



ROLE OF MUCOSAL-ASSOCIATED INVARIANT T CELLS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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The etiology of inflammatory and autoimmune diseases is complex and not yet fully understood. Their pathogenesis includes mechanisms in which both innate and adaptive immune cells are involved. Mucosal-associated invariant T (MAIT) cells are immune cells expressing an invariant TCR α chain (Va7.2-J α 33 in human and Va19-J α 33 in mice) and recognize the conserved MHC-I-related molecule MR1, which presents bacterial metabolites derived from the synthesis of vitamin B. Although most of the studies support a hazardous role of MAIT cells in tissue inflammation and destruction, few studies suggest a protective role. MAIT cells have tissue homing properties with the production of inflammatory cytokines, signifying that they may play an essential role in autoimmune and inflammatory diseases. In the current study, we clarified the present knowledge on MAIT cells in systemic lupus erythematosus.

INTRODUCTION

Mucosal-associated invariant T (MAIT) cells are defined as a subset of innate-like T lymphocytes first described in 1999¹. They are present abundantly in humans and have the property of rapidly expressing a range of pro-inflammatory cytokines. MAIT cells differ from conventional T cells in that they express an $\alpha\beta$ T-cell receptor (TCR) that has a limited TCR diversity, mostly including a semi-invariant TCR- α chain associated with a limited TCR- β chain repertoire². Another difference is that MAIT cells are not MHC-restricted but are restricted by the non-classical antigen-presenting molecule; class Ib MHC-related protein 1 (MR1)^{3&4}. MR 1 acts by presenting non-protein antigens which contain precursors and derivatives from highly

conserved riboflavin and folic acid metabolism biosynthetic pathways in bacteria, mycobacteria, and yeast^{5&6}.

MAIT cells were initially named after their unique location in the gut lamina propria. A previous study reported that germ-free mice lack MAIT cells, indicating their link with mucosal immunity³. A monoclonal antibody recognizing human Va7.2 TCR was produced in 2009 by Martin et al.⁷ and showed that Va7.2TCR+ cells with high expression of CD161 were MAIT cells. MAIT cells are abundant in peripheral human blood and constitute up to 10% of blood CD3+ cells. The level of iNKT cells in human peripheral blood represents 0.01-1%, and MAIT cell frequency is 10-1,000 folds more than iNKT cells.

Although little is known about the roles that MAIT cells play in disease, there is a

growing understanding of these cells' role in host protection from intracellular pathogens. Many features suggest potential importance to immune-mediated pathology. MAIT cells display an intrinsic effector memory phenotype i. e. without the need for previous clonal expansion⁸. They can rapidly secrete a range of pro-inflammatory cytokines, including interferon- γ (IFN- γ), tumor necrosis factor- α (TNF- α), interleukin-17 (IL-17), and the type 2 cytokine IL-4 on TCR ligation^{9&10}.

Systemic lupus erythematosus (SLE) is an autoimmune disease with multi-system involvement, factors like genetic susceptibility, environmental triggers including infections, and dysregulation of innate and adaptive immunity can predispose to the disease^{11&12}.

Within tissues, the local cytokine production by MAIT cells could lower the quantitative threshold of immune signaling, which is believed to affect the genetic predispositions that contribute to the initial pathogenesis in SLE. Also, several non-MHC loci contribute to the genetic predisposition to SLE¹², so polymorphisms in MR1 or other MAIT cell-related genes could lead to such predispositions. Till now, these have not been described. Cho et al. (2014) reported a decrease in the level of MAIT cells in peripheral blood of patients with SLE and rheumatoid arthritis¹³, mainly in the CD8+ and double-negative subsets, which correlated with disease activity scores in both diseases. Also, the frequencies of MAIT cells secreting IFN- γ (though not IL-17 or IL-4) were reduced in peripheral blood in SLE.

Because of the disease's unpredictable nature, SLE patients still suffer from disease flares, Conventional biomarkers are suboptimal in detecting flares, its sensitivity 50%, and specificity is 75%^{14&15}. Multiple studies showed that interferon (IFN) signaling pathway had an essential role in SLE. A high level of IFN in the serum of patients with SLE had been shown in previous studies^{16&17}. Recently, gene expression studies showed an overexpression of IFN-stimulated genes (ISGs) in the blood of SLE patients, which indicated the significant role of IFN in SLE^{18&19}. Another study on ISG products has recognized IFN regulated chemokines and established the correlation of these chemokines with disease activity making them promising biomarker candidates²⁰. One of

the IFN-regulated chemokines that has the strongest correlation with SLE disease activity is IFN gamma inducible protein 10 (IP-10) or chemokine ligand 10 (CXCL10)²⁰.

Markers of disease activity, including anti-double-stranded DNA antibodies (dsDNA antibodies), erythrocyte sedimentation rate (ESR), and C3 levels, are widely used but several patients present obvious disease-related signs and symptoms with normal or almost average values for these parameters. For example, in more than 40% of SLE patients, anti-dsDNA antibodies were not detected²¹, Also up to 15% of clinically - asymptomatic patients had high anti-dsDNA antibody titers^{22, 23}. Furthermore, some patients with central nervous system lupus or high SLEDAI had low anti-dsDNA antibody titers²⁴. Therefore, there is a need for new markers to predict and monitor disease activity. Increased classical signs of T-cell activity, such as the level of soluble interleukin-2 receptor (IL-2R) in serum^{25, 26}, or upregulation of HLA-DR and IL-2R on circulating T lymphocytes^{27&28}, have been reported that make them have a pivotal role in the immune response. Up till now, HLA-DR expression on T-cell subsets in SLE patients has never been studied in a large cohort and has never been compared with other conventional parameters²⁹.

MAIT Cells

Although most T cell studies are focusing on 'conventional' CD4+ and CD8+ T cells that distinguish peptides presented by MHC class II or I, there are several prominent populations of T cells referred to as "unconventional" T cells that recognize non-peptide antigens presented by specialized MHC class I-like molecules^{8&30}. These MHC class I-like molecules are monomorphic, and the T cells that recognize them have unique and conserved TCR repertoires, and consisting of an invariant TCR α -chain paired with a restricted TCR β -chain repertoire that differs from the highly polymorphic MHC class I molecules that present antigen to a diverse population of T cells². Also, these cells have unique effector functions by the recognition of these MHC class I-like targets during intrathymic development confers on the cells' developmental pathways that diverge from those of their peptide-MHC-restricted

counterparts. So, their distinct TCRs and antigenic targets are central to the biology of these cells. Invariant TCR α -chains in humans were first described in 1993 when a study of human CD4⁺CD8⁻ T cells discovered two distinct TCR α sequences². One was the α -chain variable region 24 and α -chain joining region 18 (V α 24J α 18) that defines type I natural killer T cells (NKT cells) restricted to the antigen-presenting molecule CD1d^{8&30}, while the other included V α 7.2 (TRAV1-2) joined to J α 33 (TRAJ33). Lantz and colleagues identified a population of T cells in mice and humans carrying the same TCR α -chain¹. In mice, these T cells expressed the orthologous V α 19J α 33 (TRAV1 TRAJ33), paired with a limited array of TCR β -chains, mainly V β 6 (TRBV19) and V β 8 (TRBV13), or V β 2 (TRBV20) and V β 13 (TRBV6) in humans¹. The nomenclature of "mucosal-associated invariant T cells" (MAIT) cells is because they are enriching mucosal locations such as gut³. Moreover, MAIT cells are restricted to the non-polymorphic MHC class I-like protein MR1³, a β 2-microglobulin-associated antigen-presenting molecule³¹. This interaction is largely deduced by the fact that MR1 and TRAV1 are highly preserved during the course of mammalian progress and have coevolved, with species that lack MR1 also selectively lacking TRAV1³²⁻³⁴. MAIT cells are very abundant in non-mucosal human tissues in which they represent up to 10% of blood T cells^{35&36} and 45% of liver T cells³⁷.

Antigens detected by MAIT cells

Studies have shown that different MR1 ligands may induce several effects on MAIT cells. Riboflavin (vitamin B2)-derivatives were observed to activate MAIT cells³⁸, but folate (vitamin B9)-derived antigens do not activate them. Riboflavin derivatives are pyrimidine products bound by MR1 of its unstable precursor, 5-Amino-6-D-Ribitylaminouraci (5-A-RU). These compounds are produced by most of the prokaryotes and fungi but not in animals lacking the riboflavin biosynthesis pathway³⁹. Furthermore, some pathogenic bacteria cannot synthesize riboflavin and have adapted to its exogenous uptake. These explain the dependence of MAIT cell development on timely commensal colonization and the changes in MAIT cell activity observed in dysbiosis⁴⁰. A small proportion of peripheral blood MAIT

cells was revealed to be reactive towards the MR1 molecule itself⁴¹. Introducing MR1-Ag tetramers [loaded with 5-(2-oxoethylideneamino)-6-D-ribitylaminouracil (5-OP-RU)] permit the determination of different phenotypical and functional MAIT cell subsets^{42 &43}. These antigens help in studying MAIT cells and in determination of the role of these cells in different diseases.

Tools for studying MAIT cells

Studying MAIT cells was done by recognizing antibodies specific for combinations of cell-surface markers, such as CD3, TRAV1-2 and CD161. Cells expressing these marker combinations are highly enriched in healthy human blood for MAIT cells, while it is uncertain how well these markers define these cells in other tissues or in the disease. The development of MR1 tetramers loaded with 5-OP-RU^{44, 45} has a key advance in the study of MAIT cells, allowing new investigations and direct evaluation of the efficacy of surrogate phenotypes for the analysis of MAIT cells in humans^{36,&45&46}.

Regarding MR1 tetramer staining, populations of blood-derived CD8⁺TRAV1-2⁺ T cells that express CD161, the dipeptidyl peptidase CD26 or the cytokine receptor CD218 in humans show considerable enrichment for MAIT cells, but not all of these are MAIT cells and not all MAIT cells are captured by this surrogate phenotype (11). Moreover, surrogate markers such as CD161 are not present on immature MAIT cells⁴⁷ and may be downregulated on MAIT cells after activation⁴⁸⁻⁵⁰, which indicate how these cells act in disease states. MR1 tetramers have also instigated rapid advances in the study of mouse MAIT cells. First study of the phenotype and function of MAIT cells was investigated in 'normal' laboratory mice (i.e., without transgenic TCR expression)⁵¹, which was previously difficult because the antibodies specific for the V α 19 (TRAV1) TCR α -chain was not detected and MAIT cells are 10- to 100-fold less frequent in mice than in humans^{1&51&52}.

Other studies used mice with transgenic expression of an invariant TRAV1+TRAJ33+ TCR and MR1-knockout mice to study mouse MAIT cells^{7, 53, 54}. The development and function of TCR-transgenic cells may differ from that of non-transgenic MAIT cells as

those TCR transgenic mice have large numbers of MAIT cells and have given valuable insight into the development and function of these cells. As, the TCR-transgenic MAIT cells⁷ mostly have a naïve phenotype and do not express the transcription factor PLZF (promyelocytic leukemia zinc finger), contrary to MAIT cells in non-transgenic mice^{51, 52}. Furthermore, TRAV1 + TRAJ33 + TCR-transgenic×TCR α -chain constant region (C α)-knockout mice on an MR1-knockout background still develop a large population of MAIT like cells^{45&55}. A study revealed that the C57BL/6. CAST- congenic mouse strain produces about ten times more MAIT cells than does the non-congenic C57BL/6 mouse strain⁵². The MAIT cells in C57BL/6.CAST- congenic mice are PLZF + and MR1 dependent⁵². One more study has described TRAJ33- knockout mice⁴⁷. The determination of MR1 tetramer allow more specific study of MAIT cells in different fields.

MAIT cell development

MAIT cells developed in a thymus-dependent manner^{1& 7} after random rearrangements in TCR-encoding genes. Cells that generate a TCR that interacts with MR1 expressed on CD4+CD8+ cortical thymocytes are selected into the MAIT cell lineage^{1&7&56}. Like the CD1d-restricted type I NKT cells that also develop after interacting with CD4+CD8+ thymocytes and contrasts with conventional T cell development, during which positive selection requires interactions of the TCR with MHC molecules on thymic epithelial cells, which suggest that MAIT cells and type I NKT cells share many transcription factors and functions⁵⁷, as highlighted by transcriptomics comparisons of these cell types^{58&59}. But, there are some differences between MAIT cells and type I NKT cells; for example, most mouse MAIT cells produce the cytokine IL-17A, and only a small subset of these cells produce the cytokine IFN- γ , while the opposite is for type I NKT cells. Moreover, in mice, type I NKT cells are more than MAIT cells by 10- to 100-fold in most tissues, while the opposite applies in humans. One common characteristic is that in contrast to conventional T cells, the number of MAIT cells and type I NKT cells varies widely between individual humans. Yet, the number of MAIT cells correlates with the

number of type I NKT cells³⁶ for reasons that remain unclear and with uncertain consequences for human immunity. The identification of immature MAIT cells and the mapping of MAIT cell development in both mice and humans was made by the use of MR1 tetramers to assess MAIT cells in the thymus⁴⁷. Studying both MAIT cells and NKT cells help in the determination of their role in SLE disease.

MAIT cell subsets

MAIT cells were first discovered as a double negative (DN) CD4-CD8- T cell population rich in the peripheral blood of healthy people and identified by expressing an invariant TCR α chain and the CD161 surface marker². These markers were used for identification and further phenotyping of human MAIT cells. MAIT cells express several surface molecules such as CD25, CD26, CD44, and CD69 surface markers also express cytokine receptors such as interleukin 7 receptor (IL-7R), IL-12R, IL-15R, and IL-18R also express transcription factors PLZF (promyelocytic leukaemia zinc finger), T-bet (T-box transcription factor) and ROR γ t (RAR-related orphan receptor gamma)⁶⁰.

The majority of human peripheral blood MAIT cells were CD8+CD4- and about 14% of the peripheral blood MAIT cells were double-negative. A minor subset was described as CD4+CD8- or CD4 + CD8 + double - positive⁴¹. These subsets differentially drop with age, signifying further alterations in their development regulation⁴¹. Different patterns of cytokine production were detected between the subsets⁴⁶. MAIT17 development was lately found to be strongly reliant on TCR signals in the thymus, being massively reduced in germ-free mice. During colonization, maturation and expansion of thymic MAIT17 cells was detected, but MAIT1 cell numbers was not affected⁶¹. Previous study confirms that the division into MAIT1 and MAIT17 subtypes occurs within the thymus and clarified other factors contributing to MAIT cell maturation and differentiation^{62, 63}. In human MAIT cells, no clear partition into MAIT1 and MAIT17 subtypes is observed, which are also strong producers of tumor necrosis factor α (TNF α)⁶⁴.

MAIT cells in autoimmunity and inflammation

Previous studies showed that in the peripheral blood of patients diagnosed with different disorders {systemic lupus erythematosus¹³, ankylosing spondylitis⁶⁵, rheumatoid arthritis (RA)⁴⁹, vasculitis⁶⁶, systemic sclerosis⁶⁷, primary Sjögren syndrome (pSS)⁶⁸, primary sclerosing cholangitis (PSC)⁶⁹ and inflammatory bowel disease^{70&71}, MAIT cells were significantly reduced. In Lupus, previous studies showed a strong positive correlation between MAIT cell deficiency and disease activity. Although, not all MAIT cell subsets decreased to the same extent. For example, a change in the expression of CD4 and CD8 coreceptors was detected in RA and pSS patients⁶⁸.

MAIT cells infiltrate the tissues affected in the immune-mediated diseases. For example, Infiltration and downregulation of activation markers in the synovium of RA and spondyloarthritis patients, which is reliable with hyporesponsiveness to potent microbial stimuli⁴⁹. Furthermore, MAIT cells infiltrating biliary ducts in primary sclerosing cholangitis, salivary glands of pSS patients⁶⁷, and intestinal lesions in inflammatory bowel disease^{70&71}. The migration of MAIT cells to the inflamed tissues may clarify the cause of why these cells decrease in the peripheral blood of patients of different disorders in different studies.

MAIT cells in cancer

While evidence of the role of MAIT cells in cancer is limited, some studies point to a possible role for MAIT cells in tumor immunity. In an investigation of diverse tumor samples, KLRB1 (encoding CD161) was the gene most significantly associated with a good prognosis. This correlated with tumor-infiltrating CD8+ T cells⁷², which may indicate that tumor-infiltrating MAIT cells may be a favorable prognostic factor.

Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus is an idiopathic connective tissue disease. Although the etiology of SLE is presumed to be multifactorial, one of the disease characteristics is the production of autoantibodies which leads to immune complex deposition, inflammation, and permanent organ damage. SLE is one of

the most known autoimmune disease of women of childbearing age (14.6 to 50.8 per 100,000 persons in this category in the USA)⁷³⁻⁷⁵. There is a female: male ratio of approximately 6-10:1, with a peak incidence between the ages of 15 and 40. On the other hand, SLE can affect all age groups, from infants to geriatric patients. Accurate clinical assessment of SLE is needed because it has a variable disease course, a complex phenotype, and cumulative morbidity over time. A new organ system may be involved over time in numerous patients, even 5-10 years after diagnosis⁷⁶. Several studies now show 5-year survival rates exceeding 90%⁷⁷⁻⁷⁹. Still, SLE patients' survival has not improved since the 1980s, with atherosclerosis remaining the major cause of death. Therefore, it is crucial to reveal new measures for diagnosing SLE, monitoring disease activity, assessing tissue damage, and recognizing effects on individual patients.⁸⁰

T cells in SLE

Particularly CD4 T-cells are of central importance, which can be found in the urine of patients with active lupus nephritis⁸¹. CD4+ T cells can occur in various subsets, such as follicular T helper cells (Tfh), regulatory T cells (Treg), Th17-, Th1- and Th2 cells. Tfh cells were elevated in SLE patients' peripheral blood and are essential for germinal centre induction, proliferation, isotype-switching and somatic hypermutation. These cells express both PD-1 and CXCR5 and produce the main cytokine IL-21, which provokes B cells to differentiate into memory B cells and plasmablasts as typically found in SLE^{82, 83}. In lupus, increased numbers of Th-17 with an imbalance to reduced Tregs have also been reported⁸⁴. IL-17 mediates inflammation, and its production is inversely correlated with IL-2. By the way, blockade of IL-2 stimulates differentiation of Th17 cells⁸⁵. IL-2 deficiency was described in SLE and represented an additional hallmark of this disease. Though, recent studies show that exogenous IL-2 cannot completely restore T-cell functions in SLE⁸⁶.

MAIT cells in SLE

The MAIT cells play important roles in the first-line defense against microbial pathogenesis as they can respond very rapidly on activation, in the absence of exogenous

antigens, by TCR signaling or cytokine stimulation, similar to other innate lymphocytes, including invariant natural killer T (iNKT) cells⁸⁷⁻⁹⁰. Several cytokines are produced by activated MAIT cells, including interferon (IFN)- γ , TNF- α , and IL-17 in addition to cytotoxic granzyme and perforin^{9&35&91&92}. MAIT cells activation is through the MR1 ligand present in microbes and drugs. Cytokines, can also activate MAIT cells including IL-12, IL-18, and IFN α , by an antigen-independent mechanism. MAIT cells express several cytokine and chemokine receptors and homing receptors. Activated MAIT cells upregulate very late antigen-4 (VLA-4) and secrete perforin and granzyme-B, Th1 and Th17 cytokines, and low levels of IL-10 (figure1)⁹³.

MAIT cells are gaining attention because of their roles in various types of immune responses and diseases due to their characteristic abundance and cytokine-producing capacity. MAIT cells are related to an increasing number of diseases of microbial, autoimmune, metabolic, and cancerous origin⁹⁴⁻⁹⁶. A Previous study established that MR1 deficiency aggravated the severity of experimental autoimmune encephalomyelitis in an animal model of multiple sclerosis⁹⁷, suggesting their protective role in this model because MR1 is necessary for the thymic development of MAIT cells (1-3). Further studies revealed that MAIT cells play role in the suppression of the severity of inflammatory colitis and the development of type 1 diabetes^{98&99}. In contrast, MAIT cells seem to play role in tissue inflammation in arthritis models and in the pancreas of NOD mice after the onset of diabetes^{9&99},

Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune disease caused by the production of autoantibodies to nuclear antigens. Deposition of this autoantibodies in the form of immune complexes in tissues cause tissue inflammation in various organs, including the skin, joints, kidneys, and central nervous system. Although the new advances in the treatment of SLE, therapeutic options are still limited. A Preceding study revealed that the frequency of MAIT cells was reduced in the peripheral blood of patients with SLE, and the MAIT cells present were activated in SLE patients more than in healthy controls, and

positively correlated with disease activity³. These findings suggest that MAIT cells may have an important role in lupus pathology. By crossing Fc γ RIIb^{-/-}Yaa mice⁴¹, a spontaneous lupus mouse model, to MR1-deficient mice that lack MAIT cells, a previous study established that MAIT cell deficiency results in reduced disease severity by decreased autoantibody production, reduced glomerulonephritis scores and reduced germinal center responses in addition to lower T cell and innate T cell immune responses in MR1-deficient lupus mice.

A previous study revealed that the treatment of mice with new synthesized non-stimulatory MR1 ligand inhibits MAIT cell activation and reduced autoantibody production and the severity of lupus nephritis. Furthermore, it showed that MAIT cells enhanced autoantibody production by B cells in vitro dependent on CD40L-CD40 and TCR pathways. So, Inhibition of MAIT cell activation by using an inhibitory MR1 ligand reduced autoantibody production by B cells¹⁰⁰. In our study we try to explain the key role of MAIT cells in SLE disease make there is a possibility of them as a therapeutic target in systemic autoimmune diseases, including SLE.

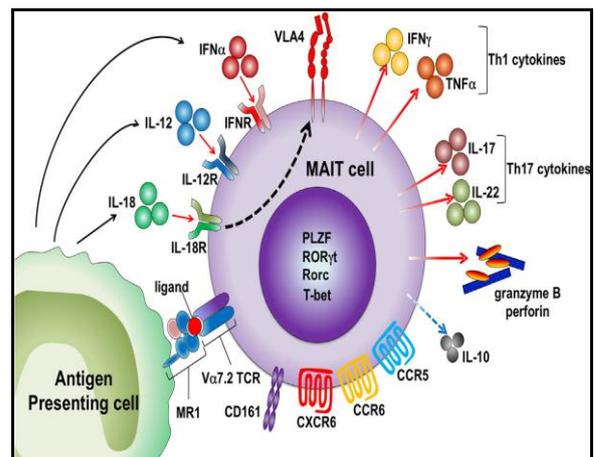


Fig. 1: Mechanisms of human mucosal-associated invariant T (MAIT) cells activation.⁹³

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دور الخلايا التائية المرتبطة بالغشاء المخاطي في الذئبة الحمراء الجهازية

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السبب في الامراض المناعية والالتهابية مازال معقد ولم يفهم كليا بعد. آلية حدوث هذه الامراض تشمل الخلايا المناعية الخلقية والمكتسبة معا. الخلايا التائية الثابتة المرتبطة بالاغشية المخاطية هي خلايا مناعية تشارك سلسلة الفا من مستقبل الخلايا التائية (في الفا ٢,٧-جية الفا ٣٣ في الانسان و في الفا ١٩-جية الفا ٣٣ في الفئران) وتتعرف على خلايا التوافق النسيجي المحافظة ١ ام ار ١ التي تقدم ايض البكتريا القادمة من تصنيع فيتامين ب. بالرغم من ان اغلب الدراسات ترجح الدور الضار الذي تقوم به هذه الخلايا في التهابات الانسجة وتدميرها، قليل من الدراسات ترجح دور وقائي لهذه الخلايا. هذه الخلايا لديها خصائص التوجه الى الانسجة مع انتاج السيتوكينات الالتهابية مما يرجح انه من الممكن ان تلعب دور هام في الامراض المناعية والالتهابية. في هذه الدراسة نحن نقدم معرفة عن هذه الخلايا في مرض الذئبة الحمراء الجهازية والتي من الممكن ان تكون مؤشر حيوي جديد للمعرفة اكثر بالمرض وتفتح تقنيات جديدة للعلاج.