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Mucosal-Associated Invariant T Cells in Chronic Inflammatory Liver Disease

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Abstract

The broadening field of microbiome research has led to a substantial reappraisal of the gut–liver axis and its role in chronic liver disease. The liver is a central immunologic organ that is continuously exposed to food and microbial-derived antigens from the gastrointestinal tract. Mucosal-associated invariant T (MAIT) cells are enriched in the human liver and can be activated by inflammatory cytokines and microbial antigens. In chronic inflammatory liver disease, MAIT cells are depleted suggesting an impaired MAIT cell-dependent protection against bacterial infections.

Keywords

mucosal-associated invariant T cells; hepatitis; inflammation; cirrhosis; liver metastases; gut–liver axis

The liver is an important immunologic organ, which receives >75% of its blood supply via the portal vein from the gastrointestinal tract. This antigen-rich blood passes through a network of fenestrated sinusoids with a unique repertoire of innate and adaptive immune cells, before it returns via the hepatic veins into the systemic circulation. Thus, the healthy liver can be regarded as a vascular firewall that prevents the entry of gut-derived antigens and bacteria into the systemic circulation.¹ Advanced liver disease often presents with spontaneous bacterial peritonitis and hepatic encephalopathy. Gastrointestinal dysbiosis, impairment of the intestinal barrier function, and increased bacterial translocation have been reported in advanced liver disease and may contribute to inflammation via disturbed host–microbial interactions.²

Keeping the close relationship of the liver and the gastrointestinal tract in mind, it is important to decipher mechanisms of intrahepatic immune cell activation and their role in liver inflammation and disease progression. In this review, we will introduce and explore the role of MAIT cells, an innate-like T cell population, in chronic inflammatory liver disease in humans.

Phenotypic and Functional Characteristics of MAIT Cells

MAIT cells are called “mucosal-associated” because they have originally been described as an abundant population of T cells in the lamina propria of the small intestine.³ However, MAIT cells are also enriched at other barrier sites, such as liver and lung (►Table 1).⁴ They constitute up to 40% of intrahepatic and up to 10% of peripheral blood T cells.^{4,5} Thus, MAIT cells represent the most abundant subset of all nonconventional T cells. The majority of MAIT cells in both liver and blood are CD8⁺ (most are CD8αα⁺, few are CD8αβ⁺), a small proportion is CD8[−]CD4[−] double negative, and only a few MAIT cells are CD4⁺.^{6–8}

MAIT cells are selected in the thymus, but remain at low frequency with an immature naïve phenotype (CD45RA^{hi}, CD45RO^{lo}, CD27^{hi}) after thymic egress and then expand preferentially in barrier tissues.^{7,9} In humans, MAIT cells have been detected as early as the second fetal trimester in the small intestine, lung, and liver.⁹ They display an effector memory phenotype (CD45RA[−], CD45RO⁺, CD62^{lo}, CD122^{int}, CD127^{hi}, CD95^{hi}) with a high proliferative capacity in these tissues as indicated by expression of the proliferation marker Ki67 and high level expression of CD127, which enables homeostatic proliferation in response to IL-7.⁹ Their maturation and functionality are dependent on the commensal flora, cytokines, and the transcription factor promyelocytic leukemia zinc finger (PLZF).^{10–12} In mice, postnatal MAIT cell development in the intestine has been shown to depend on the commensal flora of the gut and on B cells as demonstrated by the absence of MAIT cells in germfree mice and mice that lack B cells.³ MAIT cells remain rare and immature in lymphoid tissues such as spleen and mesenteric lymph nodes.⁴

MAIT cells are strikingly different from conventional T cells. First, MAIT cells express a conserved invariant T cell receptor (TCR) α chain (Vα7.2-Jα33)^{13,14} and a limited repertoire of β chains (predominantly Vβ6 and Vβ20).¹⁵ Second, MAIT cells are not reactive to peptides. They recognize vitamin B (riboflavin) metabolites from microorganisms that are presented on major histocompatibility complex (MHC) class I-like molecules, called MR1.^{16,17} Microorganisms that possess the riboflavin-synthesizing pathway include enterobacteriaceae, staphylococci, mycobacteria, and fungi. All have been shown to activate MAIT cells.^{18,19} This appears to be an evolutionary conserved mechanism because the sequence of the antigen-presenting MHC class I-like molecule is shared among mammals.^{20,21} MR1 is expressed at mRNA level in multiple tissues,²² but its surface expression is tightly regulated and depends on antigen exposure.^{23–25} This contrasts with classical MHC class I molecules, which are highly expressed on cells even in the absence of antigens. Stimulation by diverse pathogen-derived ligands results in antigen-dependent expansion of individual MAIT cell clones and in a distinct TCR repertoire of the MAIT cell population in each individual.²⁶ Third, MAIT cells express high levels of the IL-18 receptor along with receptors for IL-12, IL-23, IL-2,^{4,12} and the C-type lectin-like receptor CD161, which they share with liver-infiltrating T cells.²⁷ Fourth, as mentioned above, MAIT cells display an effector memory phenotype and rapidly respond to antigen (TCR dependent) and cytokine (TCR independent) stimulation in an innate-like fashion. Their effector response includes a mixed T_H1/T_H17 profile with the production of proinflammatory cytokines including IFN-γ, TNF-α, and IL-17.^{4,20,27} In addition, MAIT cells exert cytotoxic effector functions by releasing granzyme B and perforin upon activation.²⁸

The anatomic location of MAIT cells along with their evolutionary conserved semi-invariant TCR and their rapid innate-like responses to bacterial products suggest that they play an essential role in the host defense at the gut–liver interface.

MAIT Cells in Chronic Liver Disease

MAIT cells can be identified in human blood and liver samples by co-staining with an antibody against CD161 and with either an antibody against the TCR V α 7.2 chain or an MR1 tetramer loaded with a vitamin B derivative (6-hydroxymethyl-8-d-ribityllumazine, rRL-6-CH₂OH).¹⁵

MAIT cells are recruited to the liver based on their expression of the tissue-homing chemokine receptors CCR6, CXCR6, and the integrin α E β 7. They lack expression of the lymph node homing receptor CCR7.^{4,8} During liver inflammation, additional recruitment occurs via the IFN-inducible chemokines CXCL9 and CXCL10 that bind to the CXCR3 receptor on MAIT cells.⁸ This is consistent with greater activation and cytotoxicity of MAIT cells in the liver than in the blood of HCV-infected patients.²⁹ Within the liver, MAIT cells have been shown to localize around the bile ducts in the portal tracts.⁸ They express the multidrug resistance transporter ABCB1 and thus are more resistant to bacterial-derived xenobiotics, drugs, and chemotherapeutic agents than other lymphocytes.⁴

MAIT cells can be activated in an antigen-dependent manner and in a cytokine-dependent manner in chronic inflammatory liver disease (►Fig. 1). As regards antigen-dependent activation, MAIT cells from the liver produce IFN- γ and degranulate upon in vitro culture with *Escherichia coli*-exposed biliary epithelial cells.⁸ Their protective role is supported by experimental studies that demonstrated a higher bacterial burden following intraperitoneal injection of *E. coli* in MR1^{-/-} mice lacking MAIT cells.^{18,30} Moreover, in a large human study Grimaldi et al showed a higher incidence of severe bacterial infections in critically ill patients with a depletion of MAIT cells in the peripheral blood.³¹

As regards to antigen-independent activation, type I IFN³² and IL-12/IL-18³³ are among the cytokines that activate MAIT cells in chronic viral hepatitis. Type I IFN is secreted by plasmacytoid dendritic cells sensing virus-infected hepatocytes^{34,35} and IL-12 and IL-18 are released by monocytes/macrophages in response to single-stranded RNA binding to intracellular toll-like receptor-8 (TLR-8).^{36,37} Indeed, it has been shown that MAIT cells along with natural killer (NK) cells are the main producers of IFN- γ after TLR-8 stimulation of monocytes.³⁸ This monocyte-dependent activation pathway extends beyond the liver and has also been described in infections with dengue virus, influenza virus, and human immunodeficiency virus (HIV).³⁹

Importantly, the frequency of MAIT cells is decreased in both liver and blood in a variety of chronic inflammatory liver diseases. These include alcoholic steatohepatitis and NASH, primary sclerosing cholangitis, and primary biliary cholangitis⁸ as well as chronic HBV and HCV infection.^{29,40–42} In chronic HCV infection, MAIT cells have been extensively characterized, and the residual MAIT cells show an activated phenotype with increased expression of the activation markers CD69, HLA-DR, and CD38. Their response to TCR-

mediated but not cytokine-mediated stimulation is impaired when compared with uninfected controls.^{29,42} As for conventional T cells, this impaired function is associated with an upregulation of the exhaustion markers PD-1, Tim-3, and CTLA-4.⁴¹ Impairment of MAIT cell function depends on the severity of liver fibrosis as demonstrated in a crosssectional study of HCV-infected patients.⁴³ However, a reduced frequency of MAIT cells is not solely found in liver disease and has also been reported in HIV infection.^{6,44} Patients with HIV/HCV co-infection have the lowest frequency of peripheral MAIT cells.⁴⁵

The frequency of MAIT cells in the liver correlates inversely with liver inflammation, as assessed by the histologic activity index (HAI score), in chronic HCV infection.²⁹ Thus, MAIT cells may be recruited from the blood to the liver where they are activated by inflammatory cytokines and undergo activation-induced cell death. This is consistent with the observation of a selective loss of CD8⁺ MAIT cells of HCV-infected patients upon in vitro stimulation with either IL-12/IL-18 or *E. coli*/IL-15.²⁹ Moreover, activation-induced death of MAIT cells has been shown by Cosgrove et al after in vitro stimulation of MAIT cells with *E. coli*⁴⁴ and a pro-apoptotic phenotype of MAIT cells with increased expression of caspase 3 and 7 has been reported by Gérard et al.⁴⁶

With the introduction of highly effective direct acting antivirals (DAA), HCV infection has become an invaluable disease model to study immune cell alterations before and after viral clearance. HCV titers typically decrease to undetectable levels within 4 weeks of treatment along with an effective reduction in liver inflammation. This results in a decrease in MAIT cell activation and an increase in MAIT cell frequency in the liver.²⁹ These changes parallel a decrease in intrahepatic monocyte activation and plasma IL-18 levels.²⁹ Overall, this underlines the predominant role of virus-induced cytokines in MAIT cell activation in chronic HCV infection.

However, despite the rapid decrease in viral titer and intrahepatic inflammation within 4 weeks of antiviral therapy, the intrahepatic MAIT cell frequency remains significantly lower than in uninfected controls.²⁹ In the blood, the MAIT cell frequency remains reduced for at least 72 weeks after successful antiviral therapy, which is the longest follow-up of sustained virologic responders to date.⁴² Importantly, successful antiviral therapy did not restore the impaired antigen-dependent effector function of MAIT cells.^{29,42} Collectively, these findings indicate that HCV infection leaves a lasting imprint on the MAIT cell population.

MAIT Cells in Metastatic Liver Disease

MAIT cells have been recognized as an attractive immunotherapeutic target in patients with colorectal cancer because they are enriched in the intestine, the primary site of colorectal cancer, and the liver, a common site of metastases, and respond rapidly to cytokine and antigen stimulation. MAIT cells infiltrate colorectal liver metastases but are less abundant in liver metastases than in healthy liver tissue.⁴⁷ Furthermore, MAIT cell function decreases with increasing proximity to metastatic liver lesions. This is not a result of decreased cytokine receptor expression on MAIT cells or prior chemotherapy.⁴⁷ Tumor-infiltrating MAIT cells are functionally impaired to produce IFN- γ in response to both cytokine (IL-12/IL-18) and antigen (staphylococcus enterotoxin B, *Klebsiella* lysate) stimulation.⁴⁷

Collectively, these findings indicate that tumor-infiltrating MAIT cells are profoundly impaired in their function by the tumor microenvironment.

MAIT Cells in Metabolic Disease

Nonalcoholic fatty liver disease (NAFLD), a disorder ranging from accumulation of fat in the liver to NASH and liver cirrhosis, is the hepatic manifestation of the metabolic syndrome.⁴⁸ With a rising prevalence, NAFLD has become the most common cause of chronic liver disease in developed countries.^{49,50} A critical factor in the progression of NAFLD to NASH is oxidative stress perpetuating liver inflammation.⁵¹ This raises the questions whether MAIT cells are activated and contribute to the disease pathogenesis. In our own studies, we found an activated MAIT cell phenotype with increased cytotoxicity but reduced cytokine production in patients with NASH.⁵² Magalhaes et al investigated MAIT cells in obesity and type 2 diabetes, which are features of the metabolic syndrome and commonly associated with NAFLD. The authors found that MAIT cells are present in adipose tissue, but they are significantly reduced in their frequency in the peripheral blood of obese and type 2 diabetic patients.²¹ The peripheral blood MAIT cells displayed an activated phenotype and, in contrast to NASH patients, enhanced cytokine production.²¹ Of note, there was also a striking increase in IL-17 production in the adipose tissue of obese patients. Both, the peripheral MAIT cell frequency and the functional alterations, were restored after bariatric surgery.²¹

In conclusion, MAIT cells represent a major T cell population in the human liver, which is capable of exerting antimicrobial and antiviral functions. Their enrichment in the liver and their location in the portal tracts close to bile ducts suggest an important role of MAIT cells in liver immune surveillance. In chronic inflammatory liver diseases, the frequency of MAIT cells is significantly reduced and their function in response to bacteria is impaired. This may impact liver immune surveillance and result in increased susceptibility to bacterial infections which is a major cause of mortality in patients with decompensated liver cirrhosis.⁵³ Further studies will help to define the role of MAIT cells in healthy and diseased livers and to identify mechanisms that contribute to both progression and complications of chronic liver disease.

Main Concepts and Learning Points

- The liver comprises an abundant population of mucosal-associated invariant T (MAIT) cells that are preferentially localized to bile ducts in the portal tracts.
- MAIT cells are innate-like T cells with an effector memory phenotype that can rapidly respond to cytokines and bacteria by production of interferon-gamma (IFN- γ), tumor necrosis factor-alpha (TNF- α), and interleukin-17 (IL-17).
- MAIT cells are severely reduced in frequency in chronic inflammatory liver diseases including chronic hepatitis B and C virus (HBV and HCV) infection, alcoholic and non-alcoholic steatohepatitis (NASH), primary sclerosing cholangitis, and primary biliary cholangitis.

- Alterations in the MAIT cell compartment in chronic liver disease may impact liver immune surveillance, resulting in increased susceptibility to infections.

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Fig. 1.

Mechanisms of MAIT cell activation in the liver. MAIT cells are characterized by their semi-invariant T cell receptor, TCR Va7.2-Ja33, the C-type lectin receptor, CD161, and the transcription factors T-bet, ROR γ t and PLZF. They express the chemokine receptors CCR6, CXCR-6, and integrin α E β 7 to home close to the bile ducts in the portal tracts. MAIT cell activation in a TCR-dependent manner by riboflavin-synthesizing bacteria and in a TCR-independent manner by cytokines is dependent on APC and results in IFN- γ , TNF- α , IL-17, granzyme B, and perforin expression. (Modified with permission from Kurioka A, Walker LJ, Klenerman P, Willberg CB. MAIT cells: new guardians of the liver. Clin Transl Immunology 2017;6(2):e132.) APC, antigen-presenting cells; B, vitamin-B metabolites; IFNR, interferon receptor; IL-17; interleukin-17; MAIT, mucosal-associated invariant T; PLZF, promyelocytic leukemia zinc finger; ROR γ t, retinoid acid-related orphan receptor gamma; TCR, T cell receptor; T-bet, T-box transcription factor; TNF- α , tumor necrosis factor-alpha.

Table 1

Distribution of MAIT cells in human tissues

Tissue	MAIT cells/CD3 ⁺ T cells [%]	References
Peripheral blood	0.1–10%	Dusseaux et al 2011 ⁴ Bolte et al 2017 ²⁹ Franciszkiewicz et al 2016 ⁵
Liver	10–40%	Dusseaux et al 2011 ⁴ Bolte et al 2017 ²⁹ Jeffery et al 2016 ⁸ Tang et al 2013 ²⁰
Lung	1–10%	Franciszkiewicz et al 2016 ⁵ Hinks et al 2016 ⁵⁴ Le Bourhis et al 2010 ¹⁸
Intestine	2–10%	Dusseaux et al 2011 ⁴ Serriari et al 2014 ⁵⁵ Howson et al 2015 ⁵⁶
Lymphoid tissue	<1%	Dusseaux et al 2011 ⁴

Abbreviation: MAIT, mucosal-associated invariant T.