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Review

MAIT-cells: A tailor-made mate in the ancient battle against infectious diseases?

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ABSTRACT

It has been almost two decades since the discovery of mucosal-associated invariant T (MAIT)-cells. Several advances in the field have been made such as the discovery of the antimicrobial activity of MAIT-cells, the abundance of these cells in human mucosa and in liver and the discovery of ligands able to bind MR1 and activate MAIT-cells. MAIT-cells are a unique subset of innate-like T-cells that express a canonical T-cell receptor with the alpha chain containing hAV7S2 and AJ33 in humans (TCRVα7.2Jα33) and respond to bacterial/fungus vitamin B2 metabolites by an MR1-dependent pathway. Indirect activation is also observed during chronic viral infections by and IL-12/IL-18 pathway. In this review, the mechanisms of activation, the timeline of MAIT-cell development in humans as well as their role in human infection are discussed. On the whole, we believe that harnessing the anti-microbial ability of MAIT-cells could contribute for the design of potent immunotherapies and vaccines against "hard-to-kill" infectious agents that remain as public health threats worldwide.

1. The discovery of mucosal-associated invariant T (MAIT) cells

It has been almost seventeen years since a unique subset of innate-like T-cells expressing a canonical T-cell receptor with alpha chain containing hAV7S2 and AJ33 (TCRVα7.2Jα33) was discovered in humans [1]. This subset was reported as a phylogenetically conserved subset of T-cells in mammals, outlined in mice and cattle by the expression homologous AV19 and AJ33.

The canonical invariant TCRVα7.2Jα33 and its murine and bovine homologues were predominantly found in double negative T-cells and in CD8αα$^+$ T-cells, a conspicuous trait shared by mucosal T-cells. This hint was later on confirmed by evidence of the TCRVα7.2$^+$T-cell abundance in mucosal tissues [2], defining this interesting subset as mucosal-associated invariant T (MAIT) cells. In addition, CD8αα expression is a hallmark of terminally differentiated human CD8$^+$ T-cells that have been primed to respond upon antigen exposure [3]. Tissue-resident MAIT-cells are primarily found in both inner and barrier tissues, where they operate as sentinels and forefront defenders of tissue integrity in response to infectious agents. MAIT-cells are preferentially located in the liver and gut lamina propria of humans and mice [2,4], however these cells can also be found in notable frequencies in lungs, lymph nodes and skin epidermis in steady state, as illustrated in Fig. 1, and can further accumulate in those sites upon infection [5–7].

2. MAIT-cells—phenotype, homing and function

At a first glance, MAIT-cells express, like invariant NKT-cells, high levels of the NK1.1 surface molecule, or CD161 in humans [8,9], which indicate that these two subsets may assign for common functions. However, the conservation between species of T-cells displaying this specific repertoire, their superior abundance in mucosal tissues and finally, their unusual restriction pattern associated with a divergence on the molecular structure of the activating antigens suggest that this population may serve a function complementary to that played by NKT-cells [1].

While some innate-like lymphocytic subsets assume almost exclusively tissue-resident behavior [1,2], MAIT-cells display significant frequencies in peripheral blood [9,10], making it possible to identify this subset using flow cytometric protocols in peripheral blood mononuclear cells (Fig. 1). In regards to MAIT cell frequency in the peripheral blood, this subset represent 0.5–0.6% of total mononuclear cells, comprising up to 10% of total circulating CD3$^+$ T-cells as

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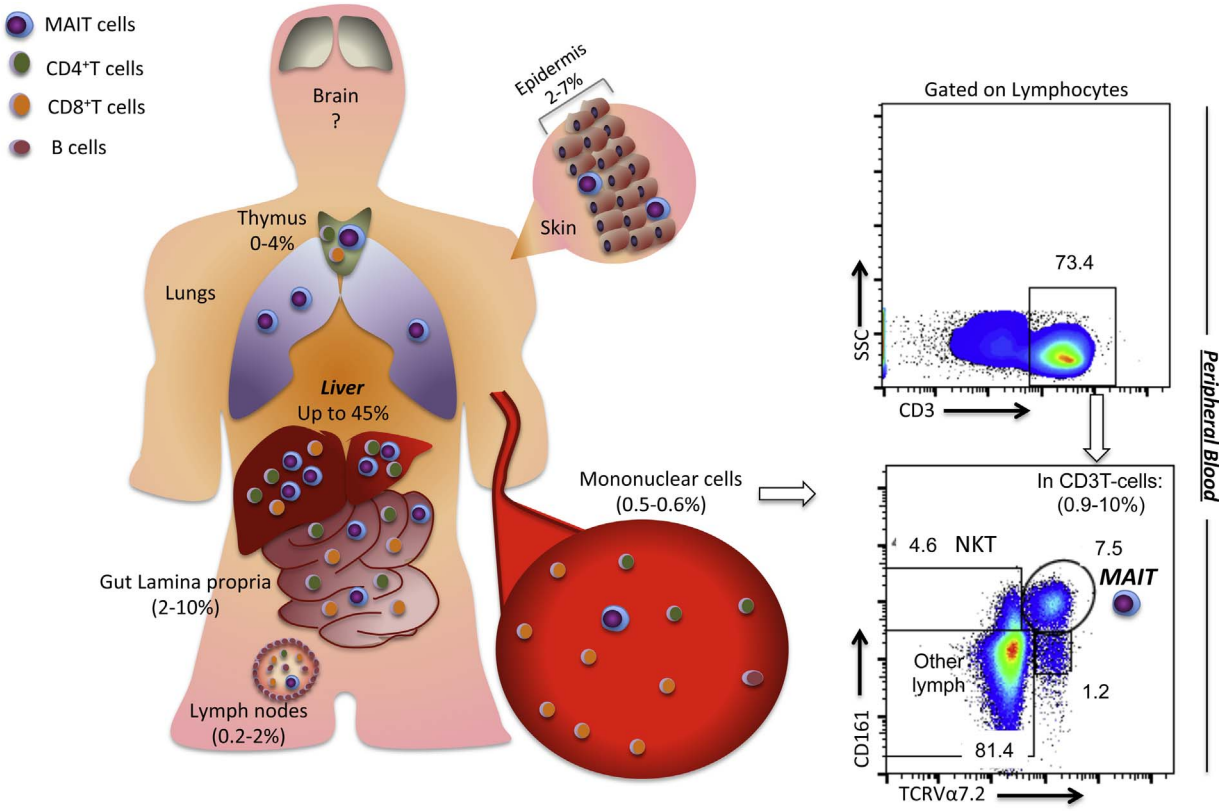

Fig. 1. Homing and phenotype of Mucosal-Associated invariant T cells (MAIT cells). MAIT cells are identified as the T cell subset expressing TCRVα7.2 and high levels of CD161, which are ubiquitous in humans and predominate in liver and gut lamina propria. Significant MAIT frequencies have been described in lungs, thymus, lymph nodes, brain, skin epidermis and, interestingly, the peripheral blood. Pseudocolor flow cytometry plots of side-scatter and CD3 allowed for selecting the percentage of MAIT cells (TCRVα7.2$^+$ CD161$^+$). Abbreviations: MAIT-cells, mucosal-associated invariant T cells; SSC, side scatter.

illustrated in the FACS plot of Fig. 1. This abundance contrasts with the frequency of other invariant NKT cells (*e.g.* TCRVα24$^+$ NKT cells represent up to 0.1% within T-cells in blood), which are rare amongst peripheral blood CD3$^+$ T-cells. It still unknown why MAIT-cells are so abundant amongst peripheral blood T-cells.

The homeostatic chemokine receptor expression pattern on the surface of MAIT-cells is composed of CCR9^{int}CCR7$^-$CCR5^{hi}CXCR6^{hi} CCR6^{hi} [9,10], confirming that MAIT-cells home preferentially in tissues, such as intestine (CCR9), liver (CXCR6 and CCR6), lungs (CCR5), in contrast with their scarcity in lymph nodes (CCR7$^-$). Human MAIT-cells display an effector memory phenotype at steady state (Fig. 2), featured by the expression of CD45RA^{lo}CD45RO$^+$CD27^{neg} [1,9,11]. A question that still remains to be fully answered is whether MAIT-cells would be able to patrol the lymphatic systems and secondary lymphoid organs, such as lymph nodes and spleen, as other effector memory lymphocytic subsets are prepared to do.

3. The lifespan of TCRVα7.2$^+$CD161^{++} T-cells in humans

As mentioned above, MAIT-cells are quite abundant in the peripheral blood of healthy adults. However, it has been reported that the MAIT cell percentage in homeostasis changes along life [12–16] as represented in Fig. 3. Percentages of TCRVα7.2$^+$CD161$^+$ T-cells are very low in newborns extending to late childhood. Between 30 and 40 years of age, the percentages of MAIT-cells seem to reach a plateau and they start to fall after 40 years of age [12]. This kinetics seems to be in agreement with thymus functionality; however, it is still under scrutiny as to whether peripheral blood MAIT-cells freshly exiting the bone marrow and egressing thymus would be mature enough to actively survey the body for infectious agents.

To partially answer this question, recent evidence showed that human MAIT-cells already display MR1 restriction even at early stages such as in cord blood and thymus [11]. However, MR1-restricted MAIT-cells found in these tissues display limited effector capacity in response to bacteria-infected antigen-presenting cells as compared to peripheral blood MAIT-cells. Cord blood and thymic MAIT-cells display a naïve memory phenotype (CD45RA$^+$CD27$^+$), indicating that they are probably yet to be functional [11,14–16].

These and other results strongly support the fact that MAIT-cells are pathogen-reactive effectors that need extrathymic education and will gain functionality after contact with peripheral tissues [11–16]. Mice born and kept in pathogen-free conditions have decreased TCRVα19 expression, indicating that the second step on MAIT-cell development after exiting the thymus is associated with commensal microbiota [10]. It was proposed that the MAIT-cell development could be divided in three stages, being stage 1 and 2 happening in the thymus and stage 3 enriched extrathymically. Prior to the latter, MAIT-cells undergo specification in the thymus mediated by MR-1, while functionality seems to be dependent upon the presence of the promyelocytic leukemia zinc finger (PLZF) and endogenous colonization of microbiota [16].

4. Non-classical MHC related protein 1: an intriguing antigen-presenting molecule

TCRVα7.2$^+$ T-cells respond upon binding to a non-classical MHC-I related protein 1 or MR1, in a restricted manner [1,2]. MR1 antigen presentation is β2m-dependent but TAP-independent [1]. Strong evidence for MR1 antigen presentation to MAIT-cells were first obtained by *in vitro* activation of MAIT-cell hybridoma and MR1 blockade promoted by the monoclonal anti-MR1 blocking antibody clone 26.5 [17]. Crystallography studies have shown that MR1 is perfectly suited to bind ligands that originate from vitamin metabolites [18–20]. MR1-restricted vitamin metabolites originated from the bacterial riboflavin