Dendritic Epidermal T Cells: Lessons from Mice for Humans

Paul R. Bergstresser, Ponciano D. Cruz, Jr., and Akira Takashima

Dendritic epidermal T cells (DETC) in mice form part of a primitive system of epithelial-resident T cells characterized by the expression of $\gamma\delta$ T-cell receptors (TCR). Critical attributes that characterize DETC include their highly restricted T-cell receptor gene utilization, proliferation and maturation within epidermis, a capacity to kill relevant skin-derived tumor targets, and the ability to modulate immune responses that are initiated and expressed in skin. Contemporary knowledge suggests that DETC and the related skin-directed $\gamma\delta$ T cells found in humans play important roles in maintaining the immunologic integrity of skin. *J Invest Dermatol 100:80S–83S, 1993*

In 1983, we and colleagues in Vienna reported an unusual population of dendritic leukocytes that expressed Thy-1 antigen to reside in normal mouse epidermis [1,2]. Not only did these cells exhibit features different from that of dendritic epidermal Langerhans cells and melanocytes, it was not possible at that time to place them with any certainty into an established system of classification. Within ten years, however, our work and the work of many others (reviewed in [3]) has led to an appreciation that these cells, dendritic epidermal T cells (DETC), represent one component of a primitive system of epithelial-resident T cells, characterized by their expression of a $\gamma\delta$ T-cell receptor (TCR). This review of contemporary knowledge about DETC places them into context, that is, into the growing awareness that $\gamma\delta$ T cells as a class may play critical roles in human disease. For a publication dedicated to the memory of our esteemed colleague, it is instructive to recognize that James N. Gilliam began his consuming interest in human autoimmune disease while working with NZB/W mice, specifically with his identification of antinuclear antibodies at the junction between dermis and epidermis [4]. Not only did Gilliam encourage the study of this unanticipated dendritic epidermal cell, he also recognized correctly that knowledge about its ontogeny, phenotype, and function would lead to new concepts concerning diseases that are expressed in skin. This brief review of DETC is a tribute to that correct assessment and to the support that followed.

CELL LINEAGE

Soon after the discovery of TCR γ and δ chains, we and others reported that DETC also express these unique molecules [5,6], which until that time were known to be expressed only by fetal thymocytes. Since then, it has been established that $\gamma\delta$ T cells localize preferentially in epithelial tissues, in marked contrast with the lymphoid organ-directed distribution of conventional $\alpha\beta$ TCR-bearing T cells (reviewed in [7]). The list of tissues that contain resident $\gamma\delta$ T cells now includes skin, intestine, lung, reproductive tract, tongue, and mammary glands.

Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, Texas, USA

Reprint requests to: Dr. Paul R. Bergstresser, Department of Dermatology, UT Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75235.

Abbreviations: APC, antigen-presenting cell; CH, contact hypersensitivity; DETC, dendritic epidermal T cell; DTH, delayed-type hypersensitivity; GM-CSF, granulocyte/macrophage- colony-stimulating factor; HSP, heat shock protein; IFN, interferon; IL-2, interleukin 2; LAK, lymphokine-activated killing; MHC, major histocompatibility complex; MoAb, monoclonal antibody; NK, natural killer cell; TCR, T-cell receptor (antigen-binding site)

CELL SURFACE PHENOTYPE

DETC share with $\alpha\beta$ T cells several cell surface molecules, including Thy-1, CD3, and CD45. DETC can be distinguished from conventional T cells, however, by their lack of the $\alpha\beta$ TCR, CD4 and CD8 (molecules associated during antigen presentation with major histocompatibility complex [MHC] class II and class I molecules, respectively), and by their unique expression of a $\gamma\delta$ TCR. DETC are also phenotypically distinct from Langerhans cells, the other resident dendritic leukocytes, most obviously by the lack of MHC class II molecules.

$\gamma\delta$ T-CELL RECEPTOR

The majority of T cells express a TCR consisting of a heterodimer of α- and β- chain polypeptides, and they recognize antigens via this receptor in the context of self-MHC molecules. TCRα and β genes encode interchangeable segments in the V, D, J, and C regions of germline DNA, and clonal diversity is generated during the course of T-cell development by the selective use of each of these segments. Moreover, pairing of α and β chains contributes to TCR diversity at the protein level [8]. The TCR γ and δ loci share many α and β loci, also permitting, at least theoretically, enormous receptor diversity [8]. A striking early observation was that DETC display extremely restricted gene usage and $\gamma\delta$ pairing: all DETC clones established in our laboratory have demonstrated an identical TCR, composed of Vγ3/Jγ1-Cγ1 and Vδ1/Dδ2/Jδ2-Cδ gene segments [5,9,10]. This feature has been confirmed at *in situ* levels by Havran and Allison, who demonstrated, using monoclonal antibodies (MoAb) specific to Vγ3, that the overwhelming majority of Thy-1$^+$, CD3$^+$ epidermal cells do express this type of TCR [11].

ONTOGENY

Radiation chimera studies have demonstrated the bone marrow derivation of DETC [12]. Although athymic (nude) mice contain a significant number of epidermal Thy-1$^+$ leukocytes, they are phenotypically and functionally distinct from those in euthymic mice, suggesting thymic dependency for complete DETC development [13]. Supporting this notion, the earliest fetal thymocytes express almost exclusively a TCR containing Vγ3, the identical TCR expressed by DETC [14]. Fetal thymic origin of DETC has been demonstrated even more definitively by the observation that intravenous injection of fetal thymocytes or transplantation of fetal thymic lobes results in reconstitution of Thy-1$^+$, CD3$^+$, TCR-Vγ3/Vδ1$^+$ DETC in the epidermis of athymic mice [15,16]. The unresolved question is whether skin-directed homing of fetal thymocytes *per se* is sufficient for full development of DETC. In fact, this may not be the case; newborn mouse skin contains only small numbers of Thy-1$^+$ epidermal cells, which increase thereafter and reach cell densities in adult mice at about 1 month after birth [17]. More importantly, these

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Thy-1$^+$ cells in neonatal skin are CD3 [18], and they appear to undergo maturation to acquire this phenotype in the epidermal microenvironment [18]. The exact mechanism by which DETC mature in skin remains to be elucidated.

FUNCTIONAL PROPERTIES

Proliferative Responses DETC isolated from skin proliferate markedly in response to conventional T-cell mitogens such as Con A, immobilized anti-CD3 MoAb, or phorbol ester and calcium ionophore [19–21]. Moreover, a significant number of DETC in normal skin have the capacity to undergo cell mitosis [22], and *in situ* proliferation becomes even more apparent after topical application of irritant or allergic chemicals [23]. These results clearly illustrate the high proliferative potential of these lymphocytes.

Cytokine Production As with $\alpha\beta$ T cells, DETC produce large amounts of interleukin 2 (IL-2) following activational stimuli, presumably serving as the major autocrine growth factor [24], They also produce γ-interferon (γIFN) but not IL-4 [20]. Our most recent study using the reverse transcription-polymerase chain reaction suggests that DETC express a variety of cytokine mRNAs upon stimulation. These include IL-1a, IL-2, IL-3, IL-6, IL-7, IFNγ, granulocyte/macrophage - colony-stimulating factor (GM-CSF), tumor necrosis factor-α (TNFα), and TNFβ [25]. In this regard, it would be interesting to examine the biologic effects of these DETC-derived cytokines on other epidermal cell populations (i.e., keratinocytes and Langerhans cells).

Growth Factor Requirement Studies from our laboratory have demonstrated progressive proliferative responses of mitogen-activated DETC to IL-2, suggesting that IL-2 serves as the major growth factor for these lymphocytes [19,24]. However, it appears unlikely that IL-2 is fully responsible for the survival of DETC in normal skin, because IL-2 is produced only by DETC, but not other epidermal cells and only after cell activation [5,24,25]. We have begun to search for a relevant factor that is constitutively present in the epidermal microenvironment and have found that IL-7, which is produced by keratinocytes [26], possess a capacity to sustain the survival and promote the growth of DETC (Matsue H, Bergstresser PR, Takashima A: Keratinocyte-derived IL-7 serves as a growth factor for dendritic epidermal T cells (manuscript submitted). These results suggest that keratinocyte-derived cytokines serve as growth factors, allowing these epidermal resident lymphocytes to survive in this location, a notion similar to that which has been proposed for Langerhans cells, the other epidermal leukocyte [27].

Cytotoxicity DETC lines and clones display non-MHC-restricted killing activity against selected tumor targets, including the YAC-1 lymphoma (NK-sensitive target) and an ultraviolet light (UVL) - induced fibrosarcoma [28,29]. Recently, we examined their target specificity and found that DETC effectively lyse melanoma and transformed keratinocyte targets as well [30]. DETC freshly isolated from normal skin, however, fail to exhibit this cytotoxic activity; rather, they acquire this capacity in culture after mitogenic stimulation and expansion in the presence of IL-2 [28]. Therefore, this activity resembles lymphokine-activated killer (LAK) activity. In this regard, however, $\gamma\delta$ T cells freshly isolated from normal mouse intestine display significant cytotoxicity, whereas cells from germ-free mice fail to exhibit this potential, suggesting that cell activation (via bacterial antigens in this case) leads to the acquisition of killing activity [31]. It is possible to speculate from this that DETC in normal epidermis have not been activated to become mature killer lymphocytes, but that once activation is achieved they then become capable of killing tumor cells, even *in situ*. The recent finding that DETCs in normal skin express mRNA for perforin, a molecule responsible for the transmembrane channel formation in target cells, supports this speculation [32]. Moreover, IL-7, which is known to enhance generation of LAK activity in $\alpha\beta$ *T* cells, may promote locally the acquisition of killing activity by these ''activated'' DETC.

Regulation of Epidermal Immune Response Unlike Langerhans cells, which play a central role in the induction of contact hypersensitivity (CH) and delayed-type hypersensitivity (DTH), DETC appear to downregulate these responses. In fact, hapten-specific unresponsiveness can be induced by intravenous infusion of hapten-derivatized DETC [33]. Furthermore, UVB radiation followed by hapten painting, a standard protocol for inducing immunologic tolerance, results in the appearance of haptenated Thy-1$^+$ cells in draining lymph nodes; these cells possess a downregulatory capacity [34]. Similarly, infusion of allogeneic DETC leads to a failure of recipients to respond to the same alloantigen in a subsequent challenge [35]. It has been shown in different mouse strains that DETC density correlates inversely with the capacity of these animals to mount CH responses [36]. Taken together, these studies suggest that DETC are not only effector cells, but that they also may downregulate immune responses that are initiated in skin.

Homing As already mentioned, $\gamma\delta$ T cells reside not only in epidermis, but also in several other epithelial tissues. The most striking feature in this respect is that cells in different tissues express predominantly different $\gamma\delta$ TCR repertoires; Vγ3-Vδ1 in epidermis, Vγ5-Vδ2/4/5/6 in intestine, Vγ2-Vδ5/6 in lung, and Vγ4-Vδ1 in the reproductive tract and tongue (reviewed in [7]). These findings even suggest that TCR molecules contribute to this tissue-specific homing. However, recent transgenic mouse studies make this unlikely as epidermis is even populated by DETC that express an incorrect transgenic $\gamma\delta$ TCR [37]. In our studies of homing mechanisms, we have observed that DETC are capable of migrating toward an undefined chemotactic activity secreted by keratinocytes (Chung, Bergstresser, and Takashima: unpublished observations), and they bind selectively to keratinocyte monolayers [38]. These results, together with the finding that DETC bind to several extracellular matrix proteins via integrin-like receptors [39], suggest that DETC possess a unique capacity to migrate through dermal connective tissue toward the epidermis and to reside among multilayered keratinocytes in this location. This scenario is supported by our recent observation that DETC isolated from the skin, when infused intravenously, will then home preferentially to the skin (and thymus) but not to other epithelial tissues [40].

Antigen Recognition The lack of diversity in TCRs expressed by DETCs implies that the antigen(s) or ligand(s) recognized by these receptors is highly restricted. Thus, DETC may recognize a set of rather limited molecules that are expressed commonly and/or frequently in the epidermal microenvironment. $\gamma\delta$ T-cell clones that specifically recognize MHC-like molecules, heat shock proteins (HSP), and mycobacterial antigens have been established from mice as well as humans, strongly supporting this notion [41–43]. Asarnow *et al* have suggested that DETC may recognize HSP or stress proteins [10], a highly conserved protein family produced by virtually all cell types in response to stressful stimuli (i.e., heat, starvation, infection, or malignant transformation) (reviewed in [44]). It is also of interest that some eukaryotic cell HSP possess striking sequence homology to mycobacterial antigens. An attractive scenario drawn from this information would be that DETC recognize HSP or related molecules expressed by ''stressed'' epidermal cells, thereby leading to an activation of DETC that allows them to eliminate otherwise harmful, neighboring cells. A recent study by Havran *et al* has provided the first evidence for this hypothesis by demonstrating that DETC activation is inducible through co-culture with transformed keratinocytes, that this activity can be transferred to other lymphocytes by transfection with Vγ3/Vδl genes, and that it can be blocked by anti-Vγ3 Moabs [45]. Obviously, further studies are required to identify the ligand(s) recognized by this receptor.

PHYSIOLOGIC ROLES AND POSSIBLE CONTRIBUTION TO HUMAN SKIN DISORDERS

An obvious question has been whether human epidermis also contains a similar $\gamma\delta$ T-cell network. The current consensus is that a DETC

equivalent does not occur, in the sense that cells with dendritic morphology, selectively localized in epidermis, and with restricted TCR diversity have not been found. On the other hand, $\gamma\delta$ T cells as a distinct subset of immunocompetent cells have been associated with the pathogenesis of several human diseases, including some that involve skin. The appearance of $\gamma\delta$ T cells in selected skin disorders, in turn, suggests that human $\gamma\delta$ T cells do play important roles in maintaining the immunologic integrity of skin.

Infection Modlin *et al* provided the first evidence that $\gamma\delta$ T cells play a role in infectious skin disorders. Several types of skin lesions in leprosy (i.e., lepromin test sites, representing the DTH reaction to *M. leprae)* are infiltrated predominantly by $\gamma\delta$ T cells, which specifically recognize mycobacterial antigens and which display strikingly limited diversity in their TCR gene rearrangement [41,46]. Similar observations have been made in localized cutaneous leishmaniasis [41]. Based on these findings, it is reasonable to postulate that DETC (and other $\gamma\delta$ T cells) may function as a first line of defense against infectious pathogens, whereas $\alpha\beta$ T cells appear to serve as a second line after the latent period required for clonal expansion [47,48].

Autoimmunity $\gamma\delta$ T cells that recognized mycobacterial antigens have been recovered from synovial fluid in patients with rheumatoid arthritis [3]. One may further speculate that those $\gamma\delta$ T cells cross-recognize autologous HSP expressed in response to local tissue damages caused by autoimmune attack [42]. In this regard, Shiohara *et al* have made the important observation that following the severe epidermal damage that is induced by the injection of autoreactive, $\alpha\beta$ TCR-bearing cytotoxic T cells, recipient skin sites then become resistant to a second challenge with the same T cells. This resistance is associated with a marked increase in DETC densities at the site of injection [49]. An attractive hypothesis is that DETC play a suppressive role, competing with the $\alpha\beta$ T cells that act as effectors in this model of autoimmunity.

Tumors As mentioned previously, DETC possess a potential to kill skin-derived tumor targets, including fibrosarcomas and melanomas. Bachelez *et al* recently found that both $\alpha\beta$ T cells and $\gamma\delta$ T cells infiltrate human melanoma skin lesions and that $\gamma\delta$ T-cell lines established from these lesions display significant killing of autologous melanoma cells [50]. These observations again reinforce the notion that the physiologic function of DETC (and other epithelial $\gamma\delta$ T cells) may be to eliminate ''stressed,'' damaged, or transformed cells.

Taken as a whole, this contemporary knowledge about functional attributes of DETC in mice and the related skin-directed $\gamma\delta$ T cells found in humans suggests strongly that they play important roles in maintaining the immunologic integrity of skin.

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