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Brief Reviews

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γδ T Cell Update: Adaptate Orchestrators of Immune Surveillance

Adrian C. Hayday

As interest in γδ T cells grows rapidly, what key points are emerging, and where is caution warranted? γδ T cells fulfill critical functions, as reflected in associations with vaccine responsiveness and cancer survival in humans and ever more phenotypes of γδ T cell–deficient mice, including basic physiological deficiencies. Such phenotypes reflect activities of distinct γδ T cell subsets, whose origins offer interesting insights into lymphocyte development but whose variable evolutionary conservation can obfuscate translation of knowledge from mice to humans. By contrast, an emerging and conserved feature of γδ T cells is their "adaptate" biology: an integration of adaptive clonally-restricted specificities, innate tissue-sensing, and unconventional recall responses that collectively strengthen host resistance to myriad challenges. Central to adaptate biology are butyrophilins and other γδ cell regulators, the study of which should greatly enhance our understanding of tissue immunogenicity and immunosurveillance and guide intensifying clinical interest in γδ cells and other unconventional lymphocytes. ***The Journal of Immunology*****, 2019, 203: 311–320.**

Running like a central artery through the biology of γδ T cells is one major question, namely, what unique host benefit is contributed by a highly conserved third lineage of cells that, together with B cells and αβ T cells, has somatically diversified surface receptors (1)? The question's significance was starkly reinforced when a wholly unrelated molecular mechanism in jawless vertebrates (agnathans) was found to likewise diversify three cell lineages (2).

γδ T cell uniqueness

For 25 years, γδ cells have highlighted atypical lymphoid effector functions, such as keratinocyte growth factor production (3), but their primary role may be to expand the breadth of immune responsiveness. Unlike αβ T cells, γδ T cells are not limited to recognition of peptides presented by MHC proteins, lipids presented by CD1, and metabolites presented by MR1, although this does not exclude such reactivities from their repertoire (4). The few TCR γδ Ags so far characterized are structurally diverse, including MHC, CD1, several other cell-bound Ags, histidyl-tRNA synthetase, and haptens that may modify cell surface proteins (5, 6). This breadth seemingly reflects an enormous potential for diversity, particularly of TCRδ (7). Moreover, this potential has been further increased in *Xenopus* by inclusion into the TCRδ locus of Ig–V_H gene segments (8) and in marsupials and sharks by the generation of TCRδ-based 3-Ig-domain receptor chains that pair with TCRγ to form TCRμ and new Ag receptor–TCR molecules, respectively (9, 10). Thus, a major challenge is to reconcile roles for γδ T cells in immunosurveillance with an unparalleled potential for diversity.

Additionally, γδ T cells may expand the spatial and temporal ranges of immune responsiveness by being activated in anatomical sites and/or ontogenetic periods not well served by B cells and αβ T cells (11). Although gray short-tailed opossums may be an exception (12), many γδ T cell subsets mature prior to αβ T cell maturation (13), with further examples continuing to emerge in mice and in humans (14–16). Predictably, therefore, some γδ T cell phenotypes are most overt prior to adulthood (17, 18).

Furthermore, the rapid response kinetics of γδ T cells (19) may critically regulate tissue immunogenicity by altering the local milieu so as to accommodate time-delayed adaptive responses of B cells and αβ T cells while promoting key elements of tissue repair and regeneration (20). Conversely, dysregulation of such activities might fuel inflammatory pathologic conditions, potentially underpinning ever more causal implications of murine γδ T cells in experimental allergic encephalomyelitis (a mouse model of multiple sclerosis), type I diabetes, skin inflammation, and cancer (21–26).

Notwithstanding these possibilities, our perspectives on how γδ T cells expand immunological range will likely require us to think more laterally about the host response to infection and tissue dysregulation. To illustrate this, we shall consider emerging data depicting three modes of γδ T cell response (Fig. 1), none of which is easily accommodated by today's immunology textbooks.

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Abbreviations used in this article: BTN3A, butyrophilin 3A; Btnl, Btn-like; DAMP, danger-associated molecular pattern; DETC, dendritic epidermal T cell; EPCR, epithelial protein C receptor; HV4, hypervariable region 4; IEL, intraepithelial lymphocyte; ILC, innate lymphoid cell; LN, lymph node; LP, lamina propria; PAg, phosphoantigen; T_{reg}, T regulatory.

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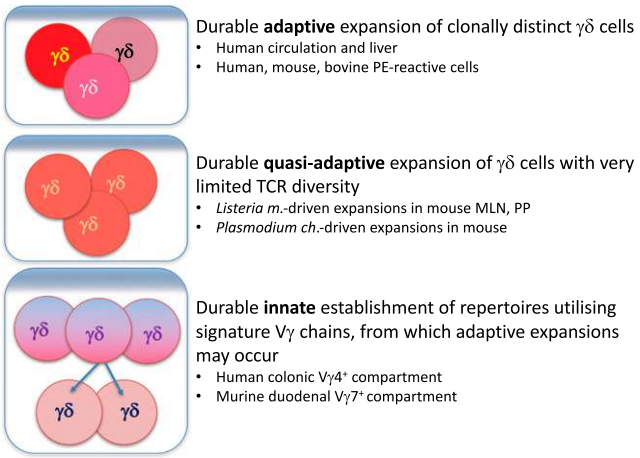

FIGURE 1. Mouse and human γδ T cells display at least three types of response: durable adaptive clonal expansion of γδ T cells, durable quasi-adaptive expansions, and durable innate repertoire selection.

How and when do γδ T cells respond?

Adaptive responses. Recent analyses of human peripheral blood and liver revealed large, durable, subject-specific expansions, commonly dominated by a few highly diverse γδ TCRs. Moreover, the expansions were enriched in $CD27^{lo}CX3CR1^{+}$ granzyme-expressing cells, consistent with clonal naive-to-effector differentiation, a signature of adaptive immunity (27–29).

The clones' specificities have yet to be deduced, but, given the potential for diversity in TCRγδ, they could be reasonably expected to include microbe-specific determinants reflecting subject-specific environmental exposures. Potentially consistent with this, hematopoietic stem cell transplantation patients displayed striking patient-specific clonal γδ T cell expansions coincident with CMV reactivation, particularly when γδ T cell reconstitution preceded αβ T cell reconstitution (30). Likewise, human monoclonal or oligoclonal γδ T cell expansions were associated with vertical CMV transmission in utero (31).

CMV is a major immunological driver, eliciting multifaceted, multilayered responses including adaptive NK cells and CMV-specific $CD8^{+}$ T cells. Hence, a γδ T cell contribution to the CMV response would seem plausible. Indeed, although neither TCRαβ-deficient nor TCRγδ-deficient mice showed impaired responses to CMV infection, mice lacking both T cell types were lethally susceptible (32). Hence, γδ T cell responses to CMV might be particularly important when αβ T cells are impaired, potentially explaining γδ T cell expansions either following transplantation or in utero. Moreover, durable clonal expansions of $TCR\gamma\delta^{+}$ effector cells in healthy human subjects might reflect transient immune deficiencies caused, for example, by sporadic holes in the TCRαβ repertoire.

Consistent with this perspective, overt γδ T cell expansions occurred in heavily immunosuppressed solid organ transplant recipients displaying reduced CMV disease and relatively few incidences of immunosuppression-associated cancer (33, 34). The isolated $TCR\gamma\delta^{+}$ clones lysed CMV-infected cells and could limit human tumor xenograft growth in mice, and, as in hematopoietic stem cell transplantation, they were subject-specific, evoking adaptive immunity to discrete stimuli. However, rather than being CMV-reactive, the first such clone to be characterized expressed a human Vγ4Vδ5 TCR specific for epithelial protein C receptor (EPCR), a CD1-like protein that can be upregulated by CMV infection and cell transformation (6, 35).

With current knowledge, this adaptive response seems puzzling: how did EPCR-reactive cells avoid immunological tolerance of self? How was their expansion favored versus the potential expansion of γδ cell clones with different specificities (e.g., CMV or self)? How do they finely distinguish virus-infected and/or transformed cells from healthy cells? And ultimately, how do they confer host benefit? Moreover, the same questions pertain to other self-reactive γδ T cells, including a human glioblastoma-reactive clone specific for annexin A2, whose surface expression is likewise promoted by CMV (36).

This puzzling scenario also arose in Lyme disease, for which the etiologic agent is *Borrelia burgdorferi.* Relative to wild-type mice, *Borrelia*-infected $TCR\delta^{-/-}$ mice display increased bacterial burden and cardiac inflammation, associated with greatly diminished αβ T cell and B cell expansions and reduced anti-*Borrelia* serum Abs, cytokines, and chemokines (37). Seemingly consistent with this important role of γδ T cells, human T cells expressing the Vδ1 gene segment were expanded in inflamed synovial joints of patients with Lyme disease. However, rather than being *Borrelia*-reactive, the expanded cells were responsive to myelomonocytic cells making TLR-dependent responses to *Borrelia* (38), and their Vδ1 TCRs bound to activated, uninfected monocytes and lymphocytes (R. Budd, personal communication).

In sum, seemingly prototypic adaptive responses have so far identified self-reactive rather than pathogen-specific γδ cells, albeit that such studies are in their infancy. Assuredly, not all TCRγδ reactivities will be self-reactive, particularly in calves and lambs, which harbor high numbers of circulating γδ T cells and in which vaccine-induced γδ responses have been reported (39). Furthermore, subsets of human, mouse, and bovine γδ T cells showed Ag-driven effector differentiation and IL-17 production in response to the microbial Ags, including PE (40, 41). This notwithstanding, we currently lack a clear physiologic natural history for an adaptive γδ T cell response spanning the cellular means of Ag exposure, drivers of clonal expansion, functional benefit to the host, and commitment to memory. It is, therefore, possible that, despite their potential for immense diversity, the uniqueness of γδ T cells may sit outside of conventional, microbe-specific adaptive immunity.

Quasi-adaptive responses. Following oral infection with an epithelial-tropic strain of *Listeria monocytogenes*, dramatic expansions of mouse γδ T cells were observed in the mesenteric lymph nodes (LN) and intestinal lamina propria (LP) (42). The expanded cells failed to recirculate following parabiosis, evoking a key component of immunological memory, namely, the cells' durable relocation to anatomical sites responsive to rechallenge (42). Consistent with this, expanded mesenteric LN and LP cells were rapidly reactivated by oral *L. monocytogenes* reinfection but not by oral *Salmonella* (live or attenuated) (42). The expanded γδ cells were the major producers of IL-17A, the blockade of which increased bacterial burden and delayed clearance. Hence, the response phenocopied host-protective adaptive immunity (42), simultaneously asserting that γδ T cells are not merely a first line of defense.

However, rather than being dominated by *L. monocytogenes*–specific clones, the expanded γδ T cells were not diverse, primarily expressing a Vγ6Vδ1 TCR present at steady state in the lungs and uterus of mice never exposed to *L. monocytogenes* and commonly found in other infectious and noninfectious scenarios (43) (below). In sum, microbe-specific γδ T cells were again difficult to identify, even in the setting of a host-beneficial, γδ-dependent effector response to an Ag-rich pathogen.

Instead, the prospect that Vγ6Vδ1$^+$ T cell responses were driven by an anatomical context of infection more than by specific microbial determinants was suggested by the cells' failure to expand in the guts, spleens, or livers of mice infected with *L. monocytogenes* i.v. despite major hepatic bacterial accumulations (42). Pathophysiologic context might also explain the selective occurrences of such responses: thus, murine Vγ6Vδ1$^+$ expansions were also provoked by repeated inhalations of *Bacillus subtilis*, whereupon they produced IL-17A that helped clear pneumonitis and resolve fibrosis (43). However, Vγ6Vδ1$^+$ cells did not expand in *Saccharopolyspora rectivirgula*–induced pulmonary fibrosis, during which IL-17A was produced by expanded CD4$^+$ Th17 cells (43). Clearly, we need a molecular explanation of how context rather than adaptive specificity can drive host-beneficial, tissue-specific γδ T cell expansions to many but not all microbial exposures.

A challenge in linking specificity to host benefit likewise pertains to malaria. The limited protection of humans induced by repeated vaccination with malarial sporozoites was associated with γδ cell activation (44), and M-CSF produced by γδ T cells expanded in the livers, lungs, and spleens of *Plasmodium chabaudi*–infected mice profoundly limited malarial recrudescence (45). However, rather than showing pathogen-specific responses to the complex, Ag-rich microbe, the expanded cells were mostly oligoclonal, innate-like Vγ1Vδ6.3$^+$ cells, which was even more surprising given that Vγ1Vδ6.3$^+$ cells, albeit with slightly different CDR3 sequences, were described among IFN-γ– and IL-4–producing NKT-like γδ cells (46) and among γδ T cells responding during bacterial infections to heat shock protein (hsp) 65–derived peptides mostly conserved from bacteria to mammals (47).

Again, the textbooks do not offer obvious mechanisms explaining the rapid, competitive expansions of oligoclonal, non–microbe-specific γδ T cells and the means by which they contribute to durable host protection. Possibly they manifest "trained immunity," as exists for nonclonal myeloid cells (48, 49). Potentially consistent with this, murine dermal IL-17–producing γδ T cells rapidly expanded in response to epicutaneous imiquimod (a TLR7 agonist), whereupon they established in nonlesional skin stable compartments of high IL-1R–expressing cells that facilitated greatly enhanced responses to imiquimod re-exposure (50). Clearly, our overall understanding of the complex immune ecologies underpinning tissue immunogenicity can benefit from improved insights into how host responses to rechallenge are promoted in tissues reprogrammed by local, durably altered oligoclonal γδ T cells.

Innate-like responses and butyrophilins. The response of primate peripheral blood γδ cells to many, albeit not all, microbes is well known and is relevant to sepsis, peritonitis, and other severe pathologies (51). However, rather than being highly specific, the responding cells detect picomolar concentrations of hydroxymethylbut-2-enyl pyrophosphate, an intermediate in sterol metabolism in myriad bacteria, including *Mycobacterium tuberculosis*, and in plastid-harboring parasites, including *Plasmodium*. Such moieties are termed "phosphoantigens" (PAgs) because responses are limited to cells expressing particular Vγ9Vδ2 TCRs that can transfer PAg reactivity to heterologous cells. Akin to adaptive immunity, PAg exposure underpins variable postnatal expansions of peripheral blood Vγ9Vδ2 cells (52).

Nonetheless, the limitation of TCR diversity to a single Vγ–Vδ pairing, the cells' rapid responsiveness, and the widespread occurrence of microbial PAgs collectively evoke innate sensing of pathogen-associated molecular patterns. Indeed, PAg-reactive cells also respond, albeit at higher concentrations, to endogenous sterol intermediates (e.g., isopentenyl pyrophosphate), a molecular pattern commonly upregulated in virus-infected or malignantly transformed cells (53). Over the past several years, it has emerged that PAg responsiveness depends on butyrophilin 3A (BTN3A) proteins (6, 54–57), which are poorly understood members of the B7 superfamily of T cell regulators that will now be considered at greater length.

Unlike TCRδ, TCRγ has little potential for diversity (58), a limitation highlighted by Vγ-specific cell expansions during murine T cell development that result in signature tissue-specific γδ T cell compartments, including canonical Vγ5$^+$Vδ1$^+$ dendritic epidermal T cells (DETC), canonical Vγ6$^+$Vδ1$^+$ uterine cells, and oligoclonal Vγ7$^+$ intestinal intraepithelial lymphocytes (IEL). Although humans lack obvious counterparts of DETC, there are skin γδ T cells (59) as well as a major intestinal huVγ4$^+$ IEL compartment (60–62) and several other human extralymphoid γδ cell compartments most likely exist. Enrichment at body surfaces might empower γδ cells with rapid surveillance of myriad types of potentially tissue-disruptive challenges. This may be an ancient function under high selective pressure, reflecting which agnathans show enrichment of γδ-equivalent VLR-C$^+$ cells in gut and skin (63); γδ T cell biology may provide a route to understanding this intriguing function.

Associations of defined Vγ elements with discrete tissues suggested that there were tissue-specific, γδTCR-specific selecting ligands, a hypothesis that gained momentum when Vγ5Vδ1$^+$ DETC development was found to depend on Skint1, a Btn-like (Btnl) molecule expressed specifically by thymic epithelial cells and differentiated suprabasal keratinocytes, among which DETC develop and reside, respectively (64–67). Likewise, intestinal moVγ7$^+$ IEL development was recently found to depend on *Btnl1*, largely restricted to intestinal epithelial cells (61, 62).

Btnl proteins most likely exist as heteromers (68), explaining the observation that moVγ7$^+$ IEL downregulated their TCRs and upregulated IL-2Rα (two signatures of TCR engagement) in response to Btnl1 plus Btnl6 but not to either alone (61, 62). Emphasizing evolutionary conservation, human BTNL3 and BTNL8, which are also largely restricted to intestinal epithelial cells, provoked TCR downregulation specifically by huVγ4$^+$ cells, the major colonic TCRγδ$^+$ IEL subtype (61, 62).

The shaping of the skin and gut γδ compartments by Skint1 and Btnl1, respectively, occurred independently of environmental factors (61), suggesting that they comprise bona fide

positive-selecting elements akin to CD1d for NKT cells or MHC class I for CD8 T cells. Consistent with this, moVγ7$^+$ and huVγ4$^+$ TCRs, respectively, conferred Btnl1+6-responsiveness and BTNL3+8-responsiveness to heterologous, nonresponsive T cells (62). These responses were largely uninfluenced by TCRδ, being primarily determined by CDR2γ and hypervariable region 4 (HV4), two Vγ subregions closely contiguous in tertiary space (62).

In conclusion, although direct evidence for binding is still lacking, it seems reasonable to consider Btnl/BTNL proteins as γδTCR ligands/Ags, but the T cell response to them is innate by virtue of it being a nonclonotypic property of essentially all TCRs with defined, germline-encoded Vγ–CDR2–HV4 sequences. Clearly, this suggests that polymorphisms in these and possibly other *Btnl/BTNL* genes contribute to the hereditary selection of TCRVγ genes. The direct impact on Vγ–CDR2–HV4 was in each case mediated by one of the two Btnl/BTNL chains (Btnl6 for moVγ7 and BTNL3 for huVγ4), with the other chains (Btnl1 and BTNL8) seemingly regulating the cellular trafficking and surface expression of the respective heteromers (62, 68).

Clearly, it may be appropriate to evaluate the degree to which this innate modality underpins PAg responses of huVγ9Vδ2 cells, particularly given recent evidence that they depend on a BTN3A1 plus BTN3A2 heteromer (68). Furthermore, recent evidence for a developmental enrichment of PAg-reactive huVγ9Vδ2 cells in utero might reflect intrinsic, BTN3A-dependent selection events akin to those shaping murine DETC and intestinal IEL compartments (16).

Adaptate integration. Clearly, the three illustrations of γδ T cell expansion need to be better understood. Does each describe a terminally differentiated state, and how do those states compare with one another and with other well-studied states (e.g., adaptive effector/memory αβ T cells, exhausted T cells, or innate-like NKT cells)? Do the durabilities of expanded adaptive γδ clones and of innately expanded tissue-associated compartments share common molecular underpinnings? By comparing and contrasting, we can determine whether γδ T cells bridge innate and adaptive immunity primarily at the population level, comprising qualitatively distinct adaptive and innate cells. That would seem consistent with the division of thymocytes into innate-like and adaptive biologies prior to the γδ/αβ T cell lineage split (69). Conversely, individual γδ T cells might combine innate and adaptive traits in cell-autonomous adaptate biology (Fig. 2).

Although huVγ4$^+$ and moVγ7$^+$ cells can be innately regulated by BTNL3 and 8 and Btnl1 and 6, respectively, they can also engage nominal Ags, including human EPCR (see above) and murine MHC-related proteins T10/T22 (35, 70). Nominal Ag responses depend on somatically-recombined CDR3 regions, consistent with their adaptive nature, albeit that gene rearrangement generates the T10/T22-reactive site fairly frequently. Such Ags may drive clonal dominance within repertoires initially selected by innate Vγ-mediated signaling. Neither the mechanism(s) by which tissue-associated γδ T cells sample nominal Ags in situ nor the cells' antigenic breadth is understood, although there seems to be some enrichment for MHC class I–related proteins (e.g., CD1, EPCR, Qa1, and T10/T22), particularly those upregulated and/or stabilized in dysregulated tissues.

γδ T cells are not intrinsically MHC-restricted. Human γδ T cell infusions induce negligible MHC-dependent graft-versus-host disease (71), and murine γδ cell compartments develop normally in mice lacking β2-microglobulin (β2m; an obligate cofactor for most MHC class I–related molecules) (72). Nonetheless, neither observation excludes the cells' reacting to nonpolymorphic MHC-related molecules. Moreover, some structural capacity of TCRγδ to complement MHC-related molecules might explain recently described Ab-like TCRγδ reactivities toward melanoma Ag-derived peptides presented by MHC (73).

In sum, adaptate biology may be an evolutionarily conserved trait by which defined γδTCRs can respond to either innate or adaptive ligands via distinct binding modalities. This is not to suggest that both are engaged simultaneously; possibly, innate ligands transduce signals that maintain the cells' competence to respond to adaptive ligands when the local milieu is dysregulated. Such biology would functionally align BTNL/Btnl

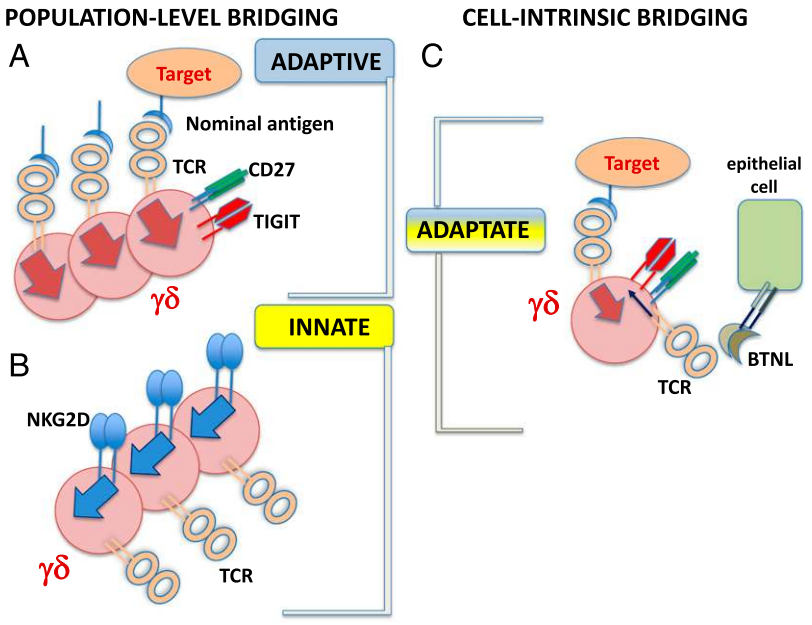

FIGURE 2. Mouse and human γδ T cells may bridge innate and adaptive immunity at the population level or at the cell-intrinsic level. (**A**) Adaptive clonal expansion of γδ T cells driven by signaling from TCR engagement of nominal Ag, regulated by examples of positive (green) and inhibitory (red) costimulation. (**B**) Innate activation of γδ T cells driven by innate receptor (e.g., NKG2D) engagement of stress ligands, without overt activation of the TCR. (**C**) Adaptate activation of γδ T cells driven by signaling from TCR engagement of nominal Ag, licensed (narrow arrow) by preceding innate TCR engagement of ligands such as BTNL.

proteins with B7 molecules (e.g., B7.1 and/or B7.2 [also known as CD80/CD86]) that inform T cells that an infected context exists, thereby licensing full, TCR-mediated, Ag-specific effector responses. This is the founding paradigm bridging innate with adaptive immunity (74).

Functional alignment of BTNL/Btnl proteins is paralleled by structural alignment, with nuclear magnetic resonance–based data showing the Skint1 ectodomain to be strikingly similar to PDL1 (75), a B7-like molecule that communicates to T cells a state of heightened immune activation, thereupon dampening TCR-mediated responsiveness. The possibility that Skint/Btnl/BTNL proteins communicate tissue status to local T cells is fueled by the restriction of their expression to postmitotic differentiated epithelial cells. In short, γδ T cells engaging Skint/Btnl/BTNL would know 1) where they were (skin/gut) and 2) the status of the tissue (homeostatic "normality"). Thereby, local γδ T cells may be uniquely well placed for tissue sensing.

The tightly regulated expression of Btnl/BTNL might be sufficient to define normality. Alternatively, the proteins may phenocopy BTN3A1, whose intracellular B30.2 domain binds PAgs (56), the concentrations of which are upregulated by cell infection and/or dysregulation and which can, therefore, be classified as danger-associated molecular patterns (DAMPs). Upon B30.2 binding, BTN3A1 is conformationally altered, purportedly promoting TCR triggering (56, 76), albeit by unknown mechanisms. Thus, there is an intriguing potential for BTNL B30.2 domains to likewise act as intracellular status sensors, and although Skint1 lacks a B30.2 domain, it includes multiple transmembrane-pass regions that may also sense cellular normality. By whichever means, *Btnl/BTNL/Skint* gene products may fulfill the roles of DAMP-sensing B7 molecules, communicating the status of the tissue to preselected sets of local T cells.

Tissue sensing by local T cells may be manifest in observations of murine gut γδ IEL dynamically engaging the basolateral sides of enterocytes (77–79). Although somewhat different observations were reported, the aggregate findings were that, following gut infection, particularly by attaching–effacing bacteria, enterocytes could provoke γδ IEL to increase their ATP utilization, facilitating their accelerated mobility up and down the villi (79). The regulators of mobility included occludin, CD103, the glucose transporter Glut1, and IL-15, and reduced mobility was associated with increased transepithelial invasiveness of *S. typhimurium* or *Toxoplasma gondii* (78, 79). For Vγ5Vδ1$^+$ DETC, tissue sensing is seemingly manifest in TCR-rich clusters that appose neighboring keratinocytes at steady state but which are disrupted upon epithelial dysregulation as a preface to full T cell activation (80) again evoking licensing.

The perception via the TCR of both tissue status and nominal Ags may require that innate and adaptive ligands transduce distinct intracellular signals. As precedent, the profound effects of microbial and/or endogenous superantigens on αβ T cells are primarily mediated by TCRβ–HV4, which transduces signals distinct from those transduced by CDRs engaging peptide–MHC (81). Indeed, innate tissue sensing may transduce signals akin to tonic signaling or chronic Ag stimulation. In this regard, *Skint/Btnl*-selected γδ T cells are rich in *Nr4a* transcriptional regulators, which compose signatures of chronically activated CD8$^+$ TCRαβ$^+$ tumor-infiltrating lymphocytes (82). However, whereas *Nr4a*$^+$ tumor-infiltrating lymphocytes are commonly regarded as exhausted, tissue-associated *Nr4a*$^+$ γδ T cells are better considered as activated-yet-resting (83), sustaining cellular competence to respond to nominal Ags.

Tissue status may also be sensed by NKG2D, an activating receptor widely expressed by NK cells, CD8$^+$ αβ T cells, and tissue-resident γδ T cells. NKG2D ligands Rae-1 (mouse) or MICA/ULBP (human) are strong candidates for DAMPs in human carcinoma because they are upregulated by DNA damage and by hyperactive epithelial growth factor receptor signaling (84, 85). Consistent with this biology, NKG2D is a coreceptor for TCR signaling on CD8$^+$ αβ T cells (86). By contrast, DETC responded rapidly in vivo to acute local Rae-1ε upregulation without overt TCR stimulation, arguing for the cells' classification as innate T cells (87, 88). Moreover, Rae-1ε–induced DETC activation initiated several downstream immunological events akin to those initiated by innately activated myeloid cells (87, 88).

However, were the Vγ5Vδ1$^+$ DETC TCR to be constitutively engaged (e.g., by Skint1), the DETC may not have been responding only to innate NKG2D ligands. Likewise, innate TCR activation may license target recognition by other innate receptors such as NKp30 (89) or WC1, an antimicrobial scavenger receptor expressed by a major subset of bovine γδ T cells (90, 91) (Fig. 2). In fact, prior *Skint1*-mediated selection is required to transform Vγ5Vδ1$^+$ DETC progenitors into T cells strongly responsive to innate receptor engagement but with relatively attenuated responsiveness to conventional TCR stimulation (92). Upon *Skint1*/*Btnl1*-mediated selection, DETC and IEL upregulate CD45RB, and when hitherto uncharacterized CD45RB^{hi} γδ cells were purified from lymphoid organs, they, too, combined atypical TCR responsiveness with strong innate responses (92), an integrated state reinforcing an adaptate view of γδ T cells.

This is not to suggest that TCR-mediated innate sensing is a unique means of tissue and/or context sensing by γδ T cells, because they express several other significant receptors, including Gpr55, JAML, CD100, 4-1BB, and the aryl hydrocarbon receptor (61, 93–96) (Fig. 2), that may make the cells particularly adept at homing to, residing within, and then discriminating the status of tissues. Likewise, γδ T cells may be inhibited by TIGIT and/or other negative regulators (Fig. 2). Importantly, expression of different receptors should facilitate receipt of different information flows from many different cell types that tissue- and tumor-resident γδ cells interact with.

What do γδ T cells do?

Functional preprogramming. Another consequence of γδ T cell selection is effector skewing. *Skint1*-mediated selection suppressed *Sox13* and *Rorc* expression, skewing DETC progenitors away from IL-17 production, which is likewise suppressed in *Btnl1*-selected Vγ7$^+$ IEL and in T10/T22-specific γδ cells that engage their ligand during development (61, 67, 97). Likewise, TCR signals are required for murine Vδ6.3$^+$ cells to skew toward either IL-4 or IFN-γ production (98).

Developmental preprogramming is not universal, as PE-reactive γδ T cells (above) were skewed toward IL-17 in the periphery following Ag priming of functionally uncommitted cells, seemingly consistent with the adaptive biology of conventional αβ T cells (40, 99). Nonetheless, its broad significance

was established when a large faction of mouse TCRγδ$^+$ thymocytes expressing CD27 and CD122 was found to be IFN-γ–skewed, with CD27 acting as a coreceptor, enabling the immature cells to survive strong TCR-mediated signals (100, 101). Indeed, IL-17 expression became epigenetically excluded in CD27$^+$ cells (102). Conversely, murine CD44^{hi}CCR6$^+$CD122^{lo}CD27$^-$ thymocytes preprogrammed toward IL-17 (100) are progenitors of several well studied, potently proinflammatory murine γδ cell compartments that respond rapidly to innate stimuli, particularly IL-1 and IL-231 (14, 15, 21, 103–105). Furthermore, the functional biases of CD27$^+$ and CD27$^-$ cells, respectively, were amplified during their expansions in *P. berghei*–infected mice (101).

Functional skewing can show striking microanatomical segregation, with IL-17 produced by subepithelial compartments (e.g., dermal and LP γδ T cells) but seemingly excluded from healthy epithelium. Note that, although DETC and IEL are IFN-γ−biased, their IFN-γ production is often minimal, suggesting that other effectors better describe their host benefit. Likewise, although most γδ subsets have high cytolytic potential, where and when such activity is ordinarily deployed is unclear. Better understanding of the microanatomical segregation of γδ T cell functions could provide useful insight into how local lymphocytes are integrated with loco-regional physiology at steady state and during tissue inflammation.

Selected or default? Related or distinct? As first noted by Born and O'Brien (105), function also segregates to some extent with TCR usage: CD27$^+$ IFN-γ producers are primarily Vγ1$^+$, whereas CD27$^-$ IL-17 producers mostly express Vγ4 or limited-diversity Vγ6 TCRs, including those showing quasi-adaptive expansion in *L. monocytogenes* infection. These observations suggest that the γδ17 phenotype can also be preprogrammed by TCRVγ-selective activation; consistent with this, γδ17 progenitors are CD44^{hi}, show strikingly attenuated TCR responsiveness (100), and are disproportionately depleted in *Skg* mice, in which the function of the TCR-proximal signaling kinase Zap70 is reduced by ~90% (92). Likewise, Vγ6$^+$ IL-17 producers are essentially ablated by haploinsufficiency of both CD3 γ- and CD3 δ-chain genes (106). The cells' innate-like activity is also suggested by their limited expression of genes encoding TCR signaling components (107).

Nonetheless, TCRVγ-specific selection is not yet established for IL-17–producing γδ T cells, and the possibility exists that they are a default state suppressed by ligand-dependent γδ selection (67, 97). Indeed, γδ17 progenitors are reportedly intolerant of strong TCRγδ signaling (108), despite the fact that strong TCR-mediated signals are seemingly required for early T cell progenitors to become γδ versus αβ T cells (109, 110).

Possibly, strength-of-signal is less significant than qualitatively distinct signals [e.g., differences in ERK activity (110)] that might reflect different TCR signaling modalities, for example, via CDR2–HV4 (62) or via ligand-independent dimerization (97), as is considered for pre–TCR signaling in αβ T cell development. Possibly, SLAM–SAP signaling in vivo permits γδ17 progenitors to survive strong TCR signals, as was recently shown for invariant NKT cell development (111). Clearly, the identification of physiologic ligands, particularly for canonical Vγ6$^+$ T cells, should resolve this and other aspects of γδ17 biology. The same would be true for oligoclonal Vγ1Vδ6.3$^+$ cells, whose TCR is critical for their adopting a defining NKT-like phenotype (98).

At the same time, TCR signals might be altered by context (e.g., coincident signals via *Notch,* cytokines, and/or other cell surface regulators, and regulation by microRNAs) (112–115). Recently, the transcription factor c-*maf* was shown to promote the developmental acquisition of the γδ17 phenotype, in part by promoting *Rorgt* activity and by suppressing *Tcf7*, whose gene product, Tcf1, promotes the γδIFN-γ phenotype (116). This may parallel the c-*maf*–driven switch of TCRαβ$^+$ T regulatory (T_{reg}) cells into IL-17 producers. Likewise, γδ17 differentiation is promoted by the transcription factor PLZF, which is generally associated with innate-like T cell phenotypes (117) and is specifically required for NKT-like γδ cells (98).

Such signature gene regulatory networks might also suggest that IFN-γ–skewed and IL-17–skewed γδ T cells arise independently from qualitatively distinct progenitors (118). This could relate to the limited and unique developmental windows during which distinct γδ T cells emerge and to the report that γδ17 cells arise from type 3 innate lymphoid cell (ILC)-like IL-17–producing thymocytes (14). This perspective would be consistent with there being many other differences between IFN-γ–skewed and IL-17–skewed γδ T cells. For example, the latter harbor low levels glutathione, making them susceptible to reactive oxygen species produced by neutrophils (119). This may reflect γδ subset–specific negative feedback regulation required to protect tissues. For example, in response to the commensal *Corynebacterium mastitidis*, ocular γδ17 cells recruit neutrophils, which release antimicrobials into tears that protect the eye from pathogenic fungi and bacteria but that, in excess, could cause immunopathologic conditions (120).

γδ T cells and disease

Complexities and controversies. An increasing sophistication of phenotyping has begun to reveal that γδ T cells are relevant to very many aspects of pathophysiologic conditions. For example, murine PLZF$^+$ Vγ6$^+$ cells resident in adipose tissue produce IL-17A and TNF, which, by regulating IL-33 production by stromal cells, indirectly maintain local type 2 ILC and T_{reg} cells that jointly regulate adipose tissue homeostasis (121). Additionally, γδ T cell–derived IL-17A and TNF directly stimulated expression of uncoupling protein 1 in adipocytes, favoring thermogenesis. As a result, TCRδ$^{-/-}$ mice displayed low body temperature and increased breathing at thermoneutrality and particularly after cold challenge (121).

The inference of γδ T cell function from TCRδ$^{-/-}$ mice is inevitably somewhat qualified by developmental adaptations to γδ cell deficiency, including ectopic potentials of replacement αβ T cell and ILC repertoires. The recent development of mice with conditional γδ T cell deficiency (122) has reduced this uncertainty, confirming that misdirection of antimicrobial potentials of dermal γδ17 cells underpins imiquimod-induced psoriasis, a phenotype that a high-fat diet exacerbates by increasing γδ17 cell numbers (122).

The thin line between tissue regulation and immunopathologic conditions is also illustrated by the relationship of γδ17 cells and commensals. IL-17 secreted by lung Vγ6Vδ1$^+$ cells responding to IL-1 and IL-23 produced by commensal-sensing myeloid cells may beneficially regulate local host–microbe interactions, akin to the induction by skin commensals of nonclassical MHC class I–restricted CD8 T cells that effected tissue

regulation (123). However, IL-17 produced by Vγ6Vδ1$^+$ cells indirectly responding to commensals in the same way drove neutrophil activation that promoted lung cancers in a transgenic "p53-loss, activated Kras" mouse model (124). Similarly, a γδ/IL-17/neutrophil axis promoted lung and LN metastasis in a murine breast cancer model (26), in part via CD8 T cell immunosuppression. IL-17 may also promote carcinomas via direct effects on epithelial cells. In addition to this, γδ17 cells may exacerbate inflammation by changing from CCR6-based homing into steady-state compartments to CCR2-dependent migration to inflammatory lesional sites (125).

Nonetheless, at least two levels of complexity provide important contexts for these studies. First, γδ17 cells can also produce IL-22, which promotes antimicrobial peptide production and epithelial repair, which can suppress inflammation and carcinogenesis (126). Indeed, retinoic acid reduces inflammation induced by either *Citrobacter* infection or dextran sodium sulfate by promoting γδ T cell–dependent IL-22 upregulation (126).

Likewise, although gingival γδ T cells can produce IL-17, a potential mediator of periodontal inflammation, their aggregate role following oral surface damage was to produce amphiregulin, which promoted barrier repair and the reestablishment of homeostasis (127). Likewise, IL-17 produced by murine γδ T cells responding to neonatal influenza infection promoted IL-33 production by lung epithelial cells (128). IL-33, in turn, promoted lung infiltration of type 2 ILC and T_{reg} cells that produced amphiregulin, which critically contributed to tissue repair. Furthermore, IL-17A, IL-33, and amphiregulin expression were correlated in influenza-infected children, although a direct linkage to γδ T cells was not shown (128). In short, it is inappropriate to assume either that IL-17 is the primary effector of γδ17 cells or that the key pathophysiologic impact of γδ17 cells is proinflammatory, and one should be cautious in interpreting experimental systems that may exaggerate that phenotype.

Second, there is strikingly little evidence for human γδ17 cells that were either preprogrammed or differentiated de novo in the periphery. Possibly, human γδ17 cells are obscure because they sit within tissues, occupy discrete ontogenetic windows, or are associated with specific pathological conditions. Indeed, rare examples of their detection in colorectal cancer and in human papillomavirus–rich vulval lesions were associated with cancer promotion (24, 25). Nonetheless, efforts to generate and/or expand human γδ17 cells have proved conspicuously challenging (129).

This potentially major difference between human and mouse γδ biologies might be because CXCL8 (whose gene is missing from the mouse genome) can replace γδ-derived IL-17 in regulating neutrophils. Possibly, the developmental pathway skewed toward γδ17 cells is less significant in humans, just as mice lack overt counterparts of PAg-reactive Vγ9Vδ2$^+$ cells. Indeed, species-specific differences are highlighted in the potent capacity of huVγ9Vδ2$^+$ cells to present Ag to T cells. Because such activity is not obviously conserved in mice, it has been somewhat understudied, with its physiologic context(s) unresolved. Recently, however, it was shown that blood and intestinal Vγ9Vδ2$^+$ cells that acquired Ag-presenting functions upon microbial activation in the presence of IL-15 could skew responding TCRαβ CD4$^+$ T cells toward IL-22 without upregulating IL-17 (130). Such selective skewing has not been shown for myeloid APCs and may reflect an additional unique contribution of γδ T cells to tissue surveillance.

In sum, the aggregate outcome(s) of γδ T cell activation can be highly case-specific and species-specific and will only be understood by better characterizing the multicomponent immune ecologies of specific responses to defined challenges. Although most human γδ T cell subsets display cytolytic IFN-γ–skewing akin to murine IEL and CD27$^+$ lymphoid γδ T cells, it is possible that pathologic reprogramming can redirect them toward IL-17 production in inflammation and/or cancer. In this vein, pathologic dysregulation of the intestinal huVγ4$^+$–BTNL3 axis was recently reported to contribute to the potent inflammatory milieu in celiac disease, for which intestinal γδ T cell expansion is a pathognomonic feature (131).

In the clinic. There are growing efforts to develop γδ T cells as immunotherapeutics in cancer. In contrast to the implication of γδ17 cells in promoting inflammation-associated cancer, a wealth of diverse studies underscore host-beneficial effects of γδ T cells in mice and humans (71, 87, 132–135). This seems consistent with the cells' potential to home to and operate in the hypoxic conditions commonplace in solid tumors; their adaptate capacity to sense tissue status and thereby to discriminate between normal and dysregulated cells; their cytolytic IFN-γ bias; their immunogenic capacity to promote other immune cell activities, including by Ag presentation; and their relative insensitivity to PD1- or T_{reg}-mediated inhibition.

Moreover, ongoing investigations of γδ T cells are casting new light onto cancer immunosurveillance. For example, activated DETC can rapidly produce IL-13, which can both promote type 2 B cell responses and promote epithelial repair (136). This intriguing link of γδ T cell–mediated lymphoid stress surveillance to atopy (88) may permit IgE to neutralize carcinogens and other toxins while tissue repair occurs. Indeed, an FcεR1-dependent IgE response driven by DETC responding to epicutaneous dimethylbenzanthracene (a dioxin-like carcinogen) protected mice against carcinogenesis, and FcεRI gene expression positively correlated with disease outcome in human squamous cell carcinoma (137). In practical terms, the recogntion of tissue dysregulation and the lack of MHC restriction of γδ T cells and other unconventional T cells have three potentially profound implications: their recognition of tumors will not be limited to those with high mutational loads required to generate peptide neoantigens; they will be unaffected by MHC loss-mediated immune evasion; and they may be efficacious in allogeneic recipients, thereby opening a door to off-the-shelf therapies.

Conclusions

In sum, many unique features of γδ T cells continue to emerge, including, but not limited to, their adaptate biology. Those features permit them to contribute to host protection in unprecedented ways, and their continued investigation promises to provide new and important insights into how tissue immunogenicity is balanced against the need to avoid inflammatory pathological conditions, and the complex interactions between multiple immune cells that will collectively compose tissue-specific immune ecologies. In this regard, understanding the specificities of adaptive γδ T cells will be essential to understanding the pressures that have presumably

maintained evolutionary selection on the capacity to generate diverse Ag receptors in three distinct cell lineages. Likewise, a greater understanding of the cells' biology may refine and optimize the clinical application of these natural orchestrators of immune surveillance.

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