A TCR-Dependent Tissue Repair Potential of MAIT Cells

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A TCR-dependent tissue repair potential of MAIT cells

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Abstract

Three studies published in *Cell Reports* (Hinks et al.; Lamichhane et al., Leng et al., 2019), describe the transcriptome of human and mouse MAIT cells after cognate and non-cognate stimulation. The results confirm the variability of MAIT cell effector functions, and provide evidence of a new tissue-repair gene signature expressed upon TCR stimulation.

Mucosal-associated invariant T (MAIT) cells represent an abundant subset of T cells expressing a semi-invariant T-cell receptor TCRα chain (TRAV1-TRAJ33), restricted by the MHC class Ib molecule, MR1 [1]. Both the TCRα chain and MR1 are highly conserved between species and appear to have co-evolved, suggesting they fulfill important non-redundant functions. MAIT cells recognize derivatives from an unstable intermediate of the vitamin B2 biosynthesis pathway, present in most bacteria and yeast, but not in animal cells [1]. In contrast to mainstream T cells, MAIT cells are selected by $CD4^+CD8^+$ thymocytes, leading to a specific differentiation program linked to the master transcription factor PLZF. This leads to tissue residency upon thymus exit, with distinct transcriptional patterns according to organ specificity [2]. In humans, MAIT cells represent a large proportion of T cells in the blood (1-8%) and in tissues (3-5% in the colon lamina propria, up to 20% in the lungs and 40% in the liver) [1]. They are much fewer in mice but their tissue distribution is similar. In humans, MAIT cells express intermediate amounts of the key transcription factors RORγt, Tbet, Eomes, and Helios, suggesting various effector functions. In contrast, mice housed in the usual laboratory facilities harbor two distinct subsets, MAIT1 and MAIT17, expressing Tbet and RORγt, respectively, each one with a specific tissue location [2]. Despite

these differences, in both species, MAIT cells can be activated either through TCR triggering or via IL-12 and IL-18 [1]. Upon activation, MAIT cells secrete various cytokines, such as IFN-γ and TNF-α, but also IL-17 or IL-22, depending on the cytokine environment.

Given their antigen specificity, MAIT cells have been implicated in various bacterial infectious diseases such as pneumonia or tuberculosis in humans with both low MAIT cell blood numbers and accumulation at sites of infection [3]. Experimental models also support an anti-bacterial function of MAIT cells. Recently, these cells have been implicated in anti-viral responses, with decreased numbers of MAIT cells in blood upon influenza virus and dengue virus infections relative to controls; and based on in vitro data showing that viruses such as influenza can induce the release of MAIT-activating cytokines [3]. Moreover, mice devoid of MAIT cells are more sensitive to influenza virus infection than wild type mice are [4]. However, despite the wealth of data on the phenotypes and transcriptomes of MAIT cells at steady state, as well as their putative roles in various infectious and metabolic diseases [3], the extent of MAIT cell functional plasticity and the nature of the functional program(s) expressed *in vivo* in pathological settings remain unclear.

Three recent articles published in *Cell Reports* provide new information regarding the potential effector functions exerted by human and mouse MAIT cells responding to specific stimuli; namely, the activation of MAIT cells via TCR or cytokine signaling, or during and after experimental bacterial infection with *Legionella longbeachae* [5-7]. Using human whole peripheral blood mononuclear cells (PBMC) [5, 6] or sorted $CD161^{hi}Va7.2^{+}$ human MAIT cells [7], the MAIT transcriptome was analyzed following i) TCR triggering (anti-CD3/CD28 antibodies, 24h) [7]; fixed *Escherichia Coli,* or the MAIT ligand precursor, 5-amino-ribityl-uracil (5-A-RU), 6h [6]; the MAIT ligand, 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU), 6h [5]); ii) cytokine activation (suboptimal IL-12/IL-18 combined with IL-15, plus the human gut-derived cytokine TL1A, 24h [7]; IL-12/IL-18, 24h [6]); or iii) a

combination of both TCR and cytokine activation [7]. The high numbers of differentially-expressed genes following the various activation protocols suggested that MAIT cell effector functions could be modulated by the nature of the initial triggering. One study further characterized the expression of various inflammatory cytokines, cytotoxic granule contents, chemokines, transcription factors and co-stimulatory molecules at the protein level [6]. While both types of stimulation efficiently activated MAIT cells, the set of effector molecules depended on the timing and mode of stimulation, with TCR triggering inducing faster and more polyfunctional responses than the examined cytokines [6]. The extensive data sets, both at the RNA and/or the protein levels, showed that human and mouse MAIT cells mounted rapid pro-inflammatory responses that were tailored to the nature of the stimuli [5-7].

The main original finding of these three papers [5-7] indicates that both human and mouse MAIT cells express a transcriptomic tissue-repair signature upon TCR stimulation, substantiating the hypothesis made a few years ago that MAIT cells would be involved in tissue repair [3]. Specifically, such a tissue-repair signature was initially identified in H2-M3-restricted $CD8^+$ T cells that accumulated in the mouse skin following *Staphylococcus epidermidis* colonization, and which were potent inducers of wound healing [8]. The shared transcriptome signature between MAIT and H2-M3-restricted $CD8^+$ T cells illustrates the commonalities between T cell subsets restricted by non-classical MHC molecules. Moreover, culture supernatants of human MAIT cells activated by *Escherichia coli* promoted the closure of a scratch on an in vitro monolayer of colonic Caco2 cells, confirming the TCR-dependent tissue repair potential of MAIT cells [7]. Furthermore, the tissue repair signature was also expressed by lung MAIT cells after *Legionella* infection in mice, both during the acute phase, and after reinfection [5]. Upon resolution of the infection, MAIT cells harbored a transcriptional profile different from the early infection phase, but similar to that of γδ T cells [5]. MAIT cells have also been shown to express both RORγt and

Tbet during influenza virus infection [9], which is different from the MAIT17 (RORγt^{+}Tbet^{-}) profile observed at steady state in mouse lungs [2, 3], yet closer to the human blood MAIT phenotype [2, 10]. Comparing these data with the transcriptome of lung MAIT cells at steady state could help decipher whether MAIT cells acquire a particular differentiation program following a pathogenic encounter. This type of analysis might also provide an explanation for the distinct MAIT1 and MAIT17 subsets in mice, contrasting with the mixed 1/17 phenotype in humans [2, 10], which is surprising considering the evolutionary conservation of MAIT cell features.

Altogether, these three articles suggest broader functions of MAIT cells in immunity, including tissue repair, rather than just harboring anti-infectious properties. Further studies are necessary to identify the pathophysiological circumstances under which MAIT cells might mediate tissue repair, and to decipher the mechanisms involved. Moreover, inappropriate tissue repair activity of MAIT cells might be involved in fibrosis or potentially promote tumor growth, and this should be investigated. Because MAIT cells reside in tissues, it will be important to determine how MAIT cell functions are specifically impacted by the organs they reside in and whether MAIT cells are directly involved in tissue homeostasis. Moreover, whether pro-inflammatory/cytotoxic vs tissue repair functions of MAIT cells are expressed simultaneously, sequentially, or even in different subpopulations during a variety of infections, remains to be elucidated. Finally, since the MAIT cell microbial ligand (5-OP-RU) from the commensal microbiota appears to easily cross the epithelia to reach the murine thymus [11], future studies should assess how MAIT cell functions are regulated at steady state based on commensal microbiota composition, or during epithelium damage in the course of pathogenic infections in relation to MAIT ligands and cytokine milieu (Fig. 1). Given the abundance of MAIT cells in humans, another exciting avenue for future studies, will be to

determine whether potential new functions of MAIT cells in wound healing can be harnessed for therapeutic purposes.

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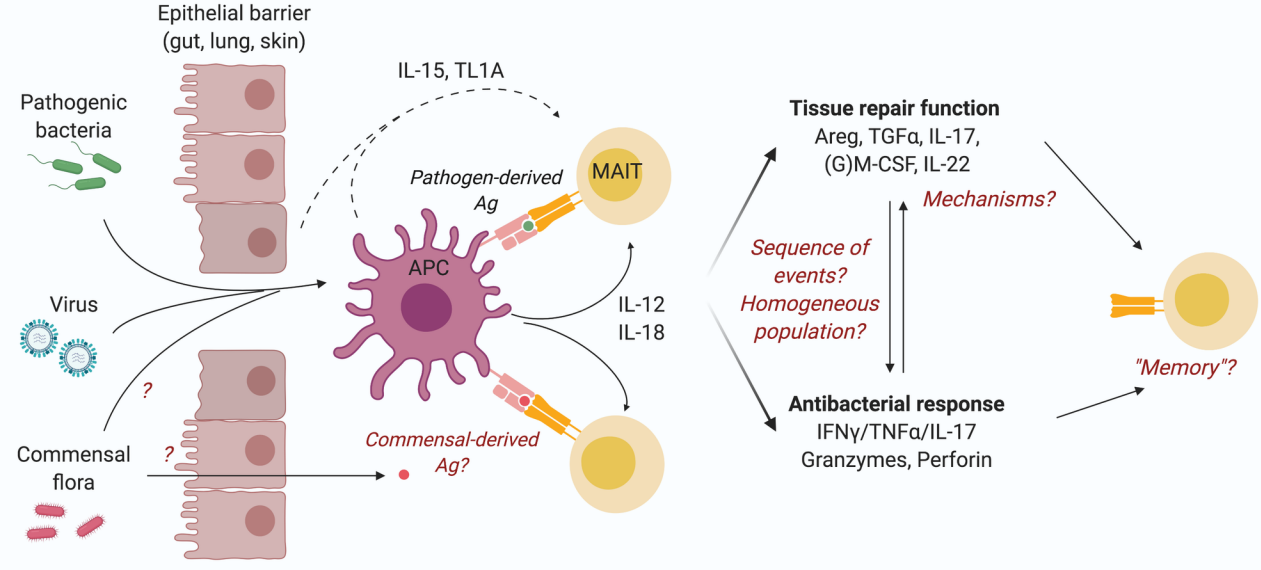
Figure Legend

Figure 1. Possible effector functions of MAIT cells. Following infection by pathogenic bacteria that produce the MAIT-activating ligand, or by viruses that do not produce it, MAIT cells underlying the intestinal (or lung or skin) epithelium can be activated following TCR-triggering and/or cytokine stimulation by interleukins IL-12 and IL-18, associated (or not) with IL-15 and TLA1 (TNF-like cytokine 1A; gut-derived). Once activated, MAIT cells have the potential to exert anti-bacterial and tissue repair responses, the latter being dependent on TCR stimulation. Pending questions regarding the potential effector functions of MAIT cells in humans and mice include assessing whether commensal bacteria also provide a cognate ligand at steady state and during infection, how this ligand might reach the antigen-presenting cell (APC), and whether the ligand derived from the commensal microbiota plays a role during infection by a pathogen unable to produce the MAIT ligand. Whether MAIT cell effector functions are performed by the same cells or by separate subpopulations remains to be investigated. Similarly, the putative tissue repair mechanisms of MAIT cells remain largely unknown. Finally, whether MAIT cells retain a specific "memory" phenotype following the resolution of infection should be clarified. Ag, antigen; Areg, amphiregulin; TGFα, Transforming growth factor α; IL, interleukin; (G)M-CSF, (granulocyte)-macrophage colony-stimulating factor; IFNγ, interferon γ; TNFα, tumor necrosis factor α.


Epithelial barrier
(gut, lung, skin)
Pathogenic
bacteria
Virus
Commensal
flora
?
?
IL-15, TL1A
Pathogen-derived
Ag
MAIT
APC
IL-12
IL-18
Commensal-derived
Ag?
Tissue repair function
Areg, TGFα, IL-17,
(G)M-CSF, IL-22
Mechanisms?
Sequence of
events?
Homogeneous
population?
Antibacterial response
IFNγ/TNFα/IL-17
Granzymes, Perforin
"Memory"?