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IL-17 Axis Driven Inflammation in Non-Alcoholic Fatty Liver Disease Progression

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Abstract

Obesity is a primary risk factor for the development of non-alcoholic fatty liver disease (NAFLD). NAFLD, the most common chronic liver disease in the world, represents a spectrum of disorders that range from steatosis (NAFL) to steatohepatitis (NASH) to cirrhosis. It is anticipated that NAFLD will soon surpass chronic hepatitis C infection as the leading cause for needing liver transplantation. Despite its clinical and public health significance no specific therapies are available. Although the etiology of NAFLD is multifactorial and remains largely enigmatic, it is well accepted that inflammation is a central component of NAFLD pathogenesis. Despite the significance, critical immune mediators, loci of immune activation, the immune signaling pathways and the mechanism(s) underlying disease progression remain incompletely understood. Recent findings have focused on the role of Interleukin 17 (IL-17) family of proinflammatory cytokines in obesity and pathogenesis of obesity-associated sequelae. Notably, obesity favors a Th17 bias and is associated with increased IL-17A expression in both humans and mice. Further, in mice, IL-17 axis has been implicated in regulation of both obesity and NAFLD pathogenesis. However, despite these recent advances several important questions require further evaluation including: the relevant cellular source of IL-17A production; the critical IL-17RA-expressing cell type; the critical liver infiltrating immune cells; and the underlying cellular effector mechanisms. Addressing these questions may aid in the identification and development of novel therapeutic targets for prevention of inflammation-driven NAFLD progression.

Keywords

IL-17; Inflammation; NAFLD; Obesity

INTRODUCTION

Obesity has become pandemic [1]. The number of over-weight and obese individuals increased from 857 million in 1980, to 2.1 billion in 2013 [2]. In this worsening pandemic,

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

the US leads the way, with the highest mean adult BMI among high-income countries [1]. Approximately 1/3 of adults and 1/5 of children are obese [3] something further marked by ethnic and racial disparities, with higher rates of obesity in Hispanics and African Americans [4]. Importantly, such trends have resulted in recent classification of obesity as a disease by the American Medical Association. Despite the clinical and public health significance of obesity, effective therapies are lacking. Few individuals on diet and exercise programs are able to maintain long term weight loss [5], and current approved medical therapies aimed at reducing energy intake through effects on brain satiety centers or intestinal absorption, are hampered by side effects and/or meager long term efficacy [6].

Obesity is pathophysiologically linked to a variety of adverse sequelae, including metabolic syndrome, type II diabetes, dyslipidemia, non-alcoholic fatty liver disease (NAFLD), atherosclerotic cardiovascular disease, Alzheimer's disease and diverse cancers [7-10]. Further, obesity-associated inflammation was directly linked to the pathogenesis of obesity related sequelae (rev. in [11]). Notably, epidemiological studies reporting increases in plasma concentrations of acute phase reactant proteins [12] and proinflammatory cytokines (e.g., TNF- α and IL-6) had initially linked obesity and T2DM with inflammation [13, 14]. Complementary studies using rodent models of disease have similarly shown that obesity is associated with broad activation of pro-inflammatory and stress response pathways in adipose tissue [13, 15, 16] and that activation of proinflammatory signaling pathways in insulin-responsive cells can directly induce insulin resistance [17-19]. Congruently, pro-inflammatory cytokine neutralization or deletion improved insulin sensitivity in these models [13, 20]. Of note, the primary reported pro-inflammatory signaling cascades activated by increased adiposity include the JNK stress kinase and IKK β /NF- κ B pathways [21, 22]. Genetic deletion of JNK pathway improved insulin resistance in mouse models of obesity [23].

Activation of pro-inflammatory cascades in obesity, are multifactorial and include: adipocyte hypoxia, ER stress and cell death [8, 24, 25]; obesity-associated changes in the intestinal microbiome [26, 27], intestinal permeability and metabolic endotoxemia [28, 29]; and activation of innate immune signaling (e.g., such as Toll-like receptors [TLRs]) by components enriched in high fat diets (e.g., free fatty acids or minimally-oxidized LDL) [30, 31], microbial products (e.g., lipopolysaccharide [LPS]) [29], or endogenous ligands uncovered during tissue injury and inflammation (e.g, fibronectin extra domain A, HMGB1) [32, 33]. Activation of pro-inflammatory signaling cascades in adipose tissue leads to adipocyte death, pro-inflammatory cytokine and chemokine production and immune cell recruitment [9]. Initial macrophage recruitment to the white adipose tissue is associated with tissue remodeling [9, 34], while continuous activation of immune pathways correlates with inflammatory macrophage polarization [35], amplification of proinflammatory mediator production and exacerbated immune cell infiltration [9]. Of note, a variety of immune cells, including neutrophils [36], dendritic cells [37], NK cells [38], NKT cells [39], T cells [40], B cells [41], eosinophils [42] and mast cells [43] have been associated with pathology of obesity-driven end-organ sequeale. Thus, the inter-linked phenomena of obesity-associated low-grade inflammation via activation of the immune system play central roles in determining the immunopathology of all of obesity's adverse sequelae, including NAFLD, the focus of this review.

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

NAFLD is the most common chronic liver disorder in the world in both adults and children [44]. NAFLD represents a spectrum of disorders ranging from simple steatosis (benign hepatic fat accumulation; NAFL) to nonalcoholic steatohepatitis (NASH) and cirrhosis [44, 45]. In the US, 1/3 of adults have evidence of NAFL [46, 47]. NASH prevalence is lower, affecting up to 30% of adults and children with NAFL [48]. Further, up to 25% of NASH patients progress to cirrhosis and hepatocellular carcinoma [49]. The underlying mechanisms for why only a portion of NAFL patients progress to NASH and cirrhosis are unknown. However, with the development of Hepatitis C therapeutics and alarming increase in obesity, it is estimated that NAFLD will soon become the leading cause for requiring liver transplantation [50]. Thus, the development of novel preventive and therapeutic approaches to NAFLD are clearly needed.

While the molecular trigger(s) and pathways underlying the pathogenesis of NAFLD are not fully understood, it is well-accepted that NAFLD pathogenesis is driven by multiple, parallel hits something often referred to as multi-hit hypothesis [51, 52]. Here specifically, the initial hit, hepatocyte triglyceride accumulation, is known to sensitize and predispose hepatocytes to subsequent sequential or parallel hits, something that drives and regulates disease progression and pathogenicity. Of note, lipotoxicity, P450-dependent or NADPH oxidase-dependent reactive oxygen species (ROS) production, fibrosis, intestinal microbiome and induction of pro-inflammatory immune mediators have all been proposed as mechanisms associated with NAFLD pathogenesis the latest being the focus of this review.

It is well established that immune responses are tightly regulated. Delayed or insufficient vigor of immune responses can result in inadequate protection from bacterial, fungal and viral infection. Conversely, too vigorous a response can itself be harmful something seen, paradigmatically, in the development of autoimmune diseases (e.g., rheumatoid arthritis, type I diabetes, psoriasis and inflammatory bowel diseases) (rev. in [53]). Further, the pathophysiology of these autoimmune diseases was directly linked to dysregulated production of pro-inflammatory cytokines (e.g., TNF- α , IL-6, IFN- γ , IL-1 β , IL-23, type I IFNs) (rev. in [54]). Although regulated production of these immune mediators is involved in the homeostasis and physiology of healthy liver, an aberrant production was associated with both obesity and NAFLD pathogenesis (e.g., hepatic inflammation, fibrosis and hepatocellular damage) (rev. in [55]). Of note, both resident liver cells (hepatocytes, hepatic stellate cells) and immune cells (Kupffer cells, NK cells, neutrophils, NKT cells, T cells) are known producers of the immune mediators described above something that further highlights the complexity of mechanistic processes associated with immune-mediated disease pathology. Of particular interest here and in addition to the above-mentioned immune mediators, the IL-17 family of cytokines has been recently shown to play an important role in pathogenesis of variety of liver diseases, including NAFLD.

INTERLEUKIN 17 (IL-17) AXIS

The IL-17 signaling axis includes a small family of proinflammatory cytokines; IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F. Of note, the expression and function of other

IL-17 family members is discussed elsewhere (rev. in [56]). Notably, IL-17A, whose production occurs largely in the skin, mucosal tissues and liver, is the best described and characterized (rev. in [56]). Th17 cells, a functionally polarized subset of effector CD4⁺ T cells, are believed to be the primary producers of both IL-17A and IL-17F. However, a variety of immune cells (e.g., $\gamma\delta$ T cells, CD8⁺ T cells, NK, NKT, neutrophils, macrophages, dendritic, lymphoid tissue inducer, and innate lymphoid cells) [57] and non-immune cells (e.g., intestinal paneth cells) [57] express IL-17A and F. As with other cytokines, the specificity of biological effects of IL-17 family members depends on their interaction with signaling receptor complexes. IL-17A and IL-17F signal through a heterodimeric receptor complex consisting of IL-17 receptor A (IL-17RA) and IL-17 receptor C (IL-17RC) subunits. IL-17B signals through a specific receptor complex consisting of IL-17 receptor B (IL-17RB) subunit. Additionally, IL-17C signals through a heterodimeric receptor complex consisting of IL-17 receptor E (IL-17RE) and IL-17RA subunits. Finally, IL-17E signals through heterodimeric receptor complex consisting of IL-17RA/IL-17RB subunits (rev. in [56]).

As a receptor for IL-17A, IL-17RA is the best described IL-17 family receptor. The expression and function of other members: in the IL-17 family of receptors is discussed elsewhere (rev. in the [56]). IL-17RA is ubiquitously expressed, including expression in the liver by hepatocytes, Kupffer cells, hepatic stellate cells, biliary epithelial cells and sinusoidal endothelial cells [58-60].

IL-17A-driven activation of IL-17RA/IL17RC heterodimeric complex was shown to activate MAPK and NF- κ B signaling pathways and to induce cytokine production by epithelial cells, endothelial cells and fibroblasts [61]. Further, such activation directly leads to production of proinflammatory and neutrophil-mobilizing cytokines and chemokines including, IL-1, IL-6, IL-8, GM-CSF, G-CSF, TNF- α , CXCL1 (KC), CCL2 (MCP-1), CXCL2 (MIP-2), CCL7 (MCP-3) and CCL20 (MIP-3A) as well as epithelial ROS and NO production [61]. Thus IL-17A signaling is essential for establishment of mucosal immunity to fungal and bacterial insults. In fact, the ability of IL-17 axis to induce the production of proinflammatory cytokines and neutrophil recruiting chemokines is central to the biological effects of IL-17 in many systems, through both expansion of the lineage through regulation of G-CSF and the G-CSF receptor as well as recruitment through regulation of chemokine expression [62]. Notably, recruitment of neutrophils correlated with increased ROS production and release of protease-enriched granules, something when combined with augmented inflammation induces mitochondrial damage, apoptosis and necrosis [63-65].

IL-17 AXIS AND LIVER DISEASE

Increased IL-17A production was reported in diverse human liver diseases, including alcoholic liver disease [60], acute liver injury [66], chronic hepatitis B and C [67, 68], primary biliary cirrhosis [69, 70], hepatocellular carcinoma [71], and acute liver transplant rejection [72, 73]. Further, the role of the IL-17 axis in the pathogenesis of liver disease has been extensively evaluated in multiple mouse models of liver injury. Specifically, genetic deletion of IL-17RA or IL-17A, or antibody-mediated neutralization of IL-17A protected from Con A-induced hepatitis [59, 74, 75]. Further, exogenous administration of IL-17A or

overexpression of IL-17 by hydrodynamic tail vein injection of IL-17A encoding plasmid has led to hepatocyte necrosis and exacerbates Con A-driven disease pathogenesis [75]. In contrast, deletion of hematopoietic IL-17A production or genetic deletion of IL-17RA protected from bile duct ligation-induced liver injury [76] and from carbon tetrachloride (CCl₄) induced liver damage something associated with decreased expression of pro-inflammatory cytokines and decreased fibrosis [66, 76]. In summary, these studies suggest that IL-17 axis plays an important role in induction and pathogenesis of various hepatic diseases.

IL-17 AXIS IN OBESITY AND NAFLD

Increased IL-17A expression was reported in obese humans and in mice something associated with increased adipose tissue Th17 cell infiltration [77-79]. In addition to the above-mentioned hepatic diseases, the IL-17 axis was implicated in both regulation of obesity and NAFLD. Specifically, previous reports have shown that mice with genetic deletion of IL-17A exhibit increased weight gain but are protected from glucose dysmetabolism [80]. Similarly, diet-induced obese mice lacking IL-17RA exhibit increased weight gain and hepatic steatosis, but are protected from glucose dysmetabolism and progression of NAFL to NASH [81]. Further, in the context of NAFLD, IL-17A seems to be the primary IL-17 family member responsible for NAFLD pathogenesis, as IL-17A neutralization protected mice from NAFLD progression [81, 82] and ameliorated liver injury in obese mice after LPS challenge [83]. Notably, the role of other IL-17 family members (e.g., IL-17B, IL-17C, IL-17D and IL-17F) or signaling receptors (e.g., IL-17RB, IL-17RC, IL-17RE) in obesity and obesity-associated sequelae remains unexamined.

Recent implications for the role of intestinal microbiome in disease development and progression have infused significant excitement into uncovering the intertwining mechanisms between immune system and intestinal microbiome in shaping disease outcomes. Of note, the development of obesity [26, 84] and progression of NAFLD [85] in humans was linked with intestinal microbiome dysbiosis. Further, experimental animal models of diet-induced obesity have shown that the intestinal microbiota are essential for development of obesity [86, 87] and play an important role in regulating NAFLD progression [88]. However, the critical molecular mechanisms linking the intestinal microbiota to immune activation in the context of obesity and NAFLD pathogenesis represent a significant allocation of current research efforts.

One potential mechanism for intestinal microbiota driven immune activation relies on activation of the IL-17 axis. Specifically, published reports have shown that germ free mice lack intestinal Th17 cells [89], while modulation of intestinal microbiota altered the balance of intestinal Th17 cells [90]. In addition, recent efforts have identified a specific intestinal commensal, segmented filamentous bacterium (SFB), as important in regulation of intestinal Th17 polarization [89] something further validated by showing that monocolonization with SFB resulted in accumulation of Th17 cells [89, 91]. Of note, SFB colonization was shown to regulate disease pathogenesis in experimental models of EAE [92], type I diabetes [93] and autoimmune arthritis [94].

These findings are also of significance to hepatic disease as SFB has been shown to colonize humans [95] and *Clostridium difficile* infection (a close relative of SFB also known to augment IL-17 production) was associated as an independent risk factor for adverse outcomes in patients with cirrhosis [96]. Further, recent reports show monocolonization of mice with SFB exacerbated hepatocellular damage in both diet-induced and genetically induced (leptin receptor deficient mice) experimental models of obesity [81]. In contrast, depletion of SFB reduced obesity-associated hepatocellular damage in this model [81]. Thus, the intestinal microbiome, at least in part via IL-17 axis regulation, modulates NAFLD pathogenesis. However, despite the clinical significance, the relevance of these findings clearly requires further validation in humans.

In support of studies discussed above, published reports employing human samples and the activation of the IL-17 axis have shown that SNPs in genes associated with IL-17 axis (e.g., *STAT4* and *RORA*) are associated with increased serum levels of hepatobiliary disease markers [97, 98]. Further, studies have shown that obesity and NAFLD correlate with increased systemic and hepatic IL-17A levels [77, 79, 81, 83] and that hepatic neutrophilic inflammation, something linked with IL-17 expression and an increased hepatic neutrophil/lymphocyte ratio, is predictive of the progression of NAFLD to NASH [99].

While unknown, potential hepatic and immune cell types critical in producing IL-17A, responding to IL-17A and mediating IL-17A's downstream effects in the context of obesity and NAFLD are discussed below.

Hepatocytes

Hepatocytes represent the primary structural cell component of the liver and play a critical role in homeostasis of hepatic function. By manufacturing, storing and exporting lipids, hepatocytes play a critical role in maintaining the metabolic function of the liver [100]. Notably, in the context of obesity and NAFLD, hepatocyte function is altered. Specifically, increased release of free fatty acids by white adipose tissue is responsible for augmented triglyceride synthesis and storage in hepatocytes (NAFL)—something that represents the “first hit” in NAFLD, and renders hepatocytes susceptible to stress mediated damage [101]. This obesity-associated lipotoxicity is inflammatory in nature and further renders the hepatocytes susceptible to parallel/sequential hits, potential cell death, and disease progression [101]. Of note, IL-17A stimulation is known to increase hepatocyte lipid uptake and hepatocyte-driven cytokine production [83]. However, whether hepatocytes are able to produce IL-17A, or other mediators from the IL-17 family, in the context of NAFLD, is yet to be determined.

Hepatic Stellate Cells

Hepatic stellate cells (HSCs) represent a major source of liver extra-cellular matrix (ECM) production [102]. While important in liver regeneration, aberrant ECM production by activated HSCs induces liver fibrosis in a myriad of hepatic disorders [102]. Notably, a variety of mediators produced by Kupffer cells (e.g., TNF- α , TGF β and MCP-1), neutrophils (e.g., IL-17, ROS), and Th17 cells (e.g., IL-17) have been shown to induce cytokine production (e.g., IL-8, MCP-1 and TGF- β) and fibrogenic machinery in HSCs [103, 104]. In

human alcoholic hepatitis, IL-17RA expression by HSCs is increased, and the HSC *in vitro* response to IL-17 leads to neutrophil recruitment via IL-8 production [60]. Additionally, experimental mouse models of bile duct ligation and CCl₄ treatment have shown that IL-17A activation of STAT3 in HSCs via induction of its upstream mediators drives increased collagen production [76, 103]. Although NAFLD pathogenesis is associated with increased HSC activation, the mechanisms underlying HSC activation and whether IL-17 induces this activation in context of NAFLD progression remain to be defined.

Kupffer Cells

Kupffer cells are the largest fixed group of macrophages in the body, representing 20% of non-parenchymal cells in the liver [100], and, as such, play a critical role in hepatic homeostasis. NAFLD is associated with an increased presence of Kupffer cells, and Kupffer cell depletion alleviates NAFLD pathogenesis [105]. As with macrophage infiltration to the adipose tissue in obesity, Kupffer cells are thought to be the initial regulators of hepatic disease pathogenesis via activation of proinflammatory cascades (e.g., JNK1, TNF- α , IL-6, IL-12), recruitment of immune cells to the liver, production of ROS, and activation of HSC-driven fibrosis [103, 106]. Notably, obese mice with a myeloid cell-specific deletion in JNK1 develop a similar degree of hepatic steatosis, compared to wild type controls, but are protected from liver inflammation and hepatic insulin resistance [107]. However, the mechanisms that drive Kupffer cell activation in hepatic diseases are not fully defined.

IL-17A stimulation of Kupffer cells *in vitro* results in robust cytokine production (e.g., IL-6, TGF- β and TNF- α) [76]. Further, in an *in vivo* setting, IL-17 axis driven activation of Kupffer cells was shown to play a role in various hepatic disease. Specifically, IL-17RA expression is upregulated by Kupffer cells in an experimental model of Con A-induced liver injury, and depletion of Kupffer cells by gadolinium chloride protected from hepatocellular damage [75]. Further, IL-17A-driven Kupffer cell activation played a critical role in hepatic neutrophil recruitment and injury in an ischemia reperfusion model [108] and to exacerbate hepatic fibrosis in a mouse model of bile duct ligation [76]. Considering the importance of Kupffer cells in NAFLD and the role of IL-17 axis in their activation, IL-17 axis-driven Kupffer cell activation may also play an important role in NAFLD pathogenesis.

NK Cells

Representing nearly a third of hepatic lymphocytes, NK cells are the primary producers of hepatic IFN- γ and a key innate immune cell involved in liver injury, fibrosis and regeneration [100, 109-112]. Specifically, the importance of NK cells in hepatic damage has been well demonstrated in models of CCl₄-driven hepatocellular injury, through direct killing of activated HSCs and inhibition of HSC-induced fibrosis by NK cell derived IFN- γ [113]. Further, NK cells were also able to produce IL-17A, and depletion of IL-17A suppressed NK cell function and reduced disease progression in TLR3-induced hepatitis [114, 115].

Obesity in humans and rodent models leads to decreased peripheral NK cell frequency and activity [116, 117]. Conversely, recent findings revealed that hepatic NK cell levels correlate with NAFLD progression [118]. Studies have also shown that NK cell produced IFN- γ may

drive hepatocyte death and NAFL to NASH progression [105]. However, whether certain subsets of NK cells play a differential role in obesity and NAFLD is unclear. Elucidating the potentially conflicting mechanisms by which NK cells play either a protective or proinflammatory role in NAFLD may be critical in understanding the mechanisms underlying disease pathogenesis.

Neutrophils

As the most abundant innate lymphoid cell population, neutrophils are an important mediator of hepatic disease. Hepatic neutrophil influx, in response to exacerbated chemokine production, was associated with detrimental effects in a variety of liver diseases including hepatic ischemia reperfusion injury [119], endotoxemia [120], sepsis [121], and alcoholic hepatitis [122]. Notably, neutrophils recruited to the liver in hepatic disease produce ROS, and release protease-enriched granules, myeloperoxidases and cathepsin G—something which alters the function of hepatocytes, endothelial cells, Kupffer cells and stellate cells through induction of inflammation, mitochondrial damage, apoptosis and necrosis [63-65]. In addition, neutrophils play an important role in NAFLD pathogenesis [123] as hepatic neutrophilia is considered a hallmark of NAFL to NASH progression [99].

The biological function of IL-17 largely depends on its ability to mediate neutrophil attractant chemokine expression, such as CXCL1 [124, 125]. Although it has been shown that the IL-17 axis regulates neutrophil-infiltration, hepatic injury and ROS induction (myeloperoxidase) in a model of liver ischemia-reperfusion [108], the role of IL-17 axis driven neutrophil recruitment and activation in NAFLD has yet to be defined. Further, only a specific subset of neutrophils expressed both the IL-17RA and IL-17RC subunits, something required for functional IL-17A response – begging the question of whether the IL-17 axis acts directly on neutrophils and whether a particular subset of neutrophils regulates disease pathogenesis [126]. These data suggest that further evaluation of the IL-17 axis's role in the modulation of neutrophil function in NAFLD may be critical to understanding the mechanisms underlying disease pathogenesis.

NKT Cells

Accounting for ~5-25% of the liver lymphocyte population, NKT cells represent an important component of hepatic immunity [127]. Invariant NKT cells are unique in their ability to produce cytokines (e.g., TNF- α , IFN- γ , and IL-17A) in response to sensing glycolipid antigens presented by CD1d expressed on Kupffer cells and hepatocytes [128]. In fact, NKT cells were shown to modulate inflammatory and fibrogenic responses in viral hepatitis, autoimmune liver disease and hepatic malignant tumor (rev. in [129]). Of note, NKT cell-driven IL-17A production was shown to activate Kupffer cells and mediate hepatocellular damage in a model of Con A-induced liver injury [75].

Although levels of CD1d expression and glycolipid antigen increase with steatosis, the effects of obesity and NAFLD on hepatic NKT cell levels are somewhat controversial [128]. Specifically, decreased levels of hepatic NKT cells were reported in ob/ob mice [130, 131] and in individuals with NAFLD [132], while other studies have demonstrated an increase in hepatic NKT cell populations in patients with NAFLD [128]. Thus, the role of NKT cells in

NAFLD progression is unclear. Further, whether NKT cell production of IL-17A plays a role in disease pathogenesis is yet to be determined.

T cells

T cells represent the largest lymphocyte population in the liver, and classical T cells (CD4 or CD8 positive) played a central role in maintaining hepatic immunity [100]. Further, NAFLD patients exhibit increased hepatic T cell levels [133, 134] something similarly seen in experimental models of NAFLD. The role of T cells (*e.g.* CD8 T cells, Th1, Th2, Tregs and $\gamma\delta$ T cells) in liver disease is described elsewhere [102, 135]. Here however, our focus will be on the role of Th17 cells, the primary IL-17 producing CD4⁺ T helper subtype [79]. Th17 function has been associated with multiple human hepatic disorders including alcoholic fatty liver disease, viral hepatitis, hepatocellular carcinoma and primary biliary cirrhosis (rev. in [136]). Hepatic Th17 enrichment and increased IL-17A production played a role in an experimental model of primary biliary cirrhosis, and T cell STAT3 activation was required for IL-17A production and hepatocellular damage in a mouse model of Con-A induced hepatitis [59]. Notably, obesity drives increased levels of tissue resident Th17 cells and both tissue and systemic IL-17 production [137, 138]. However, the role of Th17 cells in the context of NAFLD has not been comprehensively studied, as only a single study has observed increased Th17 presence in murine NAFLD [83]. Given the role Th17 cells play in obesity and other liver diseases, evaluation and manipulation of Th17 cells in obesity and NAFLD may hold promise into understanding mechanisms associated with disease pathology.

IL-17 AXIS AND NAFLD: MOVING FORWARD

Despite considerable progress in recent years toward elucidating the immunological mechanisms of NAFLD pathogenesis, no specific therapies exist. Although published findings clearly suggest the IL-17 axis plays an important role in NAFLD pathogenesis, further evaluation of biological processes underlying such effects is required. Specifically, defining the role of other IL-17 family members (*e.g.*, IL-17B, IL-17C, IL-17D and IL-17F) or signaling receptors (*e.g.*, IL-17RB, IL-17RC, IL-17RE); initial loci of increased IL-17 production; the primary cellular source(s) of production of IL-17 family members; the critical IL-17 receptor family members expressing cell type(s); the critical immune infiltrating cells during NAFLD progression; and the role of intestinal microbiome in IL-17 axis activation, represent essential studies for defining the underlying cellular and molecular effector mechanism(s) regulating NAFLD pathogenesis. Importantly, completion of such studies will have to be complemented with the development and availability of novel, innovative tools (*e.g.* conditional knockout and transgenic mouse lines; efficient and specific neutralizing antibodies; and specific chemical inhibitors). In terms of mechanisms underlying IL-17 axis-driven effects in NAFLD, it is postulated that increased accumulation of IL-17A in the liver directly acts on resident hepatic and immune cells to amplify the proinflammatory chemokines and cytokines that lead to immune cell infiltration, ROS production, and disease pathogenesis.

Finally, although the role of the IL-17 axis in NAFLD pathogenesis is not fully understood, its relevance in regulation of wide spectrum of diseases is obvious. Human mutations in pathways critical to the IL-17 axis (e.g., IL-17RA, IL-17F, IL-17RC) and Th17 function (e.g., STAT3, TYK2, IL-12B, IL-12RB, DECTIN1, CARD9, STAT1, AIRE, and ACT) have been identified and may represent novel therapeutic targets (rev. in [139]). Further, use of IL-17A or IL-17RA specific antibodies (Ixekizumab, Secukinumab and Brodalumab), for treatments of psoriasis, psoriatic arthritis, rheumatoid arthritis, and ankylosing spondylitis are in the final stages of clinical testing something shown to be as safe and efficacious as the current standard-of-care in Phase II trials [139]. Notably, if combined with better insights into the cellular and molecular mechanisms underlying IL-17 axis-driven NAFLD progression, similar approaches are envisioned for development of novel therapeutics to NAFLD.

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Biography

Senad Divanovic

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Fig. (1). Overview of the role of the IL-17 axis in NAFLD pathogenesis

In addition to increased hepatocyte lipid uptake, obesity drives increased IL-17 production systemically and in the liver by NKT, Th17 and NK cells. IL-17 activates IL-17RA on a variety of cells. Such activation leads to proinflammatory cytokine and chemokine production, neutrophil recruitment, ROS production and increased collagen deposition biological processes known to mediate NAFLD progression.