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Our modern understanding of the way that T cells identify target Ag, as a foreign peptide bound to cell-surface molecules encoded within the MHC, can be traced back to the seminal studies in the mid-1970s by Rolf Zinkernagel and Peter Doherty. In their paradigm-shifting “altered-self” hypothesis from 1974 (1), they proposed that T cells see some form of complex between an MHC molecule and foreign Ag. We now readily accept that this complex is the antigenic peptide embedded within the groove of the MHC molecule; however, for nearly a decade after the enunciation of altered self, the nature of the association between Ag and MHC products was largely opaque. The journey to its ultimate resolution (2) prompted a number of discoveries, often initiating completely new and exciting areas of research. The discovery of cross-priming, primarily by Michael Bevan (3, 4), then working at the Salk Institute in California, and the theory put forth to explain this phenomenon is a case in point.

Bevan contributed to both the clarification of altered self and spin-off discoveries, such as the description of the positive selection that gives rise to a self-restricted T cell repertoire during development in the thymus. For much of this work he used minor histocompatibility Ags as the targets of his CTL. These “minors” arise from allelic variations in background or non-MHC genes, which result in slow graft rejection, as distinct from differences in the MHC genes, which drive vigorous T cell-mediated reactions. His typical system involved immunizing mice with cells that differed at these minor histocompatibility loci (e.g., priming H-2 d BALB/c mice with H-2 d B10.D2 cells) and showing that recognition of the minor Ags (i.e., products of the background non-MHC genes that differed between BALB/c and B10 inbred lines) was dependent on matching the MHC between the animal from which the CTL had been derived and the target of the CTL response (in this case, both had to be H-2 b). The experiments largely confirmed the findings of Zinkernagel and Doherty that one needed a strict histocompatibility match for CTL killing, at least as measured using an in vitro [Cr]-release killing assay. However, when Bevan examined this histocompatibility requirement in animals that had mixed MHC haplotypes, especially in the context of the in vivo environs during priming, the strict restriction rules seemed to break down. Specifically, he immunized F1 mice from a BALB/c and BALB.B mating (H-2 lb) with cells from a B10 (H-2 b) mouse. As expected, this generated CTLs that killed B10 cells, the same cells used during immunization. Based on the altered-self hypothesis, he concluded that the minor B10 Ags were being recognized in complex with the H-2 b MHC elements that were found on the immunizing cells. Unexpectedly, however, he found that priming with the B10 cells also generated CTLs that killed the MHC-mismatched B10.D2 targets (H-2 b), which shared minor Ags but did not carry the appropriate H-2 b-restricting elements. He used the term “cross-priming” to describe this ability to prime across an apparent MHC mismatch between immunizing cell and target cell. Over the course of experiments described in those papers (3, 4), he excluded the possibilities that he was simply observing a cross-reaction at the level of Th cells, that T cells had independent receptors that recognized MHC and Ag and that Ag alone could prime, or that there may have been some form of flexible imprinting of MHC restriction during the in vitro phase of the assay. Ultimately, he settled on the notion that the B10 minor Ags were somehow being transferred from the priming B10 splenocytes to professional APCs in the host that carried both H-2 b and H-2 d restricting elements.

Although such an interpretation might seem obvious today, at the time this was far from the case. The modern immunologist recognizes that priming requires a phalanx of coreceptors, adhesion molecules, and cytokines that are uniquely expressed by professional APCs, such as macrophages or dendritic cells. In addition, we now know that the foreign Ag recognized by the TCR is a peptide fragment produced from intracellular degradation or processing. But the nature of the processing required for class I-restricted presentation and even its existence were completely unknown at the time of Bevan’s original studies. The combined issues of cross-priming, processing, and professional APC involvement intersected again in Bevan’s subsequent contribution to this field. Shortly after Alain Townsend’s stunning demonstration that MHC class I-restricted Ag was a peptide fragment (5), and just before it was shown that its formation involved some form of cytosolic processing not normally accessible to exogenous Ag (6, 7), Bevan proposed that there was a specialized cell uniquely capable of shuttling exogenous Ag into this cross-priming pathway (8), because not all cells had such capabilities. Critically, he argued that such cells would be particularly important in the context of infections confined to peripheral compartments away from the secondary lymphoid organs. Although the macrophage was the APC of choice at the time that Bevan first speculated on the identity of the cell orchestrating cross-priming, years later, and armed with the latest knowledge, he finally identified the dendritic cell subset involved in this event (9). Interestingly, a decade later it is still largely a mystery how exogenous Ag accesses the cytosolic MHC I pathway.

Although cross-priming is generally well accepted by modern-day immunologists, one cannot ignore that debate remains as to its relevance. Rolf Zinkernagel has long maintained that cross-
priming and many of the elements normally associated with it play only minor roles in shaping CTL immunity (10). The final word on cross-priming remains to be written, and arguments about its importance and the mechanisms that underlie its existence will persist for some time to come. In many ways this is the special feature of these papers. Not many of us will put forward a mechanism that will still be the topic of active debate and investigation more than 30 years later.

References