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EDITORIAL

Cross talk of the immune system in the adipose tissue and the liver in non-alcoholic steatohepatitis: Pathology and beyond

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Abstract

Non-alcoholic steatohepatitis (NASH) is considered to be the hepatic manifestation of the metabolic syndrome, thus has a tight correlation with systemic metabolic impairment. The complex mechanisms underlying the pathogenesis of NASH involve different organs and systems that cross talk together contributing to the onset of NASH. A crucial role is played by inflammatory mediators, especially those deriving from the adipose tissue and the liver, which are involved in the cascade of inflammation, fibrosis and eventually tumorigenesis. In this setting cytokines and adipokines as well as immunity are emerging drivers of the key features of NASH. The immune system participates in this process with disturbances of the cells constituting both the innate and the adaptive immune systems that have been reported in different organs, such as in the liver and in the adipose tissue, in clinical and preclinical studies. The role of the immune system in NASH is increasingly studied, not only because of its contribution to the pathogenetic mechanisms of NASH but also because of the new potential therapeutic options it offers in this setting. Indeed, novel treatments acting on the immune system could offer new options in the management of NASH and the correlated clinical consequences.

Key words: Non-alcoholic steatohepatitis; Immune system; Adipokines; Inflammation; Fibrosis

Core tip: Non-alcoholic steatohepatitis (NASH) is considered to be the hepatic manifestation of the metabolic syndrome, thus has a tight correlation with systemic metabolic impairment. The complex mechanisms underlying the pathogenesis of NASH involve different organs, including liver, adipose tissue and immune system, which cross talk together contributing to the onset of NASH. Increasing interest has been aroused by the role of the immune system in NASH, not only because of its

contribution to the pathogenetic mechanisms of NASH but also considering the new potential therapeutic options in this setting.

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INTRODUCTION

The increasing burden of non-alcoholic fatty liver disease (NAFLD) is a major health concern. The NAFLD worldwide prevalence shows an upward trend over time and has reached "pandemic" proportions. In the general population it is estimated to be 20%-30% in Western countries and 5%-18% in Asia and is associated with an increased prevalence of obesity, insulin resistance, metabolic syndrome and diabetes, which are often paired to NAFLD[1]. Indeed in at risk patients, such as patients with diabetes mellitus, the prevalence of NAFLD increases up to 40%-70%[2]. In addition, NAFLD can run a unfavourable course, given the possible evolution to cirrhosis and hepatocellular carcinoma and can constitute an indication for liver transplantation[3].

NAFLD and more specifically non-alcoholic steatohepatitis (NASH) are closely related to metabolic impairment, such as visceral adiposity, hyperinsulinaemia or diabetes, dyslipidaemia and arterial hypertension, which define the metabolic syndrome. NAFLD and NASH are considered the hepatic manifestation of the metabolic syndrome[4]. Moreover patients with NAFLD, and a fortiori NASH, are at higher risk of developing diabetes mellitus and are at increased risk of morbidity and mortality related to cardiovascular diseases[3,5].

These considerations arise the need of understanding the complex mechanisms underlying the onset of NASH. At the basis of a wide clinical spectrum of NAFLD that includes metabolic impairment at different levels, there is a complex interaction between different organs at the pathogenetic level. This is conceptualized in the "multiple parallel hit hypothesis"[6] and has been substantiated by further research. The liver damage, driven by insulin-resistance, iron accumulation, oxidative stress and hepatocyte death, can be triggered by an imbalance in anti- and pro-inflammatory factors originating from the liver itself or from extrahepatic sites that cross talk with the liver, particularly the adipose tissue and the gut[7]. Another key player in the pathogenesis of NASH is the immune system, including both the innate[8] and the adaptive[9] immune cells[10]. The specific role of the different cell-subsets and the reciprocal role of pro- and anti-inflammatory pathways, however, have not yet been fully clarified and is object of interest in NASH research. Understanding the reciprocal role of these cells in NAFLD should help identifying possible targets for treatment, as nowadays there is no pharmacological treatment licensed for NAFLD[4].

LIVER, ADIPOSE TISSUE AND THE IMMUNE SYSTEM

NAFLD and NASH are associated with the presence of low-grade inflammation. Numerous studies have demonstrated that both the innate and the adaptive immune system play an important role in the pathogenesis of NAFLD/NASH (for review see[10]) and, moreover, that the organ-specific immunity is involved in the onset and progression of this disease.

When considering the whole population of T lymphocytes ($CD3^+$ leucocytes) in the liver, it appears relatively stable in NASH. A variation of the various subtypes of $CD3^+$ cells, however, has been described in NASH, namely a relative increase of the hepatic $CD8^+$ cells in comparison with the $CD4^+$ cells (hence a higher $CD8^+/CD4^+$ ratio)[11]. Among the $CD4^+$ cells, an imbalance between the T helper (Th)1 and Th2 profile towards the pro-inflammatory Th1 has also been described[12]. Moreover a liver specific and reversible depletion of the regulatory T-cells (Tregs) was observed under high fat diet (HFD) in an animal model[13]. The Treg decrease in NASH can in part be explained by dendritic cells (DC) induced down-regulation. *In vitro* studies indeed demonstrated that intrahepatic DC are able to blunt the $CD25^+FOXP3^+$ Treg phenotype within the $CD4^+$ cells[11].

Opposite to these findings, in liver biopsies from a group of NAFLD patients, including NASH patients, the forkhead/winged helix transcription factor (FOXP3) positive cells (Tregs)[14] were more expressed in NASH patients with a more severe disease[15] in comparison with no-NASH patients, hence showing a Treg proliferation with the progression of the disease.

The Th17 pathway is another key player in liver disease, including NAFLD and NASH. In preclinical and clinical studies an increase of the Th17 cells was described together with an up-regulation of the Th17-related genes. Moreover interleukin 17 (IL17) appeared to be crucial in the induction of liver injury in a HFD context and is implicated in metabolic damage by interfering with the insulin signalling pathway[16]. A stimulation of the Th17 occurs, at least in part, *via* interaction between liver and adipose tissue. Indeed, leptin, an anorexigenig and pro-inflammatory adipokine which is increased in obesity due to a mechanism of leptin resistance[17], is able to increase the number of Th17 and the gene expression of the Th17-specific transcription nuclear factor RAR-related orphan receptor (ROR)γt and to stimulate the IL17 production[18]. In addition, the IL17 pathway is implicated in the onset of liver fibrosis: liver injury induces IL17 signalling, which in turn stimulates collagen deposition from the hepatic stellate cells (HSC) and hence the onset of fibrosis[19]. An impairment of the balance between Tregs and Th17 is hence potentially of relevance for the onset and development of NASH, which opens perspectives for new treatment.

Natural killer T (NKT) cells are reduced in hepatic steatosis[20-22], but are increased in hepatic fibrosis in the context of NASH[20,23]. Indeed, human liver biopsies with advanced fibrosis showed increased levels of osteopontin and hedgehog, which are secreted by NKT, in comparison with early stages of fibrosis[24].

The resident macrophages in the liver, the Kupffer cells (KC), are sensitive to gut-derived endotoxin and modulate the activation of different cells in the liver, such as DCs, T lymphocytes and neutrophils[25]. They are actively implicated in the development and progression of NASH by the secretion of tumour necrosis factor (TNF)α, which plays an important role in the early phase of the disease, and of IL6, which is important in the liver disease evolution and in de onset of insulin resistance[7].

DCs in NASH are enrolled in the early phases. They display a decreased plasmocytoid and lymphoid fraction and an increased myeloid fraction and produce higher levels of pro-inflammatory cytokines and to mediate an allogenic T cell proliferation, an antigen-restricted $CD4^+$ T cell stimulation and a Treg down-regulation[11].

The adipose tissue is another key organ in the pathogenesis of NASH and the associated metabolic impairment. Moreover the NASH-related immune system impairment involves also the immune cells infiltrating this organ.

Considering the T lymphocytes, $CD8^+$ and $CD4^+$ are enriched in the adipose tissue[11]. Moreover there is a shift towards the pro-inflammatory Th1 cytokines in comparison with the anti-inflammatory Th2 ones, particularly in the visceral adipose tissue[12]. Interestingly, the Th1 stimulation, *via* INFγ, induces the infiltration of the adipose tissue by other pro-inflammatory cells, such as the M1-polarized macrophages[26].

The abdominal adipose tissue (but not the subcutaneous adipose tissue) is a preferential source of Tregs in mice fed a normal diet with a time-dependent kinetic. In insulin-resistant models of obesity Tregs are specifically reduced in the abdominal site[12,27], which can be explained, at least in part, by the suppression of Treg proliferation by leptin[28]. Moreover in obese patients FOXP3 RNA was expressed at a higher level in the subcutaneous adipose tissue and a negative correlation between body mass index (BMI) and the FOXP3 to CD3 ratio in omental *vs* subcutaneous fat was reported in these patients[27]. In leptin deficient obese mice Treg depletion leads to increased fasting blood glucose level, impaired insulin sensitivity and renal impairment, while Treg adoptive transfer improves insulin resistance[29]. In addition, in type 2 diabetes a deregulation of the balance between Tregs and Th17 occurs: there is a decrease of the Tregs/Th17 ratio and Tregs appear to be more prone to cell death[30]. Opposite to these findings, other studies suggested a potential beneficial effect of the IL17 in blunting the phenotypic and metabolic characteristics correlated to obesity. Preclinical studies showed a reduction of the Th17 in the visceral adipose tissue of mice fed a HFD[12] and demonstrated the role of IL17 as a negative regulator of adipogenesis and glucose metabolism in mice, delaying the onset of obesity[31]. In these experiments, IL17 deficiency enhanced diet-induced obesity, early adipose tissue accumulation and altered glucose homeostasis. In addition IL17 acted on preadipocytes and adipocytes to inhibit adipogenesis and moderate lipid and glucose uptake[31].

A depletion of invariant NKT cells (iNKT) has been reported in obesity, in correlation with pro-inflammatory macrophage infiltration. Indeed, iNKT-depleted NASH animal models show larger adipocytes while iNKT adoptive transfer decreases fat accumulation, leptin levels and insulin sensitivity[32].

In adipose tissue, an infiltration of DC has been shown in preclinical and clinical studies. In humans, the subcutaneous adipose tissue-derived DC have been described to correlate with metabolic impairment [high BMI and insulin resistance] and with increased Th17[33].

Considering the B lymphocytes, they contribute to the onset of insulin resistance. Mice fed a HFD display and increase of B lymphocytes in serum and adipose tissue, while when feeding B-cell-deficient mice a HFD lower insulin resistance is determined. Accordingly, adoptive transfer of B cells or IgG isolated from mice fed a HFD into B-cell-deficient mice induces insulin resistance. In addition, insulin-resistant patients have a distinct IgG profile compared to patients without it[34].

Macrophages derive from circulating monocytes and play a crucial role in the adipose tissue. They can activate as the "classically activated" pro-inflammatory M1 or as the "alternatively activated" anti-inflammatory M2 states. In obesity animal models pro-inflammatory M1 polarized macrophages infiltrate the adipose tissue[32] and create the characteristic "crown like" structures around necrotic adipocytes[32].

The obesity-related switch from the M2 to the M1 polarization is driven by a C-C chemokine receptor 2 (CCR2)-dependent monocyte recruitment[35]. CCR2 is therefore a potential target of therapy. Indeed, blunting macrophage accumulation, also *via* monocyte chemoattractant protein 1/chemokine (C-C motif) ligand 2 (MCP-1/CCL2) inhibition, induces an improvement of inflammation activity, insulin resistance and liver fibrosis[7].

These data summarize the multiple immune cell subtypes involved in the onset of NAFLD and NASH, which draw complex pathways and offer various possible targets to interfere with the onset of NASH.

A relevant role in the pathogenesis of NASH is played by adipose tissue-derived mediators, such as adiponectin and leptin[6], and other molecules such as ghrelin, visfatin and resistin[36,37].

Adiponectin and leptin are produced mainly by the adipose tissue. The former acts as an insulin sensitizing and an anti-inflammatory mediator. Hypoadiponectinemia has been found to be associated with the metabolic

Table 1 Treatment perspectives: Novel agents acting on the immune system

Treatment	Target	Effect
Anti-CD3 moAb	CD3	Reduction of liver enzymes and glucose and insulin levels
Imm124-E	Treg stimulation	Improvement of glucose metabolism parameters, lipid profile and liver injury
Adoptive transfer		
Tregs		Reduction of TNFα-related inflammation
$CD4^+$ T cells		Reverses weight gain and insulin resistance
NKT cells		Decreases body fat, triglyceride levels, leptin levels, hepatic steatosis and insulin sensitivity
RORγt ligands	RORγt	Th17 inhibition
Cenicriviroc	CCR2/5 inhibitor	Improvement of lipid metabolism and liver fibrosis
VAP-1	Lymphocytes recruitment	Anti-inflammatory en anti-fibrogenic effect

TNF: Tumour necrosis factor; ROR: RAR-related orphan receptor; CCR2: C-C chemokine receptor 2; VAP-1: Vascular adhesion protein-1; NKT: Natural killer T; Th17: T helper cell 17; Tregs: Regulatory T-cells; moAb: Monoclonal antibody.

syndrome and its components, including NASH[38]. The latter, under physiological conditions, has anorexigenic effects decreasing appetite and increasing energy expenditure, while in obese patients hyperleptinemia associated to leptin resistance has been described[17]. Moreover leptin has pro-inflammatory and pro-fibrogenic properties that play a role in liver disease, including NASH[37,39,40].

Adiponectin exerts its anti-inflammatory function inhibiting the pro-inflammatory cytokines (TNFα) and stimulating the anti-inflammatory cytokines (IL10 secreted by KC)[41] and *via* direct suppression of the macrophage function[42]. Adiponectin attenuates also oxidative stress and fibrogenesis, the latter through suppression of the activated HSC function[38].

Leptin is able to affect the production of acute-phase-reactants, such as IL1 and TNFα, to alterate the Th1/Th2/Tregs balance promoting a Th1 differentiation and a Treg down-regulation[40]. Hyperleptinemia is a condition correlated with obesity and can favour pro-inflammatory mechanisms. Namely it can induce a proliferation of Th1 cells in the adipose tissue, of $CD8^+$ T cells, macrophages and mast cells and stimulates pro-inflammatory cytokines (as TNFα, IL6 and IL12). Moreover they induce a down-regulation of the Treg in the adipose tissue, as previously described[40].

Ghrelin is a gut peptide that is involved in regulation of food intake and energy balance. Ghrelin has been reported to have protective effects on the liver and reduced levels of this hormone have been found in NAFLD patients[43].

Resistin, which is produced by adipose tissue and macrophages, is involved in insulin resistance, has pro-inflammatory (*via* stimulation of the secretion of TNFα and IL12 by macrophages and *via* regulation of IL6 and IL1β production) and pro-fibrogenic (acting on the HSC)[36]. Resistin has been correlated with the progression of liver damage in NAFLD and with the onset of NASH[44].

NASH patients show lower adiponectin, higher leptin and resisitin and unaltered ghrelin levels in comparison with control subjects. In these patients antioxidant treatment can induce an reversal of the hypoleptinemia and hypoadiponectinemia and is able to arise the ghrelin levels[37].

Visfatin is an insulin mimicking adipokine. It is able to induce IL6 secretion from $CD4^+$ T cells[45]. The specific contribution in NASH, however, has not been fully clarified.

TREATMENT PERSPECTIVES

Currently there is no approved pharmacological treatment available for NASH. Among the treatments used in the pharmacotherapy of NASH, some agents have failed to give a satisfactory improvement of NASH, such as metformin, statins and ursodeoxycholic acid. Vitamin E and thiazolidinediones have shown beneficial effects on liver histology in randomized control trials and can hence be used for the treatment of NASH, but are not approved for this indication[4]. Furthermore, there is some concern about the potential side effects associated with these drugs, which should hence be prescribed with caution[46]. Pioglitazone finds a possible indication in older patients with aggressive NASH and Vitamin E can be used in non-diabetic pre-cirrhotic adults[4]. Of note pioglitazone is also able to increase adiponectin levels[47] (Table 1).

Very recent preclinical data show the ability of the adiponectin receptor agonist AdipoRon to significantly ameliorate glucose metabolism and serum lipid levels. In the liver the AdipoRon reduces triglyceride content, oxidative stress, and inflammatory cytokine expression, suggesting its potential role in the treatment of NASH[48].

Another treatment approach exploits the possibility to interfere with the immune system, which is actively involved in the physiopathology of NASH, through immune-regulation[49].

Some data are available regarding the anti-CD3 monoclonal antibody (moAb), which prevents the onset and the evolution of inflammatory and autoimmune diseases.

The anti-CD3 moAb or its Fragment anti-binding $F(ab^1)_2$ have been shown to be effective in ameliorating insulin resistance in leptin deficient *ob/ob* mice where they restored Tregs in the visceral adipose tissue and improved glucose tolerance and insulin sensitivity[12].

The anti-CD3 moAb can be also administered in combination with β-glucosylceramide, which is able to mediate the interaction with other immune cells such as NTK. Oral anti-CD3 antibody is rapidly absorbed by the gut-associated lymphoid tissue and induces $CD4^+CD25$-latency-associated peptide-positive Tregs, which act in a tumor growth factor-β-dependent manner. Treatment of *ob/ob* mice resulted in a better metabolic control and an improvement of the liver damage. A decrease in pancreatic islet cell hyperplasia, fat accumulation in the liver and inflammation in adipose tissue, accompanied by lower blood glucose and liver enzymes were observed[50].

The systemic administration of anti-CD3 moAb, however, can be hampered by serious side effects such as the cytokine release syndrome, a "cytokine storm" released as a consequence of generalized T cell activation, or the antiglobulin response[51]. To minimize the side effects of the systemic administration of the anti-CD3 moAb and to maximize its local effects, anti-CD3 can be orally administered. A single-blind randomized placebo-controlled phase 2a study showed the safety of oral anti-CD3 moAb in 36 NASH patients with impaired glucose control up to type-2 diabetes. Oral anti-CD3 moAb showed safety and were able to improve liver damage and glucose metabolism. This effect was coupled with a persistent Treg level increase[51].

The Treg-induction can be either antigen-specific or antigen nonspecific. The induction of antigen-specific Tregs has the potential advantage of inducing a specific immune modulation and of reduced side effects. This is, however, not achievable in conditions such as type 2 diabetes or NASH where there are to date no well-defined target antigens. In these conditions the induction of antigen non-specific Tregs by anti-CD3 may be a valid option. Further research will investigate the possibility of developing a combination of mucosal anti-CD3 with a given antigen[51].

Moreover Tregs are an important possible target for immunotherapy. Different therapeutic approaches have been used to modulate these cells. The Imm124-E, an anti-lipopolysaccharide hyperimmune bovine colostrum, has been tested, in an open label trial, in patients with biopsy-proven NASH and insulin resistance. Imm124-E was safe and effective in ameliorating the glucose metabolism parameters, the lipid profile and the liver injury. The improvement of the clinical parameters was paired with a Treg enhancement[52].

A redistribution of the Tregs, paired to an increase in NKTs, was reached in leptin deficient *ob/ob* and HFD mice treated with DT56a, a molecule contained in soybean able to activate estrogen receptors and to improve glucose homeostasis, the lipid profile and the liver enzymes[53].

Adoptive cell transfer refers to the transfer of immune cells into a recipient host aiming at transferring the immunological functionality into the host. In particular the Treg cell transfer is able to preserve and restore tolerance to self-antigens and alloantigens. The benefits of this treatment are the potential for antigen specificity, the lack of general immunosuppression and the long-lasting regulation[54]. Treg expansion in obese mice tempers TNFα-related inflammation[13] but it is not able to restore metabolic function in obesity[27].

Cellular therapy has also been tested with other cell subtypes. The $CD4^+$ Tcell transfer into obese mice reversed weight gain and insulin resistance[12]; iNKT transfer decreased body fat, triglyceride levels, leptin levels, hepatic steatosis and insulin sensitivity[32].

Although cellular therapy shows positive preliminary result and constitutes a conceptually potentially effective therapy, these treatments raise feasibility concerns in the clinical setting[55] and need further development and evaluation.

A further possible therapeutic approach involves the ROR pathway. RORα and RORγ are transcription factors implicated in the control of lipid and glucose metabolism, besides various immune functions. The absence of RORα protects against diet-induced obesity, adipose tissue-associated inflammation, liver injury (namely steatosis), and insulin resistance[56]; RORγ deficiency also protects against diet-induced insulin resistance[57]. Therefore, ROR antagonists may provide a novel therapeutic target in the management of various aspect of the metabolic syndrome.

Recently RORγt ligands have been studied in autoimmune diseases. They blunt the production of IL17 from the stimulated Th17 cells, by counteracting nuclear receptor specific for Th17 RORγt. These compounds constitute a promising strategy in the therapy of NASH, considering the central role of the Th17 pathway in the induction and progression of both the liver damage and the metabolic impairment.

Antioxidants constitute another potential therapy in NAFLD. Polyphenols, such as resveratrol contained in grapes and wine, are molecules of interest. Indeed resveratrol is able to improve insulin sensitivity and to modulate mitochondrial energetics[58]. Moreover resveratrol has been shown to be effective in ameliorating liver enzymes, insulin resistance and glucose and lipid metabolism in patients with NAFLD. Furthermore it induced a reduction of pro-inflammatory and pro-fibrogenic cytokine levels (namely TNFα, cytokeratin 18 fragment, and fibroblast growth factor) and an elevation of adiponectin levels[59].

Another potential target is the fibrosis pathway. The Chemokine receptors type 2 and 5 (CCR2-CC5) are expressed by cells involved in fibrogenesis, such as monocytes, macrophages, Kupffer cells and hepatic stellate cells. Preclinical studies in NASH and liver fibrosis animal models showed that a dual CCR2 and CCR5 inhibitor, cenicriviroc (CVC), has an anti-fibrogenic effect[60]. A clinical study conducted in human immunodeficiency virus (HIV) patients has shown that CVC is able to improve lipid metabolism (decreasing the total cholesterol, low-density lipoprotein and triglycerides levels and increasing the high-density lipoprotein levels) and the fibrosis scores aspartate aminotransferase to platelet ratio index (APRI)[61] and fibrosis-4 (FIB-4)[62,63]. This, together with the preclinical data, makes CVC a good candidate for the treatment of NASH.

Very recently a new potential target of treatment for NAFLD has been identified. The Vascular adhesion protein-1 (VAP-1) is an amino-oxidase constitutively expressed on human hepatic endothelium that promotes lymphocyte recruitment in the liver. This molecule is increased in various models of liver disease, including NAFLD, and is implicated in both inflammation and fibrosis. In a NAFLD preclinical model VAP-1 inhibition leads to less leucocyte recruitment in the liver and, more specifically, a reduction of the $CD4^{+}$ T lymphocytes and of the NKT lymphocytes. This, together with its anti-fibrogenic effect, makes the VAP-1 inhibition a potential therapeutic target[64].

Further research is, however, urgently needed to unravel the exact pathogenetic mechanisms of NAFLD/NASH, also aiming at discovering new effective therapeutic options, given the increasing burden of this disease and its potential evolutive course.

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