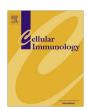
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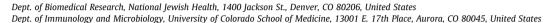
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Dermal $\gamma\delta$ T cells – What have we learned?

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ABSTRACT

Over the last several years, a number of papers have called attention to a distinct population of $\gamma\delta$ T cells preferentially found in the dermis of the skin of normal mice. These cells appear to play an important role in promoting the development of psoriasis, but also are critical for host resistance to particular pathogens. They are characterized by the expression of a limited subset of $\gamma\delta$ T cell receptors and a strong propensity to secrete IL-17. Perhaps most importantly, humans appear to carry an equivalent dermal $\gamma\delta$ T cell population, likewise biased to secrete IL-17 and also implicated as playing a pathogenic role in psoriasis. This review will attempt to summarize and reconcile recent findings concerning the dermal $\gamma\delta$ T cells.

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1. How were phenotypically distinct dermal $\gamma\delta$ T cells identified?

Historically, one of the first characteristics of $\gamma\delta$ T cells that distinguished them from classical $\alpha\beta$ T cells was their relative abundance in certain anatomical sites, particularly in epithelial tissues. Moreover, the distribution of $\gamma\delta$ T cells was found to be non-random in these tissues, and $\gamma\delta$ T cells bearing certain T cell receptors (TCRs) predominated in distinct sites. One of the earliest examples of this was the discovery that nearly all T cells present in the epidermis of mice, known as dendritic epidermal T cells (DETC), are $\gamma\delta$ T cells expressing identical TCRs, composed of $V\gamma$ 5- and $V\delta$ 1-containing TCR chains that also carry identical or nearly identical junctional sequences [1] (note: the Tonegawa nomenclature for mouse $V\gamma$ chains will be used throughout this review [2]). Furthermore, cells bearing this canonical TCR were not found at any other location in the periphery of the mouse, and they evidently represent a specialized subset for the epidermis only. These cells are derived from thymic precursors generated only in the fetal/newborn stage of development [3], which home to the skin after exiting the thymus, and then persist throughout the life of the mouse by limited peripheral expansion. The invariant

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TCR that the DETC express is composed of germline-encoded components only. This feature is thought to be representative of the fetal development of these T cells, which occurs before deoxynucleotidyl transferase, the enzyme needed for N and P nucleotide additions, is expressed [4].

Though the reason for a need for a particular T cell type in the epidermis having a predetermined specificity is still not understood, in the last few years it has become clear that another skinassociated $\gamma\delta$ T cell population also exists, residing in the dermis rather than epidermis. The existence of these cells was first suggested by a finding from our laboratory in a study involving mice with collagen-induced arthritis. In this model, a disease with many of the same characteristics as human rheumatoid arthritis can be induced by intradermal injection of DBA/1 mice with a collagen/ Complete Freund's Adjuvant (CFA) emulsion. Upon examining the T cells present in the draining lymph nodes of mice with collagen-induced arthritis, we found a preferential increase in $\gamma\delta$ T cells expressing a $V\gamma 4V\delta 4$ TCR, and also showing a strong bias to secrete IL-17A. A more in-depth analysis revealed that these cells also express nearly invariant TCR junctions [5], which could either suggest the oligoclonal expansion of $\gamma\delta$ T cells having a certain specificity, or that the cells represent, like DETC, a fetal-derived subset. This strong response by $V\gamma 4V\delta 4+\gamma\delta$ cells was not dependent upon the mice developing arthritis, required CFA but not collagen in the immunizing inoculum [5], and depended upon immunization via the skin, by intradermal or subcutaneous inoculation, which we confirmed in a later study [6]. This requirement implied that the

Abbreviations: TCR, T cell receptor; DETC, dendritic epidermal T cells; CFA, Complete Freund's Adjuvant.

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preferentially responding $\gamma \delta$ T cells originate from the murine dermis. In fact, a paper by Kisielow et al. in 2008 reported that $\gamma\delta$ T cells with these properties are present in the dermis, and showed that the skin-draining lymph nodes as well as the dermis contain a population of IL-17-biased predominantly V γ 4+ $\gamma\delta$ T cells, representing about 20% of the dermal $\gamma\delta$ T cells, also distinct in that they express high levels of the scavenger receptors Scart1 and Scart2. The Scart2-expressing $\gamma\delta$ T cell subset was not detected among lymphocytes obtained from mesenteric lymph nodes or the spleen [7]. Soon after this publication, in a study involving an autoimmune uveitis model, a similar subset of $\gamma\delta$ T cells was found to expand preferentially when cultured in the presence of IL-23; these cells likewise predominantly expressed $V\gamma4$ and $V\delta4$ in their TCRs and were strongly biased to produce IL-17A [8]. The disease in this instance, which like collagen-induced arthritis is exacerbated by IL-17 [8.9], was again provoked by a subcutaneous immunization, using an ocular antigen peptide emulsified in CFA. As with collagen-induced arthritis, subcutaneous emulsified CFA alone was sufficient to elicit the response of these $\gamma\delta$ T cells, again suggesting a possible dermal origin for the dominantly responding $\gamma \delta$ T cell subset. Interestingly, the production of IL-17 by these $\gamma \delta$ T cells, which was elicited by culture with IL-23, required the presence of both $\gamma\delta$ and $\alpha\beta$ T cells, and the ability of the two cell types to make physical contact [8].

2. What are the characteristics of dermal $\gamma\delta$ T cells?

In 2011, nearly simultaneous publications from three different laboratories [10–12] described the presence of a major $\gamma\delta$ T cell subset present in the normal dermis having many characteristics in common with those we and others had noted among the $\gamma\delta$ T cell subset responding preferentially following immunization with intradermal or subcutaneous CFA. In particular, the dermis-associated $\gamma\delta$ T cells predominantly expressed IL-17 when stimulated with PMA/ionomycin [10–12], and about half expressed a $V\gamma4+$ TCR [11,12]. These dermal $\gamma\delta$ T cells were shown to differ from the epidermal DETC subset in terms of the type of TCR they express (few were $V\gamma5+$, whereas DETC are virtually all $V\gamma5+$), in the amount of TCR present on their surfaces (DETC are TCR-bright whereas the dermal $\gamma \delta$ T cell were found to be TCR-intermediate), and in the amount of the chemokine receptor CCR6 that they expressed (which is essentially absent on DETCs but abundant on dermal $\gamma\delta$ T cells) [10]. The latter finding is interesting because CCR6, whose ligand CCL20 is expressed by epidermal keratinocytes, endothelial cells, and dendritic cells during skin inflammation, has been shown to play an important role in promoting the infiltration of activated T cells into the skin [13]; thus, CCR6 expression may imply that the dermal $\gamma\delta$ T cells largely represent previously activated cells that have been recruited to the skin. An equally striking difference noted between the dermal $\gamma\delta$ T cells and DETC was their motility: whereas DETC are sessile and remain in close contact with surrounding keratinocytes, the dermal $\gamma\delta$ T cells were highly motile [10] (Table 1).

A number of other distinct properties of dermal $\gamma\delta$ T cells were also noted. First, they were found to depend for their maintenance on IL-7 but not IL-15 [12], unlike DETC [14,15] and splenic $\gamma\delta$ T cells [16,17] which depend upon both IL-7 and IL-15. Like the V γ 4V δ 4+ T cells elicited by intradermal CFA immunization [5], the dermal $\gamma\delta$ T cells were found to carry additional cell surface molecules characteristic of T cells that have been pre-activated: virtually all were CD69-positive, CD44-high, and CD25-low [10,12]. Second, as had been previously reported for naïve splenic ROR γ t-expressing IL-23R-positive $\gamma\delta$ T cells [18], naive dermal $\gamma\delta$ T cells could be induced to proliferate and secrete IL-17 when cultured with cytokine as the only stimulant. This was

evident either after 2 days in culture with IL-23 [11] or within 8 h with IL-23 plus IL-1 β [10]. Including ligands for TLRs or dectin in these cultures enhanced the effect of IL-23, perhaps by stimulating IL-1 β production as well, because the ability to express IL-1 β was found to be essential for this response [11]. Production by these cells of the other "IL-17 type" cytokines IL-17F and IL-22 as well as IL-17A was reported in two of these studies [10,11], even though lymph node CFA-elicited V γ 4V δ 4+ cells when stimulated with PMA/ionomycin appeared to produce only IL-17A but not IL-17F or IL-22 [6]. When likewise stimulated with PMA/ionomycin, dermal $\gamma\delta$ T cells produced large amounts of IL-17 plus an intermediate amount of TNF α and IL-22 [11]. Lymph node $\gamma\delta$ T cells tested side-by-side also produced these same cytokines, but they also secreted IFN γ .

3. What is the immunological role of dermal $\gamma\delta$ T cells?

Based on our findings with $V\gamma 4V\delta 4+$ cells in the skin-draining lymph nodes of mice immunized intradermally with emulsified CFA, we anticipated that they would have an overall pro-inflammatory effect, and hence could play either a positive or negative role depending upon the disease in question. When we examined their role in mice with collagen-induced arthritis, inactivation/depletion of V γ 4+ cells by injection of a V γ 4-specific monoclonal antibody resulted in milder disease, indicating a disease-exacerbating role for this subset [5]. A negative role for dermal IL-17-producing $\gamma\delta$ T cells has now been shown in several other studies involving induced dermatitis. When dermatitis was provoked by topical application of TPA, a phorbol ester, Scart1+ $\gamma\delta$ T cells present in the skin increased in the dermis nearly 9-fold [19]. In two other studies [11,20], mice were treated topically with Imiquimod cream, a TLR7 agonist that stimulates IL-23 production and thereby induces a psoriasis-like disease characterized by epidermal hyperplasia, parakeratosis, and dermal inflammatory infiltrates containing neutrophils and T cells [21]. Here, $TCR\delta$ -/- mice developed much milder disease than did wildtype mice. Because the IL-17 axis is known to be essential for psoriasis induction in these models [21], the relative resistance of the TCR δ -/- mice was attributed to their lack of dermal IL-17-producing $\gamma\delta$ T cells rather than to their lack of DETC, since Imiquimod treatment induces dermal $\gamma\delta$ T cells but not DETC to produce copious amounts of IL-17. In a similar psoriasis model in which the disease is induced by direct intradermal injection of IL-23, nearly identical results were obtained and CCR6+ dermal $\gamma\delta$ T cells were again implicated as the source of pathogenic IL-17 [22]. Production of IL-23 by Langerhans cells has in fact now been shown to be required for the development of psoriasis in Imiquimod-treated mice, and for inducing IL-17 production from CCR6+ $\gamma\delta$ T cells [23]. When skin from human psoriasis patients was examined, it was also found to contain elevated numbers of dermal $\gamma\delta$ T cells compared to normal controls, increasing from an average of about 1% of the CD3+ cells in normal control samples to an average of 15% in psoriasis samples [11]. The psoriasis-associated human $\gamma\delta$ T cells produced IL-17 when stimulated in culture, strongly implying that dermal $\gamma\delta$ T cell subsets in mice and humans are in fact functional analogues of one another. Epidermal $\gamma\delta$ T cells in humans also had similar functions as the murine DETC $\gamma\delta$ T cells [24], although unlike mouse DETC they do not contain a TCR-invariant $\gamma \delta$ T cell population.

Evidence for a positive role for dermal IL-17-producing $\gamma\delta$ T cells in infectious disease was documented in mice infected intradermally with *Mycobacterium bovis*-BCG. Infection of these mice resulted in a rapid induction of IL-17 secretion among their dermal $\gamma\delta$ (but not $\alpha\beta$) T cells, and this process appeared to be important in subsequent neutrophil recruitment, because neutrophil numbers in the skin were much reduced in TCR δ -/- mice

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