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PDZ Domains and the Politics of Polarity in Lymphocytes

In this issue of *Immunity*, Ludford-Menting et al. (2005) show that scaffold proteins previously implicated in the control of epithelial cell polarity also play an important role in determining the macroscopic organization of the engaged T cell.

Signaling and politics have much in common—both are organized processes spanning diverse constituencies that somehow come to consensus and initiate actions while vigorously maintaining the appearance of complete irrationality to the average observer. Making sense of signaling requires a detailed understanding of the elements of the decision process, as well as the design rules that govern the behavior of the interacting constituencies.

T cells encountering a novel environment must make complex decisions regarding the significance of antigenic peptides presented to them. They must weigh the presence or absence of counter receptors, hormonal mediators, cytokines, and their own developmental history in deciding how best to respond. Within the cell, a signaling apparatus of formidable complexity and considerable spatial extent must integrate this information. Because biology borrows from itself as much as it invents, the signaling apparatus of T cells is a patchwork of elements from other biological processes. In this issue, the Russell lab makes a highly fruitful connection between the molecules that determine cellular polarity in epithelial cells and those that shape the antigen response (Ludford-Menting et al., 2005). The molecules in question belong to a relatively large collection of interesting proteins known as the PDZ family, after the initial recognition of a common architecture in the PSD-95, Discs Large, and Zona Occludens 1 proteins (Nourry et al., 2003). Recent studies have demonstrated that PDZ domain proteins facilitate signal transduction in lymphocytes, where scaffold proteins containing PDZ domains stabilize HTLV-1 envelope glycoprotein complexes at the viral synapse, mediate NF-κB signaling, and localize ion channels (Blot et al., 2004; Hanada et al., 1997; Jun and Goodnow, 2003; Lin and Wang, 2004; Xavier et al., 2004).

Adaptor molecules of the PDZ family recognize C-terminal conserved residues of modest complexity, as well as one another; as such, they are well positioned to serve as scaffold proteins to create complex architectures adorned with additional adaptors and enzymes (Songyang et al., 1997). Much has been made of the similarity between the transitory architecture of the antigen-presenting and the antigen-responsive cell in the immunological synapse; but as in many biological analogies, the superficial similarities belie deep differences. In this example we find convincing evidence that a major reorientation of cell shape and polarity attends the antigen response.

The authors have shown that the PDZ domain proteins Scribble, Discs large 1–4, Lgl, Crb3, and PAR3 are expressed in primary T cells. In the resting (or more precisely, in the basal, wandering) state, the Scribble complex trails the cell body in the distal uropod. However, upon contact with an antigen presenting cell bearing an activating peptide, the uropod is disassembled and Scribble localizes to the contact site between cells. Although it would be sensible to assume that this reorganization is triggered by antigen recognition, the bulk of the T cell receptor does not become recruited to the contact zone until somewhat later in the process. That Scribble is a legislator in the cellular parliament is shown by siRNA knockdown experiments, which demonstrate that Scribble hypomorphs have a more rounded shape and less evidence of uropodial extension. In these cells, the distal pole complex (Cullinan et al., 2002) components ezrin, Dlg and CD44 are less localized, suggesting that the Scribble complex plays an important role in polarization of T cell proteins. Scribble hypomorphs display a markedly reduced ability to form stable conjugates with antibody-coated beads, and both CD3 and PKC θ are not drawn to the bead contact site. In well-designed rescue experiments the authors show that expression of an engineered Scribble designed not to be knocked down by the siRNA results in reversion of the rounded phenotype in the presence of the siRNA. The authors also demonstrate that CRIPT peptides, which target PDZ domain 3 of Dlg4, abrogate uropod formation when delivered to the cell with the aid of a protein transduction domain. These data indicate that Dlg4 is also a voting member of the PDZ delegation.

Scribble is a broadly expressed cytoplasmic protein that contains 16 N-terminal leucine rich repeats (LRRs), as well as four PDZ domains (Bilder and Perrimon, 2000). It is a member of the phylogenetically conserved LAP family, whose members are scattered widely through the metazoan lineages. In Drosophila, the Scribble LRR domain has been found to be necessary for both epithelial cell polarity and control of proliferation (Zeitler et al., 2004). In mice, the circle tail mutation that leads to premature termination of Scribble after the second PDZ domain gives rise in homozygous animals to a syndrome of perinatal mortality and profound neural tube defects (Murdoch et al., 2003). Extensive phenotypic pleiotropy is common among PDZ family knockout phenotypes – consistent with their role as important scaffolds – suggesting that progress in understanding the roles of these important proteins will have to await the development of experimentally tractable conditional null alleles.

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