

dissociate rapidly enough from the TCR so that a productive signal cannot occur but so that a limiting intracellular effector can nonetheless be depleted (8). TCR engagement by such fast-dissociating ligands induces a unique pattern of intracellular events that is not observed after stimulation with any concentration of an optimal ligand (5, 9, 10). With three concatenated ITAMs and six potential tyrosine phosphorylation sites, CD3- ζ can generate many discrete phospho-species and constitute a very appropriate gauge of the early tyrosine phosphorylation events that follow TCR engagement. Previous reports showed that resting T cells express a 21-kD phosphoform of CD3- ζ (p21) (5, 9). After full stimulation of their TCR, the phosphorylation of p21 increases and a 23-kD species (p23) appears. CD3- ζ phosphorylation also occurs after stimulation with suboptimal TCR ligands. In these cases, however, p21 is produced in large excess over p23.

Using antisera specific for each of the six phosphotyrosine motifs present in CD3- ζ , Neumeister Kersh *et al.* (2) have now deciphered the sites of phosphorylation in p21 and p23 and have made several important observations. First, p21 consists of two or three monophosphorylated ITAMs, an unexpected finding in view of the fact that the ZAP-70 tyrosine kinase is constitutively associated with p21 and preferentially associates with biphosphorylated ITAMs. Second, all six tyrosines in p23 are phosphorylated, allowing it to form a 1:3 complex with ZAP-70 molecules. Third, the reactions leading from basal to full phosphorylation of CD3- ζ proceed in a hierarchal mode and by way of discrete intermediates. These new results suggest that CD3- ζ is a molecular processor that can translate the variations in the half-lives of the TCR-ligand interactions into discrete phosphoforms and, by inference, distinct biological outcomes. Interestingly, as shown by Torigoe *et al.*, when stimulated with high- and low-affinity ligands, the Fc ϵ RI can also produce a diverse range of responses, but without incorporating a transducing subunit with concatenated ITAMs or relying on differential ITAM phosphorylation.

The data of Torigoe *et al.* and Neumeister Kersh *et al.* clearly reveal how antigen receptors translate quantitative differences in ligand binding into qualitatively different biological responses. We are still far from a quantitative understanding of the activation events triggered by those receptors. Nevertheless, the next steps—understanding how these various molecular components interact under the more compartmentalized circumstances of an intact cell—will be a story worth following.

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NOTA BENE: COMPUTERS

Softening Support for Macintoshes

The overall market share of Apple Computer's popular Macintosh system has been declining in recent years, falling from 6.7% of the total personal computer market in 1996 to 4.1% in 1997 (1). Although the popularity of the Macintosh computer remains high in scientific laboratories, even this previously secure niche of Apple's computer market may now be in trouble.

MacSciTech is an independent professional organization promoting use of the Macintosh computer in laboratories. With its broad range of services, the group has its finger on the pulse of scientific Macintosh computing. From MacSciTech's offices comes the popular *SciTech Journal*, which reaches 60,000 scientists and engineers each year, and Web sites geared to Macintosh users in laboratories (www.scitech-comp.org, www.macscitech.org). They also produce CD-ROMs to assist with data acquisition, imaging, math and simulation, earth-space sciences, and engineering, as well as the annual "Top 10 Wish List for Science and Engineering," which is a popular missive to Apple from scientists on their needs for Macintosh software.

MacSciTech has had a long history, which parallels Macintosh scientific usage. It sprang from the Consortium for Laboratory and Industrial Applications of the Macintosh (CLIAM), a trade organization formed independently of Apple to promote the use of the Macintosh in science and engineering. CLIAM's early success convinced Apple to provide financial and personnel resources to technical markets. In 1991, CLIAM spawned MacSciTech, which grew rapidly, ultimately reaching a core membership of 2000 highly influential scientists, engineers, and information systems (IS) professionals.

Partly as a result of MacSciTech's efforts, Macintosh sales have always been disproportionately higher to scientists than to the general public. Industry insiders point out that Macintosh scientific software makes up 40% of some markets, with particular strength in molecular biology, cognitive psychology, and chemistry. Between 1996 and 1997, however, academic market share for Macintoshes fell from 41.6% to 27.1% of total personal computer sales (1). MacSciTech speculates that this may be because IS departments of many research-based organizations do not buy Macintoshes because they require less support than Windows-based computers, threatening the departments' power base (2). Other factors may include Apple's opposition to Macintosh clones and a perceived price differential compared to Intel-based systems.

Another reason for the declining sales may be related to Apple's diminishing support for scientific developers and organizations. In the past, powerful Mac-only software products with unique features, such as Textco's Gene Construction Kit, have provided justification for the purchase of Macintosh equipment in otherwise hostile environments. Reduced support from Apple is driving Macintosh-only software developers to make dual-platform products, removing Apple supporters' historically powerful wedge to justify purchases of Macintoshes. Some developers, such as The MathWorks (3) are dropping Macintosh software support altogether. MacSciTech itself will soon reorganize as SciTech Computing Association, a new entity that will continue to support the Macintosh but will also support UNIX, Windows, and Linux systems. MacSciTech's decision comes on the heels of an announcement by Merck & Co. that it will eventually convert its 6000-plus base of lab Macintosh machines to Windows NT systems (4).

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