World Journal of Gastrointestinal Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Oncol 2024 December 15; 16(12): 4543-4547

DOI: 10.4251/wjgo.v16.i12.4543

ISSN 1948-5204 (online)

EDITORIAL

Gene targets with therapeutic potential in hepatocellular carcinoma

Syifaus Shodry, Yuliono Trika Nur Hasan, Iwal Reza Ahdi, Zulvikar Syambani Ulhaq

Specialty type: Oncology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade B

P-Reviewer: Tchilikidi KY

Received: June 27, 2024
Revised: August 3, 2024
Accepted: August 13, 2024
Published online: December 15, 2024
Processing time: 138 Days and 5.7 Hours

Syifaus Shodry, Yuliono Trika Nur Hasan, Iwal Reza Ahdi, Faculty of Medicine and Health Sciences, Maulana Ibrahim Islamic State University of Malang, Malang 65144, Jawa Timur, Indonesia

Zulvikar Syambani Ulhaq, Research Center for Preclinical and Clinical Medicine, National Research and Innovation Agency Republic of Indonesia, Cibinong 16911, Indonesia

Corresponding author: Zulvikar Syambani Ulhaq, MD, PhD, Research Scientist, Research Center for Preclinical and Clinical Medicine, National Research and Innovation Agency Republic of Indonesia, Cibinong Science Center, Jl. Raya Jakarta-Bogor, Cibinong 16911, Indonesia. zulvikar.syambani.ulhaq@brin.go.id

Abstract

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide. Major treatments include liver transplantation, resection, and chemotherapy, but the 5-year recurrence rate remains high. Late diagnosis often prevents surgical intervention, contributing to poor patient survival rates. Carcinogenesis in HCC involves genetic alterations that drive the transformation of normal cells into malignant ones. Enhancer of zeste homolog 2 (EZH2), a key regulator of cell cycle progression, is frequently upregulated in HCC and is associated with advanced stages and poor prognosis, making it a potential biomarker. Additionally, signal transducer and activator of transcription 3, which binds to EZH2, affects disease staging and outcomes. Targeting EZH2 presents a promising therapeutic strategy. On the other hand, abnormal lipid metabolism is a hallmark of HCC and impacts prognosis. Fatty acid binding protein 5 is highly expressed in HCC tissues and correlates with key oncogenes, suggesting its potential as a biomarker. Other genes such as guanine monophosphate synthase, cell division cycle associated 5, and epidermal growth factor receptor provide insights into the molecular mechanisms of HCC, offering potential as biomarkers and therapeutic targets.

Key Words: Hepatocellular carcinoma; Enhancer of zeste homolog 2; Target genes; Biomarkers; Potential therapeutic

Core Tip: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related deaths due to late diagnosis and high recurrence rates. Key biomarkers such as enhancer of zeste homolog 2 and fatty acid binding protein 5, along with other genetic biomarkers provide insights into HCC progression and potential therapeutic targets.

Citation: Shodry S, Hasan YTN, Ahdi IR, Ulhaq ZS. Gene targets with therapeutic potential in hepatocellular carcinoma. *World J Gastrointest Oncol* 2024; 16(12): 4543-4547
URL: https://www.wjgnet.com/1948-5204/full/v16/i12/4543.htm
DOI: https://dx.doi.org/10.4251/wjgo.v16.i12.4543

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer, accounting for 80% of all cases[1,2]. HCC imposes a substantial health and economic burden worldwide, especially in Asia[3]. Moreover, HCC is the third leading cause of cancer-related deaths globally, with a 5-year survival rate around 18%[3]. In 2020, there were about 906000 new cases and 830000 deaths from HCC, with Asia bearing 80% of the global disease burden[4]. Various treatments are available for managing HCC, including transcatheter arterial chemoembolization, liver transplantation (LT) or resection, transarterial radioembolization, radiofrequency ablation, and targeted systemic chemotherapy[5]. While surgical treatment is often viewed as the standard curative option for early-stage HCC[6-8], it is not a complete solution since the majority of patients are diagnosed at a more advanced stage with poor prognoses. Despite various treatment efforts, the 5-year recurrence rate remains high at approximately 70% following surgery[9]. Consequently, there is a critical need for more effective treatments to enhance the long-term survival of HCC patients.

Indeed, HCC is prevalent and frequently linked to a poor prognosis for patients[2]. The disease's incidence and mortality rates have been rising globally, particularly in regions such as eastern and southeastern Asia and Africa[10]. Chronic infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) are well-established primary contributors to liver cirrhosis and HCC. Furthermore, exposure to aflatoxin B1 and long-term alcohol abuse are notable risk factors for the development of HCC[11,12]. Despite advancements in surgical techniques that have improved overall survival (OS) rates among patients with HCC, the 5-year OS remains low at 15%, and cancer-specific survival is less than 20%[13]. This is likely because many patients are not eligible for surgical resection or LT, primarily due to late diagnosis[14]. Furthermore, the disease is marked by a significant recurrence rate, with more than 40%-70% of patients experiencing a relapse within 5 years of surgical intervention[15]. The process of cancer development is generally understood to be a multistep phenomenon, driven by the accumulation of genetic changes that activate multiple signaling pathways, and ultimately leading to the transformation of normal cells into cancerous ones[16].

Genetics plays a crucial role in understanding the structure and function of organisms and have been widely applied in clinical diagnosis, drug development, and disease prediction[17-19]. Genes that play a role in DNA replication and maintaining proper sister chromatid cohesion are crucial for cell division, and any disruptions in these processes can greatly influence the onset and progression of malignant diseases[20]. In HCC, the genes related to this condition, along with their interacting counterparts, create a network of gene interactions[21]. Several molecules in this network are integral to the development and progression of HCC. For example, genes such as signal transducer and activator of transcription 3 (STAT3) and centrosomal protein of 55 kDa (CEP55) are involved in cell migration and invasion[22,23]. Additionally, EZH2, the catalytic subunit of polycomb repressive complex 2, is functionally associated with cell cycle regulation. Abnormal regulation of EZH2 can accelerate cell proliferation and extend cell survival, which may contribute to the onset and progression of cancer[24]. Study indicates that EZH2 is overexpressed in other cancers, including breast and prostate cancers, and its presence is linked to advanced disease and unfavorable outcomes[25].

The correlation between EZH2 and lymph node metastasis is more pronounced in EZH2-expressing tumor cells within lymph nodes compared to their matched primary tumor cells[25]. This suggests that elevated EZH2 expression is linked to higher tumor grade and increased likelihood of lymph node metastasis[25]. EZH2 also interacts with CEP55, worsening the prognosis in HCC[22]. Moreover, STAT3 causes carcinogenesis by binding to and being activated by EZH2 [26,27]. STAT3 and EZH2 are both promising molecular biomarkers for tumor progression and are associated with poor prognosis[25]. Their activation shows a strong correlation with tumor-node-metastasis (TNM) stage and patient survival, indicating that the combined expression of STAT3 and EZH2 may aid in determining the clinical TNM stage and predicting disease outcomes. STAT3 can be downregulated by EZH2 knockdown, making EZH2 a potential therapeutic target and biomarker for HCC diagnosis and prognosis[25].

Given the liver's crucial role in lipid metabolism, including the synthesis of most of the body's cholesterol and fatty acids[28,29], disrupted lipid metabolism is a key feature of metabolic reprogramming in HCC and significantly impacts its prognosis[30]. In HCC, this disruption is characterized by alterations in lipid oxidation processes, increased cholesterol esterification, elevated endogenous lipid synthesis, and changes in lipid uptake and efflux[30]. These changes closely correlate with tumor survival, growth, proliferation, and metastasis[30]. It is notable that FABP5 is highly expressed in human HCC tissues and cell lines compared with normal liver tissues and hepatocytes. FABP5, a specific isoform of FABPs, binds various long-chain fatty acids and retinoids. It is involved in transporting lipids to cellular compartments for membrane synthesis, storage, trafficking, and transcriptional regulation[31,32]. FABP5 increases the activity of the nuclear receptor peroxisome proliferator-activated receptor β/δ, which drives cell migration, growth, and survival, thus

displaying tumor-promoting properties[33]. High FABP5 expression correlates with cancer hallmarks and oncogenes such as polo like kinase 1 and baculoviral IAP repeat containing, which are master regulators in cell cycle progression and inhibition of cell death[32]. Positive FABP5 expression is associated with worse prognoses and higher recurrence rates[32]. Together, these data strongly suggest that both EZH2 and FABP5 may be useful as markers and novel therapeutic targets for treating HCC, providing valuable insights for potential therapeutic development.

OTHER POTENTIAL THERAPEUTIC GENE TARGET FOR HCC

The pathomechanism of liver cancer involves a complex interplay of various risk factors, including race, age, HBV, and HCV, which all contribute to abnormal gene expression linked to the onset and progression of HCC. Current research is focused on identifying key genes crucial for the initiation as well as the progression of HCC as a potential treatment strategy. With the advancement of genomics, numerous gene sequencing data have been stored in public databases, providing valuable resources for bioinformatic mining of gene expression profiles related to cancer[34]. In 2017, Zhang *et al*[35] identified key genes and pathways related to HCC through bioinformatic analysis of differentially expressed genes (DEGs) between HCC samples and normal samples. In HCC, 10 deregulated genes include: KRAS proto-oncogene, GTPase (KRAS), epidermal growth factor receptor (EGFR), B-cell lymphoma 2, acetyl-CoA carboxylase alpha, cluster of differentiation 8A, guanine monophosphate synthase (GMPS), transforming growth factor beta 1, STAT3, human epidermal growth factor receptor 2. Among these, albumin combined with bilirubin (albumin–bilirubin grade) displayed higher prognostic value. GMPS, essential for the synthesis of purines, has been recognized as a significant target for repression by p53, and its upregulation disrupts the tumor-suppressive p53 network in liver cancer, making GMPS a potential therapeutic target. EGFR overexpression contributes to HCC progression by enhancing cell proliferation, migration, and invasion, establishing it as an effective drug target and prognostic biomarker.

On the other hand, in 2021, Li and Xu[36] identified six genes that serve as potential therapeutic targets for HCC. Among these, cell division cycle associated 5 (CDCA5) plays a crucial role in the accurate separation of sister chromatids during the S and G2/M phases of the cell cycle[37,38]. Overexpression of CDCA5 has been clinically associated with a poor prognosis in HCC patients[39]. Opa interacting protein 5 (OIP5) regulates HCC growth and metastasis through the AKT/mammalian target of rapamycin signaling pathways[40]. DNA topoisomerase 2 alpha (TOP2A) is highly expressed in HCC tumors and is associated with shorter patient survival and increased resistance to chemotherapy[41]. Protein regulator of cytokinesis 1 (PRC1) overexpression enhances chemoresistance and inhibits apoptosis in HCC patients undergoing chemotherapy[42]. Abnormal spindle-like microcephaly-associated protein (ASPM) overexpression serves as a marker for increased metastatic potential and poor prognosis in HCC[43]. Additionally, nucleolar and spindle-associated protein 1 (NUSAP1) overexpression is associated with significantly lower survival rates in patients with HCC [44], with microRNA 193a-5p implicated in hepatocarcinogenesis suppression by regulating NUSAP1 Levels. Cyclin A2 (CCNA2) and kinesin family member 20A (KIF20A) also demonstrate elevated expression levels in HCC tissues compared to normal tissues[45].

In 2018, Hu *et al*[46] identified 56 upregulated and 8 downregulated DEGs in HCC. Their analysis revealed significant enrichment of genes involved in cell cycle arrest, transcription regulation, protein amino acid phosphorylation, cell cycle, and apoptosis. They proposed JUN, early growth response protein 1 (EGR1), MYC, and cyclin-dependent kinase inhibitor 1A (CDKN1A) as potential diagnostic and therapeutic molecular biomarkers for HCC. c-JUN prevents apoptosis by antagonizing p53 activity, contributing to early-stage HCC[47]. EGR1 contributes to HCC radio resistance by upregulating autophagy-related 4B, yet paradoxically, its upregulation by beta-lapachone inhibits hepatoma cell progression and metastasis[48]. MYC controls various cellular processes, including cell cycle progression, proliferation, and apoptosis, with miR-320a acting as a tumor suppressor by targeting MYC in HCC[49]. CDKN1A, a prominent cell cycle inhibitor, arrests cell cycle progression at the G1/S and G2/M transitions by blocking the activity of CDK4/6-cyclin D and CDK2-cyclin E complexes[28,50]. In summary, ongoing research continues to uncover crucial genes and pathways involved in HCC, offering new insights into potential therapeutic targets and prognostic biomarkers.

CONCLUSION

In conclusion, both EZH2 and FABP5 serve as biomarkers for poor outcomes in HCC and show potential as therapeutic targets for patients with this disease. Additionally, other markers such as GMPS, CDCA5, EGFR, OIP5, TOP2A, PRC1, ASPM, NUSAP1, CCNA2, JUN, EGR1, MYC, and CDKN1A contribute to a detailed understanding of the molecular mechanisms underlying HCC occurrence and progression. These molecules hold promise as both biomarkers and therapeutic targets.

FOOTNOTES

Author contributions: Shodry S wrote the original manuscript; Hasan YTN and Ahdi IR supervised the project; Ulhaq ZS conceived the study, wrote the original draft and revised the manuscript, and supervised the study; Ulhaq ZS was the main contributor to this manuscript.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Country of origin: Indonesia

ORCID number: Zulvikar Syambani Ulhaq 0000-0002-2659-1940.

S-Editor: Lin C
L-Editor: Filipodia
P-Editor: Zhao S

REFERENCES

1 **Foglia B**, Turato C, Cannito S. Hepatocellular Carcinoma: Latest Research in Pathogenesis, Detection and Treatment. *Int J Mol Sci* 2023; **24** [PMID: 37569600 DOI: 10.3390/ijms241512224]
2 **Ladju RB**, Ulhaq ZS, Soraya GV. Nanotheranostics: A powerful next-generation solution to tackle hepatocellular carcinoma. *World J Gastroenterol* 2022; **28**: 176-187 [PMID: 35110943 DOI: 10.3748/wjg.v28.i2.176]
3 **Kim DY**. Changing etiology and epidemiology of hepatocellular carcinoma: Asia and worldwide. *J Liver Cancer* 2024; **24**: 62-70 [PMID: 38523466 DOI: 10.17998/jlc.2024.03.13]
4 **Sim YK**, Chong MC, Gandhi M, Pokharkar YM, Zhu Y, Shi L, Lequn L, Chen CH, Kudo M, Lee JH, Strasser SI, Chanwat R, Chow PKH; Asia-Pacific Hepatocellular Carcinoma Trials Group. Real-World Data on the Diagnosis, Treatment, and Management of Hepatocellular Carcinoma in the Asia-Pacific: The INSIGHT Study. *Liver Cancer* 2024; **13**: 298-313 [PMID: 38756144 DOI: 10.1159/000534513]
5 **Kotsifa E**, Vergadis C, Vailas M, Machairas N, Kykalos S, Damaskos C, Garmpis N, Lianos GD, Schizas D. Transarterial Chemoembolization for Hepatocellular Carcinoma: Why, When, How? *J Pers Med* 2022; **12** [PMID: 35330436 DOI: 10.3390/jpm12030436]
6 **Lin S**, Hoffmann K, Schemmer P. Treatment of hepatocellular carcinoma: a systematic review. *Liver Cancer* 2012; **1**: 144-158 [PMID: 24159579 DOI: 10.1159/000343828]
7 **Tabori NE**, Sivananthan G. Treatment Options for Early-Stage Hepatocellular Carcinoma. *Semin Intervent Radiol* 2020; **37**: 448-455 [PMID: 33328700 DOI: 10.1055/s-0040-1720950]
8 **Cucchetti A**, Elshaarawy O, Han G, Chong CCN, Serra C, O'Rourke JM, Crew R, Felicani C, Ercolani G, Shah T, Vogel A, Lai PBS, Johnson PJ. 'Potentially curative therapies' for hepatocellular carcinoma: how many patients can actually be cured? *Br J Cancer* 2023; **128**: 1665-1671 [PMID: 36807338 DOI: 10.1038/s41416-023-02188-z]
9 **Llovet JM**, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, Lencioni R, Koike K, Zucman-Rossi J, Finn RS. Hepatocellular carcinoma. *Nat Rev Dis Primers* 2021; **7**: 6 [PMID: 33479224 DOI: 10.1038/s41572-020-00240-3]
10 **Yang JD**, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 589-604 [PMID: 31439937 DOI: 10.1038/s41575-019-0186-y]
11 **Chu YJ**, Yang HI, Wu HC, Lee MH, Liu J, Wang LY, Lu SN, Jen CL, You SL, Santella RM, Chen CJ. Aflatoxin B(1) exposure increases the risk of hepatocellular carcinoma associated with hepatitis C virus infection or alcohol consumption. *Eur J Cancer* 2018; **94**: 37-46 [PMID: 29533866 DOI: 10.1016/j.ejca.2018.02.010]
12 **El-Serag HB**. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* 2012; **142**: 1264-1273.e1 [PMID: 22537432 DOI: 10.1053/j.gastro.2011.12.061]
13 **Orcutt ST**, Anaya DA. Liver Resection and Surgical Strategies for Management of Primary Liver Cancer. *Cancer Control* 2018; **25**: 1073274817744621 [PMID: 29327594 DOI: 10.1177/1073274817744621]
14 **Abdelhamed W**, El-Kassas M. Hepatocellular carcinoma recurrence: Predictors and management. *Liver Res* 2023; **7**: 321-332 [DOI: 10.1016/j.livres.2023.11.004]
15 **Wen T**, Jin C, Facciorusso A, Donadon M, Han HS, Mao Y, Dai C, Cheng S, Zhang B, Peng B, Du S, Jia C, Xu F, Shi J, Sun J, Zhu P, Nara S, Millis JM; MDT of West China Hospital*. Multidisciplinary management of recurrent and metastatic hepatocellular carcinoma after resection: an international expert consensus. *Hepatobiliary Surg Nutr* 2018; **7**: 353-371 [PMID: 30498711 DOI: 10.21037/hbsn.2018.08.01]
16 **Niu ZS**, Niu XJ, Wang WH. Genetic alterations in hepatocellular carcinoma: An update. *World J Gastroenterol* 2016; **22**: 9069-9095 [PMID: 27895396 DOI: 10.3748/wjg.v22.i41.9069]
17 **Ulhaq ZS**, Garcia CP. Estrogen receptor beta (ESR2) gene polymorphism and susceptibility to dementia. *Acta Neurol Belg* 2021; **121**: 1281-1293 [PMID: 32335869 DOI: 10.1007/s13760-020-01360-z]
18 **Ulhaq ZS**, Nurputra DK, Soraya GV, Kurniawati S, Istifiani LA, Pamungkas SA, Tse WKF. A systematic review on Treacher Collins syndrome: Correlation between molecular genetic findings and clinical severity. *Clin Genet* 2023; **103**: 146-155 [PMID: 36203321 DOI: 10.1111/cge.14243]
19 **Ulhaq ZS**, Garcia CP. Inflammation-related gene polymorphisms associated with Parkinson's disease: an updated meta-analysis. *Egypt J Med Hum Genet* 2020; **21**: 14 [DOI: 10.1186/s43042-020-00056-6]
20 **Ulhaq ZS**, Soraya GV, Milliana A, Tse WKF. Association between GPER gene polymorphisms and GPER expression levels with cancer predisposition and progression. *Heliyon* 2021; **7**: e06428 [PMID: 33748487 DOI: 10.1016/j.heliyon.2021.e06428]
21 **Su SG**, Li QL, Zhang MF, Zhang PW, Shen H, Zhang CZ. An E2F1/DDX11/EZH2 Positive Feedback Loop Promotes Cell Proliferation in Hepatocellular Carcinoma. *Front Oncol* 2020; **10**: 593293 [PMID: 33614480 DOI: 10.3389/fonc.2020.593293]
22 **Li M**, Gao J, Li D, Yin Y. CEP55 Promotes Cell Motility *via* JAK2–STAT3–MMPs Cascade in Hepatocellular Carcinoma. *Cells* 2018; **7** [PMID: 30096813 DOI: 10.3390/cells7080099]
23 **Ulhaq ZS**, Tse WKF. PFHxS Exposure and the Risk of Non-Alcoholic Fatty Liver Disease. *Genes (Basel)* 2024; **15** [PMID: 38254982 DOI:

10.3390/genes15010093]
24 **Yu TY**, Zhan ZJ, Lin Q, Huang ZH. Computed tomography-based radiomics predicts the fibroblast-related gene *EZH2* expression level and survival of hepatocellular carcinoma. *World J Clin Cases* 2024; **12**: 5568-5582 [DOI: 10.12998/wjcc.v12.i24.5568]
25 **Bae AN**, Jung SJ, Lee JH, Lee H, Park SG. Clinical Value of EZH2 in Hepatocellular Carcinoma and Its Potential for Target Therapy. *Medicina (Kaunas)* 2022; **58** [PMID: 35208478 DOI: 10.3390/medicina58020155]
26 **Kim E**, Kim M, Woo DH, Shin Y, Shin J, Chang N, Oh YT, Kim H, Rheey J, Nakano I, Lee C, Joo KM, Rich JN, Nam DH, Lee J. Phosphorylation of EZH2 activates STAT3 signaling *via* STAT3 methylation and promotes tumorigenicity of glioblastoma stem-like cells. *Cancer Cell* 2013; **23**: 839-852 [PMID: 23684459 DOI: 10.1016/j.ccr.2013.04.008]
27 **Park SH**, Fong KW, Mong E, Martin MC, Schiltz GE, Yu J. Going beyond Polycomb: EZH2 functions in prostate cancer. *Oncogene* 2021; **40**: 5788-5798 [PMID: 34349243 DOI: 10.1038/s41388-021-01982-4]
28 **Ulhaq ZS**, Tse WKF. Perfluorohexanesulfonic acid (PFHxS) induces oxidative stress and causes developmental toxicities in zebrafish embryos. *J Hazard Mater* 2023; **457**: 131722 [PMID: 37263022 DOI: 10.1016/j.jhazmat.2023.131722]
29 **Ulhaq ZS**, Boncan DAT, Chan TF, Tse WKF. Insights from metabolomics and transcriptomics studies on Perfluorohexanesulfonic acid (PFHxS) exposed zebrafish embryos. *Sci Total Environ* 2023; **904**: 166833 [PMID: 37673246 DOI: 10.1016/j.scitotenv.2023.166833]
30 **Feng XC**, Liu FC, Chen WY, Du J, Liu H. Lipid metabolism of hepatocellular carcinoma impacts targeted therapy and immunotherapy. *World J Gastrointest Oncol* 2023; **15**: 617-631 [PMID: 37123054 DOI: 10.4251/wjgo.v15.i4.617]
31 **Ohira M**, Yokoo H, Ogawa K, Fukai M, Kamiyama T, Sakamoto N, Taketomi A. Serum fatty acid-binding protein 5 is a significant factor in hepatocellular carcinoma progression independent of tissue expression level. *Carcinogenesis* 2021; **42**: 794-803 [PMID: 33754641 DOI: 10.1093/carcin/bgab025]
32 **Ohata T**, Yokoo H, Kamiyama T, Fukai M, Aiyama T, Hatanaka Y, Hatanaka K, Wakayama K, Orimo T, Kakisaka T, Kobayashi N, Matsuno Y, Taketomi A. Fatty acid-binding protein 5 function in hepatocellular carcinoma through induction of epithelial-mesenchymal transition. *Cancer Med* 2017; **6**: 1049-1061 [PMID: 28374947 DOI: 10.1002/cam4.1020]
33 **Kawaguchi K**, Senga S, Kubota C, Kawamura Y, Ke Y, Fujii H. High expression of Fatty Acid-Binding Protein 5 promotes cell growth and metastatic potential of colorectal cancer cells. *FEBS Open Bio* 2016; **6**: 190-199 [PMID: 27047747 DOI: 10.1002/2211-5463.12031]
34 **Xu H**, Huang J, Hua S, Liang L, He X, Zhan M, Lu L, Chu J. Interactome analysis of gene expression profiles identifies CDC6 as a potential therapeutic target modified by miR-215-5p in hepatocellular carcinoma. *Int J Med Sci* 2020; **17**: 2926-2940 [PMID: 33173413 DOI: 10.7150/ijms.51145]
35 **Zhang C**, Peng L, Zhang Y, Liu Z, Li W, Chen S, Li G. The identification of key genes and pathways in hepatocellular carcinoma by bioinformatics analysis of high-throughput data. *Med Oncol* 2017; **34**: 101 [PMID: 28432618 DOI: 10.1007/s12032-017-0963-9]
36 **Li C**, Xu J. Identification of Potentially Therapeutic Target Genes in Ovarian Cancer via Bioinformatic Approach. 2021 IEEE 9th International Conference on Bioinformatics and Computational Biology (ICBCB); 2021 May 25-27 [DOI: 10.1109/icbcb52223.2021.9459203]
37 **Shen A**, Liu L, Chen H, Qi F, Huang Y, Lin J, Sferra TJ, Sankararaman S, Wei L, Chu J, Chen Y, Peng J. Cell division cycle associated 5 promotes colorectal cancer progression by activating the ERK signaling pathway. *Oncogenesis* 2019; **8**: 19 [PMID: 30808873 DOI: 10.1038/s41389-019-0123-5]
38 **Hu H**, Xiang Y, Zhang XY, Deng Y, Wan FJ, Huang Y, Liao XH, Zhang TC. CDCA5 promotes the progression of breast cancer and serves as a potential prognostic biomarker. *Oncol Rep* 2022; **48** [PMID: 36004470 DOI: 10.3892/or.2022.8387]
39 **Tian Y**, Wu J, Chagas C, Du Y, Lyu H, He Y, Qi S, Peng Y, Hu J. CDCA5 overexpression is an Indicator of poor prognosis in patients with hepatocellular carcinoma (HCC). *BMC Cancer* 2018; **18**: 1187 [PMID: 30497429 DOI: 10.1186/s12885-018-5072-4]
40 **Li H**, Zhang J, Lee MJ, Yu GR, Han X, Kim DG. OIP5, a target of miR-15b-5p, regulates hepatocellular carcinoma growth and metastasis through the AKT/mTORC1 and β-catenin signaling pathways. *Oncotarget* 2017; **8**: 18129-18144 [PMID: 28184024 DOI: 10.18632/oncotarget.15185]
41 **Meng J**, Wei Y, Deng Q, Li L, Li X. Study on the expression of TOP2A in hepatocellular carcinoma and its relationship with patient prognosis. *Cancer Cell Int* 2022; **22**: 29 [PMID: 35033076 DOI: 10.1186/s12935-021-02439-0]
42 **Wang Y**, Shi F, Xing GH, Xie P, Zhao N, Yin YF, Sun SY, He J, Wang Y, Xuan SY. Protein Regulator of Cytokinesis PRC1 Confers Chemoresistance and Predicts an Unfavorable Postoperative Survival of Hepatocellular Carcinoma Patients. *J Cancer* 2017; **8**: 801-808 [PMID: 28382142 DOI: 10.7150/jca.17640]
43 **Zhang H**, Yang X, Zhu L, Li Z, Zuo P, Wang P, Feng J, Mi Y, Zhang C, Xu Y, Jin G, Zhang J, Ye H. ASPM promotes hepatocellular carcinoma progression by activating Wnt/β-catenin signaling through antagonizing autophagy-mediated Dvl2 degradation. *FEBS Open Bio* 2021; **11**: 2784-2799 [PMID: 34428354 DOI: 10.1002/2211-5463.13278]
44 **Roy S**, Hooiveld GJ, Seehawer M, Caruso S, Heinzmann F, Schneider AT, Frank AK, Cardenas DV, Sonntag R, Luedde M, Trautwein C, Stein I, Pikarsky E, Loosen S, Tacke F, Ringelhan M, Avsaroglu SK, Goga A, Buendia MA, Vucur M, Heikenwalder M, Zucman-Rossi J, Zender L, Roderburg C, Luedde T. microRNA 193a-5p Regulates Levels of Nucleolar- and Spindle-Associated Protein 1 to Suppress Hepatocarcinogenesis. *Gastroenterology* 2018; **155**: 1951-1966.e26 [PMID: 30165047 DOI: 10.1053/j.gastro.2018.08.032]
45 **Wu C**, Qi X, Qiu Z, Deng G, Zhong L. Low expression of KIF20A suppresses cell proliferation, promotes chemosensitivity and is associated with better prognosis in HCC. *Aging (Albany NY)* 2021; **13**: 22148-22163 [PMID: 34491228 DOI: 10.18632/aging.203494]
46 **Hu WQ**, Wang W, Fang DL, Yin XF. Identification of Biological Targets of Therapeutic Intervention for Hepatocellular Carcinoma by Integrated Bioinformatical Analysis. *Med Sci Monit* 2018; **24**: 3450-3461 [PMID: 29795057 DOI: 10.12659/MSM.909290]
47 **Eferl R**, Ricci R, Kenner L, Zenz R, David JP, Rath M, Wagner EF. Liver tumor development. c-Jun antagonizes the proapoptotic activity of p53. *Cell* 2003; **112**: 181-192 [PMID: 12553907 DOI: 10.1016/s0092-8674(03)00042-4]
48 **Peng WX**, Wan YY, Gong AH, Ge L, Jin J, Xu M, Wu CY. Egr-1 regulates irradiation-induced autophagy through Atg4B to promote radioresistance in hepatocellular carcinoma cells. *Oncogenesis* 2017; **6**: e292 [PMID: 28134935 DOI: 10.1038/oncsis.2016.91]
49 **Xie F**, Yuan Y, Xie L, Ran P, Xiang X, Huang Q, Qi G, Guo X, Xiao C, Zheng S. miRNA-320a inhibits tumor proliferation and invasion by targeting c-Myc in human hepatocellular carcinoma. *Onco Targets Ther* 2017; **10**: 885-894 [PMID: 28243124 DOI: 10.2147/OTT.S122992]
50 **Khan MGM**, Boufaied N, Yeganeh M, Kandhi R, Petkiewicz S, Sharma A, Yoshimura A, Ferbeyre G, Labbé DP, Ramanathan S, Ilangumaran S. SOCS1 Deficiency Promotes Hepatocellular Carcinoma *via* SOCS3-Dependent CDKN1A Induction and NRF2 Activation. *Cancers (Basel)* 2023; **15** [PMID: 36765862 DOI: 10.3390/cancers15030905]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com