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WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, etc.

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Gene targets with therapeutic potential in hepatocellular carcinoma

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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

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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.

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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

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