Chromodomain-helicase-DNA-binding protein 4: a novel therapeutic target in liver cancer stem cells

Kouki Nio[1,2], Taro Yamashita[1], Shuichi Kaneko[1]

[1]Department of Gastroenterology, Kanazawa University Graduate School of Medical Science, Kanazawa, Ishikawa, Japan; [2]Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Correspondence to: Taro Yamashita, MD, PhD. Department of General Medicine/Gastroenterology, Kanazawa University Graduate School of Medical Science, 13-1 Takara-Machi, Kanazawa, Ishikawa 920-8641, Japan. Email: taroy@m-kanazawa.jp.

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First of all, we appreciate the precious comments written by Professors Dr. Ochiya and Dr. Willoughby to our study (1,2). As commented, hepatocellular carcinoma (HCC) is one of the most common cancers with poor outcome worldwide, partly due to the lack of effective treatment options for patients with advanced-stage disease (3,4). Treatment with cytotoxic reagents did not show clear survival benefit in advanced HCC patients. Although a receptor tyrosine kinase inhibitor sorafenib, mainly targeting the vascular endothelial growth factor receptor 2 (VEGFR2) signaling in vascular endothelial cells, is the current standard therapy for advanced HCC, its effect is modest (5). The novel therapeutic strategy is clearly required to prolong the survival in advanced HCC patients.

We have been exploring the malignant nature of HCCs based on the stem/maturational status of the tumors by evaluating the expression of stem cell and hepatocyte markers such as epithelial cell adhesion molecule (EpCAM), alpha-fetoprotein (AFP), Sal-like protein 4 (SALL4), organic anion transporter polypeptides 1B3 (OATP1B3), and hepatocyte nuclear factor 4 alpha (HNF4α) (6-9). We found that the expression of stem cell markers is very heterogeneous even in established HCC cell lines, and these cells show the feature of so-called "cancer stem cells" (CSCs) in terms of self-renewal and differentiation capacity, tumorigenic capacity, and chemoresistance against cytotoxic reagent 5-fluorouracil (10,11). Our previous studies indicated that HCCs with stem cell features [hepatic stem cell-like HCC (HpSC-HCC)] show poor prognosis after surgery, suggesting the requirement to develop novel adjuvant therapy effective to treat CSCs as well as non-CSCs population in HpSC-HCC.

We have made a concentrated effort on clarifying the molecular events activated in HCC CSCs. SALL4 is known as a recruiter of nucleosome remodeling and deacetylase (NuRD) complex as well as a transcription factor activating the genes regulating the stemness (12). NuRD complex contains histone deacetylases (HDACs) to regulate the histone modification. Indeed, our previous study indicated that SALL4-positive HCCs have high HDAC activity and are chemosensitive to an HDAC inhibitor SBHA (9). However, SBHA treatment alone had a limited efficacy to suppress the tumorigenesis in patient-derived xenograft (PDX) mouse model (unpublished data), suggesting the need to search additional targets activated in HCC CSCs. Since NuRD complex is composed of HDACs, chromodomain-helicase-DNA-binding proteins (CHDs), and metastasis-associated proteins (MTAs), we focused on the characterization of these protein expressions in HCC CSCs.

In our current study, we evaluated the expression of chromodomain helicase DNA-binding protein 4

(CHD4) in HCC. Although CHD4 is known as relatively ubiquitous protein detected in proliferating cells, we found that CHD4 is highly expressed in EpCAM-positive HCCs compared with -negative HCCs, and the abundant expression of CHD4 correlates with poor prognosis in HCC patients. Interestingly, forced expression of CHD4 conferred chemoresistance against epirubicin, consistent with the previous studies suggesting the role of CHD4 on DNA double strand break repair through interaction with poly (ADP-ribose) polymerase (PARP) (13-15). Sorted EpCAM-positive CSCs showed the strong expression of CHD4, suggesting that CHD4 plays a crucial role in chemoresistance as a core member of NuRD complex and may be a potential therapeutic target in HCC CSCs. We tried to suppress the molecular activity of CHD4 as a regulator of HDAC and PARP by combination of an HDAC inhibitor (SBHA) and a PARP inhibitor (AG-014699) in PDX mouse model, and demonstrated the utility of the combination of HDAC and PARP inhibitor to suppress the HCC growth *in vitro* and *in vivo* (16).

Since several evidence have demonstrated that the aberrant expression of HDACs is associated with poor prognosis and survival rates in HCC (17), HDAC inhibitor alone or in combination with sorafenib has been recently tested in some clinical trials (18,19). Our findings offer new mechanistic insights into the chemoresistance of HCC CSCs and suggest clinical utility of HDAC/PARP inhibitors combination therapy. We hope that our findings will provide a novel therapeutic option for patients with advanced HCC in near future.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Ochiya T. Novel therapeutic strategies targeting liver cancer stem cells. Chin Clin Oncol 2016;5:59.
2. Willoughby CE, Reeves HL. Combination PARP and HDAC inhibition as a therapeutic strategy targeting liver cancer stem cells? Chin Clin Oncol 2016;5:60.
3. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
4. de Lope CR, Tremosini S, Forner A, et al. Management of HCC. J Hepatol 2012;56 Suppl 1:S75-87.
5. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90.
6. Yamashita T, Budhu A, Forgues M, et al. Activation of hepatic stem cell marker EpCAM by Wnt-beta-catenin signaling in hepatocellular carcinoma. Cancer Res 2007;67:10831-9.
7. Yamashita T, Forgues M, Wang W, et al. EpCAM and alpha-fetoprotein expression defines novel prognostic subtypes of hepatocellular carcinoma. Cancer Res 2008;68:1451-61.
8. Yamashita T, Honda M, Nakamoto Y, et al. Discrete nature of EpCAM+ and CD90+ cancer stem cells in human hepatocellular carcinoma. Hepatology 2013;57:1484-97.
9. Zeng SS, Yamashita T, Kondo M, et al. The transcription factor SALL4 regulates stemness of EpCAM-positive hepatocellular carcinoma. J Hepatol 2014;60:127-34.
10. Yamashita T, Ji J, Budhu A, et al. EpCAM-positive hepatocellular carcinoma cells are tumor-initiating cells with stem/progenitor cell features. Gastroenterology 2009;136:1012-24.
11. Yamashita T, Wang XW. Cancer stem cells in the development of liver cancer. J Clin Invest 2013;123:1911-8.
12. Lu J, Jeong HW, Kong N, et al. Stem cell factor SALL4 represses the transcriptions of PTEN and SALL1 through an epigenetic repressor complex. PLoS One 2009;4:e5577.
13. Larsen DH, Poinsignon C, Gudjonsson T, et al. The chromatin-remodeling factor CHD4 coordinates signaling and repair after DNA damage. J Cell Biol 2010;190:731-40.
14. Pan MR, Hsieh HJ, Dai H, et al. Chromodomain helicase DNA-binding protein 4 (CHD4) regulates homologous recombination DNA repair, and its deficiency sensitizes cells to poly(ADP-ribose) polymerase (PARP) inhibitor treatment. J Biol Chem 2012;287:6764-72.
15. Polo SE, Kaidi A, Baskcomb L, et al. Regulation of DNA-damage responses and cell-cycle progression by the chromatin remodelling factor CHD4. EMBO J 2010;29:3130-9.
16. Nio K, Yamashita T, Okada H, et al. Defeating EpCAM(+) liver cancer stem cells by targeting chromatin remodeling enzyme CHD4 in human hepatocellular carcinoma. J Hepatol 2015;63:1164-72.
17. Rikimaru T, Taketomi A, Yamashita Y, et al. Clinical significance of histone deacetylase 1 expression in patients

with hepatocellular carcinoma. Oncology 2007;72:69-74.
18. Bitzer M, Horger M, Giannini EG, et al. Resminostat plus sorafenib as second-line therapy of advanced hepatocellular carcinoma - The SHELTER study. J Hepatol 2016. [Epub ahead of print].
19. Yeo W, Chung HC, Chan SL, et al. Epigenetic therapy using belinostat for patients with unresectable hepatocellular carcinoma: a multicenter phase I/II study with biomarker and pharmacokinetic analysis of tumors from patients in the Mayo Phase II Consortium and the Cancer Therapeutics Research Group. J Clin Oncol 2012;30:3361-7.

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