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Gary A. Koretzky

The field of T cell biology was ushered in with a series of discoveries in the 1960s demonstrating that the thymus was not a vestigial organ lacking important biologic function but instead was critical for the host to mount both humoral and cell-mediated immune effector functions (1). Why the thymus was critical for both arms of the adaptive immune system became clear with the subsequent demonstration of two nonoverlapping but functionally interdependent subsets of lymphocytes, later designated B and T cells (2). As reagents were being developed (predominantly mAbs raised against purified cell populations) to distinguish these two lymphocyte subsets, it quickly became clear that neither B nor T cells were uniform in their expression of cell surface molecules. T cells populating the peripheral blood or secondary lymphoid organs were distinguished early on by the mutually exclusive expression of either CD4 (designated originally as T4, L3T4, Ly1, or Leu3) or CD8 (T8, Leu2, or Ly2/Ly3), based on the use of particular mAbs (3). Subsequently, data emerged suggesting that expression of CD4 or CD8 was linked to different T cell functions; in the case of CD4, augmenting the ability of B cells to produce Abs (4), and in the case of CD8, causing direct cytoxicity of infected target cells (5, 6). Whether CD4 and CD8 were merely markers for cells that possessed different functions or were in fact important themselves in mediating these functions was an unanswered question.

Insight into the potential role of CD4 and CD8 came from the seminal discovery that expression of these coreceptors was not linked as much to the effector functions of the different T cell subsets as to the restricting element that initiated the T cell response (reviewed in Ref. 7). The finding that CD4-positive T cells respond to Ag presented by MHC class II proteins [and the subsequent observation of direct binding of CD4 to MHC class II (8)] and that CD8 has a similar relationship to MHC class I proteins (9) also provided important insight into the observation that coligation of either CD4 or CD8 with the TCR could augment effectiveness of the engaged TCR. It was easy to understand why cross-linking the TCR with the coreceptors could stabilize interactions, thus potentiating the ability of the TCR to signal (10–12). In vivo, the impact of CD4 and CD8 on TCR signaling was shown to be, at least in part, through binding nonpolymorphic regions of MHC class II or class I, allowing CD4 and CD8 to act as auxiliary binders to tighten the key interaction between the TCR and peptide within the binding pocket of MHC. However, a number of investigators speculated that, in addition to serving as a means to stabilize interactions, the coreceptors might participate directly in signal transduction, either by initiating unique signals or by affecting signals known to be driven by TCR engagement (13–15). Although many studies using Abs directed against either CD4 or CD8 suggested that these proteins might transduce signals, it was not until the two Pillars of Immunology papers reprinted in this issue of The Journal of Immunology (16, 17) were published that a molecular basis for this action could be proposed.

These two papers came at an extremely exciting time for the community interested in the molecular basis of signal transduction and, for immunologists, how engagement of receptors on the surface of T cells results in cellular activation. Most of the attention in the field was directed toward probing signal transduction events mediated by the TCR itself, where it was just becoming appreciated that ligation of the TCR might, like growth factor receptors, stimulate protein tyrosine kinase (PTK) activity in the cell (18, 19). Unlike growth factor receptors (such as the epidermal growth factor or platelet-derived growth factor receptors), which have intrinsic PTK activity, sequence analysis of the components of the TCR/CD3 complex failed to reveal any potential enzymatic, much less PTK, function. Hence, it was suggested that the TCR might operate by recruiting a cytoplasmic PTK to initiate a signal transduction cascade.

One excellent candidate for the recruited PTK was Lck, a relatively T cell-selective member of the src family of PTKs that was identified (in its oncogenic form) from a T cell lymphoma (20–22). Further studies revealed that Lck is activated in stimulated T cells and led investigators to explore the possible role of this PTK in T cell activation (23). It was this backdrop that stimulated the work described in the two complementary 1988 papers from the Schlossman (16) and Bolen (17) groups. These two reports described biochemical approaches to ask whether CD4 (16) or both CD4 and CD8 (17) were associated with PTK activity. The answer in both cases was yes, demonstrating clearly that in addition to functional extracellular domains (mediating interactions with MHC molecules), the cytoplasmic domains of both CD4 and CD8 were critical for coreceptor function. The finding that CD4 and CD8 participated so directly in both the recognition of Ag/MHC by the TCR (through their binding to nonpolymorphic MHC residues) and in the ability of the TCR to initiate an activation program (by positioning a key proximal signaling element near the receptor) dramatically impacted our concept of the importance of coreceptors in T cell function and set the stage for numerous studies investigating other molecules later identified as key regulators of T cell activation.

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Abbreviation used in this paper: PTK, protein tyrosine kinase.

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As with all good scientific studies, the discoveries made by Rudd et al. (16) and Veillette et al. (17) led to the next series of questions. How did CD4 and CD8 bind lck, and was this interaction direct or indirect? Was the CD4 or CD8/lck interaction absolutely necessary for TCR signaling, or did the juxtaposition of lck with the TCR through CD4 and CD8 merely augment responses to weak Ags? Was lck itself regulated, or was it just localization that dictated its activity as a transducer of TCR signaling? Are there other yet undiscovered functions of CD4 or CD8, or was the biology of these coreceptors solved? How do T cells become activated if they lack both CD4 and CD8? Is it MHC binding and/or CD4/CD8-mediated lck recruitment that is so critical for lineage choice in the thymus?

As the readers are well aware, we have answers to some but not all of these questions. The work described in these two Pillars papers (16, 17), extending from their conceptual framework to the state-of-the-art biochemistry, is important reading for students of modern immunology, as these manuscripts represent an elegant synthesis of ideas and data that took a field to the next level of understanding. Importantly, these papers are prime examples of how seminal discoveries in immune cells have informed the larger biomedical research community, in this case by describing a mechanism by which receptors with no intrinsic enzymatic activity may recruit and use essential cytosolic signaling components.

Disclosures
The author has no financial conflicts of interest.

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