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Analysis of γδ T Cell Functions in the Mouse

Willi K. Born,‡§ Zhinan Yin,‡ Youn-Soo Hahn,‡ Deming Sun,‡ and Rebecca L. O’Brien,*‡

Mouse models of disease and injury have been invaluable in investigations of the functional role of γδ T cells. They show that γδ T cells engage in immune responses both early and late, that they can function both polyclonally and as peripherally selected clones, and that they can be effector cells and immune regulators. They also suggest that functional development of γδ T cells occurs step-wise in thymus and periphery, and that it is governed by γδ TCR-signaling and other signals. Finally, they indicate that γδ T cell functions often segregate with TCR-defined subsets, in contrast to conventional T cells. From the functional studies in mice and other animal models, γδ T cells emerge as a distinct lymphocyte population with a unique and broad functional repertoire, and with important roles in Ab responses, inflammation and tissue repair. They also are revealed as a potentially useful target for immune intervention. The Journal of Immunology, 2010, 184: 4055–4061.

Unlike B cells and αβ T cells, γδ T cells were discovered through molecular means instead of by way of their functions. Key questions remain concerning possible functional differences between αβ T cells and γδ T cells, the significance of the organization of γδ T cells into a system of specialized subsets, and the function of the γδ TCR. Explanations are needed for why γδ T cells often respond faster than αβ T cells and how sometimes in very small numbers they exert powerful effects on inflammatory responses and tissue physiologies. Answers to these questions could revise conventional immunological concepts, and they might open new avenues for immunotherapy. In this brief review, we examine in vivo γδ T cell functions as revealed in mouse models.

Development of γδ T cell function

From the studies in mouse models, it appears that the development of γδ T cell function begins in the thymus and continues in the periphery, where environmental influences modulate developmental pathways. Fig. 1 shows a speculative scenario of the development of γδ T cell function in three major stages.

Early functional commitment in the thymus (stage 1)

The γδ T lymphocytes arise from a common thymocyte progenitor for αβ and γδ T cells during development in the thymus. Lineage commitment and potential appear to be influenced by several factors (1, 2), and commitment may occur at more than one developmental stage (3). Although the TCR type per se does not determine the lineage decision, TCR signal strength appears to determine lineage fate and developmental stage of lineage choice (4, 5). TCR signals and their different strengths may continue to be important in subset-specific functional differentiation and commitment (Ref. 6 and below). Studies with γδ TCR-expressing thymocytes indicated early on that certain subsets already acquire functional competence while in the thymus. Thus, thymocytes expressing TCR-γδ and resembling NKT cells were found to produce IL-4 (7), and a subset of adult γδ TCR+ thymocytes that expressed Thy-1 at low levels could be induced to secrete IL-3, IL-4, IL-10, and IFN-γ, in contrast to Thy-1hi cells that only secreted IFN-γ (8). The Thy-1lo γδ T cells were barely detectable in newborn mice and increased during the first 2 wk after birth (8), but a later study suggested that most originated from fetal precursors (9). Vγ1+ γδ T cells represent one of the major subsets in the secondary lymphoid organs and circulation of mice (10), and they are associated with distinct functional roles (see below). In keeping with the idea of subset-specific differentiation, the IL-4–producing thymocytes all express TCRs encoded by Vγ1 (8, 9). While investigating γδ TCR+ thymocytes for their ability to regulate allergic airway hyperresponsiveness (AHR), we found that in vivo-transfered Vγ1+ thymocytes enhanced AHR, whereas Vγ4+ thymocytes had no effect (11), preempting at least in part the functional pattern we had noted for peripheral γδ T cells (12). Interestingly, the γδ lineage-derived AHR enhancers are not those that produce IL-4 and IL-13 (11), unlike the above-mentioned NKT-like γδ T cell population. This indicates that the Vγ1+ thymocyte population contains more than functionally committed cell type.

*Integrated Department of Immunology, National Jewish Health, Denver, CO 80206; ‡University of Colorado at Denver Health Sciences Center, Denver, CO 80220; §College of Life Sciences, Nankai University, Tianjin, China; †Department of Pediatrics, College of Medicine and Medical Research Institute, Chungbuk National University, Cheongju, Korea; and Department of Ophthalmology, Doheny Eye Institute, University of Southern California, Los Angeles, CA 90033

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Address correspondence and reprint requests to Dr. Willi K. Born, Integrated Department of Immunology, National Jewish Health, 1400 Jackson Street, GB K409, Denver, CO 80206. E-mail address: bornw@njhealth.org

Abbreviations used in this paper: AHR, airway hyperresponsiveness; DC, dendritic cell; DETC, dendritic epidermal T cell.

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Many γδ TCRγδ thymocytes are already capable of producing TNF-α and IFN-γ upon activation in vitro (11), a bias that is maintained in the periphery (13). Thymocytes expressing γδ TCRs with a known specificity for the T10/22 nonclassical class I molecules may express different Vγs and Vδs and only share a common D6 motif (14, 15). These cells were shown to differentiate into IFN-γ rather than IL-17 producers dependent on TCR-avid interactions in the thymus (16). However, development of IL-17–producing γδ T cells in the thymus has its own particular requirements (17). Finally, functional differentiation of thymocytes expressing the invariant Vγ5Vδ1 TCR of dendritic epidermal T cells (DETCs) in mice depends on thymic expression of Skint 1, an Ig-like molecule expressed on epithelial cells (18), which might be a ligand of this TCR.

These data in mice show that many, if not all, thymic precursors of peripheral γδ T cells leave the thymus with a defined and limited functional potential.

Polyclonal functional induction in periphery (stage 2)

Many peripheral γδ T cells in mice appear to be “resting yet activated” (19) (i.e., they acquire an intermediate state of activation from whence polyclonal responses might be elicited with little further stimulation). Perhaps this intermediate state depends on tonic signaling by cross-reactive γδ TCRs, as envisaged some time ago for certain γδ T cells (20). The unexplained “spontaneous” reactivity of hybridomas expressing Vγ1+ γδ TCRs described many years ago might be an in vitro correlate, at least for this subset (21). Peripheral γδ T cells, which leave the thymus as functionally committed precursors, are either already functionally competent or can be induced to become competent in short order. With the exception of two related populations in mice that express invariant TCRs and directly colonize peripheral epithelia and mucosae (22), most peripheral γδ T cells seem to recirculate and temporarily reside in the lymphoid tissues.

A detailed comparison of murine and human γδ T cell populations is still lacking. We examined the mouse Vγ1+ and Vγ4+ γδ T cells, because these subsets resemble the much-studied recirculating γδ T cells present in human peripheral blood. Both reside in the murine spleen, and both depend for their functional development on CD8+ dendritic cells (DCs) (11, 23), a cell type present in thymus and secondary lymphoid organs including the spleen, but not in peripheral nonlymphoid tissues (24). Our data suggest that although both of these γδ T cell types are already functionally committed, they differ in their requirement for peripheral functional induction (12, 25).

When transferred into secondary recipients, splenic Vγ1+ γδ T cells can exert dramatic functional effects in various mouse models of disease (see Table I). In models of allergic AHR and in the primary IgE response to OVA/alum (a model of adjuvant-supported vaccination), where they have a response-enhancing effect, these cells do not need to be induced in any way (12, 42). In fact, even as HSA+ thymocytes, they already have the ability to enhance AHR, following transfer into γδ T cell-deficient recipients (11). Whereas the IgE-enhancing γδ T cells may be contained within the NKT-like fraction of Vγ1+ γδ T cells (39), the AHR-enhancing cells are not (see below) (42). Nevertheless, the AHR-enhancing cells also do not require induction. However, AHR-enhancing γδ T cells are functionally incompetent in mice lacking certain cytokines and receptors. In these mice, they can be induced to become fully functional by peripheral stimulation with OVA/alum (11), revealing some flexibility in their developmental pathway. It thus appears that several types of Vγ1+ γδ T cells, if not all, experience early intrathymic programming/functional induction.

Vγ4+ γδ T cells also affect disease outcome in various mouse models, but unlike the Vγ1+ cells, they require peripheral signals to become functional. In contrast to Vγ1+ cells, we observed that Vγ4+ cells suppress AHR and the primary IgE response to OVA/alum but require immunization or repeated challenge with Ag to develop (25, 39, 43). Thus, Vγ4+ cells might bypass some of the intrathymic programming that defines the Vγ1+ cells. However, their functional dependence on CD8+ DCs in donor mice suggests that they receive developmental signals as well, whether in thymus or periphery (23). Moreover, although Vγ4+ cells can be peripherally induced to suppress AHR and IgE, Vγ1+ cells cannot. Such suppressor-inducing conditions do not seem to have any effect on the Vγ1+ AHR enhancers but rendered Vγ1+ IgE enhancers nonfunctional, although they did not turn them into IgE suppressors (39). Thus, although there is some functional plasticity within either subset, the two do not functionally overlap. Both Vγ1+ and inducible Vγ4+ type cells are highly effective regulators of AHR and IgE in vivo (38, 39, 42) but appear to exert their functional effects as polyclonal unselected populations because they express diverse TCRs, and the treatments used to induce function do not lead to substantial changes in their TCR repertoires (25, 39).

Peripheral induction of Ag-presenting functions

Studies with ovine, human, and murine cells established that peripheral γδ T cells can be induced to acquire Ag-presenting functions (44–46), and a recent report characterized human γδ T cells as professional phagocytes (47). Because all of these studies were done in vitro, it remains to be seen whether Ag-presenting γδ T cells develop in vivo and are capable of influencing Ag-specific immune responses.

In contrast to human γδ T cells, which express MHC class II, in vitro expression of MHC class II molecules by murine cells γδ T cells has been detected but is limited to recently activated...
Table I.  Contribution of murine γδ T cells to pathogenesis and pathology

<table>
<thead>
<tr>
<th>Model</th>
<th>γδ T Cells (Net Effect)</th>
<th>Vγ1+</th>
<th>Vγ4+</th>
<th>VγδVδ1+ (Invariant)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin wound</td>
<td>Protective</td>
<td></td>
<td></td>
<td>Protective (promote wound healing)</td>
<td>26, 27</td>
</tr>
<tr>
<td>L. monocytogenes bacterial infection</td>
<td>Protective</td>
<td>Pathogenic</td>
<td>No effect</td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>West Nile virus infection</td>
<td>Protective</td>
<td>Protective</td>
<td>Pathogenic</td>
<td>(promote encephalitis)</td>
<td>29</td>
</tr>
<tr>
<td>Respiratory syncytial virus infection</td>
<td>Pathogenic</td>
<td></td>
<td></td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>Bacillus subtilis exposure; hypersensitivity pneumonitis</td>
<td>Protective</td>
<td></td>
<td></td>
<td></td>
<td>31</td>
</tr>
<tr>
<td>Coxsackievirus B3-induced myocarditis</td>
<td>Protective</td>
<td>Protective</td>
<td>Pathogenic</td>
<td>(proinflammatory)</td>
<td>32</td>
</tr>
<tr>
<td>Experimental autoimmune uveitis</td>
<td>Pathogenic</td>
<td></td>
<td></td>
<td></td>
<td>33</td>
</tr>
<tr>
<td>Collagen-induced arthritis</td>
<td>Variable</td>
<td>No effect</td>
<td>Pathogenic</td>
<td>(proinflammatory)</td>
<td>34</td>
</tr>
<tr>
<td>Heymann’s nephritis; adriamycin-induced nephritis</td>
<td>Protective</td>
<td></td>
<td></td>
<td></td>
<td>35, 36</td>
</tr>
<tr>
<td>Allergic AHR</td>
<td>Variable</td>
<td>Pathogenic</td>
<td>Protective</td>
<td>(anti-inflammatory)</td>
<td>12, 37</td>
</tr>
<tr>
<td>Primary IgE response to OVA/alum (vaccination)</td>
<td>Variable</td>
<td>Enhancing</td>
<td>Inhibitory</td>
<td></td>
<td>38, 39</td>
</tr>
<tr>
<td>Subcutaneous melanoma</td>
<td>Protective</td>
<td>No effect</td>
<td>Protective</td>
<td></td>
<td>40; Z. Yin, personal communication</td>
</tr>
<tr>
<td>Environmental exposure (ozone)-induced AHR</td>
<td>Pathogenic</td>
<td>Pathogenic</td>
<td>No effect</td>
<td></td>
<td>41</td>
</tr>
</tbody>
</table>
cells (46). When highly enriched γδ T cells were restimulated in vitro with plate-bound anti-CD3ε and anti-CD28 mAbs, activated γδ T cells lost surface γδ TCR expression while gaining MHC class II. Because of the absence of surface TCR, these cells became essentially “invisible” but could be identified as γδ T cells by intracellular staining for TCR-δ (46). It is thus conceivable that MHC class II+ γδ T cells in vivo have escaped investigator scrutiny because of a loss of TCR expression. Taken together with MHC class II+, the in vitro-restimulated γδ T cells expressed CD40 and CD80, and they were capable of presenting peptide Ags to MHC class II-restricted αβ T cells with specificities for the uvetogenic peptide IRBP1–20 (48) and the encephalitogenic peptide MOG35–55 (49). These data suggest that stimulation of peripheral γδ T cells via the TCR can induce an alternative functional program that converts them (transiently) to APCs. However, activation with cytokines might induce the conversion also (46), and the relative importance of these mechanisms remains to be determined.

Clonal selection in the periphery (stage 3)

Studies in humans (50, 51) and mice (34, 52, 53) suggest that functionally committed γδ T cells can be peripherally selected via TCR-ligand interactions. The putative TCR ligands are still unknown. This peripheral selection appears to be a slow process, perhaps largely limited to chronic disease conditions, and less effective than clonal selection of Ag-specific αβ T cells.

A recent study in the collagen-induced arthritis model in DBA/1 mice illustrates this process (34). In these mice, γδ T cells responded to injections of collagen in CFA, Vγ4+ cells in particular became activated, expanded, infiltrated the joints, and were shown to exacerbate the disease. Intracellular staining showed that the infiltrating Vγ4+ γδ T cells expressed IL-17, a cytokine associated with T cell pathogenicity in several models of autoimmune disease. In the course of this response, the TCR repertoire within the Vγ4+ subset became much more focused, suggesting that the oligoclonal response was driven by a specific ligand (34). The putative ligand driving this peripheral response does not appear to be collagen, but it might be contained within CFA or be induced through inflammation (34).

Two TCR-defined γδ T cell subsets in mice, the DETCs in the skin expressing invariant Vγ5Vδ1 TCRs and the γδ T cells expressing the related invariant Vγ6Vδ1 TCRs, which colonize the mucosa of the female reproductive tract and the lung, resemble clonally expanded γδ T cell populations (“I” in Fig. 1), although their invariant TCR appears to be selected in the thymus. These cells are activated by inducible autologous ligands (54, 55), and they exert relatively uniform functions. The activated DETCs promote epithelial repair and wound healing (26, 56). Vγ6Vδ1+ γδ T cells seem to respond to inflammation (55, 57), might play an immune-regulatory role during pregnancy (58), exert antibacterial activities in the lung, and inhibit the development of pulmonary fibrosis (31). The evolutionary conservation of these pseudoclonal γδ T cell populations in rodents—there is no human equivalent—might reflect a particular need for their rapid responses early in development.

Evidence that the TCR remains involved in all stages of functional development

At the onset of development, TCR-signaling supports the lineage decision between αβ and γδ T cells, with strong signals through the γδ TCR favoring γδ T cell development (3–5). Subsequently, innate TCR interactions with autologous ligands seem to play a role in the functional commitment of γδ T cells (6, 16). It is not yet clear whether such TCR signals determine subset differences in functional commitment (19). However, although still in the thymus, cells expressing different γδ TCRs already exhibit different functional potentials in vitro and in vivo (11). Autologous ligands and their in situ expression patterns in the thymus might be detectable using soluble variants of the γδ TCRs in question, as has been demonstrated in principle in vitro (59, 60).

Polyclonal activation and functional induction of committed cells in the peripheral lymphoid organs do not necessarily involve the TCR and might be accomplished with cytokines alone. However, γδ T cells at this stage can be activated via the TCR, with subsequent changes in function. Most obviously perhaps, the polyclonal conversion to Ag-presenting functions in vitro can be induced by TCR engagement (46). A role for poly- or oligoclonal TCR engagement is also suggested by data linking the expression of certain VγVδ pairs with distinct functions. Thus, only Vγ1Vδ5+ cells promote AHR in mice hypersensitized to OVA, and Vγ1Vδ6+ γδ T cells express a unique cytokine profile when compared with other Vγ1+ cells (8, 9). The ability of polyclonal Vγ1+ hybrids to secrete cytokines “spontaneously” suggests that their TCRs might detect self-determinants (21, 61–64).

Finally, clonal expansion in the periphery implicitly involves TCR-ligand interactions, but putative ligands remain to be identified.

Terms of functional engagement

Early and very rapid responses of γδ T cells were found both in models of infection and exposure to injury. Thus, the influence of γδ T cells can be detected within a few hours of exposure to ozone, in this case mediating nonspecific AHR (41). In this short time frame, expansion of γδ T cells is not expected to play a role in their function. In contrast, γδ T cells can undergo large expansions, and the largest expansions were found relatively late in infectious and chronic inflammation, with several 100-fold increases of local γδ T cell populations (31, 34). During inflammation, γδ T cells often assume a regulatory role, as was first suggested in a model of pulmonary infection with influenza virus (65), and later demonstrated in mice infected with Listeria monocytogenes (66). In Listeria infection of the liver, γδ T cells were found to be required for the resolution of neutrophilic inflammation and the subsequent infiltration of macrophages (67). However, the same γδ T cell types that respond in infectious inflammation can also respond in sterile inflammation (55). Elegant studies with γδ T cells in the skin expressing an invariant TCR revealed that these cells respond locally, and very rapidly, to tissue injury (27). Histological analyses of recent skin wounds showed activated γδ T cells proximal to the wound edge, and further studies determined that the γδ T cells must be able to recognize keratinocytes (68) and induce them to produce hyaluronan, which in turn attracts macrophages that are instrumental in the repair process (26, 69).

However, the influence of γδ T cells is also evident in the absence of injury and inflammation, most notably perhaps in B cell development. That γδ T cells can provide B cell help and support Ab production in immunized or infected mice has been known for some time (70, 71). There is also evidence that they might regulate peripheral levels of specific Abs (38,
least some of these cells appear to be capable of recognizing and increase vastly in numbers as the placenta develops (58). At 56). Apparently, this function is so important that it justifies in which they reside. Perhaps the most impressive example of likely that they also have specific functions related to the tissues variant gd sequences for immune functions. Even prior to birth, of productive tract in female mice harbors a distinct population were shown to be required for host resistance against this pathogen (78). In contrast, in adult mice, T cells in young mice might be due to an early Th2 bias of these cells so that gd T cells come to function as a Th1 substitute (79). Human neonates harbor highly active gd T cells. By comparison with gd T cells, these cells exhibit stronger, pleiotropic functional responsiveness, and they lack deficits in IFN-γ production present in neonatal αβ T cells (80). The gd T cells in infants respond strongly to immunization with bacillus Calmette-Guérin vaccine (81), and environmental factors are likely to shape the neonatal repertoire of gd T cells (82), with possible long-term consequences for immune functions. Even prior to birth, gd T cells might protect the developing organism. The reproductive tract in female mice harbors a distinct population of gd T cells (83). During pregnancy in mice, gd T cells increase vastly in numbers as the placenta develops (58). At least some of these cells appear to be capable of recognizing determinants on trophoblasts (84). Whether such cells play an immune-regulatory role or perhaps protect the fetus against infections remains to be determined (85, 86).

Because gd T cell subsets are locally segregated, it seems likely that they also have specific functions related to the tissues in which they reside. Perhaps the most impressive example of this is the DETCs in rodents, which selectively colonize the epidermis and play a distinctive role in wound healing (26, 27, 56). Apparently, this function is so important that it justifies the existence of an entire gd T cell subset expressing an invariant gd TCR (Vγ5/Vδ1) (87). Whether these cells are also functionally homogeneous remains to be tested rigorously (88).

A second type of γδ T cell in mice and rats expressing an invariant TCR (Vγ6/Vδ1) also has local functions in the tissues. In contrast to the DETCs, however, these cells form smaller steady-state populations, which expand to a much larger size only when their functions are required (57). Cells expressing Vγ6/Vδ1 invariant γδ TCRs in the lung (89) expand during chronic exposure with live bacteria (31). Importantly, cells within this subset help preventing pulmonary fibrosis (90). Vγ6/Vδ1 TCR+ cells also expand in nephritis of mice and rats (35, 36, 91) and in testicular inflammation in mice (55), in either tissue with a protective effect. The heterogeneous γδ T cells in the lymphoid tissues likely have multiple functions. For example, Vγ1+ cells seem to play a role in driving and regulating background levels of B cell differentiation (39, 73, 74), without apparent need for stimulation. When the immune system is challenged through vaccination or during infections (70, 71), they continue to support B cell differentiation, but now the help from αβ T cells becomes dominant (39). The γδ T cells, which can be found in the lymphoid organs, reappear in the peripheral nonlymphoid tissues where they can be engaged to functionally (Table 1). Vγ4+ cells, for example, contain inducible regulators of lung function, capable of inhibiting bronchoconstriction (43). They also contain inducible proinflammatory effectors, as demonstrated in mouse models of coxsackievirus B3 infection (32, 92), of respiratory syncytial virus infection of the lung (30), and of collagen-induced arthritis (34). Vγ1+ cells in the lymphoid tissues tend to oppose the effects of Vγ4+ cells in the tissues (12, 32, 39), though not always. Besides Vγ4+ and Vγ1+ γδ T cells, there are other γδ T cells in the lymphoid tissues (e.g., up to 50% of splenic γδ T cells), whose functions have not yet been studied separately. Investigations of such cells in mice likely will broaden the perspective of distinct γδ T cell functions. In contrast, the main experimental source of human γδ T cells continues to be peripheral blood, which contains a more limited spectrum of γδ T cells (93).

**Is participation in the stress response a distinguishing function of γδ T cells?**

The idea that γδ T cells play a key role in immune surveillance of stress in the tissues can be traced back to early days in this field of research (94), and it continues to stimulate speculation. A comprehensive analysis of this idea has been recently published by A. Hayday (19), who concluded that γδ T cells indeed play a significant role in the immune responses to stress. However, γδ T cells are by no means the only lymphocytes capable of recognizing and responding to cellular stress. Furthermore, there are constitutive γδ T cell functions that are difficult to reconcile with a focus on cellular stress, because they occur under steady-state conditions. An example is the already mentioned role of γδ T cells in B cell differentiation and the development of Abs. Although earlier studies showed an involvement of γδ T cells in B cell differentiation and the development of Abs, recent observations suggest a far more critical influence of γδ T cells on the development of polyclonal noninduced Abs (39, 73, 74), with potential downstream effects on immune competence (97). Moreover, assuming that the immune responses to stress are immediate and polyclonal, the slow peripheral selection of oligo- or monoclonal γδ T cells (34, 98) does not fit well either.

**Functional balance**

Comparisons of the roles of Vγ1+ and Vγ4+ γδ T cells now have been made in a number of mouse models of disease (Table 1), and the functional contributions of these subsets often appear to be opposed. Thus, when cells contained within one subset exacerbate disease pathology, cells within the other diminish it (12, 28, 29, 32, 33, 37, 40) (Z. Yin, unpublished results). Functional equilibrium may be reached at different levels, depending on external influences. For example, we found that airway allergen challenge strengthens the IgE-suppressive capability of Vγ4+ cells while at the same time diminishing the IgE-enhancing capability of Vγ1+ cells (39). It is still unclear whether the example of Vγ1+ and Vγ4+ γδ T cells can be generalized. Perhaps functional equilibrium is also achievable between cell types of less closely related lineages (e.g., γδ T cells and αβ T cells). In any case, one lesson from these studies is that depleting or reconstituting total γδ T cells might reveal little in terms of functional effects when functions are balanced, and the full regulatory range of these populations can easily be missed (38, 39, 42, 75).

**When and where γδ T cell functions are needed**

Because γδ T cells are the first T lymphocytes to arise in ontogeny (76, 77), it seems likely that they play an important role in immune protection early in development. Studies in mouse models and with human cells support this notion. Specifically, in young mice infected with Eimeria vermiformis, an intestinal parasite responsible for coccidiosis, γδ T cells were shown to be required for host resistance against this pathogen (78). In contrast, in adult mice, αβ T cells are both necessary and sufficient for protection. The relative ineffectiveness of αβ T cells in young mice might be due to an early Th2 bias of these cells so that γδ T cells come to function as a Th1 substitute (79). Human neonates harbor highly active γδ T cells. By comparison with αβ T cells, these cells exhibit stronger, pleiotropic functional responsiveness, and they lack deficits in IFN-γ production present in neonatal αβ T cells (80). The γδ T cells in infants respond strongly to immunization with bacillus Calmette-Guérin vaccine (81), and environmental factors are likely to shape the neonatal repertoire of γδ T cells (82), with possible long-term consequences for immune functions. Even prior to birth, γδ T cells might protect the developing organism. The reproductive tract in female mice harbors a distinct population of γδ T cells (83). During pregnancy in mice, γδ T cells increase vastly in numbers as the placenta develops (58). At least some of these cells appear to be capable of recognizing determinants on trophoblasts (84). Whether such cells play an immune-regulatory role or perhaps protect the fetus against infections remains to be determined (85, 86).
However, the response to stress likely is one of several natural responses that can be achieved with human beings. Studies in mice already have generated a far more comprehensive picture of T cells that modulate airway hyper-reactivity. J Immunol. 186: 2657–2679.

Disclosures
The authors have no financial conflicts of interest.

References


Conclusions
Animal models and especially mouse models of disease provide some γδ T cells subsets and their functions in a manner that is not achievable with human beings. Studies in mice already have generated a far more comprehensive picture of γδ T cell functions than could be obtained with human cell culture, and they are likely to provide first-hand information in the future. Because differences between γδ T cells in primates and rodents exist, any finding in mice must be validated in humans, but mice and other animal models remain irrelevant as discovery tools.

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