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Altered Self, Altered World

Michael J. Bevan¹



Throughout the 1960s and early 1970s, it was apparent to immunologists that the products of the MHC had a profound influence on immune responsiveness. So-called Ir genes that mapped within the MHC controlled the level of response, high vs low, to certain simple Ags. Another intriguing and well-studied finding—and the easiest T cell response to study in those days—was the whopping reaction of T cells from one individual to the inactivated cells of another member of the species, provided that the responder and stimulator differed at the MHC, a phenomenon referred to as “alloreactivity.” However, no one understood how the effects of MHC genes were mediated, nor why the MHC genes were the most polymorphic loci known.

Toward the end of this age of darkness, results began to appear suggesting that the MHC also controlled Ag-specific interactions between T cells and other cells such as B lymphocytes and APCs. Benacerraf, Kindred, and their colleagues' investigations of T:B interactions, and Shevach and Rosenthal's studies of T:macrophage interactions, had provided evidence for the control of these cellular interactions by the MHC. In April 1974, Rolf Zinkernagel and Peter Doherty, at the John Curtin School in Canberra, Australia, published their finding that CTLs from lymphocytic choriomeningitis virus-infected mice would only kill infected target cells that shared MHC type with the responder strain (1). The beauty of this report was that the restriction could be observed in a simple, short, *in vitro* chromium-release assay involving only T cells and fibroblast targets, but the real bombshell came from Zinkernagel and Doherty 6 months later, when they proposed that the explanation for the MHC restriction was that T cells recognize self-MHC molecules that have been altered in some way by infection or Ag. The altered self hypothesis was born (2).

The paper in *Nature* of August 1974 presented some evidence to support this novel interpretation for the MHC restriction of T cell function. It was known that MHC heterozygous CTL could interact with and kill target cells from either parent. Thus, CTL from an infected AxB mouse killed infected A targets and infected B targets, but not infected C or infected D targets. Zinkernagel and Doherty reasoned that an “intimacy” model, which required T cells to share self-MHC markers with targets, could explain this pattern of specificity. For example, there could be a requirement for a like:like interaction between MHC molecules on the T cell and its target. The virus-specific receptor on the T cell would be separate from this intimacy

receptor, and in all likelihood, the same AxB CTL that killed infected A targets would also kill infected B targets. In contrast, the altered self hypothesis predicted that virus modified the A and B MHC molecules differently and that the receptor on the T cell would be different for each complex and clonally distributed, such that the T cells recognizing infected A targets would be different from those recognizing infected B targets. The experiment aimed at discriminating these two ideas took primed CTL from an AxB mouse and restimulated them on virus-infected presenting cells of either parent A or parent B before assaying the levels of killing against infected A or infected B targets. The results supported the idea that the T cell repertoire contains separate pools of T cells that see Ag in association with each MHC type. The results did not prove the altered self hypothesis because, as the authors pointed out, intimacy receptors for self-MHC could also be distributed clonally on T cells. Nevertheless, the altered self hypothesis just felt correct. For many of us, it was a blinding insight that explained all of the MHC-associated immune phenomena.

It even went further. If T cells bore receptors that were specific for foreign Ag only when seen in the context of a self-MHC molecule, the hypothesis predicted that T cells had found a way to ignore any form of Ag not associated with the surface of a relevant presenting cell, whether it was a target to kill or a B lymphocyte to help. It was the job of Ab to bind and neutralize Ag, and the job of T cells to engage in cell:cell interactions and not be diverted by binding free Ag.

Over the years that followed, it was realized that Th cells, now referred to as CD4 T cells, recognize Ag-plus MHC class II molecules, which are selectively expressed on B cells, dendritic cells, macrophages, and a few other locations. In contrast, CTLs, or CD8 T cells, recognize Ag in association with MHC class I molecules, which are widely expressed, as one would expect, to allow any infected cell to be targeted for cytolysis. The altered self model of T cell recognition also led to the realization that the repertoire of TCRs present in any individual is selected by self-MHC molecules in the thymus to be the assortment of receptors best able to interact with Ag-altered self. It would be quite a few more years before the nature of the alteration of self-MHC by Ag was discovered or the precise pathway of positive selection was revealed. However, MHC restriction of T cell recognition, and the altered self interpretation set the stage for this subsequent work. Who could have predicted that MHC molecules would turn out to be peptide binding grooves that (due to their polymorphism) determine which fragments of protein Ags are presented to T cells? With this elucidation of the nature of altered self came the insight that the universe of Ags for T cells was roughly divisible into two

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separate sources: exogenous Ag, degraded into peptides for class II binding in endosomes to be perused by CD4 T cells, and endogenous or cellular Ag, processed by proteasomes for MHC class I binding and surveillance by CD8 killer cells.

This was the future, and 1974 was the beginning of the revolution. For me it was the most intellectually exciting time to argue and debate with colleagues at the Salk Institute, Mel Cohn, Rod Langman, and Polly Matzinger, about the implications of MHC restriction. It was no surprise when Peter and

Rolf were awarded the Nobel Prize for Physiology and Medicine in 1996 for their classic work.

References

1. Zinkernagel, R. M., and P. C. Doherty. 1974. Restriction of in vivo T cell-mediated cytotoxicity in lymphocytic choriomeningitis within a syngeneic or semiallogeneic system. *Nature* 248:701.
2. Zinkernagel, R. M., and P. C. Doherty. 1974. Immunological surveillance against altered self components by sensitised T lymphocytes in lymphocytic choriomeningitis. *Nature* 251:547.