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The role of IL-17 signaling in regulation of the liver-brain axis and intestinal permeability in Alcoholic Liver Disease

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Abstract

Alcoholic liver disease (ALD) progresses from a normal liver, to steatosis, steatohepatitis, fibrosis and hepatocellular carcinoma (HCC). Despite intensive studies, the pathogenesis of ALD is poorly understood, in part due to a lack of suitable animal models which mimic the stages of ALD progression. Furthermore, the role of IL-17 in ALD has not been evaluated. We and others have recently demonstrated that IL-17 signaling plays a critical role in development of liver fibrosis and cancer. Here we summarize the most recent evidence supporting the role of IL-17 in ALD. As a result of a collaborative effort of Drs. Karin, Gao, Tsukamoto and Kisseleva, we developed several improved models of ALD in mice: 1) chronic-plus-binge model that mimics early stages of steatohepatitis, 2) intragastric ethanol feeding model that mimics alcoholic steatohepatitis and fibrosis, and 3) diethylnitrosamine (DEN)+alcohol model that mimics alcoholic liver cancer. These models might provide new insights into the mechanism of IL-17 signaling in ALD and help identify novel therapeutic targets.

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Conflict of Interest

Hsiao-Yen Ma, Jun Xu, Xiao Liu, Yunheng Zhu, Bin Gao, Michael Karin, Hidekazu Tsukamoto, Dilip V. Jeste, Igor Grant, Amanda J Roberts, Candice Contet, Cedric Geoffroy, Binhai Zheng, David Brenner and Tatiana Kisseleva declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

Animal studies are approved by IACUC Protocol S07088 at UCSD

Keywords

alcoholic liver disease; ethanol metabolism; activated myofibroblasts; regression of liver fibrosis; hepatocellular carcinoma; Innate Immunity; Adaptive Immunity; Cytokines; Inflammation

I. Introduction

Alcoholic liver disease (ALD) is a major cause of cirrhosis and liver failure, which is the 12th leading cause of death in patients in the United States[1]. ALD progresses from steatosis, to steatohepatitis, fibrosis, cirrhosis, and finally hepatocellular carcinoma (HCC)[1]. Several injury-triggered events (see below) play a critical role in the pathogenesis of ALD. To-date there is no effective treatment of ALD, in part because there are no pre-clinical models available to study ALD progression. Furthermore, the majority of preclinical models focuses on the effect of chronic alcohol consumption on pathology of a single organ, such as liver, brain, heart or kidneys. In reality, alcohol-induced injury produces a systemic effect, and the failure of the damaged liver to perform detoxifying function also has a profound effect on the brain, and other organs. Here we summarize the recent evidence for the role of IL-17 signaling pathway in alcohol-induced injury of the liver and the brain, and regulation of the intestinal permeability, the critical factors that drive development of alcoholic liver disease, .

II. ALD progression in patients

Progression of ALD from steatohepatitis to fibrosis

ALD studies have been hampered by the absence of suitable animal models. In patients ALD progresses from fatty liver to steatohepatitis and fibrosis, and often leads to development of HCC. Each stage is characterized by specific morphological changes and upregulation of specific sets of cytokines. Recently, we developed a chronic-plus-binge ethanol feeding model, which induces significant liver inflammation and neutrophil infiltration but not fibrosis [2,3], and reflects early stages of steatohepatitis. Alcohol-induced damage to hepatocytes is induced via up-regulation of cytochrome P4502E1, SREBP-1c causing accumulation of fat droplets (mainly triglycerides and phospholipids), centrilobular ballooning of hepatocytes, and formation of Mallory–Denk hyaline inclusions[4]. Serum levels of about 250IU/L ALT and 420 IU/L AST were found post single binge gavage, and correlated with increased expression of inflammatory cytokines IL-8, IL-6, IL-1β and development of hepatic oxidative stress [1,4]. Neutrophilic infiltration is the major feature of alcoholic steatohepatitis. Apoptotic hepatocytes release TGF-β1 and factors, including IL-8, CXCL1 (Gro-α), and IL-17, that facilitate recruitment of inflammatory cells to the fatty liver. Infiltrating BM-derived neutrophils kill sensitized hepatocytes, and further exacerbate alcohol-induced liver injury[5]. A rodent model of ASH has demonstrated a pivotal role of neutrophils in pathogenesis of ALD [1,2]. Recruited T and B lymphocytes also contribute to liver damage causing activation liver resident Kuppfer cells, which secrete TGF-β1 and activate hepatic myofibroblasts. Myofibroblasts are the primary source of extracellular matrix (ECM) in fibrotic liver[6–11]. Activated Hepatic Stellate Cells (aHSCs) have been recently demonstrated to serve as a major source of myofibroblasts in alcohol-damaged liver Under physiological conditions HSCs store Vitamin A and function as liver pericytes, but in

response to sustained exposure to alcohol, HSCs rapidly differentiate into fibrogenic myofibroblasts, start producing Collagen Type I, the major component of extracellular matrix, and make liver fibrotic. Up-to-date the intragastric model of ethanol feeding (Tsukamoto-French model)[12] is the best rodent model of alcohol-induced liver fibrosis mimics this stage of alcoholic fibrosis in patients, and these mice develop significant level of liver fibrosis after 2 months of alcohol[12,13]. This stage is characterized by release of TGF-β1, mostly by Kupffer cells[4], and activation of Hepatic stellate cells (HSCs)[13,14]. Furthermore, a recent study has demonstrated that addition of ethanol to drinking water increased tumor incidence in DEN-injected male mice[15], suggesting that this model can be used to study the effects of ethanol on HCC progression.

Hepatocellular carcinoma (HCC)

HCC is the firth most common cancer worldwide and the third most common cause of cancer death[16]. HCC is a malignant tumor made of cells resembling hepatocytes with a plate-like organization around sinusoids[17], usually arises in a cirrhotic liver of patients with ALD[16,18], and is identified by expression of alpha-fetoprotein (AFP), CD90, CD133, YAP and EpCAM expression[19]. Several mechanisms contribute to development of HCC in patients with alcoholic cirrhosis, including sustained inflammation, immunosuppressive effect of alcohol, impaired hepatocyte proliferation, loss of cell cycle checkpoints and increased tumor cell survival, telomere shortening and chromosomal instability[1,2]. Three potential cellular sources of HCC have been suggested: 1) mature hepatocytes as unipotential stem cells which rapidly regenerate to restore the liver mass in response to acute injury, 2) oval cells as bipotential stem cells which are activated and proliferate in response to chronic injury when proliferation of hepatocytes is exhausted or inhibited, 3) BM-derived stem cells[20,21]. Accumulating evidence suggests that HCC originates from dedifferentiation and transformation of mature hepatocytes, or maturation arrest of oval cells[18,19]. Progression of HCC in patients with ALD is associated with upregulation of IL-6[22], IL-17[23,24] and IL-22[25] and constitutive activation of Stat3[26]. Consistent with this, IL-22-/- mice are less susceptible to DEN-induced HCC than wild type mice. In addition to Stat3[27], NFκB, Wnt/β-catenin, and Hedgehog signaling pathways were implicated in HCC development[23,28–31].

After injury and loss of hepatic mass, the liver regenerates mainly via proliferation of remaining adult hepatocytes. Oval cells (ductular reaction) activate when proliferation of hepatocytes is inhibited or exhasted[1]. Oval cells are bipotential liver progenitor cells, which reside in the Canal of Herring[32], and give rise to hepatocytes and cholangiocytes[20,33]. Oval cells exhibit a $CD45^{-}/11b^{-}/31^{-}/MIC1\text{-}1C3^{+}/133^{+}/26^{-}$ phenotype[34]. Several studies indicate that these may originate from *Sox9*-expressing clonogenic progenitors[33–36]. Therefore, recently generated *Sox9creER*^{T2}*-R26R*^{YFP} mice[34] may be useful for lineage tracing of oval cells. The oval cell reaction includes a broader progenitor population which can be identified by expression of A6, AFP, FoxJ1[34,36] and other markers[37] in mice. Chronic alcohol consumption inhibits hepatocyte proliferation, increasing the number of oval cells in patients with ALD. Proliferation of oval cells correlates with the severity of ALD and risk of alcoholic HCC. It has been suggested that tumor progenitors may originate from the oval cell reaction emerging in response chronic alcohol exposure[38]. Recent studies have implicated IL-22 in the regulation of alcohol-induced oval cell response and HCC

progression. Thus, overexpression of IL-22 in the liver (IL-22TG mice) drives exaggerated oval cell proliferation via Stat3 activation[26,39], suggesting that IL-22/Stat3 signaling may be critical in HCC[40].

Systemic effect of alcohol on liver-brain axis and intestinal permeability

Liver metabolizes alcohol, and therefore, is directly affected by chronic alcohol consumption. In turn, liver dysfunction contributes to systemic release of proinflammatory microbial products, toxic lipids (such as ceramides) and cytokines into the circulation, and exacerbates cytotoxic effect of alcohol on other organs, including development of insulin resistance and oxidative stress. The central nervous system (CNS) is the other major target of alcohol toxicity and degeneration. In addition to its direct neurotoxic effects, alcohol misuse establishes a liver-brain axis of neurodegeneration mediated by toxic lipid trafficking across the blood-brain barrier, leading to a range of complications that begin with mild neurocognitive impairment but can progress to more severe dementing disorder. The neuroanatomic underpinnings of these neurocognitive disorders include disruption of white matter integrity as evidenced by reduction in fractional anisotropy and increase in diffusivity measures on diffusion tensor imaging; and loss of volume in hippocampus, frontal cortex, subcortical structures and cerebellum. On structural brain imaging brain volume loss may be manifested by cortical thinning, white matter loss, and corresponding enlargement of sulci and ventricles. These changes may be accompanied by neuropathologic findings of astrogliosis, loss of synaptodendritic complexity, loss of cytoskeleton, and ultimately neuronal loss. When complicated by thiamine deficiency there may be additional damage to thalamus, and mammillary bodies with clinical presentation of Wernicke Korsakoff syndrome [amnestic-confabulatory syndrome][41–45].

III. Evidence of the role of IL-17 signaling pathway in ALD

Interleukin 17 (IL-17)

Interleukin-17 (IL-17)-producing effector $CD4^+$ T (Th17) cells[46,47] originate from naïve T cells via activation of lineage specific transcription factors[48,49], regulated by TGF-β1 and IL-6, and other cytokines[50,51]. IL-17 is mainly produced by $CD4^+$ Th17 cells, but also by a variety of cells, including γδ T cells, $CD8^+$ T cells, NKT cells, NK cells, innate lymphoid cells, eosinophils, neutrophils, and monocytes[52]. Th17 cells secrete IL-17 cytokines, a family of cytokines comprised of IL-17A, IL-17F, IL-17B, IL-17C and IL-17E[53]. IL-17A homodimers (also known as IL-17) is the most abundant in Th17 cells, exhibit higher biological activity, and signal through their cognate receptors IL-17RA and IL-17RC[52]. IL-17RA is ubiquitously expressed, but is strongly induced in hematopoietic cells[54] and fibroblasts[55] in response to stress. IL-17A signaling activates inflammatory signaling in target cells, including Stat3, TRAF6, Act1, JNK, ERK, NF-κB[54,56]. IL-17 mediates autoimmunity, and the autoimmune inflammatory diseases psoriasis and rheumatoid arthritis respond to anti-IL-17 biological therapies[57]. Most recently, IL-17 has been implicated in liver, lung, and skin fibrosis, and in tumorigenesis[52,53,58–60,5,61–64]. Although anti-TNF-α therapy has been ineffective in patients with ALD[1,65], the corollary of our underlying hypothesis is that anti-IL-17 therapy is a potential novel therapy for ALD. The autoimmune inflammatory diseases psoriasis and rheumatoid arthritis respond to anti-IL-17 biological

therapies[57]. Most recently, IL-17 has been implicated in liver, lung, and skin fibrosis, and in tumorigenesis [52,66]. We have demonstrated that IL-17 is a critical mediator of liver fibrosis of different etiologies[2,67].

IL-17 in liver fibrosis

Patients with ALD have a high serum level of IL-17. Accumulation of Th17 cells was significantly increased in the livers of patients with ALD, and the numbers of Th17 cells correlated with fibrosis score[5]. Several events play a critical role in progression of alcohol-related liver fibrosis. Hepatocyte apoptosis causes recruitment of inflammatory cells to the damaged liver and release of pro-fibrogenic cytokines (TGF-β1, IL-6, IL-1β, TNF-α). Our group has recently demonstrated that IL-17A and its receptor IL-17RA are highly upregulated in injured livers, and IL-17 signaling plays a critical role in the pathogenesis of liver fibrosis. IL-17 regulates production of TGF-β1 by activated Kupffer cells, and can directly activate Collagen Type I production by HSCs, the major source of fibrogenic myofibroblasts in fibrotic liver. Deletion of IL-17 signaling in mice resulted in inhibition of liver fibrosis by 75%. Abrogation of IL-17 signaling in hematopoietic cells (as demonstrated by deletion of either IL-17A or IL-17RA in BM) decreases liver fibrosis by 50%. Kupffer cells are the primary targets of IL-17, IL-17 regulates approximately 30% of TGF-β1 production by Kupffer cells. Meanwhile, deletion of IL-17RA in non-immune liver resident cells decreases liver fibrosis by 25%[67]. In this case, HSCs are the primary non-parenchymal targets of IL-17 in fibrotic liver, and IL-17A can directly stimulate activation of HSCs or induce IL-6 production, which stimulates Collagen Type I production in HSCs[67]. Increased expression of IL-17A was detected in livers from patients with liver fibrosis and cirrhosis of different etiologies (compared to patients with no fibrosis), and correlated with the severity of the disease[23].

Regulation of Th17 differentiation in liver fibrosis

TGF-β1, IL-6 are strongly upregulated during development of ALD-induced fibrosis. In the mean time, TGF-β1, IL-6 and IL-21 drive differentiation of Th17 cells from naïve Th0 cells[50] via activation of retinoid-related orphan receptor γt (ROR γt)[48]. IL-23 is required for Th17 proliferation[52]. IL-23 is expressed by the macrophages and DCs, signals through IL-12Rbeta1 and IL-23R receptors, and activate Jak2/STAT3 signaling pathway[68]. Mice deficient of IL-23p19, have very few Th17 cells[69,70], suggesting that and the main biological functions of IL-23 is regulation of Th17 cell expansion. IL-23 is upregulated along with IL-17 in fibrotic liver, and IL-23$^{-/-}$ deficient mice develop less fibrosis in response to cholestatic and toxic liver injury[67], indicating that the IL-23/Th17 axis may become a promising target for suppressing liver inflammation during ALD[71,72]. Furthermore, IL-23 is upregulated in multiple human cancers, and ablation of IL-23p19 gene resulted in reduced tumorigenesis in a mouse model of skin cancer[73], colitis-associated cancer (CAC)[66]. There is emerging evidence that IL-23 also promotes HCC development[74–76]. IL-27 antagonizes expansion of Th17 via inhibition of IL-23-producing cells. is formed from IL-27p28 and Ebi3 subunits [77] and IL-27p28$^{-/-}$[78] and Ebi3$^{-/-}$[79] knockout mice have been generated. IL-27 signals via IL-27RA and common receptor chain gp130, activating STAT3 and Stat1 in target cells[77,80]. IL-17RA$^{-/-}$ mice[81] exhibit a dramatic increase in Th17 activity,

demonstrating that IL-27 suppresses *de novo* Th17 cell differentiation driven by IL-6 and TGF-β1[78].

IL-25 also blocks Th17 cell proliferation via inhibition of IL-23, IL-1β1 and IL-6 secretion by dendritic (and other) cells [52]. IL-25 propagates allergic responses[82–84]. IL-25 binds to IL-17RA and IL-17RB heterodimers (of which IL-17RB represents an IL-25 specific moiety[85,86]), and induces Act1-dependent activation of NFκB signaling pathway in target cells[87]. IL-25 drives the expression of IL-13[88], which is required for suppression of Th17 responses[82–84,89,90]. We have demonstrated that IL-25 attenuates liver fibrosis in mice, suggesting that IL-25 agonists may become targets for ALD treatment[67].

IL-17 in brain and spinal cord

In addition to immune cells, glial cells in the CNS also express IL-17 under physiological conditions[91]. IL-17R is widely expressed within the CNS and upregulated under inflammatory conditions[92]. Genetic deletion of IL-17 increased the number of adult-born neurons. Furthermore, IL-17 deletion altered the network of the cytokines, facilitated basal excitatory synaptic transmission, enhanced intrinsic neuronal excitability, and increased expression of proneuronal genes in neuronal progenitor cells (NPCs), suggesting a profound role of IL-17 in the negative regulation of adult hippocampal neurogenesis under physiology conditions[93]. In an ischemic brain injury model, IL-17, highly expressed by γδ T lymphocytes, has been shown to play an important role in mediating the evolution of brain infarction and accompanying neurological deficits in the delayed phase of injury[94]. In a spinal cord injury model, IL-17 deletion improved tissue sparing and locomotor recovery without significantly affecting microglial activation and astroglial reactivity[95].

IL-17 in blood-brain barrier

In addition, Th17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation[92,96]. Aging augments T cell-derived release of IL-17 and granzyme B that mediate neuronal cell death. IL-17 and IL-22 receptors are expressed on blood-brain barrier endothelial cells (BBB-ECs), and elevated levels of IL-17 and IL-22 disrupt BBB tight junctions in vitro and in vivo. Furthermore, Th17 lymphocytes transmigrate efficiently across BBB-ECs, highly express granzyme B, and kill neurons and promote CNS inflammation through recruitment of $CD4^+$ lymphocytes.

IL-17 and intestinal permeability

The translocation of bacteria and bacterial products into the circulation, and subsequent changes in the microbiome composition are associated with chronic alcohol consumption. Thus, overgrowth of Bacteroidetes and Verrucomicrobia bacteria was observed in alcohol-fed mice (compared with a predominance of Firmicutes bacteria in control mice), and was associated with downregulation in gene and protein expression of bactericidal c-type lectins Reg3b and Reg3g in the small intestine[97]. Commensal bacteria regulate efficiency of immune response, and vice versa. For example, mono-colonization of mice with segmented filamentous bacteria (SFB) results in induction of proinflammatory factors that favor expansion and accumulation of Th17 cells in the small intestine, and elicits a systemic Th17

response. Intestinal microbiota have also been shown to play a critical role in the absorption of lipopolysaccharide (LPS)[98].

IL-17 and aging

Aging is associated with change of liver function caused by increased steatosis, inflammation, and fibrosis[99]. Changes in hypothalamic-pituitary-adrenal (HPA) activity are one of several proposed mechanisms involved in brain aging[100]. Recent studies have also implicated IL-17 in the process of aging in humans and mice[101]. For example, it has been suggested that aging is associated with changes in the immune system that affect specific T cell functions. The immune response to infection, immunization, and tumors in aged individuals is quite different from that found in the young. Specifically, aged naive CD4 T cells do not differentiate well to Th1 and Th2 effector subsets, but exhibit an increased ability to generate functional Th17 effectors, which can be found readily in older individuals. Therefore, the levels of IL-17 are highly increased in older individuals. Th17 effectors produce high levels of IL-17 family cytokines (IL-17, IL-21, and IL-22). In addition to the greater prevalence of Th17 effectors, aging is associated with expansion of regulatory T cells (Treg)[101]. Since IL-2 was shown to inhibit the expression of IL-17, and blocking IL-2 promotes the differentiation of Th17 effectors[102]. Therefore, it has been suggested that the presence of regulatory T cells during an immune response may favor the development of a Th17 polarized response because the regulatory cells consume IL-2, which is needed for the development of Th1 and Th2 but not Th17 effectors. These observations also suggest that aging has very specific effects on CD4 T cell populations and does not lead simply to an overall downregulation of T cell function[101].

IL-17 and HIV

Th17 cells play a crucial role in protection against infections. Therefore, it is not surprising that IL-17-producing T cells play an important role in pathogenesis of HIV and opportunistic infections observed in AIDS patients[103]. Specifically, the loss of balance between Th17 cells and Tregs was linked to increased immune activation and HIV progression. Although the numbers of Th17 cells in the peripheral blood often vary in AIDS patients, Th17 cells are substantially depleted from the gastrointestinal tract, leading to a loss of mucosal integrity, increased microbial translocation, and further impairment of systemic immune responses[103]. Furthermore, excessive alcohol use is common among AIDS patients, and greatly augments HIV-associated neurocognitive deficits[104]. However, the role of IL-17 signaling in HIV progression complicated by chronic alcohol abuse has not been evaluated. A longitudinal assessment of functional changes in circulating and tissue Th17 cells is urgently needed in order to better determine the dynamic of Th17 cells in peripheral blood, and IL-17-specific regulation of liver-brain axis and intestinal permeability in AIDS patients with a history of chronic alcohol abuse.

Regulation of Th17 differentiation by gut microbiota

The composition of microbiota has been linked to the differentiation of Th17 cells in the gut, specifically in the small intestine lamina propria. In vitro, IL-17 expressing T-helper cells are induced by the interactions of cytokines TGF-β, IL-6, IL-21 & IL-23; these cytokines also play an important role in Th17 differentiation *in vivo* and regulation of inflammatory

immune response. Recent studies have demonstrated the correlation between Th17 *in vivo* differentiation and induction in the small intestine lamina propria with the presence of intestinal Cytophaga-Flavobacter-Bacteriodes bacteria[105]. Here, Th17 differentiation was observed independent of IL-21 & IL-23 signaling, the cytokines typically associated with regulation of Th17 expansion. Additionally, the abrogation of Th17 inducing bacteria in the gut microbiota was linked to increased Foxp3+ T regulatory cells in the lamina propria. These findings implicate gut microbiota composition in the induction of Th17 cells and the regulation of Th17:Treg balance in the lamina propria; this in turn suggests that certain populations of bacteria influence host defense and predisposition to inflammatory bowel diseases[105]. A subsequent investigation narrowed the search for Th17 inducing bacteria down to segmented filamentous bacteria (SFB). Germ-free mice were used as a model for Th17 deficient mice; the colonization of SFB in these mice led to the expression of IL-17 and IL-22 in the CD4+ T cells found in the intestine lamina propria. SFB colonization was also associated with a more potent host defense against *Citrobacter rodentium*, an intestinal pathogen. SFB is the first specific microbiota component that has been linked to Th17 cell differentiation, an important step in the still-growing understanding of the commensal mechanisms that shape host immunity[106]. The discovery that microbiota induce CD4+ T cells expressing IL-17 arouses speculation that alcoholic liver disease can be curbed through antibiotics that target specific microbiota components. However, studies have found that germ free mice associated with immune deficiency exhibit elevated levels of cirrhosis compared to those with active microbiota. Given this, the implications commensal bacteria carry for alcoholic liver disease[97], as well as any roles they may hold in its treatment[107], have yet to be conclusively defined.

IV. Conclusion

Considerable progress has been made in our understanding of the effects of alcohol on liver function, brain function, intestinal permeability, composition of the gut microbiota, and dysregulation of immune responses. However, we are still far from achieving a comprehensive understanding of the systemic interactions between affected organs, and mechanisms underlying pathological changes associated with chronic alcohol abuse. Therefore, further interdisciplinary collaborative studies are required to identify targets which mediate a crosstalk among injured organs, and that can either protect from or exacerbate alcohol-induced systemic multi-organ damage. IL-17 signaling may function as one of these potential targets, and more studies are required to address this question. The new animal models described above might provide new insights into the mechanism of IL-17 signaling in ALD and identify novel therapeutic targets.

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Abbreviations

Col collagen α1(I)

α-SMA	α-smooth muscle actin
qHSCs	quiescent Hepatic Stellate Cells
aHSCs	activated Hepatic Stellate Cells
iHSCs	inactivated Hepatic Stellate Cells

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