The Journal of Immunology

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J Immunol 2005; 174:1143; ;
doi: 10.4049/jimmunol.174.3.1143
http://www.jimmunol.org/content/174/3/1143

The Journal of Immunology is published twice each month by
The American Association of Immunologists, Inc.,
1451 Rockville Pike, Suite 650, Rockville, MD 20852

Print ISSN: 0022-1767 Online ISSN: 1550-6606.

First Sighting of the Elusive T Cell Antigen Receptor

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In his textbook, *Immunology: The Science of Self-Nonself Discrimination*, published in 1982, Jan Klein stated, "The TCR—the molecule in the T cell membrane capable of specifically binding Ags—is the San Andreas Fault of immunology: here the plates rub against each other and a major 'earthquake' may occur at any moment" (1). Indeed, such a seismic event occurred that year, but in Smithville, Texas, at the University of Texas Science Park, when Allison, McIntyre, and Bloch reported the first biochemical description of the $\alpha\beta$-T cell Ag receptor in *The Journal of Immunology* (2). As reprinted in this issue, using a mAb against a "tumor-specific Ag," Allison et al. described the presence of a glycoprotein on the cell surface of a mouse T cell lymphoma that was composed of two disulfide-bonded subunits, and they proposed that it "may be a clonally expressed epitope of a normal T cell-specific cell surface marker" (2).

In the early 1980s, several laboratories were zeroing in on the elusive T cell Ag receptor. Although some groups proposed that Ig itself or some variant of an Ig molecule was responsible for T cell recognition, there was mounting evidence that this hypothesis was incorrect. However, the assumption that T cells would use the same general strategy as B cells to generate Ag-receptor diversity seemed a good bet. Based on the fact that individual B cells and B cell tumors express a unique Ig "Id" that confers Ag-binding specificity, if T cells behaved in a similar fashion this would provide an experimental approach to identify the TCR. Antisera were generated that would uniquely bind to a particular T cell clone or tumor (i.e., demonstrate "clonotypic" or "idiotypic" binding) or inhibit Ag-specific T cell responses of functional T cell clones (3, 4). Based on the prediction that T cell tumors, like B cell tumors, would express a single unique Ag receptor, Allison et al. immunized mice with the X-irradiation-induced C6XL T cell lymphoma and selected a mAb, designated 124-40, that reacted only with the immunizing T lymphoma, but not other T cell tumors, thymocytes, or splenic T lymphocytes. Biochemical analysis of the Ag recognized by 124-40 mAb revealed a disulfide-bonded heterodimer, consisting of two glycoprotein subunits of 39 and 41 kDa with very distinct isoelectric points: one acidic and the other basic. The conceptual link between this "tumor-specific" Ag on this T cell lymphoma and the TCR on normal T lymphocytes took advantage of the fact that disulfide-bonded protein complexes are easily separated from most cell surface proteins when a heterogeneous mixture of proteins, such as cell surface proteins, are first separated by SDS-PAGE under nonreducing conditions and then run again on another SDS-PAGE gel under reducing conditions. Monomeric proteins, in general, will migrate with the same or almost the same mobility under nonreducing and reducing conditions. Thus, the majority of cell surface proteins, which are not disulfide-bonded to another protein, will form a "diagonal" array of spots on the second gel. However, proteins that are disulfide-bonded together will fall "below the diagonal" on the second gel, because after reduction the individual subunits migrate more rapidly. Goding and Harris (5) had previously used this technique to identify surface Ig and CD8, which appeared "off-diagonal" in the analysis of B and T cells, respectively. Allison et al. noted that the "tumor-specific" Ag on the C6XL T lymphoma demonstrated migration properties similar to "off-diagonal" proteins expressed on normal thymocytes and T cells, but not B cells, and suggested that this protein may represent "a variable-region determinant of a T cell-specific surface component" (2).

My first sighting of the TCR was at the University of California Los Angeles Keystone Symposium on B and T cell Tumors: Biological and Clinical Aspects held at Squaw Valley, California, March 1–5, 1982. At the poster session, Jim Allison presented the experiments published later that year in *The Journal of Immunology*. I clearly recall Jim pointing to the "off-diagonal" spots on the two-dimensional SDS-PAGE gel of splenocytes and thymocytes (Fig. 8, *D* and *E*, in this paper) and testifying "that's the TCR!".

Publications from several laboratories appeared in 1983 reporting the presence of similar glycoproteins on human and mouse T cell clones (6–9). This was also the year when a major "immunological earthquake" indeed occurred on the San Andreas Fault, specifically at Stanford University in Palo Alto, California (and previously at the National Institutes of Health), where Mark Davis and colleagues cloned the mouse TCR β-chain (presented at the International Congress of Immunology in Kyoto, Japan, August 1983). But because of the prior biochemical analysis of the TCR by Allison and others, it was clear that the cloning was only half done; the TCR α-chain gene still needed to be found!

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0022-1767/05/$02.00