A Discussion on the Relationship among Hepatic Stellate Cells, Hepatic Sinusoidal Endothelial Cells and Hepatic Sinusoidal Capillarization in the Development of Hepatic Fibrosis

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Abstract Hepatic stellate cells, hepatic sinusoidal endothelial cells and hepatic sinusoidal capillarization are closely related to the occurrence and progression of hepatic fibrosis. The pathological activation of hepatic stellate cells is the central link of hepatic fibrosis, and hepatic sinusoidal capillarization also promotes the occurrence and development of liver diseases. In the course of hepatic fibrosis, there is always a mutually reinforcing relationship between the activation of hepatic stellate cells and the capillarization of hepatic sinusoids. This paper strives to find an effective way to intervene or even reverse this vicious cycle by deeply investigating the effect of hepatic stellate cells and hepatic sinusoidal capillarization on hepatic fibrosis and their mutual promotion, and provide a new idea for the treatment of hepatic fibrosis, which is of great significance for relieving and reversing hepatic fibrosis.

Keywords Hepatic stellate cells; Hepatic sinusoidal endothelial cells; Hepatic sinusoidal capillarization; Hepatic fibrosis

The liver is the largest gland in the animal body and one of the important parenchymal organs of the body, with many physiological functions such as metabolizing nutrients, secreting bile, detoxifying and defending, and regulating blood volume. Viral infection, drug damage, chemical damage, excessive alcohol, *etc*., can cause liver damage, leading to acute and chronic hepatitis, fatty liver, alcoholic liver, and even cirrhosis, liver cancer and other diseases.

1 Hepatic Stellate Cells and Hepatic Fibrosis

Hepatic stellate cells, which were discovered and named by German scholar Karl Wilhelm von Kupffer in 1876, are the core cells in the development of hepatic fibrosis and the main source of myofibroblasts. Hepatic stellate cells are polygonal, with elongated protuberances extending outward, distributed in the Disse space of the liver. They are liver-specific mesenchymal cells, accounting for approximately 13% –15% of the total number of liver cells and about 30% of liver non-parenchymal cells. The activation of hepatic stellate cells is the central link of hepatic fibrosis[1].

When various injury factors invade the liver and stimulate hepatic stellate cells, hepatic stellate cells are stimulated, activated and transformed into myofibroblasts, which express α-smooth muscle actin[2], and have contraction function, resulting in the emergence and development of hepatic fibrosis.

In addition, the level of extracellular matrix secreted by activated hepatic stellate cells is greatly increased, mainly type I, III and IV collagen. The secretion of type IV collagen increases mainly in the early stage of hepatic fibrosis, and when the disease progresses to the stage of cirrhosis, there are more secretions of type I and III collagen, mainly type I collagen[3].

In addition to collagen, the formation of hepatic fibrosis is also closely related to glycoproteins, including fibronectin, laminin, *etc*., which are closely related to activated hepatic stellate cells. In the early stage of liver injury caused by various factors, the secretion of fibronectin and laminin is significantly increased[5]. Studies have shown that fibronectin can accelerate the phenotypic transformation of hepatic stellate cells into myofibroblasts in the early stage of hepatic fibrosis, and laminin is also positively correlated with the degree of hepatic fibrosis[4].

The activated hepatic stellate cells can release a large number of cytokines such as transforming growth factor, con-

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nective tissue growth factor, platelet derived growth factor, epidermal growth factor and endothelin in addition to activating phenotype, *i.e.* secreting collagen and glycoprotein. Transforming growth factor can promote the activation of hepatic stellate cells, increase the synthesis and decrease the degradation of extracellular matrix. Transforming growth factor-β1 is the strongest factor known to induce hepatic fibrosis[5]. Both transforming growth factor and C-transforming growth factor increase the expression of platelet derived growth factor in hepatic stellate cells. C transforming growth factor, platelet derived growth factor and epidermal growth factor can all promote the proliferation and activation of hepatic stellate cells[6], expand the scope of disease and accelerate the process of hepatic fibrosis. Endothelin is originally derived from hepatic sinusoidal endothelial cells, but activated hepatic stellate cells can also secrete endothelin, which can enhance vasoconstriction, trigger hepatic sinusoidal constriction, and lead to liver ischemia and hypoxia.

2 Hepatic Sinusoidal Capillarization and Hepatic Fibrosis

Hepatic sinusoidal endothelial cells account for 70% of the non-parenchymal cells of the liver. Due to the large number of fenestrae on its surface and the lack of basement membrane characteristics, hepatic sinusoidal endothelial cells become the most permeable endothelial cells in the body, and participate in the pathological process of most hepatic diseases, being of great significance for the occurrence and development of hepatic diseases. When the liver is damaged by various acute and chronic causes, the hepatic sinuses endothelial cells show pathological changes such as loss of fenestration, continuous basement membrane, and pathological vascular hyperplasia, which are collectively referred to as hepatic sinusoidal capillarization[7]. Studies have shown that the pathological changes of hepatic sinusoidal capillarization are manifested in the early stage of hepatic fibrosis, and some scholars declare that hepatic sinusoidal capillarization is the starting link of hepatic fibrosis. Therefore, the study of hepatic sinusoidal capillarization is of great significance for the study of hepatic fibrosis[8].

The most characteristic structures of hepatic sinusoidal endothelial cells are fenestra and basement membrane. When hepatic fibrosis occurs, declined number and narrowed diameter of fenestra, expanded area of basement membrane and even the formation of continuous sheets of basement membrane, pathological angiogenesis and remodeling are all manifestations of hepatic sinusoidal capillarization. These changes lead to liver microcirculation disorders, and nutrients are unable to enter the liver, thus accelerating the process of hepatic fibrosis[9].

Fenestra structure is a characteristic structure of hepatic sinusoidal endothelial cells. There are a large number of fenestra structures distributed on the surface of hepatic sinusoidal endothelial cells, which are gathered into "sieve plates" and become the places for material exchange between hepatic sinusoids and Disse lumen. Hepatocytes exchange materials and communicate information with hepatic sinusoids through the fenestra structure. In the early stage of hepatic fibrosis, the fenestra structure of hepatic sinusoidal endothelial cells is changed, which is manifested in the reduction of the number and diameter of fenestrae, while the large deposition of extracellular matrix also leads to the reduction of fenestrae, which are positively correlated. In addition, the destruction of cytoskeleton structure and ischemia and hypoxia caused by hepatic fibrosis may also lead to the loss of fenestration of liver sinusoidal endothelial cells[10]. However, hepatocytes can exchange materials and information with hepatic sinusoids through the fenestra structure. Therefore, the diameter and number of fenestrae are closely related to the physiological functions of the liver, and regulating the fenestra of hepatic sinusoidal endothelial cells is of great significance for liver fibrosis[11].

Both fenestra and basement membrane are unique physiological structures of hepatic sinusoidal endothelial cells, and they work together to act as screening barriers. Fenestra is the main pathway of material exchange, while basement membrane can block the process of material exchange[12]. When hepatic fibrosis occurs, the basement membrane expands its area and even forms a continuous basement membrane, which blocks nutrients from entering the liver, leads to liver microcirculation disorders, and accelerates the process of hepatic fibrosis, eventually promoting the development of the course to the direction of liver cirrhosis.

Angiogenesis is an important process to maintain liver physiology, which can provide blood and nutrients to the ischemic and damaged parts, and build a more suitable vascular network. When the liver is damaged, there will be pathological reconstruction of hepatic vessels and a large number of capillary angiogenesis, but these vessels have no practical function and can not promote blood supply. On the contrary, the vascular reconstruction will consume a lot of energy, aggravate ischemia and hypoxia of hepatocytes, and further aggravate hepatic fibrosis[13].

Hepatic sinusoidal capillarization will directly lead to ischemia and hypoxia of hepatocytes and insufficient supply of nutrients, and the hepatocytes are damaged, which will stimulate hepatic stellate cells and release extracellular matrix. A large amount of extracellular matrix is deposited in the Disse space, which accelerates the process of hepatic fibrosis, and promotes the transformation of hepatic fibrosis into cirrhosis, eventually leading to liver failure [14]. Studies have confirmed that hepatic sinusoidal capillarization will weaken the exchange of substances between hepatocytes and hepatic sinusoids, which is an

important factor leading to cirrhosis and even liver failure.

Hepatic sinusoidal capillarization not only leads to the substance metabolism disorder of hepatocytes, but also changes the liver hemodynamics and participates in the formation or exacerbation of portal hypertension. Malnutrition caused by hepatic sinusoidal capillarization will lead to hepatocyte atrophy and hepatic sinusoids collapse, increased resistance of hepatic sinusoids, damage of intrahepatic vascular network and decreased number of effective blood vessels[15]. Meantime, the formation of continuous basement membrane narrows the hepatic sinusoidal cavity and increases blood flow resistance, thus forming portal hypertension[16]. Studies have also shown that hepatic sinusoidal capillarization is the main source of portal vascular resistance in patients with cirrhosis. Therefore, hepatic sinusoidal capillarization is critical for the formation of portal hypertension.

Hepatic sinusoidal capillarization not only aggravates the degree of hepatic fibrosis in patients, increases the probability of the disease transforming into cirrhosis or liver cancer, but also increases the resistance of hepatic blood flow, leading to portal hypertension, and even causes a series of complications such as hepatic encephalopathy and hepatorenal syndrome.

3 Hepatic Fibrosis

As a common pathological process of most liver-related diseases, hepatic fibrosis is the only way for many chronic liver diseases to develop into cirrhosis and liver cancer. Hepatic fibrosis is not a static result, but a dynamic pathological change process, which is a pathological change characterized by the continuous stimulation of the liver by various pathogenic factors, resulting in the accumulation of extracellular matrix. In acute liver injury diseases, excessive extracellular matrix will be absorbed and degraded, but in chronic liver disease, a large amount of deposited extracellular matrix will lead to the activation of hepatic stellate cells into myofibroblasts and the formation of scar tissue, leading to irreversible fibrosis pathological manifestations. With the continuous effect of liver injury factors, the course of hepatic fibrosis continuously progresses, manifesting as gradually increased extracellular matrix deposition, severe damage of liver microcirculation and severer hepatocyte ischemia and hypoxia phenotype, which promotes the aggravation of hepatic fibrosis and the development of liver cirrhosis[17].

Hepatic fibrosis not only leads to the loss of liver nutrients, but also causes hepatocyte atrophy, skeleton collapse, intrahepatic vessel damage, reduced effective circulating blood flow, and aggravated ischemia and hypoxia symptoms. Vascular injury also lead to increased liver blood flow resistance, increased vascular pressure, arterialization of liver tissue blood supply, and increased portal vein pressure, thus leading to a series of subsequent liver diseases such as cirrhosis[18]. Hence, hepatic sinusoidal capillarization will not only increase the degree of hepatic fibrosis, but also increase the risk of patients suffering from cirrhosis, liver cancer and other diseases, and seriously affect the quality of life of patients.

Nitric oxide is the scavenger of blood vessels and the second messenger that makes blood vessels dilate[19]. Physiologically, liver sinusoidal endothelial cells can synthesize and secrete nitric oxide, but when hepatic fibrosis occurs, the synthesis of nitric oxide is reduced, resulting in weakened vasomodulation and angiotonia. In addition, endothelin, a cytokine released by hepatic stellate cells, strongly constricts blood vessels. Many factors work together to cause abnormal contraction of hepatic vessels and poor blood circulation, inducing portal hypertension and compensatory reconstruction of hepatic vessels. However, these new vessels have no practical effect and can not alleviate the status quo of liver ischemia and hypoxia or have poor relief effect. Moreover, massive vascular reconstruction requires energy and oxygen consumption, which further aggravates liver ischemia and hypoxia, stimulates hepatic stellate cells activation, and aggravates hepatic fibrosis.

4 Relationship of Hepatic Stellate Cells and Hepatic Fibrosis

Hepatic stellate cells, belonging to liver non-parenchymal cells, are polygonal, with multiple prominences, shaped like five-pointed stars, so they are called hepatic stellate cells. Their physiological function is to synthesize extracellular matrix. However, when the liver is stimulated by chronic injury, neighboring cells release a series of cytokines, such as transforming growth factor-β and platelet derived growth factor, to act on hepatic stellate cells. Hepatic stellate cells will undergo phenotype transformation when stimulated, manifesting as fibroblasts, and the ability of activated hepatic stellate cells to synthesize and secrete extracellular matrix is greatly improved. Because of large deposition of collagen, laminin, proteoglycan, *etc*., it directly leads to the occurrence of hepatic fibrosis[20].

Activated hepatic stellate cells are closely related to hepatic fibrosis and are the central link in the pathogenesis of hepatic fibrosis[21]. Physiologically, hepatic stellate cells are in a static state, and there are several lipid droplets rich in vitamin A in the cells, whose main function is to store retinene[22]. In pathological conditions, hepatic stellate cells are activated by cytokines, and the activated hepatic stellate cells will differentiate into myofibroblasts, secrete various collagen, glycoprotein and other extracellular matrix, and release a large number of cytokines, such as transforming growth factor, C-transforming growth factor, platelet derived growth factor, etc. Meantime, a large number of released cytokines in turn activate new hepatic stellate cells and secrete a large number of extracellular matrix,

thus forming a vicious cycle. In addition, a large amount of transforming growth faction-β1 released by activated hepatic stellate cells inhibits the expression level of matrix metalloproteinases, which reduces the degradation of extracellular matrix and leads to a large amount of extracellular matrix deposition, thus accelerating or aggravating the course of hepatic fibrosis[23].

When a variety of chronic injuries, inflammation, etc. continue to stimulate hepatic stellate cells, the hepatic stellate cells activate and secrete a large amount of extracellular matrix, whereas large deposition of extracellular matrix is the most important cause of hepatic fibrosis. Although a variety of cells can synthesize and secrete extracellular matrix, the extracellular matrix secreted by activated hepatic stellate cells is the main source in the process of hepatic fibrosis in various liver diseases[24].

Extracellular matrix deposition is both a product and a cause of hepatic stellate cell activation[25]. It is clearly known that activation of hepatic stellate cells is the cytological basis for the formation of hepatic fibrosis, and activated hepatic stellate cells are also the main source of large deposition of extracellular matrix. Hepatic fibrosis is a pathological process in which the activation of hepatic stellate cells and their activation product extracellular matrix play an important role. Therefore, we hold the opinion that activated hepatic stellate cells are closely related to hepatic fibrosis and are the central link in the occurrence of hepatic fibrosis.

5 Relationship of Hepatic Sinusoidal Capillarization and Hepatic Fibrosis

Liver sinusoidal endothelial cells are thin layer of flatten cells covering the hepatic sinusoids, and account for a large proportion of liver non-parenchymal cells. Due to large number of fenestrae on their surface and the lack of basement membrane characteristics, they become the most permeable endothelial cells in the body, which is a unique morphological structure that distinguishes them from other endothelial cells. The fenestra mainly acts as a screening barrier in the process of material exchange between blood and liver cells. In addition, there is no complete basement membrane in human liver endothelial cells, which makes material exchange smoother. It is just because of this unique physiological structure that the liver sinusoidal endothelial cells become the most permeable physiological structure in the human body, and the material exchange between blood and liver cells can be carried out.

Fenestra and basement membrane are the most characteristic structures of hepatic sinusoidal endothelial cells. When hepatic fibrosis occurs, hepatic stellate cells are stimulated and activated to synthesize and secrete a large amount of extracellular matrix, and increased synthesis and decreased decomposition of these extracellular matrix results in large deposition. These deposits narrow the diameter and decrease the number of fenestrae, or even make them disappear; the basement membrane expands or even joins into slices; hepatic microcirculation is impaired, which is not conducive to the uptake of nutrients by liver cells from the blood, resulting in ischemia and hypoxia of hepatocytes. These are collectively referred to as hepatic sinusoidal capillarization, which is one of the characteristic pathological changes of hepatic fibrosis and is of great significance in the pathological process of various acute and chronic liver diseases[26]. Hepatic sinusoidal capillarization causes changes in the fenestra structure of liver sinusoidal endothelial cells and loss of function, which weakens the material communication between hepatocytes and blood. As hepatocytes lack the support of oxygen and nutrients and lack of energy, they can not maintain the normal shape of cytoskeleton, and the skeleton collapses, resulting in loss of its supporting and fixed function. As a result, the fenestra structure is further destructed, which further aggravate the liver injury, forming a vicious circle. Hepatic sinusoidal capillarization can promote the occurrence and development of hepatic fibrosis, accelerate liver failure, lead to portal hypertension, and trigger a series of complications[27].

Hepatic sinusoidal capillarization will directly lead to ischemia and hypoxia of hepatocytes, insufficient supply of nutrients, and hepatocyte injury, which will stimulate hepatic stellate cells to release extracellular matrix, and a large amount of extracellular matrix are deposited in the Disse space, which accelerates the process of hepatic fibrosis and promotes the transformation of hepatic fibrosis into cirrhosis, ultimately leading to liver failure. Studies have confirmed that hepatic sinusoidal capillarization will weaken the exchange of substances between hepatocytes and hepatic sinusoids, which is an important factor leading to cirrhosis and even liver failure[28].

6 Relationship of Hepatic Stellate Cells and Hepatic Sinusoidal Capillarization

Hepatic sinusoidal capillarization is closely related to the activation of hepatic stellate cells. Hepatic sinusoidal capillarization refers to the loss of fenestration of hepatic sinusoidal endothelial cells, the appearance of continuous basement membrane and pathological angiogenesis. The liver cells are stimulated to secrete a variety of substances, mainly extracellular matrix secreted by activation of hepatic stellate cells. There are many kinds of extracellular matrix, including type I, II, IV collagen, glycoprotein, proteoglycan and various cytokines, including transforming growth factor, platelet derived growth factor, epidermal growth factor, endothelin, *etc*.[29]. Transforming growth factor-β1, as

the strongest factor known to induce hepatic fibrosis, can not only promote the secretion of extracellular matrix, but also inhibit matrix metalloproteinases, thereby inhibiting the degradation of extracellular matrix. These extracellular matrixes are deposited in large quantities on the surface of hepatic sinusoids, resulting in narrowed or even disappeared fenestra structure of hepatic sinusoidal endothelial cells, which is the so-called "loss of fenestration". Moreover, laminin and type IV collagen in extracellular matrix are the material basis for the synthesis of basement membrane. When hepatic fibrosis occurs, the amount of laminin and type IV collagen increases and there are abundant materials for the synthesis of basement membrane, so the basement membrane is enlarged in area and even forms continuous basement membrane, which is one of the characteristic manifestations of hepatic sinusoidal capillarization. A large number of new basement membranes in the hepatic sinusoids lead to reduced space in the hepatic sinusoids and increased blood flow resistance, and some blood vessels in the liver are damaged, resulting in hepatic microcirculation disorders.

Hepatic fibrosis leads to weakened or lost function of some liver cells, liver ischemia and hypoxia, and insufficient energy, and is unable to maintain the physiological structure of cytoskeleton, resulting in the atrophy and collapse of cell structure, which further accelerates the loss of fenestrae of hepatic sinusoidal endothelial cells. Fibronectin secreted by activated hepatic stellate cells accelerates the phenotypic transformation of hepatic stellate cells and helps them to transform into myofibroblasts, secreting various types of collagen and laminin, which are the main material sources for the formation of the basement membrane of hepatic sinusoidal endothelial cells. In addition, hepatic ischemia and hypoxia can lead to compensatory hyperplasia of blood vessels, which is the main cause of pathological angiogenesis in hepatic sinusoidal capillarization. Activated hepatic stellate cells can release endothelin and vascular endothelial growth factor, in which endothelin causes intense contraction of blood vessels, leading to hepatic sinusoid contraction and aggravating hepatic ischemia and hypoxia. At the same time, V epidermal growth factor can induce angiogenesis, and the two work together to accelerate pathological angiogenesis.

In addition, because of the unique cellular structure, liver sinusoidal endothelial cells are the pathway of hepatic sinusoid hemofiltration, and also an important source of nutrients and oxygen required by liver cells. In chronic liver injury diseases, normal hepatic sinusoidal endothelial cells can intercept related cytokines and effectively prevent or even help reverse the activation of hepatic stellate cells. Some researchers have co-cultured freely activated hepatic stellate cells with hepatic sinusoidal endothelial cells, and found that the expression of α-smooth muscle actin, a marker of hepatic stellate cell activation, is significantly reduced. However, when the hepatic sinusoidal capillarization occurs, hepatic cell ischemia and hypoxia caused by poor blood circulation and nutrient delivery will aggravate the activation of hepatic stellate cells. It can be seen that hepatic sinusoidal endothelial cells have a bidirectional regulatory effect on hepatic stellate cells, and hepatic sinusoidal capillarization will accelerate the activation of hepatic stellate cells. Therefore, inhibition of hepatic sinusoidal capillarization is a potential target to reverse hepatic fibrosis.

7 Conclusions

In summary, hepatic stellate cells and liver sinusoidal endothelial cells have a close relationship with hepatic sinusoidal capillarization. Whether it is the activation of hepatic stellate cells or the capillarization of hepatic sinusoids, it will aggravate liver injury, accelerate the process of hepatic fibrosis, promote the occurrence and development of cirrhosis, and even lead to a series of serious diseases such as liver cancer and hepatic encephalopathy. Therefore, it is of great significance for improving or even reversing hepatic fibrosis by actively repairing hepatic sinusoidal capillarization, preventing or reversing hepatic stellate cells. Slowing down the progression of liver diseases by regulating hepatic microcirculation, and increasing the exchange of substances between blood and liver cells is a research hotspot nowadays. At present, the research on hepatic stellate cells and hepatic sinusoidal capillarization is becoming more and more thorough, and has made a lot of achievements, but the relationship between hepatic stellate cells and hepatic sinusoidal capillarization and the mechanism of action are still unclear, which still needs to be explored.

We hope to further clarify the relationship between hepatic stellate cells and hepatic sinusoidal capillarization, try to relieve the vicious cycle between them, and find an effective treatment to prevent or even reverse this situation, in order to provide a new idea for the treatment of hepatic fibrosis. It is of great significance for relieving and reversing hepatic fibrosis, and is conducive to relieving the pain of patients with liver disease, reducing social pressure, and improving the health level and quality of life of patients.

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