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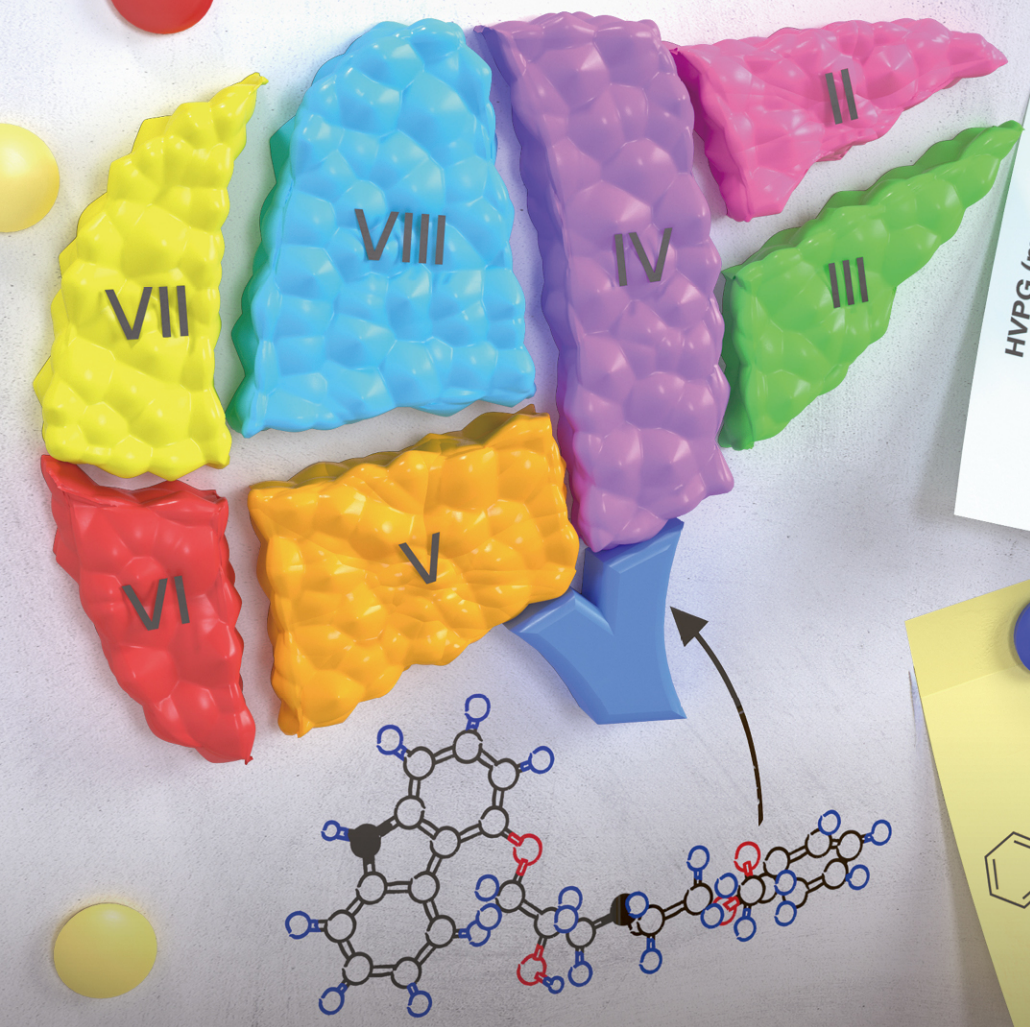

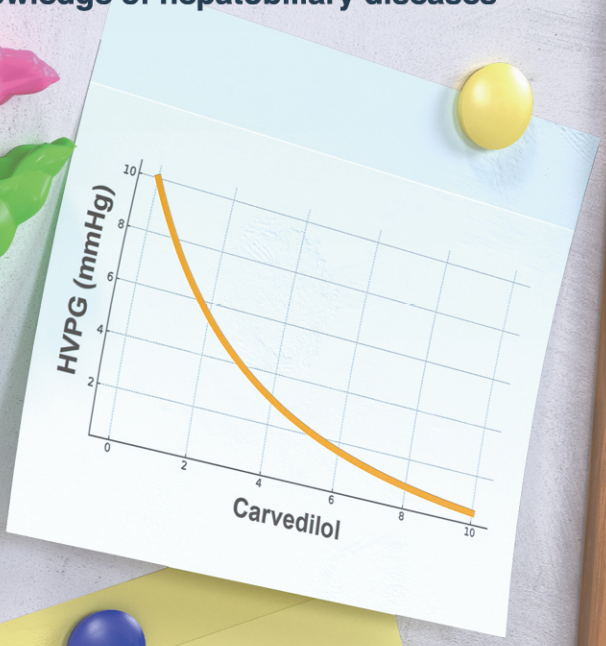

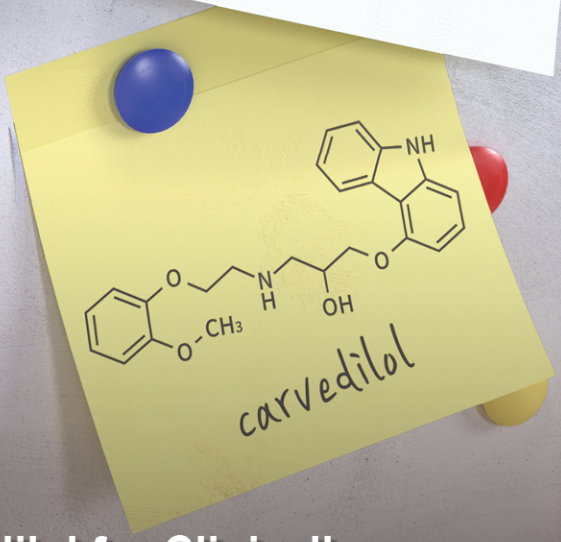

Non-invasive Model guiding Carvedilol for Clinically Significant Portal HTN

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Editorial

Identification of KCTD17 as a Ras stabilizer in hepatocellular carcinoma: Editorial on "KCTD17-mediated Ras stabilization promotes hepatocellular carcinoma progression"

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Hepatocellular carcinoma (HCC) is the 6th most common cancer and the 4th leading cause of cancer mortality worldwide.[1] Most HCC patients present at an advanced stage when surgery and liver transplantation are not curative treatment options. For these patients, targeted therapies, including administration of sorafenib and lenvatinib, are applied. [2] However, survival benefits are limited following these therapies owing to the development of drug resistance.[3,4] Therefore, it is crucial to identify reliable biomarkers and develop novel therapeutic strategies for HCC. On the basis of previous findings showing the role of potassium channel tetramerization domain-containing 17 (KCTD17) in glucose and lipid metabolism, especially in HCC patients with metabolic dysfunction-associated steatotic liver disease (MASLD),[5,6] Jung et al.[7] investigated the clinical significance and functional mechanistic roles of KCTD17 in HCC in an issue of *Clinical and Molecular Hepatology*.

Jung et al.[7] reported the upregulation of KCTD17 in both human and mouse HCC. This finding is clinically relevant; analysis of publicly available HCC datasets revealed the upregulation of this gene in HCC. KCTD17 overexpression was correlated with advanced tumor-node-metastasis stage. Survival analysis revealed that KCTD17 can serve as an independent prognostic marker for poor disease-free survival. These results show that KCTD17 is a potentially reliable diagnostic and prognostic marker for HCC. On the basis of these encouraging data, these researchers performed functional analyses via knockout and doxycycline-inducible KCTD17 knockdown approaches. Interestingly, the reduction in KCTD17 suppressed the proliferative, self-renewal, and invasive abilities of HCC cells. Conversely, overexpression had the opposite effect. Notably, the overexpression of KCTD17 conferred resistance to sorafenib and 5-FU via the inhibition of the Akt and MAPK pathways.

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To understand the molecular mechanism of KCTD17 in HCC, Jung et al. reported significant enrichment of Ras-related signaling features, including KRAS and extracellular signal-regulated kinase 1/2 signaling. Consistently, elevated levels of the Ras protein were detected despite unaltered mRNA levels, suggesting that KCTD17 regulates MAPK signaling through stabilizing the Ras protein. KCTD17 is a soluble, non-channel protein that functions as a substrate adapter for Cul3-based ubiquitin-conjugating enzyme E3 ligases and has a role distinct from its counterparts.[8-10] This observation, together with previous studies showing the role of leucine zipper-like transcription regulator 1 (Lztr1) in promoting the polyubiquitination and degradation of Ras family members by recruiting a Cul3 ubiquitin ligase complex,[11-13] suggests that Kctd17 affects Ras stability by interfering with the Lztr1-Ras interaction. Consistent with this hypothesis, Kctd17 physically binds to Lztr1 and regulates its expression through ubiquitination, thereby affecting MAPK activation by stabilizing Ras. Lztr1 was found to be significantly downregulated in HCC cells.[14]

To further examine the tumor-promoting role of KCTD17 in HCC, Jung et al.[7] demonstrated a significant decrease in tumor growth upon knockdown and knockout approaches. To determine the role of KCTD17 in HCC development, they administered a choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD) to hepatocyte-specific Kctd17 knockout (L-Kctd17) mice that were previously treated with diethylnitrosamine (DEN). Compared with wild-type mice, L-Kctd17 mice exhibited slower tumor growth. Next, on the basis of these encouraging data, they assessed the thera-

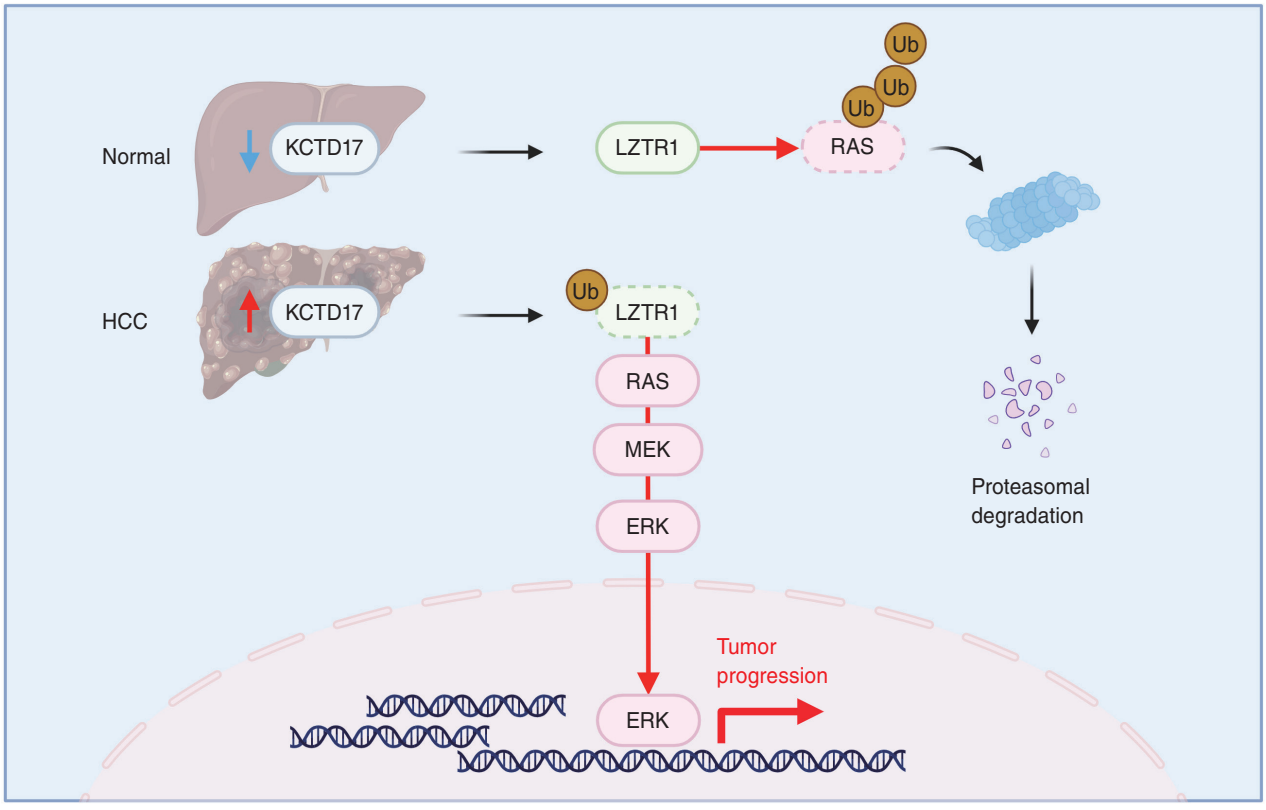

Figure 1. Schematic representation of the role of KCTD17/LZTR1 in regulating Ras stability in HCC. HCC, hepatocellular carcinoma; KCTD17, potassium channel tetramerization domain-containing 17; LZTR1, leucine zipper-like transcription regulator 1; ERK, extracellular signal-regulated kinase.

Abbreviations:

ASO, anti-sense oligo; CDAHFD, choline-deficient, L-amino acid-defined, high-fat diet; DEN, diethylnitrosamine; Dox, doxycycline; ERK1/2, extracellular signal-regulated kinase1/2; HCC, hepatocellular carcinoma; KCTD17, potassium channel tetramerization domain-containing 17; L-Kctd17, hepatocyte-specific Kctd17 knockout mice; Lztr1, leucine zipper-like transcription regulator 1; MASLD, metabolic dysfunction-associated steatotic liver disease; TNM, tumor-node-metastasis

peutic potential of targeting KCTD17. They employed hydrodynamic-induced and DEN-CDAHFD-induced HCC mouse models, and they demonstrated that reducing Kctd17 through the use of an antisense oligo suppressed the growth of HCC tumors without notable side effects; furthermore, this was accompanied by an increase in LZTR1 and a concurrent decrease in Ras expression.

Overall, this study describes an unprecedented role for KCTD17 in HCC, with new mechanistic insights and clinical implications. First, this study revealed that KCTD17 can function as a new diagnostic and prognostic marker for HCC. Second, KCTD17 expression is increased in different etiologies of HCC, such as those caused by viruses and MASLD. Third, this study provides new mechanistic insights into how KCTD17 regulates the Ras signaling pathway (Figure 1). Finally, this study provides a novel therapeutic strategy for HCC treatment via the suppression of KCTD17 expression. Although the *in vitro* and *in vivo* data obtained by Jung et al.[7] are novel and encouraging, several questions still need to be explored. Given the existence of several isoforms of Ras proteins, including NRAS, KRAS, and HRAS,[15] it is important to determine whether KCTD17 affects the expression of isoforms in addition to KRAS. Since KRAS/MAPK signaling has been found to play a role in immune modulation,[16] targeting KCTD17 may complement current immune therapies. Considering the significant therapeutic potential of targeting KCTD17 in HCC, researchers are eagerly awaiting the synthesis of small-molecule inhibitors and protein degraders against KCTD17 to facilitate the translation of these findings.

Authors' contribution

R.W.L drafted the manuscript. T.K.L reviewed and finalized the manuscript.

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Conflicts of Interest

The authors have no conflicts to disclose.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-249.
2. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-390.
3. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34.
4. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163-1173.
5. Kim K, Ryu D, Dongiovanni P, Ozcan L, Nayak S, Ueberheide B, et al. Degradation of PHLPP2 by KCTD17, via a glucagon-dependent pathway, promotes hepatic steatosis. Gastroenterology 2017;153:1568-1580.e10.
6. Oh AR, Jeong Y, Yu J, Minh Tam DT, Kang JK, Jung YH, et al. Hepatocyte Kctd17 Inhibition ameliorates glucose intolerance and hepatic steatosis caused by obesity-induced Chrebp stabilization. Gastroenterology 2023;164:439-453.
7. Jung YH, Lee YJ, Dao T, Jung KH, Yu J, Oh AR, et al. KCTD17-mediated Ras stabilization promotes hepatocellular carcinoma progression. Clin Mol Hepatol 2024;30:895-913.
8. Teng X, Aouacheria A, Lionnard L, Metz KA, Soane L, Kamiya A, et al. KCTD: A new gene family involved in neurodevelopmental and neuropsychiatric disorders. CNS Neurosci Ther 2019;25:887-902.
9. Ji AX, Chu A, Nielsen TK, Benlekbir S, Rubinstein JL, Privé GG. Structural Insights into KCTD Protein Assembly and Cullin3 Recognition. J Mol Biol 2016;428:92-107.
10. Pinkas DM, Sanvitale CE, Bufton JC, Sorrell FJ, Solcan N, Chalk R, et al. Structural complexity in the KCTD family of Cullin3-dependent E3 ubiquitin ligases. Biochem J 2017;474:3747-3761.
11. Abe T, Umeki I, Kanno SI, Inoue SI, Niihori T, Aoki Y. LZTR1 facilitates polyubiquitination and degradation of RAS-GTPases. Cell Death Differ 2020;27:1023-1035.
12. Bigenzahn JW, Collu GM, Kartnig F, Pieraks M, Vladimer GI, Heinz LX, et al. LZTR1 is a regulator of RAS ubiquitination and

signaling. Science 2018;362:1171-1177.
13. Steklov M, Pandolfi S, Baietti MF, Batiuk A, Carai P, Najm P, et al. Mutations in LZTR1 drive human disease by dysregulating RAS ubiquitination. Science 2018;362:1177-1182.
14. Yi T, Luo H, Qin F, Jiang Q, He S, Wang T, et al. LncRNA LL22NC03-N14H11.1 promoted hepatocellular carcinoma progression through activating MAPK pathway to induce mitochondrial fission. Cell Death Dis 2020;11:832.
15. Castellano E, Santos E. Functional specificity of ras isoforms: so similar but so different. Genes Cancer 2011;2:216-231.
16. Hamarsheh S, Groß O, Brummer T, Zeiser R. Immune modulatory effects of oncogenic KRAS in cancer. Nat Commun 2020; 11:5439.