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Review

Dysfunctions of Circulating Adaptive Immune Cells in End-Stage Liver Disease

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Abstract: End-stage liver disease (ESLD) from acute liver failure to compensated advanced chronic liver disease and decompensated cirrhosis at different stages (chronic decompensation, acute decompensation with or without acute-on-chronic liver failure) has high disease severity and poor patient outcome. Infection is a common complication in patients with ESLD and it is associated with a high mortality rate. Multiple mechanisms are involved in this marked susceptibility to infections, noticeably the inadequate immune response known as immune paresis, as part of cirrhosis-associated immune dysfunction (CAID). Specifically in the adaptive immune arm, lymphocyte impairments—including inadequate activation, reduced ability to secrete effector molecules and enhanced immune suppressive phenotypes—result in compromised systemic immune responses and increased risk of infections. This review summarises current knowledge of alterations in adaptive immune responsiveness and their underlying mechanisms in ESLD. Understanding these mechanisms is of crucial importance in the identification of potential therapeutic targets and applications of targeted treatments beyond antimicrobials, such as immunotherapy.

Keywords: adaptive immune; T cell; B cell; immune paresis; end-stage liver diseases; cirrhosis-associated immune dysfunction (CAID)

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1. Introduction

End-stage liver disease (ESLD) covers a large spectrum of disease severities; it includes acute liver failure (ALF) without underlying chronic liver disease, compensated advanced chronic liver disease (cACLD) (defined according to the Baveno VII criteria [1]) complicated cirrhosis at different stages (chronic decompensation (CD) and acute decompensation (AD) without or with organ failure, referred to as acute-on-chronic liver failure (ACLF). ESLD patients' outcome is significantly impaired compared to the general population, with a poor prognosis associated with disease severity (>90% 1-year survival in compensated cirrhotic patients versus 60% in decompensated cirrhotic patients [2]). Following AD, a 27% 1-year mortality rate has been reported in a European multicentric cohort in the absence of organ failure [3], whereas the highest mortality risk has been described for patients with multiple organ failure (79% 3-month mortality for grade-3 ACLF patients [4]). Several complications, including bacterial infections, contribute to the impairment of cirrhotic patients' survival at any stage.

Twenty years ago, in the first study based on the US National Hospital Discharge Survey (NHDS), the authors showed that cirrhotic patients were more likely to be admitted for sepsis and exhibited a higher mortality rate compared to the general population [5]. The incidence of bacterial infections among hospitalised cirrhotic patients has been reported

in multiple studies, suggesting a rate of bacterial infection between 25% and 47% in this specific population and even higher in the most severely ill patients (in the presence of ascites or ACLF) [4,6–9]. This high rate of infectious complications in patients with cirrhosis represents a crucial issue because of its dramatic impact on clinical outcomes. In a French prospective study of patients with viral hepatitis-induced cACLD, infections were reported to be the most frequent precipitating event for cirrhosis decompensation, leading to an increased mortality risk [10]. A recent European multicentric prospective study based on almost 1500 patients showed that infectious events account for the most frequent precipitating factor for AD and ACLF [11]. Bacterial infections significantly impair patients' outcomes compared to other cirrhosis complications, as demonstrated by a meta-analysis from 2010, showing a higher mortality rate for admitted cirrhotic patients with infections compared to non-infected patients [12].

Multiple mechanisms are likely involved in this high infection susceptibility and these poor outcomes following an infectious event [13]. Bacterial translocation from the gut could promote bacterial infection, facilitated by intestinal barrier alterations and dysfunctions and gut dysbiosis. Cirrhosis-associated immune dysfunction (CAID), described in several studies [14–16], could also be involved in infection development and outcomes. CAID has been defined as an immune paresis in response to excessive pro-inflammatory stimulations [14], as previously described in sepsis in the general population [17]. Different studies have then consolidated this hypothesis of an excess of baseline inflammation and/or myeloid cell stimulation, leading to an impaired innate immunity-driven anti-microbial response (at cellular and molecular levels) [18–20]. Alterations in resident or peripheral immune cells' phenotype and function in patients with liver failure could be required to promote inflammation resolution, while contributing to infection susceptibility because of their anti-inflammatory profile. High plasma levels of pro-inflammatory cytokines and repeated stimulation of Pathogen-Associated Molecular Patterns (PAMPs) receptors or release of Damage-Associated Molecular Patterns (DAMPs) have been suggested to drive the immune-regulatory phenotype and function of innate immune cells [20–23]. Notably, pro-resolution monocyte phenotypes have been described to be associated with in vitro impaired anti-bacterial functions and poor clinical outcomes [21,24,25].

Recent studies have also described changes in systemic adaptive immune response in the setting of ESLD, which could impact clinical course [26–29]. The adaptive immune response is essential for antigen-specific responses: humoral immune response and infected cell and/or pathogen killing. Besides the response to infectious events, effective adaptive immunity is crucial to establish immune memory and so to limit the occurrence of further severe infectious events. Vaccine response, which is a major issue in the setting of liver transplantation patients, also depends on the efficacy of the adaptive immune response. In this review, we report adaptive immune response alterations described in ESLD, clinical consequences and future research areas.

2. Clinical Definitions and Main Pathophysiological Concepts

2.1. Acute Liver Failure

ALF is a rapid-onset clinical syndrome occurring in the absence of pre-existing chronic liver disease [30]. ALF cases can present with jaundice, coagulopathy (raised INR) and hepatic encephalopathy [31]. It is a rare but severe condition in which coagulopathy and neurological disorders due to hepatic encephalopathy and systemic inflammation associated with elevated risk of secondary infection result in high mortality [31]. Rapid overwhelming hepatocyte damage can be seen histologically as widespread necrosis and apoptosis of hepatocytes [31]. This contributes to high sterile inflammation, leading to the promotion of pro-resolution monocytes/macrophages and $CD4^+$ T cells [22,23,26]. However, this compensatory anti-inflammatory immune response leads to high infection susceptibility, infections and multi-organ failure, representing the most frequent causes of death in ALF patients [32].

2.2. Natural Evolution of Cirrhosis: From cACLD to AD and ACLF

Chronic liver diseases may lead to progressive intrahepatic fibrosis development, finally resulting in cirrhosis, which is defined by annular fibrosis and the destruction of normal liver histological architecture [33]. While alcohol is the most common underlying cause of liver disease in Europe, viral hepatitis is responsible for most cirrhosis diagnosed in Asia-Pacific regions. The early stage of cirrhosis is usually poorly symptomatic, also referred to as non-complicated cirrhosis or compensated cirrhosis. Recently, the concept of compensated advanced chronic liver disease (cACLD) has been proposed by the Baveno VII conference to reflect the continuum between severe fibrosis and compensated cirrhosis. cACLD is defined by the absence of previous cirrhosis complications and liver stiffness above 10 kPa (a liver stiffness between 10 and 15 kPa being suggestive of cACLD and a value > 15 kPa highly suggestive of cACLD). These values are also relevant to rule out the risk of clinically significant portal hypertension and a 3-year risk of liver decompensation or related death (<1% for liver stiffness < 10 kPa) [1].

The sudden onset of one or more events related to cirrhosis complications (ascites, gastrointestinal haemorrhage, hepatic encephalopathy) defines acute decompensation of cirrhosis. Whether bacterial infection should be considered a cirrhosis complication or just a precipitating event is still under debate [1,34]. While an acute event occurring within a 2-week period determines AD, the slow development of cirrhosis complications defines non-acute decompensation of cirrhosis [35]. Chronic decompensation of cirrhosis encompasses the persistence of decompensation following AD and non-acute decompensation of cirrhosis.

The occurrence of organ failure in association with AD characterises a specific condition named acute-on-chronic liver failure (ACLF). The CANONIC study by the European Foundation for the study of Chronic Liver Failure (EF-CLIF) consortium aimed to define ACLF in AD patients with the worst clinical course and prognosis, which led to the CLIF ACLF definition: cirrhosis AD associated with no organ failure (or single organ failure without renal and brain dysfunction) or multiple organ failures [4].

The definition of ACLF remains controversial due to the various distinct descriptions published by different organisations. Another definition is given by the Asian Pacific Association for the Study of the Liver (APASL): underlying chronic liver disease (cirrhotic or non-cirrhotic, excluding isolated steatosis) with an acute hepatic insult (viral hepatitis, alcohol consumption or drug-induced liver toxicity) causing liver failure (defined by jaundice and coagulopathy) [36]. The negative criteria in the APASL definition exclude prior decompensation, and bacterial infection is not considered as an acute hepatic insult. The two definitions have different aims, which might explain the discrepancies: the APASL definition identifies a syndrome that anticipates extrahepatic organ failure, and the targeted population has a large proportion of viral hepatitis; the EASL-CLIF definition identifies a syndrome with organ failure and high short-term mortality for cirrhotic patients with mainly alcohol-induced liver disease.

2.3. Inflammation Hypothesis

Inflammation has been proposed to play a central role in the pathophysiology of ESLD. Besides its implication in CAID, inflammation may be crucial in the natural history of cirrhosis, being the main driver for the evolution of compensated cirrhosis toward decompensated diseases [37]. Bacterial translocation or other pro-inflammatory triggers (alcohol, infections, etc.) can induce a hyperinflammatory state, leading to AD and immune dysfunction. Interleukin (IL)-6 and IL-8 levels have been mostly associated with disease severity in decompensated cirrhotic patients, with or without ACLF [25,38–40]. The prognostic value of C-reactive protein (CRP) levels to determine outcomes following admissions for cirrhotic patients has also contributed to developing this hypothesis [41]. Recently, an association between CRP, plasma IL-6 levels and the severity of cirrhosis has been confirmed in different studies [34,37,42]. IL-6 levels and CRP have been reported as independent predictive factors of 1-year death or liver transplantation in cACLD patients (IL-6) and chronic decompensated cirrhotic patients (IL-6 and CRP) [42]. Regarding AD

course, IL-6 and CRP levels are increased in cirrhotic patients who develop toward unstable decompensated cirrhosis following a first AD episode, being even higher for patients who will develop ACLF in the future, and IL-6 levels rise with ACLF grade [34,37]. Enhanced baseline inflammasome activation (defined as high levels of circulating IL-1α and IL-1β) may be determinant for future ACLF development in AD and CD cirrhotic patients [43]. The highly inflammatory status of AD and ACLF patients has also been supported by a study of plasma lipid mediators' profile, showing a pro-inflammatory balance in AD and ACLF compared to healthy volunteers and an association with disease severity [39]. ACLF accounts for a specific cirrhosis decompensation, associated with multiple organ failure, more pronounced immune paresis and the highest risk of death. In this setting, inflammation parameters vary from those described in cACLD, CD and AD, with notably high circulating levels of pro-inflammatory cytokines involved in innate immunity (such as TNF-α, MIP-1β, IL-10) [25,40]. In a recent study combining mice models and patients' data, Hackstein et al. demonstrated a relationship between microbiota-induced inflammation and impaired adaptive immune response [19]. This corroborates previously reported in vitro models in which alterations in immune cells' phenotype and function were reproduced in vitro through conditioning with ESLD patients' plasma [20,26,28].

3. Circulating T Cell Alterations in End-Stage Liver Disease

3.1. Changes in CD4 Subsets in Cirrhosis

In a cohort of cACLD and decompensated cirrhotic patients, Lario et al. showed that bacterial translocation could induce hyperactivated HLA-DR$^+$ CD4$^+$ T helper (Th) cells, shifting naïve Th cells towards effector and effector memory lineages. This sustained activation also drove increased apoptosis in all Th subsets, therefore participating in Th depletion, despite increased proliferation rates (Ki67$^+$ cells) observed in all memory Th subsets [44]. In agreement with this, Marquez et al. found both higher frequencies of memory CD4$^+$ T cells expressing the CD95 apoptosis marker and of activated CD4$^+$ T cells in viral- and alcohol-related cirrhosis. These changes were equally observed regardless of the severity of cirrhosis and were not influenced by the presence of ascites or high levels of lipoprotein binding protein (LBP) [45]. Conversely, other authors found that an imbalance between naïve and activated CD4$^+$ T cells was specifically marked in ascitic patients with high levels of LBP, suggesting bacterial translocation as a key driver of CD4$^+$ T cell impairment [46].

Recent data from mouse models of liver cirrhosis demonstrated the crucial role of liver sinusoidal endothelial cells (LSECs) to induce in vitro activation of CD4$^+$ T cells independently of the presence of concomitant bacterial infection [47]. Interestingly, in these models, norfloxacin may reverse pro-inflammatory Th subset activation and promote regulatory T cell (Treg) differentiation through LSEC modulation. In a clinical trial of ascitic patients receiving norfloxacin or placebo, norfloxacin treatment restored the unbalanced ratio between naïve Th cells and memory CD4$^+$ Th cells [46]. In another experimental model of liver cirrhosis, propranolol improved Th cell depletion by modulating adrenergic receptors of CD4$^+$ T cells [48].

Besides phenotypic shifts, several reports suggest functionally altered T cells in cirrhosis (encompassing both CD4$^+$ and CD8$^+$ compartments). In a recent study, the authors suggested that impairment of CD4$^+$ T cell function occurs even at the early stage of cirrhosis. In a cohort of cACLD patients recently vaccinated against hepatitis B virus (HBV) or SARS-CoV-2, they reported lower IL-21 and IFN-γ production by CD4$^+$ T cells following antigen-specific stimulation [49]. In other studies, cytokine production appears to be impaired only in the most severe patients, with defective production of IFN-γ and TNF-α by T cells in AD patients [50]. In line with this, the T cells of patients with alcoholic hepatitis (AH) produce less pro-inflammatory IFN-γ following in vitro lipopolysaccharide (LPS) stimulation and more anti-inflammatory IL-10 [51]. Finally, following in vitro stimulation, T cells of cirrhotic patients display impaired proliferation ability [52]. In patients, mechanisms sustaining CD4$^+$ T cell impairment remain to be fully deciphered. Notably,

the exact role of circulating factors such as PAMPs, DAMPs and microRNA is yet to be clarified. In mice models, Hackstein et al. suggested that the antigen-specific impaired $CD4^+$ T cell response was IL-10-driven following gut-derived inflammation. IL-10 receptor blockade allowed the restoration of $CD4^+$ T cell proliferation and IL-21 secretion following antigen-specific stimulation [49]. The characterisation of circulating activated Th cells has still not been achieved. Some data suggest preferential polarisation towards the Th17 lineage [53,54]. Hence, in HBV and alcohol-related cirrhosis, circulating Th17 frequency was higher compared to chronic HBV infection and healthy controls, and the surface expression of IL-23 receptor on Th17 was positively correlated with severity scores of cirrhosis and could predict mortality [53]. The proportion of circulating Th17 can also positively predict mortality in HBV-ACLF patients as persistent elevation of the Th22 subset [54,55].

3.2. Impairment of Circulating $CD4^+$ T Helper Cells in Acute Liver Failure

In ALF, the naïve peripheral $CD4^+$ pool expands while the effector memory $CD4^+$ T cell subset is markedly decreased compared to healthy controls and to cirrhotic patients [26]. Khamri et al. showed that $CD4^+$ T cells displayed an immunosuppressive phenotype characterised by the increased expression of checkpoint CTLA-4, known to negatively regulate T cell activation. The frequency of $CTLA\text{-}4^+CD4^+$ T cells positively correlated with MELD score and was even more elevated in ALF patients who developed secondary infections. However, no change in CTLA-4 expression was found in ACLF patients. Furthermore, $CD4^+$ T cell functionality was impaired in ALF patients, with decreased proliferative capacity specifically mediated by the CTLA-4 pathway in contrast to cirrhotic patients. The authors demonstrated that the secretion of soluble B7 ligands (sCD80 and sCD86) by injured hepatocytes sustained the activation of the CTLA-4 pathway in $CD4^+$ T cells, and thus plasma exchange may be considered as a therapy for immune dysfunction in ALF [26].

3.3. Expansion of Regulatory T Cells in Cirrhosis

Tregs inhibit both the proliferation and cytokine production of other $CD4^+$ and $CD8^+$ T cells. Tregs could thus prevent host immune-mediated damage but could also participate in cirrhosis-associated immune dysfunction. However, previous studies on circulating Tregs in the setting of cirrhosis are inconsistent. Some authors reported a significant down-regulation of Tregs in cirrhosis or AH [56,57], while others found them to increase in all cirrhotic patients [29,58] regardless of the severity [50] or found them to be higher in ACLF patients [59,60].

Bacterial translocation has been proposed to promote Treg preferential differentiation since patients with elevated levels of LBP display a significantly higher frequency of Tregs than those with normal levels [45]. The pathogenicity of Tregs in cirrhosis is currently not established, but a previous report has suggested a detrimental role, with an increase in peripheral Tregs being predictive of subsequent bacterial infections in cirrhotic patients [58].

Apart from thymic-derived $CD25^+CD127^-$ Tregs, Khamri et al. recently reported the expansion of non-classical $CD4^+$ regulatory T cells in AD expressing the tolerogenic marker HLA-G [27]. These cells suppressed peripheral blood mononuclear cells' (PBMCs) proliferation and pro-inflammatory cytokine production in in vitro experiments, an effect that was both HLA-G- and CTLA-4-mediated. Interestingly, the expansion of regulatory $HLA\text{-}G^+CD4^+$ T cells was induced by Kupffer cells through IL-35 secretion and these unconventional Tregs specifically down-regulated Th17-related cytokine production [27].

In patients with AH, compared to alcohol-related cirrhotic patients and healthy controls, Markwick et al. demonstrated that T cell responses were skewed toward a dominating immunosuppressive response, as witnessed by a marked increase in different inhibitory receptors' surface expression on $CD4^+$ (PD-1 and Gal-9) and $CD8^+$ (PD-L1, TIM-3 and Gal-9) T cells [51]. The overexpression of these inhibitory receptors, known to promote immune exhaustion when expressed in a sustained manner, was mediated by LPS binding to TLR-4 and CD14 on monocytes. It was also noted that blockade of PD-1 and TIM-3 improved the IFN-γ/IL-10 ratio in AH by improving CD4, CD8, Treg and NK cell functions [51].

3.4. Alterations in Circulating CD8⁺ T Cells in Cirrhosis: Activation to Exhaustion Profile

Regarding circulating $CD8^+$ T cells, previous studies reported either a reduction in the absolute numbers of both naïve and memory subsets or only of naïve cells [46,50]. Additionally, the phenotypic profile of peripheral $CD8^+$ T cells may change with disease severity with the co-expression of activation and exhaustion/senescence markers.

In a recent study, Rueschenbaum et al. demonstrated that $CD8^+$ T cells of cirrhotic patients exhibited simultaneously increased surface expression of activation markers (HLA-DR, CD38, CD69), inhibitory receptors (KLRG1, PDPN, TIM3) and the apoptotic marker CD95 [50]. In this cohort, changes in the $CD8^+$ phenotype were observed in patients with cACLD and chronic decompensated cirrhosis and in AD and ACLF patients. The expansion of activated $CD8^+$ T cells has been previously suggested in another cohort of cirrhotic patients, where $CD8^+$ lymphocytes displayed an altered phenotype with elevated surface expression of the activation marker HLA-DR and checkpoint inhibitor TIM-3 compared to healthy subjects. While HLA-DR expression on $CD8^+$ T cells was increased in AD patients with concomitant infections, TIM-3 expression was associated with disease severity and the co-expression of HLA-DR and PD-1 was predictive of poor disease outcome in all cirrhotic patients. Interestingly, this $CD8^+$ T cell subset may have been primed in the liver, as $HLA\text{-}DR^+CD8^+$ T cells were enriched in the hepatic compartment, especially in the lobular area compared to non-cirrhotic liver tissue. $HLA\text{-}DR^+CD8^+$ T cells may contribute to the alterations in innate immunity related to cirrhosis, as these cells reduced the in vitro proliferation of PBMCs and induced phenotypic and functional dysfunctions in monocytes and neutrophils in co-culture experiments [28]. In mice models of cirrhosis, $CD8^+$ T cells exhibited the exhaustion phenotype according to RNA sequencing and impaired antiviral function. The authors suggested that gut microbiota induced IFN response and IL-10 release, contributing to impaired adaptive immune response [49].

Finally, the expansion of memory $CD8^+$ T cells overexpressing the apoptotic marker CD95 in the $CD8^+CD45RO^+CD57^+$ subset, reported as an effector senescent population, has been highlighted in viral- and alcohol-related cirrhosis [45]. An exhausted-like profile in peripheral $CD8^+$ T cells was also reported in HBV-related ACLF, with increased expression of inhibitory checkpoints PD-1, CTLA-4 and LAG-3 but down-regulation of perforin, granzyme B and FasL expression [61]. Other quiescence/exhaustion markers, such as FOXP1, are heavily involved in lymphoproliferative diseases and tumour microenvironment and were shown to be related to cirrhosis progression towards hepatocellular carcinoma [62,63]. However, the expression of FOXP1 in T cells is yet to be investigated in ESLD.

3.5. Alterations in Circulating Follicular T Helper Cells Linked to Impaired Humoral Immunity

Follicular T helper cells (Tfh) are specialised $CD4^+$ T cells that enable the emergence of effective antibody responses against microbial pathogens through B cell activation and differentiation. A reduction in the frequency of this T cell population has been reported in cirrhosis [57,61]. In alcoholic liver disease, the level of circulating Tfh cells, as reflected by the level of the soluble CD40 ligand (sCD40L), was significantly lower compared to controls. sCD40L, released into circulation upon Tfh activation, was an independent predictor of mortality [64].

Recently, Basho et al. investigated the exact role of Tfh in decompensated liver cirrhosis in a cohort of patients with hepatitis C virus (HCV), alcohol-related or non-alcoholic steatohepatitis (NASH)-related underlying liver diseases [29]. Patients with decompensated cirrhosis had significantly fewer liver resident Tfh and circulating Tfh cells compared to compensated cirrhosis patients and healthy controls. The Tfh cells of cirrhotic patients exhibited phenotypic ($CD25^{high}OX40^{high}CD127^{high}$) and transcriptional changes (low expression of TCF1 ad FOXP3) compared to healthy controls. These alterations were systemic effects, likely driven by elevated circulating pro-inflammatory IL-2 levels in these patients. In vitro, IL-2 exposure impaired Tfh helper function in co-culture experiments with naïve B cells, with reduced secretion of both immunoglobulin classes G and M. As

high immunoglobulin levels were correlated with improved survival in decompensated cirrhosis, Tfh cell dysfunction likely contributes to CAID [29].

Conversely, other authors have provided conflicting results regarding the frequency of circulating Tfh in liver cirrhosis. Zhao et al. reported an increase in circulating Tfh cells in HBV- and non-HBV-related cirrhosis, correlated with an enrichment in splenic Tfh cells [65]. These cells displayed an increased surface expression of the inhibitory receptor PD-1 and co-stimulatory receptor ICOS compared to healthy controls and positively correlated with the percent of plasma cells and disease severity. Functionally, they produced more IL-21 and splenic Tfh cells from cirrhotic patients and robustly induced plasma cell differentiation in vitro [65]. The relative numbers of circulating Tfh cells were also reported to be increased in patients with HBV-related ACLF compared to patients with chronic HBV infection and healthy controls and correlated with MELD score and clinical outcome [66].

4. Alterations in Circulating B Cell Subset

4.1. Global B Cell Depletion

Like T cells, the B lymphocyte absolute count has been reported to decrease in patients with chronic liver disease. However, B cell frequency varies according to disease stage and cirrhosis aetiology. Decreased B cell frequency is found in alcoholic liver disease [67]. Increased B cell frequency is reported in decompensated cirrhotic patients, consisting of a mixed-aetiology population [68], while no change in B cell frequency is reported in HCV-related decompensated cirrhotic patients [69].

4.2. Loss of Memory Subset

Depletion in $CD27^+$ memory B cells is widely reported in decompensated cirrhosis [68–70] as well as in ACLF [71]. The loss of the memory subset is associated with high susceptibility towards infections [68,69], and it might also contribute to the poor B cell response to vaccination observed in cirrhotic patients [72,73].

4.3. Hyperglobulinaemia

In cirrhotic patients, B cells show an up-regulation of the activation markers HLA-DR and CD86. Doi et al. also reported the up-regulation of TLR9 and BAFF in memory B cells. This hyperactivation of B cells leads to enhanced production of immunoglobulins A and G [69,70,74], which is commonly observed in advanced cirrhosis. Data regarding the significance of immunoglobulin levels are contradictory. In a cohort of 119 patients, Basho et al. suggested that the absence of hypergammaglobulinaemia in cirrhosis might be associated with a poorer prognosis [29]. In contrast, a recent study on 245 patients with different stages of cirrhosis suggested that increased levels of IgA, and to a lesser extent IgG1, were correlated with a higher risk of liver-related death or decompensation [75]. In the same study, IgG1 and IL-6 levels were the only biomarkers associated with the risk of infection development in multivariate analysis. The shift of naïve B cells to memory subsets and plasmablasts has been reported [71], indicating B cell response. However, the effect of antigen-specific B cell response is questionable, as B cells in cirrhosis are hyporesponsive towards CD40/TLR9 stimulation and less capable of inducing Th proliferation [69].

4.4. Regulatory B Cells

Regulatory B cells are a small subset of the B cell population involved in immunomodulation. One of the best-known mechanisms of immune suppression used by regulatory B cells is the secretion of the anti-inflammatory cytokine IL-10. The loss of regulatory B cells is a well-described contributing factor to autoimmune hepatitis. In cirrhosis, alterations in regulatory B cell populations may contribute to the effector B cell hyporesponsiveness. The expansion of circulating $CD19^+CD24^{high}CD38^{high}$ regulatory B cells has been reported in HBV-related chronic decompensated cirrhotic patients [76]. Regulatory B and T cells contribute to the elevated serum IL-10 levels observed in ACLF and are associated with

higher 90-day mortality and disease severity [40,77]. Factors favouring the emergence and the exact role of these cells have yet to be explored.

5. Decrease in Circulating Mucosal-Associated Invariant T Cells

Mucosal-associated invariant T (MAIT) cells are innate-like T cells abundant in blood, mucosal tissues and the liver [78]. MAIT cells express a semi-invariant T cell receptor consisting of Va7.2-Ja12/20/33 combined with limited β chain variable region (Vb) diversity. They recognise riboflavin metabolites of bacteria or fungi with the help of MHC class-I and thus contribute to immune defence against pathogens. Circulating MAIT cells have been reported to be severely diminished in cirrhosis from the early stages [79,80]. Conflicting results have been published regarding whether they accumulate in liver fibrotic septa [79] or not [80]. In ascites, MAIT cells increase together with monocytes, innate lymphoid cells and NK cells [80]. Circulating MAIT cells displayed an activated phenotype, typified by high surface expression of HLA-DR, CD56, CD25 and CD38, and high proliferation levels indicated by Ki-67 detection. However, cytokine production and degranulation ability following in vitro stimulation are less efficient compared to matched peritoneal MAIT cells, which are critical to local immunity during spontaneous bacterial peritonitis [80].

6. Perspectives and Remaining Questions

A description of adaptive immune response in the setting of ESLD is in progress. Most studies based on patient data and/or animal models have suggested a strong link between inflammation and impaired adaptive immune response (Figure 1). The mechanisms involved in inflammation could be different according to the type of ESLD: gut microbiota may be the most important inflammation trigger in cACLD and decompensated cirrhosis, whereas cell death may induce immune paresis in acute liver failure syndromes [26,49]. In cACLD, gut microbiota could be an interesting target to reverse immune dysfunction, and different therapeutic strategies have been studied [81].

However, studies reporting adaptive immune features in ESLD are heterogeneous, with sometimes conflicting data, reflecting the complexity of deciphering adaptive immune response mechanisms in general and the wide spectrum of ESLD clinical presentations. In addition, most currently published studies focus on phenotypic alterations, without investigating the induction mechanism and the cells' functionality or the potential clinical consequences. Analogies with other pathologies, such as sepsis [82,83], suggest a potential role for these altered cell populations and more data are needed to better define CAID.

Many questions need to be addressed before moving forward in the description of adaptive immune response and clinical incidence in ESLD, such as standard conditions and methodology to study immune responses in ESLD, the relevance of studies focused on circulating cells and clinical endpoints to study according to disease stages. Inflammation level, associated with disease severity, hepatic venous pressure gradient and any acute event, may influence the phenotype and function of circulating immune cells [29,49,51]. Substantial alterations in the adaptive immune response observed in ESLD may be biased by concomitant acute episodes (infection, bleeding, alcoholic hepatitis). An initial characterisation of peripheral immune cells in baseline conditions for patients with cACLD and then according to a long-term longitudinal follow-up is likely necessary to avoid bias induced by acute events or by underlying liver disease. Studies on ALF are likely easier to perform since the spectrum of disease is more restricted and the time course is shorter.

Inflammation and host immune response could also influence the natural history of the underlying liver disease. In a recent study, Waller et al. described peripheral immune cell phenotype changes driven by steatosis, in comparison to healthy volunteers. However, the main changes in this study were observed between patients with simple steatosis and patients with NASH and fibrosis, suggesting that both inflammation and fibrosis lead to alterations in peripheral immune cells' phenotype [84].

Most of the clinical studies describe peripheral immune cells' phenotype and function as a reflection of peripheral immune compartments. Blood samples are indeed easy to

collect, with high acceptability from patients and ethics committees, but they provide restrictive data on immune responses. Simultaneous combined study of different immune compartments should be performed, especially the liver, spleen, medullar and gut compartments. Recent studies on animal models bring new insights to understand mechanisms involved in immune response alterations in ESLD [19,49,85]. Changes in immune metabolites have recently been discovered in ESLD [86,87]. Modulation of the immune metabolism could act as a potential mechanism of immune suppression. Identifying key metabolites provides novel biomarkers as well as potential interventional pathways.

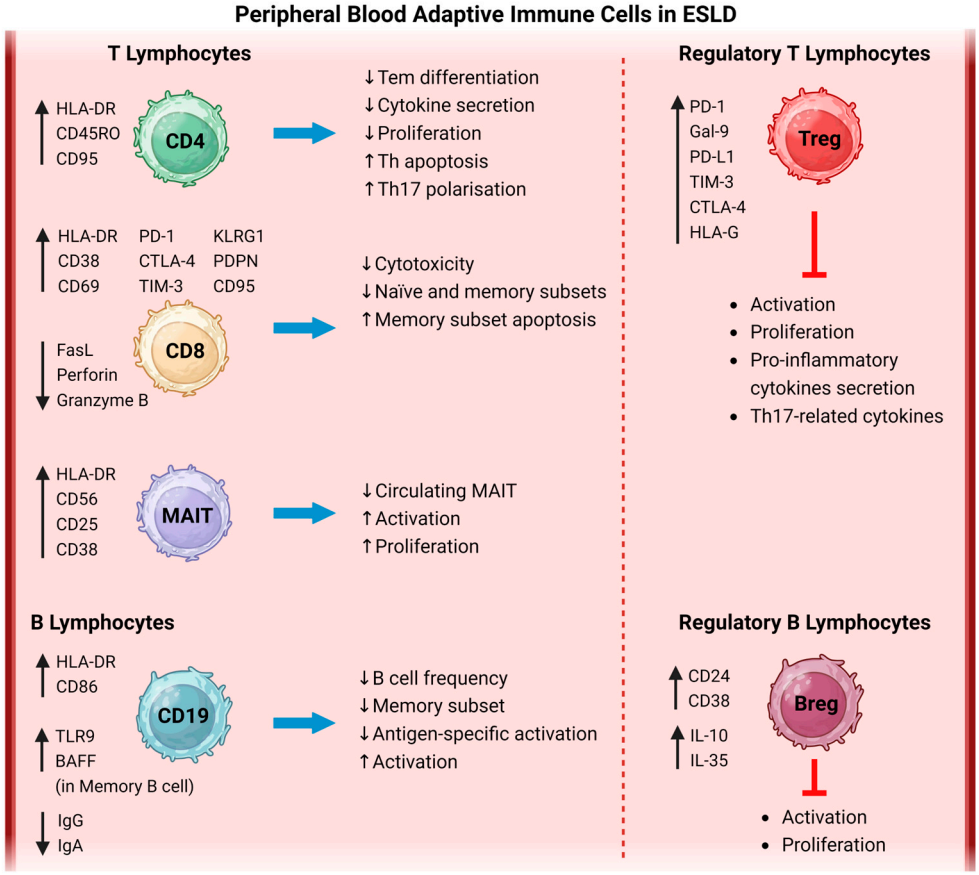

Figure 1. Changes in peripheral blood adaptive immune cells in end-stage liver disease (ESLD). Lymphocytes are in a persistent state of activation while co-expressing exhaustion/senescence/apoptosis markers. The expansion of regulatory T and B cells further suppresses lymphocyte activation and proliferation. (HLA-DR, human leukocyte antigen-DR; Tem, effector memory T cell; Th, T helper cell; PD-1, programmed cell death protein 1; CTLA-4, cytotoxic T lymphocyte-associated protein 4; TIM-3, T cell immunoglobulin and mucin domain-containing protein 3; KLRG1, killer cell lectin-like receptor G1; PDPN, podoplanin; FasL, Fas ligand; MAIT, mucosal-associated invariant T cell; TLR9, Toll-like receptor 9; BAFF, B cell activating factor; IgG, immunoglobulin G; IgA, immunoglobulin A; Gal-9, galectin-9; PD-L1, programmed cell death ligand 1; HLA-G, human leukocyte antigen-G; IL-10, interleukin-10; IL-35, interleukin-35).

Finally, the clinical impact of alterations in the adaptive immune response may be described, and relevant clinical outcomes need to be defined according to disease stages. Response to vaccine and the cumulative risk of first decompensation driven by primary infection is likely to be an interesting outcome to study in cACLD patients, whereas the occurrence of secondary infection, organ dysfunction and survival without liver transplantation represent relevant outcomes in AD and ACLF patients. To answer these questions, correlation with functional assays may be required, although the correlation between in vitro assays and clinical incidence may be minimal.

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