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All hands on DE(T)C: Epithelial-resident $\gamma\delta$ T cells respond to tissue injury

Kevin Ramirez, Deborah A. Witherden, and Wendy L. Havran*

Department of Immunology and Microbial Science, The Scripps Research Institute, La Jolla, CA, USA

Abstract

Immunology has traditionally focused on the lymphocytes circulating among primary lymphoid organs while the large reservoir of tissue-resident T cells have received relatively less attention. In epithelia, these populations are comprised of significant, and sometimes exclusive, subsets of $\gamma\delta$ T cells that are highly specialized in promoting tissue homeostasis. As the epithelial layers of the skin and gut are permanently exposed to the environment, they are continually subject to injury and therefore require highly efficient repair processes to maintain barrier functions. Here, we review the role of $\gamma\delta$ T cells in promoting wound healing, a critical and complex process occurring in the skin and other barrier sites.

Keywords

Epithelial $\gamma\delta$ T cell; dendritic epidermal T cell; DETC; skin wound repair

Introduction

As the interface between an organism and its environment, epithelial surfaces provide essential protection against water and nutrient loss, pathogen entry and physical damage. Mechanisms to efficiently detect breaches in barrier integrity and promote return to homeostasis are therefore critical for host survival. $\gamma\delta$ T cells are found in the surface-contacting epithelia of all mammals [1]. These lymphocytes have evolved to meet the site-specific challenges encountered at barrier tissues: anti-microbial defense, tumor surveillance, tissue homeostasis and repair after damage [2–5]. Indeed, by regulating inflammation after wounding and epithelial cell growth and survival, epidermal-resident $\gamma\delta$ T cells appear to have specialized roles in promoting the repair of damaged skin [6–8].

The skin is constantly exposed to physical, chemical and radiant energy damage from the environment. After cutaneous injury, a complex intercellular crosstalk regulates distinct but

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*Correspondence: Wendy L. Havran, Department of Immunology and Microbial Science, The Scripps Research Institute, 10550 North Torrey Pines Road, IMM-8, La Jolla, CA 92037 USA, havran@scripps.edu.

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overlapping phases of wound repair [9]. Critically, keratinocytes at wound edges migrate and proliferate to fill wounded areas and reestablish a protective barrier [9]. Reepithelialization and other wound repair responses are highly dependent upon resident $\gamma\delta$ T cells, evidenced by the delayed wound closure observed in the skin of mice lacking $\gamma\delta$ T cells [6]. Importantly, the wound healing functions of epithelial resident T cells extends beyond the skin, as $\gamma\delta$ T cells resident to the epithelia of the gut, lungs and eyes also contribute to damage repair at these sites [10–15].

While we now appreciate the importance of epithelial $\gamma\delta$ T cells in the maintenance of tissues, we are only beginning to dissect the mechanisms regulating the function of these cells and the pathways they use to promote homeostasis. A more complete understanding of how epithelial-resident $\gamma\delta$ T cells are functionally controlled would have a clear impact on the treatment of a number of human disease conditions.

Distribution of epithelial-resident $\gamma\delta$ T cells

In contrast to conventional T cells, $\gamma\delta$ TCR-bearing cells are rare in lymphoid organs but abundant in surface epithelia [1]. This tropism is associated with highly restricted TCR $\gamma\delta$ gene rearrangements, in some tissues resulting in oligo- or mono-clonal populations [1]. $\gamma\delta$ T cells also differ from conventional T cells in that they do not require priming to elaborate effector activity and appear partially activated in the resting state [16]. Collectively, these properties have led to the notion that epithelial-resident $\gamma\delta$ T cells recognize and respond to tissue-specific distress. The vanguard nature of tissue-resident $\gamma\delta$ T cells is highlighted by the fact that they are the first T cells to develop during ontogeny; the initial wave of progenitors to emerge from the embryonic thymus are V γ 3V δ 1+ (Garman nomenclature [17]) cells that home to the epidermis followed by V γ 4V δ 1+ progenitors that seed the reproductive tract [18]. Subsequently, waves of $\gamma\delta$ T cell progenitors emerge from the thymus and migrate to the lung, lymphoid sites and intestines and that coincide with the first appearance of cells bearing diverse $\alpha\beta$ TCRs [18].

The skin is the largest barrier organ and the first site colonized by $\gamma\delta$ T cells [19]. The most superficial skin layer, the epidermis, is 3–5 cells deep in mice (6–10 cell layers in humans) and overlays a much thicker dermal layer. While keratinocytes comprise the majority of cells in the epidermis and serve as the primary physical barrier to the environment, resident T cells, myeloid-derived cells and melanocytes comprise functionally integral components of epidermal tissue [9]. In the mouse, the epidermis is home to a single prototypic $\gamma\delta$ T cell population. Termed dendritic epidermal T cells (DETC), these cells are the sole epidermal-resident T cell population in wildtype mice and uniformly express a V γ 3V δ 1 (V γ 5V δ 1, alternative nomenclature [20]) TCR gene rearrangement [17, 21, 22]. DETC form a dense stationary network of cells amongst basal keratinocytes and display a highly dendritic morphology. The majority of these dendrites are long and sessile extensions, polarized toward the apical epidermal layer, which coordinate with multiple surrounding keratinocytes while shorter, basally oriented projections frequently extend and retract [23]. While the significance of this morphology is unclear, it likely facilitates the tissue surveillance function of DETC.

In contrast to mice, the distribution of T cells in human skin appears much more complex. The epidermis contains a mixture of both $\alpha\beta$ and $\gamma\delta$ -expressing compartments, the latter being enriched for V δ 1+ T cells [7, 24, 25]. While there is not a human T cell population with a dendritic morphology, analysis of clinical skin samples has revealed that both $\alpha\beta$ and $\gamma\delta$ epidermal T cells have the capacity to regulate epidermal homeostasis by producing insulin-like growth factor 1 (IGF-1), a critical growth and survival factor for epithelial cells [7]. Importantly, T cells isolated from chronic skin wound samples lack the capacity to produce IGF-1 and appear functionally anergic [7]. Dysfunction of epidermal T cells could therefore be a factor in the development of non-healing skin wounds.

Similar to the epidermis, the epithelium of the gut is a large barrier tissue and home to vast numbers of $\gamma\delta$ T cells, in some species accounting for half of all the T cells in the organism. Often referred to as intraepithelial lymphocytes (IEL), these highly motile gut-resident cells are comprised of both $\alpha\beta$ and $\gamma\delta$ T cell populations, the latter being biased toward V γ 1 and V γ 5 TCR expression in mice and V δ 1 usage in humans [26, 27]. While the functions of intestinal-resident T cell populations has been enigmatic, studies using models of intestinal injury repair have revealed that $\gamma\delta$, but not $\alpha\beta$, IELs in the gut can secrete epithelial cell growth factors, akin to epidermal-resident T cells, that maintain intestinal epithelia and promote repair after injury [11, 28, 29].

Responses of $\gamma\delta$ T cells to wounding

In normal healthy skin, keratinocyte proliferation, maturation, migration, terminal differentiation and corneocyte shedding are all perfectly balanced to continually replenish and maintain the epidermis. In this steady state, DETC critically regulate keratinocyte survival via low but constitutive production of IGF-1 [30, 31]. After skin trauma, a complex multi-cellular tissue response is orchestrated to cleanse and repair damaged areas. Almost immediately after injury, coagulation and vasoconstriction occur to prevent blood loss [9]. DETC are one of the first cellular components of the skin to respond following cutaneous damage [32]. Within hours of injury, DETC bordering the wound edge begin to retract their dendrites and become rounded [33]. This striking change in morphology is accompanied by upregulation of the activation marker, CD69, and the release of soluble factors that regulate various aspects of tissue repair: recruitment of inflammatory cells, deposition of matrix proteins and production of epithelial cell mitogens [34]. Importantly, DETC activation and responses to injury are completely dependent upon V γ 3V δ 1 TCR engagement of an unknown ligand on wound-proximal keratinocytes [33–35].

Nearly concurrent to DETC activation, myeloid-derived cells, attracted by soluble factors released by damaged tissue, begin to enter wound sites. Neutrophils are the first circulating leukocytes to arrive and begin to phagocytose bacteria and debris as well as produce reactive-oxygen species to sterilize damaged tissue [36, 37]. Within 24 hours, circulating monocytes have entered damaged tissue and differentiate into functional macrophages, the predominant inflammatory cell 3 days after injury [37]. Macrophages have a pivotal role in wound repair by removing dead cells, particularly spent neutrophils, and secreting factors that promote angiogenesis and tissue growth [36, 37]. In the absence of DETC, neutrophils appear to infiltrate wounds normally but macrophage accumulation is significantly delayed

[38]. As DETC are able to produce CCL3 and CCL4, chemokines important for macrophage homing, this defect could be due to an inability to attract inflammatory cells to the wound sites [39]. In addition to providing chemotactic signals, DETC are able to promote macrophage recruitment by regulating production of hyaluronan, a glycosaminoglycan that accumulates in damaged tissues and is required for inflammatory cell motility [38]. DETC do not produce hyaluronan but production can be induced in keratinocytes via DETC-derived keratinocyte growth factor (KGF) signaling [38, 40]. DETC therefore possess multiple pathways to promote macrophage recruitment, a critical component in the early repair process.

In addition to the antimicrobial activities of inflammatory cells, epithelial cells are able to upregulate production of antimicrobial peptides and proteins (AMP) upon wounding to prevent infection and promote repair [41]. β -defensin 3, S100A8 and RegIII γ are three AMPs that are induced in keratinocytes after damage [42–44]. A subset of DETC appears to possess the ability to regulate keratinocyte AMP production via IL-17 release [45]. While murine epidermal $\gamma\delta$ T cells have previously been shown to produce this proinflammatory cytokine, the ability of human epidermal $\gamma\delta$ T cells to release IL-17 is unknown [46]. However, both human and mouse dermis contains significant populations of $\gamma\delta$ T cells that are able to release IL-17 and therefore may impact AMP production [47, 48].

Beyond regulating the early and inflammatory wound repair phases, DETC regulate the reestablishment of a physical protective barrier by keratinocytes. TCR δ -deficient mice display reduced hyperepithelial thickening at wound sites and delayed reepithelialization, defects that can be attributed to reduced cellular proliferation and/or increased keratinocyte apoptosis in the tissue [30]. As epithelial cell mitogens, KGF-1 and KGF-2 can potentially induce keratinocyte proliferation. While resting DETC do not produce these factors, the genes for KGF-1 and KGF-2 become highly transcribed in DETC upon activation [28]. The importance of DETC-derived KGF in mediating the proliferative response of keratinocytes is apparent during *in vitro* skin wound cultures, in which the defective healing response of TCR δ -deficient skin samples can be rescued by introduction of activated DETC or addition of exogenous KGF-1[6].

Tissue maintenance by $\gamma\delta$ T cells extends beyond the skin as gut-resident $\gamma\delta$ +, but not as $\alpha\beta$ +, IELs appear to possess the ability to regulate intestinal homeostasis via KGF production [28]. The functional importance of $\gamma\delta$ intestinal IELs is observed in the DSS mouse model of ulcerative colitis, which replicates the repair of epithelial erosion found in human inflammatory bowel disease. In this experimental system, mice given dextran sulfate sodium (DSS) in drinking water develop intestinal epithelial lesions that heal several weeks after DSS treatment is stopped [49]. In animals recovering from DSS exposure, $\gamma\delta$ IELs accumulate near epithelial gut ulcers and become activated for local KGF-1 production [28]. Compared to wildtype mice, TCR δ -deficient mice develop a more severe colitis and the rate of epithelial cell proliferation is severely reduced, due in part to the lack of KGF-1 production [11]. These findings indicate a gut-protective role for $\gamma\delta$ IELs in humans and raises an interesting possibility that dysregulation of gut-resident $\gamma\delta$ IELs could be a contributing factor for the development of inflammatory bowel diseases and underscores the specialization of epithelial-resident $\gamma\delta$ cells for barrier tissue maintenance.

In addition to influencing keratinocyte proliferation, DETC promote the survival of epithelial cells in wounds by upregulating IGF-1 production. DETC are the primary source of IGF-1 in the epidermis and, when this hormone is absent, the epidermis appears underdeveloped and an increased spontaneous rate of keratinocyte apoptosis is observed [30]. Interestingly, TCR stimulation also triggers upregulated expression of the IGF-1 receptor on DETC, suggesting that autocrine survival signaling might promote a positive feedback loop that enhances DETC potency during repair [30].

Epithelial signals of damage

In addition to activation by physical cutaneous injury, DETC are also responsive to keratinocyte tumors [6, 50]. Given this dual sensitivity towards injured or transformed cells, universal expression of an invariant TCR and exclusive epidermal localization, DETC have been postulated to recognize a stress-induced self-antigen [35]. Indeed, by using a modified DETC TCR as a staining reagent (a V γ 3V δ 1 TCR tetramer), this stress antigen appears to be transiently expressed by keratinocytes bordering skin wounds *in vivo* whereas undamaged keratinocytes do not appear to express stress ligand [33].

Interestingly, *in vivo* imaging studies indicate that the apical dendrites of steady state DETC form immunological synapse-like contacts, enriched in TCR clusters and phosphorylated CD3 ζ , with keratinocyte tight junctions [23]. These findings suggest that resting DETC normally engage ligand and receive constitutive TCR signals, which could explain the semi-activated state of these T cells. In this model, reorganization of a signaling complex caused by tissue injury, rather than changes in TCR signal strength, would control DETC activation. While identification of a keratinocyte stress-induced antigen will allow the possibility of constitutive TCR ligand engagement to be examined, defining the stress molecule activating DETC has proved challenging; the few known ligands for $\gamma\delta$ TCRs appear highly diverse in chemical nature, leaving little insight into the identity of the molecules seen by specific populations of $\gamma\delta$ T cells.

In humans, some skin-homing $\alpha\beta$ subsets have been identified that respond to the MHC class I-like molecule, CD1a [51]. CD1a is expressed on antigen presenting cells and, like other CD1 family molecules, is able to bind and present lipids for T cell activation [52]. The stimulatory potential of CD1a is dependent on the hydrophobic characteristics of bound lipids; apolar lipids appear stimulatory whereas polar oils are inhibitory to CD1a-reactive $\alpha\beta$ T cells [53]. This dichotomy may be due to disruption of antigenic TCR binding to CD1a by the bulky headgroups of polar lipids. Interestingly, while the extracellular apolar lipid content of most tissues is relatively low, sebaceous gland secretions coat the epidermal surface with highly hydrophobic lipids, such as squalene and wax esters, that contribute to the waterproofing of the stratum corneum. As CD1a expression in the skin is restricted to dendritic cells found in the basal layers of the epidermis, the spatial separation of stimulatory lipids on the surface of the skin from deeper cutaneous antigen presenting cells might normally only allow for CD1a presentation of inhibitory polar lipids. However, damage to the skin by injury or infection could allow dendritic cell access to apolar lipids for CD1a presentation. In this model, oily skin antigen would therefore serve as a cutaneous damage signal for T cells [53]. While some $\gamma\delta$ T cell populations have been shown to

recognize a variety of endogenous and exogenous lipid antigens, further work is necessary to determine whether activation by CD1-presented lipids extends to $\gamma\delta$ T cells in the skin [54–59].

The V δ 2- subset of human blood $\gamma\delta$ cells has been demonstrated to respond to CMV-infected cells or intestinal epithelial tumors [60]. By using a V γ 4V δ 5+ clone to typify this population, the dual reactivity of these cells was revealed to be TCR-mediated recognition of the MHC I-like protein, endothelial protein C receptor (EPCR) [61]. Upregulated on virally infected endothelial cells and transformed intestinal epithelia, EPCR may serve a broad stress signal in these tissues recognized by some blood $\gamma\delta$ T cell populations. Interestingly, EPCR is also expressed on human keratinocytes and is implicated in cutaneous wound repair via a critical role in the cytoprotective protein C pathway [62]. While epidermal $\gamma\delta$ T cell recognition of EPCR is unknown, it is interesting to speculate whether this molecule may also regulate skin wound healing by serving as a cutaneous stress signal recognized by skin resident $\gamma\delta$ T cells.

In humans, up to 90% of gut $\gamma\delta$ IELs are V δ 1+ cells and it has been reported that a subset of these recognize the MHC Class I-like molecules, MICA and MICB [63]. These proteins are inducibly expressed by damaged enterocytes and target epithelial tumors for killing by V δ 1+ T cells. MICA and MICB have therefore been proposed to be stress molecules signaling gut epithelial injury or dysregulation to T cells. However, V δ 1+ populations also express NKG2D, an NK cell activating receptor, which engages MICA and may compete with $\gamma\delta$ TCR binding. [64]. The role of MICA-TCR interactions in regulating gut $\gamma\delta$ IELs therefore remains unclear.

Interestingly, NKG2D also activates epidermal T cells in the mouse. Expression of the murine NKG2D ligand, H60c, is upregulated on keratinocytes after damage or transformation and, in concert with TCR signaling, can stimulate DETC killing of stressed cells or mediate DETC production of KGF1 [50, 65, 66]. However, whether NKG2D acts as a costimulatory receptor, requiring simultaneous TCR signaling, or is a primary immunoreceptor that drives DETC activation is unclear; RAE1 is another NKG2D ligand upregulated by stress in the skin and is able to stimulate DETC in the absence of TCR engagement [67, 68]. It may be that alternative skin ligands for NKG2D are expressed depending on the form or severity of the epidermal stressor and that differential expression of these molecules gives context for the DETC response.

Interactions modulating T cell responses

While the damage signals detected by $\gamma\delta$ T cells are mostly unknown, the necessity of TCR signaling in DETC function is clear; the V γ 3V δ 1 TCR is necessary for detection of epithelial stress ligand and ectopic expression of this TCR can transfer reactivity against distressed keratinocytes [35]. For $\alpha\beta$ T cells, TCR signals alone are insufficient for cellular activation as costimulatory signals are needed to elaborate effector functions and prevent T cell anergy [69]. $\gamma\delta$ T cells do not express the classic receptors known to mediate $\alpha\beta$ costimulation, leaving the $\gamma\delta$ T cell requirement for a “second signal” unresolved [25, 35]. However, recent studies using epidermal T cells as a model system clearly indicate that

secondary signals, in addition to TCR signaling, are required to stimulate $\gamma\delta$ T cell functions.

The primary example of an epithelial $\gamma\delta$ T cell-specific costimulatory receptor is junctional adhesion molecule-like (JAML). Low levels of JAML are constitutively expressed on DETC and gut $\gamma\delta$ IEL, but not other $\gamma\delta$ T cell populations, and stimulation of epithelial $\gamma\delta$ T cells results in upregulation of JAML [70]. In the epidermis, JAML engages a ligand, coxsackie and adenovirus receptor (CAR), expressed on keratinocytes [70]. Upon wounding, CAR expression is upregulated by keratinocytes proximal to damage and concomitant with DETC activation [70]. JAML-CAR interactions are required for efficient KGF-1 production by DETC and, importantly, a severe *in vivo* defect in wound closure is observed when this interaction is disrupted [70]. While regulation of IEL wound responses by JAML-CAR interactions in the gut remains to be tested, the responsiveness of intestinal $\gamma\delta$ T cells to JAML costimulatory signals makes this an interesting prospect.

Upon wounding, one of the first observable DETC responses is cellular rounding [33]. This morphological change is controlled by CD100 signaling on DETC after engagement of its ligand, plexin B2, expressed by keratinocytes [71]. While the functional significance of this response is unknown, failure to round is associated with defects in wound closure. *In vivo*, DETC at wound borders of CD100-deficient mice remain dendritic after injury and wound closure is delayed by 1–2 days compared to wildtype mice [71]. In contrast to DETC, resident T cells in the gut do not display a dendritic morphology and are highly motile [27]. However, CD100-plexin B2 interactions on respective gut-resident $\gamma\delta$ IELs and intestinal epithelial cells also appears involved in the repair processes of gut injury as CD100-deficient mice also display delayed healing and exacerbated colitis when given DSS compared to wildtype mice [29].

Conclusions

The maintenance of epithelial barrier tissues is necessary for the critical separation of an organism and the environment. Epithelial-resident $\gamma\delta$ T cells promote barrier tissue homeostasis by producing factors that regulate the growth and survival of epithelia in the skin and gut. In the mouse, DETC and intestinal $\gamma\delta$ IELs function as sentinels that detect breaches in barrier integrity caused by injury or disease. DETC regulate tissue level responses to injury by promoting inflammatory cell recruitment, keratinocyte growth and epithelial cell survival (Summarized in Figure 1). $\gamma\delta$ IELs in the gut play a similar tissue protective role by releasing KGFs that regulate tissue repair after intestinal injury. While less studied, resident $\gamma\delta$ T cells found in the epithelia of the lungs, urogenital tracts, and eyes also appear to possess tissue repair capacity. This distribution, coupled with conservation in the epithelia of all mammals, highlights the evolutionary specialization of these lymphocytes in barrier tissue homeostasis.

Human diseases of barrier sites such as chronic non-healing skin wounds, skin cancers and inflammatory bowel diseases are becoming increasingly common and take a heavy toll on both afflicted patients and society. Work aimed at understanding the signals regulating the functions of epithelial-resident $\gamma\delta$ T cells and the pathways used by these lymphocytes to

promote tissue repair might one day be used to clinically modulate $\gamma\delta$ T cell functions for disease therapies.

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- Epithelial-resident $\gamma\delta$ T cells respond to stress-induced self-antigens
- Epithelial-resident $\gamma\delta$ T cells promote repair of tissue injury
- Molecules that regulate tissue-resident $\gamma\delta$ T cell and $\alpha\beta$ T cell functions differ

Figure 1.

Dendritic epidermal T cells (DETC) respond to skin injury by detecting an unknown self-antigen (Stress Antigen) expressed on distressed keratinocytes at wound sites. Activated DETC regulate inflammatory cell recruitment directly, by producing CCL3 and CCL4, and indirectly, by controlling hyaluronan deposition by keratinocytes. DETC stimulate keratinocyte proliferation via release of keratinocyte growth factors (KGFs) and promote epithelial cell survival by upregulating production of insulin-like growth factor-1 (IGF-1).