

World Journal of *Gastroenterology*

World J Gastroenterol 2016 November 7; 22(41): 9039-9250



**EDITORIAL**

- 9039** Emerging role of obeticholic acid in the management of nonalcoholic fatty liver disease

Makri E, Cholongitas E, Tziomalos K

REVIEW

- 9044** Concise review: Interferon-free treatment of hepatitis C virus-associated cirrhosis and liver graft infection

Weiler N, Zeuzem S, Welker MW

- 9057** Mesenchymal stromal cell-based therapy: Regulatory and translational aspects in gastroenterology

Dothel G, Raschi E, Rimondini R, De Ponti F

- 9069** Genetic alterations in hepatocellular carcinoma: An update

Niu ZS, Niu XJ, Wang WH

MINIREVIEWS

- 9096** Th17 involvement in nonalcoholic fatty liver disease progression to non-alcoholic steatohepatitis

Chackelevicius CM, Gambaro SE, Tiribelli C, Rosso N

ORIGINAL ARTICLE**Basic Study**

- 9104** Dysregulation of innate immunity in ulcerative colitis patients who fail anti-tumor necrosis factor therapy

Baird AC, Mallon D, Radford-Smith G, Boyer J, Piche T, Prescott SL, Lawrance IC, Tulic MK

- 9117** Altered pattern of tumor necrosis factor-alpha production in peripheral blood monocytes from Crohn's disease

Loganes C, Pin A, Naviglio S, Girardelli M, Bianco AM, Martelossi S, Tommasini A, Piscianz E

- 9127** Esophagogastric anastomosis in rats: Improved healing by BPC 157 and L-arginine, aggravated by L-NAME

Djakovic Z, Djakovic I, Cesarec V, Madzarac G, Becejac T, Zukanovic G, Drmic D, Batelja L, Zenko Sever A, Kolenc D, Pajtak A, Knez N, Japjec M, Luetic K, Stancic-Rokotov D, Seiwert S, Sikiric P

- 9141** HER2-induced metastasis is mediated by AKT/JNK/EMT signaling pathway in gastric cancer

Choi Y, Ko YS, Park JJ, Choi Y, Kim Y, Pyo JS, Jang BG, Hwang DH, Kim WH, Lee BL

Retrospective Cohort Study

- 9154 Effect of airplane transport of donor livers on post-liver transplantation survival

Huang Y, MacQuillan G, Adams LA, Garas G, Collins M, Nwaba A, Mou L, Bulsara MK, Delriviere L, Jeffrey GP

Retrospective Study

- 9162 First-line endoscopic treatment with over-the-scope clips significantly improves the primary failure and rebleeding rates in high-risk gastrointestinal bleeding: A single-center experience with 100 cases

Richter-Schrag HJ, Glatz T, Walker C, Fischer A, Thimme R

- 9172 Presepsin teardown - pitfalls of biomarkers in the diagnosis and prognosis of bacterial infection in cirrhosis

Papp M, Tornai T, Vitalis Z, Tornai I, Tornai D, Dinya T, Sumegi A, Antal-Szalmas P

- 9186 Impact of IL28B and OAS gene family polymorphisms on interferon treatment response in Caucasian children chronically infected with hepatitis B virus

Domagalski K, Pawłowska M, Zalesna A, Pilarczyk M, Rajewski P, Halota W, Tretyn A

- 9196 Simplified criteria for diagnosing superficial esophageal squamous neoplasms using Narrow Band Imaging magnifying endoscopy

Dobashi A, Goda K, Yoshimura N, Ohya TR, Kato M, Sumiyama K, Matsushima M, Hirooka S, Ikegami M, Tajiri H

- 9205 Assessment of scoring systems for acute-on-chronic liver failure at predicting short-term mortality in patients with alcoholic hepatitis

Kim HY, Kim CW, Kim TY, Song DS, Sinn DH, Yoon EL, Jung YK, Suk KT, Lee SS, Lee CH, Kim TH, Kim JH, Yim HJ, Kim SE, Baik SK, Lee BS, Jang JY, Kim YS, Kim SG, Yang JM, Sohn JH, Lee HJ, Park SH, Choi EH, Kim DJ;
Korean Acute-on-Chronic Liver Failure Study Group

Prospective Study

- 9214 Molecular detection of *Helicobacter pylori* antibiotic resistance in stool vs biopsy samples

Brennan DE, Omorogbe J, Hussey M, Tighe D, Holleran G, O'Morain C, Smith SM, McNamara D

CASE REPORT

- 9222 Two cases of pancreatic ductal adenocarcinoma with intrapancreatic metastasis

Fujita Y, Kitago M, Masugi Y, Itano O, Shinoda M, Abe Y, Hibi T, Yagi H, Fujii-Nishimura Y, Sakamoto M, Kitagawa Y

- 9229 Collision tumor of hepatocellular carcinoma and neuroendocrine carcinoma involving the liver: Case report and review of the literature

Choi GH, Ann SY, Lee SI, Kim SB, Song IH

- 9235** Reoperation in an adult female with "right-sided" Hirschsprung's disease complicated by refractory hypertension and cough

Wei ZJ, Huang L, Xu AM

- 9242** Metabolic imaging for guidance of curative treatment of isolated pelvic implantation metastasis after resection of spontaneously ruptured hepatocellular carcinoma: A case report

Hao B, Guo W, Luo NN, Fu H, Chen HJ, Zhao L, Wu H, Sun L

Letters to The Editor

- 9247** Hepatic epithelioid hemangioendothelioma: Dilemma and challenges in the preoperative diagnosis

Hu HJ, Jin YW, Jing QY, Shrestha A, Cheng NS, Li FY

ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Peng Hou, PhD, Professor, Department of Endocrinology, The First Affiliated Hospital of Xi'an Jiaotong University School of Medicine, Xi'an 710061, Shaanxi Province, China

AIMS AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 1375 experts in gastroenterology and hepatology from 68 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

INDEXING/ABSTRACTING

World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents[®]/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch[®]), Journal Citation Reports[®], Index Medicus, MEDLINE, PubMed, PubMed Central, Digital Object Identifier, and Directory of Open Access Journals. The 2015 edition of Journal Citation Reports[®] released by Thomson Reuters (ISI) cites the 2015 impact factor for *WJG* as 2.787 (5-year impact factor: 2.848), ranking *WJG* as 38 among 78 journals in gastroenterology and hepatology (quartile in category Q2).

FLYLEAF

I-IX Editorial Board

EDITORS FOR
THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Cai-Hong Wang*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Jing Yu*
Proofing Editorial Office Director: *Jin-Lei Wang*

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Damian Garcia-Olmo, MD, PhD, Doctor, Professor, Surgeon, Department of Surgery, Universidad Autonoma de Madrid; Department of General Surgery, Fundacion Jimenez Diaz University Hospital, Madrid 28040, Spain

Stephen C Strom, PhD, Professor, Department of Laboratory Medicine, Division of Pathology, Karolinska Institutet, Stockholm 141-86, Sweden

Andrzej S Tarnawski, MD, PhD, DSc (Med), Professor of Medicine, Chief Gastroenterology, VA Long Beach Health Care System, University of Cali-

fornia, Irvine, CA, 5901 E. Seventh Str., Long Beach, CA 90822, United States

EDITORIAL BOARD MEMBERS
All editorial board members resources online at <http://www.wjgnet.com/1007-9327/editorialboard.htm>

EDITORIAL OFFICE
Jin-Lei Wang, Director
Yuan Qi, Vice Director
World Journal of Gastroenterology
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

PUBLICATION DATE
November 7, 2016

COPYRIGHT
© 2016 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS
Full instructions are available online at <http://www.wjgnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION
<http://www.wjgnet.com/esps/>

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

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

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

Author contributions: Chackelevecius CM and Rosso N designed the research; Chackelevecius CM and Gambaro SE analyzed data and wrote the manuscript; Tiribelli C participated in the writing and revision of the manuscript; Rosso N revised the study and the manuscript.

Supported by the PhD Fellowship from the Italian Ministry of Foreign Affairs to Chackelevecius CM.

Conflict-of-interest statement: The authors have no conflict of interest to report in this work.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

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

Received: June 17, 2016
Peer-review started: June 19, 2016
First decision: August 8, 2016
Revised: August 22, 2016
Accepted: September 14, 2016
Article in press: September 14, 2016
Published online: November 7, 2016

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 macrophages (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

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

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.

Chackelevicius CM, Gambaro SE, Tiribelli C, Rosso N. Th17 involvement in nonalcoholic fatty liver disease progression to non-alcoholic steatohepatitis. *World J Gastroenterol* 2016; 22(41): 9096-9103 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v22/i41/9096.htm> DOI: <http://dx.doi.org/10.3748/wjg.v22.i41.9096>

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 macrophages (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"

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.

"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.

Th17 CELLS

Th17 differentiation

CD4 T helper cells that recognize antigens in the context of Major 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-1 β , 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 anti-microbial 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 one is phosphoinositide-3-kinase (PI3K) through the nuclear factor- κ B (NF- κ B)^[15,16]. STAT3 and/or NF- κ B, respectively, translocate to the nucleus to promote IL-17 production (Figure 1).

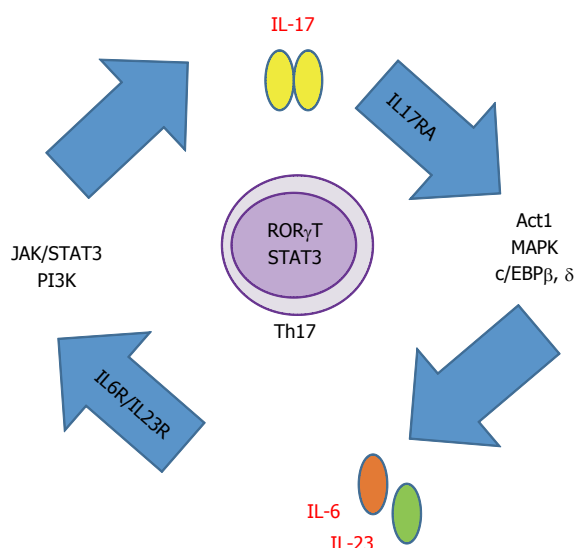


Figure 1 Interleukin-17 signaling cascade and amplification loop. IL-17 upregulates the production of pro inflammatory cytokines IL-6 and IL-23 through a complex intracellular signal involving IL-17 RA downstream Act1, MAPK and C/EBP transcription factors and kinases. IL-6 and IL-23 after binding their receptors, stimulate IL-17 production by PI3K and JAK/STAT3 that release NF- κ B 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.

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- κ B activator 1 (Act1), CCAAT/enhancer binding protein beta (C/EBP β), CCAAT/enhancer binding protein delta (C/EBP δ) and mitogen-activated protein kinase (MAPK) activation, followed by NF- κ B 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 ROR γ t function)^[22,23].

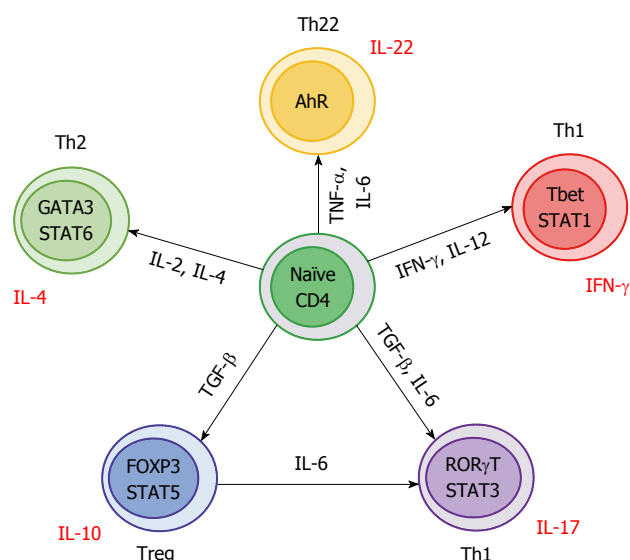


Figure 2 T cell differentiation and plasticity. A naïve CD4 T cell differentiates into different T effector cell subsets depending on the cytokines present in the environment. Effector T cells secrete their characteristic cytokines represented in red. In the presence of pro-inflammatory IL-6, already 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 .

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

Table 2 Th17 in mouse models of liver injury

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

limited to CD4+ and CD8+ T cells. Natural Killer T cells, macrophages, neutrophils, $\gamma\delta$ T cells and Innate Lymphoid Cells also 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 CCL4 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- α 1 through STAT3 signaling. Stimulation of HSCs with IL-17 results in Collagen- α 1 up-regulation via IL-17RA. Moreover, in a STAT3-deficient mice, HSCs do not up-regulate Collagen- α 1 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-1 β , 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- α 1 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 IL17 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 <i>et al</i> ^[4]
				PBC	Shi <i>et al</i> ^[62]
				CH - CIRR	Tan <i>et al</i> ^[46]
VAT			↑↑	MO	McLaughlin <i>et al</i> ^[59]
				MO	Zapata-Gonzalez <i>et al</i> ^[58]
SAT			↑	MAO	Fabbrini <i>et al</i> ^[57]
				MO	McLaughlin <i>et al</i> ^[59]
PBMC	↑↑↑	↑↑		NAFLD - MO	Rau <i>et al</i> ^[4]
				T2D	Zeng <i>et al</i> ^[60]
				Obesity	Łuczynski <i>et al</i> ^[64]
				PBC	Shi <i>et al</i> ^[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+ cells infiltration were 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 Łuczynski *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 this 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 is been widely argued if the 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.

REFERENCES

- Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ; American Association for the Study of Liver Diseases, American College of Gastroenterology, American Gastroenterological Association. The diagnosis and management of non-alcoholic fatty liver disease: Practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Am J Gastroenterol* 2012; **107**: 811-826 [PMID: 22641309 DOI: 10.1038/ajg.2012.128]
- LaBrecque DR, Abbas Z, Anania F, Ferenci P, Khan AG, Goh KL, Hamid SS, Isakov V, Lizarzabal M, Peñaranda MM, Ramos JF, Sarin S, Stimac D, Thomson AB, Umar M, Krabshuis J, LeMair A. World Gastroenterology Organisation global guidelines: Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *J Clin Gastroenterol* 2014; **48**: 467-473 [PMID: 24921212 DOI: 10.1097/MCG.0000000000000116]
- Marra F, Lotersztajn S. Pathophysiology of NASH: perspectives for a targeted treatment. *Curr Pharm Des* 2013; **19**: 5250-5269 [PMID: 23394092]
- Rau M, Schilling AK, Meertens J, Hering I, Weiss J, Jurowich C, Kudlich T, Hermanns HM, Bantel H, Beyersdorf N, Geier A. Progression from Nonalcoholic Fatty Liver to Nonalcoholic Steatohepatitis Is Marked by a Higher Frequency of Th17 Cells in the Liver and an Increased Th17/Resting Regulatory T Cell Ratio in Peripheral Blood and in the Liver. *J Immunol* 2016; **196**: 97-105 [PMID: 26621860 DOI: 10.4049/jimmunol.1501175]
- Harley IT, Stankiewicz TE, Giles DA, Softic S, Flick LM, Cappelletti M, Sheridan R, Xanthakos SA, Steinbrecher KA, Sartor RB, Kohli R, Karp CL, Divanovic S. IL-17 signaling accelerates the progression of nonalcoholic fatty liver disease in mice. *Hepatology* 2014; **59**: 1830-1839 [PMID: 24115079 DOI: 10.1002/hep.26746]
- Nati M, Haddad D, Birkenfeld AL, Koch CA, Chavakis T, Chatzigeorgiou A; World Gastroenterology Organisation. The role of immune cells in metabolism-related liver inflammation and development of non-alcoholic steatohepatitis (NASH). *Rev Endocr Metab Disord* 2016; **17**: 29-39 [PMID: 26847547 DOI: 10.1007/s11154-016-9339-2]
- Rother N, van der Vlag J. Disturbed T Cell Signaling and Altered Th17 and Regulatory T Cell Subsets in the Pathogenesis of Systemic Lupus Erythematosus. *Front Immunol* 2015; **6**: 610 [PMID: 26648939 DOI: 10.3389/fimmu.2015.00610]
- Marinoni B, Ceribelli A, Massarotti MS, Selmi C. The Th17 axis in psoriatic disease: pathogenetic and therapeutic implications. *Auto Immun Highlights* 2014; **5**: 9-19 [PMID: 26000152 DOI: 10.1007/s13317-013-0057-4]
- Steinman L. A brief history of T(H)17, the first major revision in the T(H)1/T(H)2 hypothesis of T cell-mediated tissue damage. *Nat Med* 2007; **13**: 139-145 [PMID: 17290272 DOI: 10.1038/nm1551]
- Stockinger B, Veldhoen M, Martin B. Th17 T cells: linking innate and adaptive immunity. *Semin Immunol* 2007; **19**: 353-361 [PMID: 18023589 DOI: 10.1016/j.smim.2007.10.008]
- Hammerich L, Heymann F, Tacke F. Role of IL-17 and Th17 cells in liver diseases. *Clin Dev Immunol* 2011; **2011**: 345803 [PMID: 21197451 DOI: 10.1155/2011/345803]
- Gaffen SL. An overview of IL-17 function and signaling. *Cytokine* 2008; **43**: 402-407 [PMID: 18701318 DOI: 10.1016/j.cyto.2008.07.017]
- Shen F, Gaffen SL. Structure-function relationships in the IL-17 receptor: implications for signal transduction and therapy. *Cytokine* 2008; **41**: 92-104 [PMID: 18178098 DOI: 10.1016/j.cyto.2007.11.013]
- Gu C, Wu L, Li X. IL-17 family: cytokines, receptors and signaling. *Cytokine* 2013; **64**: 477-485 [PMID: 24011563 DOI: 10.1016/j.cyto.2013.07.022]
- Eljaafari A, Robert M, Chehimi M, Chanon S, Durand C, Vial G, Bendridi N, Madec AM, Disse E, Laville M, Rieusset J, Lefai E, Vidal H, Pirola L. Adipose Tissue-Derived Stem Cells From Obese Subjects Contribute to Inflammation and Reduced Insulin Response in Adipocytes Through Differential Regulation of the Th1/Th17 Balance and Monocyte Activation. *Diabetes* 2015; **64**: 2477-2488 [PMID: 25765019 DOI: 10.2337/db15-0162]
- Cho ML, Kang JW, Moon YM, Nam HJ, Jhun JY, Heo SB, Jin HT, Min SY, Ju JH, Park KS, Cho YG, Yoon CH, Park SH, Sung YC, Kim HY. STAT3 and NF-kappaB signal pathway is required for IL-23-mediated IL-17 production in spontaneous arthritis animal model IL-1 receptor antagonist-deficient mice. *J Immunol* 2006; **176**: 5652-5661 [PMID: 16622035]
- Chang SH, Dong C. Signaling of interleukin-17 family cytokines in immunity and inflammation. *Cell Signal* 2011; **23**: 1069-1075 [PMID: 21130872 DOI: 10.1016/j.cellsig.2010.11.022]
- Brucklacher-Waldert V, Carr EJ, Linterman MA, Veldhoen M. Cellular Plasticity of CD4+ T Cells in the Intestine. *Front Immunol* 2014; **5**: 488 [PMID: 25339956 DOI: 10.3389/fimmu.2014.00488]
- Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M, Weiner HL, Kuchroo VK. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. *Nature* 2006; **441**: 235-238 [PMID: 16648838 DOI: 10.1038/nature04753]
- Zhou L, Ivanov II, Spolski R, Min R, Shenderov K, Egawa T, Levy DE, Leonard WJ, Littman DR. IL-6 programs T(H)-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways. *Nat Immunol* 2007; **8**: 967-974 [PMID: 17581537 DOI: 10.1038/ni1488]
- Korn T, Bettelli E, Gao W, Awasthi A, Jäger A, Strom TB, Oukka M, Kuchroo VK. IL-21 initiates an alternative pathway to induce proinflammatory T(H)17 cells. *Nature* 2007; **448**: 484-487 [PMID: 17581588 DOI: 10.1038/nature05970]
- Ueno A, Ghosh A, Hung D, Li J, Jijon H. Th17 plasticity and its changes associated with inflammatory bowel disease. *World J Gastroenterol* 2015; **21**: 12283-12295 [PMID: 26604637 DOI: 10.3748/wjg.v21.i43.12283]
- Zhou L, Lopes JE, Chong MM, Ivanov II, Min R, Victora GD, Shen Y, Du J, Rubtsov YP, Rudensky AY, Ziegler SF, Littman DR. TGF-beta-induced Foxp3 inhibits T(H)17 cell differentiation by antagonizing RORgamma function. *Nature* 2008; **453**: 236-240 [PMID: 18368049 DOI: 10.1038/nature06878]
- Omenetti S, Pizarro TT. The Treg/Th17 Axis: A Dynamic Balance Regulated by the Gut Microbiome. *Front Immunol* 2015; **6**: 639 [PMID: 26734006 DOI: 10.3389/fimmu.2015.00639]
- Xu L, Kitani A, Fuss I, Strober W. Cutting edge: regulatory T cells

- induce CD4+CD25-Foxp3- T cells or are self-induced to become Th17 cells in the absence of exogenous TGF-beta. *J Immunol* 2007; **178**: 6725-6729 [PMID: 17513718]
- 26 **Wilson MS**, Madala SK, Ramalingam TR, Gochoico BR, Rosas IO, Cheever AW, Wynn TA. Bleomycin and IL-1beta-mediated pulmonary fibrosis is IL-17A dependent. *J Exp Med* 2010; **207**: 535-552 [PMID: 20176803 DOI: 10.1084/jem.20092121]
 - 27 **Gasse P**, Riteau N, Vacher R, Michel ML, Fautrel A, di Padova F, Fick L, Charron S, Lagente V, Eberl G, Le Bert M, Quesniaux VF, Huaux F, Leite-de-Moraes M, Ryffel B, Couillin I. IL-1 and IL-23 mediate early IL-17A production in pulmonary inflammation leading to late fibrosis. *PLoS One* 2011; **6**: e23185 [PMID: 21858022 DOI: 10.1371/journal.pone.0023185]
 - 28 **Okamoto Y**, Hasegawa M, Matsushita T, Hamaguchi Y, Huu DL, Iwakura Y, Fujimoto M, Takehara K. Potential roles of interleukin-17A in the development of skin fibrosis in mice. *Arthritis Rheum* 2012; **64**: 3726-3735 [PMID: 22833167 DOI: 10.1002/art.34643]
 - 29 **Feng W**, Li W, Liu W, Wang F, Li Y, Yan W. IL-17 induces myocardial fibrosis and enhances RANKL/OPG and MMP/TIMP signaling in isoproterenol-induced heart failure. *Exp Mol Pathol* 2009; **87**: 212-218 [PMID: 19527710 DOI: 10.1016/j.yexmp.2009.06.001]
 - 30 **Cătană CS**, Berindan Neagoe I, Cozma V, Magdaş C, Tăbăran F, Dumitraşcu DL. Contribution of the IL-17/IL-23 axis to the pathogenesis of inflammatory bowel disease. *World J Gastroenterol* 2015; **21**: 5823-5830 [PMID: 26019446 DOI: 10.3748/wjg.v21.i19.5823]
 - 31 **Gálvez J**. Role of Th17 Cells in the Pathogenesis of Human IBD. *ISRN Inflamm* 2014; **2014**: 928461 [PMID: 25101191 DOI: 10.1155/2014/928461]
 - 32 **Kolbinger F**, Huppertz C, Mir A, Di Padova F. IL-17A and multiple sclerosis: signaling pathways, producing cells and target cells in the central nervous system. *Curr Drug Targets* 2016; Epub ahead of print [PMID: 26953244]
 - 33 **Melnikov M**, Belousova O, Murugin V, Pashenkov M, Boyko A. The role of dopamine in modulation of Th-17 immune response in multiple sclerosis. *J Neuroimmunol* 2016; **292**: 97-101 [PMID: 26943966 DOI: 10.1016/j.jneuroim.2016.01.020]
 - 34 **Dos Passos GR**, Sato DK, Becker J, Fujihara K. Th17 Cells Pathways in Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorders: Pathophysiological and Therapeutic Implications. *Mediators Inflamm* 2016; **2016**: 5314541 [PMID: 26941483 DOI: 10.1155/2016/5314541]
 - 35 **Qin L**, Feng J, Hu C, Li Y, Niu R. [Th17/Treg imbalance mediated by IL-8 in RSV-infected bronchial epithelial cells]. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2016; **41**: 337-344 [PMID: 27241142 DOI: 10.11817/j.issn.1672-7347.2016.04.001]
 - 36 **Gavino AC**, Nahmod K, Bharadwaj U, Makedonas G, Tweardy DJ. STAT3 inhibition prevents lung inflammation, remodeling, and accumulation of Th2 and Th17 cells in a murine asthma model. *Allergy* 2016; Epub ahead of print [PMID: 27225906 DOI: 10.1111/all.12937]
 - 37 **Bi HS**, Liu ZF, Cui Y. Pathogenesis of innate immunity and adaptive immunity in the mouse model of experimental autoimmune uveitis. *J Chin Med Assoc* 2015; **78**: 276-282 [PMID: 25769932 DOI: 10.1016/j.jcma.2015.01.002]
 - 38 **Peverill W**, Powell LW, Skoien R. Evolving concepts in the pathogenesis of NASH: beyond steatosis and inflammation. *Int J Mol Sci* 2014; **15**: 8591-8638 [PMID: 24830559 DOI: 10.3390/ijms15058591]
 - 39 **Meng F**, Wang K, Aoyama T, Grivennikov SI, Paik Y, Scholten D, Cong M, Iwaisako K, Liu X, Zhang M, Osterreicher CH, Stickel F, Ley K, Brenner DA, Kisseleva T. Interleukin-17 signaling in inflammatory, Kupffer cells, and hepatic stellate cells exacerbates liver fibrosis in mice. *Gastroenterology* 2012; **143**: 765-766.e1-3 [PMID: 22687286 DOI: 10.1053/j.gastro.2012.05.049]
 - 40 **Kang Z**, Altuntas CZ, Gulen MF, Liu C, Giltiay N, Qin H, Liu L, Qian W, Ransohoff RM, Bergmann C, Stohman S, Tuohy VK, Li X. Astrocyte-restricted ablation of interleukin-17-induced Act1-mediated signaling ameliorates autoimmune encephalomyelitis. *Immunity* 2010; **32**: 414-425 [PMID: 20303295 DOI: 10.1016/j.immuni.2010.03.004]
 - 41 **Zenewicz LA**, Yancopoulos GD, Valenzuela DM, Murphy AJ, Karow M, Flavell RA. Interleukin-22 but not interleukin-17 provides protection to hepatocytes during acute liver inflammation. *Immunity* 2007; **27**: 647-659 [PMID: 17919941 DOI: 10.1016/j.immuni.2007.07.023]
 - 42 **Jie Z**, Liang Y, Hou L, Dong C, Iwakura Y, Soong L, Cong Y, Sun J. Intrahepatic innate lymphoid cells secrete IL-17A and IL-17F that are crucial for T cell priming in viral infection. *J Immunol* 2014; **192**: 3289-3300 [PMID: 24600029 DOI: 10.4049/jimmunol.1303281]
 - 43 **Cua DJ**, Tato CM. Innate IL-17-producing cells: the sentinels of the immune system. *Nat Rev Immunol* 2010; **10**: 479-489 [PMID: 20559326 DOI: 10.1038/nri2800]
 - 44 **Rosso N**, Chavez-Tapia NC, Tiribelli C, Bellentani S. Translational approaches: from fatty liver to non-alcoholic steatohepatitis. *World J Gastroenterol* 2014; **20**: 9038-9049 [PMID: 25083077 DOI: 10.3748/wjg.v20.i27.9038]
 - 45 **Sun XF**, Gu L, Deng WS, Xu Q. Impaired balance of T helper 17/T regulatory cells in carbon tetrachloride-induced liver fibrosis in mice. *World J Gastroenterol* 2014; **20**: 2062-2070 [PMID: 24616573 DOI: 10.3748/wjg.v20.i8.2062]
 - 46 **Tan Z**, Qian X, Jiang R, Liu Q, Wang Y, Chen C, Wang X, Ryffel B, Sun B. IL-17A plays a critical role in the pathogenesis of liver fibrosis through hepatic stellate cell activation. *J Immunol* 2013; **191**: 1835-1844 [PMID: 23842754 DOI: 10.4049/jimmunol.1203013]
 - 47 **Ogata H**, Chinen T, Yoshida T, Kinjo I, Takaesu G, Shiraishi H, Iida M, Kobayashi T, Yoshimura A. Loss of SOCS3 in the liver promotes fibrosis by enhancing STAT3-mediated TGF-beta1 production. *Oncogene* 2006; **25**: 2520-2530 [PMID: 16474852 DOI: 10.1038/sj.onc.1209281]
 - 48 **Tag CG**, Sauer-Lehnen S, Weiskirchen S, Borkham-Kamphorst E, Tolba RH, Tacke F, Weiskirchen R. Bile duct ligation in mice: induction of inflammatory liver injury and fibrosis by obstructive cholestasis. *J Vis Exp* 2015; **(96)**: [PMID: 25741630 DOI: 10.3791/52438]
 - 49 **Zhang S**, Huang D, Weng J, Huang Y, Liu S, Zhang Q, Li N, Wen M, Zhu G, Lin F, Gu W. Neutralization of Interleukin-17 Attenuates Cholestatic Liver Fibrosis in Mice. *Scand J Immunol* 2016; **83**: 102-108 [PMID: 26484852 DOI: 10.1111/sji.12395]
 - 50 **Caballero F**, Fernández A, Matías N, Martínez L, Fúcho R, Elena M, Caballeria J, Morales A, Fernández-Checa JC, García-Ruiz C. Specific contribution of methionine and choline in nutritional nonalcoholic steatohepatitis: impact on mitochondrial S-adenosyl-L-methionine and glutathione. *J Biol Chem* 2010; **285**: 18528-18536 [PMID: 20395294 DOI: 10.1074/jbc.M109.099333]
 - 51 **Liu Y**, She W, Wang F, Li J, Wang J, Jiang W. 3, 3'-Diindolylmethane alleviates steatosis and the progression of NASH partly through shifting the imbalance of Treg/Th17 cells to Treg dominance. *Int Immunopharmacol* 2014; **23**: 489-498 [PMID: 25281898 DOI: 10.1016/j.intimp.2014.09.024]
 - 52 **Rolla S**, Alchera E, Imarisio C, Bardina V, Valente G, Cappello P, Mombello C, Follenzi A, Novelli F, Carini R. The balance between IL-17 and IL-22 produced by liver-infiltrating T-helper cells critically controls NASH development in mice. *Clin Sci (Lond)* 2016; **130**: 193-203 [PMID: 26558403 DOI: 10.1042/CS20150405]
 - 53 **Giles DA**, Moreno-Fernandez ME, Stankiewicz TE, Cappelletti M, Huppert SS, Iwakura Y, Dong C, Shanmukhappa SK, Divanovic S. Regulation of Inflammation by IL-17A and IL-17F Modulates Non-Alcoholic Fatty Liver Disease Pathogenesis. *PLoS One* 2016; **11**: e0149783 [PMID: 26895034 DOI: 10.1371/journal.pone.0149783]
 - 54 **Ma X**, Hua J, Mohamood AR, Hamad AR, Ravi R, Li Z. A high-fat diet and regulatory T cells influence susceptibility to endotoxin-induced liver injury. *Hepatology* 2007; **46**: 1519-1529 [PMID: 17661402 DOI: 10.1002/hep.21823]
 - 55 **Tang Y**, Bian Z, Zhao L, Liu Y, Liang S, Wang Q, Han X, Peng Y,

- Chen X, Shen L, Qiu D, Li Z, Ma X. Interleukin-17 exacerbates hepatic steatosis and inflammation in non-alcoholic fatty liver disease. *Clin Exp Immunol* 2011; **166**: 281-290 [PMID: 21985374 DOI: 10.1111/j.1365-2249.2011.04471.x]
- 56 **Vonghia L**, Magrone T, Verrijken A, Michielsen P, Van Gaal L, Jirillo E, Francque S. Peripheral and Hepatic Vein Cytokine Levels in Correlation with Non-Alcoholic Fatty Liver Disease (NAFLD)-Related Metabolic, Histological, and Haemodynamic Features. *PLoS One* 2015; **10**: e0143380 [PMID: 26599575 DOI: 10.1371/journal.pone.0143380]
- 57 **Fabbrini E**, Cella M, McCartney SA, Fuchs A, Abumrad NA, Pietka TA, Chen Z, Finck BN, Han DH, Magkos F, Conte C, Bradley D, Fraterrigo G, Eagon JC, Patterson BW, Colonna M, Klein S. Association between specific adipose tissue CD4⁺ T-cell populations and insulin resistance in obese individuals. *Gastroenterology* 2013; **145**: 366-374.e1-3 [PMID: 23597726 DOI: 10.1053/j.gastro.2013.04.010]
- 58 **Zapata-Gonzalez F**, Auguet T, Aragonès G, Guiu-Jurado E, Berlanga A, Martinez S, Martí A, Sabench F, Hernandez M, Aguilar C, Sirvent JJ, Jorba R, Del Castillo D, Richart C. Interleukin-17A Gene Expression in Morbidly Obese Women. *Int J Mol Sci* 2015; **16**: 17469-17481 [PMID: 26263971 DOI: 10.3390/ijms160817469]
- 59 **McLaughlin T**, Liu LF, Lamendola C, Shen L, Morton J, Rivas H, Winer D, Tolentino L, Choi O, Zhang H, Hui Yen Chng M, Engleman E. T-cell profile in adipose tissue is associated with insulin resistance and systemic inflammation in humans. *Arterioscler Thromb Vasc Biol* 2014; **34**: 2637-2643 [PMID: 25341798 DOI: 10.1161/ATVBAHA.114.304636]
- 60 **Zeng C**, Shi X, Zhang B, Liu H, Zhang L, Ding W, Zhao Y. The imbalance of Th17/Th1/Tregs in patients with type 2 diabetes: relationship with metabolic factors and complications. *J Mol Med (Berl)* 2012; **90**: 175-186 [PMID: 21964948 DOI: 10.1007/s00109-011-0816-5]
- 61 **Roohi A**, Tabrizi M, Abbasi F, Ataie-Jafari A, Nikbin B, Larijani B, Qorbani M, Meysamie A, Asgarian-Omran H, Nikmanesh B, Bajouri A, Shafiey N, Maleki A. Serum IL-17, IL-23, and TGF- β levels in type 1 and type 2 diabetic patients and age-matched healthy controls. *Biomed Res Int* 2014; **2014**: 718946 [PMID: 24995325 DOI: 10.1155/2014/718946]
- 62 **Shi T**, Zhang T, Zhang L, Yang Y, Zhang H, Zhang F. The Distribution and the Fibrotic Role of Elevated Inflammatory Th17 Cells in Patients With Primary Biliary Cirrhosis. *Medicine (Baltimore)* 2015; **94**: e1888 [PMID: 26554784 DOI: 10.1097/MD.0000000000001888]
- 63 **Fabre T**, Kared H, Friedman SL, Shoukry NH. IL-17A enhances the expression of profibrotic genes through upregulation of the TGF- β receptor on hepatic stellate cells in a JNK-dependent manner. *J Immunol* 2014; **193**: 3925-3933 [PMID: 25210118 DOI: 10.4049/jimmunol.1400861]
- 64 **Łuczyński W**, Grubczak K, Moniuszko M, Głowińska-Olszewska B, Bossowski A. Elevated levels of Th17 cells in children with central obesity. *Scand J Clin Lab Invest* 2015; **75**: 595-601 [PMID: 26216210 DOI: 10.3109/00365513.2015.1066845]
- 65 **Bossowski A**, Moniuszko M, Idzkowska E, Grubczak K, Singh P, Bossowska A, Diana T, Kahaly GJ. Decreased proportions of CD4⁺ IL17⁺/CD4⁺ CD25⁺ CD127⁻ and CD4⁺ IL17⁺/CD4⁺ CD25⁺ CD127⁻ FoxP3⁺ T cells in children with autoimmune thyroid diseases (.). *Autoimmunity* 2016; **49**: 320-328 [PMID: 27206624 DOI: 10.1080/08916934.2016.1183654]
- 66 **Wang X**, Chen X, Tang H, Zhu J, Zhou S, Xu Z, Liu F, Su C. Increased Frequency of Th17 Cells in Children With Mycoplasma pneumoniae Pneumonia. *J Clin Lab Anal* 2016; Epub ahead of print [PMID: 27240139 DOI: 10.1002/jcla.22005]

P- Reviewer: Khedmat H, Laguna JC, Streba LA **S- Editor:** Gong ZM
L- Editor: A **E- Editor:** Wang CH





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



ISSN 1007-9327



9 771007 932045