Novel therapeutic strategies targeting liver cancer stem cells

Takahiro Ochiya

Division of Molecular and Cellular Medicine, National Cancer Center Research Institute, Tokyo, Japan

Correspondence to: Takahiro Ochiya. Chief, Division of Molecular and Cellular Medicine, National Cancer Center Research Institute, Tokyo, Japan. Email: tochiya@ncc.go.jp.

Submitted Feb 25, 2016. Accepted for publication Feb 29, 2016. doi: 10.21037/cco.2016.03.10

View this article at: http://dx.doi.org/10.21037/cco.2016.03.10

Novel strategies against treatment-resistant tumor cells remain a major challenge but a promising therapeutic method. Over the past decade, despite accumulated evidence suggesting the presence of highly malignant cell populations within tumors, the issues such as in vivo targeting and clinical relevance remain unsolved. In liver cancer, which is the 5th most common cancer in worldwide, several hepatic stem/progenitor markers are found for isolating a subset of liver cells with stem cell features, such as cancer stem cells (CSCs) which are responsible for tumor drug resistance, relapse, and metastasis (1). Currently, Yamashita’s group focused on chromodomain helicase DNA binding protein 4 (CHD4), a component of the histone deacetylase NuRD complex which participates in the remodeling of chromatin by deacetylating histones (2). They found that CHD4, which is specifically expressed in CSC fractions with [epithelial cell adhesion molecule (EpCAM)]++, could be a therapeutic approach against liver CSCs.

Among primary liver cancers, hepatocellular carcinoma (HCC) represents the major histological subtype, accounting for around 80% of cases of primary liver cancer (3). The poor prognosis of patients with HCC is credited to recurrence of the disease after treatment and the emergence of chemoresistance, which may be explained partly by the existence of liver CSCs. Liver CSCs have been recognized as an important therapeutic target against HCC. Several liver CSCs markers identified include EpCAM, CD133, CD90, CD44, CD24, CD13, oval cell markers (OV6, A6, and OV1), cytokeratin 7, CK19, fetal hepatocytes (alphafetoprotein), as well as aldehyde dehydrogenase activities (4). Those liver CSC markers may functionally support their malignant phenotypes with highly invasiveness and chemoresistance (1,5). Therefore, these surface markers serve not only as tools for identifying liver CSCs but also as therapeutic targets for eradicating these cells (6,7). Although numerous therapeutic agents have been developed targeting liver CSC markers, their clinical significance have not been confirmed. Other possible approaches for targeting liver CSCs examine CSC-specific molecular signatures that are involved in high therapeutic resistance. In the current publication by Nio et al., the authors highlighted chromatin remodeling enzyme CHD4 (2). This unique molecule is known for their roles in DNA-damage response and cell cycle progression (8). Furthermore, as part of NuRD, it participates in regulating p53 acetylation status, thereby indirectly regulating the G1/S cell cycle checkpoint. Nio et al. surveyed large HCC samples and found that CHD4 was abundantly expressed in cell fraction with EpCAM+ HCC CSCs. It was also identified that the patients with CHD4-high EpCAM+ HCCs showed worse prognosis in two independent cohort analyses. Most importantly, the authors conducted in vitro and in vivo model studies that assessed the efficacy of the histone deacetylase inhibitors such as suberohydroxamic acid and poly(ADP-ribose) polymerase inhibitor and found that the combination of these two inhibitors effectively inhibited tumor growth in a mouse xenograft model. They also indicated the reduction of EpCAM+ CSCs after the treatment of these inhibitors, thus suggesting that the CHD4 targeting agents can be a promising new molecular therapy in HCC.

Acknowledgements

This work was supported in part by Japan Agency for Medical Research and Development (AMED).
footnote

Provenance: This is a Guest Editorial commissioned by the Section Editor Haitao Zhao, MD, PhD, Associate Professor (Department of Liver Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China).

Conflicts of Interest: The author has no conflicts of interest to declare.


References


cite this article as: Ochiya T. Novel therapeutic strategies targeting liver cancer stem cells. Chin Clin Oncol 2016;5(5):59. doi: 10.21037/cco.2016.03.10