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Research Progress on Bilirubin Metabolism based on FXR Agonist Regulation and the Treatment of Jaundice in Traditional Chinese Medicine

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Abstract: ***Jaundice is a common clinical symptom caused by bilirubin metabolism disorders and is closely related to diseases of the liver, biliary tract and blood system. As a core nuclear receptor regulating bile acid metabolism, farnesol X receptor (FXR) maintains metabolic homeostasis by regulating bile acid synthesis (inhibiting CYP7A1), transport (promoting BSEP, MRP2), and enterohepatic circulation (inducing IBABP and FGF19). Traditional Chinese medicine takes 'dissolving dampness and facilitating urination' as the core treatment principle, showing multi-target advantages in the treatment of jaundice. Emodin and gardenoside and other active ingredients of traditional Chinese medicine can directly activate FXR, reduce bile acid synthesis through "downregulation of FXR→SHP→CYP7A1", and promote bile acid and bound bilirubin excretion by upregulation of BSEP and MRP2; some traditional Chinese medicines can also enhance bilirubin-binding conversion by regulating UGT1A1 activity, or indirectly affect the FXR signalling pathway by remodeling the intestinal flora (e.g., inhibiting BSH activity and enriching beneficial bacteria) and regulating the microbiota-bile acid-FXR axis. Studies have shown that FXR agonists (such as obeticholic acid) and traditional Chinese medicine have a multi-dimensional intersection in regulating bilirubin metabolism, and the combination of the two forms an innovative strategy of "targeted intervention and systematic regulation". In the future, it is necessary to deeply explore the structure-activity relationship and synergistic mechanism between traditional Chinese medicine ingredients and FXR, verify the efficacy through multi-centre trials, promote the development of new drugs and the advancement of precision diagnosis and treatment of integrated traditional Chinese and Western medicine, and provide a scientific basis for the treatment of jaundice and related hepatobiliary diseases.***

Keywords: FXR agonists, Bilirubin metabolism, Jaundice, Chinese medicine, Research progress.

1. Introduction

Jaundice is a common clinical symptom caused by yellow discolouration of the skin and mucous membranes due to elevated serum bilirubin levels, usually caused by bilirubin metabolism disorders. The pathogenesis of jaundice mainly involves abnormal bilirubin metabolism, including bilirubin production, binding, transport and excretion. When bilirubin is produced too much or excretion is blocked, serum bilirubin levels rise, leading to the development of jaundice. Jaundice is an important clinical manifestation of many diseases and has important diagnostic value. It is not only a common symptom of liver disease, but may also indicate diseases of the biliary system, blood system, or other systems [1] [2].

Farnesol X receptor (FXR, NR1H4) is a nuclear receptor widely found in tissues involved in bile acid metabolism, such as the liver, intestines, and kidneys. The natural ligand of FXR is bile acids, which play a key role in maintaining bile acid homeostasis by regulating their synthesis, transport, and excretion. In recent years, FXR agonists have received significant attention for their potential therapeutic effects in metabolic diseases. The regulatory role of FXR agonists in bilirubin metabolism is one of the hot topics of current research [3].

Traditional Chinese medicine has the characteristics of multi-target effect, which can simultaneously regulate bilirubin metabolism, bile acid secretion and liver detoxification function. It has high safety, few side effects, and no dependence, especially suitable for long-term treatment and chronic disease management. Modern research has found that certain TCM ingredients can regulate bile acid metabolism by activating FXR (farnesate X receptor), which in turn affects the excretion of bilirubin. Clinical studies have shown that traditional Chinese medicine has significant efficacy in the treatment of viral hepatitis, cirrhosis jaundice, obstructive jaundice, etc. Studying the synergistic mechanism of traditional Chinese medicine and FXR agonists will help further reveal the targets and molecular mechanisms of traditional Chinese medicine, and provide a scientific basis for the modernization of traditional Chinese medicine [4].

This paper reviews the relevant literature in recent years, deeply explores the regulatory mechanism of FXR agonists in bilirubin metabolism, further reveals the targets and molecular mechanisms of traditional Chinese medicine, provides a scientific basis for the modernisation of traditional Chinese medicine, and promotes the theoretical innovation of integrated traditional Chinese and Western medicine. It promotes multidisciplinary interdisciplinary cooperation, aiming to provide a reference for in-depth research in this field.

2. Mechanisms by which FXR Agonists Regulate Bilirubin Metabolism

2.1 Physiological Functions of FXR

FXR (farnesate X receptor) is a nuclear receptor that plays a central regulatory role in bile acid metabolism. The following are its main functions and mechanisms of action [5]:

1) Inhibition of bile acid synthesis: FXR inhibits bile acid

synthesis by regulating the expression of CYP7A1, a key enzyme in bile acid synthesis. After bile acids bind to FXR, activated FXR induces the expression of small heterodimer chapermates (SHPs) [5]. SHP can inhibit the activity of transcription factors LRH-1 and HNF4α, thereby inhibiting the transcription of CYP7A1. This negative feedback mechanism helps maintain stable bile acid levels and prevent liver damage caused by excessive bile acid accumulation [5].

2) Promote bile acid binding and transport: In hepatocytes, FXR activation can promote bile acid binding and transport. FXR promotes the secretion of bile acids from hepatocytes into bile by inducing the expression of bile acid output pumps such as BSEP. In addition, FXR can upregulate the expression of multidrug resistance protein 3 (MDR3) and multiple drug resistance-related protein 2 (MRP2), further promoting the excretion of bile acids [6].

3) Regulate the enterohepatic circulation of bile acids: In the intestine, FXR promotes the absorption and transport of bile acids in the intestine by inducing the expression of intestinal bile acid-binding protein (IBABP) [7]. In addition, FXR can upregulate the expression of the organic solute transporter α/β (OSTα/OSTβ), promoting the return of bile acids from the intestine to the liver. This process is essential for maintaining the enterohepatic circulation of bile acids [7].

(4) Interaction with other signalling pathways: FXR not only plays a role by directly regulating the expression of genes related to bile acid metabolism but also interacts with other signalling pathways [6]. For example, FXR activation can induce the expression of fibroblast growth factor 19 (FGF19), which further inhibits the expression of CYP7A1 by binding to the FGFR4 receptor. In addition, FXR also plays a comprehensive regulatory role in metabolic diseases by regulating lipid metabolism, glucose metabolism, and inflammatory responses [8].

2.2 Mechanism of Action of FXR Agonists

FXR agonists regulate the expression of genes related to bile acid metabolism by activating FXR, thereby affecting bilirubin metabolism. FXR agonists can inhibit the expression of CYP7A1, a key enzyme in bile acid synthesis, by activating the FXR-expressed Shp protein, which directly inhibits the transcription of CYP7A1. In addition, FXR activation promotes the expression of bile acid output pump BSEP and increases the excretion of bile acids. FXR agonists can also induce the expression of the bile acid-binding protein IBABP, promoting the reabsorption of bile acids in the intestine [9].

Under the action of FXR agonists, the synthesis and excretion of bile acids are balanced, preventing liver damage caused by excessive accumulation of bile acids. FXR agonists induce SHP expression through the FXR/RXR heterodimer form, bind to LRH-1, inhibit the expression of CYP7A1, thereby reducing bile acid synthesis. At the same time, FXR agonists activate FXR and promote the excretion of bile acids, which is achieved through the FXR target gene BSEP. In addition, FXR agonists can also affect bilirubin metabolism by regulating the expression of transporters such as MRP2 [9].

Obeticholic acid (OCA), as an FXR agonist, has been used clinically in the treatment of cholestatic diseases such as primary biliary cholangitis (PBC). Several studies have shown that OCA significantly improves liver function in animal experiments by modulating bile acid metabolism and reducing the inflammatory response in the liver. Verbeke et al. [10] evaluated the effects of OCA on liver fibrosis and inflammation in a rat model of thioacetamide (TAA)-induced cirrhosis, and found that OCA reduces liver inflammation and reduces pro-inflammatory cytokine levels (e.g., MCP-1, IL-6) by inhibiting the NF-κB pathway. A Dash et al. [11] verified the regulatory mechanism of OCA on bile acid metabolism through in vitro experiments and transcriptome analysis, and found that OCA inhibits bile acid synthesis genes (e.g., CYP7A1, CYP27A1) by activating FXR, and upregulates bile acid transporters (ABCB4, ABCB11, OSTα/β) to promote bile excretion. In an animal experiment in a mouse model of high-fat diet-induced non-alcoholic fatty liver disease (NAFLD) [12], OCA was found to promote the conversion of primary bile acids to secondary bile acids by modulating the gut microbiota (e.g., enrichment of Akkermansia muciniphila), reducing liver fat deposits and inflammation. After antibiotics cleared the gut microbe, the therapeutic effect of OCA disappeared, suggesting microbiota dependence.

2.3 Effects of FXR Agonists on Bilirubin Metabolism

FXR (farnesate X receptor) agonists can indirectly affect bilirubin metabolism by regulating bile acid metabolism. FXR is highly expressed in tissues involved in bilirubin metabolism, such as the liver, intestine and kidney, and its activation can inhibit the rate-limiting enzymes CYP7A1 and CYP8B1 (by inducing the expression of small heterodimer chaperone SHP), and promote the binding and excretion of bile acids, thereby reducing the liver accumulation of bile acids and bilirubin. As the first FXR agonist approved for the second-line treatment of PBC, OCA significantly reduced bilirubin levels and improved other liver function markers in clinical trials. In a rat model of pyrazinamide (PZA)-induced cholestasis, Guo et al. found that OCA activated FXR significantly upregulated the expression of hepatocyte bile acid export pump (BSEP, ABCB11) and multidrug resistance-related protein 2 (MRP2, ABCC2), promoting the synergistic excretion of bile acids and bound bilirubin. It also inhibits the bile acid uptake protein NTCP (SLC10A1) and reduces the reabsorption of bile acids and bilirubin in hepatocytes, thereby reducing serum total bilirubin (T-BIL) levels (down 38%) and direct bilirubin (D-BIL) levels (down 42%). The study confirmed that the above effects of OCA completely disappeared in FXR gene knockout ($FXR^{-/-}$) mice, confirming FXR dependence.

3. Regulation of Bilirubin Metabolism and FXR Signalling Pathway by Traditional Chinese Medicine

3.1 Traditional Chinese Medicine Treatment of Jaundice

The understanding of jaundice in traditional Chinese medicine began in the “Huangdi Neijing”, and Zhang Zhongjing in the Eastern Han Dynasty systematically classified and created classic prescriptions such as Yinchen Hao Tang and Yinchen Wuling San for the first time in the “Essentials of Jinkui”, laying the foundation for clinical treatment in later generations. The core of the pathogenesis of jaundice is

"damp evil", which often combines heat, cold, epidemic poison, stasis and other evils, and the disease is mainly located in the spleen, stomach, liver, and gallbladder, following the basic treatment principle of "dissolving damp evil and facilitating urination". Modern research has also confirmed that many traditional Chinese medicines and prescriptions have the effects of promoting bile secretion, regulating bilirubin metabolism, anti-inflammatory properties and protecting the liver, etc., providing theoretical and practical support for the treatment of jaundice with integrated traditional Chinese and Western medicine.

3.2 Effects of Traditional Chinese Medicine Components on Bilirubin Metabolism

The active ingredients of some traditional Chinese medicines play a therapeutic role by regulating the activity of enzymes related to bilirubin metabolism and the expression of transporters, promoting the binding and excretion of bilirubin, and reducing accumulation in the body. For example, rhubarb, gardenia, knotweed, yinchen and other traditional Chinese medicines contain emodin, rhubarbic acid, resveratrol, gardeniside and other chemical components, all of which are FXR agonists, which reduce bile acid synthesis through "FXR → SHP → CYP7A1/CYP8B1 downregulation", while "FXR → BSEP/MRP2/Ost-β upregulation" to enhance bile acid and bind bilirubin excretion.

Emodin is mainly found in traditional Chinese medicines such as Rhubarb and Knotweed in the Polygonaceae family. Emodin specifically activates the nuclear receptor FXR (farnesol X receptor), regulates the expression of the downstream target gene BSEP (bile salt export pump) through FXR, and enhances the ability of hepatocytes to excrete bile acids and binding bilirubin into the bile tubules [14]. At the same time, the activation of FXR upregulates the expression of MRP2 (multidrug resistance-associated protein 2), further promoting the excretion of bound bilirubin through the bile duct membrane [15]. It has also been found that emodin can increase the activity of UGT1A1 (uridine diphosphate glucuronyltransferase 1A1), promote the conversion of unconjugated bilirubin (fat-soluble) to conjugated bilirubin (water-soluble), and lay the foundation for subsequent excretion [16]. Gardeniside is found in gardenia, a plant of the madder family, and is the main active ingredient in gardenia for the treatment of jaundice. Studies have found that gardeniside can directly upregulate the mRNA and protein expression of UGT1A1, and improve the water solubility of bilirubin by enhancing its catalytic activity and promoting the binding of unbound bilirubin to glucuronic acid [17]. By activating FXR signalling, the expression and localisation of MRP2 on the bile duct membrane of hepatocytes are increased, and the excretion of binding bilirubin into bile is accelerated [18].

3.3 Regulation of FXR Signalling Pathway by Traditional Chinese Medicine

As a core regulator of bile acid metabolism, the activity of farnesol X receptor (FXR) is regulated by multiple levels of traditional Chinese medicine components. In addition to directly activating or inhibiting FXR, TCM ingredients can also affect FXR signalling pathways by remodelling the structure of the gut microbiota and regulating the enterohepatic circulation of bile acids.

1) Direct regulation of FXR by traditional Chinese medicine components: For example, hyperoside [19], by directly binding to the FXR ligand binding domain, activates the FXR/SHP signalling pathway, inhibits key enzymes in liver fatty acid synthesis (e.g., SCD1, SREBP1), and promotes fatty acid β-oxidation. In the nonalcoholic fatty liver disease (NAFLD) model, hypericin can also promote bile acid excretion and reduce intrahepatic cholestasis by activating FXR to upregulate BSEP (bile salt export pump).

2) Special mechanism of inhibition of FXR pathway: Astragalus polysaccharide in Astragalus Chifeng Decoction (Astragalus, Red Peony, Fangfeng) can deregulate FXR expression, relieve its inhibition of CYP7A1 and CYP8B1, and promote bile acid synthesis. This mechanism is manifested in cholestasis models as enlarged bile acid pools and improved cholesterol metabolism [20].

3) Interaction of microbiota-bile acid-FXR axis: Baicalin reduces the debinding of primary bile acids (such as bile acid) and increases its hepatointestinal circulation efficiency by inhibiting bile saline hydrolase (BSH) activity in the intestinal flora. Bound bile acids (e.g., taurinecholic acid) promote bile acid excretion by activating hepatic FXR, upregulating the expression of BSEP and MRP2 [21]. At the same time, baicalin enriches beneficial bacteria in the gut that produce SCFAs (such as Bifidobacteria), which indirectly inhibit hepatic CYP7A1 activity by activating intestinal FXR, promoting FGF19 secretion, and indirectly inhibiting hepatic CYP7A1 activity [21].

4. Summary

As the core regulator of bile acid-bilirubin metabolism, FXR (farnesol X receptor) has a multi-dimensional intersection between the mechanism of agonist and the intervention effect of traditional Chinese medicine, and the combination of the two provides innovative ideas for the treatment of jaundice. FXR agonists achieve precise regulation of bilirubin metabolism by regulating transporters, binding enzymes and the enterohepatic axis. Traditional Chinese medicine directly targets FXR or indirectly regulates intestinal flora through active ingredients, playing a multi-dimensional intervention role. The combination of the two not only provides an innovative strategy of "targeted intervention and systematic regulation" for the treatment of jaundice, but also promotes the integration and development of traditional Chinese and Western medicine theories, opening up a new path for the precise diagnosis and treatment of hepatobiliary diseases.

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