the promoter region and inhibit the messenger RNA expression of E-cadherin. In the context of HCC, the regulation of ZEB1 occurs post-transcriptionally through the action of the microRNA-200 family, which is down-regulated frequently in HCC. This downregulation subsequently contributes to the upregulation of ZEB1.[1] Moreover, the stabilization of the ZEB1 protein in human HCC is facilitated by the deubiquitinase activity of ubiquitin specific peptidase 22.[2] The overexpression of ZEB1 has been associated with HCC metastasis via its influence on liver cancer stem cell formation. ZEB1 achieves this by binding to the promoters of *CD13*, *CD24*, and *EpCAM* genes, leading to the up-regulation of *CD13* and *CD24*, and the down-regulation of *EpCAM*.[1] In addition to this, ZEB1 has been shown to promote the expression of vascular endothelial growth factor A, which in turn facilitates angiogenesis.[2] Despite these insights, a more in-depth and comprehensive understanding of the role of ZEB1 in HCC metastasis warrants further investigation.

In a recent research article published in *Cellular and Molecular Gastroenterology and Hepatology*,[3] a team of scientists led by Li and Jiang, explored the function of ZEB1 in modulating the metabolic reprogramming of HCC. The researchers developed a liver-specific ZEB1 knockout mouse model and discovered that ZEB1 knockout hindered the formation of N-nitrosodiethylamine (DEN)-carbon tetrachloride (CCl4)-induced HCC, indicating the crucial role of ZEB1 in HCC development. Using Liquid Chromatography/Mass Spectrometry analysis on ZEB1 knockdown MHCC97H cells, the team found that multiple metabolites in the serine synthesis pathway (SSP) were altered considerably, which could be restored by overexpression of ZEB1. SSP is a derivative pathway of glycolysis that encompasses 3 essential enzymatic reactions performed by the enzymes: phosphoglycerate dehydrogenase (PHGDH), phosphoserine aminotransferase, and phosphoserine phosphatase. The initial reaction involves the Nicotinamide adenine dinucleotide^{+}-dependent oxidation of 3-phosphoglycerate to 3-phosphohydroxypyruvate by PHGDH. Subsequently, phosphoserine aminotransferase mediates a transamination reaction that converts 3-phosphohydroxypyruvate to 3-phosphoserine (3PS) using glutamate as an amino donor, resulting in the generation of α-ketoglutarate. In the final step, phosphoserine phosphatase catalyzes the dephosphorylation of 3PS, yielding serine, a crucial metabolite that is intricately connected to the folate cycle and plays a vital role in the production of antioxidants. The impairment of SSP in ZEB1 knockdown HCC cells was owing to the down-regulation of PHGDH. Wang et al[3] showed that ZEB1 binds to the promoter of PHGDH between -254 to -214 nt, thus activating the expression of PHGDH. [U-^{13}C]-glucose tracing experiments further confirmed that 3-phosphoglycerate, the substrate of PHGDH, was accumulated upon ZEB1 knockdown, while the products of SSP, such as 3PS, serine, and glycine, were depleted. Importantly, these metabolic changes could be reversed by re-expression of ZEB1 or PHGDH, suggesting that ZEB1 modulates SSP in HCC through PHGDH.

PHGDH and SSP increasingly are recognized as key players in human carcinogenesis. Recent studies have suggested that PHGDH is implicated in redox homeostasis and sorafenib resistance in human HCC.[4] In this study, the investigators showed that PHGDH also plays a crucial role in ZEB1-stimulated HCC tumorigenicity and metastasis. Activation of SSP enhanced pyrimidine biosynthesis, providing building blocks for DNA/RNA synthesis in rapidly proliferating HCC cells. Moreover, SSP is the primary pathway for Glutathione biosynthesis. The authors showed that Glutathione counteracts the reactive oxygen species insults and enhances anoikis resistance of HCC cells, thereby promoting HCC metastasis. Targeting PHGDH holds significant potential for HCC therapy. The inactivation of PHGDH by small-molecule inhibitors has been shown to suppress HCC growth and sensitize sorafenib treatment.[4] The findings from Li and Jiang's groups[3] illustrate the role of PHGDH in ZEB1-mediated HCC metastasis, highlighting the opportunity to use PHGDH inhibitors as an adjuvant treatment to prevent postoperative HCC recurrence. This study not only sheds light on the complex molecular mechanisms behind HCC development and progression, but also highlights promising therapeutic avenues for future research.

FOR-FAN CHAN
CHUN-MING WONG
State Key Laboratory of Liver Research
Department of Pathology
School of Clinical Medicine
Li Ka Shing Faculty of Medicine
The University of Hong Kong
Hong Kong

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Correspondence
Address correspondence to: Chun-Ming Wong, PhD, State Key Laboratory of Liver Research, Department of Pathology, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, No. 5 Sassoon Road, Room 711, Hong Kong. e-mail: jackwong@pathology.hku.hk.

Conflicts of interest
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