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MINIREVIEWS

Review of the potential value of serum interleukin levels as prognostic biomarkers of liver failure

Yong Lin, Geng-Jie Yan, Mei-Yan Liu, Yin Cao, Kan Zhang, Na Wang, Fu-Li Long, De-Wen Mao

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Abstract

Liver failure (LF) is prevalent in China and is characterized by complex pathogenesis, challenging clinical management, poor prognosis, and rising incidence and mortality rates. The immune status is an important factor affecting LF prognosis. Interleukins (Ils) are a type of cytokine that act and interact with multiple cells, including immune cells. These signaling molecules play important roles in intercellular information transmission, including the regulation of immune cells; mediation of the activation, proliferation, and differentiation of T and B cells; and orchestration of the inflammatory response. To date, many studies have explored the correlation between IL expression and liver disease prognosis, but few studies have evaluated Ils as the prognostic biomarkers of LF. This article reviews the potential use of Ils as the prognostic biomarkers of LF. Particularly, it evaluates the predictive values of IL-21, IL-22, and IL-31, the three often overlooked yet promising prognostic biomarkers, in predicting susceptibility to LF. Harnessing biomarkers for early prognostic insights can facilitate tailored treatment strategies and enhance patient survival. Thus, this article focuses on the identification of IL-21, IL-22, and IL-33 as biomarkers in preclinical

and clinical studies on LF and reviews their role as biomarkers in the pathogenesis and diagnosis of LF.

Key Words: Interleukin-21; Interleukin-22; Interleukin-31; Liver failure; Biological markers; Potential value

Core Tip: This review highlights the potential of interleukins (Ils), particularly IL-21, IL-22, and IL-31, as the prognostic biomarkers of liver failure. The article emphasizes the crucial role of immune responses in liver failure pathogenesis and explores the complex interplay between these Ils and various immune cells, signaling pathways, and liver diseases. Moreover, it critically analyzes existing literature, identifying limitations and suggesting future directions for further research.

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INTRODUCTION

Liver failure (LF) is the end result of various acute or chronic liver diseases. Its pathological essence is the complete loss of hepatic metabolic and detoxification functions due to the extensive death of hepatocytes[1]. Liver transplantation is a fast and effective treatment for advanced LF. However, the stark incongruity between the substantial demand for liver donors and the limited supply is not expected to be effectively resolved in the near future. Active and effective comprehensive medical intervention, encompassing energy and nutrition supplement, electrolyte acid-base balance maintenance, anti-inflammatory liver protection, immunomodulation, artificial liver support, and complication prevention and treatment, is still the preferred approach for the treatment of this disorder[2,3]. However, the massive consumption of medical resources and high medical costs because of comprehensive treatment, difficulty in fully controlling inflammatory reactions, and complication prevention and management lead to a heavy burden on patients and society. Consequently, LF has emerged as a critical and challenging condition in the realm of liver diseases and needs to be comprehensively analyzed with regard to its complex pathogenesis. In addition, it is necessary to develop early assessment methods and formulation for evidence-based diagnostic and therapeutic strategies targeting its core pathological processes. In LF treatment plans, numerous countries emphasize the importance of comprehensive prognostic evaluation throughout the diagnosis and treatment course, particularly emphasizing early assessment. Kuroda *et al*[4] used the time interval between the time to peak of hepatic artery and liver parenchyma to accurately predict the prognosis of acute LF (ALF) patients, and this strategy may be helpful for clinical decision-making. Bernal *et al*[5] used the admission variables of age, Glasgow coma scale, arterial pH and lactate levels, creatinine level, international normalized ratio, and cardiovascular failure to develop an initial predictive model. It accurately predicts the quality of life for patients with paracetamol-induced ALF at an early stage and thus aids in emergency liver transplantation and medical decision-making. Xiao *et al*[6] found that patients receiving the treatment of artificial liver support had a higher short-term survival rate than those receiving standard drug treatment. Notably, the authors observed that among the patients who received artificial liver support, those receiving mixed artificial liver support demonstrated a higher short-term survival rate than those undergoing plasma exchange, confirming the efficacy of the artificial liver support system. Clearly, early recognition and proactive intervention may improve the prognosis of patients with ALF. Therefore, reliable prognostic markers that can distinguish between patients at high risk of death and those with the potential for recovery following treatment may help reduce ALF-associated mortality, and these biological indicators are mostly closely related to the disease mechanism of LF[7]. The underlying mechanism of LF fundamentally involves a sequence of critical clinical conditions that emerge when a substantial number of hepatocytes undergo pathological passive death, compromising the structure and function of the liver[8]. Concurrently, the rapid and massive death of hepatocytes is accompanied by hepatic injury caused by hyperimmunity (immune responses that are heightened beyond normal physiological levels) and inflammatory stress[9]. Moreover, an Increasing amount of research evidence suggests that immune hyperactivity may be the main factor leading to the rapid hepatocyte death in the early stages of LF[10-16]. Kupffer cells, which are resident macrophages in the liver, produce large amounts of interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), and interleukin 1 (IL-1), capable of inducing rapid hepatocyte death and causing hepatic damage[10]. Additionally, natural killer (NK) and NKT cells have been shown to induce hepatocyte death through the Fas/Fas ligand (FasL) and NKG2D/NKG2DL signaling pathways[11]. Likewise, cytotoxic T cells can induce rapid hepatocyte death through the perforin-1/granzyme, Fas/FasL, TNFR1/TNF, and receptor interaction protein kinase 1 (RIP-1)/RIP-3 signaling pathways[12]. Moreover, T helper 17 cells (Th17) cells can contribute to hepatocyte death and hepatic inflammatory damage by secreting the key inflammatory factor IL-17, which enhances the function of tumor necrosis factor and expression of cell adhesion molecule[13]. Hyperimmunity combined with cytokine storm triggers a "domino effect" of rapid hepatocyte death in LF[14]. These findings suggest that the development and exacerbation of LF are related to severe systemic inflammation. Systemic inflammatory

responses are recognized as the indicators of LF that affect the prognosis of LF[15,16]. In this context, the recruitment and differentiation of immune cells at inflammatory sites are facilitated by pro-inflammatory cytokines[17]. As a type of proinflammatory factor, IL often interacts with white blood cells and immune cells, thereby participating in intercellular information transmission, activating and regulating immune cells, and mediating inflammatory reactions such as activation, proliferation, and differentiation of T and B cells[18]. Therefore, ILs may be a kind of mediator that promotes the occurrence of immune response in LF.

The present article explores the relationship between the levels of IL-21, IL-22, and IL-31 and prognosis of LF, shedding light on the potential of ILs as prognostic biomarkers of LF.

IL-21

Research has found that IL-21, as one of the main immune modulators, plays a crucial role in the induction, initiation, progression, and deterioration of various diseases[19]. It is mainly expressed in activated CD4+ T cells and regulates various immune responses by modulating many immune cells[20] (Figure 1). The IL-21R gene encodes the receptor for IL-21. IL-21 receptor (IL-21R) belongs to the type I cytokine receptor family and complexes with the common γ chain (γc), forming a heterodimer receptor complex. The subunit γc is also a common receptor for IL-2, IL-4, IL-7, IL-9, and IL-15 [21]. The IL-21R transduces the growth-promoting signal of IL-21, which is of great significance for the proliferation and differentiation of T, B, and NK cells[22]. Binding of the ligand to the receptor results in the activation of multiple downstream signaling molecules, including Janus kinase 1 (JAK1), JAK3, signal transducer and activator of transcription 1 (STAT1), and STAT3[23] (Figure 2). Studies have demonstrated that IL-21 can be upregulated in various subsets of T helper cells, including Th2, Th17, and follicular T cells[24]. In addition, IL-21 is expressed in NKT cells, which oversee the functions of these cells[22]. Investigations on IL-21R have revealed that this receptor plays a vital role in regulating immunoglobulin production in both animals and humans[25,26]. Notably, IL-21 has been linked to inflammatory diseases, and studies suggest the existence of a positive autocrine loop that can enhance and stabilize IL-21-driven, T cell-mediated responses[27,28]. Moreover, IL-21 exhibits anticancer properties and stimulates autoimmune reactions[29]. IL-21 has garnered significant attention as a potential therapeutic and predictive target of LF. A study has shown that IL-21 may participate in the regulation of inflammatory mediators of liver injury by modulating the functions of cells associated with innate and adaptive immunities[30]. Additionally, it may contribute to LF by changing the expression of other pro-inflammatory cytokines. Specifically, research has revealed that IL-21 can increase IL-1β, IL-6, IL-10, IFN-γ, and TNF-α levels in peripheral blood monocytes, potentially contributing to the development of ALF triggered by the hepatitis B virus (HBV)[30]. However, in a mouse model of ALF induced by the hepatitis virus 3 strain, significant upregulation of the Th17-related cytokine IL-21 was observed after 72 h of infection[31]. Importantly, this upregulation demonstrated a positive correlation with the degree of liver function impairment in the infected mice. Liu *et al*[32] used high-resolution melting to genotype five single nucleotide polymorphisms in 546 HBV-infected Chinese patients and 353 healthy subjects, and the results revealed that the IL-21R (rs2285452 AA) genotype was associated with an increased risk of developing HBV-related cirrhosis and liver cancer in Chinese patients. Chen *et al*[33] observed significantly higher serum IL-21 levels in patients with chronic hepatitis B (CHB) or HBV-related acute-on-chronic LF (ACLF) than in healthy individuals, whereas there was no such increase in patients with liver cirrhosis. The relatively high serum IL-21 levels in CHB patients may play a causal role in the persistence of HBV infection. Additionally, the proportion of CD4+ T cells in the peripheral blood of HBV-ACLF patients was higher than in healthy individuals and correlated with the number and proportion of lymphocytes in the blood. This suggests that elevated serum IL-21 levels lead to the activation of T and B cells, stimulating them to release pro-inflammatory cytokines to combat the virus, although this immune response can inadvertently lead to liver damage. The same study compared patients with moderate CHB (M-CHB), severe CHB (S-CHB), and HBV-ACLF. Compared with M-CHB patients and the control group, both HBV-ACLF and S-CHB patients showed higher frequencies of IL-21 secretion by CD4+ T cells. HBV-ACLF patients had the highest mean serum IL-21 levels, which positively correlated with the "Model for End-Stage Liver Disease"(MELD) score and mortality rate. The recovery of the HBV-ACLF patients was found to be associated with decreased serum IL-21 level and decreased CD4+ T cell proportion. Moreover, IL-21 stimulation has been shown to significantly increase serum IL-6, IL-10, and TNF-α levels [31]. Pan *et al*[34] showed a positive correlation between serum IL-21 level and alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBIL) levels in HBV-ACLF patients and a negative correlation with albumin (ALB) level. These observations suggest that IL-21 plays a causative role in the progression of severe hepatic inflammation and is associated with the severity of liver diseases. T follicular helper cells (Tfh) are considered a unique subset of CD4+ T cells that mediate the development of long-term humoral immunity and play an important role in the process of hepatic viral infection[35,36]. CD4+ T cells in the immune system produce IL-21, which is crucial for the development of CD8+ tissue-resident memory cells during persistent viral infections, particularly in the central nervous system[37,38]. A recent study showed that HBV-ACLF patients have elevated proportions of Tfh cells and high serum IL-21 levels, displaying a strong correlation with MELD scores. Notably, in HBV-ACLF patients, CD4+ T cells tend to differentiate into Tfh cells under the influence of the IL-21-rich serum, a process effectively suppressed by IL-21 antibodies. Furthermore, the induced Tfh cells facilitate the proliferation and IgG production of B cells, as indicated by significant increases in the number of CD19+ B cells and in serum and hepatic IgG/M levels[39]. These findings underscore the importance of IL-21 in the pathogenesis of liver diseases and its potential as a therapeutic target in LF.

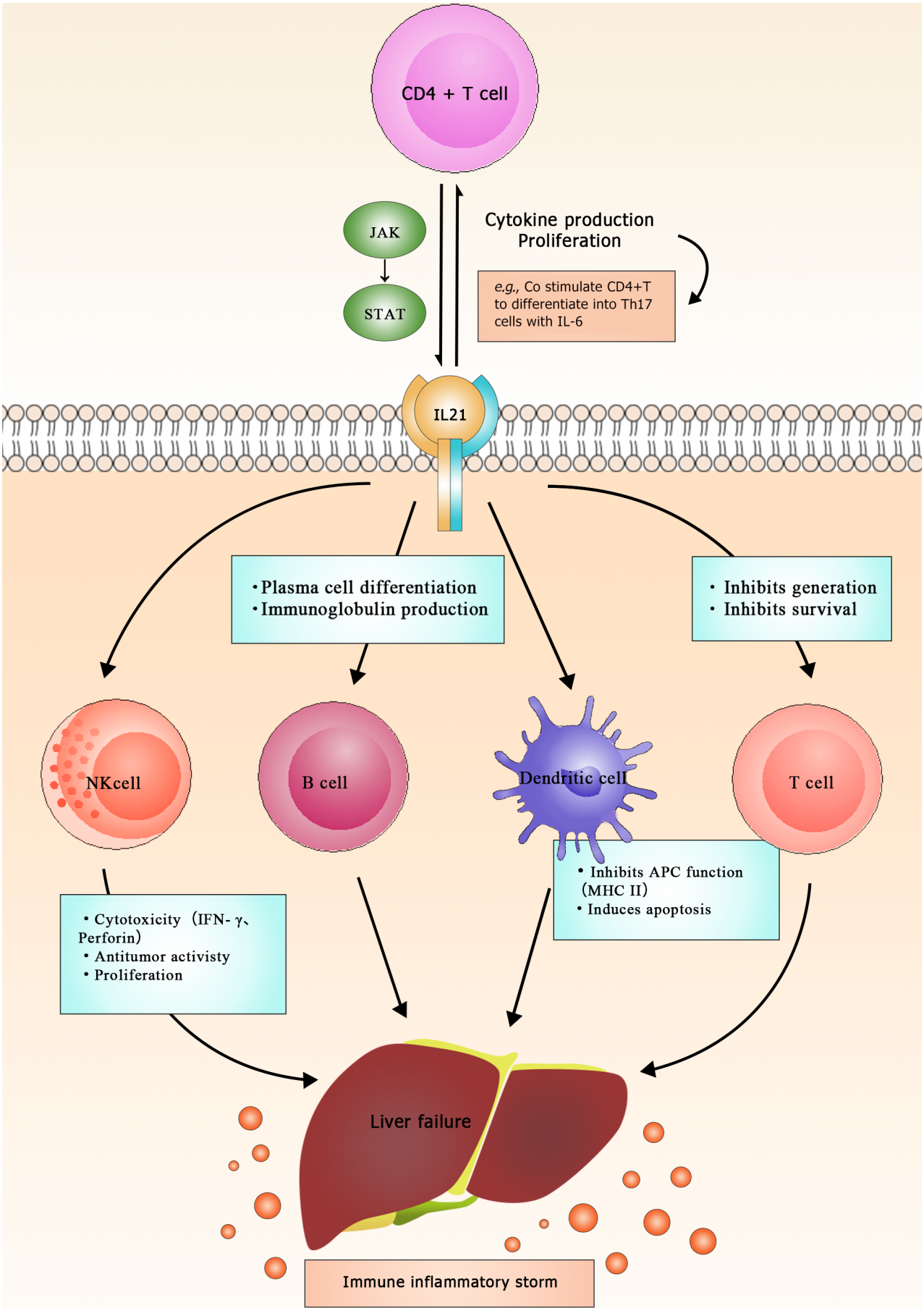

Figure 1 Mechanism of interleukin 21 in liver failure (diagram depicts various immune cells, including CD4+ T cells, natural killer cells, B cells, T cells, and dendritic cells, along with their interactions and functions). The central role of interleukin 21 (IL-21) is highlighted, as it is secreted

by CD4+ T cells and influences the differentiation of B cells into plasma cells, leading to immunoglobulin production, while also inhibiting T cell survival and generation. Additionally, IL-21 can stimulate dendritic cells to induce apoptosis, further impacting the immune response). APC: Anaphase-promoting complex; IFN-γ: Interferon gamma.

IL-22

IL-22, discovered in 2000, is secreted by activated T cells. It is a member of the IL-10 family of cytokines, which consists of IL-19, IL-20, IL-24, IL-26, IL-28, and IL-29. IL-22 is expressed by various types of lymphocytes, including innate and acquired immune cells, such as CD4+ T cells (especially Th17 cells), δγ T cells, and NK cells[40]. All of these different cell subpopulations express IL-22 with similar features (*e.g.*, similar activation receptors and transcription factors) as well as unique features. For example, IL-22 is produced by activated immune cells during inflammation or infection. Its primary mechanism involves binding to IL-22Rs specifically expressed on the surface of epithelial and stromal cells, thereby exerting its effects on these cell types[41]. Upon binding to the IL-22R, IL-22 triggers processes such as cell proliferation and tissue remodeling and repair in diverse tissues and organs. This process supports the innate defense mechanism of the host against pathogenic intrusion, thereby playing a crucial role in fostering antibacterial immunity, inflammation, and tissue repair at barrier surfaces[42]. The IL-22R is a heterodimer complex composed of IL-22R1 and IL-10R2, which belong to the type II cytokine receptor family[43]. IL-22R1 is expressed in various non-immune organs, such as the liver, skin, lungs, small intestine, colon, kidneys, and pancreas, whereas IL-10R2 is widely expressed in immune cells[44]. In addition to its functional receptor, IL-22 has an endogenous antagonist called IL-22-binding protein (IL-22BP, also known as IL-22RA2)[45]. Upon binding to its receptor, IL-22 activates STAT3 primarily through the JAK-STAT pathway, in addition to STAT1 and STAT5. It can also trigger the nuclear factor kappa B (NF-kB), mitogen-activated protein kinase, and phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathways[46-48] (Figure 2). IL-22-induced signaling pathways can upregulate genes that counteract inflammation or apoptosis and those promoting cell proliferation, thereby contributing to the cellular mechanisms associated with local tissue regeneration and host defense[49,50]. Clinical studies have indicated that patients with chronic HBV or hepatitis C virus infections exhibit elevated levels of IL-22 and an abundance of IL-22-producing cells in the liver compared with healthy individuals [51,52]. Numerous *in vitro* and animal experiments have shown that IL-22 has a strong protective effect against hepatocyte damage[53,54]. The specific actions of IL-22 include stimulating STAT3-dependent cell division in injured hepatocytes and liver stem cells, enhancing hepatocyte fibroblast growth factor 3 expression and restoring hepatocyte function. It has several mechanisms of action. First, it prevents hepatocyte apoptosis by regulating lipid metabolism, alleviating oxidation, and attenuating endoplasmic reticulum stress[57]. Second, it shields hepatocytes from oxidative stress by inhibiting mitochondrial apoptosis and boosting antioxidant protein levels[58]. Third, it regulates immune cells *via* certain pathways such as nuclear factor erythroid 2-related factor 2/heme oxygenase 1, TNF-α/NF-κB, and JNK/STAT3 signaling to induce the production of anti-inflammatory and antibacterial proteins, thereby restraining immune cell infiltration[59,60]. Finally, it binds to the highly expressed receptors IL-22R1 and IL-10R2 to activate STAT3 in hepatic stellate cells, thereby upregulating inhibitory factors in these cells, reducing liver fibrosis, and ameliorating alcoholic liver injury[61,62] (Figure 3). LF mainly encompasses ALF and ACLF. In a rat model of ALF induced by d-galactosamine-positive (D-GalN+) lipopolysaccharides (LPS), the mortality rate of the rats was 20% after 48 h of D-GalN/LPS administration, along with increased levels of indicators such as AST, ALT, alkaline phosphatase, TBIL, prothrombin time, TNF-α, and cyclooxygenase-2 (COX-2). However, IL-22 treatment completely reversed the mortality, improved the abnormal biochemical and serological parameters, and reduced TNF-α and COX-2 levels in the liver[63]. Similarly, IL-22 has shown promise in acetaminophen (APAP)-induced acute liver injury, notably reducing serum ALT levels and liver necrosis in mice with early intervention. These processes may be related to factors that induce the IL-22/STAT3 axis, including cyclin signal-3, lipocalin-2, and alpha 1-antichymotrypsin. Furthermore, after 2 h of APAP administration, IL-22 showed unique antioxidant and anti-inflammatory effects[64], possibly due to IL-22 controlling the activity of metabolic regulators and enzymes by inducing AMP-activated protein kinase, AKT, and mTOR. This process aids in restoring mitochondrial integrity, reducing reactive oxygen species accumulation, and suppressing mitochondrial dysfunction[65] (Figure 3). IL-22 has shown a similar effect in cases of concanavalin A (ConA)-induced ALF[66,67]. A study showed that recombinant IL-22 could suppress ConA-induced ALF, whereas IL-22 deficient mice were more sensitive to ConA-induced ALF than wild-type mice. This pattern is also evident in the liver-injury model induced by carbon tetrachloride (CCl4)[68]. Similarly, IL-22Fc treatment 24 h after CCl4-induced acute liver injury in rats increased their survival rate, reduced serum ALT levels, and improved the bacterial load. This effect is achieved by IL-22Fc reprogramming the liver-regeneration signaling pathway, *i.e.* boosting liver regeneration by activating the STAT3 pathway while suppressing the STAT1 pathway. In addition, Schwarzkopf *et al*[69] observed in clinical practice that high levels of IL-22 and low IL-22BP/IL-22 ratios are associated with ACLF and mortality in patients with liver cirrhosis. High levels of IL-22BP in ACLF patients may inhibit hepatocyte IL-22 signaling, where excessive secretion of IL-22BP can neutralize IL-22, potentially preventing the hepatoprotective effects of IL-22 in patients with liver cirrhosis[69]. Mo *et al*[70] found that patients with HBV-ACLF had increased peripheral blood Th22/Th17 cells as well as elevated plasma IL-22 and IL-17 levels but decreased Th1 cells compared with healthy controls. Subsequent analyses have confirmed these findings, showing that elevated plasma levels of IL-22 were associated with lower survival rates in HBV-associated ACLF patients[70]. A study by Khanam *et al*[71] supported these conclusions but also indicated that serum IL-22 levels was positively correlated with CCR6 and ALT levels in HBV-ACLF[71-75].

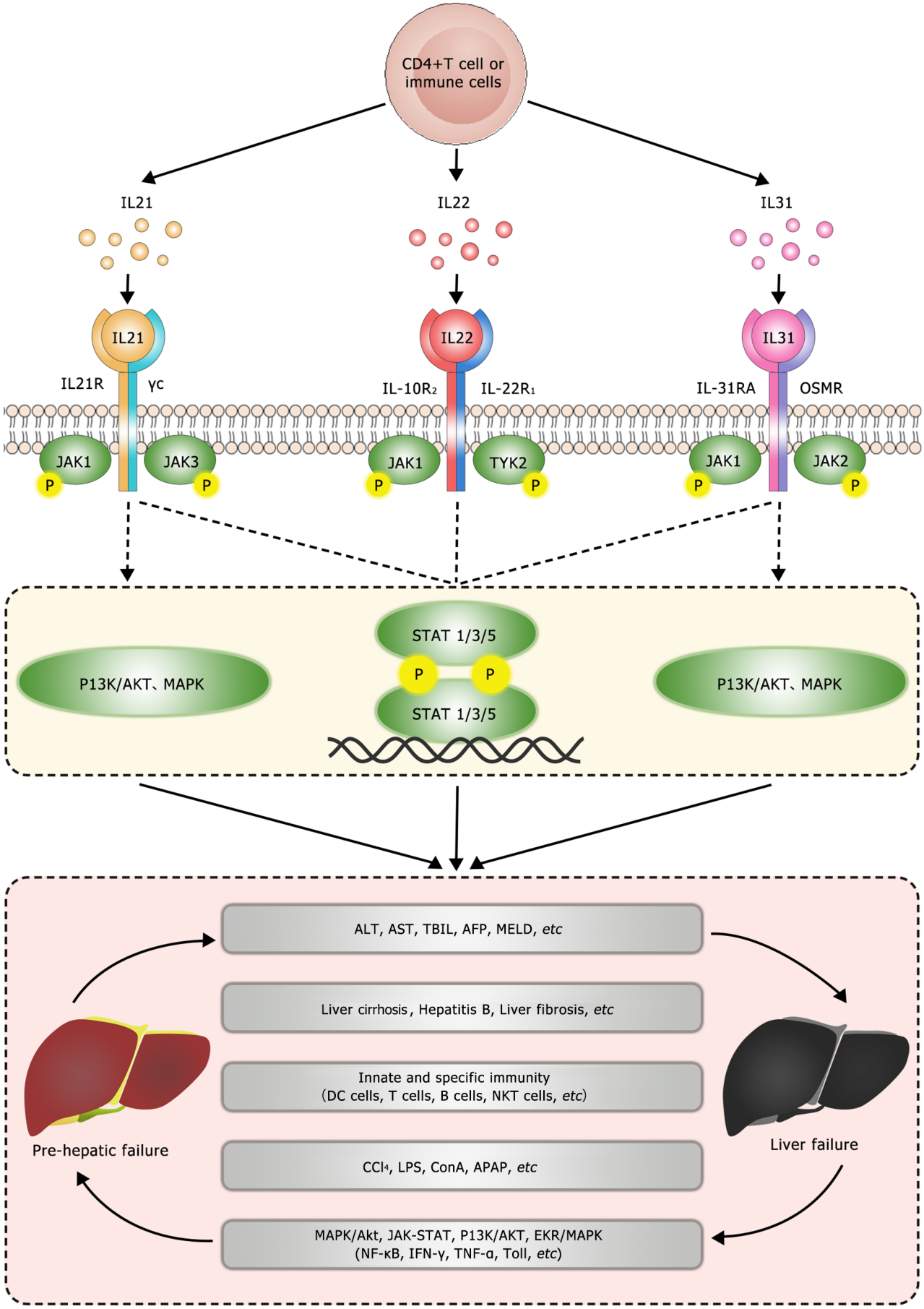

Figure 2 Molecular mechanisms underlying the involvement of interleukin 21 (IL-21), IL-22, and IL-31 in liver failure (diagram depicts the signaling pathway of ILs and their involvement in liver failure). It starts with a CD4+ T cell or immune cell at the top, which secretes three different types

of interleukin (IL): IL-21, IL-22, and IL-31. Each IL binds to its specific receptor on the cell surface: IL-21 binds to the IL-21 receptor (IL-21R), IL-22 binds to the IL-10R2 and IL-22R1, and IL-31 binds to the IL-31RA and oncostatin M receptor (OSMR). These receptors activate downstream signaling pathways involving Janus kinase 1 (JAK1), JAK2, JAK3, and tyrosine kinase 2 (TYK2), which phosphorylate signal transducer and activator of transcription (STAT) proteins. The activated STAT proteins then translocate to the nucleus and regulate gene expression, activating phosphoinositide 3-kinase (PI3K)/AKT and mitogen-activated protein kinase (MAPK) signaling pathways. The diagram shows that these signaling events ultimately lead to liver failure through various mechanisms, including increased levels of liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin [TBIL], alpha-fetoprotein [AFP], model for end-stage liver disease [MELD]), liver cirrhosis, hepatitis B, and liver fibrosis, which highlights the complex interplay between immune cells, ILs, and signaling pathways in the pathogenesis of liver failure.) APAP: Acetaminophen; CCl4: Carbon tetrachloride; ConA: Concanavalin A; LPS: Lipopolysaccharides.

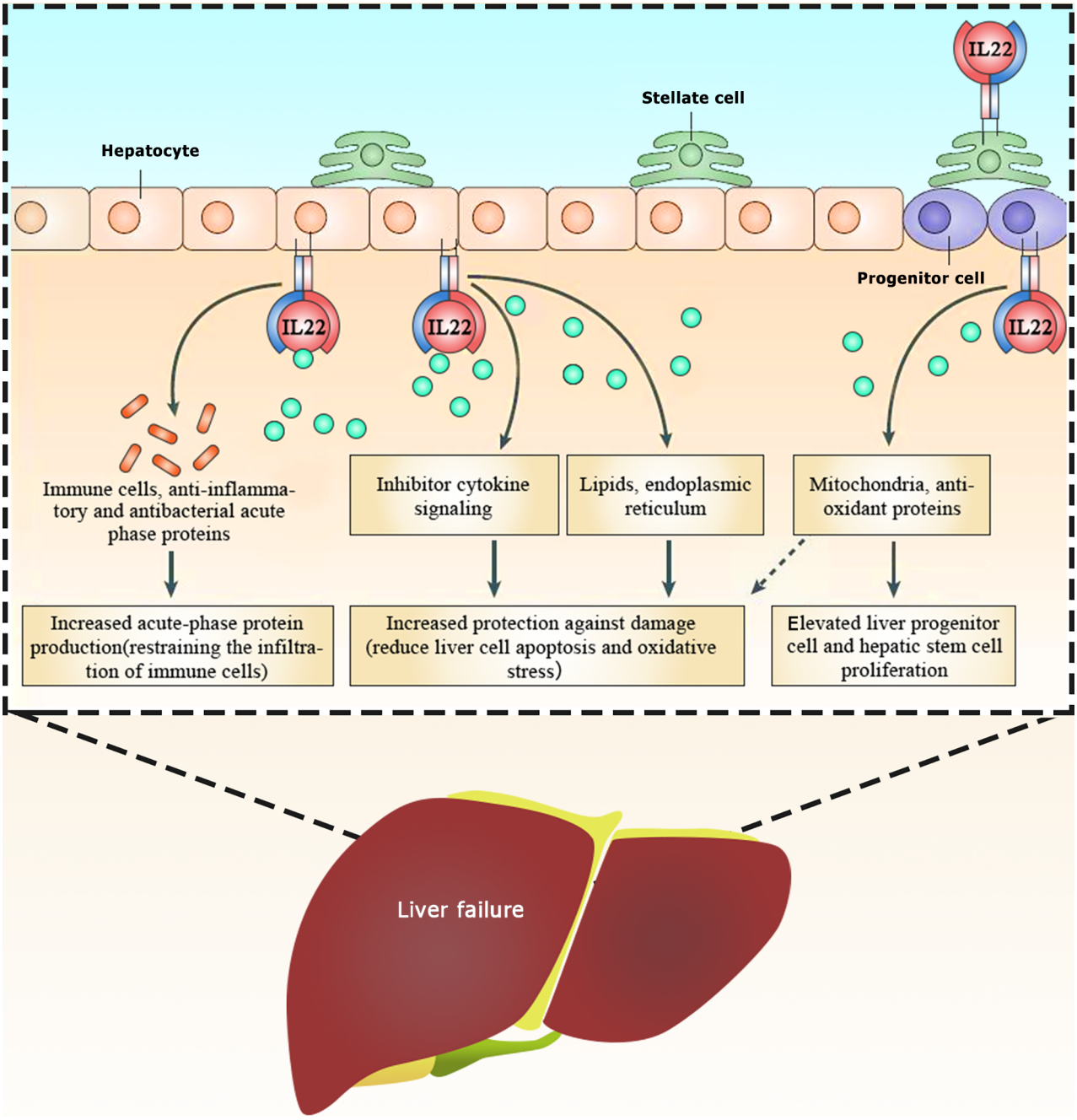

Figure 3 Mechanism of interleukin 22 (IL-22) in liver failure (diagram illustrates the protective role of IL-22 in liver health and its potential benefits in preventing liver failure). Interleukin 22 (IL-22) is secreted by immune cells, specifically progenitor cells, and binds to receptors on the surface of hepatocytes, stellate cells, and progenitor cells. This binding triggers a series of downstream effects: (1) Hepatocytes: IL-22 acts on hepatocytes by increasing the production of acute-phase proteins, which help fight infection and inflammation. This, in turn, helps restrain the infiltration of immune cells, reducing inflammation and protecting the liver from damage; (2) Stellate cells: IL-22's interaction with stellate cells increases protection against damage and reduces liver cell apoptosis (cell death) and oxidative stress; (3) Progenitor cells: IL-22 stimulates the production of mitochondria and antioxidant proteins in progenitor cells. This promotes the proliferation of liver progenitor cells and hepatic stem cells, which are crucial for liver regeneration).

IL-31

IL-31, a four-helix cytokine discovered by Dillon *et al*[75] in 2004, belongs to the IL-6 cytokine family. It is primarily secreted by activated CD4+ T lymphocytes, especially activated helper Th2 cells, mast cells, monocytes/macrophages, and dendritic cells[72]. Studies have shown that monocytes can express the IL-31RA subunit when co-stimulated with IFN-γ and LPS[73,74]. Notably, LPS can activate cells *via* Toll-like receptor 4, which is crucial for driving adaptive Th1 responses. Moreover, IL-31 has been observed to induce Th2 responses in mouse models of allergic sensitization[75], suggesting that it aids antigen presentation through monocytes or dendritic cells. Furthermore, IL-31 has been identified as a significant player in cell proliferation, activation, migration, inflammation, and allergic reactions, engaging with signaling pathways such as MAPK/Akt, JAK/STAT, PI3K/AKT, and extracellular signal-regulated kinase (ERK)/MAPK [76-78] (Figure 2). In studies on LF, IL-31 was positively correlated with the serum levels of transforming growth factor-β1 (TGF-β1), TBIL, and alpha-fetoprotein (AFP) in patients with HBV-ACLF. Conversely, recovery of the liver damage in HBV-ACLF was accompanied by decreased levels of IL-31 and TGF-β1, which were significantly upregulated in deceased HBV-ACLF patients. Notably, the levels of IL-31/TGF-β1 exhibited high sensitivity and specificity in predicting the survival rates of patients with HBV-ACLF[79]. Furthermore, the TGF-β/IL-31 axis has been implicated in HBV-associated cirrhosis. Increased serum levels of TGF-β1 and IL-31 have been observed, demonstrating a positive correlation with albumin, AFP, creatinine, white blood cell count, and platelet level, in individuals with HBV-associated cirrhosis. This association serves as a potential early warning indicator in cirrhotic patients without esophageal varices[80]. Recent studies have connected serum IL-31 levels to cholestatic diseases complicated by nonalcoholic steatohepatitis, where IL-31 mRNA levels were closely related to the concentration of bile acid and determined the degree of pruritus in such patients [81]. In terms of its function, TGF-β1 is a 25-kDa homologous dimer protein consisting of two subunits linked by disulfide bonds and is a potent inhibitor of DNA synthesis and cell proliferation[82]. Relevant studies have found that serum and hepatic TGF-β1 levels are significantly increased in patients with fulminant LF compared with healthy individuals[83]. Additionally, TGF-β1 has been shown to inhibit liver regeneration in mice with fulminant LF by promoting fibrosis and hepatocyte apoptosis[84].

CONCLUSION

The liver has a strong regenerative capacity, offering potential for intervention at various stages of LF through timely warnings and appropriate treatments. However, the management of LF is currently challenging due to its intricate pathogenesis and diverse etiologies, leading to limitations in diagnostic and therapeutic approaches. IL-21, IL-22, and IL-31 have emerged as promising candidates for diagnosing, predicting, and treating LF, with correlations observed in liver biochemical function (ALT, AST, TBIL, and AFP), underlying liver diseases (cirrhosis, hepatitis B, and liver fibrosis), immune system dynamics (DC, T, B, NKT, and CD4+ T cells), LF inducers (CCl4, LPS, ConA, and APAP), and inflammatory pathways (MAPK/Akt, JAK/STAT, PI3K/AKT, and ERK/MAPK) that involve factors such as NF-κB, IFN-γ, TNF-α, and Toll-like receptors. To enhance our understanding of LF, future efforts should focus on identifying effective early warning signs and therapeutic indicators. The exhaustive exploration and validation of IL-21, IL-22, and IL-31 and their associations with liver and inflammatory disorders may provide promising avenues for advancing our comprehension and devising efficient interventions.

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