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EDITORIAL

# Targeting Kupffer cells in non-alcoholic fatty liver disease/non-alcoholic steatohepatitis: Why and how?

Nicolas Lanthier

Nicolas Lanthier, Service d'Hépato-gastroentérologie, Cliniques Universitaires Saint-Luc, Université catholique de Louvain, 1200 Brussels, Belgium

Nicolas Lanthier, Laboratory of Hepatogastroenterology, Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, 1200 Brussels, Belgium

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Correspondence to: Dr. Nicolas Lanthier, MD, PhD, Service d'Hépatogastroentérologie, Cliniques Universitaires Saint-Luc, Université catholique de Louvain, Avenue Hippocrate, 10, 1200 Brussels, Belgium. nicolas.lanthier@uclouvain.be
Telephone: +32-2-7645275
Fax: +32-2-7645346

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## Abstract

Mechanisms for non-alcoholic steatohepatitis (NASH) development are under investigation in an era of increased prevalence of obesity and metabolic syndrome. Previous findings have pointed to the role of adipose tissue, adipose tissue macrophages and their secretory products in the development of a chronic inflammatory status inducing insulin resistance and a higher risk of liver steatosis called non-alcoholic fatty liver disease. The activation of resident macrophages [Kupffer cells (KC)] and the recruitment of blood derived monocytes/macrophages into the diseased liver have now been identified as key elements for disease initiation and progression. Those cells could be activated through gut flora modifications and an altered gut barrier function but also through the internalization of toxic lipid compounds in adjacent hepatocytes or in KC themselves. Due to the role of activated KC in insulin resistance, fibrosis development and inflammation amplification, they became a target in clinical trials. A shift towards an anti-inflammatory KC phenotype through peroxisome proliferator activator-receptorδ agonists, an inhibition of macrophage recruitment through anti-C-C chemokine receptor 2 action and a specific blocking of internalization of toxic lipoxidation or glycation compounds into KC by galectin-3 receptor inhibitors are now under investigation in human NASH.

**Key words:** Steatosis; Non-alcoholic steatohepatitis; Insulin; Non-alcoholic fatty liver disease; Macrophage



**Core tip:** Previous findings in the context of obesity have pointed to the role of macrophages from the adipose tissue in the development of a chronic inflammatory status inducing insulin resistance and non-alcoholic fatty liver disease (NAFLD). However, nowadays, the activation of liver macrophages called Kupffer cells (KC) and the recruitment of monocytes have been identified as key elements for disease initiation and progression towards steatohepatitis and cirrhosis. What are the possible reasons for this deleterious KC activation in

NAFLD? Are our current therapeutic approaches in NAFLD targeting KC and how? Those two important questions are raised in this paper, supported by recent studies in the field.

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## INTRODUCTION

The metabolic syndrome is characterized by a low grade inflammatory state. Macrophages polarized towards a pro-inflammatory phenotype infiltrating the white adipose tissue particularly in its visceral location are known to play a major role in this setting, producing inflammatory circulating mediators[1]. Similar to the adipose tissue, the liver also contains macrophages, called Kupffer cells (KC), which represent the largest tissue resident macrophage population. In parallel with the growing prevalence of the metabolic syndrome, liver steatosis (*i.e.,* increased fat deposition into the hepatocytes) associated with this condition becomes now a common finding, affecting one third of the population in Western countries. Liver steatosis called non-alcoholic fatty liver disease (NAFLD) could be the source of insulin resistance and is known to be associated with increased morbidity and mortality, particularly due to an increased cardiovascular risk[2,3]. Apart from that, the severity of NAFLD is also linked to the fact that a subset of patients with steatosis can progress to an inflammatory liver disease with hepatocyte damage called non-alcoholic steatohepatitis (NASH), which is able to induce fibrosis and potential cirrhosis development[2,4,5].

## DO KC PLAY A ROLE IN NAFLD/NASH?

In animal as in human studies, we have now arguments sustaining that KC are implicated in NAFLD, both at disease initiation and for disease progression.

First, previous animal experiments in our lab demonstrated a rapid onset of liver steatosis and hepatic insulin resistance upon introduction of a high fat diet concurrently with an inflammatory activation of KC[6]. We proved that the rapid KC activation in mice played a pathological role in hepatic insulin resistance[6], as well as in whole body insulin resistance and adiposity during chronic high fat feeding[7]. Clodronate loaded liposomes were used to selectively deplete KC[8]. Blunting hepatic macrophage response prior to the initiation of the diet prevented the development of hepatic insulin resistance and ameliorated whole body insulin resistance and decreased body weight in chronic experiments[6,7]. The implication of KC in NASH was also addressed using methionine/choline deficient (MCD) diet by other authors[9]. This diet induces NASH lesions together with KC clustering next to injured hepatocytes[9], as seen in the human NASH[10]. In this situation, KC depletion also ameliorated NASH injuries[9]. Moreover, KC are known to produce profibrogenic factors (for example transforming growth factor beta) able to activate the collagen producing hepatic stellate cells (HSC). We showed that *in vivo* KC depletion in a fibrosis mouse model decreased HSC activation and fibrosis development[11].

Second, in humans, a recent elegant study explored the key inflammatory steps in NAFLD development[12]. Interestingly, KC expansion was the first difference seen in liver biopsies of patients with steatosis compared to control patients. The study also revealed that KC expansion was the first step of liver inflammatory activation, preceding the recruitment of other inflammatory cells. Further macrophage infiltration particularly next to the portal tracts as well as apparition of lymphocytes and neutrophils were seen in more advanced fibrotic and inflammatory stages of the disease[12]. This well designed observation supports a key role for KC activation in disease initiation as well as in further fibrosis and inflammatory development. Previous findings on hepatic gene expression patterns in controls, obese patients with normal liver histology, obese and steatotic patients and obese patients with NASH corroborates this observation highlighting an increased liver macrophage expression (CD68 mRNA) with obesity, even more pronounced in case of NASH, together with the upregulation of many genes involved in neutrophil and macrophage recruitment including monocyte chemoattractant protein-1 (MCP-1) also named chemokine ligand 2 (CCL2)[13].

## WHAT ARE THE POTENTIAL ACTIVATORS OF KC?

Following the previous observations, an interesting question is arising: what are the possible reasons for this deleterious KC activation in NAFLD? Why do the cells initiate an inflammatory condition while they are normally present to fight against foreign particles or bacteria? Indeed, KC belongs to the innate immune system and their main function is the elimination by phagocytosis of exogenous material including microorganisms, apoptotic cells and debris. KC also participates to the adaptive immune system, presenting specific antigens to cytotoxic and regulatory T cells[14].

At disease initiation, KC can thus be activated by pathogen-associated molecular patterns (PAMPs), including modified gut microbiome (dysbiosis) and increased gut-derived bacterial translocation described in patients with obesity[15]. They can also be activated directly through the uptake or the metabolization of toxic lipids like oxidized lipoproteins, ceramides and cholesterol crystals recognized as foreign particles[16]. With liver disease progression, in addition with the amplification of those mechanisms, KC activation can also be linked

to the presence of endogenous molecules released by adjacent damaged hepatocytes constituting damage-endogenous-associated molecular patterns (DAMPs)[15]. Collectively, PAMPs and DAMPs well known to be able to activate various toll like receptors (TLR) like TLR2, 4, 9 present on KC[15] but also intracellular lipid content of KC[16] could be responsible for the inflammatory reaction at different disease stages. Altogether, those mechanisms explain the deleterious adaptation of the liver innate immune system to the metabolic condition associated with mal- and/or overnutrition.

## CURRENT CLINICAL TRIALS IN NAFLD/NASH: ARE THEY TARGETING MACROPHAGES?

Despite their usefulness for the determination of the role of KC in disease initiation or amplification, experimental techniques depleting KC in animal models of NAFLD or NASH using clodronate loaded liposomes are not appropriate in a long term clinical human setting due to the important roles of macrophages in health and host defense as well as to the potential anti-inflammatory benefits of the cells. Indeed, next to the classical "Mister Hyde" inflammatory M1 phenotype of KC investigated in animal and human studies, a possible "Dr Jekyll" anti-inflammatory alternative M2 phenotype has been described with specific activators and releasing factors[17]. Therefore, targeting specific pathways of KC seems to be preferable to deleting a whole KC population and its related function. Interestingly, a high proportion of studies or current clinical trials in NAFLD/NASH potentially target KC activation, by different methods which could be classified as follows.

### *Reduction of KC activation*

**Nutritional counseling:** As we know, KC activation occurs in humans in the setting of obesity and early steatosis before the development of NASH and fibrosis. Further KC recruitment occurs with disease progression[12,13]. Many studies have investigated the role of dietary counseling in the disease management. Few of them have a paired liver biopsy[18], and none evaluated the changes in macrophage content to assess the impact of such a nutritional approach on KC response. In a recent trial[19], weight loss was shown to significantly ameliorate NAFLD activity scores in 47% of the subjects. However, KC evaluation does not participate to this score. Furthermore, portal inflammation which contains mainly macrophages[12] remained unchanged in the high weight loss group (> 5%) compared to the low weight loss group (< 5%)[19], possibly meaning that the portal inflammatory condition initiated in NAFLD could perpetuate despite adequate nutritional counseling.

**Specific modulation of gut microbiota:** The benefice of fecal microbiota transplantation of lean donors on obese subjects has been demonstrated on insulin sensitivity[20]. However, its impact on NAFLD and KC activation remains to be established. Intestinal dysbiosis could also be targeted through prebiotic[21] or probiotic[22] treatments. Whether those treatments are effective in human NAFLD/NASH and KC activation remains also to be experimentally addressed.

### *KC shift towards an anti-inflammatory phenotype*

As mentioned before, experimental studies have highlighted an alternative activation of KC, in some circumstances, favoring glucose metabolism and fatty acid oxidation. This alternative pathway is activated by STAT-6 and interleukin 4 (IL-4) and maintained by the fatty acid sensor peroxisome proliferator activator-receptor delta (PPARδ). Unsaturated fatty acids act in synergy with IL-4, activating PPARδ[17]. In the first publication demonstrating the shift towards an anti-inflammatory phenotype, oleic acid was used in conjugation to IL-4 to stimulate PPARδ[23].

**Eicosapentaenoic acid:** The administration of this polyunsaturated fatty acid has been tested in NAFLD/NASH. In combination with docosahexaenoic acid, an indirect impact on liver steatosis (on imaging) has been described, maybe restricted to early NAFLD stages, because an impact on fibrosis was not demonstrated[24]. In contrast, in well-established biopsy proven NASH with fibrosis, the treatment supplementation was not efficacious. Indeed, in patients with NAFLD activity scores $\geqslant$ 4 with at least stage 1a fibrosis, a double blind placebo controlled study did not evidence any beneficial impact[25].

**PPARδ:** GFT505, a double PPARα and PPARδ agonist known to ameliorate NASH in mice induced by the MCD diet[26] was also tested in 22 individuals with metabolic syndrome showing an amelioration of insulin sensitivity, as well as a significant decrease in liver enzyme abnormalities[27]. A large phase 2b trial is now conducted in order to test the benefice of such molecule on NASH patients with fibrosis (NCT01694849).

### *Blocking macrophage recruitment*

Recruitment of hepatic macrophages is proven to be mediated through the C-C chemokine receptor 2 (CCR2) for which the main ligand is CCL2 or MCP-1. Cenicriviroc, a dual CCR2/CCR5 antagonist was tested in diabetic mice fed a high fat diet, showing a decrease in NASH components together with a decrease of fibrosis[28]. A phase 2 trial addressing the role of cenicriviroc is now conducted in NASH patients with fibrosis (NCT02217475).

### *Targeting specific macrophage pro-inflammatory activation*

Galectins are a family of 15 proteins having a carbohydrate binding domain for the terminal galactose residues of macromolecules such as glycoproteins. KC express galectin-3 which is the main scavenger receptor

involved in the hepatic uptake of advanced lipoxidation and glycation endproducts. This scavenger receptor is involved in inflammation and fibrosis. Indeed, galectin-3 null mice are resistant to steatohepatitis, stellate cell activation and fibrosis under an atherogenic diet[29]. Treatment with galactoarabino-rhamnogalacturonan polysaccharide (GR-MD-02) which has side chains including galactose and arabinose will thus be able to block the galectin-3 receptor. Through this mechanism, the treatment was shown to decrease fibrosis in an experimental model in rats[30]. In a NASH model, the treatment abrogated the expression of galectin-3 on KC in areas of hepatocellular damage, as well as the number of activated HSC while preserving normal KC number[31]. Results of an early phase 1 clinical trial with this galectin-3 inhibitor drug (administered through intravenous injections) were presented at the American Association congress[32] and a phase 2 trial is planned on NASH with advanced fibrosis (NCT02421094).

Other scavenger receptors like CD36, macrophage scavenger receptor 1 mediate modified cholesterol lipoproteins uptake into KC and have been described in animal models of NASH to be implicated in the disease pathogenesis[33]. The specific targeting of those pro-inflammatory pathways through adequate therapy represent attractive possibilities in order to blunt the onset of hepatic inflammation by affecting intracellular lipid content of KC.

## CONCLUSION

We are facing a new metabolic era with an increased prevalence of metabolic syndrome and NAFLD, but also of new findings regarding disease evolution in humans and potential pathophysiological mechanisms. KC represents attractive targets in this setting and numerous clinical studies specifically point to this pathogenic pathway. Due to the importance of KC in NAFLD and NASH, evaluation of their response in clinical trials targeting other pathways like biliary salts (for obeticholic acid), collagen synthesis (for simtuzumab) or insulin secretion and satiety (for liraglutide) are of major interest. However, due to the possible anti-inflammatory role of KC, such evaluation remains difficult and has not to be dissociated from other inflammatory pathways analysis. Further studies are also needed addressing the precise mechanisms of KC activation in humans, as well as the nature of factors secreted from inflammatory KC.

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