Modulation of liver injury by interleukin-10

H. Louis[1], O. Le Moine[1], M. Goldman[2], J. Devière[1]

Laboratory of Experimental (1) Gastroenterology and (2) Immunology, Faculty of Medicine, Université Libre de Bruxelles, Brussels, Belgium.

Abstract

Inflammation is commonly observed in liver diseases and is frequently complicated by fibrosis and cirrhosis in end-stage disease. The only curative treatment for cirrhotic patients is liver transplantation. However, organ shortage as well as an increasing organ demand call for early treatment of liver disease and prevention of fibrosis. Experimental data have shown the critical role of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) in the development of liver injury. Here, we review our work on the role of endogenously produced interleukin-10 (IL-10), a potent anti-inflammatory cytokine, in several experimental models of acute and chronic liver injury. First, in acute macrophage-mediated hepatitis induced by galactosamine/lipopolysaccharide administration, IL-10 neutralisation led to a more severe liver damage, whereas IL-10 injection, even delayed, was able to limit liver necrosis. A similar protective effect of IL-10 was observed in acute T cell-mediated hepatitis induced by concanavalin A (Con A) injection. The immunoregulatory role of IL-10 was then established after repeated exposition to Con A. In carbon tetrachloride liver injury, two other properties of IL-10 have been suggested : modulation of hepatocyte proliferation and modulation of liver fibrosis. Finally, the potential therapeutic applications in human liver disease as well as the potential side effects are discussed. (Acta gastroenterol. belg., **2003**, 66, **7-14**).

Key words : liver, inflammation, hepatitis, liver injury, cytokines, mice, interleukin-10, tumor necrosis factor-alpha.

Introduction

For more than a decade, experimental data from animal models and clinical data from patients have suggested that pro-inflammatory cytokines are involved in the development of liver injury. One of these mediators, TNF-α, induced toxic side effects when used as an anticancerous agent, and produced a rise in serum bilirubin and transaminases, indicating a direct cytotoxic role of TNF-α on hepatocytes (1). Since then, experimental data have established the critical role of TNF-α in inducing hepatocyte cell death in many models of liver injury. Among other cytokines, the role of IFN-γ was demonstrated in fulminant hepatitis in transgenic mice expressing the hepatitis B surface antigen in a constitutive manner (2), and in IFN-γ transgenic mice which develop a chronic hepatitis after a few weeks (3). In humans, an increased expression of IFN-γ is observed in autoimmune, viral and in liver allograft rejection (4-6).

Interleukin-10 (IL-10) was initially discovered in 1989, as a cytokine synthesis inhibitory factor for T lymphocytes (7). Studies later showed that IL-10 deeply inhibits many macrophage functions, including cytokine and NO production and the expression of costimulatory molecules produced by macrophages and lymphocytes, and limits the proliferation of lymphocytes (8). Since then, numerous studies have shown that IL-10 is produced by other cells of the immune system, but also by various cell types in other organs, including the liver. Within the liver, production of IL-10 has been documented within hepatocytes, sinusoidal endothelial cells, Kupffer cells, stellate cells and liver-associated lymphocytes (9). Being exposed to bacterial endotoxin (lipopolysaccharide, LPS) flowing in the liver through the portal circulation, Kupffer cells express IL-10 in physiological LPS concentrations, avoiding a perpetual liver inflammation (10,11). Like other cytokines, IL-10 is pleiotropic : it has multiple effects on diverse cell types ; it is also redundant by having similar properties like other cytokines, although there is no homology of structure or sequence between these cytokines. One of the most important properties of IL-10 is an anti-inflammatory inhibitory action which will restrain and limit the immune response under various stimuli, which would otherwise pursue with deleterious consequences for the individual. Evidence of in vivo function of IL-10 indicated that in the absence of IL-10 (in genetically IL-10 deficient animals), an exaggerated inflammatory response can lead to inflammatory states like inflammatory bowel disease (12,13).

The interest of our laboratory for IL-10 began 10 years ago in the context of liver diseases. After the detection of IL-10 in several human hepatic disorders like reperfusion of a transplanted liver or unbalanced production in alcoholic cirrhosis (14,15), we undertook studies to investigate the role played by this cytokine *in vivo* .

Role of IL-10 in acute liver injury

It has been hypothesised that in acute or fulminant hepatitis in humans, an overproduction of pro-inflammatory cytokines often precludes deleterious effects. Indeed, increased TNF-α, IL-1 and IL-6 serum levels have been detected in fulminant liver failure, persistent high levels being associated with a bad prognosis (16). Moreover, an imbalance between pro-inflammatory, like IL-1, and anti-inflammatory cytokines, like IL-1 receptor antagonist, was demonstrated in patients who will

Address where reprints are to be sent : Dr. Hubert Louis, Department of Gastroenterology, Erasme Hospital, 808 route de Lennik, 1070 Brussels.

die, suggesting a defective anti-inflammatory response in this situation (17). Concerning IL-10, elevated levels of IL-10 were detected in the serum of patients presenting fulminant liver failure, and were significantly higher in surviving cases (18). A massive induction of pro-inflammatory cytokines in patients with fulminant hepatitis was also demonstrated in the hepatic tissue, and was apparently not counterbalanced by an induction of IL-10 expression (19). Beside increased TNF-α serum levels and a mononuclear liver infiltrate expressing TNF-α, an increased expression of the TNF receptor type 1 was demonstrated on the surface of hepatocytes in cases of fulminant hepatitis (16). The interaction between TNF-α and its type 1 receptor is a major pathway of cell death in hepatocytes, and we can thus speculate that the blockade of this pathway might be of therapeutic interest (20-23). Finally, costimulatory molecules on hepatocytes and their respective ligands on T cells seem to be also overexpressed in this dramatic clinical situation (24). It must be noted, however, that raised serum levels of cytokines in liver failure cases might be also the consequence of an impaired liver metabolism, the liver being an important organ for the elimination of cytokines (25).

Like in cirrhosis, infections and endotoxemia are common complications in fulminant hepatitis, probably partly due to a defective function of the scavenger function of Kupffer cells and sinusoidal endothelial cells (26-28). Bacterial LPS can then activate peripheral macrophages/monocytes, and in that circumstance, an imbalance between the burst of immune activation and the anti-inflammatory response will lead to catastrophic consequences. The filter function of the liver downstream of the gut puts liver sinusoids and Kupffer cells in contact with bacterial endotoxins which would be continuously activated, in the absence of an anti-inflammatory defence, with deleterious effects. IL-10, produced locally in hepatic sinusoids by Kupffer cells, is a natural anti-inflammatory mediator acting on sinusoidal cells in a paracrine fashion, or peripherally in an endocrine fashion (10,11).

The overactivation of the pro-inflammatory cascade and a potentially defective anti-inflammatory response in fulminant hepatitis compelled us to investigate the production and the role of IL-10 in two animal models of acute hepatitis (29,30). In the first model, mice were injected with galactosamine, an inhibitor of hepatocyte transcription, which sensitizes hepatocytes to normally innocuous doses of LPS. After Gal/LPS injection, mice develop in a few hours an acute and potentially fatal liver necrosis whose histology resembles acute liver injuries in humans. Kupffer cells are activated by LPS to produce TNF-α, which can induce hepatocyte apoptosis and further activate other cells of the immune system, thereby contributing to the propagation of the inflammatory cascade (31,32). Transendothelial migration of neutrophils is observed in the liver parenchyma, where these cells will exert cytotoxicity (33). In this experimental model of hepatitis, we detected IL-10 very early in the serum, and after neutralisation of endogenously produced IL-10 with a monoclonal antibody, we observed increased TNF-α serum levels and a more severe hepatic necrosis. Conversely, administration of exogenous recombinant IL-10 prevented the release of TNF-α and the subsequent liver damage, and a protective effect was still observed when IL-10 was administered after Gal/LPS injection, indicating that IL-10 might be of therapeutic value after the peak of secretion of TNF-α and after the onset of liver injury. Several mechanisms can explain the protective effect of IL-10 in this acute hepatitis : an inhibition of the secretion of TNF-α by Kupffer cells, an inhibition of the adherence of neutrophils to the endothelium through the downregulation of adhesion molecules, and an inhibition of the secretion of toxic mediators by neutrophils. Others have demonstrated that an anti-inflammatory response is also important in drug-induced liver injury, as demonstrated in IL-10 deficient mice which exhibit a more severe acetaminophen-induced liver injury (34). A potential clinical use of IL-10 can so be foreseen in human liver failure of various aetiologies.

Activation of Kupffer cells has been proved to play a deleterious role in several models of liver injury (35). Interestingly, Kupffer cells may be activated in other pathologies with systemic complications. In acute pancreatitis for example, TNF-α is produced in several organs, like the liver (in Kupffer cells). IL-10, produced among other organs within the liver, will limit the severity of the pancreatitis in mice (36), and its administration before ERCP in humans has proven to reduce the severity of acute pancreatitis complicating this endoscopic procedure (37). These results show that IL-10 is able to restrain the inflammatory cascade leading to liver cell death, and the systemic inflammatory response in situations where Kupffer cells are activated.

Activated lymphocytes infiltrating portal tracts are commonly observed in viral or autoimmune hepatitis (38). In a second model of acute liver injury, we assessed the role of IL-10 in mice challenged with concanavalin A (Con A), a potent polyclonal activator of T lymphocytes (39). Once injected in vivo, Con A induces an inflammatory cascade and a cytokine release syndrome, among which cytokines TNF-α, IL-4, IL-12 and IFN-γ play a critical role in the development of liver injury (40-43). In this model, we observed that IL-10 is produced concomitantly with the pro-inflammatory cytokines (30). The role of endogenous IL-10 was also addressed by the use of a blocking monoclonal antibody, whose administration led to increased levels of TNF-α, IL-12 and IFN-γ, and to a more severe hepatic necrosis. On the other hand, administration of recombinant IL-10 in mice challenged with Con A dramatically reduced the secretion of pro-inflammatory cytokines, the apoptosis of hepatocytes, the hepatic neutrophilic infiltrate and the extent of delayed hepatic necrosis. IL-10 dosages on tissue homogenates also suggested that the cytokine was produced locally in the liver.

Following a massive liver insult, for example after partial hepatectomy or liver necrosis, remaining hepatocytes proliferate, enabling the liver to regenerate. It has been established that TNF-α and IL-6 are key cytokines to trigger hepatocyte proliferation (44). We studied the role of IL-10 in the phase of tissue reparation following acute liver necrosis induced by carbon tetrachloride (CCL4) in IL-10 deficient mice, with a targeted disruption of the IL-10 gene (12). Our data show that IL-10 restrains the proliferative response of hepatocytes after liver damage (45). This is in line with previous reports establishing that the production of IL-10 by Kupffer cells limits the expression of TNF-α, avoiding an overexpression that would lead to enhanced proliferation of hepatocytes (46). Transforming growth factor-beta 1 (TGF-β1), another cytokine able to limit the production of TNF-α, is produced later than IL-10, and exerts its inhibitory effects on cell mitosis later. In IL-10 deficient mice, TGF-β1 secretion is increased after exposition to CCL4, presumably explaining why the proliferation of hepatocytes is not sustained after 72 hours. Thus, a complex network of cytokines with redundant effects on the cell cycle is involved in the control of liver regeneration.

Interleukin-10 and alcoholic liver disease

In alcoholic liver disease, a comparable immune activation is observed, involving LPS and its macrophage receptors CD14 and Toll-like-receptor 4 (Tlr4), Kupffer cell activation and the production of TNF-α (47-50). In humans, a genetic polymorphism of the CD14 gene and of the promoter of the TNF-α gene is associated with an increased susceptibility to alcohol liver injury (51,52). Interestingly, the biological effects of TNF-α, whose increased production has been demonstrated in alcoholic hepatitis (53-55), are often observed in these patients : fatigue, anorexia, cachexia, low grade fever, hypoalbuminemia, jaundice, hepatocyte apoptosis and neutrophil recruitment to the liver (together with IL-8, leading to the histological image of satellitosis) .

An excessive pro-inflammatory response might here also be the consequence of a defective anti-inflammatory response. Indeed, Le Moine *et al.* suggested that a defective IL-10 production might explain the excessive secretion of TNF-α in human alcoholic liver disease (15). This can be the consequence of a genetic predisposition, since the ability to secrete IL-10 depends on the genetic composition of the IL-10 locus, some haplotypes being associated with an increased production of IL-10 in response to LPS (56). In alcoholic hepatitis, the allele conferring a low production of IL-10 is more frequently encountered, adding to this hypothesis (57). Beside a genetic predisposition to produce lower amounts of IL-10, a blunted response to adenosine, a stimulator of IL-10 secretion, and an increased activity of adenosine deaminase was observed in these patients (58). A direct toxic effect of alcohol on the liver might also explain lower hepatic levels of IL-10 mRNA, as observed in rats

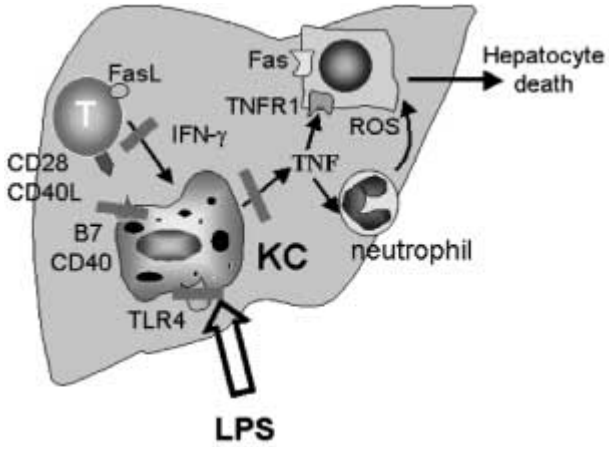

Fig. 1. — Potential targets of IL-10 in acute liver injury. IL-10 inhibits (red bars) several pathways of the inflammatory cascade leading to hepatocyte apoptosis. Abbreviations : KC : Kupffer cells, ROS reactive oxygen species, T : T lymphocyte.

fed with alcohol (59). Finally, other factors like a stimulation of TNF-α production by macrophages due to IgA deposits in liver sinusoids (60) and a defective synthesis of anti-inflammatory acute phase proteins (61) might also explain this imbalance. In alcoholic hepatitis also, there is thus evidence that IL-10 might be of therapeutic value by interfering with TNF-α pathways of hepatocyte cell death (Fig. 1).

Interleukin-10 in chronic viral liver injury

In viral hepatitis, expression of TNF-α and IFN-γ is induced, which is beneficial for viral clearance (62-64). If the infected individual is unable to mount a vigorous antiviral response, chronic infection will ensue, due to a genetic predisposition to secrete certain types of cytokines, and to the viral variability with apparition of mutants escaping to the immune response (65). Patients with a strong Th1 response (high levels of TNF-α and IFN-γ) during acute HCV infection will clear the virus, while patients presenting with a Th2 response (low levels of TNF-α and IFN-γ and high levels of IL-4, IL-5 and IL-10) will evolve to chronicity (66,67). In chronic hepatitis, intrahepatic clones of lymphocytes continue to produce TNF-α and IFN-γ, whose expression is correlated to the extent of liver damage (5,6). This persistent silent inflammation, unable to clear the virus or at the best controlling partially its replication, will pursue during years, eventually ending in cirrhosis. Interestingly, some HCV epitopes like the core protein and the NS3 epitope, can stimulate the production of IL-10 by CD4 + T cells and stimulate the apparition of regulatory T cells able to inhibit Th1 cells (68,69). This might explain why increased serum levels of IL-10 are often observed in chronic HCV infection, highest levels being associated to a less favourable response to interferon treatment (70). Here also, the genetic profile of patients can help to predict the response to treatment :

patients with the haplotype conferring a high production of IL-10 have a lower rate of response to interferon therapy in chronic HCV infection (71,72). In hepatitis B, patients having the haplotype conferring a high production of IL-10 develop a chronic progressive liver disease, while patients with a lower production of IL-10 tend to be asymptomatic carriers. (73). This cytokinic profile with a high IL-10 secretion might also be viewed as a state of tolerance (see infra), regulatory T cells developed in a state of continuous antigenic exposition limiting an excessive immune response. In the optic of cytokine modulation as a treatment for chronic viral hepatitis, two ways are possible. The first aims to boost the Th1 immune response to mount an effective viral clearance. IFN-α and ribavirin act partly through that mechanism (74,75). IL-12, a potent cytokine for the induction of a Th1 response, has been used in clinical trials, nevertheless with disappointing results (76). The second way, if a viral clearance cannot be obtained as a primary endpoint, is to limit the futile intrahepatic inflammation and to prevent fibrosis. For this purpose, IL-10 has been tried in patients with chronic HCV hepatitis who did not respond to interferon therapy (77). After 12 weeks of treatment, histological scores of liver fibrosis and inflammation, as well as serum transaminases, were significantly reduced in the group treated with IL-10. Predictably, the viral load was not modified by IL-10 treatment. ALT and AST serum levels returned to basal levels after cessation of treatment. An interesting feature was a decrease in serum TNF-α levels in these patients, while systemic manifestations of chronic HCV infection (myalgias, arthralgias, fatigue) were improved under IL-10 treatment, suggesting that pro-inflammatory cytokines secreted in periphery might be involved in these symptoms. Prolonged treatment with IL-10 during one year in a larger group of patients did however not confirm the enthusiastic antifibrogenic results, and at the end of treatment, viral load was even three times higher, when compared to levels before treatment (78).

Role of interleukin-10 in liver fibrogenesis

Hepatic stellate cells are centrally involved in liver fibrogenesis. Activation of these cells after liver injury depends on many soluble factors like cytokines and chemokines (79). In vitro experiments on fibroblasts have shown that these cells express the IL-10 receptor and that IL-10 can modulate the remodelling of the extracellular matrix. Liver stellate cells also express IL-10 receptor (80) and produce IL-10, which inhibits collagen synthesis and stimulates collagenase secretion by these cells (81,82). Wang *et al.* also showed that after bile duct ligation in the rat, which induces liver fibrosis, IL-10 is strongly expressed on stellate cells (81). These observations prompted us to investigate the role of IL-10 in liver fibrogenesis in vivo (45). Carbon tetrachloride induces acute as well as chronic liver injury when exposition to the toxic is repeated. Hepatotoxicity involves in a first step the production of highly reactive oxygen species, and in a second step an inflammatory response which both lead to centrilobular necrosis. Chronic exposition in the animal induces liver fibrosis and cirrhosis. Here, the role of IL-10 was assessed by the use of IL-10 deficient mice. If acute liver necrosis after a single exposition to CCL4 was not modified by the presence of IL-10, we showed that IL-10 controls the neutrophilic infiltrate in the liver through the control of TNF-α secretion. Moreover, after 7 weeks of repeated exposition to CCL4, IL-10 deficient animals had a persistent increased inflammatory infiltrate, and developed a more extensive fibrosis than the animals able to synthesise IL-10, indicating that IL-10 is involved in the control of fibrogenesis. Beside a direct effect on the production of collagen and collagenases by stellate cells, IL-10 might indirectly limit the fibrogenic response by a control of TGF-β1 secretion, and a dampening of the inflammatory response (Fig. 2). Indeed, inflammation and fibrogenesis are often linked, and stimulate each other in a vicious circle : activated stellate cells produce chemokines which will attract neutrophils and macrophages but also stellate cells themselves. In turn, activated inflammatory cells secrete reactive oxygen species which activate stellate cells (83-87).

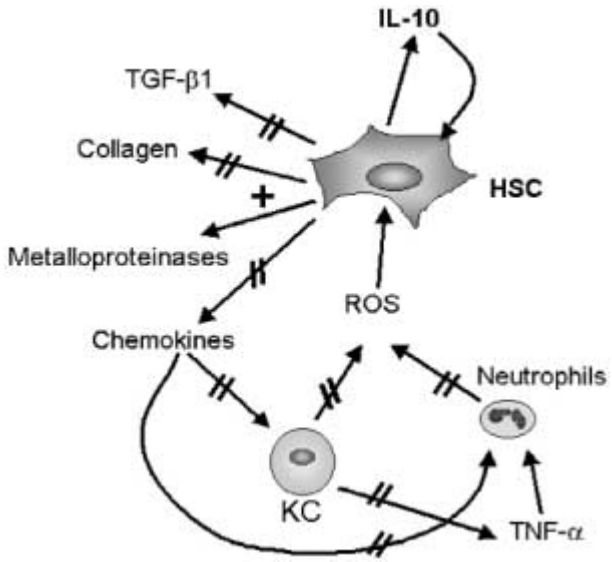

Fig. 2. — Possible mechanisms explaining the antifibrogenic properties of IL-10. // :inhibitory effect of IL-10 ; + : stimulatory effect of IL-10. Abbreviations : KC : Kupffer cells, ROS reactive oxygen species, T : HSC : hepatic stellate cell.

Other experimental studies have indicated that IL-10 is not always anti-fibrogenic in the liver or the lung, depending on the fibrogenic stimulus and on the type of immune response (Th1 or Th2 type). Indeed, Th1 cytokines like IFN-γ are rather anti-fibrogenic, while Th2 cytokines like IL-4, IL-5 or IL-13 are pro-fibrogenic (88-91). As mentioned above, antifibrogenic effects in human chronic hepatitis due to HCV infection were

disappointing, after initial enthusiasm following a small pilot trial (77,78). At the present time, IL-10 can thus certainly not be proposed as a magic antifibrogenic bullet (92).

Interleukin-10 as a regulatory cytokine : implications for tolerance

It has become evident that IL-10 plays a role in antigen tolerance by inducing T cell anergy, through the blockade of costimulatory signals, and by the development of regulatory T cells (93-96). In the liver, IL-10 limits T cell activation by inhibiting antigen presentation and the costimulatory activity of sinusoidal endothelial cells (97). Interestingly, these cells can induce antigen-specific T cell tolerance, which is certainly mandatory, regarding the number of soluble food antigens that are absorbed in the gut and enter the circulation via the portal vein (98). Oral antigens also generate regulatory T cells in the liver, secreting IL-4, IL-10 and TGF-β1, and suppressing other T cells, as recently demonstrated (99).

We evaluated the effect of a repeated exposition to Con A in mice (100). This repeated T cell stimulation led rapidly to a modified profile of cytokine secretion : the polyclonal T cell profile was replaced after 3 injections of Con A by a dramatic increase in IL-10 secretion, while serum levels of TNF-α, IL-2 and IFN-γ were rapidly almost abolished. The increased production of IL-10 was responsible for the decrease in the secretion in the other cytokines : this is a regulatory mechanism which avoids a deleterious and potently lethal massive activation of the immune system : large areas of liver necrosis, observed after the first injection of Con A, were no more observed when exposition to Con A was repeated. TGF-β1 was also increasingly expressed in the liver, together with an accumulation of stellate cells and the apparition of liver fibrosis within the sinusoids. TGF-β1 is a major cytokine involved in liver fibrogenesis, is also involved in oral tolerance and produced by regulatory T cells (95). In our model of repeated injections of Con A, CD4+ lymphocytes were seemingly the cellular source of IL-10, as attested by cellular depletion experiments. It is thus tempting to postulate that regulatory T cells have developed, producing high levels of IL-10 and TGF-β1. It remains to investigate if these cells, by their production of TGF-β1, are involved in liver fibrogenesis. In human chronic viral injury also, as HCV proteins induce the development of regulatory T cells (69), these cells could be linked to fibrogenesis. If massive inflammation and subsequent liver necrosis is no more observed after each additive exposition to Con A, a silent hepatic inflammation persists, with an infiltrate surrounding portal tracts and central veins. This mild persistent inflammation could be due to IL-10, as this cytokine has also immunostimulatory effects. This is probably the price to pay to avoid a catastrophic immune activation as seen after a single injection of Con A in naive animals.

IL-10 potential side effects

The anti-inflammatory properties of IL-10 have led to clinical studies in human inflammatory and autoimmune pathologies. First, IL-10, administered subcutaneously or intravenously, is well tolerated without serious side effects. In a chronic setting, daily subcutaneous injection of IL-10 led to a moderate anaemia (77). By its immunosuppressive activity and the inhibition of bactericidal activity, IL-10 might increase the susceptibility to infections (101). Beside its anti-inflammatory and immunosuppressive properties, one has to keep in mind that IL-10 has also immunostimulatory properties due to its isoleucine in position 87 of the protein (102). IL-10 stimulates the recruitment, the proliferation and the cytotoxic activity of CD8+ and NK cells, the proliferation of mast cells and B lymphocytes, and the secretion of immunoglobulins by B cells (8). These immunostimulatory effects have interesting applications, for example the stimulation of an immune response against tumours (103). However, IL-10 was implicated in the pathogenesis of autoimmune disorders like systemic lupus erythematosus (104), and its use might precipitate an autoimmune disorder or precipitate graft rejection in transplanted patients (105). The time of administration, the way of administration and the dosage are probably critical to determine the response to this cytokine, the therapeutic interval being narrow, with side effects at higher dosages (106-108). In chronic HCV infection also, the increased peripheral production of IL-10 might lead to B cell proliferation and be responsible of autoimmune complications observed in these patients : auto-antibodies, cryoglobulinemia and lymphoma.

A cytokine can have multiple effects, depending on the cellular target and the tissue. The inhibition of certain factors involved in cell reparation or cell proliferation by IL-10 (TNF-α, IL-6, NFkB) could be disadvantageous in some situations, like liver regeneration. Finally, the future might be to target the delivery of cytokines locally in a tissue to avoid systemic side effects and a low biodisponibility. For example, IL-10 can be produced by transgenic bacteria in the gut (109) or by regulatory T cells that will home in the gut (110,111), which may be useful in the treatment of inflammatory bowel disease. In the liver, IL-10 was delivered locally with an adenovirus (112). By this more targeted approach, anti-inflammatory cytokines might have a future in the treatment of liver injury and the prevention of its complications.

References

1. CREAVEN P.J., BRENNER D.E., COWENS J.W. *et al.* A phase I clinical trial of recombinant human tumor necrosis factor given daily for five days. *Cancer Chemother. Pharmacol*., 1989, **23** : 186-191.
2. ANDO K., MORIYAMA T., GUIDOTTI L.G. *et al.* Mechanisms of class I restricted immunopathology. A transgenic mouse model of fulminant hepatitis. *J. Exp. Med*., 1993, **178** : 1541-1554.

3. TOYONAGA T., HINO O., SUGAI S. *et al.* Chronic active hepatitis in transgenic mice expressing interferon-gamma in the liver. *Proc. Natl. Acad. Sci. U.S.A*., 1994, **91** : 614-618.
4. NAPOLI J., BISHOP G.A., MCCAUGHAN G.W. Increased intrahepatic messenger RNA expression of interleukins 2, 6, and 8 in human cirrhosis. *Gastroenterology*, 1994, **107** : 789-798.
5. NAPOLI J., BISHOP G.A., MCGUINNESS PH., PAINTER D.M., MCCAUGHAN G.W. Progressive liver injury in chronic hepatitis C infection correlates with increased intrahepatic expression of Th1-associated cytokines. *Hepatology*, 1996, **24** : 759-765.
6. SCHWEYER S., MIHM S., RADZUN H.J., HARTMANN H., FAYYAZI A. Liver infiltrating T lymphocytes express interferon gamma and inducible nitric oxide synthase in chronic hepatitis C virus infection. *Gut*, 2000, **46** : 255-259.
7. MOSMANN T.R., CHERWINSKI H., BOND M.W., GIEDLIN M.A., COFFMAN R.L. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J. Immunol*., 1986, **136** : 2348-2357.
8. MOORE K.W., DE WAAL M., COFFMAN R.L., O'GARRA A. Interleukin-10 and the interleukin-10 receptor. *Annu. Rev. Immunol*., 2001, **19** : 683-765.
9. LE MOINE O., LOUIS H., SERMON F., GOLDMAN M., DEVIERE J. Interleukin-10 and liver diseases. *Acta Gastroenterol. Belg*., 1999, **62** : 1-8.
10. KNOLLE P.A., UHRIG A., PROTZER U. *et al.* Interleukin-10 expression is autoregulated at the transcriptional level in human and murine Kupffer cells. *Hepatology*, 1998, **27** : 93-99.
11. KNOLLE P.A., GERKEN G. Local control of the immune response in the liver. *Immunol. Rev*., 2000, **174** : 21-34.
12. KUHN R., LOHLER J., RENNICK D., RAJEWSKY K., MULLER W. Interleukin-10-deficient mice develop chronic enterocolitis. *Cell*, 1993, **75** : 263-274.
13. RENNICK D., DAVIDSON N., BERG D. Interleukin-10 gene knock-out mice : a model of chronic inflammation. *Clin. Immunol. Immunopathol*., 1995, **76** : S174-S178
14. LE MOINE O., MARCHANT A., DURAND F. *et al.* Systemic release of interleukin-10 during orthotopic liver transplantation. *Hepatology*, 1994, **20** : 889-892.
15. LE MOINE O., MARCHANT A., DE GROOTE D., AZAR C., GOLDMAN M., DEVIERE J. Role of defective monocyte interleukin-10 release in tumor necrosis factor-alpha overproduction in alcoholics cirrhosis. *Hepatology*, 1995, **22** : 1436-1439.
16. STREETZ K., LEIFELD L., GRUNDMANN D. *et al.* Tumor necrosis factor alpha in the pathogenesis of human and murine fulminant hepatic failure. *Gastroenterology*, 2000, **119** : 446-460.
17. SEKIYAMA K.D., YOSHIBA M., THOMSON A.W. Circulating proinflammatory cytokines (IL-1 beta, TNF-alpha, and IL-6) and IL-1 receptor antagonist (IL-1Ra) in fulminant hepatic failure and acute hepatitis. *Clin. Exp. Immunol*., 1994, **98** : 71-77.
18. YUMOTO E., HIGASHI T., NOUSO K. *et al.* Serum gamma-interferon-inducing factor (IL-18) and IL-10 levels in patients with acute hepatitis and fulminant hepatic failure. *J. Gastroenterol. Hepatol*., 2002, **17** : 285-294.
19. LEIFELD L., CHENG S., RAMAKERS J. *et al.* Imbalanced intrahepatic expression of interleukin 12, interferon gamma, and interleukin 10 in fulminant hepatitis B. *Hepatology*, 2002, **36** : 1001-1008.
20. LEIST M., GANTNER F., BOHLINGER I., TIEGS G., GERMANN P.G., WENDEL A. Tumor necrosis factor-induced hepatocyte apoptosis precedes liver failure in experimental murine shock models. *Am. J. Pathol*., 1995, **146** : 1220-1234.
21. LEIST M., GANTNER F., JILG S., WENDEL A. Activation of the 55 kDa TNF receptor is necessary and sufficient for TNF-induced liver failure, hepatocyte apoptosis, and nitrite release. *J. Immunol.*, 1995, **154** : 1307-1316.
22. LEIST M., GANTNER F., NAUMANN H. *et al.* Tumor necrosis factor-induced apoptosis during the poisoning of mice with hepatotoxins. *Gastroenterology*, 1997, **112** : 923-934.
23. BRADHAM C.A., PLUMPE J., MANNS M.P., BRENNER D.A., TRAUTWEIN C. Mechanisms of hepatic toxicity. I. TNF-induced liver injury. *Am. J. Physiol*., 1998, **275** : G387-G392
24. LEIFELD L., TRAUTWEIN C., DUMOULIN F.L., MANNS M.P., SAUERBRUCH T., SPENGLER U. Enhanced expression of CD80 (B7-1), CD86 (B7-2), and CD40 and their ligands CD28 and CD154 in fulminant hepatic failure. *Am. J. Pathol*., 1999, **154** : 1711-1720.
25. ANDUS T., BAUER J., GEROK W. Effects of cytokines on the liver. *Hepatology*, 1991, **13** : 364-375.
26. LUMSDEN A.B., HENDERSON J.M., KUTNER M.H. Endotoxin levels measured by a chromogenic assay in portal, hepatic and peripheral venous blood in patients with cirrhosis. *Hepatology*, 1988, **8** : 232-236.
27. ALEXANDER G.J.M., GOKA A.J., SHERON N. The relationship between sepsis, endotoxaemia and cytokines in patients with acute liver failure. In : WILLIAMS R., HUGHES R.D. (eds). Acute liver failure. Proceedings of the eleventh BSG.SK&F International Workshop. London : Smith Kline Beecham, 1991 : 22-25.
28. NOLAN J.P. The role of endotoxin in liver injury. *Gastroenterology*, 1975, **69** : 1346-1356.
29. LOUIS H., LE MOINE O., PENY M.O. *et al.* Hepatoprotective role of interleukin 10 in galactosamine/lipopolysaccharide mouse liver injury. *Gastroenterology*, 1997, **112** : 935-942.
30. LOUIS H., LE MOINE O., PENY M.O. *et al.* Production and role of interleukin-10 in concanavalin A-induced hepatitis in mice. *Hepatology*, 1997, **25** : 1382-1389.
31. CHOJKIER M., FIERER J. D-Galactosamine hepatotoxicity is associated with endotoxin sensitivity and mediated by lymphoreticular cells in mice. *Gastroenterology*, 1985, **88** : 115-121.
32. HISHINUMA I., NAGAKAWA J., HIROTA K. *et al.* Involvement of tumor necrosis factor-alpha in development of hepatic injury in galactosamine-sensitized mice. *Hepatology*, 1990, **12** : 1187-1191.
33. JAESCHKE H., SMITH C.W. Mechanisms of neutrophil-induced parenchymal cell injury. *J. Leukoc. Biol.*, 1997, **61** : 647-653.
34. BOURDI M., MASUBUCHI Y., REILLY T.P. *et al.* Protection against acetaminophen-induced liver injury and lethality by interleukin 10 : role of inducible nitric oxide synthase. *Hepatology*, 2002, **35** : 289-298.
35. WINWOOD P.J., ARTHUR M.J. Kupffer cells : their activation and role in animal models of liver injury and human liver disease. *Semin. Liver Dis*., 1993, **13** : 50-59.
36. VAN LAETHEM J.L., ESKINAZI R., LOUIS H., RICKAERT F., ROBBERECHT P., DEVIERE J. Multisystemic production of interleukin 10 limits the severity of acute pancreatitis in mice. *Gut*, 1998, **43** : 408-413.
37. DEVIERE J., LE MOINE O., VAN LAETHEM J.L. *et al.* Interleukin 10 reduces the incidence of pancreatitis after therapeutic endoscopic retrograde cholangiopancreatography. *Gastroenterology*, 2001, **120** : 498-505.
38. VOLPES R., VAN DEN OORD J.J., DESMET V.J. Memory T cells represent the predominant lymphocyte subset in acute and chronic liver inflammation. *Hepatology*, 1991, 13 : 826-829.
39. TIEGS G., HENTSCHEL J., WENDEL A. A T cell-dependent experimental liver injury in mice inducible by concanavalin A. *J.Clin.Invest*., 1992, **90** : 196-203.
40. MIZUHARA H., O'NEILL E., SEKI N. *et al.* T cell activation-associated hepatic injury : mediation by tumor necrosis factors and protection by interleukin 6. *J. Exp. Med*., 1994, **179** : 1529-1537.
41. KUSTERS S., GANTNER F., KUNSTLE G., TIEGS G. Interferon gamma plays a critical role in T cell-dependent liver injury in mice initiated by concanavalin A. *Gastroenterology*, 1996, **111** : 462-471.
42. NICOLETTI F., DI MARCO R., ZACCONE P. *et al.* Murine concanavalin A-induced hepatitis is prevented by interleukin 12 (IL-12) antibody and exacerbated by exogenous IL-12 through an interferon-gamma-dependent mechanism. *Hepatology*, 2000, **32** : 728-733.
43. KANEKO Y., HARADA M., KAWANO T. *et al.* Augmentation of Valpha14 NKT cell-mediated cytotoxicity by interleukin 4 in an autocrine mechanism resulting in the development of concanavalin A-induced hepatitis. *J. Exp. Med*., 2000, **191** : 105-114.
44. MICHALOPOULOS G.K., DEFRANCES M.C. Liver regeneration. *Science*, 1997, **276** : 60-66.
45. LOUIS H., VAN LAETHEM J.L., WU W. *et al.* Interleukin-10 controls neutrophilic infiltration, hepatocyte proliferation, and liver fibrosis induced by carbon tetrachloride in mice. *Hepatology*, 1998, **28** : 1607-1615.
46. RAI R.M., LOFFREDA S., KARP C.L., YANG S.Q., LIN H.Z., DIEHL A.M. Kupffer cell depletion abolishes induction of interleukin-10 and permits sustained overexpression of tumor necrosis factor alpha messenger RNA in the regenerating rat liver. *Hepatology*, 1997, **25** : 889-895.
47. THURMAN R.G. II. Alcoholic liver injury involves activation of Kupffer cells by endotoxin. *Am. J. Physiol*., 1998, **275** : G605-G611.
48. UESUGI T., FROH M., ARTEEL G.E. *et al.* Role of lipopolysaccharide-binding protein in early alcohol-induced liver injury in mice. *J. Immunol*., 2002, **168** : 2963-2969.
49. UESUGI T., FROH M., ARTEEL G.E., BRADFORD B.U., THURMAN R.G. Toll-like receptor 4 is involved in the mechanism of early alcohol-induced liver injury in mice. *Hepatology*, 2001, **34** : 101-108.
50. YIN M., BRADFORD B.U., WHEELER M.D. *et al.* Reduced early alcohol-induced liver injury in CD14-deficient mice. *J. Immunol*., 2001, **166** : 4737-4742.
51. JARVELAINEN H.A., ORPANA A., PEROLA M., SAVOLAINEN V.T., KARHUNEN P.J., LINDROS K.O. Promoter polymorphism of the CD14 endotoxin receptor gene as a risk factor for alcoholic liver disease. *Hepatology*, 2001, **33** : 1148-1153.

52. GROVE J., DALY A.K., BASSENDINE M.F., DAY C.P. Association of a tumor necrosis factor promoter polymorphism with susceptibility to alcoholic steatohepatitis. *Hepatology*, 1997, **26** : 143-146.
53. DEVIERE J., CONTENT J., DENYS C. *et al.* Excessive in vitro bacterial lipopolysaccharide-induced production of monokines in cirrhosis. *Hepatology*, 1990, **11** : 628-634.
54. BIRD G.L., SHERON N., GOKA A.K., ALEXANDER G.J., WILLIAMS R.S. Increased plasma tumor necrosis factor in severe alcoholic hepatitis. *Ann. Intern. Med*., 1990, **112** : 917-920.
55. FELVER M.E., MEZEY E., MC GUIRE M. *et al.* Plasma tumor necrosis factor alpha predicts decreased long-term survival in severe alcoholic hepatitis. *Alcohol Clin. Exp. Res.*, 1990, **14** : 255-259.
56. ESKDALE J., GALLAGHER G., VERWEIJ C.L., KEIJSERS V., WESTENDORP R.G., HUIZINGA T.W. Interleukin 10 secretion in relation to human IL-10 locus haplotypes. *Proc. Natl. Acad. Sci. U.S.A*., 1998, **95** : 9465-9470.
57. GROVE J., DALY A.K., BASSENDINE M.F., GILVARRY E., DAY C.P. Interleukin 10 promoter region polymorphisms and susceptibility to advanced alcoholic liver disease. *Gut*, 2000, **46** : 540-545.
58. LE MOINE O., QUERTINMONT E., GULBIS B., DEVIERE J. Blunted anti-inflammatory response to adenosine in alcoholic cirrhosis. *J. Hepatol*., 1999, **31** : 457-463.
59. NANJI A.A., JOKELAINEN K., RAHEMTULLA A. *et al.* Activation of nuclear factor kappa B and cytokine imbalance in experimental alcoholic liver disease in the rat. *Hepatology*, 1999, **30** : 934-943.
60. DEVIERE J., VAERMAN J.P., CONTENT J. *et al.* IgA triggers tumor necrosis factor alpha secretion by monocytes : a study in normal subjects and patients with alcoholic cirrhosis. *Hepatology*, 1991, **13** : 670-675.
61. LE MOINE O., DEVIERE J., DEVASTER J.M. *et al.* Interleukin-6 : an early marker of bacterial infection in decompensated cirrhosis. *J. Hepatol*., 1994, **20** : 819-824.
62. GONZALEZ-AMARO R., GARCIA-MONZON C., GARCIA-BUEY L. *et al.* Induction of tumor necrosis factor alpha production by human hepatocytes in chronic viral hepatitis. *J. Exp. Med.*, 1994, **179** : 841-848.
63. GUIDOTTI L.G., ROCHFORD R., CHUNG J., SHAPIRO M., PURCELL R., CHISARI F.V. Viral clearance without destruction of infected cells during acute HBV infection. *Science* 999, 284 : 825-829.
64. GUIDOTTI L.G., CHISARI F.V. Cytokine-mediated control of viral infections. *Virology*, 2000, **273** : 221-227.
65. FARCI P., SHIMODA A., COIANA A. *et al.* The outcome of acute hepatitis C predicted by the evolution of the viral quasispecies. *Science*, 2000, **288** : 339-344.
66. TSAI S.L., LIAW Y.F., CHEN M.H., HUANG C.Y., KUO G.C. Detection of type 2-like T-helper cells in hepatitis C virus infection : implications for hepatitis C virus chronicity. *Hepatology*, 1997, **25** : 449-458.
67. KAMAL S.M., RASENACK J.W., BIANCHI L. *et al.* Acute hepatitis C without and with schistosomiasis : correlation with hepatitis C-specific CD4(+) T-cell and cytokine response. *Gastroenterology*, 2001, **121** : 646-656.
68. KAKUMU S., OKUMURA A., ISHIKAWA T., IWATA K., YANO M., YOSHIOKA K. Production of interleukins 10 and 12 by peripheral blood mononuclear cells (PBMC) in chronic hepatitis C virus (HCV) infection. *Clin. Exp. Immunol*., 1997, **108** : 138-143.
69. MAC DONALD A.J., DUFFY M., BRADY M.T. *et al.* CD4 T helper type 1 and regulatory T cells induced against the same epitopes on the core protein in hepatitis C virus-infected persons. *J. Infect. Dis*., 2002, **185** : 720-727.
70. KUZUSHITA N., HAYASHI N., KATAYAMA K. *et al.* High levels of serum interleukin-10 are associated with a poor response to interferon treatment in patients with chronic hepatitis C. *Scand. J. Gastroenterol*., 1997, **32** : 169-174.
71. EDWARDS-SMITH C.J., JONSSON J.R., PURDIE D.M., BANSAL A., SHORTHOUSE C., POWELL E.E. Interleukin-10 promoter polymorphism predicts initial response of chronic hepatitis C to interferon alfa. *Hepatology*, 1999, **30** : 526-530.
72. YEE LJ, TANG J., GIBSON A.W., KIMBERLY R., VAN LEEUWEN D.J., KASLOW R.A. Interleukin 10 polymorphisms as predictors of sustained response in antiviral therapy for chronic hepatitis C infection. *Hepatology*, 2001, **33** : 708-712.
73. MIYAZOE S., HAMASAKI K., NAKATA K. *et al.* Influence of interleukin-10 gene promoter polymorphisms on disease progression in patients chronically infected with hepatitis B virus. *Am. J. Gastroenterol*., 2002, **97** : 2086-2092.
74. TAM R.C., PAI B., BARD J. *et al.* Ribavirin polarizes human T cell responses towards a Type 1 cytokine profile. *J. Hepatol*., 1999, **30** : 376-382.
75. CRAMP M.E., ROSSOL S., CHOKSHI S., CARUCCI P., WILLIAMS R., NAOUMOV N.V. Hepatitis C virus-specific T-cell reactivity during interferon and ribavirin treatment in chronic hepatitis C. *Gastroenterology*, 2000, **118** : 346-355.
76. CARRENO V., ZEUZEM S., HOPF U. *et al.* A phase I/II study of recombinant human interleukin-12 in patients with chronic hepatitis B. *J. Hepatol.*, 2000, **32** : 317-324.
77. NELSON D.R., LAUWERS G.Y., LAU J.Y., DAVIS G.L. Interleukin 10 treatment reduces fibrosis in patients with chronic hepatitis C : a pilot trial of interferon nonresponders. *Gastroenterology*, 2000, **118** : 655-660.
78. MC HUTCHISON J.G., PATEL K. Future therapy of hepatitis C. *Hepatology*, 2002, **36** : S245-S252.
79. Friedman S.L. Cytokines and fibrogenesis. *Semin. Liver Dis*., 1999, **19** : 129-140.
80. MATHURIN P., XIONG S., KHARBANDA K.K. *et al.* IL-10 receptor and coreceptor expression in quiescent and activated hepatic stellate cells. *Am. J. Physiol. Gastrointest. Liver Physiol.*, 2002, **282** : G981-G990
81. WANG S.C., OHATA M., SCHRUM L., RIPPE R.A., TSUKAMOTO H. Expression of interleukin-10 by in vitro and in vivo activated hepatic stellate cells. *J. Biol. Chem*., 1998, **273** : 302-308.
82. THOMPSON K.C., TROWERN A., FOWELL A. *et al.* Primary rat and mouse hepatic stellate cells express the macrophage inhibitor cytokine interleukin-10 during the course of activation In vitro. *Hepatology*, 1998, **28** : 1518-1524.
83. MARRA F. Hepatic stellate cells and the regulation of liver inflammation. *J. Hepatol*., 1999, **31** : 1120-1130.
84. MARRA F., VALENTE A.J., PINZANI M., ABBOUD H.E. Cultured human liver fat-storing cells produce monocyte chemotactic protein-1. Regulation by proinflammatory cytokines. *J. Clin. Invest.*, 1993, **92** : 1674-1680.
85. MARRA F., ROMANELLI R.G., GIANNINI C. *et al.* Monocyte chemotactic protein-1 as a chemoattractant for human hepatic stellate cells. *Hepatology*, 1999, **29** : 140-148.
86. THOMPSON K., MALTBY J., FALLOWFIELD J., MC AULAY M., MILLWARD-SADLER H., SHERON N. Interleukin-10 expression and function in experimental murine liver inflammation and fibrosis. *Hepatology*, 1998, **28** : 1597-1606.
87. DE BLESER PJ., XU G., ROMBOUTS K., ROGIERS V., GEERTS A. Glutathione levels discriminate between oxidative stress and transforming growth factor-beta signaling in activated rat hepatic stellate cells. *J. Biol. Chem.*, 1999, **274** : 33881-33887.
88. GRANSTEIN R.D., MURPHY G.F., MARGOLIS R.J., BYRNE M.H., AMENTO E.P. Gamma-interferon inhibits collagen synthesis in vivo in the mouse. *J. Clin. Invest*., 1987, **79** : 1254-1258.
89. BARONI G.S., D'AMBROSIO L., CURTO P. *et al.* Interferon gamma decreases hepatic stellate cell activation and extracellular matrix deposition in rat liver fibrosis. *Hepatology*, 1996, **23** : 1189-1199.
90. WYNN T.A., CHEEVER A.W., JANKOVIC D. *et al.* An IL-12-based vaccination method for preventing fibrosis induced by schistosome infection. *Nature*, 1995, **376** : 594-596.
91. SHI Z., WAKIL A.E., ROCKEY D.C. Strain-specific differences in mouse hepatic wound healing are mediated by divergent T helper cytokine responses. *Proc. Natl. Acad. Sci. U.S.A.*, 1997, **94** : 10663-10668.
92. TSUKAMOTO H. Is interleukin-10 antifibrogenic in chronic liver injury ? *Hepatology*, 1998, **28** : 1707-1709.
93. AKDIS C.A., BLESKEN T., AKDIS M., WUTHRICH B., BLASER K. Role of interleukin 10 in specific immunotherapy. *J. Clin. Invest*., 1998, **102** : 98-106.
94. GROUX H., BIGLER M., DE VRIES J.E., RONCAROLO M.G. Interleukin-10 induces a long-term antigen-specific anergic state in human CD4+ T cells. *J. Exp. Med*., 1996, **184** : 19-29.
95. GROUX H., O'GARRA A., BIGLER M. *et al.* A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. *Nature*, 1997, **389** : 737-742.
96. MALOY K.J., POWRIE F. Regulatory T cells in the control of immune pathology. *Nat. Immunol.*, 2001, **2** : 816-822.
97. KNOLLE P.A., UHRIG A., HEGENBARTH S. *et al.* IL-10 down-regulates T cell activation by antigen-presenting liver sinusoidal endothelial cells through decreased antigen uptake via the mannose receptor and lowered surface expression of accessory molecules. *Clin. Exp. Immunol.*, 1998, **114** : 427-433.
98. LIMMER A., OHL J., KURTS C. *et al.* Efficient presentation of exogenous antigen by liver endothelial cells to CD8+ T cells results in antigen-specific T-cell tolerance. *Nat. Med.*, 2000, **6** : 1348-1354.
99. WATANABE T., YOSHIDA M., SHIRAI Y., YAMORI M., YAGITA H., ITOH T., CHIBA T., KITA T., WAKATSUKI Y. Administration of an antigen at high dose generates regulatory CD4+ T cells expressing CD95 ligand and secreting IL-4 in the liver. *J.Immunol*., 2002, **168** : 2188-2199.

100. LOUIS H., LE MOINE A., QUERTINMONT E. *et al.* Repeated concanavalin A challenge in mice induces an interleukin 10-producing phenotype and liver fibrosis. *Hepatology*, 2000, **31** : 381-390.
101. KALECHMAN Y., GAFTER U., GAL R. *et al.* Anti-IL-10 therapeutic strategy using the immunomodulator AS101 in protecting mice from sepsis-induced death : dependence on timing of immunomodulating intervention. *J. Immunol*., 2002, **169** : 384-392.
102. DING Y., QIN L., KOTENKO S.V., PESTKA S., BROMBERG J.S. A single amino acid determines the immunostimulatory activity of interleukin 10. *J. Exp. Med*., 2000, **191** : 213-224.
103. BERMAN R.M., SUZUKI T., TAHARA H., ROBBINS P.D., NARULA S.K., LOTZE M.T. Systemic administration of cellular IL-10 induces an effective, specific, and long-lived immune response against established tumors in mice. *J. Immunol*., 1996, **157** : 231-238.
104. LLORENTE L., ZOU W., LEVY Y. *et al.* Role of interleukin 10 in the B lymphocyte hyperactivity and autoantibody production of human systemic lupus erythematosus. *J. Exp. Med*., 1995, **181** : 839-844.
105. QIAN S., LI W., LI Y. *et al.* Systemic administration of cellular interleukin-10 can exacerbate cardiac allograft rejection in mice. *Transplantation*, 1996, **62** : 1709-1714.
106. WISSING K.M., MORELON E., LEGENDRE C. *et al.* A pilot trial of recombinant human interleukin-10 in kidney transplant recipients receiving OKT3 induction therapy. *Transplantation*, 1997, **64** : 999-1006.
107. FEDORAK R.N., GANGL A., ELSON C.O. *et al.* Recombinant human interleukin 10 in the treatment of patients with mild to moderately active Crohn's disease. The Interleukin 10 Inflammatory Bowel Disease Cooperative Study Group. *Gastroenterology*, 2000, **119** : 1473-1482.
108. BLAZAR B.R., TAYLOR P.A., PANOSKALTSIS-MORTARI A. *et al.* Interleukin-10 dose-dependent regulation of CD4+ and CD8+ T cell-mediated graft-versus-host disease. *Transplantation*, 1998, **66** : 1220-1229.
109. STEIDLER L., HANS W., SCHOTTE L. *et al.* Treatment of murine colitis by Lactococcus lactis secreting interleukin-10. *Science*, 2000, **289** : 1352-1355.
110. VAN MONTFRANS C., HOOIJBERG E., RODRIGUEZ P.M. *et al.* Generation of regulatory gut-homing human T lymphocytes using ex vivo interleukin 10 gene transfer. *Gastroenterology*, 2002, **123** : 1877-1888.
111. VAN MONTFRANS C., RODRIGUEZ P.M., PRONK I., TEN KATE F.J., TE V.A., VAN DEVENTER S.J. Prevention of colitis by interleukin 10-transduced T lymphocytes in the SCID mice transfer model. *Gastroenterology*, 2002, **123** : 1865-1876.
112. QUATTROCCHI E., DALLMAN M.J., DHILLON A.P., QUAGLIA A., BAGNATO G., FELDMANN M. Murine IL-10 gene transfer inhibits established collagen-induced arthritis and reduces adenovirus-mediated inflammatory responses in mouse liver. *J. Immunol*., 2001, **166** : 5970-5978.