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## Psoriasis and the MAITing game: A role for IL-17A+ invariant TCR CD8+ T cells in psoriasis?

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### Abstract

Recent findings have indicated that the majority of IL-17A+CD8+ T-cells in the blood belong to a subset of innate T-cells named mucosa-associated invariant T-cells (MAIT). In this issue, Teunissen and colleagues (Teunissen *et al.*, 2014) demonstrate that while MAIT cells are found in psoriatic skin, they are not increased in abundance and that the majority of IL-17A+CD8+ T-cells in plaques of psoriasis are devoid of MAIT cell characteristics.

Mucosa-associated invariant T-cells (MAIT) are a recently-characterized T-cell subset that together with  $\gamma\delta$  T-cells and invariant natural killer T-cells (iNKT) joins the ranks of the unconventional T-cells (Figure 1). Like other subsets of innate T-cells (Laggnier *et al.*, 2011), attempts have been made to implicate these cells in the pathogenesis of psoriasis (Bonish *et al.*, 2000), especially because IL-17 is now known to have a prominent role in the pathogenesis of psoriasis, and because MAIT cells have been shown to account for the majority of the IL-17A-producing CD8+ T-cells in the blood (Dusseaux *et al.*, 2011). In their article, Teunissen and colleagues (Teunissen *et al.*, 2014) show that while the number of IL-17A-producing CD8+ T-cells in the blood correlates with psoriasis disease severity and while MAIT cells are found in psoriatic skin, they are not increased in frequency compared with normal skin; moreover a large proportion of the IL-17A-producing CD8+ T-cells in skin plaques are conventional CD8+ T-cells.

MAIT cells are evolutionarily conserved, and they express an invariant T cell receptor  $\alpha$ -chain (V $\alpha$ 7.2 and J $\alpha$ 33) that is restricted by the non-classical major histocompatibility complex (MHC) class I molecule MHC-related protein 1 (MR1) (reviewed in (Le Bourhis *et al.*, 2011)). In contrast to conventional T-cells that have a lag in terms of generating effector cells and mounting immune responses, these innate T-cell subtypes express an effector-memory phenotype upon maturation, and they have a capacity for rapid effector function (Le Bourhis *et al.*, 2011). One of the striking differences between MAIT cells and conventional CD8+ T-cells is that MAIT cells are uniquely activated by vitamin B2 (riboflavin) metabolites that are presented in the context of the MR1 protein on antigen presenting cells (APC) and on epithelial cells. Mammals do not synthesize vitamin B2, relying on certain bacteria and yeasts for this. Interestingly, only microbes with functional

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biosynthetic pathways for vitamin B2 have been shown to activate MAIT cells (e.g., *Escherichia coli*, *Staphylococcus aureus* and *Mycobacterium tuberculosis* but not *Streptococcus* or *Listeria*) which may also explain the lack of response by MAIT cells to virus-infected cells. Thus MAIT cells might provide a means to control certain commensals and/or to offer a novel mechanism to detect the overgrowth or cellular infection by certain pathogens. This might occur by detecting the presence of their biosynthetic intermediates, which would be akin to  $\gamma\delta$  T-cells' recognition of intermediates of the alternative pathway of cholesterol synthesis used by some bacteria and eukaryotic pathogens but not by mammalian cells. No studies have been reported to address the role of MR1 in psoriasis, but its mRNA expression in lesional psoriatic skin is decreased by approximately 30% compared with normal healthy skin (unpublished observation).

In contrast to mice, where this subset is relatively rare, MAIT cells constitute a significant proportion of T-cells in humans, accounting for between 1 and 10% of T-cells in peripheral blood, as well as representing a significant population of T-cells in the human liver, gut mucosa and mesenteric, but not peripheral, lymph nodes. MAIT cells are defined as CD3+CD4- cells expressing TCR V $\alpha$ 7.2, with high levels of the NK receptor CD161 (previously associated with all IL-17 producing T-cells), together with the IL-18 receptor (IL-18R $\alpha$ ) and the Th17-associated transcription factor ROR $\gamma$ t (reviewed in (Le Bourhis *et al.*, 2011)). MAIT cells also express high levels of the chemokine receptors CCR6 and CXCR6, with intermediate expression of CCR9; such chemokine receptor expression likely explains the abundance of these cells in the periphery, particularly the gut and liver. The multidrug efflux transporter protein ABCB1 is also expressed strongly by MAIT cells. ABCB1 is typically expressed by long-lived non-cycling (G<sub>0</sub>) cells, which together with their expression of CD45RO and CD95, suggests that these cells are long-lived effector T-cells.

MAIT cell activation occurs when APCs, epithelial cells or fibroblasts present a vitamin B2 metabolite (typically containing a ribityl carbohydrate group) in the groove of the MR1 molecule to the responding MAIT cell. The precise pathway for such antigen presentation is poorly defined, but it is independent of TAP and invariant chains (i.e., the typical class I and class II presentation pathways), and it is independent of Toll-like receptor signaling, because MyD88, TRIF and NLRP3 knock-down had no effect on MAIT cell activation by APC. Isolated human MAIT cells secrete IFN- $\gamma$ , TNF- $\alpha$ , CCL20 and granzyme B rapidly after stimulation with CD3/CD28 antibodies or bacterially infected APC, although PMA-ionomycin stimulation is required for the reported large amounts of IL-17 to be secreted. This may reflect the intensity of *in vitro* stimulation required to elicit IL-17 production from both CD8+ T-cells and MAIT cells, or it might suggest that MAIT cells require more co-stimulation from a cytokine or cell surface ligand expressed by the APC, e.g. NKG2D or CD161 ligation, to drive the MAIT cell response fully.

Lesional psoriasis skin is highly enriched with IL-17+CD8+ T-cells (Ortega *et al.*, 2009; Res *et al.*, 2010). A recent report by Dusseaux and colleagues indicated that the majority of IL-17A-producing CD8+ T-cells in the blood are MAIT cells (Dusseaux *et al.*, 2011), thus the true identity of the IL-17+CD8+ T-cells in the skin has been questioned. CD8+ T-cells have long been implicated as critical players in the pathogenesis of psoriasis. In contrast to

CD4<sup>+</sup> T-cells that are predominantly found in the upper dermis of psoriatic skin lesions, CD8<sup>+</sup> T-cells are the predominant T-cell in the epidermis (Baker *et al.*, 1984). There is a strong correlation between the presence of epidermal T-cells and the development of epidermal hyperplasia, a key feature of psoriasis, and studies blocking the entry of T-cells into the epidermis, through blocking of the  $\alpha 1\beta 1$  integrin, prevent development of psoriasis in a xenograft mouse model of psoriasis (Conrad *et al.*, 2007). Conventional CD8<sup>+</sup> T-cells detect and respond to peptide antigens presented on MHC class I molecules, such as HLA-Cw6, which is the most prominent risk gene for the development of psoriasis (Nair *et al.*, 2006). Consistent with the potential role of conventional CD8<sup>+</sup> T-cells in the pathogenesis of psoriasis is the finding that the CD8<sup>+</sup> T-cells in the psoriatic epidermis show oligoclonal expansion with preferential expansion of particular V $\beta$  families (reviewed in (Valdimarsson *et al.*, 2009)).

About 50 to 60% of epidermal T-cells secrete IL-17A (Kryczek *et al.*, 2008). IL-17A has been shown to be a critical cytokine in the pathogenesis of psoriasis. This has been determined through genetic studies, with the identification of genetic risk variants within, or close to, several genes involved in IL-17A responses and by the therapeutic responses seen in psoriasis when treated with drugs that target IL-17A. IL-17A has wide-ranging pro-inflammatory effects. It induces secretion of cytokines such as IL-6, IL-8, CCL20 and GM-CSF by keratinocytes and fibroblasts, resulting in recruitment of T-cells, macrophages and neutrophils to skin. Furthermore, IL-17A synergizes with other pro-inflammatory cytokines such as IFN- $\gamma$  (Kryczek *et al.*, 2008), and its effects are amplified by TNF- $\alpha$ . The cellular source of IL-17A in psoriatic skin has not been identified with certainty.

Immunohistochemistry demonstrates that the major portion of staining for IL-17A in psoriatic skin is associated with mast cells and neutrophils, with a minor portion being from T-cells (Lin *et al.*, 2011). However, as T-cells express and secrete IL-17A rapidly, the main source of IL-17A in skin appears to be lesional CD4<sup>+</sup> and CD8<sup>+</sup> T-cells (Res *et al.*, 2010). Interestingly, when compared to healthy normal skin, the frequency of CD4<sup>+</sup>IL-17A<sup>+</sup> T-cells (Th17) is unchanged, whereas CD8<sup>+</sup>IL-17<sup>+</sup> T-cells (Tc17) are highly enriched (Res *et al.*, 2010). This does not necessarily mean that Th17 cells do not contribute to IL-17 production in psoriatic skin, as these cells are activated in psoriatic lesions but are resting in normal healthy skin. In addition, Tc17 cells do not produce IL-17 exclusively, as most CD8<sup>+</sup>IL-17<sup>+</sup> cells also secrete TNF- $\alpha$  and about half produce IFN- $\gamma$  along with IL-17 (Ortega *et al.*, 2009), a feature that can also be attributed to MAIT cells.

In the light of the information presented here it is important to determine whether the IL-17<sup>+</sup>CD8<sup>+</sup> T-cells in psoriatic skin are conventional MHC class I restricted T cells or belong to the MAIT subset. In this manuscript Teunissen *et al.* demonstrate that although MAIT cells are found in psoriatic skin, they represent only a proportion of IL-17A<sup>+</sup> expressing CD8<sup>+</sup> T cells and that majority of Tc17 clones derived from psoriatic epidermis are conventional T-cells (Teunissen *et al.*, 2014). In addition, the investigators demonstrate that the frequency of Tc17 cells in peripheral blood correlates with disease severity, although they did not take the next step by determining whether the cells belong to the MAIT subset rather than conventional CD8<sup>+</sup> T-cells. Taken together, this data suggest that MAIT cells are unlikely to play a major role in the pathogenesis of psoriasis and, instead,

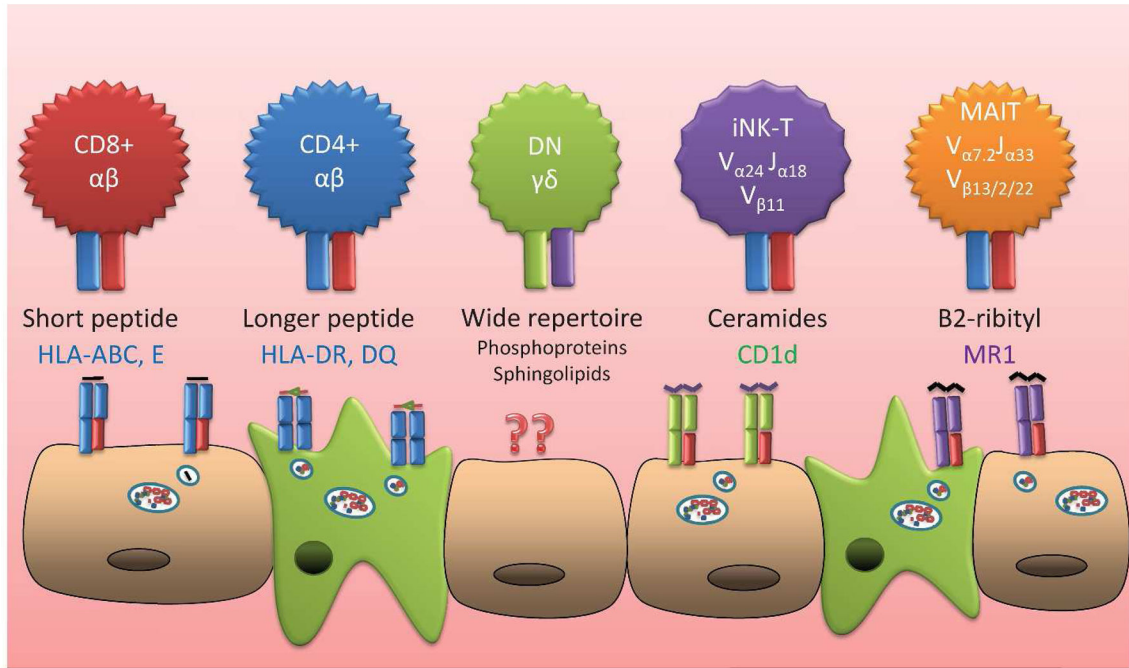
focus the spotlight back on conventional Tc17 cells as the critical CD8+ T-cell population in psoriasis pathogenesis. This, along with other evidence supporting the role of CD8+ T-cells in psoriasis (Elder *et al.*, 2010), indicates that these cells may have either being selectively recruited to, or expanded in, the epidermis of psoriatic skin. Expansion might occur after recognition of antigens in the context of MHC class I, with HLA-Cw\*0602 being the most likely restriction element in a large proportion of patients with psoriasis (Nair *et al.*, 2006). This is a relatively unexplored avenue of research in psoriasis, but addressing the nature of the antigen specificity of conventional CD8+ T-cells in psoriasis is very attractive. It holds considerable promise, because it is the most likely approach to eventually “cure” psoriasis.

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**CLINICAL IMPLICATIONS**

- IL-17 secreting CD8+ T-cells in the epidermis may have a major role in driving the psoriasis disease process.
- The majority of lesional psoriatic IL-17A-producing CD8+ T-cells are conventional T-cells, which are driven by antigen-specific responses.
- Targeting or blocking the function of IL-17A+CD8+ T-cells in the psoriatic epidermis is an attractive avenue for future therapeutics.



**Figure 1. Mucosa-associated invariant T-cells (MAIT) join the ranks of the unconventional T-cells**

Characterized by their limited TCR rearrangements, unconventional T-cells respond more quickly than their conventional counterparts, stationed in peripheral tissues poised to act. These cells expand the repertoire of antigens recognized by T-cells; with the invariant natural killer (iNK) T-cells responding to lipid antigens presented by CD1d, and several clones of  $\gamma\delta$  T-cells recognizing a diverse array of structures including phospho-antigens and sphingolipids apparently independent of MHC-antigen presentation. Like conventional  $\alpha\beta$  T-cells and, MAIT cells recognize antigens presented in the context of an MHC-like molecule, MR1, on the surface of antigen presenting cells (green) or epithelia (brown). Thus far, antigens derived from the structures of vitamins B2 and B9 containing a ribityl carbohydrate group have been identified to activate MAIT cells. MAIT cells express many of the markers associated with Th17 cells (RORC, CD161, CCR6) and account for the majority of IL17-producing CD8<sup>+</sup> T-cells in the blood, but only a fraction of epidermal IL-17+CD8<sup>+</sup> cells.