T CELLS

γδ T cells: pre-determined specificity?

The known ligands of γδ T cells are diverse and are recognized directly, without the requirement for antigen processing and presentation. However, only a few γδ T-cell ligands have been defined, and it is unclear how they are recognized by γδ-T-cell receptors (γδ-TCRs). Now, reporting in *Science*, Sunny Shin and colleagues show that a naturally occurring population of γδ T cells have a germline-encoded motif in the complementarity-determining region 3 (CDR3) of the TCR δ-chain, the presence of which correlates strongly with recognition of their ligand. This finding was supported by a crystallography study by Erin Adams and colleagues that was published in the same issue of *Science*.

Previous studies have shown that the ligands for a high proportion (0.1–2%) of γδ T cells in unimmunized mice are the highly homologous non-classical MHC class I molecules T10 and T22, so Shin *et al.* set out to determine how this γδ-TCR repertoire is generated. First, they isolated T22-specific γδ T cells from both the spleen and the small intestine, using a T22-tetramer staining reagent, and determined the sequence of individual γδ-TCRs. Because tissue-specific distribution of γδ T cells correlates strongly with Vγ (variable gene segment of TCR-γ) usage, it has been postulated that Vγ-encoded residues mediate the recognition of tissue-specific antigens. However, Shin *et al.* found that a variety of Vγ and Vδ gene segments were associated with T22-specific TCRs, and after comparing the TCR sequences of T22-tetramer-positive and -negative γδ T cells, they concluded that Vγ usage is reflective of tissue origin rather than antigen specificity.

Although there were no sequences conserved among TCR γ-chains, most T22-specific γδ T cells from the spleen (~40–60%) and intestine (~90%) had a conserved sequence — W-(S)EGYEL — in the CDR3 of TCR-δ, and this sequence was absent in T22-tetramer-negative γδ T cells. The motif was found to be encoded by the Vδ or Dδ1 (diversity) gene segment (W), the Dδ2 gene segment (SEGYE; as γδ-TCRs can incorporate two D segments into a single TCR δ-chain) and a P-nucleotide addition (L), indicating that recognition results from a sequence that is mainly germline encoded (SEGYE).

These findings were supported by the crystal structure of T22 complexed with the TCR of the γδ T-cell clone G8, which was determined by Adams and colleagues. Most of the contact residues between G8 (which also contains the TCR-δ CDR3 motif) and T22 are contributed by the CDR3. Moreover, the CDR3 loop seems to be anchored by the W, G, Y, E and L residues of the identified motif.

This finding is in contrast to recognition by the αβ-TCR, which uses all three CDRs to contact antigen and in which the most crucial residues (in the CDR3 of TCR-α and TCR-β) are not germline encoded but encoded by N nucleotides incorporated during junctional recombination.

The germline-encoded nature of the motif is unexpected given that the possible use of two D regions in TCR-δ provides γδ TCRs with the highest possible diversity of all antigen receptors, as a result of the increased potential for junctional diversity. Shin *et al.* showed that variation in the residues adjacent to the CDR3 motif resulted in the population of T22-specific γδ T cells having a range of affinities for T22. They speculate that this could be useful for flexible responses to the self-antigen T22 and that, if specificity for other antigens is encoded in a similar manner, then γδ T cells are likely to recognize relatively few antigens (compared with B-cell receptors and αβ-TCRs) but at a high frequency.

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References and links

ORIGINAL RESEARCH PAPERS Shin, S. *et al.* Antigen recognition determinants of γδ T cell receptors. *Science* **308**, 252–255 (2005) | Adams, E. J., Chien, Y.-H. & Garcia K. C. Structure of a γδ T cell receptor in complex with the nonclassical MHC T22. *Science* **308**, 227–231 (2005)

IN BRIEF

T-CELL SIGNALLING

A novel E3 ubiquitin ligase TRAC-1 positively regulates T cell activation.

Zhao, H. *et al. J. Immunol.* **174**, 5288–5297 (2005)

When screening for molecules involved in T-cell activation downstream of T-cell receptor (TCR) ligation, Zhao *et al.* identified a cDNA encoding a carboxy (C)-terminally truncated form of an uncharacterized protein. As the full-length protein contained a RING (really interesting new gene)-finger domain at its amino terminus, the authors named the new molecule T-cell RING protein identified in activation screen 1 (TRAC1). Consistent with the presence of a RING-finger domain, TRAC1 had RING-finger-dependent E3 ubiquitin ligase activity. And endogenous TRAC1 functioned as a positive regulator of T-cell activation downstream of TCR ligation. By contrast, C-terminally truncated TRAC1 inhibited TCR-induced CD69 upregulation, indicating the importance of this domain for TRAC1 function.

MAST CELLS

Stem cell factor promotes mast cell survival via inactivation of FOXO3a mediated transcriptional induction and MEK regulated phosphorylation of the pro-apoptotic protein Bim.

Möller, C. *et al. Blood* 26 Apr 2005 (doi:10.1182/blood-2004-12-4792)

Möller *et al.* investigated the molecular mechanisms by which stem-cell factor (SCF) promotes mast-cell survival. SCF induced phosphorylation of forkhead box O3A (FOXO3A) in bone-marrow-derived cultured mast cells (BMCMCs). Consistent with phosphorylation of FOXO3A resulting in its inactivation, SCF prevented expression of BIM (B-cell lymphoma 2 (BCL-2)-interacting mediator of cell death), a pro-apoptotic member of the BCL-2 family, the gene encoding which is a FOXO3A target. Further analysis indicated that SCF also induced phosphorylation of BIM, which has been linked with proteasome-mediated degradation. Together with the observation that *Bim*$^{-/-}$ BMCMCs showed increased viability following SCF withdrawal, these data characterize a mechanism for SCF-regulated mast-cell survival.

ALLERGY

Antigen-specific CD4$^+$ T cells drive airway smooth muscle remodeling in experimental asthma.

Ramos-Barbon, D. *et al. J. Clin. Invest.* 2 May 2005 (doi:10.1172/JCI19711)

The relationship between airway smooth muscle (ASM) growth and T-cell-mediated airway inflammation in asthma is poorly understood. So, to study this, antigen-specific CD4$^+$ T cells were isolated from sensitized rats and transfected with green fluorescent protein before being transferred to naive recipients. After repeated antigen challenge, the transferred cells induced a marked inflammatory response with CD4$^+$ T-cell infiltration in the airways. The infiltrating T cells co-localized with ASM cells and led to increased ASM growth. This T-cell–myocyte crosstalk was also evident *in vitro*: ASM cells proliferated on direct contact with activated CD4$^+$ T cells, and reciprocally, activation-induced T-cell death was inhibited in a contact-dependent manner. These data implicate CD4$^+$ T cells as promoters of pathology in asthma.