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Advances in the Role and Mechanism of the 14-3-3 Protein Family in Hepatocellular Carcinoma

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Abstract: ***The 14-3-3 protein family contains multiple isoforms that are expressed in different tissues and play key roles in cellular physiological functions through binding to related molecules. This article discusses in detail the role of 14-3-3 proteins in the progression of hepatocellular carcinoma, highlights their regulatory role in cell proliferation, migration, invasion, apoptosis, and autophagy, and emphasizes the potential of using 14-3-3 proteins as therapeutic targets in hepatocellular carcinoma. The article provides a comprehensive review of the role of the 14-3-3 protein family in hepatocellular carcinoma and its mechanisms.***

Keywords: 14-3-3 protein, Liver cancer, Isoforms, Research progress**.**

1. Introduction

Hepatocellular carcinoma is a malignant tumor that occurs in the liver and originates in the epithelial or mesenchymal tissues of the liver. In recent years, global incidence and mortality rates have continued to rise, making it the sixth most common cancer worldwide and the third most common cause of cancer deaths [1]. Since the pathogenesis of hepatocellular carcinoma has not been fully clarified, in-depth study of the molecular mechanisms of hepatocellular carcinoma and active search for reliable biomarkers are of crucial importance to improve the accuracy of clinical diagnosis and the effectiveness of treatment.14-3-3 protein family is a class of highly conserved proteins widely expressed in eukaryotes, with a total of seven isoforms, β, γ, ζ, η, θ, σ, and ε. 14-3-3 protein family plays a key role in cell biology, especially in phosphorylation-dependent protein interactions. These interactions are critical for several key biological processes, including control of cell cycle progression, activation and maintenance of DNA damage checkpoints, activation of MAP kinases, prevention of apoptosis, and coordination of integrin signaling and cytoskeletal dynamics [2]. The aim of this paper is to summarize the role of 14-3-3 protein family in hepatocellular carcinoma and to summarize the progress of research on the relevance of 14-3-3 protein family in hepatocellular carcinoma. The 14-3-3 protein family is involved in a wide range of biological activities by interacting with a variety of intracellular target proteins. Many of these target proteins regulate tumor cell genesis and progression. It has been shown that the 14-3-3 family of proteins is closely related to the development of various cancers.

2. 14-3-3 Protein Family Overview

2.1 Structural and Biological Characteristics

14-3-3 proteins are a family of proteins with multiple isoforms, whose structure consists of nine anti-parallel α-helical monomers, which exist as homo- or heterodimers, forming a horseshoe-like structure. Different isoforms are expressed in different tissues and are involved in the regulation of cellular physiological functions through binding to related molecules. The mechanism of action of 14-3-3 proteins is to influence a variety of physiological and pathological processes including tumorigenesis and development by altering the target protein's localization, stability, phosphorylation status, activity, and intermolecular interactions, and in cellular signaling, 14-3-3 proteins are involved in the regulation of the cell cycle, apoptosis, cell differentiation and other key processes [3].

2.2 Relationship with Tumors

The 14-3-3 protein family plays an important role in tumorigenesis and progression. 14-3-3σ protein levels are usually down-regulated in chronic granulocytic leukemia, nasopharyngeal carcinoma, as well as lung, breast, esophageal, uterine, ovarian, and skin cancers. In addition, CpG methylation of the 14-3-3σ promoter was observed in different types of tumors such as breast, lung, liver and pancreatic cancers, resulting in low expression of 14-3-3σ in these tumors [4]; However, in breast, gastric, and pancreatic cancers, 14-3-3σ showed high expression, and studies have suggested that this high expression is an independent risk factor for poor patient survival [5]. At the other hand, elevated expression of 14-3-3ζ in gliomas, ovarian cancers, and NK/T-cell lymphomas was significantly associated with tumorigenesis, progression, and poor prognosis [6]. Overexpression of 14-3-3ζ was significantly associated with more advanced pathologic stages, grades, and poorer clinical outcomes in patients with ovarian cancer, and it may play an important role in ovarian cancer progression [7].

In summary, the 14-3-3 protein family plays a complex and multifaceted role in tumorigenesis and development. They show different expression patterns in different types of tumors, thereby affecting tumor behavior and patient prognosis. For example, low expression of 14-3-3σ is associated with worse clinical outcomes in many cancers, whereas high expression of 14-3-3ζ is strongly associated with worse tumor prognosis. These findings suggest that members of the 14-3-3 protein family may be potential targets for future cancer therapy and prognostic assessment. As we gain a better understanding of the role of these proteins in tumors, their potential for application in cancer diagnosis, treatment and prognostic assessment will become increasingly apparent.

3. Role of the 14-3-3 Protein Family in the Development of Hepatocellular Carcinoma

3.1 The 14-3-3 Protein Family Regulates Hepatocellular Carcinoma Cell Proliferation

Hepatocellular carcinoma cells are characterized by rapid proliferation and intense aggressiveness, which makes hepatocellular carcinoma a highly lethal cancer.14-3-3 protein family plays an important regulatory role in the proliferation of hepatocellular carcinoma cells. By activating multiple signaling pathways, including Raf-1 kinase, mitogen-activated protein kinase, and extracellular regulated kinases, the 14-3-3 protein family can directly promote the proliferation of hepatocellular carcinoma cells.

3.1.1 14-3-3σ

Nitidine chloride (NC) regulates G2/M phase by modulating the p53/14-3-3σ/CDK1 signaling pathway, in which 14-3-3σ has been identified as a molecule critical in this signaling pathway and involved in the regulation of hepatocellular carcinoma cell proliferation by NC [8].

3.1.2 14-3-3ζ

A study by Ma et al [9] found that hanobufotalin inhibited the proliferation of hepatocellular carcinoma cells by regulating the miR-27b-5p/14-3-3ζ signaling pathway. In addition, 14-3-3ζ enhanced tumor cell invasion and proliferation by inducing Epithelial-Mesenchymal Transition (EMT) and activating the ERK signaling pathway [10]. A study indicated that 14-3-3ζ stabilizes heme oxygenase-1 (HO-1) and prevents its degradation via ubiquitin-mediated degradation, thereby promoting cell proliferation. In addition, 14-3-3ζ binds to HO-1, regulates its stability, and promotes cancer cell proliferation through activation of STAT3 signaling, revealing an important role of the 14-3-3ζ/HO-1/STAT3 axis in hepatocellular carcinoma cell proliferation [11].

Wei et al [12] showed that 14-3-3ζ is a target of miR-451a to inhibit the progression of hepatocellular carcinoma. miR-451a achieves its inhibitory effect on the proliferation, metastasis and epithelial-mesenchymal transition of hepatocellular carcinoma cells by targeting and regulating the expression of 14-3-3ζ. In tumor therapy, RNA interference to reduce the expression of 14-3-3ζ can activate the JNK and p38/MAPK signaling pathways, thereby inhibiting the proliferation of tumor cells and enhancing the anticancer effect of the chemotherapeutic drug cisplatin on hepatocellular carcinoma cell lines [13].

3.1.3 14-3-3ε

14-3-3ε is overexpressed in hepatocellular carcinoma, and 14-3-3ε is involved in the proliferation of hepatocellular carcinoma cells by regulating AKR1B10 expression through activation of β-catenin signaling [14].

3.1.4 14-3-3η

It was found that overexpression of 14-3-3η in hepatocellular carcinoma tissues was present not only in tumor cells but also in blood vessels within the tumor. By activating the ERK1/2 signaling pathway, it enhanced the proliferation and angiogenesis of hepatocellular carcinoma cells while reducing the inhibitory effect of sorafenib on tumor cells. 14-3-3η formed a functional positive feedback loop with phosphorylated ERK1/2 to promote hepatocellular carcinoma growth. These findings suggest that 14-3-3η may be a potential target for hepatocellular carcinoma treatment and a biomarker for predicting response to sorafenib therapy [15].

3.2 The 14-3-3 Protein Family Regulates Hepatocellular Carcinoma Cell Migration and Metastasis

3.2.1 14-3-3 σ

The expression level of 14-3-3σ was significantly increased in hepatocellular carcinoma cells, especially in suspension cells. Song J et al [16] found that 14-3-3σ enhanced the non-adhesion resistance and metastatic ability of hepatocellular carcinoma (HCC) cancer cells, possibly by inhibiting the degradation of epidermal growth factor receptor and modulating the The ERK1/2 signaling pathway, which is dependent on the epidermal growth factor receptor, exerts important effects on drug resistance and metastatic ability of hepatocellular carcinoma cells. In addition, 14-3-3σ promoted hepatocellular carcinoma cell migration and tumor development by regulating the β-catenin/HSF-1α/HSP70 pathway [17]. At the same time, 14-3-3σ may act synergistically with other signaling molecules in its microenvironment to regulate the development of hepatocellular carcinoma in conjunction with tumor-associated stromal cells. In addition, hypermethylation of the 14-3-3σ gene and the resulting deletion of its expression play a crucial role in the development and progression of hepatocellular carcinoma [18]. 14-3-3σ plays a key role in HCC progression by interacting with the epidermal growth factor receptor, inhibiting its degradation and activating the EGFR-dependent ERK1/2 signaling pathway [16].

3.2.2 14-3-3β

In hepatocellular carcinoma patients, 14-3-3β protein expression was strongly associated with extrahepatic tumor metastasis, overall survival, and quality of survival. Specifically, 14-3-3β enhanced the expression of Matrix metalloproteinase2 (MMP2) and Matrix metalloproteinase9 (MMP9) through activation of the PI3K/Akt/NF-κB signaling pathway, which promoted hepatocellular carcinoma cells' migration and invasion ability of liver cancer cells [19]. This overexpression phenomenon is considered to be a prognostic factor for poor prognosis of hepatocellular carcinoma patients. In addition, the co-expression of 14-3-3β with phosphorylated Akt provided a more precise predictor of the prognosis of hepatocellular carcinoma patients [20]. In terms of clinical applications, high levels of serum 14-3-3β have been proposed as a potential biomarker for early HCC diagnosis because of its significant association with metastasis and poor prognosis of hepatocellular carcinoma [21]. These findings not only reveal the important role of 14-3-3β in the progression of hepatocellular carcinoma, but also provide new directions for early diagnosis and treatment of hepatocellular carcinoma.

3.2.3 14-3-3γ

14-3-3γ plays a key role in the metastatic process of hepatocellular carcinoma. It affects the apoptotic process through its interaction with Bad protein. Specifically, decreased expression of 14-3-3γ leads to the translocation of Bad protein to mitochondria and promotes mitochondrial membrane instability, thereby activating the apoptotic pathway. In addition, 14-3-3γ is involved in regulating the growth and migration of hepatocellular carcinoma cells [22]. In hepatocellular carcinoma tissues, overexpression of 14-3-3γ was significantly associated with extrahepatic metastasis. 14-3-3γ overexpressing HCC patients had a higher probability of extrahepatic metastasis within five years, and this overexpression was associated with worse overall and progression-free survival of the patients [23].

3.2.4 14-3-3ζ

14-3-3ζ protein is significantly upregulated in the microenvironment of hepatocellular carcinoma, suppresses the anti-tumor function of infiltrating T cells, and may be delivered from HCC cells to T cells via exosomes to further influence tumor progression [24]. At the cell signaling level, 14-3-3ζ induces autophagy in HCC cells by binding and stabilizing phospho-beclin 1S295, thereby enhancing resistance to chemotherapy [25]. In addition, it promotes malignant transformation of cells by activating multiple signaling pathways (e.g., NF-κB, PI3K/AKT, JAK-STAT, etc.), which enhances the proliferation, invasion, and angiogenesis of cancer cells. In the specific setting of hepatocellular carcinoma, 14-3-3ζ interacts with HIF-1α and plays a key role in portal vein tumor thrombosis and hepatocellular carcinoma metastasis [26]. miR-22 reduces cell migration and invasion by targeting 14-3-3ζ [27].

3.3 Role of the 14-3-3 Protein Family in Apoptosis and Autophagy in Hepatocellular Carcinoma

14-3-3 proteins regulate the survival and death of hepatocellular carcinoma cells through various cell signaling pathways, such as the AKT/14-3-3 and c-Myc/p53 pathways. These proteins affect the apoptosis and autophagy process of hepatocellular carcinoma cells by interacting with cell cycle-related proteins and apoptosis regulators [28-29]. Tumor suppressor effect of miR-613 on hepatocellular carcinoma by targeting and regulating the expression of 14-3-3ζ [30]. YAP and 14-3-3γ are involved in the effect of hydrogen sulfide-releasing oleanolic acid (HS-OA) on hepatocellular carcinoma cells, and HS-OA induced significant apoptosis in HepG2 hepatocellular carcinoma cells [22]. 14-3-3θ regulates apoptosis in hepatocellular carcinoma cells through interaction with RAI16 protein. RAI16 exerts its anti-apoptotic effects through PKA-mediated phosphorylation of HSP70, whereas 14-3-3θ can inhibit its mediated phosphorylation of HSP70 by binding to phosphorylated RAI16, which in turn affects the apoptotic process of hepatocellular carcinoma cells [15].

3.4 14-3-3 Protein Family Promotes EMT in Hepatocellular Carcinoma Cells

In hepatocellular carcinoma, overexpression of 14-3-3ε promotes cell migration and facilitates EMT by decreasing the expression of E-calmodulin and inducing the expression of N-calmodulin and waviness proteins [31]. miR-660-5p/14-3-3η axis activates the PI3K/AKT pathway and promotes EMT and the cell cycle process [32]. In addition, 14-3-3ε selectively induces the expression of Zeb-1 and Snail. overexpression of 14-3-3ε in HCC cells induces migration and promotes EMT [31].

4. Mechanism of Action of the 14-3-3 Protein Family in Hepatocellular Carcinoma

4.1 Regulation of the PI3K/AKT Signaling Pathway

The phosphatidylinositol-3 kinase/protein kinase (PI3K-AKT) pathway is an important intracellular signaling pathway that is critical for the response of extracellular signals to promote biological processes such as metabolism, proliferation, cell survival, growth, and angiogenesis, and is closely related to a variety of disease processes such as neoplasia and inflammation. Xie et al [33] found that the ITGB1/PXN/14-3-3ζ/AKT axis accelerated the growth progression of HCC tumors by accelerating cell proliferation. wu et al [32] found that miR-660-5p was significantly upregulated in HCC tissues and cell lines, and an in-depth study of its targets revealed that miR-660-5p affected the progression of HCC cells through its interaction with the 14-3-3η-PI3K/ AKT axis interaction affects HCC cell progression. 14-3-3ζ promotes hepatocellular carcinoma progression by acting on HIF-1α through direct binding to HIF-1α and through the PI3K/Akt/NF-κB signaling pathway and upregulating its expression in HCC [34]. Tang et al [19] found that 14-3-3β overexpression in HCC cells activates PI3K/Akt/NF-κB signaling pathway, which in turn enhanced the expression of MMP2 and MMP9, thereby enhancing the migration and invasion of hepatocellular carcinoma cells.

4.2 Regulation of the JAK-STAT Signaling Pathway

The JAK-STAT signaling pathway is an important cell signaling pathway. This signaling pathway plays a key regulatory role in mammalian cells and is mainly involved in cellular value-addition, differentiation, apoptosis, and immune regulation.14-3-3ζ promoted the proliferation of HCC by inhibiting the degradation of Heme Oxygenase-1 (HO-1). Specifically, 14-3-3ζ interacted with HO-1 and inhibited the degradation process of HO-1, which led to an increase in the stability of HO-1, and the increase in HO-1 promoted the proliferative capacity of HCC cells [11].

4.3 Regulation of the MAPK/ERK Signaling Pathway

The MAPK/ERK signaling pathway is one of the important pathways in eukaryotic cells involved in cell proliferation, differentiation, apoptosis, adhesion, migration, and inflammatory and stress responses. 14-3-3ζ is involved in the regulation of MAPK by affecting the expression of KSR2, which may specifically interact with 14-3-3ζ to promote HCC cell growth [35]. The RDIVpSGP structural domain of the ASPP2 protein binds to 14-3-3ζ to form the ASPP2/k18/14-3-3ζ complex. This complex helps to promote the inhibition of the BRAF/MEK/ERK signaling pathway, thereby inhibiting the proliferation of hepatocellular

carcinoma cells [37].

4.4 Regulation of the NF-κB Signaling Pathway

The NF-κB signaling pathway is involved in the regulation of many biological processes and plays a key role in inflammation and immune response, regulating the expression of inflammatory factors, apoptosis-related factors, and cell adhesion molecules. In cancer, NF-κB is commonly over-activated and promotes tumorigenesis, growth and metastasis, making it one of the important targets for cancer therapy.14-3-3ζ plays an important role in the inhibition of NF-κB and STAT-3 signaling pathways by caffeic acid and thus suppresses the inflammatory response in human hepatocellular carcinoma cell lines and murine macrophage cell lines [38]. 14-3-3η, on the other hand, affects NF-κB activity by interacting with key molecules in the NF-κB signaling pathway, which in turn regulates NF-κB-mediated gene expression. On the other hand, 14-3-3β plays a key role in the PI3K/Akt/NF-κB signaling pathway and further exacerbates the migration and invasion process of hepatocellular carcinoma by regulating the expression of MMP2 and MMP9 [32]. In this process, PI3K and Akt were activated and subsequently activated NF-κB, and the activation of NF-κB led to the overexpression of MMP2 and MMP9, which in turn promoted the migration and invasion of hepatocellular carcinoma cells [19].

4.5 Regulation of the TGFβ Signaling Pathway

The TGF-β signaling pathway plays an important role in the development of hepatocellular carcinoma. It promotes the proliferation, invasion and metastasis of hepatocellular carcinoma cells and is closely related to the degree of tumor malignancy and prognosis. MEG8 achieves its promotional effect on hepatocellular carcinoma by regulating the miR-367-3p/14-3-3ζ/TGFβR1 signaling pathway [39]. Axl interacted with 14-3-3ζ and regulated mesenchymal gene expression in HCC cells. This interaction led to an aberrant phosphorylation of Smad3L by 14-3-3ζ and induced the expression of mesenchymal genes in HCC cells. The aberrant phosphorylation of Smad3L contributed to tumor progression and enhanced the function of TGF-β, resulting in an autocrine TGF-β signaling pathway activated by Axl/14-3-3ζ in hepatocellular carcinoma, which in turn promoted the progression of hepatocellular carcinoma [40].

4.6 Regulation of the p53 Signaling Pathway

The p53 signaling pathway is an important cellular regulatory pathway that plays a key role in cellular stress response, DNA damage repair, cell cycle regulation, and apoptosis. p53 signaling pathway plays an important role in cell cycle regulation, especially in the G1/S and G2/M phases. Zhang et al. found that NC inhibited the proliferation of hepatocellular carcinoma cells by regulating the p53/14-3-3σ/CDK1 axis, inhibited the G2/M phase of hepatocellular carcinoma cells and suppressed the proliferation of hepatocellular carcinoma cells [8].

5. Summary and Outlook

The 14-3-3 protein family plays an important role in the development of hepatocellular carcinoma, and its mechanism of action involves multiple signaling pathways and biological processes, and its regulation has a significant impact on the occurrence, development and prognosis of hepatocellular carcinoma. Studies have shown that this family of proteins plays a key role in the development of hepatocellular carcinoma by affecting various aspects of cell proliferation, migration, metastasis, invasion, apoptosis and autophagy, etc. 14-3-3 proteins regulate the behavior of hepatocellular carcinoma cells by interacting with multiple signaling pathways. These findings emphasize the value of 14-3-3 proteins as potential targets for hepatocellular carcinoma therapy and provide new perspectives and possibilities for future therapeutic strategies for hepatocellular carcinoma.

References

[1] 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.

[2] BALLONE A, CENTORRINO F, OTTMANN C. 14-3-3: A Case Study in PPI Modulation[J]. Molecules, 2018, 23(6):1386.

[3] Tang Tao, Meng Jun. Research progress on 14-3-3 protein function [J]. Laboratory Medicine and Clinical Practice, 2015, 12 (11): 1628-1631

[4] Tang Yufu, Zhang Yibing, Feng Xiaodong, et al. Research progress of 14-3-3 protein in human diseases [J]. World Chinese Digestive Journal, 2017, 25 (06): 509-520.

[5] ALJABAL G, YAP B K. 14-3-3σ and Its Modulators in Cancer[J]. Pharmaceuticals (Basel), 2020,13(12)

[6] YANG X, CAO W, WANG X, et al. Down-regulation of 14-3-3zeta reduces proliferation and increases apoptosis in human glioblastoma[J]. Cancer Gene Ther, 2020, 27(6):399-411.

[7] KIM H J, SUNG S H, KIM C Y, et al. 14-3-3ζ Overexpression is Associated with Poor Prognosis in Ovarian Cancer[J]. Yonsei Med J, 2018, 59(1):51-56.

[8] ZHANG B, ZHOU B, HUANG G, et al. Nitidine chloride inhibits G2/M phase by regulating the p53/14-3-3 Sigma/CDK1 axis for hepatocellular carcinoma treatment[J]. Heliyon, 2024, 10(1):e24012.

[9] MA M Y, WANG Q, WANG S M, et al. Wogonin inhibits hepatoma cell proliferation by targeting miR-27b-5p/YWHAZ axis[J]. J Biochem Mol Toxicol, 2023, 37(12):e23508.

[10] ZHANG C, LIU L X, DONG Z R, et al. Up-regulation of 14-3-3ζ expression in intrahepatic cholangiocarcinoma and its clinical implications[J]. Tumour Biol, 2015, 36(3):1781-1789.

[11] SONG J, ZHANG X, LIAO Z, et al. 14-3-3ζ inhibits heme oxygenase-1 (HO-1) degradation and promotes hepatocellular carcinoma proliferation: involvement of STAT3 signaling[J]. J Exp Clin Cancer Res, 2019, 38(1):3.

[12] WEI G Y, HU M, ZHAO L, et al. MiR-451a suppresses cell proliferation, metastasis and EMT via targeting YWHAZ in hepatocellular carcinoma[J]. Eur Rev Med Pharmacol Sci, 2019, 23(12):5158-5167.

[13] CHOI J E, HUR W, JUNG C K, et al. Silencing of 14-3-3ζ over-expression in hepatocellular carcinoma inhibits tumor growth and enhances chemosensitivity to

cis-diammined dichloridoplatium [J]. CANCER LETTERS, 2011, 303(2):99-107.
[14] LIU T A, JAN Y J, KO B S, et al. Regulation of aldo-keto-reductase family 1 B10 by 14-3-3ε and their prognostic impact of hepatocellular carcinoma[J]. Oncotarget, 2015, 6(36):38967-38982.
[15] SHEN, JIAN, JIANG, et al. 14-3-3 is a novel growth-promoting and angiogenic factor in hepatocellular carcinoma[J]. JOURNAL OF HEPATOLOGY, 2016, 65(5):953-962.
[16] SONG J, LIU Y, LIU F, et al. The 14-3-3σ protein promotes HCC anoikis resistance by inhibiting EGFR degradation and thereby activating the EGFR-dependent ERK1/2 signaling pathway[J]. Theranostics, 2021, 11(3):996-1015.
[17] LIU C C, JAN Y J, KO B S, et al. 14-3-3σ induces heat shock protein 70 expression in hepatocellular carcinoma[J]. BMC Cancer, 2014, 14:425.
[18] MHAWECH P, BENZ A, CERATO C, et al. Downregulation of 14-3-3sigma in ovary, prostate and endometrial carcinomas is associated with CpG island methylation[J]. Mod Pathol, 2005, 18(3):340-348.
[19] TANG Y, LV P, SUN Z, et al. 14-3-3β Promotes Migration and Invasion of Human Hepatocellular Carcinoma Cells by Modulating Expression of MMP2 and MMP9 through PI3K/Akt/NF-κB Pathway[J]. PLoS One, 2016, 11(1):e0146070.
[20] LIU T A, JAN Y J, KO B S, et al. Increased expression of 14-3-3β promotes tumor progression and predicts extrahepatic metastasis and worse survival in hepatocellular carcinoma[J]. Am J Pathol, 2011, 179(6):2698-2708.
[21] LIN H, JIAO X, YU B, et al. Clinical significance of serum 14-3-3 beta in patients with hepatocellular carcinoma[J]. Cancer Biomark, 2017, 20(2):143-150.
[22] XU G, WANG J, WU F, et al. YAP and 14-3-3γ are involved in HS-OA-induced growth inhibition of hepatocellular carcinoma cells: A novel mechanism for hydrogen sulfide releasing oleanolic acid[J]. Oncotarget, 2016, 7(32):52150-52165.
[23] KO B S, LAI I R, CHANG T C, et al. Involvement of 14-3-3γ overexpression in extrahepatic metastasis of hepatocellular carcinoma[J]. Hum Pathol, 2011, 42(1):129-135.
[24] WANG X, SHEN H, ZHANGYUAN G, et al. 14-3-3ζ delivered by hepatocellular carcinoma-derived exosomes impaired anti-tumor function of tumor-infiltrating T lymphocytes[J]. Cell Death Dis, 2018, 9(2):159.
[25] TANG Y, ZHANG Y, LIU S, et al. 14-3-3ζ binds to and stabilizes phospho-beclin 1S295 and induces autophagy in hepatocellular carcinoma cells[J]. J Cell Mol Med, 2020, 24(1):954-964.
[26] TANG Y, LIU S, LI N, et al. 14-3-3ζ promotes hepatocellular carcinoma venous metastasis by modulating hypoxia-inducible factor-1α[J]. Oncotarget, 2016, 7(13):15854-15867.
[27] CHEN M, HU W, XIONG C L, et al. miR-22 targets YWHAZ to inhibit metastasis of hepatocellular carcinoma and its down-regulation predicts a poor survival[J]. Oncotarget, 2016, 7(49):80751-80764.
[28] PENG Z, WANG Y, FAN J, et al. Costunolide and dehydrocostuslactone combination treatment inhibit breast cancer by inducing cell cycle arrest and apoptosis through c-Myc/p53 and AKT/14-3-3 pathway[J]. Sci Rep, 2017, 7:41254.
[29] LEE Y K, HUR W, LEE S W, et al. Knockdown of 14-3-3[zeta] enhances radiosensitivity and radio-induced apoptosis in CD133[plus] liver cancer stem cells[J]. EXPERIMENTAL AND MOLECULAR MEDICINE, 2014, 46(2):e77.
[30] JIANG X, WU J, ZHANG Y, et al. MiR-613 functions as tumor suppressor in hepatocellular carcinoma by targeting YWHAZ[J]. Gene, 2018, 659:168-174.
[31] LIU T A, JAN Y J, KO B S, et al. 14-3-3ε overexpression contributes to epithelial-mesenchymal transition of hepatocellular carcinoma[J]. PLoS One, 2013, 8(3):e57968.
[32] WU Y, ZHANG Y, WANG F, et al. MiR-660-5p promotes the progression of hepatocellular carcinoma by interaction with YWHAH via PI3K/Akt signaling pathway[J]. Biochem Biophys Res Commun, 2020, 531(4):480-489.
[33] XIE J, GUO T, ZHONG Z, et al. ITGB1 Drives Hepatocellular Carcinoma Progression by Modulating Cell Cycle Process Through PXN/YWHAZ/AKT Pathways[J]. Front Cell Dev Biol, 2021, 9:711149.
[34] TANG Y, LV P, SUN Z, et al. 14-3-3ζ up-regulates hypoxia-inducible factor-1α in hepatocellular carcinoma via activation of PI3K/Akt/NF-κB signal transduction pathway[J]. Int J Clin Exp Pathol, 2015, 8(12):15845-15853.
[35] GAO C, WANG S W, LU J C, et al. KSR2-14-3-3ζ complex serves as a biomarker and potential therapeutic target in sorafenib-resistant hepatocellular carcinoma[J]. Biomark Res, 2022, 10(1):25.
[36] HUANG X Y, KE A W, SHI G M, et al. αB-crystallin complexes with 14-3-3ζ to induce epithelial-mesenchymal transition and resistance to sorafenib in hepatocellular carcinoma[J]. Hepatology, 2013, 57(6):2235-2247.
[37] YANG T, ZHU C, SHI Y, et al. RDIVpSGP motif of ASPP2 binds to 14-3-3 and enhances ASPP2/k18/14-3-3 ternary complex formulation to promote BRAF/MEK/ERK signal inhibited cell proliferation in hepatocellular carcinoma[J]. Cancer Gene Ther, 2022, 29(11):1616-1627.
[38] Lu Ming. The role and mechanism of NF-κ B/IL-6/STAT-3 pathway in the inhibition of liver cancer inflammation microenvironment by caffeic acid [D], 2020.
[39] LOU J, YAN W, LI Q Y, et al. LncRNA MEG8 plays an oncogenic role in hepatocellular carcinoma progression through miR-367-3p/14-3-3ζ/TGFβR1 axis[J]. Neoplasma, 2021, 68(2):273-282.
[40] REICHL P, DENGLER M, VAN ZIJL F, et al. Axl activates autocrine transforming growth factor-β signaling in hepatocellular carcinoma[J]. Hepatology, 2015, 61(3):930-941.