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Review

Dual effect of T helper cell 17 (Th17) and regulatory T cell (Treg) in liver pathological process: From occurrence to end stage of disease

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ABSTRACT

Liver disease is a complicated pathological status with acute or chronic progressions, causing a series of damages to liver and massive burden to public health and society. Th17 and Treg, two subsets of $CD4^+$ T helper cells, seem to keep a subtle balance in the maintenance of organic immune homeostasis including liver. The dysfunction of Th17/Treg balance in liver has been proved associated with hepatic injury and disease. Herein, we summarized the research advance of Th17 and Treg cells in different phenotypes of liver diseases in the past decade. It is known to all that hepatic diseases start from stimulations or infections like virus, autoimmune, alcohol and so on in the early stage, which would cause inflammation. With the disease consistently existed, severe outcomes like cirrhosis and hepatocellular carcinoma appear finally. In conclusion, it is found that Th17 and Treg cells serve as an important role in the immune response imbalance of liver diseases from the beginning to the end stage. However, the effect of these two subsets of $CD4^+$ T helper cells is not a stereotype. Pathological role which exacerbates the disease and protective character which inhibits damage to liver are co-existed in the effect of Th17 and Treg cells. Still, more studies should be carried out to enrich the understandings of liver disease and Th17/Treg immune balance in the future.

1. Introduction

Liver disease is a type of damage or pathological status in liver, which composed of a series of processes, causing a massive burden to public health and society. There are many different types of liver injuries and disease with common process. From the beginning of disease, inflammation occurs in liver. With the inflammation sustains, it starts to hurt liver permanently. In the end stage of liver disease, the transformation of liver is irreversible and the normal function of liver could be hardly maintained. Innate immune and some immune cells have been thought relevant in different phenotypes of liver injuries and diseases [1]. T helper cell 17 (Th17), as a subset of $CD4^+$ T helper (Th) cell, is

Abbreviations: ACLF, Acute-on-chronic liver failure; AH, Alcoholic hepatitis; AHA, Acute hepatitis A; AIH, Autoimmune hepatitis; AILD, Autoimmune liver disease; AKT, Protein Kinase B; ALD, Alcoholic liver disease; ALT, Alanine aminotransferase; APAP, Acetaminophen; AST, Aspartate aminotransferase; BA, Biliary atresia; BDL, Bile duct ligation; CCL, Chemokine (C-C motif) ligand; CD, Cluster of differentiation; CEACAM1, Carcinoembryonic antigen-related cell adhesion molecule 1; CHB, Chronic hepatitis B; CHC, Chronic hepatitis C; COX, Cyclooxygenase; DCs, Dendritic cells; DILI, Drug-induced liver injury; DNA, Deoxyribonucleic acid; Fas, Apoptosis antigen 1; Foxp3, Forkhead box P3; Gal, Galectin; HAV, Hepatitis A virus; HCC, Hepatocellular carcinoma; HCV, Hepatitis C virus; HMGB1, High mobility group box-1 protein; HSC, Hepatic stellate cell; ICP, Intrahepatic cholestasis of pregnancy; IL, Interleukin; IL-6R, Interleukin-6 receptor; JAK, Janus-activated kinase; JNK, c-Jun N-terminal kinases; miR155, MicroRNA-155; MMP, Matrix metalloproteinase; mTOR, Mammalian target of rapamycin; MxA, Myxovirus resistance A; NAFLD, Nonalcoholic fatty liver disease; NASH, Nonalcoholic steatohepatitis; OAS, Oligoadenylate synthetase; OLT, Orthotopic liver transplantation; PBC, Primary biliary cirrhosis; PBMCs, Peripheral blood mononuclear cells; PD-L1, Programmed death-ligand 1; PGE2, Prostaglandin E2; PSC, Primary sclerosing cholangitis; ROR-γt, RAR-related orphan receptor γt; SOCS, Suppressor of cytokine signaling; STAT, Signal transducers and activators of transcription; TGF, Transforming growth factor; TGFBR2, Transforming growth factor beta receptor 2; Th, T helper cell; Tim, T-cell immunoglobulin and mucin-domain containing; TIMP, Tissue inhibitors of matrix metalloproteinase; TLR, Toll-like receptor; TP, Triptolide; Treg, Regulatory T cell; TWHF, Tripterygium wilfordii Hook F; VDR, Vitamin D receptor; YAP, Yes-associated protein; α-SMA, α-smooth muscle actin

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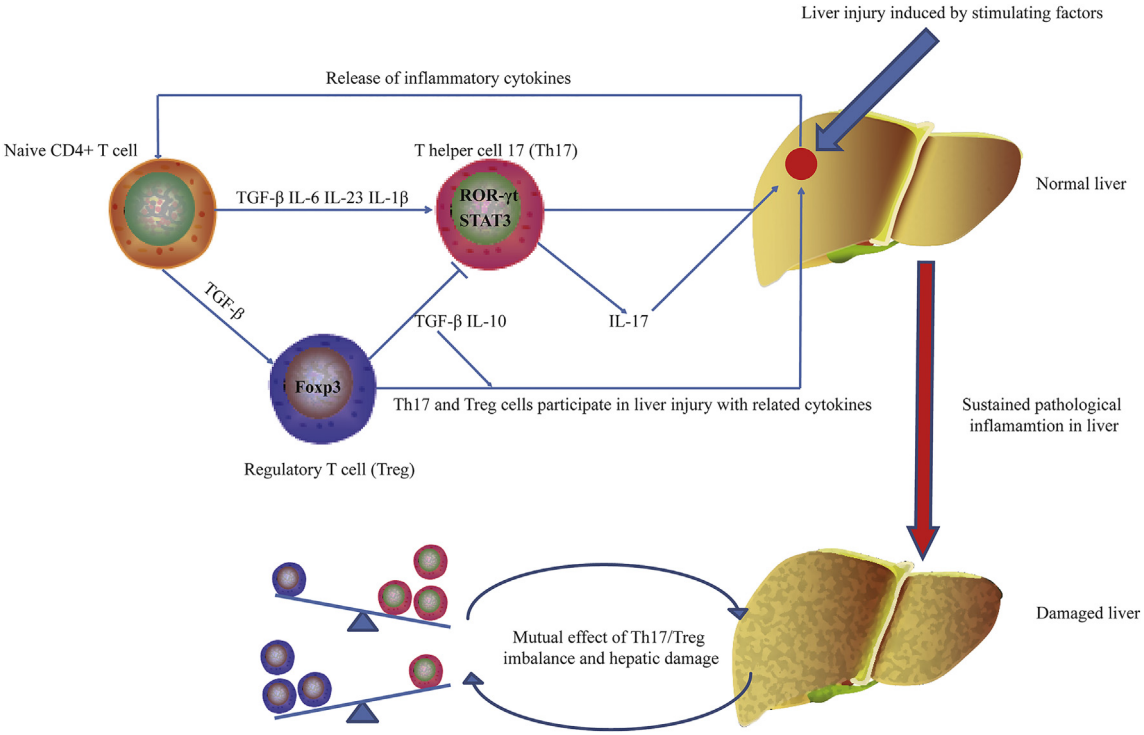

Fig. 1. Role of Th17 and Treg cells in liver disease. In the initiation of liver disease, it is certain that some parts of the liver are damaged with inflammation, which induced by some pathogenic factors such as virus and autoimmune. Meanwhile, the release of inflammatory cytokines induce Naïve $CD4^+$ T cells start to differentiate into Th17 and Treg cells in the context of inflammation in liver. Then, the mature Th17 and Treg cells in liver are able to participate in the pathological process of liver disease together with their related cytokines such as IL-17 and IL-10. The status of liver becomes worse for the duration of inflammation. Th17/Treg imbalance promotes the development of disease in an acute or chronic way. In addition, Th17/Treg imbalance existed extensively in the damaged liver. This mutual effect constantly exacerbates the condition of liver till the end stage of hepatic disease.

involved in the host defense against fungi and extracellular bacteria, which is important for the protection of body from pathogen infected. In recent years, studies reveal that a subset of Th17 is pathogenic and participant in the injury of liver disease [2]. Another subset of $CD4^+$ T cells in immune system which function as "immune-suppressor" is regulatory T (Treg) cells. It is widely accepted that Treg cells play a protective role in the control of excessive inflammation in physiological condition or some pathological contexts. Moreover, current studies also pay attention to the promotion of Treg cells in liver injury and disease. Th17 and Treg cells seem to keep a subtle balance in the maintenance of liver immune homeostasis. Furthermore, the dysfunction of Th17/Treg balance in liver has been proved associated with hepatic injury and disease. The development, differentiation, interaction and effect of Th17 and Treg cells in liver disease (Fig. 1) are not completely understood. Thus, it is of great necessity to explore the inner connection between Th17/Treg balance and liver injury in order to discover potential cures for liver disease, which not only makes us have a better understanding of immune system function but serves as an inspiration in the overcoming of organ injury and disease. In this review, we summarized the research advance of Th17/Treg balance related liver injury in the past decade. The effect of Th17 and Treg cells from occurrence to end stage of liver injury will be demonstrated separately.

2. The effect of Th17 and Treg cells in the occurrence of liver disease induced by some pathological factors

Despite different types of hepatic disease, they all start from disturbances or infections caused by some pathogenic factors. Liver injury initiates with slight inflammation and activation of immune system. The occurrence of immune response relies on coordination of innate and adaptive immune system. T helper cells can be considered a 'bridge' to link and make this two unique paths work as one. Consequently, it is reasonable to take Th17 and Treg cells into consideration. Under this circumstance, the imbalance of Th17 and Treg cells has been found participant in the initiation of disease which induced by pathogenic factors. In this part of review, we concluded roles of Th17 and Treg cells in liver injury and disease triggered by six inducements: virus, autoimmune, alcohol, obesity, cholestasis and drug.

2.1. Viral hepatitis

Viral hepatitis is pathology of liver inflammation due to viral infection, which may present in chronic or acute forms. It is detected that Th17 and Treg cells participate in the occurrence and development of the viral hepatitis. However, the role of Th17 and Treg cells is complicated. Herein, we mainly focus on the effect of Th17 and Treg cells in hepatitis induced by HAV (Hepatitis A virus), HBV (Hepatitis B virus) and HCV (Hepatitis C virus) (Tables 1, 2).

2.1.1. Hepatitis A

In the serum of pediatric patients with AHA (Acute hepatitis A), high level of Interleukin-17E (IL-17E) and IL-17F were found, correlating with increased level of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), indicating liver injury in the HAV infection. Th17-related cytokine proliferation seemed to be associated with HAV infection and play a role on the modulation of HAV-infected induced allergies [3]. As for Treg cells, it was found that both circulating and total Treg cells in peripheral blood were decreased in AHA patients, negative correlated with higher level of serum ALT and AST. With highly expressed death receptor Fas, Treg cells decreased in the AHA, and induced by apoptosis antigen 1 (Fas)-mediated apoptosis mechanism. Decreased number of Treg cells result in less suppressive effect in immune mediated liver injury in AHA [4].

Table 1
Variations of Th17 and Treg cells in viral hepatitis and autoimmune liver disease have been concluded, as well as the liver condition that affected by these changes.

Disease	Frequency or number of Th17	Frequency or number of Treg	Ratio of Th17/Treg	Liver condition	Reference
Hepatitis A	–	↓	–	Severe liver injury	[4]
Hepatitis B	↑	↑	↑	Chronic hepatitis B	[8–10]
	↑	↑	↓	Suppression of HBV clearance	[13]
	–	↑	–	Chronic hepatitis B	[21]
Hepatitis C	↑	–	–	Liver inflammation and damage	[22]
	–	↑	–	Restriction of fibrosis	[23]
	–	↑	–	Profibrogenesis	[24,25]
	↑	–	–	Infection resolved	[26]
	↓	↑	↓	Viral persistence	[26]
Autoimmune hepatitis	–	↑	–	Reduced severity of hepatitis	[34]
	–	↓	–	Loss of IL-17 suppression	[35]
	↓	–	–	Inflammation and severity in disease	[36]
Primary sclerosing cholangitis	–	–	–	–	
Primary biliary cirrhosis	↑	–	–	Promotion of hepatic fibrosis	[41,44]
	–	↓	–	Pathogenesis of disease	[46]

Note: The symbol "↑" represents increased frequency or number of the cells. Similarly, symbol "↓"represents decreased frequency or number of the cells. The "–" symbol represents that the change is not mentioned in article. Besides, this table was only generalized from articles which possess data from the clinical cases. Research articles using murine models were not taken into consideration in this chart.

2.1.2. Hepatitis B

Treg and Th17 immune imbalance is believed existing in chronic hepatitis B (CHB) [5]. Th17 cells can contribute to the immune activation and disease aggravation in CHB [6]. In an article about Chinese pediatric patients with CHB, Th17 cell frequency was associated closely with grades of liver inflammation [7]. The frequency of Th17 cells increased together with the same tendency of Treg cells. But the Treg/Th17 ratio decreased. This imbalance of Th17 and Treg is considered playing an important role in the pathology of CHB [8]. Besides, elevated number and ratio of Th17 is positively associated with increasing serum ALT levels in CHB patients but had no correlation with serum HBV DNA load, which means that Th17 cells may contribute to the disease progression instead of clearing the virus in CHB [9]. Similar results were found in CHB-induced cirrhosis and liver failure [10]. As for Treg cells, its inhibition effect to Th17 cells have been found and reported in CHB [11]. However, in another research, this effect of inhibition was not considered existed [12]. In another article about de novo hepatitis B virus infection after orthotopic liver transplantation, Th17 cells increased with clearance of virus. The level of IL-17 didn't significantly correlate with ALT. Conversely, Treg cells increased in the initiation of the infection and then decreased with the clearance of virus. This change of Th17/Treg frequency indicated that in the clearance of HBV, Th17 cells play a positive role. Instead, Treg cells could lead to immune suppression resulting in immune escape and chronicity [13].

The underlying mechanism of how Th17 and Treg cells influence hepatitis B and CHB process is still under study. Some cytokines, targets and related pathways were taken into consideration. As a major cytokine that Th17 cells secreted, IL-17 appears to be 'dual functional'. In the prevention of HBV, IL-17A effectively suppressed HBV replication in a non-cytopathic manner by enhancing the expression of antiviral protein myxovirus resistance A (MxA) and oligoadenylate synthetase (OAS) [14]. Besides, its pathological function in hepatitis B is widely noticed. Transforming growth factor β (TGF-β) and IL-21 levels were found to positively correlate with The levels of Th17 cells [15,16]. IL-6R expression on $CD4^+$ T cells also contributes to enhanced Th17 response in patients with CHB [17]. IL-22 has hepatoprotective and antifibrotic functions in acute liver injury models, but it is also found that IL-22 plays a pathological role in exacerbating chronic liver inflammation and fibrosis by recruiting hepatic Th17 cells in HBV-infected patients [18]. IL-23 is indispensable for the naïve T cell differentiating into Th17 cells (Fig. 1), and IL-23/IL-23R axis closely correlated with Th17 cells, liver damage and clinical phenotypes of hepatitis B patients [19]. HMGB1 was found in modulating Th17/Treg ratio balance via toll-like receptor 4 (TLR4)-IL-6 pathway in CHB patients [20]. Programmed death-ligand 1 (PD-L1) expression increased significantly with higher frequency of Treg cells in CHB patients, with positively correlating with the levels of ALT and AST. PD-L1 could be a potential indicator in the monitor of liver injury [21].

Table 2
Regulation of Th17 and Treg cells in viral hepatitis and autoimmune liver disease. Significant pathway, cytokine and target protein have been concluded.

Disease	Th17 related significant pathway, cytokine or target protein	Treg related significant pathway, cytokine or target protein
Hepatitis A	IL-17E and IL-17F [3]	Fas-mediated apoptosis [4]
Hepatitis B	IL-17, TGF-β, IL-21, IL-22 and IL-23 [14–16,18,19]	PD-L1 [21]
	IL-6 receptor [17]	
	HMGB1 and TLR4-IL-6 pathway [20]	
	MxA and OAS [14]	
Hepatitis C	IL-23/Th17 axis [29]	IL-8 [24,25]
	IL-21 [26]	TLR2 and HCV core protein [27]
		Gal-9 [26]
Autoimmune hepatitis	IL-17, IL-6 [31,32]	CEACAM1, IL-2 and STAT5 [37]
Primary sclerosing cholangitis		IL-12 [40]
Primary biliary cirrhosis	IL-17 [41–43]	
	IL-23p19 and IL-23/Th17 pathway [44]	
	VDR-miR155-SOCS1 pathway [45]	
	CCL20 [41]	

Note: The cytokine IL-17 family includes several members: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, IL-17F. IL-17A is the most studied one, and usually used the abbreviation "IL-17". When talking about the exact member in this family, strict differentiations must be used such as IL-17A and IL-17F. In addition, the abbreviations in this table have been concluded in the "Abbreviation" part in the manuscript.

2.1.3. Hepatitis C

Compared with Hepatitis B, hepatitis C is a long-term, chronic illness for most of infected people, causing serious diseases and resulting in health problems. Circulating and liver-infiltrating Th17 cells were found increased in chronic hepatitis C (CHC). This HCV-specific Th17 cells correlated with severity of liver inflammation and damage but not effect to viral replication [22]. This finding demonstrates that Th17 cells are related with the infection of HCV. The effect of Treg cells in CHC seems to be a 'double-edged sword'. On one hand, an increasing number of Treg cells were found localizing in liver and highly activated, which may result in restricting further fibrosis [23]. On the other hand, a subset of Treg cells were found to promote fibrogenesis in CHC, which have the ability producing IL-8 and activating hepatic stellate cells (HSCs) in an IL-8 dependent manner [24]. Similar phenomenon was detected in another research [25]. Research about the imbalance of Th17 and Treg cells in hepatitis C is also involved. In acute hepatitis C, this imbalance partially resulted in loss of $CD4^+$ T cell help and further virus persistence [26].

The mechanism of hepatitis C is ambiguous, but there are some important discoveries. TLR2 and its ligands such as HCV core protein [27] triggered Treg activation and expansion to inhibit host immune responses, resulting in viral persistence [28]. The IL-23/Th17 axis also plays a significant role in development of CHC and antiviral response [29]. T-cell immunoglobulin and mucin-domain containing 3 (Tim-3)/Galectin 9 (Gal-9) pathway was found activated in viral persistence with less $CD4^+$ and $CD8^+$ T cells. It is limited by IL-21 producing Th17 cells and enhanced by Gal-9 producing Treg cells in acute hepatitis C [26].

2.2. Autoimmune liver disease

Autoimmune liver disease is a general definition for autoimmune hepatitis, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC) and autoimmune cholangitis. The common characteristic of these diseases is excessive activation of body's immune system. Th17 cells have been recognized a promotion in autoimmune disease. But the effect of Treg cells is barely certain (Tables 1, 2). The ratio of Forkhead box P3 (Foxp3)/RAR-related orphan receptor γt (ROR-γt), which represent the transcriptional factors of Th17 and Treg cells, had been noticed in assessing the disease activity [30].

2.2.1. Autoimmune hepatitis

Th17 is believed involved in autoimmune diseases including autoimmune hepatitis (AIH). IL-17, the cytokine secreted by Th17 cells, contributes to the pathogenesis of AIH by inducing hepatic IL-6 expression [31], and inhibition of IL-17 promotes generation of stable Treg cells [32]. Regulatory T cells that increased [33] and accumulated in the liver are able to reduce the severity of T-cell mediated hepatitis in vivo, which play a key protective role in liver against inflammation [34]. A reduced subset of $CD39^+$ Treg cells failed to efficiently suppress IL-17 production [35]. Conversely, this subset of Treg cells displays a proinflammatory profile in AIH. Interestingly, in an article about juvenile autoimmune liver disease (AILD) including AIH patients, a special subset of Th17, $CD39^{++}$ Th17 cells also express immunosuppression property. This subset of Th17 decreased in number and defected in function, leading to inflammation and severity in disease [36]. Studies about $CD39^+$ $CD4^+$ T cells in AIH are worthy further investigations in the future.

The mechanism of how Treg works is rare. Carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) were analyzed for the promotion of IL-2 production and signal transducers and activators of transcription 5 (STAT5) phosphorylation, leading to enhanced Treg induction and stability [37].

2.2.2. Primary sclerosing cholangitis

Primary sclerosing cholangitis is a slow, progressive and cholestatic disease that damages the bile ducts inside and outside the liver. Some infection-related pathogens which cultured in PSC patients' bile fluid could stimulate a higher level of Th17 generation in patients with PSC compared with healthy controls and other groups [38]. Treg cells were thought a protect role by decreasing hepatic $CD8^+$ T cells [39]. Reduced numbers of regulatory T cells have also been reported in PSC, but in vivo hepatic Treg expansion failed to improve the course of cholangitis, which was related to the effects of hepatic IL-12 on Treg cells. IL-12 receptor knockout was able to maintain the functionality of hepatic Treg cells [40].

2.2.3. Primary biliary cirrhosis

Primary biliary cirrhosis, also known as primary biliary cholangitis, is an autoimmune disease of the liver. It results from a long-term and progressive destruction of the small bile ducts of the liver, causing cholestasis. In PBC patients, circulating and hepatic Th17 cells were found elevated. With progression of disease, Th17 population decreased in the circulation but great accumulated in liver, which regulated by chemokine (C-C motif) ligand 20 (CCL20). IL-17 may be involved in the process of PBC fibrosis for promoting activation of HSCs [41]. Periductal produced IL-17 was found associated with chronic inflammation of bile ducts in PBC, which contribute to the pathogenesis [42]. Similar results were established in another article. Increased level of IL-17 was detected in liver tissue from PBC patients. The upgrading frequency of Th17 was also found distributing in liver compared with periphery in an IL-2 receptor α knockout murine model of human PBC. Hence, researchers assumed that an inflamed liver microenvironment maybe a preference for the induction of Th17 cells, which might help explain a number of liver diseases [43]. In the maturation of Th17 from naïve $CD4^+$ T cells, IL-23 is of vital importance, and IL-23/Th17 pathway may be considered as a potential target for PBC therapeutic intervention [44]. The vitamin D receptor (VDR)-microRNA-155 (miR155)-suppressor of cytokine signaling 1 (SOCS1) pathway was proved involved in the Th17/Treg related pathogenesis of PBC and PSC as well. As a constraint of inflammation, VDR targets miR155-SOCS1 axis. In peripheral blood mononuclear cells (PBMCs) of PSC and PBC patients, VDR and SOCS1 protein expression was reduced considerably. The decreased protein level of SOCS1 was found fulfilled by enhanced miR155 expression in PBC patients [45].

The role of Treg cells in PBC is controversial. In general thoughts, Foxp3 serves as a vital nuclear factor for the function of Treg cells. However, the exact role of transcriptional factor Foxp3 in Treg cells has been challenged. Because a research found that $CD4^+$ $CD25^+$ but not $CD4^+$ $Foxp3^+$ Treg cells were observed as a regulatory role in PBC [46].

2.3. Alcoholic liver disease

Alcoholic liver disease is a series of disorders that encompasses the liver manifestations of alcohol overconsumption. The activation of the innate immune response may promote the development of alcoholic liver disease (ALD). The research about Th17 and Treg cells in ALD is insufficient by now (Tables 3, 4). It was reported that elevation of serum Th17-assosiated interleukins, IL-17A, IL-17F, and IL-22 correlated with the progression of liver damage in ALD [47]. In alcoholic hepatitis, peripheral blood Treg cells are significantly decreased in patients with alcoholic hepatitis (AH) not only compared to the healthy but the alcoholic patients without liver disease [48], indicating the relation of Treg cells and AH. More studies about T helper cells in alcoholic liver disease and further investigations aimed at potential mechanisms still need to keep working on.

2.4. Nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease is a clinicopathological syndrome characterized by excessive fat deposition in liver [49] that caused by

Table 3
Variations of Th17 and Treg cells in alcoholic liver disease, nonalcoholic fatty liver disease, cholestatic liver disease, drug-induced liver injury, cirrhosis, liver failure and hepatocellular carcinoma have been concluded, as well as the liver condition that affected by these changes.

Disease	Frequency or number Th17	Frequency or number Treg	Ratio of Th17/Treg	Liver condition	Reference
Alcoholic liver disease	–	↓	–	Alcoholic hepatitis	[48]
Nonalcoholic fatty liver disease	↑	–	↑	Progression to nonalcoholic steatohepatitis	[50]
		↑		Nonalcoholic steatohepatitis	[55]
	↑	↓	↑	Nonalcoholic steatohepatitis	[56]
Biliary atresia	↑	↓	↑	Biliary duct damage	[62,64]
Drug-induced liver injury	–	–	–	–	
Liver fibrosis	↑	–	–	Leading to cirrhosis	[78]
Cirrhosis of liver	↑	↑	↑	Development of HBV-associated cirrhosis	[79,81]
Acute-on-chronic liver failure	↑	↓	↑	Liver Injury in liver failure	[85]
	–	–	↑	Poor survival rate of patients	[86,87]
	–	↑	–	Poor outcomes	[90]
Hepatocellular carcinoma	↑	–	–	Promotion of tumor progression	[92]
	↑	–	–	Angiogenesis and poor survival rate	[93]
	↓	↑	↓	Promotion of tumor development	[96]

Note: The symbol "↑" represents increased frequency or number of the cells. Similarly, symbol "↓"represents decreased frequency or number of the cells. The "–" symbol represents that the change is not mentioned in article. Besides, this table was only generalized from articles which possess data from the clinical cases. Research articles using murine models were not taken into consideration in this chart.

explicit factors except alcohol, which result in liver injuries. Two types of nonalcoholic fatty liver disease (NAFLD) are simple fatty liver (Nonalcoholic Fatty Liver) and nonalcoholic steatohepatitis. In simple fatty liver, there is little or no inflammation or liver cell damage. Instead, In nonalcoholic steatohepatitis (NASH), inflammation and liver cell damage happens in addition to fat in liver, and the immune system becomes activated.

Th17 cells are believed to play a pathological role in NAFLD (Tables 3, 4). It has been reported that, an elevated frequency of Th17 in liver with an increased Th17/Treg ratio in peripheral blood and liver marked the progression from nonalcoholic fatty liver to nonalcoholic steatohepatitis [50]. Similarly, in a mouse model of high fat diet, NASH was developed. $CD4^+$ $ROR\gamma t^+$ Th17 cells were significantly increased in the liver, together with upregulated inflammatory cytokines [51]. The cytokine IL-17 was thought to be associated with hepatic steatosis and proinflammatory response in NAFLD [52]. In a further study, DNA damage in hepatocytes were observed to trigger inflammation via Th17 and IL-17A, inducing white adipose tissue neutrophil infiltration, mediating insulin resistance and fatty acid release, which stored in liver as triglycerides, causing NASH. NASH is a common cause of hepatocellular carcinoma with disease sustained. Pharmacological suppression of Th17 cell differentiation, IL-17A blocking, and ablation of the IL-17A receptor are able to prevent NASH and subsequently hepatocellular carcinoma (HCC) [53]. The molecular mechanisms of the hepatotoxic action of IL-17 might be associated with increased c-Jun N-terminal kinases (JNK) activation of steatotic hepatocytes [54].

Research about Treg cells in NAFLD is rare, and the role of Treg cells is neither clear (Tables 3, 4). In liver tissues obtained from patients with NASH, hepatocytes with microvesicular steatosis seem to be expressing more inflammatory markers and an increased number regulatory T cells [55], indicating the dynamic change of Treg cells in NAFLD. Besides, in a current study about imbalance of Th17/Treg in NASH, there seemed to be an increasing ratio of Th17 cells, and a lower proportion of Treg cells in liver [56]. The change of Treg in NAFLD and underlying molecular mechanism still need to further investigated.

2.5. Cholestatic liver disease

Cholestasis is a chronic condition caused by an impairment of the biliary system, provoking a decrease or obstruction of bile secretion from liver to intestine. Degeneration of liver tissues, chronic inflammation and fibrosis happen in the progression of cholestasis. Th17 and Treg cells now are found intimate in the development of cholestatic liver disease (Tables 3, 4). In an article about patients with intrahepatic cholestasis of pregnancy, the level of serum and placental tissues IL-17 is increased together with lower IL-35 level, a new-discover subset of IL-12 cytokine family with potent effect of immunosuppression. The Th17/Treg ratio may be modulated by dendritic cells (DCs) in ICP [57].

Table 4
Regulation of Th17 and Treg cells in alcoholic liver disease, nonalcoholic fatty liver disease, cholestatic liver disease, drug-induced liver injury, cirrhosis, liver failure and hepatocellular carcinoma. Significant pathway, cytokine and target protein have been concluded.

Disease	Th17 related significant pathway, cytokine or target protein	Treg related significant pathway, cytokine or target protein
Alcoholic liver disease	IL-17A, IL-17F, and IL-22 [47]	
Nonalcoholic fatty liver disease	IL-17 [51–53]	
	JNK [54]	
Intrahepatic cholestasis of pregnancy	IL-17, IL-35, TGF-β1 and, TGF-β2 [57,58]	
Biliary atresia	IL-17A, IL-1β, IL-6 and TGF-β1 [62]	
Drug-induced liver injury	IL-17 [68,71]	
Fibrosis	IL-17, IL-6, TGF-β and IL-1β [73–75,78]	MMPs/TIMPs balance [77]
	α-SMA [73]	
Cirrhosis	COX-PGE2 pathway [84]	
	IL-35, IL-6 and IL-1β [80,84]	
Acute-on-chronic liver failure	IL-6 and mTOR-STAT3 pathway [89]	
Hepatocellular carcinoma	IL-17 and IL-17 receptor E [94]	TGF-β [98,99]
	IL-6/JAK2/STAT3-AKT pathway [95]	CCL20-IL-17-IL-6 transcriptional network [100]
		YAP-1 and TGFBR2 [101]

Note: The cytokine TGF-β family belongs to the transforming growth factor superfamily. TGF-β1, TGF-β2, TGF-β3 and TGF-β4 are several members of the isoforms. TGF-β1 is the most studied one, and usually used the abbreviation "TGF-β" just like IL-17. When talking about the exact member in this family, strict differentiations must be used such as TGF-β1 and TGF-β2. In addition, the abbreviations in this table have been concluded in the "abbreviation" part in the manuscript.

In another cholestasis model of bile duct ligation, pro-fibrogenic cytokines IL-17, TGF-β1 and, TGF-β2 were found increased. The source of IL-17 may be Th17 cells [58]. Besides, the number of Treg cells in bile duct ligation (BDL) model was observed to increase. This elevated Treg cells caused impairment of liver T lymphocyte function, modulated liver cholestasis and fibrosis, and limited liver injury [59]. Depletion of $Foxp3^+$ Treg cells enhanced Th17 cell response and promotes increase of IL-17 cells and related gene expressions [60]. However, it is controversial whether Treg cells are protective in BDL induced cholestatic liver injury. Because in another report, Treg cells were found capable in suppressing symptom development, but not altering liver injury in BDL mice [61].

2.5.1. Primary sclerosing cholangitis and primary biliary cirrhosis

PSC and PBC are liver diseases with biliary obstruction and activation of autoimmune. Role of Th17 and Treg in PSC and PBC have been mentioned in the 'Autoimmune liver disease' section.

2.5.2. Biliary atresia

Biliary atresia (BA) is a rare disease of infants with ducts blockage. The bile flow from the liver to the gallbladder is blocked, leading to liver damage and cirrhosis of the liver. Several studies have reported that Th17 and Treg participate in the progression and pathogenesis in BA (Tables 3, 4). In patients with BA, it was found that the ratio of Th17/Treg significantly increased with higher level of Th17 and lower Treg cells. Meanwhile, related cytokine mRNA and proteins level such as Foxp3, ROR-γt, IL-17A, IL-1β, IL-6 as well as TGF-β1 were also elevated. The changed proportion of Th17 and Treg cells, along with cytokine level, may be involved in the biliary duct damage in BA [62]. However, in another investigation, the source of elevated IL-17 is believed not from Th17 but γδT cells in BA patients [63]. Compared with Th17, effect of Treg cells in BA is quite clear. Liver Treg cells were decreased in number, activation marker expression and suppressive function in a mouse model of BA. Adoptive transfer Treg cells to BA mice significantly increased survival rate. Depletion of Treg cells in model mice resulted in increased bile duct injury [64].

The possible mechanism and key modulation of Th17 and Treg cells in BA is still blurring. DCs were found playing an important role in regulating Treg-Th17 axis and aggravating progressive inflammatory injury in ductal obstruction [65]. Methylation of CpG islands in Foxp3 promoter seems to be a vital modification in Treg cells in BA. Demethylation-modified Treg cells with decreased function were shown to significantly improve BA phenotypes when adoptively transferred to BA model mice [66].

2.6. Drug-induced liver injury

Drug-induced liver injury is a cause of acute and chronic liver disease. More than 900 drugs, toxins, and herbs have been reported to cause liver injury and it is the most common reason for a drug to be withdrawn from the market [67]. Acetaminophen, as one of the most studied drugs causing direct liver injury, is generally considered to metabolize in liver. The overdose of acetaminophen leads to over consumption of glutathione, which will result in accumulation of toxic metabolite in liver and induce liver injury. However, in a research about acetaminophen-induced liver failure, elevated IL-17 was also found, and the source of IL-17 was mostly Th17, indicating that Th17 may play a exacerbation role in APAP-induced hepatotoxicity [68]. Traditional Chinese Medicine tripterygium wilfordii Hook F, which exhibits unique immune regulative effects in the treatment of rheumatoid arthritis and systemic lupus erythematosus, has a notable hepatotoxicity in the use of medication [69]. Triptolide is isolated from TWHF and serves as a major active ingredient of TWHF, but its clinical applications are limited due to severe toxicities especially hepatotoxicity [70]. In the study of our laboratory, it was found that TP could induce the imbalance of Th17 and Treg with expansion of Th17 cells and suppression of the production of Treg cells during liver injury [71], and the cytokine IL-17 mediated this injury [69]. Adoptive transfer of Treg cells could ameliorate the injury [72], which may represent a new pathogenesis of TP-induced liver injury.

3. The function of Th17 and Treg cells in the end stage of liver disease

With the development of disease progression, a transform concerning the entire organ even the whole body is taking place. The liver ends up with some damaging outcomes like cirrhosis, failure and carcinoma in an acute or chronic manner. Th17 and Treg cells are also found participant in the progression and end stage of liver injury and disease. In this part of review, we summarized the function of Th17 and Treg cells in the severe outcomes of liver disease process (Tables 3, 4).

3.1. Cirrhosis of liver

Cirrhosis is a chronic disease of the liver. The liver does not function properly due to long-term damage which characterized by the replacement of normal liver tissue by scar tissue. In the pathological process of cirrhosis, liver fibrosis plays an important role in early stage. If not treated in time, the liver would end up in cirrhosis even HCC. In the progression of cirrhosis, inflammatory infiltration serves as a curial factor. Th17 cells have been found closely connected with fibrosis and cirrhosis of liver, but effect of Treg cells is not easy to determine. The change of Th17/Treg ratio exists and acts as a pathological role in process of liver cirrhosis.

3.1.1. Liver fibrosis

Fibrosis is the first stage of liver scarring. In a mouse model of liver fibrosis, the frequency of Th17 cells in the model group was increased but the frequency of Treg cells decreased gradually. The imbalance of Th17/Treg ratio appeared with higher levels of IL-6, TGF-β and α-smooth muscle actin (α-SMA) which indicating the activation of HSCs [73]. The cytokine IL-17 was found localizing in the fibrosis region and promoting pathogenesis of liver fibrosis through HSCs activation [74,75]. Th17 served as an important source of IL-17. Identically, down-regulation of Th17 was involved in the reduced process of fibrosis caused by Schistosomiasis [76]. Interestingly, the effect of Treg cells do not seem opposite to Th17. Treg cells were found to suppress fibrosis resolution and maintain liver fibrosis by regulating the balance of Matrix metalloproteinases (MMPs)/Tissue inhibitors of matrix metalloproteinases (TIMPs), which left a debatable role to keep investigating [77]. In hepatitis C induced liver allograft fibrosis, HCV specific $CD4^+$ Th17 cells which induced by proinflammatory mediators such as IL-17, IL-1β and IL-6 increased and led to cirrhosis in orthotopic liver transplantation (OLT) recipients [78].

3.1.2. Cirrhosis

Cirrhosis is a slow, long-term disease with scar tissue takes the place of healthy liver tissue, eventually preventing the liver from functioning properly. Upregulated Th17 and IL-17 level, imbalance ratio of Th17 and Treg cells and activation of HSCs are common characters in cirrhosis. In an article studying HBV-associated liver cirrhosis, the decreased Treg/Th17 proportion led to exacerbation in disease progress [79]. IL-35, as an inhibitory factor in the differentiation of Th17 cells, were thought to be concerned with the pathogenesis of hepatitis B-related liver cirrhosis [80]. In patients with CHB related liver fibrosis, proportions of peripheral Th17 and Treg cells were found both significantly increased and correlated with the severity of disease. However, a lower Treg/Th17 ratio indicated more liver injury and disease progression [81]. HSCs activation was thought associated with the cirrhosis and severity of disease [82,83]. In addition, HSCs are also considered as a promote mediator in the genesis of abundant Th17-induced fibrosis progress. Release of IL-1β, IL-6 as well as the activation

of Cyclooxygenase (COX)-Prostaglandin E2 (PGE2) pathway may partially account for this HSCs' promotion effect for Th17 [84].

3.2. Acute-on-chronic liver failure

"Acute on chronic liver failure (ACLF)" is said to exist when someone with chronic liver disease, such as HBV infection, develops features of liver failure. Th17 and Treg cells are observed involved in the pathology of ACLF. In HBV-related ACLF, the ratio of Treg to Th17 cells frequency decreased, with more Th17 but less Treg cells. Higher frequency of Th17 positively correlated with liver injury and severity of ACLF, as a role of exacerbating liver damage during chronic HBV infection [85]. In another research, this low Treg/Th17 frequency predicts poor survival rate, and patients ended up with death or liver transplantation [86,87]. Similar phenomenon about change of Th17 cells has been confirmed in a rat model of ACLF [88]. IL-6 may be crucial in upregulating Th17 response via mammalian target of rapamycin (mTOR)-STAT3 pathway [89].

However, the role of Treg cells may be unusual, and more work need to be done to explore the possible mechanism. It was found that Treg cells amounts were higher and positively associated with worse severity and poorer outcomes in ACLF [90]. Meanwhile, a subset of Treg cells ($CD4^+$ $CD25^{high}$ Treg), was also found significantly increased in peripheral blood of ACLF patients and positively correlated with HBV DNA load, which may be used in helping diagnosis and treat patients with ACLF. But the role of Treg cells in the disease was not mentioned [91]. On the contrary, in a rat model of ACLF, the proportion of Treg cells were observed to gradually decrease and become stable, indicating a dysfunction of regulatory T cells [88].

3.3. Hepatocellular carcinoma

Hepatocellular carcinoma is a cancer that starts from liver. Hepatitis B or hepatitis C, cirrhosis, alcohol, obesity and diabetes could be the causes of HCC. Recently, Th17 and Treg have been concentrated on in the participant of HCC process. In HBV-related HCC, intratumoral densities of Th17 cells were augmented [92]. These Th17 cells were thought to promote tumor progression and correlate with poor survival rate through fostering angiogenesis [93]. IL-17 is a crucial cytokine for the function of Th17 in HCC. In patients with HCC, high expression of intratumoral IL-17 and IL-17 receptor E were reported, associated with poorer survival rate and increased recurrence [94]. It is likely that IL-17 boosts tumor progression through IL-6/janus-activated kinase (JAK2)/STAT3 induction by activating the protein kinase B (AKT) pathway [95].

The balance of Th17 and Treg cells seems existed in HCC, and Treg cells also play a significant role in HCC. The density of liver infiltrated Treg cells was increased in a stepwise manner from CHB to HCC, while the density of Th17 cells was decreasing. This imbalance promotes HCC development and affects the prognosis of HCC [96]. In a model of tumor bearing mice, Treg cells were observed increased compared with normal mice, which was thought to be associated with the suppression of anti-tumor immunity [97]. In the studies about Treg cells in HCC, some cytokines and chemokine were focused. TGF-β, a multifunctional cytokine belonging to the transforming growth factor superfamily, was reported. Cancer-secreted TGF-β1 increase Treg cells, and TGF-β1 knockdown impaired immunosuppression in the tumor microenvironment by decreasing Treg cells [98]. Identical result was also found that TGF-β is necessary for HCC progression, acting by inducing Treg cell polarization [99]. Besides, CCL20-IL-17-IL-6 transcriptional network was observed and facilitated Treg activity in advanced grades and metastasis in HCC [100]. About the mechanism of Tregs in HCC, Yes-associated protein (YAP-1) was reported to promote Treg cells' differentiation in HCC by enhancing Transforming growth factor beta receptor 2 (TGFBR2) transcription [101].

4. Discussion

It is generally believed that the body's immune organ contains central immune organ (bone marrow and thymus) and peripheral immune organ (lymph node and spleen). Liver, as the largest organ in body, is usually considered important in the metabolism of multiple substances. As a matter of fact, liver has been recognized an important organ in host defense in recent years' research. In addition, it is observed that liver serves as a significant organ for T cells differentiation. In a word, liver is also function as an important immune-regulate organ. Recent years, pathological immune activation in liver diseases has been focused, and role of Th17/Treg cells has been revealed gradually. In this review, we concluded a dual effect of Th17 and Treg cells in liver diseases. On the one hand, Th17 cells have function in host defense against exogenous infection, because a proper level of inflammation is beneficial for foreign matter's clearance and self-healing. However, if this immune response of Th17 loses control, the situation would be different. Over activated immune system lacks suppressive regulation, leading to severe outcomes. Similarly, Treg cells have the function of immune suppression, and act as a "suppressor" role in the resolution of inflammatory under physiological condition. But this over-suppressed status is also harmful for liver immune homeostasis if Treg cells are activated permanently without any limitation. Too much restriction of immune system result in sustained low level of immune response, which end up with chronic disease even cancer. Thus, it is necessary to combine the physiological and pathological effects of Th17 and Treg cells in liver disease.

In the writing of this manuscript, we also found something which is worth to discuss. As summarized in four tables (Tables 1–4), there are much more articles studying Th17 cells, and Treg cells seem to be "ignored and forgettable". We also generalized the possible regulation of Th17 and Treg cell in hepatic diseases, and here is the summary. So far, there are mainly three kinds of regulations of Th17/Treg balance in liver disease after going through all the papers we collected. The first type of regulation is about proinflammatory pathways, including cytokines with its receptors and significant target protein inside the pathway. In brief, inflammation is essential in hepatic function and inevitable in liver disease. Thus, it is reasonable for proinflammatory pathways such as TLR pathway and COX-PGE2 pathway to be activated in Th17 mediated liver disease, together with crosstalk of a series of cytokines like IL-17, IL-6 and so on. The keywords of the second type of regulation are "life" and "death". Many of the articles focused on how $CD4^+$ T cells proliferate and differentiate in liver disease, thus the pathways about cell proliferation and survival such as Jak2-STAT3-AKT and mTOR-STAT3 pathway were investigated and found closely associated with Th17/Treg imbalance in disease. In addition, when coming to how a subset of $CD4^+$ T cells decrease in liver disease, the pathway concerning cell death such as Fas mediated apoptosis would also be considered. The third type of regulation is about immunosuppression. Some significant proteins such as PD-L1 and SOCS serve as regulated and controlled characters in immune homeostasis. Once expression level of these proteins changed in $CD4^+$ T cells, overwhelming inflammation or sustained immunosuppressed status would occur, leading to acute or chronic process in the exacerbation of liver disease.

However, most of the articles prefer to describe a phenomenon in a kind of liver disease, but the deep research about the mechanisms is hardly involved. As we all know, samples from clinical cases are valuable and important in the scientific research. It needs to dig out to find more substantial results about the effect of Th17 and Treg cells in liver disease. In addition, there are still some paradoxical results in the research of one same disease in the available data, which remind us of the need to keep exploring. Last but not least, in most articles studying Th17 and Treg cells in liver disease, leaving Th17 and Treg cells alone is less rigorous. $CD4^+$ T cell is like a "bridge" not the "killer". We ought to take other immune cells even other types of cells in liver microenvironment together to evaluate its effects in liver disease.

In conclusion, the roles of Th17 and Treg cells in different liver disease are summarized in this review; Th17 and Treg cells serve as an important role in the disorder of immune response all through liver injuries and diseases. Inflammation, cell proliferation and immunosuppression are three significant aspects in the regulation of Th17/Treg balance. More works should be carried on to figure out the substantial character and regulation of Th17 and Treg cells in liver pathogenesis.

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Declaration of interest

None.

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