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# Regulation of MAIT cells through host-derived antigens

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Mucosal-associated invariant T (MAIT) cells are a major subset of innate-like T cells that function at the interface between innate and acquired immunity. MAIT cells recognize vitamin B2-related metabolites produced by microbes, through semi-invariant T cell receptor (TCR) and contribute to protective immunity. These foreign-derived antigens are presented by a monomorphic antigen presenting molecule, MHC class I-related molecule 1 (MR1). MR1 contains a malleable ligand-binding pocket, allowing for the recognition of compounds with various structures. However, interactions between MR1 and self-derived antigens are not fully understood. Recently, bile acid metabolites were identified as host-derived ligands for MAIT cells. In this review, we will highlight recent findings regarding the recognition of self-antigens by MAIT cells.

KEYWORDS

**MAIT cell, MR1 ligand, bile acids, T cell development, self-antigen**

## 1 Introduction

Mucosal-associated invariant T (MAIT) cells are the most abundant T cell subset in humans (1). They recognize non-peptidic antigens presented on a monomorphic antigen presenting molecule, MR1 (2–4). T cell receptor (TCR) repertoires of MAIT cells are composed of restricted TCRα and β chains (mice, TRAV1- TRAJ9/12/33–TRBV13/19; human, TRAV1-2- TRAJ12/20/33–TRBV6/20) that recognize riboflavin-based metabolites produced in microbes but not in mammals (2, 5, 6).

MAIT cells are positively selected in the thymus through the interaction with MR1-expressing double-positive (DP) thymocytes (7) and/or thymic epithelial cells (8). The development of MAIT cells is severely impaired in germ-free (GF) mice and microbiota-derived antigen 5-OP-RU is reported to contribute to their thymic selection (8, 9). Judging from its structure, 5-OP-RU is unlikely to cross the plasma membrane and, as no transporter proteins have been identified thus far, it is still unclear how unstable 5-OP-RU is transferred from gut to the thymus. Additionally, a small but significant number of MAIT cells have been detected in the thymi of GF mice (5, 8, 10), potentially suggesting the presence of endogenous antigen(s) that influence thymic development of MAIT cells (11).

Conventional T cells, which recognize peptidic antigens presented by classical MHC molecules using variant TCRs, are positively selected by weak affinity of self-peptides (12). In the periphery, self-peptides also contribute to the survival and maintenance of conventional T cells (13–15). Since the affinity of bacteria-derived 5-OP-RU to MAIT TCR is strong enough to induce negative selection (8), it is possible that host-derived weak antigen(s) may also be involved in the development and/or maintenance of MAIT cells. However, it is still unclear whether the strength of antigen affinity can differentially regulate the fate and function of MAIT cells, as is reported for conventional T cells.

One of the tissues in which human MAIT cells are most abundant is the liver, particularly in the hepatic sinusoid around bile ducts (16–19). Liver MAIT cells constitutively express activation markers, suggesting that MAIT cells receive continuous TCR signaling even in a steady state (20, 21). Thus, the unique localization and/or maintenance of tissue residency may also be regulated by tissue-derived endogenous factor(s) abundant in the liver. However, such self-antigens have not been identified thus far.

# 2 Diverse ligands presented by MR1

## 2.1 Diversity and specificity of MR1 ligands

MR1 is a well-conserved MHC class I-like molecule and present small compounds unlike CD1 molecules which can accommodate large lipids. For ligand binding, MR1 utilizes the A-pocket, which is flexible and accommodates a large variety of ligands (22, 23). Within the A-pocket, K43 mediates a covalent bond with some typical antigens (5-OP-RU, 6-FP and Ac-6-FP) (24, 25). Neutralization of this positively charged K43 is required for the stabilization of MR1 (22). However, some other ligands (RL-7-Me, RL-6, 7-diMe, diclofenac (DCF), DB28 and NV18.1) non-covalently bind to MR1 (2, 22, 23, 26, 27). It is unknown whether these 'non-covalent' ligands induce MR1 stabilization beyond K43 neutralization. MR1 additionally requires the ligand to possess a hydroxy group to be 'pinched' by two Arg residues found on MR1 (R9 and R94) (2, 6, 22). However, a comprehensive screening of potential MR1 ligands demonstrates that MR1 can actually present a notably broader range of small molecules regardless of these requirements, including mono- and multi-cyclic chemical compounds (22, 23). It is therefore possible that MR1 can bind to previously unappreciated endogenous metabolites.

## 2.2 Self recognition by MAIT cells

There are some studies that support the possibility of self-recognition by MAIT cells. Young et al. reports that a cell line expressing a MAIT TCR was activated in the presence of MR1-expressing antigen presenting cells (APC) in the absence of infection (28). Additionally, cancer cells have been shown to be targeted by MAIT cells utilizing an MR1-dependent mechanism, although with an unidentified ligand (29). Some atypical MR1-related T cells (MR1T cells) are reported to respond to self-derived antigen(s) (30, 31). Recently, Chancellor et al. discovered the rare occurrence of self-reactive MAIT cells that display unique T-helper functions (32). However, endogenous MAIT cell antigen(s) presented by MR1 are yet to be identified.

# 3 Bile acid metabolites as host-derived ligands

## 3.1 Cholic acid 7-sulfate is a MAIT cell ligand

We recently purified and identified cholic acid 7-sulfate (CA7S) as a host-derived ligand for MAIT cells (33). CA7S has a structure that is distinct from those of previously-reported MR1 ligands in that it uniquely possesses four rings. In addition to previously-demonstrated small ligands (2, 6, 22), a large cholane skeleton can also be accommodated within the MR1 pocket. Notably, a competition assay (34) revealed that CA7S binds to the A-pocket of the MR1 molecule (33) similar to known ligands (2, 25). However, the chemical structure of CA7S and its ability to increase surface expression of MR1 lacking K43 (K43A) suggested that CA7S could bind to MR1 without forming a Schiff base. Indeed, the relative affinity of CA7S to MR1 was estimated to be as weak as that of DCF (33), which is also a non-covalent ligand (22). One of the structural characteristics of CA7S is the presence of carboxy group at position 24. This moiety might be interacted with cationic residues in the A-pocket, which warrants further structural analysis. Although we reported a potential function of CA7S on MAIT cell development, comprehensive understanding of its role in MAIT cell biology need further investigation.

## 3.2 Role of CAS in bile acid metabolic pathway

CA7S is a primary bile acid produced from cholic acid by sulfotransferase 2a (Sult2a), which is bile acid-specific sulfotransferases (35–37) (Figure 1). As amphiphilic bile acids are sometimes toxic, sulfotransferase function is essential for neutralization and detoxification of bile acids like cholic acid. To do this, Sult2a adds a hydrophilic $SO_3^-$ group to the hydrophobic cholane skeleton, which generates sulfated cholic acids for excretion in feces and urine (35, 38). Thus, the significance of CA7S was previously thought to be as an excreted bile acid metabolite, and only a few additional roles were reported (39, 40).

Although CA7S is biosynthesized in the host, levels of CA7S were decreased in GF mice (33). This is likely due to the lack of deconjugation of tauro-CA7S (TCA7S) by symbiotic bacteria (Figure 1), as TCA7S was increased in GF mice (33, 41). Thus, CA7S is an endogenous metabolite, but its quantities are largely influenced by symbiotic bacteria. This is consistent with the observation that MAIT cells dramatically decreased in GF mice (5, 8, 9). These results suggest that the reduction in CA7S levels might also contribute to the impairment of MAIT cell development in GF mice in combination with the lack of microbial antigens like 5-OP-RU.

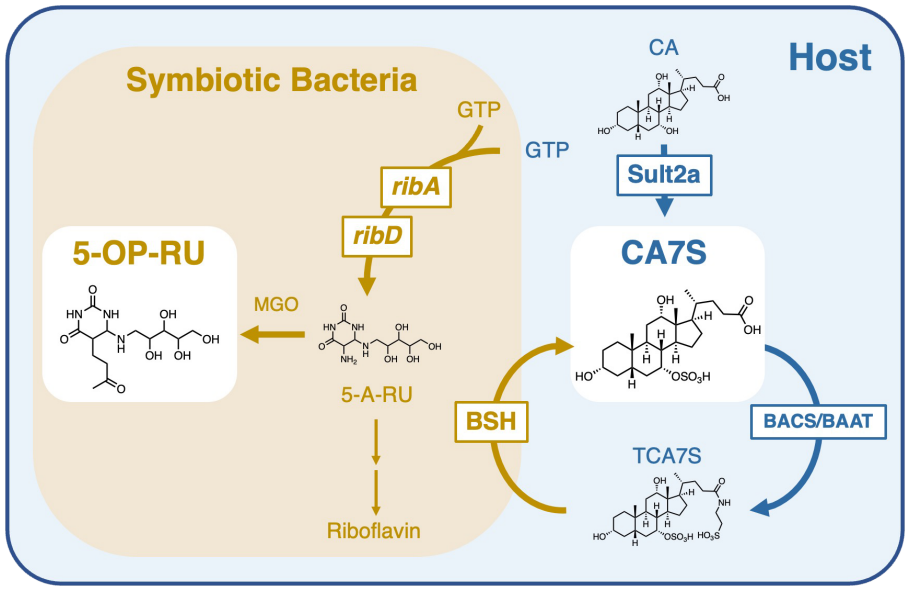


FIGURE 1
Role of symbiotic bacteria in the generation and modification of MAIT cell antigens. Bacterial riboflavin biosynthesizing enzymes, such as *ribA* and *ribD*, generate 5-A-RU, which is converted to 5-OP-RU in the presence of methylglyoxal (MGO) (left). CAS is produced by sulfation of cholic acid (CA) by sulfotransferase 2a (Sult2a) in the host. CAS is further taurine-conjugated in the host by bile acid–CoA:amino acid N-acyltransferase (BAAT) or bile acid–CoA synthetase (BACS) to generate TCA7S. Most intestinal bacteria have deconjugation enzymes, bile salt hydrolases (BSH), which metabolize TCA7S to CA7S. Symbiotic bacteria are therefore required for the maintenance of both 5-OP-RU and CA7S.

## 3.3 Role of CAS in MAIT cell development

As CA7S is weakly recognized by MAIT cells, it may contribute to the development of MAIT cells in the thymus (Figure 2). CA7S was detected in the thymus, and in mice lacking all Sult2a isoforms, thymic development of MAIT cells was impaired (33). Among thymic MAIT cells, the most mature stage, stage 3 ($CD44^{+}CD24^{-}$) (10), was severely affected. In mature thymic MAIT cells, MAIT17 occurs more frequently than MAIT1, whereas MAIT17 was fewer than MAIT 1 in Sult2a-deficient mice (33). These phenotypes were similar to those of GF mice (8, 10). While CA7S has been detected in the thymus, it is still unclear whether CAS is taken up and presented by thymocytes (Figure 2). Alternatively, Sult2a is also expressed in thymus as well as hepatocytes, implying that CAS might be synthesized within thymocytes when its substrate CA is available (Figure 2). Conditional deletion of all Sult2a isoforms will answer the key question whether CAS is *de novo* generated in thymocytes.

## 3.4 Effect of CA7S on MAIT cells in peripheral tissues

The role of CA7S in MAIT cells in peripheral tissues is not well understood. Unlike GF mice, the number of MAIT cells in the liver was not significantly decreased in Sult2a-deficient mice (33), implying that the antigen(s) utilized for the maintenance of MAIT cells vary by tissue. However, among liver-resident T cells, only MAIT cells lost the expression of multiple T cell signature genes, which is in contrast to invariant natural killer T (iNKT) cells and conventional T cells. Thus, CA7S might play an important role in shaping the identity of MAIT cells in the liver. MAIT cell-dependent protective immunity in the absence of CA7S function would be a worthy subject of further investigation utilizing infection models. Liver MAIT cells localize in the hepatic sinusoid, close to bile duct where CA7S is abundantly present; however, it is currently unknown whether bile acid metabolites play a role in MAIT cells in 'distant' tissues, such as the skin or lungs. Quantitative analysis of bile acid metabolites in these tissues would be required for further clarification. Although Sult2a is mainly expressed in hepatocytes, its transcript is also highly detected in other tissues (42), such as in some regions of the small intestine (Figure 2) (42, 43). CA7S produced in non-liver tissues might contribute to the maintenance of MAIT cells locally, which is a potential area of further investigation.

In humans, instead of CA7S, CA3S is an abundant cholic acid sulfate (35). Although the position of sulfation is different, CA3S can be presented by MR1 and recognized by MAIT TCR. In contrast to 5-OP-RU which triggers proliferation of peripheral MAIT cells, CA3/7S only induces survival, not proliferation. Thus, CA3/7S appears to induce qualitatively distinct MAIT cell responses. Indeed, while 5-OP-RU upregulates pro-inflammatory genes, CA3/7S induces gene signatures characterized by homeostatic and tissue repair responses (33). Among these is *CXCR4*, which contributes to migration and residency of lymphocytes in the tissues. It is therefore possible that CA3/7S, which is abundant in bile, may contribute to the residency of MAIT cells in the liver sinusoid where MAIT cells are most enriched

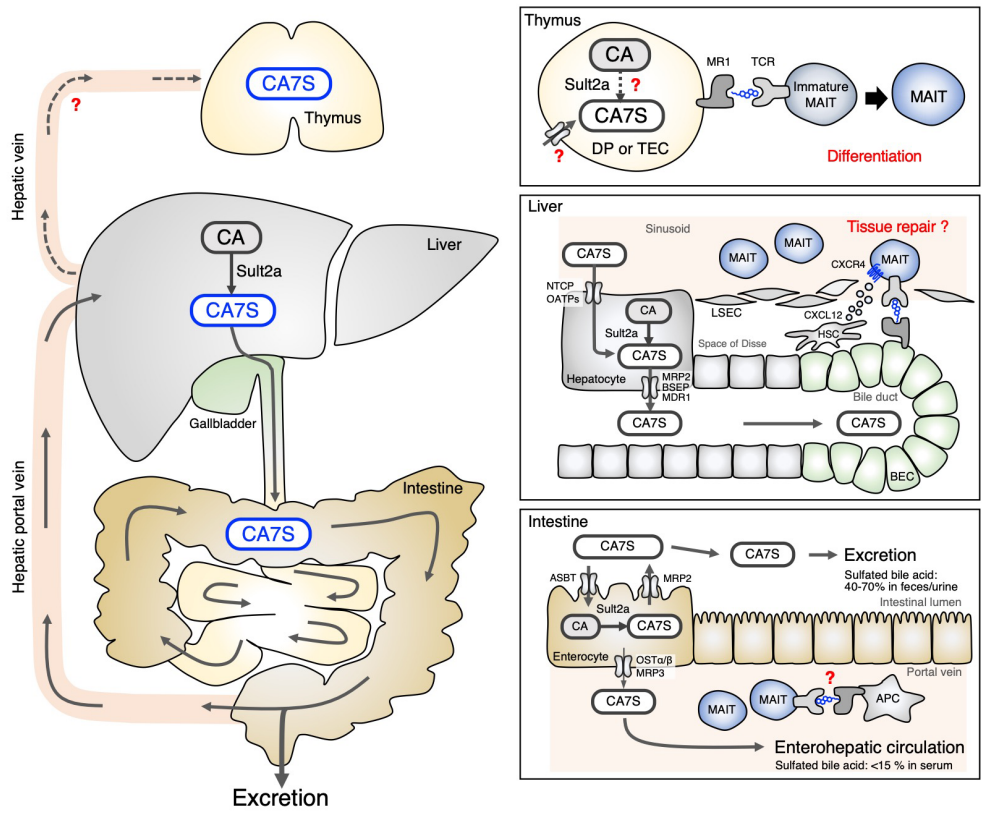


FIGURE 2
Circulation of CA7S in the body. CA7S is mainly biosynthesized in the liver from CA, stored in the gallbladder and excreted through the intestine (left). The source of thymic CA7S is unknown (Thymus). CA7S in the bile duct may be presented to liver MAIT cells surrounding biliary epithelial cells (BEC) expressing MR1 (Liver). Sult2a expressed by enterocytes can locally produce CA7S in some intestinal areas, which might control the homeostasis of intestinal MAIT cells. Enterocyte-derived CA7S may also be transported through the enterohepatic vein (Intestine). .

particularly in humans (16, 18, 19). Since the barrier composed of liver sinusoidal endothelial cells (LSEC) is fragile, upon liver damage, MAIT cells will likely come into contact with cholangiocytes/biliary epithelial cells (BEC) that express MR1 (16, 44). One might speculate that bile acid metabolites presented by MR1 on BEC promote tissue repair responses. Additionally, MAIT cells may act as a sensor of bile acid homeostasis.

Recently, roles of secondary bile acid metabolites, which are produced by the microbiota from primary bile acids, have been highlighted in T cell development. 3-oxo-litho cholic acid (3-oxo-LCA) has been shown to inhibit Th17 differentiation through the interaction with RORγt (45). Furthermore, the 3-oxo-LCA derivative, iso-allo-LCA, promotes regulatory T cell (Treg) differentiation via mitochondria-mediated epigenetic regulation (45) through Nr4a1 (46), which is supported by bacterial genetics (47). A similar secondary bile acid, iso-deoxycholic acid (iso-DCA), antagonizes FXR and the impairs immunogenic properties of dendritic cells, leading to pTreg maturation (48). In contrast to these indirect effects of secondary bile acids on T cells, CA3S and CA7S are endogenous primary bile acids that are directly recognized by TCR as antigens. Nevertheless, since CA3/7S also potentially act on nuclear receptor and/or GPCR families (39), sulfated bile acids may serve unknown pleiotropic functions within the immune system.

## 3.5 Role of CAS in disease settings

Thus far we have discussed CAS in a homeostatic context. However, quantitative variations in CAS have been reported in several diseases (35, 49–51). Furthermore, the expression of SULT2A1 is reported to be decreased in cholestatic diseases (52–55). Examination of the involvement of the CAS-MAIT cell axis in these disorders would be intriguing (18, 56). In particular, cholestatic autoimmune diseases, such as primary biliary cholangitis (PBC) and primary sclerosis cholangitis (PSC), have been associated with MAIT cells (57–60). The role of MAIT cells in immune diseases related to bile duct abnormalities is therefore an exciting area for future research.

# 4 Future perspective

Why should bile acids metabolites be recognized by MAIT cells? Currently, there is still no clear answer to this teleological question. The correlation of CAS-rich sites (bile duct) and MAIT cell-rich sites (liver sinusoid) raise several hypotheses regarding their role in tissue residency. As bile acids can sometimes harm the body, excessive cholic acids are continuously excreted as sulfated forms. Excreted forms are therefore stably and abundantly present in the

body, which make them effective for the maintenance of a host cell lineage. Moreover, recycling 'waste' metabolites is considered as an efficient strategy to make use of limited metabolites in the body. Nevertheless, at present, the localization of MAIT cells in other tissues, such as lung and skin where CAS is presumably less abundant, cannot be simply explained by bile acids. Additionally, the discovery of the 'peculiar' antigenic structure of the bile acid skeleton may suggest that MR1 can present a far greater variety of molecules than previously assumed, and that the MAIT TCR, despite its lack of diversity, can recognize complexes of such diverse antigens with MR1. It is exciting to imagine that further diverse self-antigen(s) for MAIT cells are present in different tissues and regulate their tissue-specific adaptation, which warrants future studies.

## Author contributions

EI: Writing – original draft, Writing – review & editing. SY: Writing – original draft, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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