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EDITORIAL

Interleukins in liver disease treatment

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Abstract

Cytokines play pleiotropic roles in human health and disease by regulating both innate and adaptive immune responses. Interleukins (ILs), a large group of cytokines, can be divided into seven families, including IL-1, IL-2, IL-6, IL-8, IL-10, IL-12, and IL-17 families. Here, we review the functions of ILs in the pathogenesis and resolution of liver diseases, such as liver inflammation (*e.g.*, IL-35), alcohol-related liver disease (*e.g.*, IL-11), non-alcoholic steatohepatitis (*e.g.*, IL-22), liver fibrosis (*e.g.*, Il-17a), and liver cancer (*e.g.*, IL-8). Overall, IL-1 family members are implicated in liver inflammation induced by different etiologies, such as alcohol consumption, high-fat diet, and hepatitis viruses. IL-2 family members mainly regulate T lymphocyte and NK cell proliferation and activation, and the differentiation of T cells. IL-6 family cytokines play important roles in acute phase response in liver infection, liver regeneration, and metabolic regulation, as well as lymphocyte activation. IL-8, also known as CXCL8, is activated in chronic liver diseases, which is associated with the accumulation of neutrophils and macrophages. IL-10 family members contribute key roles to liver immune tolerance and immunosuppression in liver disease. IL-12 family cytokines influence T-cell differentiation and play an essential role in autoimmune liver disease. IL-17 subfamilies contribute to infection defense, liver inflammation, and Th17 cell differentiation. ILs interact with different type I and type II cytokine receptors to regulate intracellular signaling pathways that mediate their functions. However, most clinical studies are only performed to evaluate IL-mediated therapies on alcohol and hepatitis virus infection-induced hepatitis. More pre-clinical and clinical studies are required to evaluate IL-mediated monotherapy and synergistic therapies.

Key Words: Interleukins; Family members; Liver disease; Treatment; Clinical trials

Core Tip: Interleukins as a large group of cytokines play pleiotropic roles in liver homeostasis and disease by regulating both innate and adaptive immune responses. They can be divided into seven families, and all of them are involved in the pathogenesis and resolution of chronic liver diseases. Currently, interleukin-mediated therapies are applied in patients with hepatitis induced by alcohol or hepatitis virus infection.

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INTRODUCTION

Cytokines coordinate both innate and adaptive immune responses, and they display pleiotropic roles in healthy and disease conditions[1]. Interleukins (ILs), a large group of cytokines, play important roles in immune cell growth, differentiation, and activation, as well as other tissue-resident cells by interacting with their receptors[2]. Acute and chronic liver diseases are characterized by liver inflammation and cell death[3,4], which are commonly associated with infiltration of different immune cells and activation of hepatic parenchymal cells to secrete ILs[5,6]. ILs as a major type of cytokines are involved in the pathogenesis and resolution of liver diseases, such as liver inflammation (*e.g.*, IL-35)[7], alcohol-related liver disease (*e.g.*, IL-11)[8], non-alcoholic steatohepatitis (*e.g.*, IL-22)[9], liver fibrosis (*e.g.*, Il-17a)[10], and liver cancer (*e.g.*, IL-8)[11].

Herein, we review the members of IL families and their functions in liver disease. Especially, we summarize the current findings for liver disease treatment by targeting different ILs in clinical trials.

INTERLEUKIN FAMILIES

Interleukins can be divided into seven families (Table 1), including IL-1 family[12,13], IL-2 family[14,15], IL-6 family[16,17], IL-8 family[18,19], IL-10 family[20,21], IL-12 family[22,23], and IL-17 family[24,25]. All the families of interleukins are involved in the liver disease. For example, IL-1 family cytokines are implicated in liver inflammation induced by different etiologies[26,27], such as alcohol consumption, high-fat diet, and hepatitis viruses. IL-2 family members mainly regulate T lymphocyte and NK cell proliferation and activation, and the differentiation of T cells[28-30]. IL-6 family cytokines play important roles in acute phase response in liver infection, liver regeneration, and metabolic regulation, as well as lymphocyte activation[31,32]. IL-8, also known as CXCL8, is activated in chronic liver diseases, which is associated with the accumulation of neutrophils and macrophages[33,34]. IL-10 family members contribute key roles to liver immune tolerance and immunosuppression in liver disease[35,36]. IL-12 family cytokines influence T-cell differentiation and play an essential role in autoimmune liver disease[37,38]. IL-17 subfamilies contribute to infection defense, liver inflammation, and Th17 cell differentiation[39,40]. Commonly, several IL families function together in each liver disease, contributing to liver disease progression and resolution. Therefore, targeting interleukins provides therapeutic strategies for liver disease.

INTERLEUKIN RECEPTORS

Cytokines such as interleukin family members can bind their receptors to activate intracellular signaling pathways (*e.g.*, Janus kinase/signal transduction and transcription activation or JAK/STAT signaling pathway) to regulate cell biological functions. Cytokine receptors are mainly classified into two classes, type 1 and type 2 receptors. Most receptors of IL family members belong to type 1 receptors (Table 2), such as IL-2 and IL-6, and IL-10 and IL-10 family cytokine (*e.g.*, IL-19) receptors belong to type 2 receptors[41,42], while IL-1 family member receptors have both type 1 and type 2 receptors [12]. Type 1 cytokine receptors have a conserved Trp-Ser-X-Trp-Ser (WSXWS) motif at their C-terminals and four conserved cysteine residues at their N-terminals, and they can interact with cytokines with four-helical bundle motifs [43]. Most type 2 cytokine receptors are heterodimers (Table 2), and their intracellular domains are linked by a Janus kinase which can activate the STAT signaling pathway[44].

IL-MEDIATED THERAPIES IN CLINICAL TRIALS

Given the important roles of ILs in liver diseases, many clinical trials are undergoing to evaluate their direct and synergistic functions in liver disease treatment. The cases (Table 3) were reviewed from the website https://www.clinicaltrials.gov/ (accessed on December 3, 2023). To date, most studies have been performed to evaluate IL-mediated therapies on alcohol and hepatitis virus infection-induced hepatitis.

Table 1 Interleukin families in liver diseases

IL family	Members	Functions
IL-1	IL-1α, IL-1β, IL-18, IL-33, IL-36, IL-37, and IL-38	Mediate inflammatory responses to a wide range of stimuli in both innate and adaptive immune systems, with pro- and anti-inflammatory functions[12,13]
IL-2	IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21	Regulate T cell proliferation and activation, NK cytolytic activity, and the differentiation of regulatory T cells[14,15]
IL-6	IL-6, IL-11, IL-27, IL-31, oncostatin M, leukemia inhibitory factor, ciliary neurotrophic factor, cardiotrophin 1, and cardiotrophin-like cytokine factor 1s	Play important roles in B-cell stimulation, the balance between regulatory and effector T cells, metabolic regulation, hepatic acute phase reaction, and many neural functions [16,17]
IL-8	IL-8, also known as CXCL8	It is a member of the chemokines, which has biological functions on cells expressing CXCR1 and CXCR2 receptors, such as polymorphonuclear leukocytes (neutrophils), epithelial cells, endothelial cells, fibroblasts, and neurons[18,19]
IL-10	IL-10, IL-19, IL-20, IL-22, IL-24, and IL-26	Display immunosuppressive functions, elicit innate defense mechanisms against viral, bacterial, and fungal infections, promote tissue repair and regeneration, and provide therapeutic targets for autoimmune diseases and cancers[20,21]
IL-12	IL-12, IL-23, IL-27 and IL-35	Regulate immune responses and influence naïve T cell differentiation in many inflammatory diseases, autoimmune diseases, and various cardiovascular diseases[22,23]
IL-17	IL-17A to IL-17F (IL-17E also known as IL-25)	Defense against microbial (bacteria, fungi, and helminth) infection, recruit neutrophils, and modify T-helper cell differentiation[24,25]

IL: Interleukins.

Table 2 Interleukins and their receptors

Interleukin	Type 1 receptors	Interleukin	Type 2 receptors	IL-1 family member	Receptor
IL-2	IL-2Rα, IL-2Rβ, IL-2Rγ	IL-10	IL-10Rα, IL-10Rβ	IL-1α, IL-1β	IL-1R1, IL-1R3
IL-3	IL-3Rα, CSF2Rβ	IL-19, IL-20, IL-24	IL-20Rα, IL-20Rβ	IL-1β	IL-1R2, IL-1R3
IL-4	IL-4R, IL-2Rγ/IL-13Rα1	IL-22	IL-22Rα1, IL-10Rβ	IL-1Rα	IL-1R
IL-5	IL-5Rα, CSF2Rβ	IL-20, IL-24	IL-22Rα1, IL-20Rβ	IL-18	IL-1R5, IL-1R7
IL-6	IL-6Rα, gp130	IL-26	IL-10Rβ, IL-20Rα	IL-33	IL-1R4, IL-1R3
IL-7	IL-7Rα, IL-2Rγ	IL-28, IL-29	IL-28Rα, IL-10Rβ	IL-36	IL-1R6, IL-1R3
IL-9	IL-9R, IL-2Rγ			IL-37	IL-1R5, IL-1R8
IL-11	IL-11Rα, gp130			IL-38	IL-1R6, IL-1R9
IL-12	IL-12Rβ1, IL-12Rβ2				
IL-13	IL-13Rα1, IL-13Rα2, IL-4R				
IL-15	IL-15Rα, IL-2Rβ, IL-2Rγ				
IL-16	CD4, CD9				
IL-21	IL-21R, IL-2Rγ				
IL-23	IL-12Rβ1, IL-23R				
IL-27	IL-27Rα, gp130				
IL-31	IL-31Rα, OSMR				
IL-34	CSF-1R				
IL-35	IL-12Rβ2, gp130				

IL: Interleukins.

Table 3 Interleukin-mediated therapies in liver disease

Clinical trials	Phase	Liver disease	Interleukin therapy
NCT00565539	1	Chronic hepatitis C virus (HCV) infection	PEGylated recombinant interleukin 29 (PEG-rIL-29) or in combination with daily oral ribavirin (an antiviral drug)
NCT03882307	1	Hepatitis C virus (HCV) infection	Test the association of serum levels of IL-6 and TGF-β in response to antiviral therapy (sofosbuvir and daclatasvir) for chronic hepatitis C patients
NCT02431312	1	Chronic hepatitis B	Evaluate the safety, tolerability, and immunogenicity of dose combinations of INO-1800 (DNA plasmids encoding hepatitis B surface antigen and hepatitis B core antigen) and INO-9112 (DNA plasmid encoding human interleukin 12) delivered by electroporation
NCT02655510	1/2	Alcoholic hepatitis	To test the efficacy of F-652, a recombinant fusion protein containing human IL-22 and human immunoglobulin G2 (IgG2)-Fc produced in CHO cells in serum-free culture
NCT03775109	2	Alcoholic hepatitis	To evaluate the potential benefits of the IL-1β antibody Canakinumab in the treatment of alcoholic hepatitis
NCT01988506	2	Autoimmune hepatitis, and other autoimmune and auto-inflammatory diseases	Low-dose IL-2 to induce regulatory T cells
NCT00196586	2	Chronic hepatitis C	Evaluate the efficacy and safety of the addition of IL-2 to pegylated interferon α-2a and ribavirin in patients with HCV/HIV coinfection
NCT01697501	3	Chronic hepatitis B	Evaluating the IL-28B polymorphism in patients with HBeAg-negative chronic hepatitis B treated with pegylated interferon α-2a
NCT03090035	3	Chronic hepatitis C	Test IL-28B (rs12979860) genotypes in patients with chronic hepatitis C infection treated with pegylated interferon α2 plus ribavirin
NCT02360592	4	Chronic hepatitis B	Evaluate the efficacy and safety of interferon α-2b therapy plus IL-2 and hepatitis B therapeutic vaccine compared to interferon α-2b alone
NCT03734783	Observational	Chronic hepatitis B	Investigate the levels of IL-35-secreting B regulatory cells in peripheral blood cells in patients with chronic hepatitis B and their functions on Th1 and Th2 cell levels

IL: Interleukins.

CONCLUSION

In summary, all seven families of ILs play pivotal roles in liver homeostasis and pathogenesis by regulating both innate and adaptive immune responses. However, current studies mainly focus on evaluating the roles of ILs in alcohol and hepatitis virus infection-induced hepatitis. Pre-clinical and clinical evaluations of IL effects in different chronic liver diseases should be further studied by testing the efficacy of interleukin monotherapy or synergistic effects with other therapies.

FOOTNOTES

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