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O-GlcNAcylation in Hepatocellular Carcinoma: Mechanisms and Implications

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Abstract: ***Hepatocellular carcinoma (HCC), a highly lethal primary liver malignancy, predominantly arises from chronic liver disease or cirrhosis. Most patients are diagnosed at advanced stage with limited therapeutic efficacy, which are closely related to its complex pathogenesis. O-GlcNAcylation is a dynamic post-translational modification (PTM) orchestrated by O-GlcNAc transferase (OGT) and O-GlcNAcase (OGA), regulates protein stability, transcriptional activity, and subcellular localization, thereby exacerbating tumor progression, immune evasion, and therapeutic resistance. Emerging evidence highlights the hyperactivation of O-GlcNAcylation in HCC, suggesting its potential as a diagnostic biomarker and therapeutic target. This review systematically summarizes the mechanisms underlying aberrant O-GlcNAcylation in HCC pathogenesis and explores its translational implications for precision oncology, providing a foundation for future research aimed at developing novel therapeutic strategies.***

Keywords: HCC, O-GlcNAcylation, OGT, OGA.

1. Introduction

HCC is the fourth most common malignant tumor in China and ranks sixth in incidence and fourth in mortality worldwide among cancers [1,2]. Its main risk factors include chronic hepatitis B (HBV) and hepatitis C (HCV), non-alcoholic fatty liver disease (NAFLD), alcohol addiction, and dietary toxins such as aflatoxin and aristolochic acid [3]. Currently, radical treatments for HCC include surgical resection, radiofrequency ablation, and liver transplantation. However, only a small proportion of patients are eligible for radical treatment, as most are diagnosed at advanced stages with poor therapeutic outcomes [4]. Additionally, patients undergoing radical treatment face a high rate of postoperative recurrence and metastasis, with a 3-year recurrence rate of approximately 50% and a 5-year recurrence rate of about 70%, which is the primary reason for the high mortality rate of HCC [5]. Therefore, in-depth research into the molecular mechanisms of HCC pathogenesis is crucial for overcoming current treatment challenges and improving prognosis.

O-GlcNAcylation is a dynamic and reversible PTM regulated by OGT and OGA. It is sensitive to cellular metabolic states and control of protein stability, transcriptional activity, and subcellular localization, playing a significant role in tumorigenesis, immune evasion, and therapy resistance [6]. Previous studies have shown that FOXA1 O-GlcNAcylation enhances its binding to chromatin, suppresses adhesion-related gene expression, and promotes breast cancer metastasis [7]. Keratin 18 (K18) is significantly upregulated in cholangiocarcinoma cells, and site-specific O -GlcNAcylation of K18 on Ser 30 stabilizes K18 promotes cholangiocarcinoma cell proliferation by regulating the expression of cell cycle checkpoint proteins [4]. O-GlcNAcylation of MITF on Ser 49 facilitates its nuclear translocation, thereby promoting resistance to CDK4/6 inhibitors in breast cancer cells through the regulation of senescence signaling [8].

In addition, O-GlcNAcylation has been shown to play an important role in the progression of HCC, although its specific mechanisms remain to be further elucidated. This review aims to systematically elucidate the molecular mechanisms by which O-GlcNAcylation promotes the development and progression of HCC, providing new theoretical insights and potential therapeutic targets for the prevention and treatment of HCC.

2. Basic Functions of O-GlcNAcylation

O-GlcNAcylation is a non-canonical PTM that attaches to serine or threonine residues of cytoplasmic, nuclear, and mitochondrial proteins. It integrates glucose, fatty acid, amino acid, and nucleotide metabolism to provide the material source for O-GlcNAcylation, utilizing uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) as a substrate through the hexosamine biosynthetic pathway (HBP). As it responds to cellular stimuli such as hypoxia and nutrient deprivation, it is referred to as a nutrient and stress sensor. O-GlcNAcylation regulates cellular processes including transcription, translation, signal transduction, protein interactions, and subcellular localization, maintaining normal cellular physiological functions [9]. Its regulation is characterized by rapid and dynamic reversibility, with OGT installs O-GlcNAc onto target proteins and OGA removes O-GlcNAc [10]. Additionally, O-GlcNAcylation of some substrate proteins can exhibit crosstalk with phosphorylation [11]

Recent studies have shown that dysregulation of O-GlcNAcylation is closely associated with the development of HCC, involving the activation of oncogenes, mechanisms of cell proliferation and apoptosis, inflammation-to-cancer transformation, remodeling of the tumor microenvironment, and tumor metabolic reprogramming. Therefore, a deeper understanding of the specific mechanisms by which O-GlcNAcylation contributes to the development and progression of HCC is of significant importance for identifying new therapeutic targets for HCC treatment.

3. O-GlcNAcylation in the Activation of HCC

3.1 O-GlcNAcylation in the Oncogene Activation of HCC

Cancer development is typically the result of multi-step

genetic mutations. These mutations may lead to uncontrolled cell growth, abnormal expression or dysregulation of enzyme activity in cell differentiation pathways, or suppression of negative cell cycle regulators, thereby promoting tumor formation. The development of HCC is associated with the activation of oncogenes or inactivation of tumor suppressor genes triggered by various endogenous or exogenous stimuli.

Receptor for Activated C Kinase 1 (RACK1) is a classical scaffold protein for multiple kinases and receptors, widely involved in biological responses, and exists in both ribosomal and non-ribosomal binding forms [12, 13]. O-GlcNAcylation of RACK1 at the S122 site on ribosomes enhances the stability of ribosomal proteins and promotes the phosphorylation of eukaryotic initiation factor 4E (eIF4E), thereby driving the translation of oncogenes and the development of HCC [13]. Additionally, 5-fluorouracil upregulates the O-GlcNAcylation level of RACK1 in HCC, while mTOR inhibitors downregulate O-GlcNAcylation level [14]. Therefore, targeting the O-GlcNAcylation of RACK1 may suppress the activation of oncogenes and reverse HCC progression, offering a potential strategy for HCC treatment.

3.2 O-GlcNAcylation in Inflammation-to-Cancer Transformation of HCC

The inflammation-to-cancer transformation is a critical mechanism promoting the development and progression of HCC. Chronic hepatitis B and Chronic hepatitis C contribute to HCC occurrence through the "hepatitis-cirrhosis-liver cancer" pathway. Studies have shown that O-GlcNAcylation plays a significant role in the progression of HCC induced by chronic HBV and HCV infections. However, the molecular mechanisms underlying their carcinogenic effects differ

Studies have shown that individuals infected with HBV have a 200-fold higher risk of developing HCC compared to uninfected individuals [15]. HBV infection upregulates the expression of glucose transporter 1 (GLUT1), promoting glucose uptake, and increases the protein stability of SAM domain and HD domain-containing protein 1 (SAMHD1) through O-GlcNAcylation, enhancing its anti-HBV activity [15]. However, this protective mechanism is not long-lasting. Persistent overexpression of the HBV X protein (HBx) upregulates YAP in HCC and further promotes HCC development by activating the YAP promoter [16]. Additionally, after HBV infection, O-GlcNAcylation of YTHDF2 significantly increases, inhibiting its ubiquitination-mediated degradation and enhancing its protein stability and oncogenic activity. Targeting YTHDF2 can significantly suppress tumor growth and progression by downregulating MCM2 and MCM5 [17].

HCV is another significant risk factor for HCC, with a 5-year tumor incidence rate of 7% and a 10-year incidence rate of 14%. The prognosis of HCV infection is closely related to tumor stage and liver function, affecting tolerance to invasive treatments [18]. HCV RNA-encoded proteins can modulate signaling pathways such as Wnt, Ras/MAPK, p53, JAK-STAT, and PI3K-AKT, thereby regulating cell cycle, proliferation, and apoptosis, and influencing the development and progression of HCC [19]. Recent studies have found that certain microRNAs, such as miR-501-3p and miR-619-3p, upregulate O-GlcNAcylation -related proteins by regulating OGT expression, altering HCV morphology and infectivity, inducing hepatocyte degeneration and necrosis, and driving the progression of liver fibrosis to HCC [20]. However, current research on the role of O-GlcNAcylation in HCC development through the regulation of HCV infection is limited, and its specific mechanisms require further exploration.

In addition, O-GlcNAcylation plays a significant role in the development of NASH-HCC, with its key mechanism closely linked to metabolic disorders that activate endoplasmic reticulum (ER) stress and induce inflammatory signaling pathways. Overexpression of OGT in the liver increases intracellular palmitic acid levels, activates ER stress, and subsequently promotes HCC development by activating oncogenic signaling cascades such as JNK/c-Jun/AP1 and NF-κB [21]. Furthermore, OGT enhances ER stress through the dual activation of JNK/c-Jun/AP1 and NF-κB signaling cascades, leading to sustained lipotoxicity and HCC progression [22]. Additionally, O-GlcNAcylation suppresses the expression and stability of RIPK3 protein [23], weakening its inhibitory effects on Caspase-8 cleavage and JNK activation, thereby removing restrictions on cell proliferation and promoting HCC development [24].

In summary, O-GlcNAcylation plays a multifaceted and critical role in driving the development of Chronic hepatitis B , Chronic hepatitis C and NASH, ultimately promoting the formation of HCC. This further underscores that O-GlcNAcylation serves as a crucial bridge connecting chronic liver diseases to the onset of HCC.

3.3 O-GlcNAcylation in the Proliferation and Growth of HCC

The proliferation of HCC cells and tumor growth are regulated by multiple molecular pathways, including the epidermal growth factor receptor (EGFR) pathway associated with cell proliferation, the SIX1 pathway related to metabolic reprogramming, the Hippo pathway, the mTOR pathway, and the nuclear transcription factor activator protein-1 (AP-1). These pathways are all modulated by O-GlcNAcylation.

The epidermal growth factor receptor (EGFR) maintains cell growth, proliferation, and survival [25]. O-GlcNAcylation enhances EGFR signaling by promoting the ubiquitination and degradation of hepatocyte growth factor-regulated tyrosine kinase substrate (HGS), thereby facilitating the development and progression of HCC [26]. SIX1, a key transcription factor in the Warburg effect of cancer, mediates metabolic reprogramming in tumor cells by increasing O-GlcNAcylation levels and inhibiting its ubiquitination -dependent degradation, promoting HCC progression [27]. Additionally, a positive feedback regulatory relationship exists between SIX1 and O-GlcNAcylation in HCC [28]. The Hippo pathway negatively regulates tumor growth, and YAP, a downstream oncogenic transcriptional regulator of this pathway, undergoes O-GlcNAcylation at Thr241 under high glucose conditions, which enhances its stability by inhibiting phosphorylation and ubiquitin-mediated degradation, thereby promoting HCC development [29]. Beyond its role in lipid accumulation, fatty acid synthase (FASN) also activates

mitogenic PI3K/AKT signaling and G protein-coupled receptors [30]. The mTOR pathway, a central regulator responsive to growth factors and hormones, is frequently hyperactivated in cancer [31]. The interaction between OGT and FASN plays a dominant role in cell proliferation, with their regulatory mechanisms linked to the strength of their interaction, which intensifies during the G1 phase, weakens in the S phase, and re-intensifies in the G2 phase. Moreover, increased OGT activity promotes mTOR pathway activation, further enhancing FASN expression. Concurrently, FASN accumulation and reduced OGA activity drive mTOR activation, creating a positive feedback loop that increases FASN protein levels, closely associated with HCC cell adhesion, migration, and proliferation [32].

However, high levels of O-GlcNAcylation can induce ferroptosis, which may represent a promising strategy for HCC treatment. Ferroptosis, a tumor suppression mechanism, can be triggered by glutathione peroxidase 4 inhibitors such as RSL3. In HCC, O-GlcNAcylation significantly enhances the sensitivity of HCC cells to RSL3-induced ferroptosis. This mechanism is associated with O-GlcNAcylation promoting the binding of YAP to the promoter region of the transferrin receptor (TFRC), upregulating TFRC mRNA expression, and thereby increasing iron uptake and ferroptosis sensitivity in HCC cells [33].

In summary, O-GlcNAcylation plays a dual role in HCC, acting both as a pro-tumor factor and a potential therapeutic target. Therefore, in-depth research into its specific mechanisms across different pathways will provide new insights and strategies for the precision treatment of HCC.

4. O-GlcNAcylation in the Metastasis and Invasion of HCC

HCC metastasis is a major cause of patient mortality and involves multiple signaling pathways. Therefore, elucidating the key molecular mechanisms underlying HCC metastasis is crucial for developing new therapies, improving patient outcomes, and advancing cancer research.

Forkhead Box Protein A2(FOXA2) is a transcriptional repressor in the epithelial-to-mesenchymal transition (EMT) process and can inhibit HCC metastasis [34]. However, O-GlcNAcylation of FOXA2 promotes its ubiquitination and degradation, downregulating FOXA2 levels and further suppressing E-cadherin gene transcription, thereby facilitating HCC metastasis [35]. Additionally, FOXA2 is a direct transcriptional activator of GFPT1, the rate-limiting enzyme of the HBP, and upregulates GFPT1 to increase intracellular O-GlcNAcylation levels. Moreover, FOXA2 inhibits apoptosis by promoting O-GlcNAcylation of NF-κB and STAT3, two apoptosis-related proteins [36]. Metabolic reprogramming is a hallmark of cancer. Tumor cells enhance aerobic glycolysis to promote HCC invasion and metastasis [37], while gluconeogenesis exerts tumor-suppressive effects in HCC by antagonizing glycolysis [38]. In HCC, the downregulation of phosphoenolpyruvate carboxykinase 1 (PCK1), a key gluconeogenic enzyme, promotes tumorigenesis by increasing O-GlcNAcylation levels. PCK1 knockdown enhances O-GlcNAcylation of CHK2 at Thr378, promoting CHK2-dependent Rb phosphorylation and HCC cell proliferation [39]. Furthermore, PCK1 depletion increases O-GlcNAcylation, inhibits KAT5 ubiquitination, activates TWIST1 expression, and enhances MMP9 and MMP14 expression through c-Myc acetylation, thereby promoting EMT and lung metastasis in HCC [40].

In summary, O-GlcNAcylation of FOXA2, CHK2, and KAT5 plays a crucial role in the metastasis and metabolic regulation of HCC, revealing the complex mechanisms underlying tumor progression and offering potential therapeutic targets for HCC treatment.

5. Conclusion

This review summarizes recent advances in the molecular mechanisms of O-GlcNAcylation in the development and progression of HCC. O-GlcNAcylation promotes the occurrence and progression of HCC by participating in the activation of oncogenes, inflammation-to-cancer transformation, multiple oncogenic pathways, metabolic dysregulation, and metastasis-related signaling pathways. However, targeting the activation of O-GlcNAcylation at T241 of YAP to induce ferroptosis may represent a promising strategy for HCC treatment. This highlights the diversity, breadth, and multidimensionality of O-GlcNAcylation regulation. O-GlcNAcylation plays a critical role at different stages of HCC development and progression. However, these stages are not independent; they interact with each other, collectively forming a complex regulatory network that governs the initiation and progression of HCC.

Currently, it is believed that the development of HCC primarily results from genetic susceptibility combined with various external and internal stimuli, which activate multiple oncogenic signaling pathways, such as inflammation, metabolism, and immunity, to promote HCC progression. Recent studies have shown that metabolic reprogramming plays a critical role in HCC, as tumor cells alter metabolic pathways and patterns to obtain energy and biosynthetic materials, supporting their rapid proliferation, invasion, and metastasis [41]. Additionally, circadian rhythm disruption, cell cycle imbalance, gut microbiota dysbiosis, and hormonal disturbances have also been demonstrated to contribute to the development and progression of HCC [42-44].

In recent years, immune checkpoint inhibitor (ICI) therapies have significantly improved the prognosis of patients with advanced HCC [45]. Among these, neoadjuvant chemotherapy regimens have increased surgical resection rates, reduced recurrence rates, and thereby enhanced long-term survival rates for patients [46] However, although approximately 30% of patients achieve a median overall survival of over 60 months after early curative treatments such as resection, liver transplantation, or local ablation, up to 70% of patients experience disease recurrence within 5 years post-surgery. Given the extensive involvement and critical role of O-GlcNAcylation in the development and progression of HCC, targeting key proteins involved in O-GlcNAcylation or combining such strategies with existing HCC treatments may provide new insights and clinical value in addressing current therapeutic challenges in HCC.

References

[1] Sia D, Villanueva A, Friedman S L, et al. Liver Cancer Cell of Origin, Molecular Class, and Effects on Patient Prognosis[J]. Gastroenterology, 2017, 152(4):745-761.
[2] Rumgay H, Arnold M, Ferlay J, et al. Global burden of primary liver cancer in 2020 and predictions to 2040[J]. J Hepatol, 2022, 77(6):1598-1606.
[3] Yang J D, Hainaut P, Gores G J, et al. A global view of hepatocellular carcinoma: trends, risk, prevention and management[J]. Nat Rev Gastroenterol Hepatol, 2019, 16(10):589-604.
[4] Lin Z F, Qin L X, Chen J H. Biomarkers for response to immunotherapy in hepatobiliary malignancies[J]. Hepatobiliary Pancreat Dis Int, 2022, 21(5):413-419.
[5] Bruix J, Takayama T, Mazzaferro V, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial[J]. Lancet Oncol, 2015, 16(13):1344-1354.
[6] Yang X, Qian K. Protein O-GlcNAcylation: emerging mechanisms and functions[J]. Nat Rev Mol Cell Biol, 2017, 18(7):452-465.
[7] Liu Y, Yu K, Kong X, et al. FOXA1 O-GlcNAcylation-mediated transcriptional switch governs metastasis capacity in breast cancer[J]. Sci Adv, 2023, 9(33): eadg7112.
[8] Zhang Y, Zhou S, Kai Y, et al. O-GlcNAcylation of MITF regulates its activity and CDK4/6 inhibitor resistance in breast cancer[J]. Nat Commun, 2024, 15(1):5597.
[9] Chatham J C, Zhang J, Wende A R. Role of O-Linked N-Acetylglucosamine Protein Modification in Cellular (Patho)Physiology[J]. Physiol Rev, 2021, 101(2): 427-493.
[10] Bond M R, Hanover J A. A little sugar goes a long way: the cell biology of O-GlcNAc[J]. J Cell Biol, 2015, 208(7):869-880.
[11] Hart G W, Slawson C, Ramirez-Correa G, et al. Cross talk between O-GlcNAcylation and phosphorylation: roles in signaling, transcription, and chronic disease[J]. Annu Rev Biochem, 2011, 80:825-858.
[12] McCahill A, Warwicker J, Bolger G B, et al. The RACK1 scaffold protein: a dynamic cog in cell response mechanisms[J]. Mol Pharmacol, 2002, 62(6): 1261-1273.
[13] Adams D R, Ron D, Kiely P A. RACK1, A multifaceted scaffolding protein: Structure and function[J]. Cell Commun Signal, 2011, 9:22.
[14] Duan F, Wu H, Jia D, et al. O-GlcNAcylation of RACK1 promotes hepatocellular carcinogenesis[J]. J Hepatol, 2018, 68(6):1191-1202.
[15] Delis S G, Bakoyiannis A, Tassopoulos N, et al. Hepatic resection for large hepatocellular carcinoma in the era of UCSF criteria[J]. HPB (Oxford), 2009, 11(7):551-558.
[16] Zhang T, Zhang J, You X, et al. Hepatitis B virus X protein modulates oncogene Yes-associated protein by CREB to promote growth of hepatoma cells[J]. Hepatology, 2012, 56(6):2051-2059.
[17] Yang Y, Yan Y, Yin J, et al. O-GlcNAcylation of YTHDF2 promotes HBV-related hepatocellular carcinoma progression in an N(6) - methyladenosine - dependent manner[J]. Signal Transduct Target Ther, 2023, 8(1):63.
[18] Di Bisceglie A M, Carithers R J, Gores G J. Hepatocellular carcinoma [J]. Hepatology, 1998, 28(4): 1161-1165.
[19] Zhao P, Malik S, Xing S. Epigenetic Mechanisms Involved in HCV-Induced Hepatocellular Carcinoma (HCC)[J]. Front Oncol, 2021, 11:677926.
[20] Herzog K, Bandiera S, Pernot S, et al. Functional microRNA screen uncovers O-linked N-acetylglucosamine transferase as a host factor modulating hepatitis C virus morphogenesis and infectivity[J]. Gut, 2020, 69(2):380-392.
[21] Santos-Laso A, Perugorria M J, Banales J M. O-GlcNAcylation: Undesired tripmate but an opportunity for treatment in NAFLD-HCC[J]. J Hepatol, 2017, 67(2):218-220.
[22] Zhou Y, Li Z, Xu M, et al. O-GlycNacylation Remission Retards the Progression of Non-Alcoholic Fatty Liver Disease[J]. Cells, 2022, 11(22).
[23] Xu W, Zhang X, Wu J L, et al. O-GlcNAc transferase promotes fatty liver-associated liver cancer through inducing palmitic acid and activating endoplasmic reticulum stress[J]. J Hepatol, 2017, 67(2):310-320.
[24] Zhang B, Li M D, Yin R, et al. O-GlcNAc transferase suppresses necroptosis and liver fibrosis[J]. JCI Insight, 2019, 4(21).
[25] Lemmon M A, Schlessinger J. Cell signaling by receptor tyrosine kinases[J]. Cell, 2010, 141(7):1117-1134.
[26] Wu L, Cheng Y, Geng D, et al. O-GlcNAcylation regulates epidermal growth factor receptor intracellular trafficking and signaling[J]. Proc Natl Acad Sci U S A, 2022, 119(10): e2107453119.
[27] Chu Y, Jiang M, Wu N, et al. O-GlcNAcylation of SIX1 enhances its stability and promotes Hepatocellular Carcinoma Proliferation[J]. Theranostics, 2020, 10(21): 9830-9842.
[28] Singh J P, Zhang K, Wu J, et al. O-GlcNAc signaling in cancer metabolism and epigenetics[J]. Cancer Lett, 2015, 356(2 Pt A):244-250.
[29] Zhang X, Qiao Y, Wu Q, et al. The essential role of YAP O-GlcNAcylation in high-glucose-stimulated liver tumorigenesis[J]. Nat Commun, 2017, 8:15280.
[30] Liu Y, An S, Ward R, et al. G protein-coupled receptors as promising cancer targets[J]. Cancer Lett, 2016, 376(2):226-239.
[31] Kamei Y, Hatazawa Y, Uchitomi R, et al. Regulation of Skeletal Muscle Function by Amino Acids[J]. Nutrients, 2020, 12(1).
[32] Raab S, Gadault A, Very N, et al. Dual regulation of fatty acid synthase (FASN) expression by O-GlcNAc transferase (OGT) and mTOR pathway in proliferating liver cancer cells[J]. Cell Mol Life Sci, 2021, 78(13):5397-5413.
[33] Zhu G, Murshed A, Li H, et al. O-GlcNAcylation enhances sensitivity to RSL3-induced ferroptosis via the YAP/TFRC pathway in liver cancer[J]. Cell Death Discov, 2021, 7(1):83.
[34] Gong Z, Yu J, Yang S, et al. FOX transcription factor family in hepatocellular carcinoma[J]. Biochim Biophys Acta Rev Cancer, 2020, 1874(1):188376.
[35] Huang H, Wu Q, Guo X, et al. O-GlcNAcylation promotes the migratory ability of hepatocellular carcinoma cells via regulating FOXA2 stability and

transcriptional activity[J]. J Cell Physiol, 2021, 236(11): 7491-7503.
[36] Huang H, Wang Y, Huang T, et al. FOXA2 inhibits doxorubicin-induced apoptosis via transcriptionally activating HBP rate-limiting enzyme GFPT1 in HCC cells[J]. J Physiol Biochem, 2021, 77(4):625-638.
[37] Gatenby R A, Gillies R J. Why do cancers have high aerobic glycolysis? [J]. Nat Rev Cancer, 2004, 4(11): 891-899.
[38] Hirata H, Sugimachi K, Komatsu H, et al. Decreased Expression of Fructose-1, 6-bisphosphatase Associates with Glucose Metabolism and Tumor Progression in Hepatocellular Carcinoma[J]. Cancer Res, 2016, 76(11): 3265-3276.
[39] Xiang J, Chen C, Liu R, et al. Gluconeogenic enzyme PCK1 deficiency promotes CHK2 O-GlcNAcylation and hepatocellular carcinoma growth upon glucose deprivation[J]. J Clin Invest, 2021, 131(8).
[40] Liu R, Gou D, Xiang J, et al. O-GlcNAc modified-TIP60/KAT5 is required for PCK1 deficiency-induced HCC metastasis[J]. Oncogene, 2021, 40(50):6707-6719.
[41] Foglia B, Beltra M, Sutti S, et al. Metabolic Reprogramming of HCC: A New Microenvironment for Immune Responses[J]. Int J Mol Sci, 2023, 24(8).
[42] Qu M, Zhang G, Qu H, et al. Circadian regulator BMAL1: CLOCK promotes cell proliferation in hepatocellular carcinoma by controlling apoptosis and cell cycle[J]. Proc Natl Acad Sci U S A, 2023, 120(2): e2080138176.
[43] Cai X, Yu X, Yang J, et al. TRPM2 regulates cell cycle through the Ca2+-CaM-CaMKII signaling pathway to promote HCC[J]. Hepatol Commun, 2023, 7(5).
[44] He W, Wang M, Zhang X, et al. Estrogen Induces LCAT to Maintain Cholesterol Homeostasis and Suppress Hepatocellular Carcinoma Development[J]. Cancer Res, 2024, 84(15):2417-2431.
[45] Llovet J M, Pinyol R, Yarchoan M, et al. Adjuvant and neoadjuvant immunotherapies in hepatocellular carcinoma[J]. Nat Rev Clin Oncol, 2024, 21(4):294-311.
[46] Schwartz J D, Schwartz M, Mandeli J, et al. Neoadjuvant and adjuvant therapy for resectable hepatocellular carcinoma: review of the randomised clinical trials[J]. Lancet Oncol, 2002, 3(10):593-603.