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Hedgehog signaling pathway as a potential therapeutic target for liver fibrosis

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Abstract: *The incidence of liver disease continues to rise, and liver fibrosis, as the early stage of cirrhosis and liver cancer, has attracted much attention. Hedgehog (Hh) signaling pathway plays a key role in the progression of liver fibrosis. In the process of liver fibrosis, Hh signaling pathway is involved in several key pathological links. It can regulate the activation, proliferation and apoptosis of hepatic stellate cells (HSC), affect the remodeling of hepatic blood vessels, regulate the function of inflammatory cells and inflammatory response, promote the proliferation of hepatic progenitor cells and epithelial-mesenchymal transdifferentiation (EMT). Many studies have shown that Hh signaling pathway is a potential therapeutic target for liver fibrosis, and related inhibitors have been shown to be effective in animal and cell experiments, but the precise mechanism of this pathway in liver fibrosis is still not fully understood, and the results of clinical trials are not clear. In the future, in-depth exploration of the role of Hh signaling pathway in the occurrence and development of liver fibrosis and the injury mechanism to achieve safe and effective regulation of it is of great significance to optimize liver regeneration and prevent liver fibrosis deterioration, and is expected to provide a reliable basis for the clinical treatment of liver fibrosis.*

Keywords: *Liver fibrosis; Hedgehog(Hh) signaling pathway; Pathogenesis; Therapeutic target*

1. Introduction

Liver disease has always been a major health problem in the world, and its incidence is increasing year by year. According to authoritative epidemiological data, about hundreds of millions of people worldwide are affected by different types of liver diseases, and the number of deaths from liver diseases is as high as millions every year[1]. As the key pathologic process of liver cirrhosis and liver cancer, liver fibrosis plays an extremely important role in this disease spectrum. Liver fibrosis is a repair response to chronic liver injury, but when the repair mechanism is out of control and a large amount of extracellular matrix is over-deposited in the liver, it will lead to serious damage to the structure and function of the liver[2]. It not only seriously affects the quality of life of patients, but also greatly increases the risk of patients developing cirrhosis and liver cancer, which in turn significantly reduces the life expectancy of patients[3, 4].

In recent years, a large number of studies have shown that Hedgehog (Hh) signaling pathway is deeply involved in the activation and proliferation of hepatic stellate cells, the aggregation of inflammatory cells, and vascular remodeling, which are closely related to liver fibrosis[5, 6]. Its abnormal activation is often associated with the occurrence and development of liver fibrosis. In view of this, this paper will conduct a comprehensive review of the role of Hh signaling pathway in liver fibrosis, aiming to deeply analyze its internal mechanism, provide a solid and reliable theoretical basis for clinical treatment of liver fibrosis, and help develop more effective treatment strategies to improve the prognosis of patients with liver fibrosis.

2. Hedgehog signaling pathway

Hh protein is a highly conserved secreted glycoprotein found in Drosophila melanoglypha and widely present in multiple species[7]. It covalently binds cholesterol and encodes a segmented polar gene, named after a mutation in this gene in fruit flies that causes the embryo to be spiny like a hedgehog[8]. In mammals, there are three homologous genes encoding Shh, Dhh and lhh proteins, all containing Hh-N and Hh-C domains. Hh-c and HH-N are produced in the endoplasmic reticulum by self-shearing and lipid modification of Hh precursor protein. Hh-c binds cholesterol to transfer to the

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carboxyl terminal of HH-N, and the amino terminal of HH-N is palmitoylated to generate 19 kD active HH-N activation signal pathway[9].

There are two kinds of transmembrane proteins, Ptch and Smo, on the membrane of Hh signal target. Ptch is encoded by tumor suppressor genes, has 12 transmembrane segments, and its sterol sensing domain can sense cholesterol[10]. Humans have Ptch1 and Ptch2, encoding proteins that can bind to Hh ligands. Smo is encoded by proto-oncogene and homologous with G protein-coupled receptor, which is essential for signal transduction and maintenance of embryonic development[11]. Abnormalities are associated with cancer. Seven transmembrane amino acid sequences were conserved outside the N-terminal cell and inside the C-terminal cell, and the C-terminal was the phosphorylation site. Smo exerts the promoter function in full length, and C-terminal hydrolysis inhibits transcription[12].

The Gi family of mammals contains three subtypes of Gi1, Gli2 and Gli3, which are multifunctional transcription factors and contain five tandem zinc finger structures[13]. The C-terminal has a transcriptional excitatory region, the N-terminal promotes intracellular transfer, Gli2 and Gli3 are hydrolyzed by proteasome, and the N-terminal has a transcriptional inhibition region, which has dual functions[14]. In addition, Hh signaling pathway is regulated by many factors. The silk/threonine protein kinase Fu promotes signal transduction, Hhip and Ptch competitively bind Hh ligands to inhibit signal transduction, and other endogenous factors such as Cos2, SuFu and PKA also inhibit signal transduction[15].

3. Correlation of Hedgehog signaling pathway with normal liver

Hh signaling pathway is important for liver production, but its role has not been fully defined. It has been reported that Hh ligands are highly expressed in the ventral foregut endoderm, which can produce liver buds, while Shh and Glil expressions disappear when liver buds are formed[16]. In embryonic liver development, Hh signal has instantaneous activation potential, and has different or even contradictory effects at different stages, so it is necessary to strictly regulate ligand expression and pathway activation to ensure normal development. Knockout Hh signal pathway can lead to embryo death[17].

In normal adult liver, Hh signaling pathway is silent. Studies have shown that the expression of Hh ligand and Gli gene is basically absent in hepatocytes of healthy adult livers. Quiescent hepatic stellate cells (Q-HSC) produce Hhip, which inhibits Hh ligand binding to Ptch receptors[18]. Ptch is rarely expressed in mature hepatocytes, but expressed in bidirectional progenitor cells. Hh signaling pathway activity is gradually inhibited when it differentiates into mature hepatocytes[6]. Evidence shows that the activity of low level Hh pathway fluctuates rhythmically with physiological changes, regulates the level of Gli factor in liver cells, and regulates liver metabolism. However, it has also been reported that mammalian livers may be influenced by and respond to extrahepatic Hh ligands[19].

4. Role of Hedgehog signaling pathway in liver fibrosis

In the course of acute and chronic liver injury, Hh ligands can be expressed in many cells in the liver to activate the Hh signaling pathway, and the degree of activation is positively correlated with the severity and duration of liver injury[10]. Studies have shown that Hh signaling pathway activation is essential for the regeneration and repair of damaged liver, and it is a common signaling pathway for different factors to trigger liver repair and reconstruction[20]. Liver fibrosis is the intermediate link of the protracted outcome of acute and chronic liver disease, the repair response of the body to chronic liver injury, and the common pathological change of chronic liver disease.When the liver is injured, hepatic stellate cells (HSC) are activated and secrete a large amount of extracellular matrix (ECM), resulting in thickening of the diaphragm and accumulation of collagen, leading to liver fibrosis[21]. Hepatoprogenitor cells migrate to the liver parenchyma after activating a large number of proliferation, which will destroy the normal liver tissue structure and may even lead to liver fibrosis and cirrhosis. Epithelial-mesenchymal transdifferentiation (EMT) occurs in cells with epithelial cell phenotype under the stimulation of various factors, which also promotes the development of liver fibrosis[22]. In the development of fibrosis, vascular structure is often changed, and vascular remodeling often precedes the formation of fibrosis. In addition, inflammatory cells in the liver promote the occurrence and development of liver fibrosis by producing inflammatory cytokines and chemokines, which is one of the core factors in the initiation of liver fibrosis. At the same time, the activity level of Hh signaling pathway was significantly correlated with the stage of liver fibrosis[23].

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4.1. Hedgehog signaling pathway is involved in the activation of hepatic stellate cells

Hepatic fibrosis is a common key pathological process of various chronic liver diseases, in which the abnormal activation of hepatic stellate cells (HSC) is the core link. HSC activation is regulated by many signaling pathways, and Hh signaling pathway may be the most prominent direct and paracrine inducer of HSC activation. Some scholars have isolated and cultured the primary HSC of mice, rats and humans, and found that HSC can express Shh, Ptch, Smo, Gli and other related factors in Hh signaling pathway. In the development of liver fibrosis, Hh signaling pathway plays a regulatory role in the fate of HSC. In vitro studies have shown that Smo small molecule inhibitors can effectively inhibit the activation of HSC. Moreover, direct interference with Gli gene expression can also hinder HSC activation[10]. In vivo, it was also found that in CCl_4 and biliary ligation induced rat hepatic fibrosis, activation of the Hh signaling pathway led to the aggregation of HSC-derived myofibroblasts (MFs), which promoted the fibrosis process and aggravated the degree of hepatic fibrosis in rats. In contrast, when mice were given Smo agonists, stationary HSCS were activated and differentiated into fibrotic phenotypic cells[24]. The study of hepatic HSC metabolism gene expression by microarray revealed that Hh pathway regulates HSC activity by regulating HSC energy metabolism[25]. In conclusion, activation of Hh signaling pathway can promote the activation of HSC, while inhibition of the activity of this pathway can inhibit the activation and proliferation of HSC, and promote its apoptosis. This indicates that Hh signaling pathway is not only a potential new target for the treatment of liver fibrosis, but also an important indicator for the diagnosis and treatment of liver fibrosis.

4.2. Hedgehog signaling pathway is involved in liver vascular remodeling

Pathological angiogenesis and hepatic sinus vascular remodeling are directly related to the degree of liver fibrosis, and have a significant impact on the treatment and prognosis of liver fibrosis. It is generally believed that primary cilia are not expressed in normal hepatic sinusoidal endothelial cells (LSEC), so the classical Hh signaling pathway cannot be activated. Only under the condition of continuous increase of hydrostatic pressure, endothelial cells will transform into ciliated state[26]. The activation of the Hh pathway can result in phenotypic changes of hepatic sinusoidal endothelial cells, loss of fenestrum, and then capillarization and vascular remodeling, eventually leading to portal hypertension[27]. In addition, when liver fibrosis occurs, activated hepatic stellate cells (HSC) around hepatic sinusoidal endothelial cells and proliferating hepatic progenitor cells are capable of producing Hh ligands. Other studies have shown that LSEC capillarization can be inhibited by regulating the Hh signaling pathway of hepatic sinusoidal endothelial cells in a mouse model of liver injury[28]. In a study of mouse liver fibrosis models induced by CCl_4, it was also found that HIF-1α, a driver of new blood vessel formation and a target gene of the Hh signaling pathway, plays an important role in liver fibrosis generation and liver injury[29]. In view of the extensive existence of angiogenesis in liver fibrosis induced by different factors, in-depth study of the mechanism of Hh signaling pathway on angiogenesis in the pathological process of liver fibrosis will help to comprehensively and deeply explore the pathological mechanism of the occurrence and development of liver fibrosis, and open up new perspectives and ideas for the treatment of liver fibrosis.

4.3. Hedgehog signaling pathway is involved in the inflammatory process

Hh signaling pathway also plays a key role in the inflammatory response. When inflammation occurs, cytokines and inflammatory mediators released by damaged tissues and immune cells activate the Hh signaling pathway. For example, in infectious inflammation, pathogen-associated molecular patterns bind to immune cell receptors, triggering intracellular cascade reactions that promote upregulation of Hh ligand expression[20]. The activation of Hh signaling pathway has a significant effect on inflammatory cells. Taking macrophages as an example, in vitro experiments have shown that Hh ligand inhibitors on liver macrophages can inhibit their anti-inflammatory M2 type polarization, highlighting the regulatory role of this pathway on macrophage polarization[30]. The Hh signaling pathway also affects other inflammatory cells. In a rat model of nonalcoholic fatty cirrhosis, its activation recruits, maintains, and promotes NK cell proliferation and promotes fibrotic progression. Studies have shown that activation of this pathway can promote the proliferation of locally pro-fibrogenic NK cells[31]. In addition, Hh pathway can regulate NKT cells in mouse primary and human peripheral blood. Shh ligands promote the activation, proliferation and differentiation of NKT cells, inhibit their apoptosis, stimulate the expression of pro-fibrocyte IL-13, and promote the formation of nonalcoholic fatty liver fibrosis[32]. In tissue repair after inflammation, Hh signaling pathway can promote the proliferation and differentiation of fibroblasts, promote the synthesis and secretion of

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extracellular matrix, and help the reconstruction of damaged tissues. It can also stimulate the proliferation of vascular endothelial cells and angiogenesis, provide nutrients and oxygen to the repair site, and accelerate the healing process. However, excessive or abnormal activation of Hh signaling pathway may lead to chronic inflammation and tissue fibrosis.

4.4. Hedgehog signaling pathway is involved in the proliferation of hepatic progenitor cells

Hepatic progenitor cells (HPCs) are static cells that are activated during liver injury and can differentiate into hepatocytes or bile duct epithelial cells to repair the damaged liver. Normal adult liver contains a small number of hepatoprogenitor cells, mainly concentrated in Hering's canals. The severity of hepatic fibrosis is closely related to the activation of hepatic progenitor cells. When the liver is damaged, liver progenitor cells are activated and proliferated to supplement the damaged liver cells and help the liver to repair and regenerate[33]. Hh signaling pathway is critical in this process. In normal liver tissue, the activity of this pathway is low. After liver injury stimulation, damaged cells release a variety of signaling molecules, change the microenvironment, and activate Hh signaling pathway. Activated cells in Hering's canals express ligands, receptors, transporters, and transcription factors of the Hh signaling pathway. Hepatic progenitor cells are Hh effector cells, and Hh ligands can inhibit apoptosis and promote proliferation. Moreover, the proliferation, apoptosis, migration and differentiation of hepatic progenitor cells all depend on the regulation of Hh signaling pathway. The activation of Hh signaling pathway affects the proliferation of hepatoprogenitor cells through complex mechanisms[34]. On the one hand, it up-regulates the expression of related transcription factors, acts on the gene regulatory region of hepatoprogenitor cells, promotes the expression of proliferation-related genes such as cyclin, promotes the hepatoprogenitor cells to enter the division phase, and accelerates the proliferation. On the other hand, it regulates the composition and structure of extracellular matrix, promotes the change of collagen, fibronectin and other components, creates a suitable microenvironment for the proliferation of liver progenitor cells, and collaborates with cell surface receptors to promote their massive proliferation[35]. Therefore, inhibiting Hh signaling pathway is expected to be an ideal target for delaying or reversing liver fibrosis.

4.5. The Hedgehog signaling pathway is involved in epithelial-mesenchymal transdifferentiation

Epithelial-mesenchymal transdifferentiation (EMT) is a process in which epithelial cells lose their epithelial characteristics and gain their mesenchymal characteristics. EMT plays an important role in tissue and organ construction during embryonic development, but abnormal EMT plays a key role in the field of disease, especially in the process of tissue fibrosis. HSC activation is the main factor that causes EMT, and epithelial phenotypic cells such as hepatic progenitor cells, bile duct epithelial cells and sinusoidal endothelial cells can also produce EMT[36]. Under normal conditions, the intracellular Hh signaling pathway activity is stable. However, this pathway is activated when the cell microenvironment is affected by changes in inflammatory factors, growth factors, or extracellular matrix. In adult liver injury repair, it has a significant effect on the occurrence and development of EMT. For example, static hepatic stellate cells (Q-HSC) overexpress Hh endogenous inhibitor Hhip. After inhibiting Hhip, Shh expression in HSC is increased, and Hh signaling pathway is activated. EMT is triggered by down-regulating epithelial cell markers and up-regulating interstitial cell marker gene expression. After Q-HSC activation and differentiation into myofibroblasts, Hh signaling pathway inhibitor cyclopamine was applied to activated HSC, which could reduce the expression of phenotypic markers in mesenchymal cells, restore the expression of phenotypic markers in epithelial cells, and effectively inhibit EMT transformation. In addition, the Hh signaling pathway activates bile duct cells and fibroblasts, which can aggravate liver fibrosis[37]. Studies of patients with chronic biliary stasis liver disease and the rat model of bile duct ligation with fibrosis found that the continuous activation of Hh signaling pathway promoted bile duct epithelial cells to develop EMT, a large number of myofibroblasts accumulated, and promoted the development of liver fibrosis[38]. In conclusion, activation of Hh signaling pathway is an important cause of EMT when liver fibrosis occurs. Further study of this mechanism is helpful to explore the pathogenesis of liver fibrosis and provide theoretical basis for the development of anti-liver fibrosis treatment strategies.

5. Conclusion and prospect

The high incidence and mortality of liver diseases worldwide highlights the urgent need for effective prevention and treatment of liver diseases such as liver fibrosis and cirrhosis. The liver

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initiates a similar wound-healing response to different injuries. However, when this repair process gets out of control and scar formation replaces normal healing, liver fibrosis occurs. More and more studies have shown that Hh signaling pathway plays a multi-faceted regulatory role in wound healing response. Abnormal activation of the pathway can not only promote the activation of HSC, lead to the capillarization and vascular remodeling of hepatic sinusoidal endothelial cells, but also stimulate the secretion of pro-fibrotic cytokines by inflammatory cells. In addition, Hh ligands can stimulate specific cells, such as immature liver epithelial cells, to proliferate and differentiate into mesenchymal cell phenotypes, thereby driving the fibrotic process. Therefore, effective intervention of Hh signaling pathway is expected to delay liver fibrosis and is a potential therapeutic target.

However, the exact mechanism of Hh signaling pathway in hepatic fibrosis has not been fully clarified. Moreover, the moderate activation of Hh signaling pathway is the embodiment of the body's physiological defense, but once excessive or continuous activation, it will lead to liver fibrosis and other liver diseases. Hh signaling pathway inhibitors, such as cyclopamine, have been shown to have significant effects on liver injury diseases in animal and cell experiments, but their clinical trial results are still unclear. In order to apply Hh signaling pathway as a therapeutic target to clinical treatment of liver fibrosis, it is necessary to further explore its role in the occurrence and development of liver fibrosis, further elucidate its mediated liver fibrosis injury mechanism, and achieve safe and effective regulation of Hh pathway, so as to optimize the regeneration process of damaged liver and prevent the deterioration of liver fibrosis.

References

[1] Xiao J, Wang F, Yuan Y, et al. Epidemiology of liver diseases: global disease burden and forecasted research trends[J]. Sci China Life Sci,2024.
[2] Gong L, Wei F, Gonzalez F J, et al. Hepatic fibrosis: Targeting peroxisome proliferator-activated receptor alpha from mechanism to medicines[J]. Hepatology,2023,78(5):1625-1653.
[3] Yasukawa K, Shimizu A, Kubota K, et al. Impact of Liver Fibrosis Severity on Oncological Prognosis in Hepatocellular Carcinoma[J]. Liver Cancer,2024,13(2):150-160.
[4] Somnay K, Wadgaonkar P, Sridhar N, et al. Liver Fibrosis Leading to Cirrhosis: Basic Mechanisms and Clinical Perspectives[J]. Biomedicines,2024,12(10).
[5] Zhang F, Hao M, Jin H, et al. Canonical hedgehog signalling regulates hepatic stellate cell-mediated angiogenesis in liver fibrosis[J]. Br J Pharmacol,2017,174(5):409-423.
[6] Hu Y, Bao X, Zhang Z, et al. Hepatic progenitor cell-originated ductular reaction facilitates liver fibrosis through activation of hedgehog signaling[J]. Theranostics,2024,14(6):2379-2395.
[7] Nellas I, Iyer K V, Iglesias-Artola J M, et al. Hedgehog signaling can enhance glycolytic ATP production in the Drosophila wing disc[J]. EMBO Rep,2022,23(11):e54025.
[8] Kaushal J B, Batra S K, Rachagani S. Hedgehog signaling and its molecular perspective with cholesterol: a comprehensive review[J]. Cell Mol Life Sci,2022,79(5):266.
[9] Rowton M, Perez-Cervantes C, Hur S, et al. Hedgehog signaling activates a mammalian heterochronic gene regulatory network controlling differentiation timing across lineages[J]. Dev Cell, 2022,57(18):2181-2203.
[10] Jiayuan S, Junyan Y, Xiangzhen W, et al. Gant61 ameliorates CCl(4)-induced liver fibrosis by inhibition of Hedgehog signaling activity[J]. Toxicol Appl Pharmacol,2020,387:114853.
[11] Mosoh D A. Widely-targeted in silico and in vitro evaluation of veratrum alkaloid analogs as FAK inhibitors and dual targeting of FAK and Hh/SMO pathways for cancer therapy: A critical analysis[J]. Int J Biol Macromol,2024,281(Pt 2):136201.
[12] Roy L, Roy A, Bose D, et al. Unraveling the structural aspects of the G-quadruplex in SMO promoter and elucidating its contribution in transcriptional regulation[J]. J Biomol Struct Dyn, 2024,42(22):12228-12243.
[13] Sanna M D, Ghelardini C, Galeotti N. Differential contribution of Galphai/o subunits in the response to food deprivation[J]. Eur J Pharmacol,2015,750:27-31.
[14] An R, Wilms E, Masclee A A M, et al. Age-dependent changes in GI physiology and microbiota: time to reconsider?[J]. Gut,2018,67(12):2213-2222.
[15] Zhang Q, Jiang J. Regulation of Hedgehog Signal Transduction by Ubiquitination and Deubiquitination[J]. Int J Mol Sci,2021,22(24).
[16] Ng S S, Saeb-Parsy K, Blackford S J I, et al. Human iPS derived progenitors bioengineered into liver organoids using an inverted colloidal crystal poly (ethylene glycol) scaffold[J]. Biomaterials, 2018, 182:299-311.
[17] Shaheen R, Alsahli S, Ewida N, et al. Biallelic Mutations in Tetratricopeptide Repeat Domain 26

ISSN 2706-6819 Vol. 7, Issue 1: 50-55, DOI: 10.25236/IJFM.2025.070108

(Intraflagellar Transport 56) Cause Severe Biliary Ciliopathy in Humans[J]. Hepatology, 2020, 71(6):2067-2079.
[18] Kumar V, Kumar V, Luo J, et al. Therapeutic Potential of OMe-PS-miR-29b1 for Treating Liver Fibrosis[J]. Mol Ther,2018,26(12):2798-2811.
[19] Marbach-Breitruck E, Matz-Soja M, Abraham U, et al. Tick-tock hedgehog-mutual crosstalk with liver circadian clock promotes liver steatosis[J]. J Hepatol,2019,70(6):1192-1202.
[20] Shen X, Peng Y, Li H. The Injury-Related Activation of Hedgehog Signaling Pathway Modulates the Repair-Associated Inflammation in Liver Fibrosis[J]. Front Immunol,2017,8:1450.
[21] Bourebaba N, Marycz K. Hepatic stellate cells role in the course of metabolic disorders development - A molecular overview[J]. Pharmacol Res,2021,170:105739.
[22] Wu Y, Ding Z, Jin G, et al. Autocrine transforming growth factor-beta/activin A-Smad signaling induces hepatic progenitor cells undergoing partial epithelial-mesenchymal transition states[J]. Biochimie,2018,148:87-98.
[23] Zhangdi H, Su S, Wang F, et al. Crosstalk network among multiple inflammatory mediators in liver fibrosis[J]. World J Gastroenterol,2019,25(33):4835-4849.
[24] Yan J, Hu B, Shi W, et al. Gli2-regulated activation of hepatic stellate cells and liver fibrosis by TGF-beta signaling[J]. Am J Physiol Gastrointest Liver Physiol,2021,320(5):G720-G728.
[25] Gao W, Sun J, Wang F, et al. Deoxyelephantopin suppresses hepatic stellate cells activation associated with inhibition of aerobic glycolysis via hedgehog pathway[J]. Biochem Biophys Res Commun,2019,516(4):1222-1228.
[26] Chen L, Gu T, Li B, et al. Delta-like ligand 4/DLL4 regulates the capillarization of liver sinusoidal endothelial cell and liver fibrogenesis[J]. Biochim Biophys Acta Mol Cell Res, 2019, 1866(10):1663-1675.
[27] Lafoz E, Ruart M, Anton A, et al. The Endothelium as a Driver of Liver Fibrosis and Regeneration [J]. Cells,2020,9(4).
[28] de Haan W, Dheedene W, Apelt K, et al. Endothelial Zeb2 preserves the hepatic angioarchitecture and protects against liver fibrosis[J]. Cardiovasc Res,2022,118(5):1262-1275.
[29] Yang L, Yue W, Zhang H, et al. Dual Targeting of Angipoietin-1 and von Willebrand Factor by microRNA-671-5p Attenuates Liver Angiogenesis and Fibrosis[J]. Hepatol Commun, 2022, 6(6):1425-1442.
[30] Hinshaw D C, Hanna A, Lama-Sherpa T, et al. Hedgehog Signaling Regulates Metabolism and Polarization of Mammary Tumor-Associated Macrophages[J]. Cancer Res,2021,81(21):5425-5437.
[31] Ustiuzhanina M O, Streltsova M A, Timofeev N D, et al. Autologous T-Cell-Free Antigen Presentation System Unveils hCMV-Specific NK Cell Response[J]. Cells,2024,13(6).
[32] Heinrichs D, Brandt E F, Fischer P, et al. Unexpected Pro-Fibrotic Effect of MIF in Non-Alcoholic Steatohepatitis Is Linked to a Shift in NKT Cell Populations[J]. Cells,2021,10(2).
[33] Overi D, Carpino G, Cardinale V, et al. Contribution of Resident Stem Cells to Liver and Biliary Tree Regeneration in Human Diseases[J]. Int J Mol Sci,2018,19(10).
[34] Byerly C D, Mitra S, Patterson L L, et al. Ehrlichia SLiM ligand mimetic activates Hedgehog signaling to engage a BCL-2 anti-apoptotic cellular program[J]. PLoS Pathog,2022,18(5):e1010345.
[35] Li B, Li F, Gu T, et al. Specific knockdown of Y-box binding protein 1 in hepatic progenitor cells inhibits proliferation and alleviates liver fibrosis[J]. Eur J Pharmacol,2022,921:174866.
[36] Cao Y. Lack of basic rationale in epithelial-mesenchymal transition and its related concepts[J]. Cell Biosci, 2024,14(1):104.
[37] Solhi R, Lotfi A S, Lotfinia M, et al. Hepatic stellate cell activation by TGFbeta induces hedgehog signaling and endoplasmic reticulum stress simultaneously[J]. Toxicol In Vitro,2022,80:105315.
[38] Wu H, Chen C, Ziani S, et al. Fibrotic Events in the Progression of Cholestatic Liver Disease[J]. Cells, 2021,10(5).