Intestinal γδ-TCR T cells: be specific!

In the inaugural issue of *Mucosal Immunology*, the News & Highlights section heralded the conquering of the frontiers of the immune system. The phrase "frontiers of the immune system," aimed at the mucosal immune system, was coined in 1988 by Charlie Janeway in a *Nature* News and Views article[1] discussing a paper in which γδ-TCR (T-cell receptor) T cells were shown to be a major component of the intestinal intraepithelial lymphocyte (IEL) compartment.[2] (In the interest of full disclosure, I am proud to say that the publication being discussed came from my laboratory at the Upjohn Company.) Other papers describing γδ-TCR IELs soon followed.[3,4] At that time, few reagents for characterizing γδ-TCR expression in the mouse were available, although several monoclonal antibodies specific for all γδ-TCRs or for various γ-TCR and δ-TCR variable regions were soon generated (thanks in large part to Armenian hamsters!). These reagents allowed a more complete characterization of γδ-TCR T cells in a variety of tissues, including the thymus, secondary lymphoid tissues, skin, lung, reproductive tract, and intestine. These were certainly halcyon days for γδ-TCR T-cell immunology, and many outstanding papers were published. Several conundrums surrounding γδ-TCR T-cell biology became evident during this time, including the large number of circulating and tissue γδ-TCR T cells in chickens and ruminants, the monoclonality of certain γδ-TCRs in specific tissues with apparent high levels of TCR diversity in other sites, the constitutively activated state of intestinal γδ-TCR IELs, and the apparent extrathymic origin of γδ-TCR IELs. The underlying reasons for these and related phenomena have yet to be completely elucidated, although progress has been made in some areas (e.g., at least some γδ-TCR IELs definitely mature extrathymically).[5]

Despite a substantial outlay of resources, some of us eventually came to a wall that seemed insurmountable, and many a junior researcher was dashed upon the rocks or diverted to other topics (as was my laboratory). Hardier researchers have shown dogged determination and continue to chip away at the problem: namely, what is the specificity of γδ-TCR cells and what is the nature of the ligands that the γδ-TCR recognizes? The few ligands that have been identified are generally "nontraditional"—at least as compared with those for αβ-TCR T cells—and run the gamut from stress-induced "self-antigens," including nonclassical major histocompatibility complex molecules, to nonpeptide bacterial products.[6,7] The inability to identify γδ-TCR antigens continues to plague the field today. Nevertheless, although it is undeniable that γδ-TCR T cells can provide protection against tumors and infection, the specificity of these γδ-TCR cells remains enigmatic. Indeed, a recent article in *Immunity* is titled "γδ T Cell Receptors Without a Job."[8] This article was written in response to reports describing a novel mechanism for triggering interleukin (IL)-17 production by γδ-TCR T cells.[9,10]

In the absence of apparent TCR triggering, peripheral γδ-TCR cells respond to TLR ligands or IL-1 and IL-23 by producing IL-17. IL-17 is important in protection against infection, and γδ-TCR cells contribute to this protection by, among other effects, enhancing neutrophil recruitment. Intestinal lamina propria, lung, and liver γδ-TCR cells are also known to produce IL-17, especially in response to bacterial infection or colonization,[11–13] but whether this requires TCR engagement is not known. Does the lack of a requirement for TCR engagement indicate that these γδ-TCR cells are memory cells of a sort, perhaps preprogrammed in the thymus similar to "natural" regulatory T cells[14–16]? Or have they encountered antigens derived from normal flora, food antigens, or stressed tissues? In the case of the γδ-TCR cells in the IEL compartment, at least some of which develop extrathymically, they are constitutively activated in part by bacterial flora, so they may be good candidates for IL-17 production. The γδ-TCRs of the IEL compartment are composed of multiple Vγ and Vδ regions and exhibit a high level of TCR junctional diversity, suggesting the ability to recognize a diverse array of antigens. However, systematic studies of the specificity of γδ-TCR IEL cells have yet to be reported. Thus, although there have been hints of possible functions and reactivities for the intestinal γδ-TCR IEL population, their TCR specificities remain mysterious. Perhaps given the current fervor over IL-17, as well as the heightened interest in the composition and physiological effects of intestinal flora, the role of γδ-TCR T cells in mediating function will come to the fore. It may be time to jump back on the bandwagon!

Leo Lefrançois, Associate Editor

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