Specialized Antitumor Functions for Skin $\gamma^\delta$ T Cells

Wendy L. Havran

*J Immunol* 2018; 200:3029-3030; doi: 10.4049/jimmunol.1800356
http://www.jimmunol.org/content/200/9/3029

Supplementary Material
http://www.jimmunol.org/content/suppl/2018/04/23/200.9.3029.DC1

References
This article cites 32 articles, 9 of which you can access for free at:
http://www.jimmunol.org/content/200/9/3029.full#ref-list-1

Why *The JI*? Submit online.
- **Rapid Reviews!** 30 days* from submission to initial decision
- **No Triage!** Every submission reviewed by practicing scientists
- **Fast Publication!** 4 weeks from acceptance to publication

Subscription
Information about subscribing to *The Journal of Immunology* is online at:
http://jimmunol.org/subscription

Permissions
Submit copyright permission requests at:
http://www.aai.org/About/Publications/JI/copyright.html

Email Alerts
Receive free email-alerts when new articles cite this article. Sign up at:
http://jimmunol.org/alerts
A central role for T cells in an immune response was well known, and their functional characterization proceeded for many years in the absence of molecular identification of the TCR. It was known that T cells could only see Ags presented on the surface of another cell and that recognition of MHC molecules was also required. Whether this was achieved through T cell expression of separate receptors for Ag and MHC or through a single receptor with dual recognition was the subject of much debate. The mid-1980s was an exciting time for T cell biologists, with isolation and molecular characterization of the TCR genes finally resolving the controversy and demonstrating a single TCR composed of α- and β-chains (1–5). However, a new controversy arose with the unexpected identification of a third TCR gene designated as γ (6). This was described in a Nature “News & Views” article in 1984 as “one more receptor gene than the protein data had led us to believe that we needed” (7). New controversy and debates ensued over the next two years on the potential role of γ until two groups reported expression of the γ-gene product on the surface of human T cells paired with a putative δ-chain (8, 9). Subsequent reports confirmed that γδ T cells were a distinct cell lineage, and the final piece of the molecular puzzle was in place with the identification of the δ-chain gene in 1987 (10).

In contrast to αβ T cells, for which rules governing Ag recognition and immune functions were described long before TCR genes were identified, the existence of a γδ TCR was unexpected, and to date, a paradigm for Ag recognition remains elusive. Little was known about specific functions of γδ T cells because of low numbers of these cells in the blood and lymphoid organs, the traditional sites for T cells. The authors of the featured Pillars of Immunology article (11) demonstrated a novel functional role for γδ T cells in skin tumor surveillance. Interestingly, γδ T cells were found to preferentially reside in epithelial tissues, including skin, intestine, and lung, where they express tissue-specific TCR with no or limited diversity (12). These body surfaces encompass large surface areas, making γδ T cells a major subset when considering all body sites. The localization to barrier tissues and limited TCR diversity led to the proposed function of γδ T cells in surveillance for stress signals upregulated in response to tissue damage or disease (13–16).

Two dermatology groups described a population of Thy-1+ cells with a highly dendritic morphology—dendritic epidermal T cells (DETC)—that were present in murine epidermis (17, 18). These cells were subsequently found to express a canonical Vγ3Vδ1 TCR [nomenclature according to Garman (19)] and to exhibit cytolytic activity in vitro (20–22). In this Pillars of Immunology article (11), the Tigelaar and Hayday labs postulated that epithelial resident γδ T cells, including DETC, recognize and control tumor development by recognition of stress signals induced during development of cutaneous malignancies. They showed that mice lacking γδ T cells exhibited increased susceptibility to three different murine models of squamous cell carcinoma (SCC) (11). Injection of PDV carcinoma cells led to development of increased numbers of tumors in TCRδ−/− compared with wild-type mice but no effect on tumor latency, in contrast to reduced latency in TCRβ−/− mice. Similarly, in two chemical carcinogen models, the absence of γδ T cells led to greater numbers of TCRδ−/− mice developing tumors compared with wild-type mice. In addition, more papillomas progressed to carcinoma tumors in mice lacking γδ T cells. These results showed, for the first time, that γδ T cells can make unique contributions to prevent tumor progression in vivo.

MHC class I–related chain A (MICA) and MHC class I–related chain B (MICB) were previously identified as stress ligands for human intestinal Vδ1+ T cells and can be recognized by the human Vδ1 TCR and NKG2D (23). MICA and MICB are upregulated on human epithelial carcinoma cells, and human Vδ1+ T cells were able to kill MICA+ and MICB+ tumor cell lines in vitro (24). Although MICA and MICB are not expressed in the mouse, Girardi et al. (11) postulated that murine skin tumors will also express NKG2D ligands (25, 26). The study elegantly showed expression of NKG2D on DETC and upregulation of MHC class I–related proteins Rae-1 or H60 on PDV tumor cells as well as on chemically induced skin tumors (11). Surface plasmon resonance analysis demonstrated direct binding of Rae-1 to NKG2D, and Ab blocking studies demonstrated a key role for NKG2D in skin tumor killing assays. Together, these results were the first to conclusively demonstrate in vivo antitumor activities for γδ T cells and, together with studies from the Groh and Spies group (23, 24), showed that NKG2D ligands expressed by tumors are key stress-induced molecules directing the cytolytic functions of γδ T cells.

Despite the progress in our understanding of γδ T cell biology made possible by the featured article and others, a continuing frustration in the γδ T cell field is the lack of...
a paradigm for TCR Ag recognition. This report did not directly address expression of TCR ligands by cutaneous tumors, although addition of anti-γδ TCR Abs significantly inhibited killing of PDV tumor cells by DETC (11), supporting a role for TCR-mediated signals. Identification of additional stress ligands for tissue-resident γδ T cells remains an area of active investigation. TCR ligands may be tissue-specific and rapidly upregulated in response to any type of tissue stress to initiate activation of these innate-like TCRs. However, it is possible that some coreceptor ligands (such as NKG2D ligands) may be differentially upregulated in response to different types of tissue stress, such as tumors, wounds, and infections. This would be a potential mechanism by which a T cell population with limited diversity could fine-tune an effector response. These molecules would then be potential candidates for therapeutic targeting.

This *Pillars of Immunology* article was the first of a series of articles by the Girardi, Tiggelaar, and Hayday groups (27–30) investigating roles for γδ T cells and NKG2D ligands in tumor immunosurveillance. This body of work has clear relevance for potential treatment of human epithelial malignancies. SCC is the second most common malignancy (after basal cell carcinoma), affecting up to 1 million patients in the United States annually (31). Although most SCC lesions are successfully treated by surgical removal, metastasis to regional lymph nodes occurs in ~5% of SCC patients and is associated with significant morbidity, demonstrating a need for additional treatment options. Other epithelial malignancies, such as metastatic melanoma, colorectal cancer, and lung cancer, affect fewer patients but are often resistant to current treatments, resulting in poor survival rates. To date, most therapeutic strategies for epithelial malignancies have largely ignored γδ T cells. The preferential localization of γδ T cells in epithelial tissues—key sites of tumor development—make them attractive targets for therapeutic intervention. Of interest, γδ T cells were recently shown to be the most significant favorable prognostic tumor-infiltrating leukocyte population across 25 human cancers (32). This highlights the need to expand on the seminal work of Girardi et al. (11) to further characterize mechanisms that regulate γδ T cell activation and antitumor functions.

**Disclosures**

The authors have no financial conflicts of interest.

**References**