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Research Progress of Traditional Chinese Medicine Intervention on TGF-B/Smad2 Signaling Pathway in Anti-Liver Fibrosis

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Abstract: liver fibrosis is a liver disease caused by early hepatic lobule endogenetic resulting from a fibrous tissue hyperplasia and normal pathological process of protein deposition process, traditional Chinese medicine for the treatment of acute liver fibrosis with the advantages of multiple targets, multi-channel, effective control of liver fibrosis development, traditional Chinese medicine (TCM) is the current reversal fibrosis, one of the highlights in agro-scientific research in the prevention and treatment of liver diseases, this paper To summarize the research literature on the intervention of TGF-β/Smad signaling pathway by traditional Chinese medicine in anti-liver fibrosis in recent years, so as to provide ideas and references for clinical medication of anti-liver fibrosis.

1. Introduction

Liver fibrosis pathological essence mainly by chronic liver disease organs has long been the cause of all sorts of all sorts of chronic complex pathological and directly after the injury or damage caused by the liver cells and cell formed by the diffuse fibrosis of perilymph matrix substrate excessive fibrosis, sedimentary formation and cell matrix of abnormal fibrosis pathological distribution, is appeared in numerous complex kinds of patients with chronic liver disease An early pathological stage that gradually evolved into the formation of various acute hepatitis toxic necrosis reactions, abnormal enzyme activation of hepaticstellate cell (HSC) fibrosis, and extracellular matrix (ECM) fibrosis. The accumulation and accumulation of extracellular matrix (ECM) and fibrosis lead to the complete degeneration of the liver structure, which destroys the important pathological changes of the liver after fibrosis. Liver fibrosis is caused by a wide range of causes, including chronic viral hepatitis, alcoholism, alcoholic hepatic steatohepatitis and other diseases and any other chronic autoimmune diseases. It is the first step of the four steps of liver cirrhosis, hepatocellular carcinoma and death[1-2]. Studies have shown that transforming growth factor beta (TGF-β) has different effects on liver fibrosis tissues and cells, and is an important fibrogenic factor.

Tgf-β can up-regulate the synthesis of ECM by HSCS and accelerate the development of liver fibrosis.[3] Liver fibrosis is the result of the regulation of a variety of cytokines and signaling pathways. HSC receptor activation mechanism is the most important in research of liver fibrosis pathological diagnosis way, research has showed activation of TGF - beta 1 / Smad signaling pathway is raised liver cell activation of HSC and promote the liver cell ECM proteins generated a kind of main active way, in order to activate the TGF - beta pathway as the target, by blocking or it could be a target to reverse liver fiber The research on the prevention and control mechanism of chemical can provide a new idea[4]. the process of liver fibrosis in China many traditional to primary liver cirrhosis development of chronic liver disease and even secondary liver cancer transformation in the development course of the first important biochemical processes, its early on the histology of reversibility, the treatment of liver fibrosis specific drugs to be clinically mining at home and abroad related research focus and hot spot of experts in the field. Treatment of Chinese medicine in recent years in the field of modern anti liver fibrosis curative effect achieved some results have certain practical value, this paper attempts to China in recent years about the traditional Chinese medicine monomer or some traditional Chinese medicine compound preparation based on TGF - beta/Smad signaling pathways of anti fibrosis treatment drug experiments clinical research were reviewed, in order to investigate the current treatment of traditional Chinese medicine resistance The study of the effective mechanism of liver fibrosis and clinical medication provide a certain basis.

2. The Role of Tgf-B/Smad2 Signaling Pathway in Liver Fibrosis

2.1 Molecules Involved in Tgf-B/Smad2 Signaling Pathway

The main functional structure of TGF-β protein /Samd signaling pathway is mainly composed of TGF-β protein superfamily, TGF-β superfamily receptor and Smads protein family receptor. TGF - beta superfamily cell growth and differentiation of active factor can directly involved in regulating the normal cells of normal growth, differentiation, apoptosis, adhesion, fast ECM gene synthesis and gene expression regulation and cancer fast sedimentation regulation and normal embryonic cells rapidly development, rapid growth, differentiation and apoptosis fast repair necrotic tumor tissue surface inflammation and cell toxicity inhibition of immune response It has a series of multiple physiological functions, such as repair, tumor suppression and fibrosis treatment. It is a fast and efficient multi-effect kinetic energy biological active cytokine factor (GDF) protein, bone morphogenicprotein (BMP), etc. TGF-β peptide is a kind of latency associated peptide composed of N-terminal amino acids peptide, LAP) and a large precursor molecule of the mature C-terminal domain. The hydrophobic residues produced in resting LAP cells bind to the resting TGF-β protein and are modified by protease and then bind in a non-covalent manner to form a small dormant resursome molecule with a smaller cell size latent complex (SLC)), and then dormant dormant LAP cells form a large-molecule dormant complex with dormant dormant TGF-β binding Protein (LTBP), a process called Tgf-β activation[5]. thrombospondin 1 (TSP-1) receptor in vivo can release TGF-β by changing the structure of platelet LTBP receptor. At the same time, high temperature, strong acid and alkali environment can also make TGF-β released from the complex[6]. At present, there are three main subtypes of TGF-β-mediated superfamily receptors in the main application research at home and abroad: TβRⅠ, TβRⅡ and TβRⅢ, respectively. Among them, TβRⅢ receptors are usually not completely and effectively directly involved in the transmission of signal pathways, while TβRⅠTβRⅡ receptors can be completely and directly mediated at the same time TGF - beta directly involved in the signal path and another in the process of transmitting signals more receptors, as the main function of T beta R Ⅱ by fitness at the same time by selective phosphorylation T and

R Ⅰ beta receptors activated T beta R Ⅰ kinase domain structure, phosphorylated activated T beta R Ⅰ signals will be further identified and further phosphorylation of transhipment to downstream of the enzyme molecule, to participate in the TGF -β signaling[7]. Smad protein family is on the human genome is currently the only known and currently the only known TGF - beta 1 across the cell membrane mass transfer downstream of the nucleus of the substrate, is currently on the human body is the most main molecules within the cell wall of the membrane effect, including nine members, according to the shape of the structure and application scope of different sizes and can be simply divided into the above three types, including receptor Regulatory type (R-Smad):Smad1, 3, 5, 8, 9, among which Smad and Smad3 mainly exist in the cytoplasm, and TβR Ⅰ mainly exists in the nucleus after activation and phosphorylation. The second type is co-regulated Smads(Co-Smad), including Smad4, one of the most important components of TGF-β family signaling proteins, which does not bind to TβR and is not phosphorylated. The third type is the inhibitory Smad(I-Smad), including Smad6 and Smad7, which competitively bind to Tβ and R-1 and block the R-Smad phosphorylation is a major inhibitor of the TGF-β1/Smad signaling pathway[8].

2.2 Relationship between Tgf-B/Smad2 Signaling Pathway and Liver Fibrosis

The process of liver fibrosis is the repair response of liver tissue after injury, which is related to the imbalance between the production and degradation of ECM, and the inhibition of matrix metalloproteinases (MMPs) and their complexes with tissue inhibitors The expression of metalloproteinases (TIMPs) is unbalanced, which increases the synthesis activity of ECM and decreases the decomposition rate. TIMPS specifically inhibits the activity of MMPs and accelerates the formation of liver fibrosis[5]. The TGF-β/ signaling pathway, the two main pathways that promote ECM signaling generation through HSC activation, is involved in almost every historical process that has witnessed the development of liver fibrosis formation, namely inflammation, tissue regeneration, and fibrosis. [9] When the liver is chronically injured, TGF-β inhibits ECM degradation, and Tgf-β1 dimers bind to TβR Ⅱ, which attracts and phosphorylates R-Smad (Smad1, and 3). After phosphorylation, R-Smad and Co-Smad(Smad4) form complex (Smad) 3, 4), enter into the nucleus to regulate the reverse transcription of target cell genes on mRNA expression. By regulating gene expression, HSC and collagenase activities are inhibited, HSC enzymes are activated, a large number of MFB are produced, and ECM(α-SMA, type Ⅰ, Ⅲ, Ⅳ, Ⅴ collagen) is increased. The negative regulatory effect of Smad6 and Smad7 in the cytoplasm can effectively reduce the formation of complex, promote the binding of Smad to activated TβR Ⅰ, prevent HSC transformation, and delay the formation of liver fibrosis[8].

3. Study on Anti-Liver Fibrosis of Traditional Chinese Medicine

There was no “liver fibrosis” in the traditional medical terms. According to the investigation of its exact pathogenesis and etiology, it was classified to the categories of “accumulation”, or “inflammation of abdomen”, or “flank pain” and “expansion of abdomen”. The main causes may include external damp heat and epidemic virus, deficiency of vital qi, qi stagnation and blood stasis, Yin deficiency of liver and kidney, etc. The clinical dialectics can be broadly divided into: liver and gallbladder damp heat, liver stagnation and spleen deficiency, qi and blood Yin deficiency damage, blood stasis blocking collaterals and other syndrome types, which are the syndrome of deficiency and excess, deficiency and excess mixed with deficiency[10]. 'TCM can effectively regulate the hepatic TGF-β and 1/Smad signaling pathway by selectively inhibiting the expression activity of hepatic fibrosis-promoting factors and indirectly inhibiting the induction and activation of hepatic

HSC proteins, thus indirectly playing an important role in anti-hepatic fibrosis. The therapeutic mechanism of traditional Chinese medicine for liver fibrosis is to inhibit the activation of hepatic HSC enzymes, reduce stem cell damage, inhibit ECM synthesis, anti-oxidation, and inhibit inflammation [11].

3.1 Chinese Medicine Monomers and Liver Fibrosis

Recently, the use of astragalus polysaccharide, tanshinone, forsythoside and other traditional Chinese medicine monomers to improve liver fibrosis through TGF-β1/Smad signaling pathway has emerged in an endless stream. May[12] and other Chinese scholars after successively by many in vitro or animal experiment analysis is naturally found in traditional Chinese medicine compound whitehead black tincture and its main anticancer pharmacological active ingredients in the steroid C - 1 and its derivatives can be directly effective through selective inhibition in vitro Smad3 Smad human plasma protein concentration and tumor cell plasma protein phosphorylation levels, lower T tumors in vivo GF-β1/Smad signaling pathway inhibits the activation of liver inflammatory cells to achieve long-term anti-liver fibrosis effect. An Zhiqiang[13] et al. 's experimental results showed that forsythoside, one of the main anti-tumor effective components of forsythiasis, could temporarily slow down the process of primary liver fibrosis by up-regulating the expression of Smad7 gene and controlling the TGF-β/Smad signaling pathway to inhibit the activation of HSC enzymes in vivo. Yue Binbin[14] et al. showed that naringenin could significantly inhibit liver fibrosis and the activation of TGF-β/Smad signaling pathway. Wang Shaozhan et al[15]. also confirmed that quercetin could selectively inhibit the abnormal receptor activation and release process and signal transduction in the TGF-β/Smad signaling pathway in patients with liver fibrosis, and had a significant and lasting bidirectional anti-liver fibrosis effect. Huang Jin[16] et al. showed that astragalus polysaccharides could effectively alleviate the degree of liver fibrosis in CCL4 rats by regulating the TGF-β/Smad signaling pathway and reducing the expression of Tgf-β1 and Smad3 in liver tissue. Curcumin is a monomer of curcuminoids in traditional Chinese medicine[17]. In recent years, researchers have found that curcumin can be used to inhibit Collagen I and Collagen by specific inhibitors III SMA and alpha receptors and the promotion of immune inflammatory factors and gene expression, such as IL - 10 to indirect inhibition of liver fibrosis in mice, relieve mild liver injury in mice caused by chronic liver fibrosis, and discovered one of its main mechanism can be further through specific inhibition of protein phosphorylation of Smad preventing proteins into the nucleus, and affect the downstream fibrous protein coding The p-65/NF-κB signaling pathway mediated by p-smad is inhibited to further achieve its effective inhibition and effect on the early occurrence and development of chronic liver fibrosis. Ferulic acid, the active component of Angelica sinensis and other drugs, can effectively reduce fibrosis of LX-cells induced by TGF-β1, and its mechanism may be through the down-regulation of Smad /3 phosphorylation and the inhibition of Smad4 translocation to the nucleus[18]]. Yang[19] et al. used isorhamnetin to play an anti-fibrosis role by down-regulating the expression of TGF-β1, p-Smad /3 and α-SMA, and had a dose-dependent reduction effect on HSC cell proliferation, hydroxyproline production, and TGF-β1, p-Smad /3 and α-SMA protein expression.

3.2 Traditional Chinese Medicine Compound and Liver Fibrosis

There are increasing studies on the mechanism of action of traditional Chinese medicine compounds such as self-made prescriptions and empirical prescriptions against liver fibrosis. Many experiments have verified that traditional Chinese medicine compounds can inhibit the development of liver fibrosis at the molecular and protein levels by inhibiting the TGF-β/Smad signaling pathway and reducing the expression of related proteins [20]. In recent years, the use of traditional Chinese

medicine compound in the treatment of liver fibrosis has increased. The traditional Chinese medicine compound pays attention to the method of nourishing and strengthening, and the characteristics based on activating blood and dredging collaterals have been highlighted, showing the unique advantages of traditional Chinese medicine compound in the clinical treatment of liver fibrosis. Su Yanqiu[21] et al. used Professor Sun Bin's self-designed formula Shipiruangan pill to perform in vitro experiments and proved that Shipiruangan pill (Codonopsis rhizoma, Atractylode rhizoma, Poria cocos, Bupleurum, Rhizoma corynesum, Xiangfu, Chaihu, Coicis seed, fried chicken internal gold and other drugs) could effectively improve liver function, reduce liver injury, reduce enzyme and protect liver. Jieyang[22] and others on the basis of peach pit gas bearing soup to add and subtract for liver spleen and activating blood, the formulas: peach kernel, turtle shell, cassia twig, rhubarb, big jujube, notoginseng powder, sweet wine, atractylodes, rhizoma zedoariae, poria cocos, salvia miltiorrhiza, liquorice, altogether plays liver spleen, soft firm fights effect, by relieving liver inflammation, to protect the liver function, reduce the collagen deposition by inhibiting liver tissue CUGBP1 table Smad7 up-regulation and TGF-β1/Smad7 reduction can inhibit the progression of liver fibrosis. Qiu-ju zhang[23] and others to add and subtract form the basis of turtle shell Fried liver collaterals and amuse oneself, composed of radix bupleuri, main astragalus root, rhizoma zedoariae, turtle shell and hovenia dulcis thunb, and found that the effective alleviate liver cell degeneration necrosis, inflammatory cells infiltration and fibrosis degree and high dose of soothing the liver and collaterals amuse oneself will also significantly reduce TGF - 1, Smad proteins with molecular expression. CGA[24] formula for (cordyceps sinensis mycelium polysaccharides, gynostemma saponins and peach kernel) and so on, by the Chinese traditional medicine compound righting capsule modified formula in the blood compatibility research form, centralizer blood capsules formula has passed approved by an official production guide recommended production and promote the use, used in traditional Chinese medicine clinical, In the treatment of acute and chronic liver fibrosis caused by hepatitis B [25] or infectious hepatitis B virus and other pathogens, Sirius red staining and liver fibrosis grading showed that collagen deposition, collagen and HYP content in the liver had comparable inhibitory effect with Fuzheng Huayu capsule, and this prescription had less effect and required less drug sources than Fuzheng Huayu capsule. As a classic traditional Chinese medicine prescription, Yiganlong recipe has also been used in clinical research for many years in China[26]. The results of a number of in vitro pharmacological experiments on Yiganlong Recipe have shown that the biomarkers of liver fibrosis, CollagenⅣ and Collagen Yggl capsule significantly reduced the expression of III, hyaluronan and laminin, and downregulated the expression of p-Smad, a protein related to liver fibrosis P-Smad3, Smad4, up-regulate the expression of Smad7 protein, accelerate the degradation of extrahepatic protein matrix of hepatocytes, block the TGF-β1/Smad signaling pathway, regulate the balance between inflammatory factors IL-4, IL-17a and INF-γ, reduce the degree of liver fibrosis and protect liver tissue damage. Cai[27] and others had by dimethyl nitrosamine compounds (DMN) induced rat experimental liver fibrosis model experiment used artemisia capillaris soup solution (artemisia capillaris, gardenia, rhubarb) treatment, the experimental observation results show that the artemisia capillaris soup solution in mice liver cancer of the liver tissue fibrosis induced by DMN pathological features are evident in the effective good clinical improvement And preventive treatment effect, make liver free protein and binding protein gradually returned to normal to basic normal bile acid level, and at the same time show that the proposed by cutting alpha SMA, TGF - beta 1, P - Smad3 receptor gene expression, regulating metabolism of bile acid synthesis of liver cells and related peroxidase metabolism to reduce induced by DMN progressive liver fibrosis and cirrhosis of the liver caused by TGF-β1/Smad/ERK signaling pathway can inhibit the inhibition and activation of HSC proliferation induced by chenodeoxycholic acid.

4. Conclusion

This article through to the domestic in recent years is given priority to with TCM intervention of TGF - beta 1 / Smad signaling pathways summarized the status quo of clinical research of anti liver fibrosis mechanism, to evaluate the method of traditional Chinese medicine treatment of chronic liver fiber lesions and may even reverse early malignant liver fibrosis effect level to provide important theoretical basis, from the macro aspects of the theory of traditional Chinese medicine knowledge and more microscopic field Method, the combination of protein molecules in the immune gene and protein molecular level against chronic liver fibrosis lesion provides a new medical theory basis, but the author through many years of research and the present situation analysis of traditional Chinese medicine were reviewed, the study found many local research work was limited to clinical animal behavior research, method of traditional Chinese medicine treatment of early pathological changes of hepatic fibrosis clinical effect observation work less In addition, this article only focuses on the positive effect of traditional Chinese medicine on blocking TGF-β1/Smad signaling pathway and treating primary liver fibrosis, and whether it also has intervention effects on other related signaling pathways is still unclear, which is also one of the deficiencies of this study.

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