DOI: 10.53469/jcmp.2025.07(01).19

Progress and Prospects of Interleukin-22 in the Treatment of Non-alcoholic Fatty Liver Disease

Yuhao Pan[1], Zebo Yu[2,*]

[1,2]The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
[1]1746722328@qq.com, [2]yuzebo2001@163.com
**Correspondence Author*

Abstract: ***Non-alcoholic fatty liver disease (NAFLD), also known as metabolism-associated fatty liver disease (MAFLD), has turned into the most prevalent chronic liver disease all over the world, with a complex pathogenesis and a lack of specific therapeutic agents. Interleukin-22 (IL-22), as a cytokine, plays a crucial role in liver physiology and pathology. The aim of this paper is to review the prospects and outlook of interleukin-22 (IL-22) in the treatment of NAFLD, introduce the biological functions of IL-22, discuss its mechanism of action in NAFLD, including its regulatory effects on liver inflammation, liver fibrosis, and lipid metabolism, etc., and analyse the current research advances on the treatment of NAFLD based on IL-22, the challenges it faces, and the possible directions for future development.***

Keywords: Non-alcoholic fatty liver disease, IL-22**.**

1. Introduction

Currently, non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease worldwide., and in China, it has replaced viral hepatitis as the number one type of chronic liver disease [1], which can progress to a range of liver diseases, including non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and even liver cancer. Over the past 20 years, the overall prevalence of non-alcoholic fatty liver disease (NAFLD) in adults in China has reached 29.6%, with the prevalence in males being 34.8%, which is higher than that in females (23.5%). The prevalence of NAFLD among the obese population and type 2 diabetes mellitus (T2DM) patients was 66.2% and 51.8%, respectively [2]. Therefore, NAFLD has become an increasing public health challenge in China.

Currently, there is a paucity of therapeutic options for the therapy method of non-alcoholic fatty liver disease (NAFLD), with the main focus being on improving lifestyle and controlling metabolic risk factors, with pharmacological treatments being less effective. Therefore, the search for novel therapeutic approaches is of great value in the management of NAFLD. Interleukin-22 (IL-22), a cytokine with diverse biological functions, is expected to be one of the focuses of NAFLD treatment.

2. Biological Properties of IL-22

1) Structure and origin of IL-22 IL-22 belongs to the IL-10 family of cytokines, and its monomer consists of six α-helices (labelled A-F) and a short N-terminal helix, forming a compact six-helix bundle of cytokines [3].Cells of the lymphoid lineage are the main cells that produce IL-22, and these IL-22-producing cells cover those in the innate and adaptive immune systems, specifically including αβ T cells, γδ T cells, natural killer T cells (NKT cells), and innate lymphoid cells (ILCs); in addition to this, non-lymphoidal lineage cells can also be produced under certain specific circumstances, e.g., lung macrophages can also produce IL-22 in response to lung injury [4].

2) Gene expression of IL-22 The IL-22 gene is located on human chromosome 12q15 [5]. The expression of the IL-22 gene is controlled by multiple factors. When it comes to cytokines like IL-2, IL-6, IL-18, IL-23, IL-1-β and TGF-β, they are significant in regulating the expression of IL-22 within cells such as Th22, Th17 and ILC3 [6,7]. In terms of transcription factors, c-Maf, AhR, Notch, BATF, IRF4, Stat3 and RORγt are involved in the regulation of IL-22 [8].

3) IL-22 receptor The interleukin-22 receptor (IL-22R) is a type II cytokine receptor, a member of the interleukin-10 receptor family [9], which is predominantly expressed in epithelial cells of the skin, lungs, and intestines, including hepatocytes, as well as the kidney [7]. It is composed of two heterodimeric subunits, namely interleukin-22 receptor 1 (IL-22R1) and interleukin-10 receptor 2 (IL-10R2). The gene that encodes human IL-22R1 is situated on chromosome 1p36.11, and the gene encoding IL-10R2 is positioned on chromosome 21q22.11 [11]. IL-22 transmits signals via a heterodimeric receptor complex that consists of the high-affinity subunit IL-22R1 and the low-affinity subunit IL-10R2. This complex triggers the tyrosine kinases Jak1 and Tyk2 to undergo phosphorylation, and then activates the signalling of transcription factors and the activators of transcription (STAT, mainly STAT1 and STAT3). STAT3 mediates the expression of tissue protective and regenerative genes that are downstream of IL-22, while STAT1 is responsible for many pro-inflammatory effects [7]. In addition to this, IL-22 binding activates the MAPK and p38 pathways [12].

3. Mechanism of Action of IL-22 in NAFLD

Currently, NAFLD is regarded as a complex metabolic disease. There are a multitude of factors that have an impact on its clinical manifestations and the progression of the disease, such as race, genetic predisposition, dietary habits, metabolism, immunity, and gut microbiota. Even though the mechanism behind its development remains unclear, the excessive build-up of toxic lipids gives rise to an inflammatory state and initiates endoplasmic reticulum / oxidative stress along with mitochondrial dysfunction, all of which play a significant part in the development of hepatocellular injury in NAFLD [13,14]. In addition, altered

gut flora is an emerging determinant of NAFLD [15]. And IL-22 can regulate NAFLD in several ways.

3.1 Hepatoprotective Effects of IL-22

IL-22 relies on signalling pathways such as STAT3 to exert its hepatoprotective properties. IL-22 triggers the expression of its downstream gene pathways, including innate immune mediators, mitotic regulators (e.g., cyclin D1, CDK4, c-myc, Rb2), anti-apoptotic regulators (e.g., myeloid cell leukaemia-1 (Mcl-1), Bcl-2, Bcl-xL), and some antioxidants (e.g., metallothionein), thus safeguarding hepatocytes against injury and facilitating survival, proliferation, and liver regeneration [16]. It has been reported that IL-22 acts through activation of JAK1/STAT3 signalling and inhibition of the apoptotic factor BAX, and is involved in the therapeutic effect of blueberries combined with probiotics in NAFLD [17].Interleukin-22 (IL-22) enhances the signalling of AMPK, mammalian target of rapamycin (mTOR), and protein kinase B (Akt) in a way that depends on signal transduction and STAT3, so as to drive metabolic adaptive reprogramming. It also boosts mitochondrial oxidative phosphorylation (OXPHOS) and glycolysis to relieve oxidative stress and preserve mitochondrial function in hepatocytes. Consequently, it can avert liver injury and steatohepatitis induced by a high-fat diet (HFD) by regulating the basic cellular metabolic processes [18].

3.2 Effects on Liver Fibrosis

Hepatic fibrosis represents a repair response to chronic liver injury, which is marked by the activation of hepatic stellate cells (HSC) and the accumulation of extracellular matrix and collagen. Inhibiting HCS activation and inducing their senescence are important strategies for treating liver fibrosis.IL-22 can inhibit HSC activation and ameliorate liver fibrosis by enhancing miR-200a expression and reducing β-catenin expression [19]. Meanwhile, IL-22 increases the expression levels of p53 and p21 genes, which are capable of inducing HSC senescence, as well as cytokine signal transduction inhibitor 3 (SOCS-3), which is a protein associated with cellular senescence, through the STAT3 signalling pathway, leading to HSC apoptosis [20]. In addition, IL-22 attenuates fibrosis in HSCs by inactivating NLRP3 inflammatory vesicle signalling and inhibiting the Notch signalling pathway [21,22].

3.3 Effects on Metabolism

Abnormal lipid metabolism leads to fat accumulation and disturbed glucose metabolism triggers insulin resistance, both of which act on the liver and contribute to the development of NAFLD.IL-22 regulates the expression of metabolism-related genes to ameliorate NAFLD. Interleukin 22 (IL-22) inhibits β-cell oxidation and endoplasmic reticulum (ER) stress, reduces local pancreatic islet inflammation, restores proper insulin production, reverses hyperglycaemia and improve insulin resistance, improve glucose metabolism and reduce hepatic steatosis [23]. Meanwhile, exogenous IL-22 mitigates MASLD by reversing diet-enhanced macronutrient uptake, a major source of hepatic lipids, through activation of STAT3 and inhibition of the WNT-β-catenin signalling pathway, thereby shrinking the number of absorptive intestinal epithelial cells [24]. Meanwhile, hepatic IL22RA1 regulates lipid homeostasis through ATF3/CYP7B1/3β HCA /LXR-α signalling, and IL-22 attenuates the effects of 3β-hydroxy-5-cholestenoic acid (3βhca)-mediated lipogenesis [25].

3.4 Regulation of Intestinal Flora

Plenty of evidence indicates that dysbiosis plays a part in the pathogenesis of NAFLD. Dysbiosis heightens the intestinal permeability to bacterial products and raises the liver's exposure to harmful substances, which promotes the progression of NAFLD; changes in the microbiome can also lead to intestinal motility disorders, intestinal inflammation, and other immune changes, which can lead to liver injury [26]. Modulation of gut flora is considered an effective strategy to improve non-alcoholic fatty liver disease (NAFLD). The combined action of intestinal epithelial cells, mucus, IgA, antimicrobial peptides, and immune cells constitutes the "mucosal firewall" [27]. IL-22 may promote intestinal recovery and reduce HFD-induced microbiota infestation and the metabolic syndrome by promoting proliferation of intestinal epithelial cells, and inducing the release of antimicrobial peptides (AMP) [28].

4. The Dilemma of IL-22 Treatment for NAFLD

IL-22 has a multifunctional role in regulating metabolic homeostasis, inflammation, and tissue repair. As a result, it shows potential as a treatment method for metabolic diseases. Nevertheless, its role in regulating immune responses might overly stimulate the immune system and give rise to inflammatory responses. For example, IL-22 induces keratinocyte migration, epidermal hyperplasia and skin inflammation [29]. The potential dual nature of IL-22 in regulating tissue immune responses may depend on the specific context in which the cytokine is expressed [30]. Its complex and sometimes contradictory biological effects are one of the difficulties in its clinical application. NAFLD is a complex disease whose pathogenesis involves several aspects such as lipid metabolism disorders, insulin resistance, and intestinal flora dysbiosis. Although IL-22 can ameliorate hepatic inflammation, promote hepatic regeneration, and ameliorate lipid metabolism disorders, its effect in alleviating NAFLD is still unstable. It has been found that high levels of biologically active IL-22 do not affect obesity and its metabolic consequences, while endogenous IL22 receptor signalling has a sex-dependent hepatoprotective and anti-apoptotic effect [31, 32]. Moreover, there are still several other bottlenecks impeding the further development of IL-22 as a treatment for NAFLD. The most significant hurdle is the pleiotropic function of IL-22, which restricts its therapeutic use due to off-target toxicity[33].

5. IL-22 for the Treatment of NAFLD

Cytokine and cytokine receptor engineering is currently being extensively investigated, and IL-22 has been extensively studied for the treatment of NAFLD. Recent studies, including structure-based design and targeted delivery strategies, offer promising solutions for clinical applications. Robert A. Saxton et al.[34] utilised structure-directed design to systematically disrupt the binding interface between IL-22

and IL-10R2 binding interface to create partial agonist analogues that achieve uncoupling of downstream STAT1 and STAT 3 signalling, thereby generating tissue-selective signalling in different tissues and exerting a tissue-protective effect without inducing local or systemic inflammation. A study of composite nanoparticles based on poly (dimethylmethomorphin) and membrane-penetrating peptides capable of targeting the delivery of the interleukin-22 gene via systemic administration in the liver that overcoming the off-target effect of IL-22, remarkably relieved hepatic steatosis,decreased excessive body weight, restored insulin sensitivity, and lessened body fat accumulation in mice fed with a high-fat diet (HFD) [35]. Moreover, through targeting the pancreas and liver, it became feasible to amplify the beneficial impacts of interleukin-22 (IL-22) on hyperglycemia, hepatic steatosis, inflammation, and fibrosis, all the while reducing its negative effects on the skin and gut [36].Combination therapies have been adopted as well. A new vascular endothelial growth factor B antibody (anti-VEGFB) / interleukin-22 (IL-22) fusion protein safeguarded db/m and high-fat diet-fed db/db mice against the impairment of diabetes-induced hepatic steatosis. It achieved this by downregulating the expression of fatty acid transporter genes, regulating glucose-lipid metabolism, decreasing renal and hepatic lipid accumulation and insulin resistance, and improving inflammatory responses through alleviating oxidative stress and mitochondrial dysfunction in db/db mice with diabetes-induced hepatic steatosis [37]. In terms of clinical applications, it is necessary to conduct further investigations into new therapeutic strategies by means of bioengineering and pharmacological techniques and assess their biosafety and bioactivity.

6. Summary and Outlook

NAFLD has emerged as a new challenge and a significant public health issue in the realm of liver disease and metabolism across the globe. IL-22 plays a role in protecting the liver, regulating metabolism and intestinal flora, and improving fibrosis, which provides a new direction and strategy for the treatment of NAFLD. Although there are still challenges in its clinical application, with further research, it is expected that its therapeutic application will be optimised in the future in a variety of ways. At the molecular structure level, IL-22 can be modified or more efficient IL-22 analogues can be designed to precisely regulate its binding activity and specificity to the receptor, enhancing efficacy and reducing side effects. In terms of the route of administration, the development of novel drug delivery systems, such as targeted nanoparticle carriers, to achieve the precise administration of IL-22 can overcome the off-target effect of IL-22. In terms of combination therapy, combining IL-22 therapy with other therapies can more comprehensively improve the liver internal environment, ameliorate liver damage, and enhance the therapeutic effect. In the future, further exploration of the internal mechanism of IL-22 to improve NAFLD and the aid of bioengineering and pharmacological technologies will explore new therapeutic approaches for NAFLD.

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