World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v18.i8.727

World J Gastroenterol 2012 February 28; 18(8): 727-735
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Role of cytokines and chemokines in non-alcoholic fatty liver disease

Vincent Braunersreuther, Giorgio Luciano Viviani, François Mach, Fabrizio Montecucco

Vincent Braunersreuther, François Mach, Fabrizio Montecucco, Division of Cardiology, Foundation for Medical Researches, Faculty of Medicine, Geneva University Hospital, 1211 Geneva, Switzerland
Giorgio Luciano Viviani, Department of Internal Medicine, Adult Diabetes Centre, University of Genoa, 16143 Genoa, Italy
Author contributions: Braunersreuther V, Viviani GL, Mach F and Montecucco F designed the research; Braunersreuther V, Viviani GL, Mach F and Montecucco F drafted the article; Braunersreuther V and Montecucco F wrote the paper; Braunersreuther V, Viviani GL, Mach F, Montecucco F revised and accepted this version of the manuscript.
Supported by The Swiss National Science Foundation, No. 32003B-134963/1 and "Sir Jules Thorn Trust Reg" Foundation, Gustave and Simone Prévot Foundation to Montecucco F; EU FP7 AtheroRemo, No. 201668 and Swiss National Science Foundation, No. 310030B-133127 and Novartis Foundation and Swiss Heart Foundation to Mach F
Correspondence to: Dr. Fabrizio Montecucco, MD, Division of Cardiology, Foundation for Medical Researches, Faculty of Medicine, Geneva University Hospital, Foundation for Medical Researches, 64 Avenue Roseraie, 1211 Geneva, Switzerland. fabrizio.montecucco@unige.ch
Telephone: +41-22-3827238 Fax: +41-22-3827245
Received: June 7, 2011 Revised: July 27, 2011
Accepted: August 4, 2011
Published online: February 28, 2012

Abstract

Non-alcoholic fatty liver disease (NAFLD) includes a variety of histological conditions (ranging from liver steatosis and steatohepatitis, to fibrosis and hepatocarcinoma) that are characterized by an increased fat content within the liver. The accumulation/deposition of fat within the liver is essential for diagnosis of NAFLD and might be associated with alterations in the hepatic and systemic inflammatory state. Although it is still unclear if each histological entity represents a different disease or rather steps of the same disease, inflammatory processes in NAFLD might influence its pathophysiology and prognosis. In particular, non-alcoholic steatohepatitis (the most inflamed condition in NAFLDs, which more frequently evolves towards chronic and serious liver diseases) is characterized by a marked activation of inflammatory cells and the up-regulation of several soluble inflammatory mediators. Among several mediators, cytokines and chemokines might play a pivotal active role in NAFLD and are considered as potential therapeutic targets. In this review, we will update evidence from both basic research and clinical studies on the potential role of cytokines and chemokines in the pathophysiology of NAFLD.

Key words: Inflammation; Non-alcoholic fatty liver disease; Cytokine; Chemokine

Peer reviewers: Maria Concepción Gutiérrez-Ruiz, PhD, Department of Health Sciences, Universidad Autónoma Metropolitana-Iztapalapa, DCBS, Av San Rafael Atlixco 186, Colonia Vicentina, México, DF 09340, Mexico; Astrid van der Velde, PhD, AMC Liver Center, Meibergdreef 69-71, 1105 BK Amsterdam, The Netherlands

Braunersreuther V, Viviani GL, Mach F, Montecucco F. Role of cytokines and chemokines in non-alcoholic fatty liver disease. *World J Gastroenterol* 2012; 18(8): 727-735 Available from: URL: http://www.wjgnet.com/1007-9327/full/v18/i8/727.htm DOI: http://dx.doi.org/10.3748/wjg.v18.i8.727

INTRODUCTION

In the last decade, there has been a remarkable scientific effort to improve our understanding of the pathogenesis, diagnosis, and treatment of non-alcoholic fatty liver disease (NAFLD). Clinical studies revealed dramatically high prevalence of NAFLD worldwide[1,2]. Worrying data on the prevalence of NAFLD in children and adolescents was also revealed[3]. Importantly, in American adolescents followed in the National Health and Nutri-

tion Examination Survey between 1999 and 2004, serum elevation of hepatic enzymes [i.e., alanine aminotransferase (ALT)] was observed in 6% to 11% of subjects (depending of ethnicity)[4]. Furthermore, serum ALT increase was positively associated with waist circumference and insulin resistance, suggesting that NAFLD might be considered as the hepatic manifestation of other epidemic diseases, such as metabolic syndrome and obesity[1,2]. In fact, in obese children and adolescents, NAFLD affects about 20% to 74%, indicating that this disease might start early during life, providing more time for its deleterious evolution[5-7]. However, we believe that NAFLD is limited to patients suffering from obesity, metabolic syndrome, or other fat-related diseases. Although NAFLD has been described as an increased hepatic accumulation of fat (steatosis), a recent scientific consensus defined it as a complex spectrum of diseases, ranging from asymptomatic steatosis with possible aminotransferase alterations to non-alcoholic steato-hepatitis (NASH), cirrhosis, and also hepatocellular carcinoma[8-10]. Whether these conditions are different stages of a common progressive disease or should be considered as different entities, is still an open question. Thus, additional pathophysiological studies on improved animal models are needed to clarify this issue. Indeed, NAFLD is often underestimated, under diagnosed, and not treated in the current medical practice; therefore, its pathophysiological history is at risk of remaining a mystery for several years.

At present, the most suitable area for improving our knowledge of the pathophysiology of NAFLD is represented by the chronic inflammation that underlies all NAFLD entities/stages[11]. Soluble cytokines and chemokines, regulating inflammatory cell function and survival, could be considered as very promising candidates. On the other hand, hormonal axes, adipocytokines, and growth factors have also received attention from NAFLD scientists. In the following paragraphs, we focus on cytokines and chemokines, updating evidence of their role in NAFLD pathophysiology, both in human (Table 1) and animal studies.

CYTOKINES

Cytokines are soluble molecules that are involved in intercellular communication and are produced by a wide variety of cells in the body, including most types of liver cells[12]. They comprise several subfamilies, including interferons, interleukins, tumor necrosis factors (TNF), transforming growth factors (TGF), colony-stimulating factors, and chemokines. Cytokines mediate several fundamental biological processes, including body growth, adiposity, lactation, hematopoiesis, as well as inflammation and immunity. However, they are also implicated in various pathologies, such as atherosclerosis, rheumatoid arthritis, systemic lupus erythematosus, psoriasis, as well as NAFLD[13-16].

Under physiological conditions, constitutive cytokine generation is absent or minimal in the liver. Nevertheless, pathological stimuli like lipid accumulation induces hepatic cells to produce these inflammatory molecules. Cytokines might play an active role in the development and the potential progression of NAFLD through stimulation of hepatic inflammation, cell necrosis and apoptosis, and induction of fibrosis. Nevertheless, they are also essential for liver regeneration following injury[16]. Evidence on the pathophysiological role of cytokine in NAFLD is reported and discussed below.

TNF-α

TNF-α is an inflammatory mediator secreted by several inflammatory cell types, including monocyte/macrophages, neutrophils, and T-cells, but also by many other tissues, such as the endothelium, adipose tissue, or neuronal tissue. In the liver, TNF-α is secreted directly by hepatocytes and Kupffer cells or indirectly by abdominal fat[17]. Several studies have shown that TNF-α is a key factor in the development of NAFLD and NASH in both humans and animals. Hotamisligil *et al*[18] showed for the first time a relationship between TNF-α expression and insulin resistance in NASH. The authors stated that adipose tissue represents an important source of obesity-induced inflammation, notably by the expression of TNF-α, which can induce inflammation and insulin resistance. Indeed, in several rodent models of obesity, TNF-α expression in adipose tissue was upregulated as compared to controls[18]. Accordingly with these study, obese mice lacking TNF-α showed an improved insulin sensibility[19]. Recently, mice treated with the anti-TNF-α drug thalidomide showed some improvements in the hepatic alterations mediated by a high-fat diet[20]. Moreover, the use of anti-TNF-α antibodies in an experimental model of NASH decreased inflammation, necrosis, and fibrosis in rats[21].

Although TNF-α inhibition in animal models of NAFLD presents encouraging therapeutic perspectives, in humans, the role of this cytokine remains controversial. In patients, TNF-α levels were shown to be higher in obese than in lean individuals, and were correlated with insulin resistance[22,23]. Moreover, a positive correlation was observed between the degree of liver fibrosis and circulating TNF-α levels in patients with NASH[24]. Another study showed increased TNF-α expression in the liver and adipose tissue in NASH patients with significant fibrosis in comparison with those with a slight or nonexistent fibrosis[25]. More recently, Hui *et al*[26] strengthened these results, showing increased TNF-α levels in subjects with steatohepatitis as compared to controls. The potential involvement of TNF-α in NAFLD pathophysiology was recently suggested by genetic studies on its polymorphisms[27,28]. Moreover, treatment with pentoxifylline (a molecule inhibiting TNF-α) decreased the serum levels of aminotransferases and displayed hepatic beneficial effects in patients with NASH[29].

Nevertheless, the involvement of TNF-α in insulin resistance and NAFLD is questionable. Some studies did

Table 1 Summary of human studies concerning the role of cytokines and chemokines in non-alcoholic fatty liver disease

Cytokine/chemokine	References	Findings	Approach/sample size	Treatment
TNF-α	Hotamisligil *et al*[22]	Increase of TNF-α in fat tissue of obese subjects Correlation between TNF-α and IR	18 control and 19 obese pre-menopausal women	-
	Dandona *et al*[23]	Higher TNF-α levels in obese subjects that contribute to IR Decrease of TNF-α levels and IR with weight loss	30 control and 38 obese women	-
	Lesmana *et al*[24]	Correlation between TNF-α serum levels and liver fibrosis	30 patients with NASH	-
	Crespo *et al*[25]	Overexpression of TNF-α in liver and adipose tissue in patient with NASH Increase of p55 TNF-α receptor expression in fibrotic liver Enhancement of TNF-α expression with advanced liver fibrosis	52 obese patients	-
	Hui *et al*[26]	Increase of TNF-α and TNFR2 in patients with NASH	109 patients with NAFLD	-
	Valenti *et al*[27]	Higher prevalence of 238 TNF-α polymorphism in patients with NAFLD	99 subjects with NAFLD	-
	Zhou *et al*[28]	238 TNF-α polymorphism association with NAFLD susceptibility	117 subjects with NAFLD	-
	Lee *et al*[29]	Reduction of aminotransferase in patients treated with Pentoxifylline	20 patients with NASH	Pentoxifylline 400 mg three time per day
	Müller *et al*[30]	No significant increase of TNF-α or its receptor levels in patients with IGT	80 subjects with IGT, 152 subjects with type II diabetes and 77 control subjects	-
	Bruun *et al*[31]	No correlation between IR and TNF-α levels	19 obese and 10 lean men	-
	Ofei *et al*[32]	No effect on insulin sensitivity	21 obese NIDDM patients	Single injection of CDP571 (anti-TNF-α antibody)
	Bernstein *et al*[33]	No effect on insulin sensitivity	56 subjects with metabolic syndrome	Etanercept (TNF-α antagonist) 50 mg 1 time per week, for 4 wk
TGF-β1	Annoni *et al*[40]	Enhancement of TGF-β1 expression in man with active liver disease	16 patients with active liver disease	-
	Castilla *et al*[44]	Association of TGF-β1 levels and fibrosis in chronic liver disease	46 patients with elevated serum ALT	-
	Milani *et al*[45]	High TGF-β1 mRNA expression in fibrotic liver	2 subjects control, 1 subject with cirrhosis, and 9 subjects with hepatitis B viral liver disease	-
	Hasegawa *et al*[47]	TGF-β1 levels are useful to differentiate between NAFLD and NASH Benefits of α-tocopherol to treat NASH	12 patients with non-alcoholic steatohepatitis and 10 patients with non-alcoholic fatty liver	α-tocopherol 300 mg/d during 1 yr
	Dixon *et al*[48]	Association of polymorphism inducing angiotensinogen and TGF-β1 and advanced hepatic fibrosis	105 obese patients	-
IL-6	Kopp *et al*[58]	Correlation between IL-6 and IR	37 obese patients	-
	Kugelmas *et al*[60]	Elevated IL-6 concentration in serum of patients with NASH Decrease of IL-6 with the treatment	16 patients with NASH	Vitamin E 800 IU/d
	Haukeland *et al*[61]	Higher levels of IL-6 in patients with NAFLD	47 patients (22 simple steatosis, 25 NASH) and 30 controls	-
	Wieckowska *et al*[63]	Higher hepatic IL-6 expression in patients with NASH Association with IL-6 levels and the disease severity Correlation between hepatic IL-6 expression and IR	50 patients with suspected NALFD	-
IL-10	Esposito *et al*[69]	Association between low levels of IL-10 and metabolic syndrome	50 obese and 50 normal-weight women	-
	Calcaterra *et al*[70]	No association between metabolic syndrome and low levels of IL-10	70 severely obese and 30 non-obese children and adolescents	-
CCL2/MCP-1	Haukeland *et al*[61]	Elevated levels of CCL2 in patients with NAFLD and NASH	47 patients (22 simple steatosis, 25 NASH) and 30 controls	-
	Westerbacka *et al*[92]	Increase of CCL2 in steatotic liver of patients with NAFLD	24 subjects (8 controls, 16 with NAFLD)	-
	Greco *et al*[93]	Correlation between CCL2 gene expression and liver fat content in patients with NAFLD	10 subjects with low and high extremes of fat liver	-
CCL5/RANTES	Wu *et al*[99]	Higher CCL5 expression in adipose tissue of obese patients than in lean controls	21 morbidly obese patients, 10 obese patients with metabolic syndrome, and 3 lean controls	-

	Kirovski *et al*[100]	Upregulation of hepatic and circulating CCL5 levels in patients with NAFLD	45 patients with NAFLD and 61 controls with normal liver	-
CXCL8/IL-8	Bahcecioglu *et al*[103]	Higher serum levels of IL-8 in patients with NASH and cirrhosis compared to control group	28 patients with NASH, 14 patients with cirrhosis, and 15 controls	-
	Torer *et al*[104]	Higher IL-8 serum levels in the patients with NASH than in patients with hepatosteatosis	57 patients with NASH and 35 patients with NALFD	-
	Jarrar *et al*[105]	Higher levels of IL-8 in NAFLD patients compared to obese and non-obese subjects Independent association of IL-8 levels with NASH	26 patients with NASH, 19 patients with simple steatosis, 38 obese controls, and 12 non-obese controls	-
	Abiru *et al*[106]	No differences of IL-8 between NASH, simple steatosis, and control groups	23 patients with NASH, 21 patients with simple steatosis, and 18 healthy controls	-
CXCL9/Mig	Wasmuth *et al*[109]	Association CXCL9 serum levels and CXCL9 liver expression with liver fibrosis due to NASH	441 individuals with HCV	

NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steato-hepatitis; TNF: Tumor necrosis factor; TGF: Transforming growth factor; IL: Interleukin; MCP: Monocyte chemotactic protein; RANTES: Regulated on activation normal T-cell expressed and secreted; Mig: Monokine induced by interferon-γ; IR: Insulin resistance; IGT: Impaired glucose tolerance; NIDDM: Noninsulin-dependent diabetes mellitus; ALT: Alanine aminotransferase; HCV: Hepatitis C virus.

not show any correlation between insulin resistance and TNF-α levels[30,31], whereas two clinical studies, using an antagonist and an anti-TNF-α antibody, did not show any improvements in insulin sensitivity[32,33]. Moreover, in a recent study, Lucero *et al*[34] did not observe any difference in circulating levels of TNF-α between patients with NAFLD as compared to controls without NAFLD.

TGF-β

TGF-β is a cytokine/growth factor with immunosuppressive, anti-inflammatory, and pro-fibrotic properties[35]. In the liver, TGF-β1 is the most abundant isoform, and it is secreted by immune cells, stellate cells, and epithelial cells[36]. TGF-β1 plays a pivotal role in hepatic fibrosis by mediating the activation of stellate cells and their production of extracellular matrix proteins[37-39]. Indeed, Kupffer and stellate cells produce TGF-β1, which induces the transformation of resting stellate cells to myofibroblasts[40]. In experimental models of hepatic fibrosis induced by CCl_4 or schistosomiasis, expression of TGF-β1 is upregulated[41-43]. Moreover, in patients with liver fibrosis, the expression of TGF-β1 mRNA is increased[40,44,45]. Stärkel *et al*[46] showed that the upregulation of TGF-β1 is an early molecular step in the progressive fibrotic steatohepatitis. A study by Hasegawa and co-workers showed that TGF-β1 levels were increased in patients with NASH as compared to hepatic steatosis. Thus, the measurement of serum levels of TGF-β1 might be useful to distinguish NASH patients in the spectrum of NAFLD[47]. Moreover, polymorphisms that induce high angiotensinogen and TGF-β1 are associated with advanced hepatic fibrosis in obese patients with NAFLD[48].

Interleukin-6

The role of interleukin-6 (IL-6) in liver pathology is very complex, and its participation in the development of NAFLD remains unclear. IL-6 activates several cells, such as immune cells, hepatocytes, hematopoietic stem cells, and osteoclasts[49]. Furthermore, IL-6 has a wide range of biological functions, including induction of inflammation and oncogenesis, regulation of immune response, and support of hematopoiesis[49]. IL-6 was initially considered as a hepatoprotector in liver steatosis, capable of reducing oxidative stress and preventing mitochondrial dysfunction[50,51]. Furthermore, this potential hepatoprotective effect of IL-6 was confirmed in other models of liver disease, such as ischemic preconditioning models and in liver regeneration after partial hepatectomy in mice[52-55].

Nevertheless, IL-6 is a key element in the acute phase response, mediating the synthesis of several acute phase proteins (such as C-reactive protein and serum amyloid A)[56]. Thus, we cannot exclude the possibility that IL-6 might also play an indirect deleterious role in NAFLD pathogenesis. In diet-induced obese mice, treatment with IL-6 antibodies improved sensitivity to insulin[57]. Furthermore, IL-6 is considered as a predictor marker of insulin resistance and cardiovascular diseases. In patients undergoing bariatric surgery, decreased IL-6 concentrations were associated with weight loss and insulin resistance improvement[58]. Serum IL-6 levels are higher in animal models and patients with NAFLD[59-61]. Recently, Mas and co-workers showed that diet-induced NASH was reduced in IL-6 knockout mice as compared to controls[62]. In humans with NASH, a positive correlation between IL-6 expression in hepatocytes and the severity of NAFLD was observed [63].

Thus, although IL-6 could improve hepatic regeneration and repair, it could also sensitize the liver to injury, stimulate hepatocyte apoptosis, induce insulin resistance, and participate in NASH development. Recent studies from Yamaguchi illustrated this paradoxical role of IL-6 in NAFLD. Indeed, IL-6 pathway neutralization with tocilizumab, a specific antibody against the IL-6 receptor, enhanced hepatic steatosis, but improved liver damage in mice with methionine choline deficient (MCD) diet-induced NASH[64]. Furthermore, Yamaguchi *et al*[65], in

a second study, showed that not only upregulation of IL-6, but also severe suppression of hepatic IL-6/signal transducer and activator of transcription 3 signaling may lead to the progression of NASH.

IL-10

IL-10 is considered as an anti-inflammatory cytokine that regulates the inflammation in several organs and tissues in physiological or pathological situations[66]. It inhibits T cell-, monocyte-, and macrophage-mediated functions. In the liver, IL-10 has been detected in several cells, including hepatocytes, stellate cells, and Knuppfer cells, but only few studies have been performed to investigate the role of endogenous IL-10 in the progression of NAFLD. A study using IL-10-deficient mice fed on high fat diet, suggested that endogenous IL-10 was protective for hepatic steatosis, but not for concomitant insulin resistance[67]. In another study, Cintra and co-workers observed that the inhibition of IL-10 (either using an anti-IL-10 antibody or an IL-10 antisense oligonucleotide) led to increased expression of pro-inflammatory markers (TNF-α, IL-6, IL-1β, and F4/80) and impaired insulin signal transduction and steatosis[68]. In humans, Esposito and co-workers showed an inverse correlation between IL-10 levels and metabolic syndrome in obese woman, suggesting a potential IL-10-mediated benefit in metabolic syndrome patients also affected by NAFLD[69]. However, Calcaterra *et al*[70] did not confirm this association in obese children and adolescents.

CHEMOKINES

Chemokines (chemotactic cytokines) are small heparin-binding proteins known to induce mainly leukocyte trafficking, growth, and activation in inflammatory sites[71,72]. Many cell types, including endothelial cells, smooth muscle cells, leukocytes, hepatocytes, and stellate cells, can secrete them. Approximately 50 currently identified chemokines are classified in four subfamilies (C, CC, CXC, CX_3C) according to their structural arrangement of N-terminal conserved cysteine residues. Chemokines need to bind to their coupled seven transmembrane protein G coupled receptors on target cells to induce cellular changes. Chemokines and their receptors have been implicated in multiple inflammatory diseases, such as atherosclerosis, multiple sclerosis, psoriasis, and insulin resistance[73]. Expression of several chemokines and chemokine receptors has been shown to be upregulated in the livers of obese patients with severe steatosis and NASH[74]. Inflammatory processes are crucial in the potential progression of NAFLD; therefore, chemokines might also play a pivotal role in NAFLD pathophysiology[75].

CCL2/monocyte chemotactic protein-1

CCL2 is a potent chemoattractant that is principally secreted by macrophages and, to a lesser extent, by activated endothelial cells, smooth muscle cells, and hepatic stellate cells[76-79]. It activates target cells (mainly macrophages) through binding with its receptor, CCR2[76-79]. It is widely secreted in adipose tissue and plasma of obese mice[80]. Monocyte/macrophage infiltration in adipose tissue has been observed in animal models and humans[81]. Monocyte/macrophage accumulation in the steatotic liver was reduced in mice fed on high-fat diet and who were deficient for *CCL2* or *CCR2* genes[82]. However, the role of CCL2 is actually more complex, extending far beyond the monocyte/macrophage chemoattractant effect. For instance, low density lipoprotein receptor and CCL2 double knockout mice showed alterations in glucose and lipid metabolism induced by high-fat diet[83]. When fed with a normal chow diet, these mice are characterized by lower alterations in the lipid and glucose profile. However, obesity is also reduced under normal diet, suggesting that different food intake might regulate CCL2-mediated inflammation in mice prone to develop obesity and atherosclerosis. Importantly, CCL2 deficiency in mice fed on a high-fat diet decreases insulin resistance and hepatic steatosis[84]. On the other hand, mice overexpressing CCL2 in adipose tissue presented increased insulin resistance and hepatic triglyceride levels[84].

Interestingly, CCL2 was also upregulated in the livers of animals with high-fat diet-induced NASH[85]. This pathophysiological aspect of CCL2 directly contributed to the lipid accumulation in hepatocytes *via* the activation of peroxisome proliferator-activated receptor α gene expression[86]. More recently, Obstfeld and co-workers showed that hepatic myeloid cells might play a crucial role in the promotion of obesity-induced hepatic steatosis. Indeed, they observed that obesity upregulates CCL2 expression in hepatocytes, leading to the recruitment of CCR2-positive myeloid cells and thus, promoting hepatosteatosis[87]. Pharmacological treatments inhibiting the CCL2/CCR2 pathway in several mouse models of metabolic diseases significantly improved obesity, insulin resistance, hepatic steatosis, and inflammation in the adipose tissue[88-90]. These benefits were not confirmed by other studies. For example, CCL2 deletion in an experimental model of MCD diet-induced steatosis did not improve liver fat accumulation and associated inflammation[91].

In humans, only few studies have been performed to investigate the role of CCL2 in NAFLD pathology. Haukeland *et al*[61] showed that patients with NAFLD had low-grade systemic inflammation and presented with higher serum levels of CCL2 compared to controls. Moreover, CCL2 has been confirmed to also be elevated in the steatotic livers of NAFLD patients[92]. More recently, another study showed that CCL2 expression was positively correlated with liver fat content in patients with NAFLD[93]. These studies suggest an important participation of CCL2 in the potential progression of simple steatosis to NASH. Therefore, although the role of CCL2 in metabolic diseases requires further investigation, these studies suggest a potential direct role of CCL2 in NAFLD and, in particular, in NASH.

CCL5/regulated on activation normal T-cell expressed and secreted

CCL5 is involved in several chronic immune-inflammatory diseases, such as atherosclerosis, acute myocardial infarction, myocarditis, rheumatoid arthritis, and multiple sclerosis[94,95]. It is secreted by various cells, such as endothelial cells, smooth muscle cells, macrophages, or hepatic stellate cells. This chemokine is mainly involved in migration of T cells, monocytes, neutrophils, and dendritic cells through binding to its cognate transmembrane receptors, CCR1, 3 and 5. The receptor CCR5 has been identified on isolated hepatic stellate cells, suggesting that these hepatic cells are both the target and source of CCL5[96,97]. The association of CCL5 with NAFLD was shown recently in humans and mice. Indeed, two studies showed that obesity increased hepatic expression of CCL5 in a murine model of NASH and in obese patients[98,99]. Hepatocytes are the major source of serum and hepatic CCL5 in NAFLD[100]. CCL5 release in the liver is mediated by hepatocellular lipid accumulation, suggesting that hepatic steatosis *per se* has pathophysiological relevance[100]. CCL5 is also involved in the progression of hepatic fibrosis in mice *via* CCR1 and CCR5 triggering[97]. More recently, Berres and co-workers defined CCL5 as a critical mediator of experimental liver fibrosis. Indeed, antagonism of CCL5 on receptor CCR5 improved experimental liver fibrosis in mice, indicating that CCL5 is a promising therapeutic target to reduce NAFLD[101].

CXCL8/IL-8

CXCL8/IL-8 is a CXC chemokine produced by several cell types, including inflammatory and endothelial cells[102]. The major role of this chemokine is to orchestrate neutrophil recruitment within inflamed tissues. There is little data documenting its potential role in NAFLD. Serum levels of CXCL8 were significantly higher in subjects with NASH as compared to hepatosteatosis or healthy control group[103,104]. More recently, Jarrar and co-workers showed that serum levels of CXCL8 were higher in NAFLD patients as compared to obese and non-obese patients[105]. In addition, CXCL8 serum levels were independently associated with NASH[105]. Conversely, the study from Abiru and co-workers did not confirm this association or any significant differences in serum CXCL8[106].

Other CXC chemokines

Chemokines CXCL9/monokine induced by interferon-γ, and CXCL10/interferon inducible protein-10, which bind the common receptor CXCR3, are generally not detectable in most non-lymphoid tissues under physiological conditions. However, in some inflammatory conditions, interferon gamma might increase their release. CXCR3 is found at high levels on activated T cells, memory T cells, and natural killer cells[107]. CXCL9 and CXCL10 mainly induce the migration of these cell types. In the liver, endothelial cells highly express CXCL9 leading to the transmigration of the CXCR3-expressing lymphocytes[108]. Recently, high levels of CXCL9 were found in the livers of patients with NASH[109]. In this study, Wasmuth and co-workers identified the CXCL9-CXCR3 axis as a potential anti-fibrotic pathway in the liver in both humans and animals.

CONCLUSION

The take-home message of the present update on the inflammatory pathophysiology of NAFLD do not recommend any optimistic insights for the near future. Much research remains to be done to clarify the pathophysiology of NAFLD and to identify selective targets for treatment. The involvement of cytokines and chemokines and their receptors in the pathogenesis of NAFLD is only partially understood. Although the first studies attempting therapeutic strategies targeting the chemokine system have been recently published, we believe that scientific interest in NAFLD should be increased. In particular, effort is required to improve the consideration of NAFLD as a dangerous condition that should not be underestimated or by-passed. Another crucial aspect is represented by the identification of common cytokines and chemokines between NAFLD and metabolic or cardiovascular diseases. The most promising mediators (such as TNF-α, CCL2 and CCL5) also require more selective inhibitory drugs to safely improve NAFLD, limiting the potential risk of deleterious immune-suppression.

REFERENCES

1 **Chen SH**, He F, Zhou HL, Wu HR, Xia C, Li YM. Relationship between nonalcoholic fatty liver disease and metabolic syndrome. *J Dig Dis* 2011; **12**: 125-130
2 **Andersen T**, Christoffersen P, Gluud C. The liver in consecutive patients with morbid obesity: a clinical, morphological, and biochemical study. *Int J Obes* 1984; **8**: 107-115
3 **Manco M**, Bottazzo G, DeVito R, Marcellini M, Mingrone G, Nobili V. Nonalcoholic fatty liver disease in children. *J Am Coll Nutr* 2008; **27**: 667-676
4 **Fraser A**, Longnecker MP, Lawlor DA. Prevalence of elevated alanine aminotransferase among US adolescents and associated factors: NHANES 1999-2004. *Gastroenterology* 2007; **133**: 1814-1820
5 **Strauss RS**, Barlow SE, Dietz WH. Prevalence of abnormal serum aminotransferase values in overweight and obese adolescents. *J Pediatr* 2000; **136**: 727-733
6 **Sartorio A**, Del Col A, Agosti F, Mazzilli G, Bellentani S, Tiribelli C, Bedogni G. Predictors of non-alcoholic fatty liver disease in obese children. *Eur J Clin Nutr* 2007; **61**: 877-883
7 **Chan DF**, Li AM, Chu WC, Chan MH, Wong EM, Liu EK, Chan IH, Yin J, Lam CW, Fok TF, Nelson EA. Hepatic steatosis in obese Chinese children. *Int J Obes Relat Metab Disord* 2004; **28**: 1257-1263
8 **Adams LA**, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, Angulo P. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 2005; **129**: 113-121
9 **Angulo P**. Diagnosing steatohepatitis and predicting liver-related mortality in patients with NAFLD: two distinct concepts. *Hepatology* 2011; **53**: 1792-1794
10 **Angulo P**. Nonalcoholic fatty liver disease. *N Engl J Med*

2002; **346**: 1221-1231
11 **Tarantino G**, Savastano S, Colao A. Hepatic steatosis, low-grade chronic inflammation and hormone/growth factor/adipokine imbalance. *World J Gastroenterol* 2010; **16**: 4773-4783
12 **Tracey KJ**, Cerami A. Tumor necrosis factor, other cytokines and disease. *Annu Rev Cell Biol* 1993; **9**: 317-343
13 **Miller AM**, McInnes IB. Cytokines as therapeutic targets to reduce cardiovascular risk in chronic inflammation. *Curr Pharm Des* 2011; **17**: 1-8
14 **Tedgui A**, Mallat Z. Cytokines in atherosclerosis: pathogenic and regulatory pathways. *Physiol Rev* 2006; **86**: 515-581
15 **O'Dell JR**. Anticytokine therapy--a new era in the treatment of rheumatoid arthritis? *N Engl J Med* 1999; **340**: 310-312
16 **Tilg H**, Diehl AM. Cytokines in alcoholic and nonalcoholic steatohepatitis. *N Engl J Med* 2000; **343**: 1467-1476
17 **Montecucco F**, Mach F. Does non-alcoholic fatty liver disease (NAFLD) increase cardiovascular risk? *Endocr Metab Immune Disord Drug Targets* 2008; **8**: 301-307
18 **Hotamisligil GS**, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. *Science* 1993; **259**: 87-91
19 **Uysal KT**, Wiesbrock SM, Marino MW, Hotamisligil GS. Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. *Nature* 1997; **389**: 610-614
20 **Pinto Lde F**, Compri CM, Fornari JV, Bartchewsky W, Cintra DE, Trevisan M, Carvalho Pde O, Ribeiro ML, Velloso LA, Saad MJ, Pedrazzoli J, Gambero A. The immunosuppressant drug, thalidomide, improves hepatic alterations induced by a high-fat diet in mice. *Liver Int* 2010; **30**: 603-610
21 **Koca SS**, Bahcecioglu IH, Poyrazoglu OK, Ozercan IH, Sahin K, Ustundag B. The treatment with antibody of TNF-alpha reduces the inflammation, necrosis and fibrosis in the non-alcoholic steatohepatitis induced by methionine- and choline-deficient diet. *Inflammation* 2008; **31**: 91-98
22 **Hotamisligil GS**, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. *J Clin Invest* 1995; **95**: 2409-2415
23 **Dandona P**, Weinstock R, Thusu K, Abdel-Rahman E, Aljada A, Wadden T. Tumor necrosis factor-alpha in sera of obese patients: fall with weight loss. *J Clin Endocrinol Metab* 1998; **83**: 2907-2910
24 **Lesmana CR**, Hasan I, Budihusodo U, Gani RA, Krisnuhoni E, Akbar N, Lesmana LA. Diagnostic value of a group of biochemical markers of liver fibrosis in patients with non-alcoholic steatohepatitis. *J Dig Dis* 2009; **10**: 201-206
25 **Crespo J**, Cayón A, Fernández-Gil P, Hernández-Guerra M, Mayorga M, Domínguez-Díez A, Fernández-Escalante JC, Pons-Romero F. Gene expression of tumor necrosis factor alpha and TNF-receptors, p55 and p75, in nonalcoholic steatohepatitis patients. *Hepatology* 2001; **34**: 1158-1163
26 **Hui JM**, Hodge A, Farrell GC, Kench JG, Kriketos A, George J. Beyond insulin resistance in NASH: TNF-alpha or adiponectin? *Hepatology* 2004; **40**: 46-54
27 **Valenti L**, Fracanzani AL, Dongiovanni P, Santorelli G, Branchi A, Taioli E, Fiorelli G, Fargion S. Tumor necrosis factor alpha promoter polymorphisms and insulin resistance in nonalcoholic fatty liver disease. *Gastroenterology* 2002; **122**: 274-280
28 **Zhou YJ**, Li YY, Nie YQ, Yang H, Zhan Q, Huang J, Shi SL, Lai XB, Huang HL. Influence of polygenetic polymorphisms on the susceptibility to non-alcoholic fatty liver disease of Chinese people. *J Gastroenterol Hepatol* 2010; **25**: 772-777
29 **Lee YM**, Sutedja DS, Wai CT, Dan YY, Aung MO, Zhou L, Cheng CL, Wee A, Lim SG. A randomized controlled pilot study of Pentoxifylline in patients with non-alcoholic steatohepatitis (NASH). *Hepatol Int* 2008; **2**: 196-201
30 **Müller S**, Martin S, Koenig W, Hanifi-Moghaddam P, Rathmann W, Haastert B, Giani G, Illig T, Thorand B, Kolb H. Impaired glucose tolerance is associated with increased serum concentrations of interleukin 6 and co-regulated acute-phase proteins but not TNF-alpha or its receptors. *Diabetologia* 2002; **45**: 805-812
31 **Bruun JM**, Verdich C, Toubro S, Astrup A, Richelsen B. Association between measures of insulin sensitivity and circulating levels of interleukin-8, interleukin-6 and tumor necrosis factor-alpha. Effect of weight loss in obese men. *Eur J Endocrinol* 2003; **148**: 535-542
32 **Ofei F**, Hurel S, Newkirk J, Sopwith M, Taylor R. Effects of an engineered human anti-TNF-alpha antibody (CDP571) on insulin sensitivity and glycemic control in patients with NIDDM. *Diabetes* 1996; **45**: 881-885
33 **Bernstein LE**, Berry J, Kim S, Canavan B, Grinspoon SK. Effects of etanercept in patients with the metabolic syndrome. *Arch Intern Med* 2006; **166**: 902-908
34 **Lucero D**, Zago V, López GI, Graffigna M, Fainboim H, Miksztowicz V, Meroño T, Belli S, Levalle O, Wikinski R, Brites F, Berg G, Schreier L. Pro-inflammatory and atherogenic circulating factors in non-alcoholic fatty liver disease associated to metabolic syndrome. *Clin Chim Acta* 2011; **412**: 143-147
35 **Douglas HE**. TGF- ß in wound healing: a review. *J Wound Care* 2010; **19**: 403-406
36 **Syn WK**, Choi SS, Diehl AM. Apoptosis and cytokines in non-alcoholic steatohepatitis. *Clin Liver Dis* 2009; **13**: 565-580
37 **Friedman SL**. Cytokines and fibrogenesis. *Semin Liver Dis* 1999; **19**: 129-140
38 **Shek FW**, Benyon RC. How can transforming growth factor beta be targeted usefully to combat liver fibrosis? *Eur J Gastroenterol Hepatol* 2004; **16**: 123-126
39 **Bissell DM**, Roulot D, George J. Transforming growth factor beta and the liver. *Hepatology* 2001; **34**: 859-867
40 **Annoni G**, Weiner FR, Zern MA. Increased transforming growth factor-beta 1 gene expression in human liver disease. *J Hepatol* 1992; **14**: 259-264
41 **De Bleser PJ**, Niki T, Rogiers V, Geerts A. Transforming growth factor-beta gene expression in normal and fibrotic rat liver. *J Hepatol* 1997; **26**: 886-893
42 **Hellerbrand C**, Stefanovic B, Giordano F, Burchardt ER, Brenner DA. The role of TGFbeta1 in initiating hepatic stellate cell activation in vivo. *J Hepatol* 1999; **30**: 77-87
43 **Czaja MJ**, Weiner FR, Flanders KC, Giambrone MA, Wind R, Biempica L, Zern MA. In vitro and in vivo association of transforming growth factor-beta 1 with hepatic fibrosis. *J Cell Biol* 1989; **108**: 2477-2482
44 **Castilla A**, Prieto J, Fausto N. Transforming growth factors beta 1 and alpha in chronic liver disease. Effects of interferon alfa therapy. *N Engl J Med* 1991; **324**: 933-940
45 **Milani S**, Herbst H, Schuppan D, Stein H, Surrenti C. Transforming growth factors beta 1 and beta 2 are differentially expressed in fibrotic liver disease. *Am J Pathol* 1991; **139**: 1221-1229
46 **Stärkel P**, Sempoux C, Leclercq I, Herin M, Deby C, Desager JP, Horsmans Y. Oxidative stress, KLF6 and transforming growth factor-beta up-regulation differentiate non-alcoholic steatohepatitis progressing to fibrosis from uncomplicated steatosis in rats. *J Hepatol* 2003; **39**: 538-546
47 **Hasegawa T**, Yoneda M, Nakamura K, Makino I, Terano A. Plasma transforming growth factor-beta1 level and efficacy of alpha-tocopherol in patients with non-alcoholic steatohepatitis: a pilot study. *Aliment Pharmacol Ther* 2001; **15**: 1667-1672
48 **Dixon JB**, Bhathal PS, Jonsson JR, Dixon AF, Powell EE, O'Brien PE. Pro-fibrotic polymorphisms predictive of advanced liver fibrosis in the severely obese. *J Hepatol* 2003; **39**: 967-971
49 **Kishimoto T**. IL-6: from its discovery to clinical applications. *Int Immunol* 2010; **22**: 347-352
50 **Cressman DE**, Greenbaum LE, DeAngelis RA, Ciliberto G,

Furth EE, Poli V, Taub R. Liver failure and defective hepatocyte regeneration in interleukin-6-deficient mice. *Science* 1996; **274**: 1379-1383
51 **El-Assal O**, Hong F, Kim WH, Radaeva S, Gao B. IL-6-deficient mice are susceptible to ethanol-induced hepatic steatosis: IL-6 protects against ethanol-induced oxidative stress and mitochondrial permeability transition in the liver. *Cell Mol Immunol* 2004; **1**: 205-211
52 **Teoh N**, Field J, Farrell G. Interleukin-6 is a key mediator of the hepatoprotective and pro-proliferative effects of ischaemic preconditioning in mice. *J Hepatol* 2006; **45**: 20-27
53 **Peters M**, Blinn G, Jostock T, Schirmacher P, Meyer zum Büschenfelde KH, Galle PR, Rose-John S. Combined interleukin 6 and soluble interleukin 6 receptor accelerates murine liver regeneration. *Gastroenterology* 2000; **119**: 1663-1671
54 **Blindenbacher A**, Wang X, Langer I, Savino R, Terracciano L, Heim MH. Interleukin 6 is important for survival after partial hepatectomy in mice. *Hepatology* 2003; **38**: 674-682
55 **Klein C**, Wüstefeld T, Assmus U, Roskams T, Rose-John S, Müller M, Manns MP, Ernst M, Trautwein C. The IL-6-gp130-STAT3 pathway in hepatocytes triggers liver protection in T cell-mediated liver injury. *J Clin Invest* 2005; **115**: 860-869
56 **Yudkin JS**, Kumari M, Humphries SE, Mohamed-Ali V. Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? *Atherosclerosis* 2000; **148**: 209-214
57 **Klover PJ**, Clementi AH, Mooney RA. Interleukin-6 depletion selectively improves hepatic insulin action in obesity. *Endocrinology* 2005; **146**: 3417-3427
58 **Kopp HP**, Kopp CW, Festa A, Krzyzanowska K, Kriwanek S, Minar E, Roka R, Schernthaner G. Impact of weight loss on inflammatory proteins and their association with the insulin resistance syndrome in morbidly obese patients. *Arterioscler Thromb Vasc Biol* 2003; **23**: 1042-1047
59 **Cai D**, Yuan M, Frantz DF, Melendez PA, Hansen L, Lee J, Shoelson SE. Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. *Nat Med* 2005; **11**: 183-190
60 **Kugelmas M**, Hill DB, Vivian B, Marsano L, McClain CJ. Cytokines and NASH: a pilot study of the effects of lifestyle modification and vitamin E. *Hepatology* 2003; **38**: 413-419
61 **Haukeland JW**, Damås JK, Konopski Z, Løberg EM, Haaland T, Goverud I, Torjesen PA, Birkeland K, Bjøro K, Aukrust P. Systemic inflammation in nonalcoholic fatty liver disease is characterized by elevated levels of CCL2. *J Hepatol* 2006; **44**: 1167-1174
62 **Mas E**, Danjoux M, Garcia V, Carpentier S, Ségui B, Levade T. IL-6 deficiency attenuates murine diet-induced non-alcoholic steatohepatitis. *PLoS One* 2009; **4**: e7929
63 **Wieckowska A**, Papouchado BG, Li Z, Lopez R, Zein NN, Feldstein AE. Increased hepatic and circulating interleukin-6 levels in human nonalcoholic steatohepatitis. *Am J Gastroenterol* 2008; **103**: 1372-1379
64 **Yamaguchi K**, Itoh Y, Yokomizo C, Nishimura T, Niimi T, Fujii H, Okanoue T, Yoshikawa T. Blockade of interleukin-6 signaling enhances hepatic steatosis but improves liver injury in methionine choline-deficient diet-fed mice. *Lab Invest* 2010; **90**: 1169-1178
65 **Yamaguchi K**, Itoh Y, Yokomizo C, Nishimura T, Niimi T, Umemura A, Fujii H, Okanoue T, Yoshikawa T. Blockade of IL-6 signaling exacerbates liver injury and suppresses anti-apoptotic gene expression in methionine choline-deficient diet-fed db/db mice. *Lab Invest* 2011; **91**: 609-618
66 **Moore KW**, de Waal Malefyt R, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. *Annu Rev Immunol* 2001; **19**: 683-765
67 **den Boer MA**, Voshol PJ, Schr öder-van der Elst JP, Korsheninnikova E, Ouwens DM, Kuipers F, Havekes LM, Romijn JA. Endogenous interleukin-10 protects against hepatic steatosis but does not improve insulin sensitivity during high-fat feeding in mice. *Endocrinology* 2006; **147**: 4553-4558
68 **Cintra DE**, Pauli JR, Araújo EP, Moraes JC, de Souza CT, Milanski M, Morari J, Gambero A, Saad MJ, Velloso LA. Interleukin-10 is a protective factor against diet-induced insulin resistance in liver. *J Hepatol* 2008; **48**: 628-637
69 **Esposito K**, Pontillo A, Giugliano F, Giugliano G, Marfella R, Nicoletti G, Giugliano D. Association of low interleukin-10 levels with the metabolic syndrome in obese women. *J Clin Endocrinol Metab* 2003; **88**: 1055-1058
70 **Calcaterra V**, De Amici M, Klersy C, Torre C, Brizzi V, Scaglia F, Albanesi M, Albertini R, Allais B, Larizza D. Adiponectin, IL-10 and metabolic syndrome in obese children and adolescents. *Acta Biomed* 2009; **80**: 117-123
71 **Rollins BJ**. Chemokines. *Blood* 1997; **90**: 909-928
72 **Gerard C**, Rollins BJ. Chemokines and disease. *Nat Immunol* 2001; **2**: 108-115
73 **Charo IF**, Ransohoff RM. The many roles of chemokines and chemokine receptors in inflammation. *N Engl J Med* 2006; **354**: 610-621
74 **Bertola A**, Bonnafous S, Anty R, Patouraux S, Saint-Paul MC, Iannelli A, Gugenheim J, Barr J, Mato JM, Le Marchand-Brustel Y, Tran A, Gual P. Hepatic expression patterns of inflammatory and immune response genes associated with obesity and NASH in morbidly obese patients. *PLoS One* 2010; **5**: e13577
75 **Lalor PF**, Faint J, Aarbodem Y, Hubscher SG, Adams DH. The role of cytokines and chemokines in the development of steatohepatitis. *Semin Liver Dis* 2007; **27**: 173-193
76 **Yl ä-Herttuala S**, Lipton BA, Rosenfeld ME, S ärkioja T, Yoshimura T, Leonard EJ, Witztum JL, Steinberg D. Expression of monocyte chemoattractant protein 1 in macrophage-rich areas of human and rabbit atherosclerotic lesions. *Proc Natl Acad Sci USA* 1991; **88**: 5252-5256
77 **Yu X**, Dluz S, Graves DT, Zhang L, Antoniades HN, Hollander W, Prusty S, Valente AJ, Schwartz CJ, Sonenshein GE. Elevated expression of monocyte chemoattractant protein 1 by vascular smooth muscle cells in hypercholesterolemic primates. *Proc Natl Acad Sci USA* 1992; **89**: 6953-6957
78 **Nelken NA**, Coughlin SR, Gordon D, Wilcox JN. Monocyte chemoattractant protein-1 in human atheromatous plaques. *J Clin Invest* 1991; **88**: 1121-1127
79 **Wobser H**, Dorn C, Weiss TS, Amann T, Bollheimer C, Büttner R, Schölmerich J, Hellerbrand C. Lipid accumulation in hepatocytes induces fibrogenic activation of hepatic stellate cells. *Cell Res* 2009; **19**: 996-1005
80 **Sartipy P**, Loskutoff DJ. Monocyte chemoattractant protein 1 in obesity and insulin resistance. *Proc Natl Acad Sci USA* 2003; **100**: 7265-7270
81 **Weisberg SP**, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 2003; **112**: 1796-1808
82 **Weisberg SP**, Hunter D, Huber R, Lemieux J, Slaymaker S, Vaddi K, Charo I, Leibel RL, Ferrante AW. CCR2 modulates inflammatory and metabolic effects of high-fat feeding. *J Clin Invest* 2006; **116**: 115-124
83 **Rull A**, Escolà-Gil JC, Julve J, Rotllan N, Calpe-Berdiel L, Coll B, Aragonès G, Marsillach J, Alonso-Villaverde C, Camps J, Blanco-Vaca F, Joven J. Deficiency in monocyte chemoattractant protein-1 modifies lipid and glucose metabolism. *Exp Mol Pathol* 2007; **83**: 361-366
84 **Kanda H**, Tateya S, Tamori Y, Kotani K, Hiasa K, Kitazawa R, Kitazawa S, Miyachi H, Maeda S, Egashira K, Kasuga M. MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. *J Clin Invest* 2006; **116**: 1494-1505
85 **Ito M**, Suzuki J, Tsujioka S, Sasaki M, Gomori A, Shirakura T, Hirose H, Ito M, Ishihara A, Iwaasa H, Kanatani A. Longitudinal analysis of murine steatohepatitis model induced by chronic exposure to high-fat diet. *Hepatol Res* 2007; **37**: 50-57

86 **Rull A**, Rodríguez F, Aragonès G, Marsillach J, Beltrán R, Alonso-Villaverde C, Camps J, Joven J. Hepatic monocyte chemoattractant protein-1 is upregulated by dietary cholesterol and contributes to liver steatosis. *Cytokine* 2009; **48**: 273-279

87 **Obstfeld AE**, Sugaru E, Thearle M, Francisco AM, Gayet C, Ginsberg HN, Ables EV, Ferrante AW. C-C chemokine receptor 2 (CCR2) regulates the hepatic recruitment of myeloid cells that promote obesity-induced hepatic steatosis. *Diabetes* 2010; **59**: 916-925

88 **Tamura Y**, Sugimoto M, Murayama T, Ueda Y, Kanamori H, Ono K, Ariyasu H, Akamizu T, Kita T, Yokode M, Arai H. Inhibition of CCR2 ameliorates insulin resistance and hepatic steatosis in db/db mice. *Arterioscler Thromb Vasc Biol* 2008; **28**: 2195-2201

89 **Yang SJ**, IglayReger HB, Kadouh HC, Bodary PF. Inhibition of the chemokine (C-C motif) ligand 2/chemokine (C-C motif) receptor 2 pathway attenuates hyperglycaemia and inflammation in a mouse model of hepatic steatosis and lipoatrophy. *Diabetologia* 2009; **52**: 972-981

90 **Tamura Y**, Sugimoto M, Murayama T, Minami M, Nishikaze Y, Ariyasu H, Akamizu T, Kita T, Yokode M, Arai H. C-C chemokine receptor 2 inhibitor improves diet-induced development of insulin resistance and hepatic steatosis in mice. *J Atheroscler Thromb* 2010; **17**: 219-228

91 **Kassel KM**, Guo GL, Tawfik O, Luyendyk JP. Monocyte chemoattractant protein-1 deficiency does not affect steatosis or inflammation in livers of mice fed a methionine-choline-deficient diet. *Lab Invest* 2010; **90**: 1794-1804

92 **Westerbacka J**, Kolak M, Kiviluoto T, Arkkila P, Sirén J, Hamsten A, Fisher RM, Yki-Järvinen H. Genes involved in fatty acid partitioning and binding, lipolysis, monocyte/macrophage recruitment, and inflammation are overexpressed in the human fatty liver of insulin-resistant subjects. *Diabetes* 2007; **56**: 2759-2765

93 **Greco D**, Kotronen A, Westerbacka J, Puig O, Arkkila P, Kiviluoto T, Laitinen S, Kolak M, Fisher RM, Hamsten A, Auvinen P, Yki-Järvinen H. Gene expression in human NAFLD. *Am J Physiol Gastrointest Liver Physiol* 2008; **294**: G1281-G1287

94 **Castellani ML**, Bhattacharya K, Tagen M, Kempuraj D, Perrella A, De Lutiis M, Boucher W, Conti P, Theoharides TC, Cerulli G, Salini V, Neri G. Anti-chemokine therapy for inflammatory diseases. *Int J Immunopathol Pharmacol* 2007; **20**: 447-453

95 **Montecucco F**, Braunersreuther V, Lenglet S, Delattre BM, Pelli G, Buatois V, Guilhot F, Galan K, Vuilleumier N, Ferlin W, Fischer N, Vallée JP, Kosco-Vilbois M, Mach F. CC chemokine CCL5 plays a central role impacting infarct size and post-infarction heart failure in mice. *Eur Heart J* 2011

96 **Schwabe RF**, Bataller R, Brenner DA. Human hepatic stellate cells express CCR5 and RANTES to induce proliferation and migration. *Am J Physiol Gastrointest Liver Physiol* 2003; **285**: G949-G958

97 **Seki E**, De Minicis S, Gwak GY, Kluwe J, Inokuchi S, Bursill CA, Llovet JM, Brenner DA, Schwabe RF. CCR1 and CCR5 promote hepatic fibrosis in mice. *J Clin Invest* 2009; **119**: 1858-1870

98 **Desai MS**, Mariscalco MM, Tawil A, Vallejo JG, Smith CW. Atherogenic diet-induced hepatitis is partially dependent on murine TLR4. *J Leukoc Biol* 2008; **83**: 1336-1344

99 **Wu H**, Ghosh S, Perrard XD, Feng L, Garcia GE, Perrard JL, Sweeney JF, Peterson LE, Chan L, Smith CW, Ballantyne CM. T-cell accumulation and regulated on activation, normal T cell expressed and secreted upregulation in adipose tissue in obesity. *Circulation* 2007; **115**: 1029-1038

100 **Kirovski G**, Gäbele E, Dorn C, Moleda L, Niessen C, Weiss TS, Wobser H, Schacherer D, Buechler C, Wasmuth HE, Hellerbrand C. Hepatic steatosis causes induction of the chemokine RANTES in the absence of significant hepatic inflammation. *Int J Clin Exp Pathol* 2010; **3**: 675-680

101 **Berres ML**, Koenen RR, Rueland A, Zaldivar MM, Heinrichs D, Sahin H, Schmitz P, Streetz KL, Berg T, Gassler N, Weiskirchen R, Proudfoot A, Weber C, Trautwein C, Wasmuth HE. Antagonism of the chemokine Ccl5 ameliorates experimental liver fibrosis in mice. *J Clin Invest* 2010; **120**: 4129-4140

102 **Bickel M**. The role of interleukin-8 in inflammation and mechanisms of regulation. *J Periodontol* 1993; **64**: 456-460

103 **Bahcecioglu IH**, Yalniz M, Ataseven H, Ilhan N, Ozercan IH, Seckin D, Sahin K. Levels of serum hyaluronic acid, TNF-alpha and IL-8 in patients with nonalcoholic steatohepatitis. *Hepatogastroenterology* 2005; **52**: 1549-1553

104 **Torer N**, Ozenirler S, Yucel A, Bukan N, Erdem O. Importance of cytokines, oxidative stress and expression of BCL-2 in the pathogenesis of non-alcoholic steatohepatitis. *Scand J Gastroenterol* 2007; **42**: 1095-1101

105 **Jarrar MH**, Baranova A, Collantes R, Ranard B, Stepanova M, Bennett C, Fang Y, Elariny H, Goodman Z, Chandhoke V, Younossi ZM. Adipokines and cytokines in non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2008; **27**: 412-421

106 **Abiru S**, Migita K, Maeda Y, Daikoku M, Ito M, Ohata K, Nagaoka S, Matsumoto T, Takii Y, Kusumoto K, Nakamura M, Komori A, Yano K, Yatsuhashi H, Eguchi K, Ishibashi H. Serum cytokine and soluble cytokine receptor levels in patients with non-alcoholic steatohepatitis. *Liver Int* 2006; **26**: 39-45

107 **Müller M**, Carter S, Hofer MJ, Campbell IL. Review: The chemokine receptor CXCR3 and its ligands CXCL9, CXCL10 and CXCL11 in neuroimmunity--a tale of conflict and conundrum. *Neuropathol Appl Neurobiol* 2010; **36**: 368-387

108 **Schrage A**, Wechsung K, Neumann K, Schumann M, Schulzke JD, Engelhardt B, Zeitz M, Hamann A, Klugewitz K. Enhanced T cell transmigration across the murine liver sinusoidal endothelium is mediated by transcytosis and surface presentation of chemokines. *Hepatology* 2008; **48**: 1262-1272

109 **Wasmuth HE**, Lammert F, Zaldivar MM, Weiskirchen R, Hellerbrand C, Scholten D, Berres ML, Zimmermann H, Streetz KL, Tacke F, Hillebrandt S, Schmitz P, Keppeler H, Berg T, Dahl E, Gassler N, Friedman SL, Trautwein C. Antifibrotic effects of CXCL9 and its receptor CXCR3 in livers of mice and humans. *Gastroenterology* 2009; **137**: 309-319, 319.e1-3

S- Editor Tian L **L- Editor** Stewart GJ **E- Editor** Li JY