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Commentary

Hepatocellular carcinoma: H-Prune gene regulatory networks

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Hepatocellular carcinoma (HCC) accounts for 90% of primary liver cancers, which represents the second leading cause of cancer-related deaths globally [1]. HCC results from the accumulation of somatic genomic and epigenomic alterations in the tissue of origin and can be mainly caused by chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), alcohol abuse, and metabolic syndromes related to diabetes or obesity. Thus far, multi-omics analyses involving genomic, transcriptomic, and/or epigenomic profiling of large cohorts of tumors have provided the basis for the molecular classification of HCC into two, equally represented, distinct subtypes named *proliferation class* and *non-proliferation class*. These proposed subclasses reflect the different biological landscapes and the promise of potential tools for both prognostics and personalized medicine [2].

In *EBioMedicine*, Liao and colleagues thoroughly analyzed the role of H-Prune in HCC [3]. H-Prune is a protein with a nucleotide phosphodiesterase (PDE) and exopolyphosphatase activities, whose overexpression was already associated with lung cancer, breast cancer, medulloblastoma and colorectal liver metastases. The authors showed that H-Prune was frequently up-regulated in HCC tissue at both mRNA and protein levels, and its overexpression correlated with poor survival outcomes. Recent studies have shown that H-Prune is an unfolded multi-domain adaptor protein that can interact with several binding partners, including Asap, Gelsolin, NM23-H1, β-tubulin and GSK3β [4]. The better-characterized interactors, NME1 and GSK3β, are both key modulators of TGF-β and WNT signaling cascades [5,6].

Liao and colleagues report that H- Prune functions as a tumor promoter in HCC. To try to identify pathways that might be responsible for boosting hepatocarcinogenesis, using available omics datasets, they showed that high H-Prune expression correlated with enhanced tumor cell proliferation through the WNT signaling pathway. Although no mention has been made regarding the metastatic status of these patients and their possible correlation with the expression of H-Prune.

The authors also showed that high expression of H-Prune in HCC was associated with a misregulated miRNome and methylome. These findings highlight the importance of a wider approach as a powerful tool to infer the dynamics of cancer.

Moreover, they provide visibility into how the CNVs would affect the gene expression pattern. By their analysis, only a subtle concordance was found between gene expression and CNVs, that it would suggest that the genetic alterations would not significantly affect the gene expression pattern. Therefore, these results need to be cautiously interpreted.

Liao et al. also analyzed the mutational landscape using whole exome sequencing data. They found that RPS6KA3 gain of function and RB1 inactivating mutations are significantly enriched in the patient with the worst outcome. Thus, indicating new potential pathways, in which H-Prune might be involved, that may drive the oncogenic proliferation in HCC.

There is the possibility that mutation identified from whole-exome sequencing of patient tumors may be false positives or considered 'passenger' mutations. Therefore, we might question how many of these alterations occur in 'passenger' genes that are not directly implicated in neoplasia, and how many genomic alterations would be considered to be 'drivers' involved in activating key signaling pathways for hepatocarcinogenesis?

However, it cannot be emphasized enough that the potential translation of this study may be the use of H-Prune as a biomarker in HCC. The WNT–β-catenin signaling in the mature healthy liver is mainly inactive but can become re-activated during the regenerative process, as well as in certain pathological conditions, such as tumor growth and dissemination [7]. As a WNT activator, H-Prune expression can be used to define a subclass of WNT-activated tumors, in the absence of driver mutations in genes that encode key components along this molecular pathway. However, like any other biomarker, the incorporation into daily clinical practice needs to be validated prospectively in a larger cohort and together with other markers defining this subgroup.

To date, a long list of H-Prune inhibitory strategies has been provided by researchers from *in vitro* to preclinical models in several different experimental settings [8,9]. Although preclinical experiments suggest the ability of these molecules to counteract H-Prune driven tumorigenesis, there are still doubts related to their full efficacy, with the risk of showing minor expected improvements in patient response in clinical trials. HCC is highly therapy-resistant and although systemic therapies have shown some clinical benefits, overall patient outcomes have been modest and we are still a long way away from the definition of an adequate treatment. Few actionable tumor-specific targets have been found and successfully used therapeutically. However, insights into the biology of the disease to design novel therapies for HCC remain an unmet medical need. Thus, further experimental validations in the context of hepatocarcinogenesis are necessary, with the possibility that these H-Prune inhibitors might be eligible for future clinical

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practice as stand-alone therapy or used as co-adjuvant treatment regimens, which are likely to become considered personalized, leading to new routes of attaining durable responses.

Disclosure

The author has no conflict of interest to declare.

References

[1] Torre LA, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015 Mar;65(2):87–108. https://doi.org/10.3322/caac.21262 [Epub 2015 Feb 4].
[2] Llovet JM, et al. Molecular therapies and precision medicine for hepatocellular carcinoma. Nat Rev Clin Oncol 2018 Oct;15(10):599–616. https://doi.org/10.1038/s41571-018-0073-4.
[3] Liao H, et al. Integrative analysis of h-prune as a potential therapeutic target for hepatocellular carcinoma. EBioMedicine 2019 Jan 18. https://doi.org/10.1016/j.ebiom.2019.01.001 pii: S2352-3964(19)30001-5. [Epub ahead of print].
[4] Diana D, et al. Mapping functional interaction sites of human prune C-terminal domain by NMR spectroscopy in human cell lysates. Chemistry 2013 Sep 9;19(37):12217–20. https://doi.org/10.1002/chem.201302168 [Epub 2013 Aug 12].
[5] Carotenuto M, et al. H-Prune through GSK-3β interaction sustains canonical WNT/β-catenin signaling enhancing cancer progression in NSCLC. Oncotarget 2014 Jul 30;5(14):5736–49. https://doi.org/10.18632/oncotarget.2169.
[6] Ferrucci V, et al. Metastatic group 3 medulloblastoma is driven by PRUNE1 targeting NME1-TGF-β-OTX2-SNAIL via PTEN inhibition. Brain 2018 May 1;141(5):1300–19. https://doi.org/10.1093/brain/awy039.
[7] Perugorria MJ, et al. Wnt-β-catenin signalling in liver development, health and disease. Nat Rev Gastroenterol Hepatol 2018 Nov 19. https://doi.org/10.1038/s41575-018-0075-9 [[Epub ahead of print] Review. PMID: 30451972].
[8] Virgilio A, et al. Novel pyrimidopyrimidine derivatives for inhibition of cellular proliferation and motility induced by h-prune in breast cancer. Eur J Med Chem 2012 Nov;57:41–50. https://doi.org/10.1016/j.ejmech.2012.08.020 [Epub 2012 Aug 23].
[9] Carotenuto M, et al. A therapeutic approach to treat prostate cancer by targeting Nm23-H1/h-Prune interaction. Naunyn Schmiedebergs Arch Pharmacol 2015 Feb;388(2):257–69. https://doi.org/10.1007/s00210-014-1035-8 [Epub 2014 Aug 20].