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REVIEW

Interleukin-10 and chronic liver disease

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Abstract

Interleukin (IL)-10 is an important immunoregulatory cytokine produced by many cell populations. Numerous investigations suggest that IL-10 plays a major role in chronic liver diseases. IL-10 gene polymorphisms are possibly associated with liver disease susceptibility or severity. Recombinant human IL-10 has been produced and is currently tested in clinical trials. These trials may give new insights into the immunobiology of IL-10 and suggest that the IL-10/IL-10 receptor system may become a new therapeutic target.

Key words: Interleukin (IL)-10; Cytokine; Chronic liver diseases; Polymorphisms

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BIOLOGICAL CHARACTERISTICS AND REGULATION OF INTERLEUKIN-10

Interleukin-10 (IL-10) first described as a cytokine synthesis inhibitory factor for T lymphocytes produced by T helper 2 (Th_2) cell clones, can inhibit interferon (IFN)-γ synthesis in Th_1 cell clones[1]. The human IL-10 gene, a homodimer with a molecular mass of 37 ku, is located on chromosome 1 and encodes for 5 exons. Each monomer consists of 160 amino acids. X-ray crystal-structure-analysis showed the two identical intertwining polypeptide chains of 160 animo acids are rotated by 180° to each other, forming two domains in a V- shape structure, each containing six helices[2-4]. Murine and human IL-10 exhibits a homology of about 80%. Various cell populations produce IL-10 in the body, including T cell subsets (Th_2, Tc_2, Tr_1, *etc*), monocytes, and macrophages. IL-10 is produced also by various cell types in other organs, including the liver[5-6]. Also, the stress axis plays a significant role in regulating IL-10 expression *in vivo*. Inflammation of the central nervous system or indirect activation of the stress axis by endotoxemia/bacteremia triggers the release of catecholamines that up-regulate IL-10 production in macrophages, particularly in the liver[7-8]. Within the liver, production of IL-10 has been documented within hepatocytes, sinusoidal endothelial cells, Kupffer cells, hepatic stellate cells and liver-associated lymphocytes[9]. These cells are stimulated to produce IL-10 through the cAMP/protein kinase A/CREB-1/ATF-1 signaling by several endogenous and exogenous factors such as stress, exdotoxin, tumor necrosis factor-α, catecholamines, and cAMP-elevating drugs. Recent data suggest that the p38 mitogen-activated kinase pathway also regulates the human IL-10 promoter via the activation of sp1 transcription factor[10]. IL-10 activity is mediated by its specific cell surface receptor-IL-10 receptor, which is expressed on a variety of cells, especially in immune cells[11]. Only a few copies of IL-10R are expressed on the surface of cells[12-13]. The expression is variable, but so far only a few regulating factors are known. IL-10R is composed of two different chains[14]. The interaction of hIL-10R with hIL-10 has been characterized recently and seems to be highly complex[15-16]. The IL-10Rβchain is essential for IL-10-mediated effects and CRFB4-deficient mice display the same phenotype as IL-10 deficient mice[17]. Only in cells expressing both IL-10R α and βchains, can the characteristic pattern of IL-10 signaling be observed[18]. The IL-10/IL-10R interaction activating the tyrosine kinases Jak1 and Tyk2, inhibiting the activity of NF-κB, results in transcriptional activation of several hundred genes[19]. The effects of IL-10 have been confirmed by experimental research in animals including IL-10 knockout mice[20] as well as by the effects of IL-10 observed in several inflammatory, autoimmune, and tumor models. IL-10 inhibits the ability of monocytes and macrophages to produce antigens to T cells[21-22] and monocytic production of IL-12. Inhibits proliferation and cytokine synthesis of $CD4^+$ T cells by exerting some direct effects of T cells, but does not exert potent direct inhibitory effects on $CD8^+$ T cells. IL-10 has various but weak stimulatory effects on B cells. IL-10 prevents apoptosis and enhances proliferation and differentiation of plasma cells as well as IgM synthesis, and inhibits the release of various chemokines by neutrophils. One of the most important properties of IL-10 is its anti-inflammatory action[23], which restrains the

immune response under various stimuli. Evidence of *in vivo* function of IL-10 indicates that inflammatory bowel disease is exacerated in the absence of IL-10.

EFFECTS OF IL-10 ON CHRONIC LIVER DISEASE AND LIVER FIBROSIS

Experimental data from animal models and clinical data from patients suggest that inflammation-associated cytokines including pro-inflammatory cytokines such as TNF-αand TGF-β, and anti-inflammatory cytokines such as IL-10 , are involved in the development of liver injury[24]. The effects of IL-10 have been observed in viral or autoimmune hepatitis, alcoholic liver disease, and animal models. Patients with a strong Th_1 response during acute HCV infection can clear the virus, while patients presenting with a Th_2 response (high levels of IL-10) evolve into chronicity[25]. In Con A-induced liver injury model[26-28], using a blocking IL-10 monoclonal antibody could lead to severe hepatic necrosis. On the other hand, administration of recombinant IL-10 in mice challenged with Con A could dramatically reduce secretion of pro-inflammatory cytokines, apoptosis of hepatocytes, hepatic neutrophil infiltrate and delay hepatic necrosis. In the model of liver injury induced by lipopolysaccharide (LPS) or staphylococcal enterotoxin B (SEB) in D-galactosamine (GalN)-sensitized mice[29-31], treatment with IL-10 could markedly reduce serum transaminase activities in a dose-dependent manner and hemorrhagic liver damage in sensitized mice exposed to toxins. IL-10 also inhibits increases in serum TNF-alpha and IFN-gamma concentrations with the toxins. Treatment with IL-10 could significantly reduce TNF-alpha mRNA and IFN-gamma mRNA expression in the liver and spleen after administration of the toxins to sensitized mice. These findings suggest that IL-10 is capable of regulating hepatic injury *in vivo* mediated by T cells macrophages. Injury of the liver requires the participation of proinflammatory cytokines and chemokines, many of which are regulated by the transcription factor, nuclear factor κB (NFκB). Other data suggest that IL-10 protects against hepatic ischemia/reperfusion injury by suppressing NFκB activation and subsequent expression of proinflammatory mediators[32]. IL-10 has been shown to be beneficial in the setting of liver transplantation[33], treatment with IL-10 can increase allograft survival. Current studies demonstrate that IL-10 may protect against surgery-or trauma related organ injuries secondary to hepatic ischemia-reperfusion. In human alcoholic liver disease or in rats fed with alcohol, defective production of IL-10 might result in chronic liver disease, suggesting that IL-10 might be of therapeutic value for alcoholic hepatitis by decreasing hepatocyte death[34]. In the model of CCl_4-induced chronic liver injury, IL-10 deficient animals had a persistently increased inflammatory infiltrate, and developed a more extensive fibrosis than the animals able to produce IL-10, indicating that IL-10 is involved in the control of fibrogenesis[35-37]. Several studies indicate that IL-10 might play an important role in antifibrogenesis during CCl_4-induced hepatic fibrogenesis[38-39]. Hepatic stellate cells (HSCs) are involved in liver fibrogenesis since, *in vitro* experiments have shown that HSCs express IL-10 receptor and produce IL-10[40-42]. In highly purified preparations of rat HSCs, messenger RNA (mRNA) for IL-10 can be detected by reverse-transcription polymerase chain reaction (RT-PCR). Long-term incubation of unstimulated mouse HSCs secrete IL-10 protein as detected by immunoblotting and specific enzyme-linked immunosorbent assay (ELISA). IL-10 protein is undetectable by immunohistochemistry in mouse HSCs during the first 3 d of culture. The percentage of IL-10-positive cells increases to 45% on d 7 and 100% on d 14, and IL-10 continues its expression in long-term culture of up to 120 d. These data indicate that IL-10 plays an important role in liver fibrosis by suppressing the function of HSC and promoting apoptosis of HSC[43-45]. IL-10 has a direct effect on the production of collagen and collagenases, modulates remodeling of the extracellular matrix[46-47], and indirectly limits the fibrogeneic response by controlling $TGF\beta_1$ secretion.

IL-10 GENE POLYMORPHISMS IN CHRONIC LIVER DISEASE

Genetic markers in cytokine genes are widely used in studies of immune-mediated diseases to determine disease susceptibility and severity[48]. In recent years, increasing attention has been paid to the role of cytokine levels in inflammatory and immune response., which may account for some of the heterogeneity observed in the outcome of chronic liver diseases, such as HBV and HCV infection, alcoholic and autoimmune hepatic disease. Possible linkage of IL-10 promoter haplotypes to disease susceptibility or severity has been reported[49]. The IL-10 promoter is highly polymorphie with two informative microsatellites, IL-10G and IL-10R. Single nucleotide polymorphisms (SNPs) in the promoter form SNP combinations (ATA, ACC, GCC) associated with differential IL-10 expression[50]. There are several lines of evidence that ATA haplotype in the IL-10 gene promoter is relevant to a genetically low capacity for IL-10 production, whereas GCC haplotype is identified as a high IL-10-producing phenotype, suggesting that the difference in disease progression of patients results from the inheritance of the IL-10 gene promoter polymorphisms. The influence of cytokine genotypes either on different clinical features of liver disease or in the response to antiviral therapy has been evaluated in several studies. Since inadequate expression of IL-10 seems to be of pathophysiological relevance in several diseases and the expression levels seem to have a genetic background. Increased serum levels of IL-10 are often observed in chronic HCV infection and inheritance of the interleukin-10 -1082 G/G may be associated with susceptibility to chronic hepatitis C infection and resistance to combined antiviral therapy[51-53], suggesting that chronic HCV infection patients with the haplotype conferring a high production of IL-10 have a lower rate of response to interferon therapy. IL-10 promoter allelic frequencies of T and A at positions -819 and -592, as well as the frequencies of ATA haplotype at positions -1082/-819/-592, are significantly higher in asymptomatic carriers than in patients with progressive chronic liver disease, suggesting that patients with haplotype

conferring a high production of IL-10 develop chronic progressive liver disease, while patients with a lower production of IL-10 tend to be asymptomatic carriers[54, 55]. Possession of the A allele at position -627 in the IL-10 promoter (low IL-10 expression) is associated with an increased risk of advanced liver disease in heavy drinkers[56, 57].

Genetic association analysis has revealed that one of the IL-10 haplotypes, IL10-ht2 (-1082A/-819T/-592C/+117T) is strongly associated with hepatocellular carcinoma (HCC) occurrence in a dose-dependent manner[58]. The frequency of susceptible IL10-ht2 is much higher in HCC patients and significantly increased in order of susceptibility to HBV progression from chronic to cirrhosis and HCC. In addition, the onset age of HCC is also accelerated among chronic hepatitis B patients who carry IL10-ht2. Increased IL-10 production mediated by IL10-ht2 suggests that up-regulation of IL-10 accelerates progression of chronic HBV infection, to HCC.

APPLICATION OF IL-10 AS A THERAPEUTIC AGENT

The promising results from IL-10 applied to several inflammatory diseases in experimental models induce the interest in clinical application of IL-10. So far human recombinant IL-10 has been tested in healthy volunteers, patients with Crohn's disease, rheumatoid arthritis, psoriasis, hepatitis C and HIV infection[59]. In phase I clinical trials, safety, tolerance, pharmacokinetics, pharmacodynamics, immunological and hematological effects of single or multiple doses of IL-10 administered by intravenous (i.v.) or subcutaneous (s.c.) route have been investigated in healthy volunteers[60]. IL-10 is well tolerated without serious side effects at the dose of 25 μg/kg and mild to moderate flu-like symptoms are observed in a fraction of recipients at the doses of 100 μg/kg.

Single i.v. or s.c. of IL-10 results in transient dose-dependent changes in white blood cell population, including increase of total white blood cells and neutrophils, lymphocytopenia and monocytosis as well as decrease in platelet counts are observed[61]. Following i.v. administration, IL-10 serum levels initially decline rapidly but yields a less steep terminal phase. IL-10 is cleared mainly through the kidneys as indicated by the increased $t_{1/2}$ and AUC of IL-10 in patients with moderate to severe renal insufficiency. Taken together, IL-10 application induces a number of immunological changes and is well tolerated[62]. IL-10 treatment does not result in significantly higher remission rate or clinical improvement for Crohn's disease compared with placebo treatment[63]. IL-10 can prevent postoperative recurrence of Chorine's disease but the clinical results are unsatisfactory[64]. The data from rheumatoid arthritis patients are rather discouraging, showing only marginal activity of the drug[65]. For psoriasis, IL-10 is likely to have antipsoriatic activity[66].

IL-10 is able to express antifibrotic properties in experimental models of liver cirrhosis[59]. It has been postulated that *in vivo* administration of IL-10 to patients with HCV infection may shift the intrahepatic immunologic balance away from Th1 cytokine predominance, thus exerting its anti-inflammatory and subsequent antifibrotic effect[67]. It was reported that long-term therapy with interleukin-10 decreases hepatic inflammatory activity and fibrosis, but leads to increased HCV viral levels[68].

IL-10 increases the susceptibility to infections due to its immunosuppressive activity and inhibition of bactericidal activity[69]. In the future, it may be used to target the delivery of IL-10 to avoid systemic side effects and low biodisponibility. IL-10 could be delivered locally with an adenovirus in the liver[70], suggesting that anti-inflammatory cytokines may have a future in the treatment of liver injury and the prevention of its complications.

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