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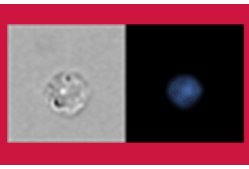
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Pillars of Immunology

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When Less Is More: T Lymphocyte Populations with Restricted Antigen Receptor Diversity

Mitchell Kronenberg

Two papers highlighted here as *Pillars of Immunology* led to the discovery, more than two decades ago, of expanded T lymphocyte populations with a limited TCR α-chain diversity (1, 2). This would be a mere factoid if these specialized cell populations were not highly conserved, suggestive of their important function, if they did not behave differently from mainstream T lymphocytes, and, also, if they did not influence many immune responses. One of these populations is known as type I or invariant NKT (iNKT) cells, and the other is known as mucosal-associated invariant T (MAIT) cells.

The first characterized population of T lymphocytes with an invariant Ag receptor was mouse γδ T cells that are found in several epithelial tissues, particularly the skin (3). This population is not found in humans, and its lack of conservation stands in contrast to iNKT and MAIT cells, which are found in most mammals (4). iNKT cells and MAIT cells are expanded T lymphocyte populations, with members of each population having identical or similar Ag specificities. Many of these cells are found in tissues such as liver, lung, and intestine, and, importantly, these lymphocytes respond rapidly to Ag stimulation, similar to innate immune cells (4). Key findings in understanding their specificity that came later include the discovery of their selecting class I–like Ag-presenting molecules, CD1d for iNKT cells (5) and MR1 for MAIT cells (6). Another key finding was the identification of the nonpeptidic molecules these class I–like molecules present: glycolipids and phospholipids for iNKT cells (7) and microbial riboflavin metabolites for MAIT cells (8). Although it is difficult to identify a singular finding regarding these two interesting T cell populations, it is important to highlight the early discovery of lymphocytes with restricted TCR α diversity, which helped to catalyze the broad interest in these cells.

Masaru Taniguchi and colleagues (9) had characterized a mouse TCR α-chain joining Vα14–Jα281, later Vα14–Jα18, which was used by a number of T cell hybridomas reported to be specific for keyhole limpet hemocyanin and alleged to have suppressor activity. This is the well-known TCR α-chain that characterizes iNKT cells. In the study highlighted from 1990 (1), they used PCR with Vα14 and Cα primers, followed by DNA sequencing, to show that the rearrangement found in the hybridomas was prevalent in the spleen and thymus. They corroborated this with RNase protection assays using probes that spanned the Vα–Jα junction, and they estimated that cells expressing this α gene rearrangement were surprisingly prevalent, that is, 0.7% of mouse thymocytes and 1.5% of splenic T cells. The transcript appeared in cells from mice at 2 wk of age and reached a plateau at 5 wk. These findings match reasonably well with later measurements of iNKT cells done with CD1d tetramers (10, 11). Haruhiko Koseki et al. (1) also observed that the abundance of mRNA from this rearrangement did not vary when congenic mouse strains with different MHC haplotypes were analyzed. They therefore suggested that cells with this TCR recognize a nonpolymorphic class I molecule, and they offered the prescient speculation that these cells might be autoreactive. T cell suppression, as described in the 1980s and earlier, has for good reasons not survived as part of the canon of contemporary immunology, and based on their TCR, the suggested keyhole limpet hemocyanin specificity of the hybridomas in the paper by Koseki et al. is not likely. Regardless, most of the findings described by Koseki et al. are on the mark in establishing the unexpected prevalence of the Vα14–Jα14 TCR rearrangement.

Missing from this study, however, was insight into the type of T cells expressing this invariant α-chain. Olivier Lantz and Albert Bendelac (12) later made the first characterization of the thymocytes expressing a Vα14–Jα18 TCR. They showed that these cells are a subset that requires β_2-microglobulin and therefore is dependent on class I Ag-presenting molecules. They also demonstrated that these cells express the NK receptor NK1.1 along with a high level of CD44, a marker for activated or memory cells. Furthermore, they are either $CD4^+$ or $CD4^-CD8^-$ double negative (DN) (12). By analyzing hybridomas made from $CD44^{high}CD4^+$ or DN thymocytes, they found that the TCR β-chain genes they expressed rearranged Vβ8.2, Vβ7, or Vβ2, but with diverse Vβ–Jβ sequences.

The second *Pillars of Immunology* paper reports research on human cells from 1993 by Steven Balk and colleagues (2). In this report, Steven Porcelli et al. focused on DN αβ TCR lymphocytes because of a possible connection of these cells to autoimmune disease pathogenesis, as well as the finding that some DN T lymphocytes were reactive to mycobacterial Ags presented by the nonclassical class I molecule CD1b (13). They used denaturing gel electrophoresis, quantitative PCR, and cloning and sequencing to show that two invariant TCR rearrangements were prevalent in DN T cells from multiple

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Abbreviations used in this article: DN, double negative; iNKT, invariant NKT; MAIT, mucosal-associated invariant T.

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donors. One of these joined Vα24 to JαQ (Vα24–Jα18 or TRAV10–TRAJ18), subsequently identified as the rearrangement in human iNKT cells (14). Antonio Lanzavecchia and colleagues (15) reported a similar finding based on the analysis of DN αβ TCR lymphocytes essentially at the same time. All of the laboratories involved noted the sequence similarity of this human TCR α rearrangement to the one reported earlier in mice (2, 12, 15). Interestingly, Porcelli et al. found a second prevalent rearrangement in the DN T cells, joining Vα7.2 to IGRJa14, later called Jα33 (TRAV1-2–TRAJ33). This rearrangement had a greater degree of diversity in the Vα–Jα junction encoding the CDR3 region than did the iNKT cell α-chain, and it is the one that Lantz and colleagues (16) later showed is characteristic of MAIT cells. Porcelli et al. demonstrated that the DN αβ TCR population has preferential transcription of a rearranged Vβ11 segment, which is similar to mouse Vβ8.2, the most prevalent Vβ gene expressed by mouse iNKT cells. Vβ2 and Vβ13 also were enriched in DN αβ T cells, and these later were shown to be prevalent in MAIT cells (16). Analysis on polyacrylamide gels indicated that, as in the mouse, the β-chain rearrangements were more diverse than those of the α-chains. This study only analyzed polyclonal DN αβ T cells, however, and therefore it could not determine which TCR β-chains were paired with the α-chains with limited diversity. In a second study from the Lanzavecchia group, Paolo Dellabona et al. (17) produced Abs to Vβ11 and Vα24 and showed that these are coexpressed in human DN T cells.

Although innate immune cells respond very rapidly, evolution does not shy away from redundancy in the immune system, and it has generated prevalent populations of T lymphocytes with a highly restricted Ag receptor diversity, tissue residence, and rapid response kinetics, similar to innate immune cells. Although there are some striking similarities between the two populations, iNKT cells are prevalent in mice and MAIT cells are relatively infrequent, whereas the opposite pattern holds true in humans, with MAIT cells being much more prevalent (4). Another distinction is that iNKT cells can respond to microbial and self-antigens but do not completely depend on microbes for their homeostasis (18), whereas MAIT cells are known to respond only to microbial metabolites of riboflavin (8), and unlike iNKT cells, they are absent in germ-free mice (6). Furthermore, recent evidence has suggested that there are functional subsets of iNKT cells analogous to Th1, Th2, and Th17 $CD4^+$ helper T cells (19, 20), whereas MAIT cells do not produce Th2 cytokines (21). Understanding the myriad effects of iNKT cells on the immune system remains an area of very active investigation, and although there are many fewer studies of MAIT cell function, this area is emerging, aided by the development of defined Ags and MR1 tetramers (22). The findings in these seminal papers from two decades ago helped to open up the vigorous fields of research on these two specialized lymphocyte populations by making the unexpected observation that some αβ TCRs are surprisingly prevalent in all individuals.

Disclosures

The author has no financial conflicts of interest.

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