해부 · 생물인류학 제 39 권 제 2 호
Anat Biol Anthropol Vol. 39, No. 2 (2026) pp. 183~189
https://doi.org/10.11637/aba.2026.39.2.183

Check for updates

Original Article

Suppressing CSTB Enhances Therapeutic Efficacy against Liver Cancer

An-Na Bae[1,†], Hajin Lee[1,†], Hanjeong Yu[1], Jinsung Yang[2], Jong Ho Park[1]

1Department of Molecular Biology, Pusan National University, Busan, South Korea
2Department of Biochemistry, Institute of Medical Science, Gyeongsang National University College of Medicine, Jinju, Republic of Korea

Abstract : Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide and remains the leading cause of cancer-related deaths. The identification of reliable biomarkers for HCC is urgently needed to improve prognosis and treatment outcomes. Cystatin B (CSTB), a member of the cysteine protease inhibitor superfamily, is known to maintain cellular homeostasis and plays a key role in neuronal stability, but its role in HCC development is not fully understood. In this study, we investigated the prognostic significance of CSTB in HCC. *CSTB* gene expression was markedly elevated in patients with HCC and high CSTB expression was significantly associated with poorer overall survival. We also found that several HCC cell lines exhibited substantially higher CSTB protein levels compared with other cancer cell lines, especially, PLC/PRF/5. Furthermore, knockdown of CSTB reduced the cell viability of HCC cell lines. These findings suggest that targeting CSTB in HCC with specific inhibitors may represent a potential therapeutic approach for HCC.

Keywords : CSTB, Hepatocellular carcinoma, Biomarker

BACKGROUND

CSTB, encoded by the *CSTB* gene, is a member of the cathepsin family of cysteine protease inhibitors and regulates key neuronal processes, including cell differentiation, mitochondrial function and synaptic transmission [1,2]. Loss of function mutation in *CSTB* causes progressive myoclonus epilepsy (PME) of Unverricht-Lundborg type, a neurodegenerative disorder featuring stimulus-sensitive myoclonus, tonic-clonic seizures and progressive neurological decline [3]. Dysregulated CSTB expression has also been implicated in oncogenesis across multiple malignancies [4]. In pancreatic cancer, CSTB sustains glycolysis to promote tumor cell survival, while in intrahepatic cholangiocarcinoma, it suppresses apoptosis [5,6]. In HCC, CSTB has been investigated primarily as a serum biomarker associated with disease-dependent changes during liver cancer development [7-9], however, its precise functional role in HCC pathogenesis remains to be fully elucidated.

[†]These authors contributed equally to this work.
This work was supported by a New Faculty Research Grant of Pusan National University, 2025.
The author(s) agree to abide by the good publication practice guideline for medical journals.
The author(s) declare that there are no conflicts of interest.
Received: March 31, 2026; **Revised:** April 13, 2026; **Accepted:** April 26, 2026
Correspondence to: Jong Ho Park (Department of Molecular Biology, Pusan National University, Busandaehak-Ro 63beon-Gil, Geumjeong-Gu, Busan 46241, Republic of Korea)
E-mail: jhp@pusan.ac.kr

www.kci.go.kr
© 2026 Korean Association of Physical Anthropologists
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/ licenses/by-nc/3.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.
ISSN 2671-566X (Online)

HCC is the primary liver malignancy, accounting for over 90% of cases and ranking among the leading causes of cancer-related deaths worldwide [10]. Despite high global incidence, its 5-year survival rate remains dismal, driven by late-stage diagnosis, high recurrence after resection and the absence of specific biomarkers for early detection or prognosis [11]. Current systemic therapies are constrained by significant limitations [12]. First-line therapeutic drug, sorafenib and lenvatinib, provide modest survival benefits but face inevitable drug resistance in most patients [13]. Meanwhile, immune checkpoint inhibitors (anti-PD-L1 and PD-1 antibody) show promise in subsets of patients, yet HCC's profoundly immunosuppressive tumor environment-characterized by regulatory T cells, myeloid-derived suppressor cells, and dysfunctional antigen-presenting cells-often leads to primary resistance [14,15]. These therapeutic challenges highlight the critical need for novel biomarkers that enable early diagnosis, accurate risk stratification and prediction of treatment response, ultimately facilitating precision medicine approaches to improve HCC outcomes.

In this study, we investigated the role of CSTB in regulating HCC, with a focus on its expression patterns. CSTB mRNA levels were significantly elevated in HCC patients compared to healthy controls. High CSTB expression strongly correlated with poor overall survival. Consistent with these findings, CSTB was markedly upregulated across multiple HCC cell lines relative to non-HCC cancer cell lines. CSTB knockdown using siRNA substantially reduced cell viability but did not affect immune-related genes. Taken together, our results position CSTB as a novel oncogene and prognostic biomarker in HCC. Targeting CSTB expression thus emerges as a promising therapeutic strategy to disrupt the immunosuppressive tumor microenvironment and enhance antitumor immunity.

METHODS

1. TCGA

RNA sequencing expression data and corresponding survival information for liver hepatocellular carcinoma (LIHC) were obtained and analyzed using the Gene Expression Profiling Interactive Analysis 2 (GEPIA2) web server, an online platform that integrates RNA-seq datasets from The Cancer Genome Atlas (TCGA) and the Genotype-Tissue Expression (GTEx) projects. GEPIA2 enables comparative analysis of gene expression between tumor and normal tissues, as well as survival analysis based on clinical outcomes, thereby providing a convenient resource for evaluating the prognostic relevance of candidate genes in LIHC.

2. Cell culture and transfection

The human HCC cell lines HepG2, Huh1, and PLC/PRF/5 (referred to as 'PLC'), the osteosarcoma cell line Saos-2, the colorectal cancer cell line HCT116, and the prostate cancer cell line DU145 were used in this study. HepG2, Huh1, PLC, Saos-2, and HCT116 cells were cultured in DMEM (Thermo Fisher Scientific, Waltham, MA, USA, Catalog no. 11995065) supplemented with 10% fetal bovine serum (FBS, Thermo Fisher Scientific, Catalog no. 16000044) and 1×penicillin-streptomycin (antibiotics, Welgene, Catalog no. LS20202) (referred to as 'D10'), whereas DU145 cells were maintained in RPMI 1640 medium (Welgene, Catalog no. LM01103) supplemented with 10% FBS and 1× penicillin-streptomycin (referred to as 'R10'). CSTB siRNA (Thermo Fisher Scientific, ID: s534225, Catalog no. 4392420; ID: s3679, Catalog no. 4392420). Transfection was performed by mixing RNAiMAX (Thermo Fisher Scientific, Catalog no. 13778150) with 100 nM siRNA in Opti-MEM medium, and a negative control siRNA (Qiagen, Hilden, Germany, Catalog no. 1027280) was transfected in parallel under the same conditions.

3. Quantitative PCR (qPCR)

Total RNA was extracted 24 h after CSTB siRNA transfection. RNA was isolated using TRIzol reagent (Thermo Fisher Scientific, Catalog no. 15596018) according to the manufacturer's instructions, and the concentration and quality of the extracted total cellular RNA were determined using a NanoDrop spectrophotometer. (IMPLEN, Munich, Germany, NanoPhotometer® N60) Reverse transcription was performed using the HighCapacity cDNA Reverse Transcription Kit (Thermo Fisher Scientific, catalog no. 4368814). Quantitative PCR analysis was carried out using the CFX Connect Real-Time PCR System (Bio-Rad, Hercules, CA, USA) and SYBR Green Real-Time PCR Master Mix (TOYOBO, Osaka, Japan, Catalog no. QPK-201). The primer sequences used for quantitative PCR were as follows: TGFB1 forward, 5′-TACCTGAACCCGTGTTGCTCTC-3′;

www.kci.go.kr

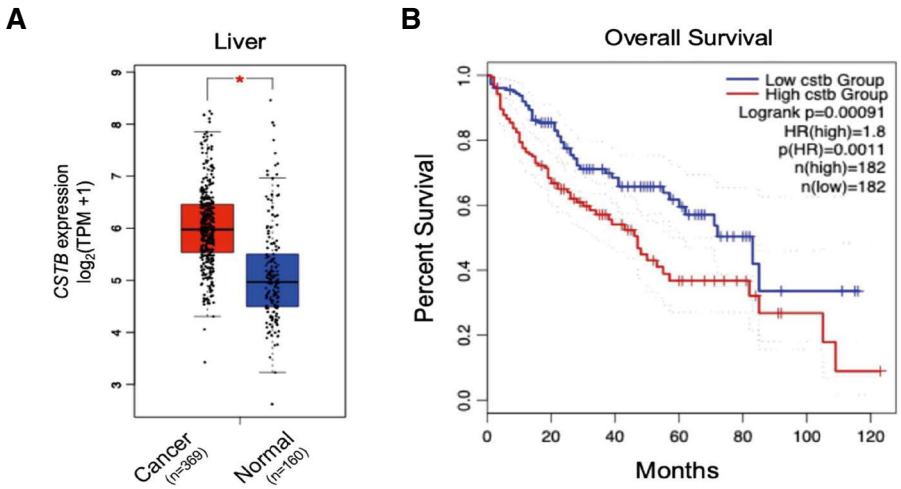

Fig. 1. Expression of CSTB and impact on the survival rate in HCC. (A) Box plot of CSTB expression in HCC versus normal liver across TCGA/GTEx datasets (*$p<0.01$, one-way ANOVA, Gene Expression Profiling Interactive Analysis database). (B) Overall survival rates of HCC patients based on high (top 30%) and low (bottom 30%) PRC1 expression levels from the TCGA database (log-rank test; gene expression profiling interactive analysis database). Red and blue dashed lines are the 95% confidence interval of each Kaplan-Meier curve.

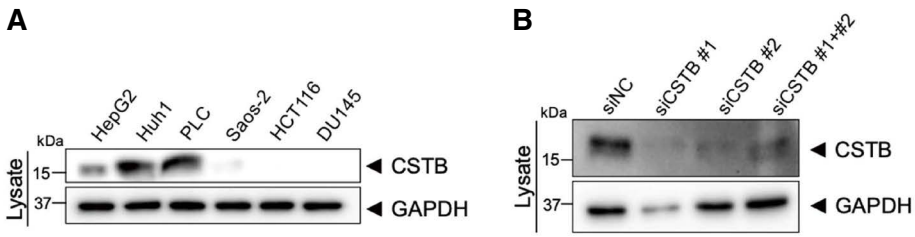

Fig. 2. Protein expression of CSTB in cancer cells. (A) Protein expression of CSTB in multiple cancer cell lines. (B) Knockdown of CSTB protein level in PLC cell lines.

reverse, 5′-GTTGCTGAGGTATCGCCAGGAA-3′; CD274 forward, 5′-GTTGCTGAGGTATCGCCAGGAA-3′; reverse, 5′-TGCAGCCAGGTCTAATTGTTTT-3′; IL 18 forward, 5′-GCGTCACTACACTCAGTCAA-3′; reverse, 5′-CATGCCCTCAATCCCAGCTACTC-3′. GAPDH forward 5′-GGAAGGTGAAGGTCGGAGTC-3’; reverse 5′-GTTGAGGTCAATGAAGGGGTC-3’.

4. Western blot

Total protein was extracted from cells using RIPA lysis buffer (Thermo Scientific, Catalog no. 89900) and separated on a 10% gel using 1× Tris/Glycine/SDS running buffer (BIO-RAD, Catalog no. 1610772). The separated proteins were transferred onto a polyvinylidene fluoride (PVDF) membrane (Roche, Basel, Switzerland, Catalog no. 03010040001) and blocked with 5% skim milk (Kisan Bio, Seoul, Republic of Korea, catalog no. MBS1667). The membrane was incubated with primary antibodies against CSTB and GAPDH at a dilution of 1 : 1000 at 4°C overnight (CSTB antibody from Abcam, Cambridge, UK, Catalog no. ab92449, GAPDH antibody from Cell signaling technology, Danvers, MA, USA, Catalog no. 5174S). The following day, the membrane was washed for 30 min with 1× Tris-buffered saline (DYNE Bio, Seongnam, Republic of Korea, Catalog no. CBT3085) containing 0.1% Tween-20 and then incubated with a rabbit secondary antibody (Jackson ImmunoResearch, West Grove, PA, USA, catalog no. 111035003) diluted 1 : 5000. Protein bands were visualized using an enhanced chemiluminescence (ECL) kit (Advansta, San Jose, CA, USA, catalog no. K-12045-D50).

5. Cell viability

PLC cells were seeded in 12-well plates at a density of 2×10^5 cells per well. CSTB knockdown was performed

www.dcig.kr

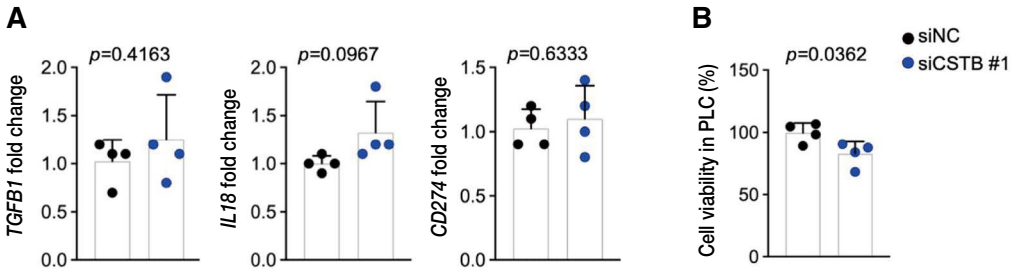

Fig. 3. CSTB regulates the cancer phenotypes. (A) mRNA levels of TGFB1, IL18 and CD274 in CSTB knockdown PLC cells with controls (n = 4). (B) Measurement of the viability of PLC cells with CSTB expression (n = 4). Graphs show mean +SD, unpaired *t*-test.

using CSTB siRNA and negative control siRNA for 24 h, after which the cells were washed with PBS. The cells were then incubated with thiazolyl blue tetrazolium bromide (MTT) solution (5 mg/mL) (Biobasic, Markham, ON, Canada, Catalog no. 298931) for 4 h, followed by the addition of dimethyl sulfoxide (DMSO, Merck, Darmstadt, Germany, Catalog no. D2650100ML) to dissolve the formazan crystals. Cell viability was measured at a wavelength of 570 nm using an Infinite M200 Pro (Tecan, Zürich, Switzerland).

6. Statistical analysis

Statistical analysis was performed using GraphPad Prism version 10 (GraphPad, San Diego, USA). Differences between groups were evaluated using an unpaired *t*-test (qPCR and cell viability) and one-way ANOVA (Box plot), and $p < 0.05$ was considered statistically significant.

RESULTS

To investigate the role of CSTB in HCC patients, we first analyzed its expression patterns and prognostic significance using the TCGA dataset. Notably, CSTB mRNA expression was significantly upregulated in HCC tumors compared to the normal group (Fig. 1A). Moreover, patients with high CSTB expression appeared to have poorer overall survival compared to those with low CSTB expression (Fig. 1B). These findings indicate that elevated CSTB levels are strongly associated with aggressive disease behavior and serve an independent predictor of unfavorable prognosis in HCC.

To validate CSTB expression across different malignancies, we performed western blotting in a panel of cancer cell lines, including those derived from HCC (HepG2, Huh1 and PLC), osteosarcoma (Saos-2), colon cancer (HCT116), prostate cancer (DU145). Interestingly, CSTB expression was selectively elevated in HCC cell lines, with PLC cells displaying the highest levels among all tested lines (Fig. 2A). This liver cancer-specific upregulation prompted us to select PLC cells for functional studies. For functional validation, we employed small interfering RNA (siRNA)-mediated knockdown of CSTB in PLC cells. Transfection with CSTB-specific siRNA (siCSTB) resulted in near-complete ablation of CSTB protein expression, as confirmed by Western blot anaylsis, whereas control siRNA (siNC) had no effect (Fig. 2B). These results confirm the feasibility of CSTB suppression in HCC cells and underscore its potential as one of the candidate biomarkers for HCC.

Next, we investigated CSTB's immunomodulatory effects in HCC, which features a highly immunosuppressive environment characterized by elevated cytokines and proteins, including TGF-β, IL-18 and PD-L1. We found that CSTB knockdown did not affect immunomodulated proteins (Fig. 3A). We also assessed CSTB's impact on tumor cell viability. CSTB suppression markedly decreased cell viability compared to siNC controls (Fig. 3B). These data demonstrate CSTB's dual role in driving HCC proliferation and sustaining immune suppression, positioning it as a candidate biomarker.

DISCUSSION

Our research demonstrates that CSTB expression in HCC regulates cancer cell phenotype and tumor progression. CSTB is significantly upregulated in HCC and associated with a poorer survival rates. Moreover, CSTB expression is specifically elevated in HCC cell lines compared to other

www.kci.go.kr

cancer types. Downregulation of CSTB markedly reduces cancer cell viability, but does not affect immunomodulated genes. Thus, our study identifies CSTB as an HCC biomarker and suggests it as one of the targets for HCC patients. Our study has limitations regarding the lack of in vivo models and supporting immune-related data. Therefore, further studies incorporating in vivo systems and additional immunological analyses will be needed in the future.

Liver diseases such as fibrosis, metabolic dysfunction-associated steatohepatitis (MASH), metabolic dysfunction-associated steatotic liver disease (MASLD), and cirrhosis are progressively worsening globally, driven by rising obesity and metabolic syndrome [16-19]. These conditions create a protumorigenic microenvironment serving as the primary risk factors for HCC development [16,20]. Therapeutic options remain limited; Rezdiffra, the first approved MASH-specific drug, improves fibrosis modestly but carries side effects like gastrointestinal issues and potential cardiovascular risks [21]. Future studies should profile CSTB expression across this disease continuum to assess its role as an early biomarker and therapeutic target for preventing HCC progression.

No specific inhibitors or Proteolysis-Targeting Chimera (PROTACs) targeting CSTB have been developed, primarily due to its small size (~11 kDa) and flat cystatin fold lacking deep hydrophobic pockets for small-molecule binding. The MAPK/ERK pathway serves as a key upstream regulator of CSTB expression in HCC, where ERK phosphorylation activates AP-1/Elk-1 transcription factors, forming a protumorigenic feedback loop [22-25]. Clinically approved MEK inhibitors, such as PD0325901 or trametinib, may suppress CSTB upregulation, reducing tumor proliferation and invasion [26]. In addition, inhibition of the ERK pathway by Micheliolide (MCL) has been shown to attenuate hepatic fibrosis, a major risk factor of HCC [27]. This antifibrotic effect suggests that targeting ERK signaling may not only mitigate liver fibrogenesis but also indirectly reduce the risk of HCC development. This strategy may extend to CSTB-related progressive myoclonic epilepsy, where MAPK hyperactivation worsens neuronal dysfunction. Future approaches could explore covalent fragment-based screening of CSTB's cathepsin-binding interface of PROTAC designs, leveraging its TRIM family E3 ligase interactions.

HCC consists of diverse cellular components, including cancer cells, hepatic stellate cells (HSCs) and Kupffer cells [28,29]. HSCs are known to secrete various factors, such as metabolic fuel, collagen and immunomodulatory cytokines, which contribute to the establishment of an immunosuppressive tumor microenvironment [30,31]. Although HCC is generally characterized by strong immunosuppressive tumor environment properties [32], our data showed no significant differences in the expression levels of immunosuppressive cytokines among the examined HCC cell lines. Therefore, further investigations using in vivo models are warranted to better elucidate the mechanisms underlying HSC-mediated immunosuppression in HCC. So, targeting not only cancer cells with CSTB but also HSCs may represent a promising strategy and help guide future research directions.

REFERENCES

1. Brannvall K, Hjelm H, Korhonen L, Lahtinen U, Lehesjoki AE, Lindholm D. Cystatin-B is expressed by neural stem cells and by differentiated neurons and astrocytes. Biochem Biophys Res Commun. 2003;308:369-74. https://doi.org/10.1016/s0006-291x(03)01386-x.
2. Gorski K, Spoljaric A, Nyman TA, Kaila K, Battersby BJ, Lehesjoki AE. Quantitative changes in the mitochondrial proteome of cerebellar synaptosomes from preclinical cystatin B-deficient mice. Front Mol Neurosci. 2020;13:570640. https://doi.org/10.3389/fnmol.2020.570640.
3. Di Matteo F, Pipicelli F, Kyrousi C, Tovecci I, Penna E, Crispino M, et al. Cystatin B is essential for proliferation and interneuron migration in individuals with EPM1 epilepsy. EMBO Mol Med. 2020;12:e11419. https://doi.org/10.15252/emmm.201911419.
4. Lin C, Yang H, Zhao W, Wang W. CTSB(+) macrophage repress memory immune hub in the liver metastasis site of colorectal cancer patient revealed by multi-omics analysis. Biochem Biophys Res Commun. 2022;626:8-14. https://doi.org/10.1016/j.bbrc.2022.06.037.
5. Jiang Y, Han L, Xue M, Wang T, Zhu Y, Xiong C, et al. Cystatin B increases autophagic flux by sustaining proteolytic activity of cathepsin B and fuels glycolysis in pancreatic cancer: CSTB orchestrates autophagy and glycolysis in PDAC. Clin Transl Med. 2022;12:e1126. https://doi.org/10.1002/ctm2.1126.
6. Zhang D, Sun BY, Wu JF, Wang ZT, Zheng SS, Sun GQ, et al. Cystatin B promotes the proliferation, migration, and invasion of intrahepatic cholangiocarcinoma. Curr Oncol. 2025;32. https://doi.org/10.3390/curroncol32020056.

www.kci.go.kr

7. Lee MJ, Yu GR, Park SH, Cho BH, Ahn JS, Park HJ, et al. Identification of cystatin B as a potential serum marker in hepatocellular carcinoma. Clin Cancer Res. 2008;14:1080-9. https://doi.org/10.1158/1078-0432.CCR-07-1615.
8. Unic A, Derek L, Duvnjak M, Patrlj L, Rakic M, Kujundzic M, et al. Diagnostic specificity and sensitivity of PIVKAII, GP3, CSTB, SCCA1 and HGF for the diagnosis of hepatocellular carcinoma in patients with alcoholic liver cirrhosis. Ann Clin Biochem. 2018;55:355-62. https://doi.org/10.1177/0004563217726808.
9. Fernandes-Ferreira R, Tenani GD, Pinhel MAS, Abrantes AMC, Botelho M, Silva R et al. Genes expression and serum biomarkers for diagnosis of hepatocellular carcinoma, cirrhosis and hepatitis C. Arq Gastroenterol. 2022;59:394-401. https://doi.org/10.1590/S0004-2803.202203000-71.
10. Mauro E, de Castro T, Zeitlhoefler M, Sung MW, Villanueva A, Mazzaferro V, et al. Hepatocellular carcinoma: epidemiology, diagnosis and treatment. JHEP Rep. 2025;7:101571. https://doi.org/10.1016/j.jhepr.2025.101571.
11. Cheishvili D, Wong C, Karim MM, Golam Kibria M, Jahan N, Chandra Das P, et al. Clinical validation of peripheral blood mononuclear cell DNA methylation markers for accurate early detection of hepatocellular carcinoma in Asian patients. Commun Med (Lond). 2024;4:220. https://doi.org/10.1038/s43856-024-00652-2.
12. Zhong C, Li Y, Yang J, Jin S, Chen G, Li D, et al. Immunotherapy for hepatocellular carcinoma: current limits and prospects. Front Oncol. 2021;11:589680. https://doi.org/10.3389/fonc.2021.589680.
13. Qi D, Qin Y, Zhu H, Li Y, Han S. Resistance of first-line targeted drugs in hepatocellular carcinoma: the epigenetic regulation mechanisms. Cell Death Dis. 2025;16:875. https://doi.org/10.1038/s41419-025-08105-x.
14. Pfister D, Nunez NG, Pinyol R, Govaere O, Pinter M, Szydlowska M, et al. NASH limits anti-tumour surveillance in immunotherapy-treated HCC. Nature 2021;592:450-6. https://doi.org/10.1038/s41586-021-03362-0.
15. Jin J, Cheng K, Chen M, Liang H, Zhang W. Immunotherapy resistance in MASLD-related hepatocellular carcinoma: special immune microenvironment and gut microbiota. Int J Biol Sci. 2025;21:5666-90. https://doi.org/10.7150/ijbs.117394.
16. Ma Y, Wang J, Xiao W, Fan X. A review of MASLD-related hepatocellular carcinoma: progress in pathogenesis, early detection, and therapeutic interventions. Front Med (Lausanne). 2024;11:1410668. https://doi.org/10.3389/fmed.2024.1410668.
17. Stefan N, Yki-Jarvinen H, Neuschwander-Tetri BA. Metabolic dysfunction-associated steatotic liver disease: heterogeneous pathomechanisms and effectiveness of metabolism-based treatment. Lancet Diabetes Endocrinol. 2025;13:134-48. https://doi.org/10.1016/S2213-8587(24)00318-8.
18. Steinberg GR, Valvano CM, De Nardo W, Watt MJ. Integrative metabolism in MASLD and MASH: pathophysiology and emerging mechanisms. J Hepatol. 2025;83:584-95. https://doi.org/10.1016/j.jhep.2025.02.033.
19. Leslie J, Krishnamurthy KA, Gopalsamy IK, Inacio P, Huch M, Gallage S, et al. Metabolic dysfunction-associated steatotic liver disease and steatohepatitis-associated hepatocarcinoma preclinical models. Nat Rev Gastroenterol Hepatol. 2026;23:286-317. https://doi.org/10.1038/s41575-025-01162-9.
20. Ray K. MASH-induced senescence and liver cancer. Nat Rev Gastroenterol Hepatol. 2025;22:152. https://doi.org/10.1038/s41575-025-01043-1.
21. Bittla P, Paidimarri SP, Ayuthu S, Chauhan YD, Saad MZ, Mirza AA, et al. Resmetirom: a systematic review of the revolutionizing approach to non-alcoholic steatohepatitis treatment focusing on efficacy, safety, cost-effectiveness, and impact on quality of life. Cureus 2024;16:e69919. https://doi.org/10.7759/cureus.69919.
22. Schmitz KJ, Wohlschlaeger J, Lang H, Sotiropoulos GC, Malago M, Steveling K, et al. Activation of the ERK and AKT signalling pathway predicts poor prognosis in hepatocellular carcinoma and ERK activation in cancer tissue is associated with hepatitis C virus infection. J Hepatol. 2008;48:83-90. https://doi.org/10.1016/j.jhep.2007.08.018.
23. Li L, Zhao GD, Shi Z, Qi LL, Zhou LY, Fu ZX. The Ras/Raf/MEK/ERK signaling pathway and its role in the occurrence and development of HCC. Oncol Lett. 2016;12:3045-50. https://doi.org/10.3892/ol.2016.5110.
24. Moon H, Ro SW. MAPK/ERK signaling pathway in hepatocellular carcinoma. Cancers (Basel). 2021;13. https://doi.org/10.3390/cancers13123026.
25. Kaminska B, Kaczmarek L, Zangenehpour S, Chaudhuri A. Rapid phosphorylation of Elk-1 transcription factor and activation of MAP kinase signal transduction pathways in response to visual stimulation. Mol Cell Neurosci. 1999;13:405-14. https://doi.org/10.1006/mcne.1999.0757.
26. Henderson YC, Chen Y, Frederick MJ, Lai SY, Clayman GL. MEK inhibitor PD0325901 significantly reduces the growth of papillary thyroid carcinoma cells in vitro and in vivo. Mol Cancer Ther. 2010;9:1968-76. https://doi.org/10.1158/1535-7163.MCT-10-0062.
27. Liu Y, Yao L, Liu Y, Yang Y, Liang A, He H, et al. Micheliolide alleviates hepatic fibrosis by inhibiting autophagy in hepatic stellate cells via the TrxR1/2-Mediated ROS/MEK/ERK pathway. Pharmaceuticals (Basel). 2025;18. https://doi.org/10.3390/ph18030287.
28. Wang BB, Cheng JY, Gao HH, Zhang Y, Chen ZN, Bian H.

www.kci.go.kr

Hepatic stellate cells in inflammation-fibrosis-carcinoma axis. Anat Rec (Hoboken). 2010;293:1492-6. https://doi.org/10.1002/ar.21173.
29. Severi T, van Malenstein H, Verslype C, van Pelt JF. Tumor initiation and progression in hepatocellular carcinoma: risk factors, classification, and therapeutic targets. Acta Pharmacol Sin. 2010;31:1409-20. https://doi.org/10.1038/aps.2010.142.
30. Trivedi P, Wang S, Friedman SL. The power of plasticity-metabolic regulation of hepatic stellate cells. Cell Metab. 2021;33:242-57. https://doi.org/10.1016/j.cmet.2020.10.026.
31. Rho H, Kim U, Song J. Ubiquitination and ubiquitin-like modifications in metabolic dysfunction-associated steatotic liver disease: mechanisms and implications. BMB Rep. 2025;58:371-88. https://doi.org/10.5483/BMBRep.2025-0014.
32. Zhou Z, Hu Y, Wu Y, Qi Q, Wang J, Chen L, et al. The immunosuppressive tumor microenvironment in hepatocellular carcinoma-current situation and outlook. Mol Immunol. 2022;151:218-30. https://doi.org/10.1016/j.molimm.2022.09.010.

www.kci.go.kr