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Shaping the T Cell Repertoire

Harald von Boehmer

Today immunologists are well aware of positive and negative selection of developing T cells. This was very different almost three decades ago when MHC-restricted Ag recognition by T cells represented an enormous puzzle in the absence of data on the molecular nature of Ag recognition by T cells. It was at this time that Bevan (1) published a report that provided a first hint for positive selection of lymphocytes.

In 1971, the Danish immunologist Niels Kai Jerne had proposed a bold theory designed to explain the high frequency of T cells specific for allogeneic MHC molecules and MHC-linked immune response genes. He assumed that germline-encoded TCRs were specific for MHC Ags of the species and that specificity for non-MHC Ags arose by somatic mutation of TCR genes in cells selected and stimulated by self-MHC molecules to proliferate in the thymus (2). At the time, Jerne did not know about MHC-restricted Ag recognition by T cells. Jerne’s ideas were nevertheless popular with some investigators who dealt with the notion of MHC-restricted Ag recognition by T cells and postulated selection of cells in the thymus according to their TCR specificity as a mechanism to focus the T cell repertoire onto recognition of self MHC. It was Bevan (1) who reported the first experiment that was consistent with such ideas. Previous experiments in chimeric mice generated by injecting T cell-depleted MHC homozygous aa bone marrow cells into MHC heterozygous ab x-irradiated recipients had shown that in this scenario the newly formed aa T cells were tolerant of b MHC molecules. After appropriate immunization, aa T cells specific for non-MHC Ags presented by either a or b MHC molecules occurred in roughly equal frequency. Bevan reversed this setup by injecting MHC heterozygous ab bone marrow cells into x-irradiated MHC homozygous aa recipients and noted that after immunization and in vitro restimulation with minor histocompatibility Ags, the thus-generated cytolytic T cells lysed preferentially targets that presented these minor H Ags in the context of a but not b MHC molecules. Importantly, he also showed that the bias was turned around when the bone marrow cells were injected into an MHC homozygous bb mouse, i.e., now T cells were mostly restricted by b MHC molecules. To explain these results, Bevan adopted and revised Jerne’s idea of T cell repertoire shaping by postulating that T cells recognized MHC molecules “altered” by other surface molecules (altered self). He further proposed that T cells selected by self-MHC molecules in the thymus would proliferate and mutate their receptors such that they would preferentially recognize “altered-self” MHC molecules, which were “similar” to self. In this hypothesis, the focus on self-MHC was imposed by MHC molecules as expressed on radioresistant tissue only as opposed to MHC molecules that were expressed on hemopoietic cells.

Even though the experiments did not directly address that point, Bevan assumed that the repertoire bias was due to intrathymic selection of cells before rather than after immunization. Although Bevan was first to publish data consistent with T cell repertoire selection by MHC molecules, it was his colleague Rolf Zinkernagel who, by letting MHC ab heterozygous bone marrow cells develop in MHC homozygous aa or bb thymus grafts before immunization, separated intrathymic repertoire selection from repertoire selection due to immunization in peripheral lymphoid tissue. Thus, these experiments convincingly showed that the thymus influenced the T cell repertoire before deliberate immunization (3).

The experiments by both Bevan and Zinkernagel had an immense impact on the scientific community in that T cell repertoire selection by thymic MHC molecules became a hotly debated and very controversial issue, even more so because the nature of the TCR was obscure at the time and the proposed selection by MHC molecules suggested to some investigators that MHC molecules and non-MHC Ags could be recognized as distinct entities. This was evident from the title of Zinkernagel’s article “On the thymus in the differentiation of ‘H-2 self-recognition’ by T cells: evidence for dual recognition?” (2). However, since the bias in terms of MHC restriction was often not found to be absolute (there were MHC b-restricted cells that had matured in a MHC homozygous aa thymus), the term “bending” of the T cell repertoire was invented, which perhaps was most appropriate for the original models proposed by Jerne (2), Bevan (1), and Zinkernagel (3), who all invoked expansion of certain cells selected by thymic MHC molecules but not other cells as a mechanism to shape the T cell repertoire.

At the time, Ag processing, peptide MHC-complexes and the nature of the TCR were not yet known. Therefore, it may not be surprising that it would take another decade to discover that the models of Jerne, Bevan, and Zinkernagel were in fact wrong in that all and not only a subset of immature T cells underwent positive selection, i.e., positive selection was required for the generation of all mature T cells. Thus, even T cells specific for allogeneic MHC Ags need to be positively selected by “self” MHC molecules. Furthermore, the mechanism of positive selection involved selective survival and maturation among moribund thymocytes rather than expansion of a selected subset. Finally, somatic mutation in Jerne’s sense played no role in the

1 Editor’s note: This month’s Pillars of Immunology commentary was previously published in the December 1, 2005, issue of The Journal of Immunology, with the incorrect Pillars Article. The commentary is reprinted here with the correct Pillars Article.

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generation of the T cell repertoire. Most importantly, it became evident that positive selection served the purpose to align the specificity of the TCR for class I and II MHC molecules with the CD4$^+$ cytolytic and CD4$^+$8$^+$ helper phenotype of TCR-expressing cells, respectively (reviewed in Ref. 4). This alignment is responsible for the well-known fact that cells presenting cytosolic peptides by class I MHC molecules (virus-infected cells) are destroyed by cytolytic CD8$^+$ T cells, whereas cells presenting peptides generated in the endocytic pathway by class II molecules (Ag-presenting B cells) induce the production of cytokines in responding CD4$^+$ T cells. The differentiation of functionally distinct subsets of T cells with expression of different surface markers was initially described by Cantor and Boyse (5), as well as Kisielow et al. (6), before the notion of positive selection and raised important questions with regard to the alignment of specificity and function of T cell subsets.

Likewise, it took a decade to discover that the T cell repertoire was not only shaped by positive but also by negative selection, i.e., elimination of potentially harmful cells. Furthermore, more recent studies have established TCR-mediated positive selection as a general mechanism of T lineage fate determination, including that of NK T and suppressor T cells (reviewed in Ref. 4).

In this context, the pioneering studies of Michael J. Bevan have to be viewed as catalytic in that their design and interpretation represented a first step in the right direction at a time when little was known about the molecular nature of MHC-restricted Ag recognition by T cells.

References