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Th17 involvement in nonalcoholic fatty liver disease progression to non-alcoholic steatohepatitis

Carla Melisa Chackelevicius, Sabrina Eliana Gambaro, Claudio Tiribelli, Natalia Rosso

Carla Melisa Chackelevicius, Sabrina Eliana Gambaro, Claudio Tiribelli, Natalia Rosso, Italian Liver Foundation, Area Science Park, Trieste, 34149 TS, Italy

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Correspondence to: Natalia Rosso, PhD, Senior Scientist, Italian Liver Foundation, Area Science Park, Ed Q, SS14 Km 163.5 Basovizza, Trieste, 34149 TS, Italy. natalia.rosso@csf.units.it
Telephone: +39-40-3757922
Fax: +39-40-3757832

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Abstract

The nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome. NAFLD encompasses a wide histological spectrum ranging from benign simple steatosis to non-alcoholic steatohepatitis (NASH). Sustained inflammation in the liver is critical in this process. Hepatic macrophages, including liver resident macropaghes (Kupffer cells), monocytes infiltrating the injured liver, as well as specific lymphocytes subsets play a pivotal role in the initiation and perpetuation of the inflammatory response, with a major deleterious impact on the progression of fatty liver to fibrosis. During the last years, Th17 cells have been involved in the development of inflammation not only in liver but also in other organs, such as adipose tissue or lung. Differentiation of a naïve T cell into a Th17 cell leads to pro-inflammatory cytokine and chemokine production with subsequent myeloid cell recruitment to the inflamed tissue. Th17 response can be mitigated by T regulatory cells that secrete anti-inflammatory cytokines. Both T cell subsets need TGF-β for their differentiation and a characteristic plasticity in their phenotype may render them new therapeutic targets. In this review, we discuss the role of the Th17 pathway in NAFLD progression to NASH and to liver fibrosis analyzing different animal models of liver injury and human studies.

Key words: Th17; Interleukin-17; Nonalcoholic fatty liver disease; Non-alcoholic steatohepatitis; Inflammation

Core tip: Interleukin-17 producing cells are important in maintaining inflammation since they are a source of pro-inflammatory cytokines and chemokines with a

critical role in fighting extracellular bacteria. In the last years, this lymphocyte subset has been linked to the pathogenesis of multiple immune mediated diseases and in some cases to the progression to fibrosis. In this review, we discuss the role of the Th17 pathway in nonalcoholic fatty liver disease progression to non-alcoholic steatohepatitis and to liver fibrosis analyzing previously published data obtained from different animal models and human studies of liver injury.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is defined as an abnormal accumulation of fat in the liver, evidenced by either imaging or histology without any known cause of secondary hepatic fat accumulation such as alcohol consumption, steatogenic medication or hereditary disorders[1]. The histological spectrum of NAFLD comprises benign simple steatosis and a more severe form with inflammation, hepatocyte injury with or without fibrosis called Non-alcoholic steatohepatitis (NASH), this last entity can progress to cirrhosis, liver failure and hepatocellular carcinoma. The incidence of NAFLD and NASH is growing worldwide associated with obesity and diabetes, becoming a common cause of chronic liver disease and need of liver transplantation. The prevalence in the European general population is between 20%-30%, reaching 90% among obese patients[2]. Sustained inflammation in the liver is critical in the progression from benign simple steatosis to NASH. Hepatic macrophages, comprising liver resident macropaghes (Kupffer cells), monocytes infiltrating the injured liver, as well as specific lymphocytes subsets play a pivotal role in the initiation and perpetuation of the inflammatory response, with a major deleterious impact on key steps of fatty liver progression to fibrosis[3]. During the last years, a specific subset of CD4 T effector cells, Th17 subpopulation has been suggested to be involved in this process[4,5]. In this review, we discuss the role of the Th17 pathway in NAFLD progression to NASH and to liver fibrosis analyzing previously published data obtained from different animal models and human studies of liver injury

LITERATURE SEARCH

For this review, we used PubMed and Google Scholar databases to search for relevant articles using the following mesh terms: "Th17 cells"; "NASH"; "NAFLD" "liver inflammation"; "liver fibrosis"; "induced liver injury" "IL17"; "Tregs"; "CD4 T cells" and "regulatory T cells". Only the articles published between 2006 and 2016 were included.

Table 1 Interleukin-17 family ligands and receptors

IL-17 family ligands	Binding receptor	Produced mainly by
IL-17 A	IL-17 RA, IL-17 RC	T cells
IL-17 A/F	IL-17 RA, IL-17 RC	T cells
IL-17 B	IL-17 RB	Numerous cells
IL-17 C	Unknown	Prostate, kidney cells
IL-17 D	Unknown	Numerous cells
IL-17 E (IL-25)	IL-17 RB (IL-25 R)	Numerous cells
IL-17 F	IL-17 RA, IL-17 RC	T cells

IL-17: Interleukin-17.

Th17 CELLS

Th17 differentiation

CD4 T helper cells that recognize antigens in the context of Mayor Histocompatibility Complex type II (MHC II) can be polarized into different types of effector T cells to coordinate different immunopathological responses[6]. Th17 cells play a role in pathogen clearance and tissue inflammation but are also implicated in the pathogenesis of autoimmune diseases[7,8]. The differentiation of naïve CD4 T cells into Th17 cells in humans is triggered by the combined action of transforming growth factor (TGF)-β, interleukin (IL)-6 and IL-1β, these cytokines induce the expression of the key lineage defining transcription factor orphan nuclear receptor (RORc). RORc is necessary and sufficient for the differentiation of Th17 cells whereas IL-23 is required only for the pathogenicity and expansion of this lineage[9,10]. Th17 pathway is suppressed by IFN-γ and IL-4 that promote Th1 or Th2 respectively[11]. The major target genes for IL-17 include pro-inflammatory chemokines, hematopoietic cytokines, acute phase response genes and antimicrobial substances[12].

IL-17 family cytokine and IL-17 family receptor

Though six IL-17 ligands have been described, IL-17A is the best characterized. IL-17F has 60% homology with IL-17A but it has 10 times less affinity for their receptors[13] (Table 1). They can form homo or heterodimers. Once they bind their cognate heterodimeric receptor IL-17RA, propagates a cascade of events that lead to neutrophil recruitment, inflammation and host defense[14]. Secretion of IL-17 is triggered and perpetuated by IL-6 and IL-23 through at least two transcription factors. The first one is Janus kinase - signal transducer and activator of transcription (JAK-STAT) and the second one is phosphoinositide-3-kinase (PI3K) through the nuclear factor-κB (NF-κB)[15,16]. STAT3 and/or NF-κB, respectively, translocate to the nucleus to promote IL-17 production (Figure 1).

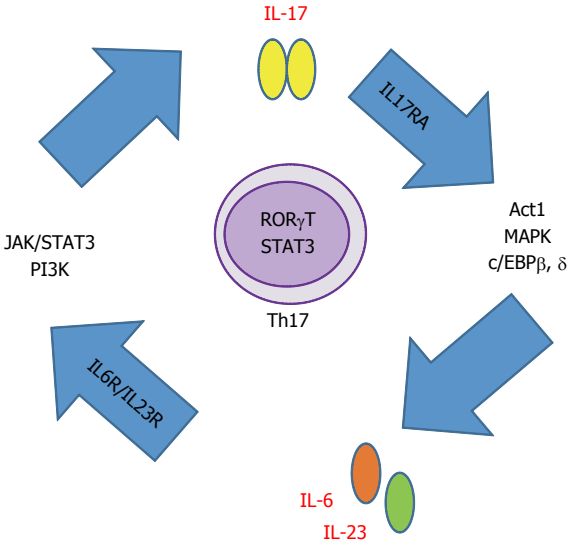

Figure 1 Interleukin-17 signaling cascade and amplification loop. IL-17 upregulates the production of pro inflammatory cytokines IL-6 and IL-23 through a complex intracellular signal involving IL-17 RA downstream Act1, MAPK and C/EBP transcription factors and kinases. IL-6 and IL-23 after binding their receptors, stimulate IL-17 production by PI3K and JAK/STAT3 that release NF-κB to translocate to the nucleus. IL-17: Interleukin-17; Act1: Activator 1; JAK/STAT3: Janus kinase/signal transducer and activator of transcription 3; PI3K: Phosphoinositide-3-kinase.

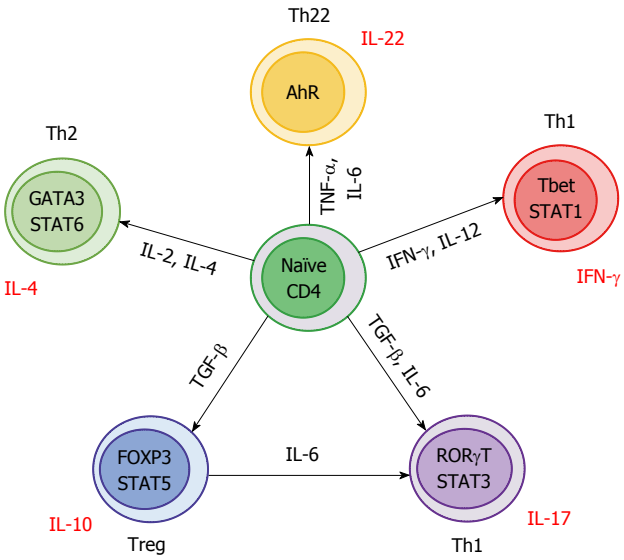

Figure 2 T cell differentiation and plasticity. A naïve CD4 T cell differentiates into different T effector cell subsets depending on the cytokines present in the enviroment. Effector T cells secrete their characteristic cytokines represented in red. In the presence of pro-inflammatory IL-6, already differentiated Tregs can switch their phenotype to Th17 and secrete IL-17. IL-17: Interleukin-17; Treg: Regulatory T cells; TGF-β: Transforming growth factor β; IFN-γ: Interferon-γ.

Regarding IL-17 receptors, there are five different heterodimeric receptors for the IL-17 family ligands. IL-17 RA is ubiquitously expressed on a wide range of tissues (liver, intestine, lung, adipose tissue) and cell types (endothelial and immune cells). IL-17RA downstream signaling involves activation of NF-κB activator 1 (Act1), CCAAT/enhancer binding protein beta (C/EBPβ), CCAAT/enhancer binding protein delta (C/EBPδ) and mitogen-activated protein kinase (MAPK) activation, followed by NF-κB and JNK nuclear translocation. Thus, leading to the production of pro-inflammatory cytokines and chemokines and subsequent myeloid cell recruitment to the inflamed tissue[15,17].

Th17 cells diversity and plasticity

Even though Th17 and T regulatory cells (Tregs) have different functions, they do share some similarities. Depending on the stimulus, both T cells populations are capable to change their regulation and function[18]. TGF-β for example, is essential for differentiation of both cell types, but in the absence of pro-inflammatory signals promotes the expansion of inducible Tregs (iTregs)[19]. On the other hand, Th17 development requires the presence of both TGF-β and IL-6[16,17].

This effect could be explained by a TGF-β concentration-dependent function. TGF-β at low concentrations acts synergistically with IL-6 and IL-21 to promote IL-23 receptor (IL-23R) expression, favoring Th17 differentiation[20,21]. On the contrary, at high concentrations, TGF-β suppresses IL-23R and Tregs development is favored by Foxp3+ expression (which in turn inhibits RORγt function)[22,23].

Several studies have established that differentiation of Foxp3+ Tregs is not static and that they can transdifferentiate into Th17 cells[24,25]. In mice, IL-6 showed to convert Foxp3+ cells into Th17 cells in the absence of TGF-β[25] (Figure 2).

IL-17 has been linked to the pathogenesis of many immune mediated diseases like psoriasis, pulmonary fibrosis, systemic sclerosis, myocardial fibrosis, systemic lupus erythematosus, inflammatory bowel disease, rhino sinusitis, encephalomyelitis, multiple sclerosis, asthma, and uveitis[7,8,26-37]. Still, the role of the Th17 pathway in human liver disease is not fully understood.

ROLE OF Th17 CELLS IN THE PROGRESSION FROM NAFLD TO NASH

The association between obesity and NAFLD/NASH implicates the crosstalk of many cells types and organs. Due to the limitation of using human samples, the best approach is to study deeply the different cell interactions in murine models.

There is evidence regarding IL-17 axis playing a broad role in multiple models of NAFLD via modulation of hepatic inflammation. Among resident hepatic cells, hepatic stellate cells (HSC), Kupffer cells, hepatocytes and endothelial cells express the IL-17RA and are known to activate inflammatory pathways which exacerbate the disease[38,39]. On the other hand, other studies showed that hepatocytes and endothelial cells do not transmit IL-17 signals despite IL-17RA expression and that they do not produce IL-17[39-41]. As regard the production of IL-17 in liver, is not only limited to CD4+

Table 2 Th17 in mouse models of liver injury

Model	Th17 cells	Th17/Tregs	IL-17 expression	Ref.
CCL4	↑	↑	↑	Meng *et al*[39] Sun *et al*[45]
BDL	↑		↑	Meng *et al*[39] Zhang *et al*[49]
MCDD	↑↑		↑	Rolla *et al*[52] Giles *et al*[53] Liu *et al*[51]
HFD	↑↑		↑	Tang *et al*[55]

IL-17: Interleukin-17; Th17: IL17 secreting T helper; Treg: Regulatory T cells; CCL4: Carbon tetrachloride; BDL: Bile duct ligation; MCDD: Methionine choline deficient diet; HFD: High fat diet.

and CD8+ T cells. Natural Killer T cells, macrophages, neutrophils, γδ T cells and Innate Lymphoid Cells are also capable of producing IL-17[39,42,43]. At least for now, only Th17 CD4 T cells, macrophages and neutrophils are known to be involved in the development of steatohepatitis inflammation process.

Th17 studies in different animal models of NAFLD

As mentioned before, the progression from NAFLD to NASH involves a wide spectrum of events such as lipid deposition, inflammation, oxidative stress, fibrosis[44]. To study the mediators involved in this process, were characterized and described several animal models.

One of the oldest model for liver fibrosis is the CCl_4 toxin-based damage. During the development of liver fibrosis by this approach, CD4+ and CD8+ T cells both exhibited increased IL-17A expression. However the major source of this interleukin was represented by neutrophils. Moreover, HSC were activated and responded by increasing IL-6, α-SMA, TNF-α and TGF-β mRNA expression[39,45,46]. Therefore, when studied the balance of Th17/Treg in the liver, it was favored toward Th17, thus promoting inflammation[45].

In vivo and *in vitro* analysis of this model demonstrated that in HSC, IL-17 increases the expression of Collagen-α1 through STAT3 signaling. Stimulation of HSCs with IL-17 results in Collagen-α1 up-regulation via IL-17RA. Moreover, in a STAT3-deficient mice, HSCs do not up-regulate Collagen-α1 in response to IL-17A, confirming that this mediator is a required target of IL-17 signaling[39,47].

Another model of liver injury is the bile duct ligation (BDL) where the bile flow is disrupted, resulting in severe inflammatory cholestatic liver injury that induces a strong fibrotic response after 21 to 28 d[48]. During the inflammatory process CD4+ T cells exhibited an increase in IL-17 expression in the liver. For the CD8+ T cells controversial results were observed, in some studies was reported that IL-17 was produced whereas others indicated the opposite[39,49]. However, neutrophils keep on representing the major source of IL-17 among the infiltrating cells in liver after BDL[49].

Inflammatory cytokines, TGF-β, IL-6, IL-1β , and TNF-α were increased after BDL, but when anti-IL-17mAb treatment or knock out (KO) IL-17RA mice was performed, a marked improvement in liver function was observed. Suppressed Kupffer cells and HSC activation (collagen-α1 production through STAT3), macrophages infiltration and decreased proinflammatory mediators level in serum and injured liver in mice were shown[39,49].

Diet induced models of liver damage have been characterized. One of the most used is the Methionine Choline deficient diet (MCDD) where steatohepatitis occurs at day 10 and fibrosis is observed by 8-10 wk in mice[50]. The main disadvantage of this model is that obesity and insulin resistance are not present. MCDD-driven NAFLD was related to increased hepatic IL-17RA expression and IL-17A/IL-17F production. Moreover, was observed an increase of Tregs (peak at 4 wk of diet) and Th17 (peak 8 wk of diet or further)[51]. When MCDD animals were treated *in-vivo* with neutralizing antibodies against CD25 or IL-17, the liver injury (measured by ALT and AST levels) was alleviated or worsen respectively. However, no evident histological changes were found[51]. On the other hand, when KO mice of IL-17RA, IL-17A or IL-17F were challenged with the diet, a reduction in proinflammatory cytokine and chemokine production, immune cell infiltration and hepatocellular damage was observed[52,53]. The anti-inflammatory and/or immune-regulatory mediators normally inhibited by the IL-17 axis were restored, for instance when IL-17A or IL-17F were missing Treg cell expansion and activation returned to normal. Rolla *et al*[52] described no changes in Treg cells but observed the presence of Th22 cells. Interestingly, was shown in IL-17 KO mice that Th22 cells seemed to be protective in NASH preventing from lipotoxicity[52].

Another widely used diet induced model of liver injury in mice is the high fat diet (HFD). Even if it is a good model for glucose intolerance and obesity, fibrosis is rarely observed and usually additional events such as LPS challenge are required to develop it. The increased oxidative stress produced in the fatty liver causes the apoptosis of Tregs, and increase the Th17 cells[54,55]. When IL-17 is neutralized in HFD mice the challenge with LPS promotes a decrease in serum transaminases levels and a reduced hepatic inflammatory cell infiltrate[55]. In *in vitro* high fat models (HepG2 and primary mice hepatocytes) the exposure to IL-17 induced a higher IL-6 release in the culture medium, higher triglyceride intracellular content and interfered insulin-signaling pathway[55] (Table 2).

Th17 studies in humans

NAFLD prevalence is higher in morbid obese (MO) patients than in the lean population, and these patients present a higher risk for developing NASH and its complications. In a prospective study that included 112 obese patients with NAFLD, the Th17/

Table 3 Th17 in human tissues

	Th17 cells	Th17/ Tregs	IL-17 expression	Disease	Ref.
Liver	↑	↑	↑	NAFLD - MO	Rau *et al*[4]
				PBC	Shi *et al*[62]
				CH - CIRR	Tan *et al*[46]
VAT			↑↑	MO	McLaughlin *et al*[59]
				MO	Zapata-Gonzalez *et al*[58]
SAT			↑	MAO	Fabbrini *et al*[57]
				MO	McLaughlin *et al*[59]
PBMC	↑↑↑	↑↑		NAFLD - MO	Rau *et al*[4]
				T2D	Zeng *et al*[60]
				Obesity	Łuczyński *et al*[64]
				PBC	Shi *et al*[62]

IL-17: Interleukin-17; Th17: IL-17 secreting T helper; Treg: Regulatory T cells; VAT: Visceral adipose tissue; SAT: Subcutaneous adipose tissue; PBMC: Peripheral blood mononuclear cells; NAFLD: Nonalcoholic fatty liver disease; MO: Morbid obesity; PBC: Primary biliary cirrhosis; CH: Chronic hepatitis; CIRR: Cirrhosis; T2D: Type II diabetes mellitus.

Tregs ratio correlated positively with NASH progression (by histology) and CK-18 expression (one of the proposed biomarkers of NAFLD progression) analyzed in peripheral blood and in intra hepatic lymphocytes. One year after bariatric surgery, there was a decrease in the Th17/Tregs ratio that became similar to healthy lean controls[4]. In Vonghia *et al*[56] prospective study, a decrease in the IL-10/IL-17A ratio marked an accentuated pro-inflammatory state in obese patients with NASH in comparison to those without NASH.

Studies with MO patients evaluated subcutaneous adipose tissue CD4 T cells content from lean, metabolically normal obese and metabolically abnormal obese subjects. They found that CD4+ gene expression was increased progressively and skewed towards Th17 phenotype. JNK activation was proposed as the mechanism responsible for IL-17 induced insulin resistance[57].

IL-17 mRNA expression from visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) of MO patients was increased in comparison to normal weight women being higher in VAT than in SAT[58]. Moreover, SAT, VAT and peripheral blood mononuclear cells (PBMC) from overweight/moderately obese and MO subjects presented a marked increase in the Th17 population (VAT higher than SAT and peripheral blood)[59]. Positive correlations between IL-17 *vs* IL-6 or Resistin at mRNA levels were found but not correlations for the percentages of Th17 cell with insulin resistance values have been established[58,59].

Contrarily to what is reported in mice[52], to our knowledge the study published by Zapata-Gonzalez *et al*[58] is the only one that reported higher plasmatic IL-17 concentration in the normal weight group than in MO patients.

Diabetes mellitus type II (T2D) is a common disorder among NAFLD patients. In the work of Zeng *et al*[60], CD4 T cells from PBMC were analyzed by flow cytometry. A reduction in the absolute number and in the percentage of Tregs was shown favoring the Th17/Tregs ratio toward Th17 cells[60]. Even though functionality of Tregs cells was conserved, their number was decreased because of impaired survival ability. Interestingly, Th17 cells were higher in patients that presented more T2D complications[57]. Conversely, no differences were found in IL-17 plasma of T2D compared to age-matched healthy controls[61].

In liver fibrosis secondary to primary biliary cirrhosis (PBC), patients presented higher peripheral Th17 cells when compared to healthy controls. In the liver, IL-17+ cells gathered around the portal areas[62]. Furthermore, in cirrhotic liver tissue IL-17+ cell infiltration was higher than controls[46].

In vitro studies of human hepatic stellate cells (HSC) exposed to IL-17 showed a dose dependent activation and proliferation response that was neutralized by an IL-17 antagonist[62]. Fabre *et al*[63] evaluated HSC activation (LX2 cell line and primary human hepatic stellate cells) by IL-17. They observed that IL-17 by itself was insufficient to activate the cells, but when combined with a suboptimal TGF-β dose generated a strong activation enhancing TGF-β response by increasing cell surface expression of its receptor and the profibrotic signaling[63].

Regarding the pediatric population, much less is known; we found only a study conducted by Łuczyński *et al*[64] in children with central obesity. They showed higher percentages of Th17 cells in the peripheral blood in comparison with healthy lean children[61]. In other pediatric diseases these T cells were involved, principally in inflammation, such as autoimmune thyroid disease or Mycoplasma pneumoniae infection[65,66] (Table 3).

CONCLUSION

A pro-inflammatory state is crucial for the initiation and maintenance of inflammation in the onset and progression of NAFLD/NASH. T cells resident in non-lymphoid tissues are able to regulate local inflammation by modulating immunological and non-immunological responses. Many studies in different animal models have proved the important role of the Th17 pathway in inflammation and HSC activation. Much less is known about human physiopathology of NAFLD due to the limitations and difficulty to obtain samples. Studies with obese or diabetic patients obtained higher Th17 cells in blood with no changes or decrease in Tregs. If IL-17 is elevated or not in plasma is still controversial. Adipose tissue and intrahepatic Th17 lymphocyte subsets have been assessed in NAFLD/obese/PBC patients, being higher compared to control individuals.

It has been widely argued if inflammation occurs first in liver than in adipose tissue or the other way around. Until now, this is still unraveled but it is

known that the adipose tissue inflammation and their adipokines, free fatty acids, and gut derived microbial products could promote Th17 differentiation in the liver, with the consequent imbalance towards inflammation. Obesity may maintain a positive feedback loop that promotes Th17 survival in the inflamed liver. This would explain how weight loss after bariatric surgery can reverse clinical and histopathological features of NASH. On the other hand, it seems that the T cell imbalance occurs in situ, but to date there is not enough evidence to explain the connection between adipose tissue inflammation and hepatic injury progression.

Studies that analyze the crosstalk between the different organs during the NAFLD/NASH progression should be promoted in order to evaluate and establish the main players in this disease.

Although there is evidence that implicates the Th17 pathway as a key player in the progression of NALFD, it seems that there is a lot more to be elucidated. Plasticity of this cell subtype may render it a therapeutic target.

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