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Pillars of Immunology

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The initiation of an adaptive immune response requires the presentation of self-antigens or foreign Ags to Ag-specific T lymphocytes. Seminal studies by R.M. Zinkernagel and P.C. Doherty (1) in the 1970s revealed that T cells only respond to their cognate Ag when it is seen in the context of specific MHC products expressed in the host, a concept called self-MHC restriction. Work by E.R. Unanue (2) and others subsequently showed that protein Ags require processing by accessory cells such as macrophages before they are recognized by MHC-restricted T lymphocytes. These and other findings led to the hypothesis that MHC products can directly bind to protein Ag–derived peptides and present them at the surface of APCs to MHC-restricted T lymphocytes. Although consistent with proposed models of MHC protein structure available at the time, this concept remained unproven until crystal structures of MHC molecules revealed a peptide-binding groove occupied by cell-derived peptides (3, 4).

In addition to conventional Ags, which are recognized by rare T cells (1 in 100,000 or less), some immunomodulatory molecules, called superantigens (SAgs), can stimulate large numbers of T cells (up to 20%) (5, 6). Similar to conventional Ags, SAgs bind to MHC molecules, but how they do so had remained unclear until the work featured in this month's *Pillars of Immunology* article by T.S. Jardetzky et al. (7). This paper documents a beautiful and insightful piece of work resulting from a long-standing collaboration between the laboratories of Don Wiley and Jack Strominger at Harvard University.

The effects of SAgs were originally identified by H. Festenstein (8) in the early 1970s, based on strong primary MLRs between MHC-identical mouse strains, a reactivity that violated the established rules of alloreactivity. The Ags responsible for these responses were called minor lymphocyte-stimulating determinants. About 15 years later, J. Kappler et al. (9) showed that *Mls* alleles could explain the mouse strain–specific deletion of T cells expressing certain TCR V_β chains (10, 11). It turned out that minor lymphocyte-stimulating Ags were encoded by endogenous retroviruses of the mouse mammary tumor virus family (12). Around that time, C.A. Janeway et al. (13) showed that certain exotoxins produced by *Staphylococci* could expand large populations of T cells in a TCR V_β-specific manner.

Since these early studies, SAg activity has been identified for a number of different bacteria and viruses (5, 6) and has been implicated in a wide range of human diseases. Staphylococcal and streptococcal SAgs are associated with food poisoning and toxic shock syndrome, and SAgs from a variety of organisms have been associated with Kawasaki disease and a number of autoimmune disorders. Endogenous exposure to retrovirally encoded SAgs causes intrathymic deletion of T cells expressing TCR V_β chains bound by the relevant SAg, a finding that was instrumental in defining thymic T cell negative selection (9, 10). When mature T cells encounter SAg, they rapidly proliferate and secrete cytokines, after which they are either deleted or rendered functionally inactive (14). Because SAgs generate holes in the TCR repertoire, their response does not benefit the host but instead appears to benefit the pathogen. This has been confirmed for mouse mammary tumor virus, which relies on a virus-encoded SAg produced by infected B cells to stimulate SAg-reactive T cells. In turn, the stimulated T cells produce costimulatory molecules and cytokines that activate the infected B cells, thus amplifying the available pool of infected B cells, which facilitates viral transport to the mammary gland for transmission to the next generation via milk (12). How SAgs might benefit bacterial pathogens is less clear, although it has been assumed that the polyclonal SAg-specific T cell response overwhelms and masks protective Ag-specific responses to the pathogen (15).

Prior to publication of the paper by Jardezky et al. (7), it had been established that SAgs exhibit specificity or preference for certain MHC class II isotypes and allotypes but that SAg-induced T cell responses lack classical MHC restriction (16). In contrast to conventional Ags, which require proteolysis for MHC binding and are not affected by denaturation, binding of SAgs to MHC class II was shown to be sensitive to limited proteolysis and denaturation (17–19). The available evidence further suggested that SAgs do not occupy the peptide-binding groove of MHC class II (20). How then does SAg bind with MHC class II proteins? The main answer to this question provided by Jardezky et al. (7) was simple yet illuminating: SAg binds as an intact protein outside the peptide-binding site of the MHC class II molecule.

Jardetzky et al. (7) reported on the three-dimensional structure of the bacterial SAg, staphylococcal enterotoxin B (SEB), bound to the human MHC class II molecule HLA-DR1, as determined by x-ray crystallography. The structure revealed that SEB binds to the DR1 α-chain via an N-terminal, low-affinity binding domain. Peptide density corresponding to a mixture of self-peptides was observed in the DR1 peptide-binding site. SEB did not interact with the peptide and did

Department of Pathology, Microbiology, and Immunology, Vanderbilt University School of Medicine, Nashville, TN 37232

ORCID: 0000-0001-5275-2309 (L.V.K.).

Address correspondence and reprint requests to Dr. Luc Van Kaer, Department of Pathology, Microbiology, and Immunology, Vanderbilt University School of Medicine, Room A-5301, Medical Center North, 21st Avenue South at Garland Avenue, Nashville, TN 37232. E-mail address: luc.van.kaer@vanderbilt.edu

Abbreviations used in this article: SAg, superantigen; SEA, staphylococcal enterotoxin A; SEB, staphylococcal enterotoxin B; TSST-1, staphylococcal toxic shock syndrome toxin-1.

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not influence the conformation of bound peptide. Details of the SEB–DR1 interface provided a structural explanation for the capacity of SEB to bind distinct DR allotypes and for its hierarchy of binding with distinct human and mouse class II isotypes. The structure also provided insight into the binding of other bacterial SAgs, such as staphylococcal enterotoxin A (SEA) and staphylococcal toxic shock syndrome toxin-1 (TSST-1), to MHC class II. Prior studies had shown that SEA, but not SEB or TSST-1, binds to MHC class II via a zinc-binding site (21). Structural alignment with the SEB-binding interface suggested that TSST-1 binds MHC class II in a manner similar to SEB and that SEA has evolved two class II binding sites, one low-affinity interaction site with the class II α-chain similar to SEB and a second zinc-mediated, high-affinity interaction site with the class II β-chain. These predictions were subsequently confirmed by crystallographic studies (22–24).

The crystal structure also allowed predictions of the ternary SEB–DR1–TCR complex. Residues of SEB previously implicated in interactions with the TCR were shown to be clustered in a region located above and to one side of the MHC peptide-binding groove. Based on mutational analyses and three-dimensional models of the TCR available at the time, Jardetzky et al. (7) proposed an interface involving the hypervariable region 4 of the TCR V_β chain. In this model, SEB was wedged in between DR1 and the TCR, and the CDRs of the TCR were situated over the MHC peptide-binding groove. This model suggested potential interactions between the TCR V_α chain and DR1, but these were nevertheless distinct from the interactions of the TCR with MHC class II molecules during antigenic peptide stimulation. Thus, this model provided structural insight into the capacity of SAgs to stimulate large numbers of T cells in a peptide Ag–independent manner. The key features of this model were confirmed in subsequent reports detailing the crystal structures of the SEB–TCR complex (25) and the ternary SEB–DR1–TCR complex (26). This general model of SAg recognition was also supported by crystallographic studies of other SAg–class II–TCR complexes (27, 28).

SAgs such as SEB induce potent cytokine responses in the host that can lead to shock and even death (6, 15). Because of their stability and potency, these toxins pose a major threat for biological warfare (29). The findings of Jardetzky et al. (7) provided a rational approach to target the interaction between SAgs and MHC class II for the development of vaccines, which has shown significant success (30, 31). A similar approach could be employed to generate antagonists interrupting SAg–class II interactions to treat SAg-mediated diseases, but this goal is yet to be achieved (31).

In summary, the structural studies of Jardetzky et al. (7) provided an elegant explanation for the capacity of SAgs to stimulate large numbers of T cells by binding outside of the peptide-binding cleft of MHC class II molecules. Since these seminal studies, SAgs have continued to intrigue, and they are employed to this day to explore principles of T cell activation, immune tolerance, and immune-mediated disease. The work of Jardetzky et al. (7) also provided a strong foundation for the rational design of interventions targeting SAg-mediated diseases.

Disclosures

The author has no financial conflicts of interest.

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