milestones

Milestone 4

MHC restriction — why do T cells only target some infected cells?

By the early 1970s, the major histocompatibility complex (MHC) had been shown by Snell, Daussett and Benacerraf to be important in the rejection of (MHC-mismatched) transplanted grafts (Milestone 6). This function of the MHC had been characterized through the use of inbred animal strains and also by the comparison of graft rejection among humans. The mouse locus had been named H-2, and similar loci were identified in other animals and birds. The MHC was also known to have weaker associations with infectious disease and autoimmunity, which implied it had unknown functions beyond graft rejection. Tellingly, studies had documented that differences in the MHC affected T cell responses, but how exactly was this working?

This set the scene for Doherty and Zinkernagel to look for what was controlling the T cell response to an infection and why there was a response to a virus-infected cell only when the responding T cell and target cell were in certain MHC combinations. At this stage, there was no clear idea of what the T cell recognized, and the concept of T cells 'seeing' fragments of pathogens was still in the future. Zinkernagel and Doherty used lymphocytic choriomeningitis virus (LCMV) and developed a method of obtaining cytotoxic T lymphocytes (CTLs) from the cerebrospinal fluid of infected mice. These CTLs could cause a lethal encephalopathy in mice, but an experiment by Oldstone, McDevitt and colleagues had suggested that different H-2 haplotypes led to different disease outcomes during LCMV infection. Infecting various mouse strains with LCMV, Zinkernagel and Doherty found that isolated T cells did not uniformly kill chromium-labelled mouse target cells — it seemed that only some H-2 haplotypes were able to generate CTLs. However, they soon realized that something else was going on: the target cells were of the H-2^k haplotype, and when these were paired with H-2^k-expressing CTLs from C3H/HE mice, there was target cell lysis. By contrast, when CTLs from BALB/c mice (H-2^d haplotype) or C57BL/6 mice (H-2^b haplotype) were used, no target-cell lysis occurred. To prove their 'MHC restriction' hypothesis, they performed the opposite experiment: they used macrophages from the peritoneal cavity of BALB/c or C57BL/6 mice as target cells and found that these were lysed by H-2^d-expressing CTLs or H-2^b-expressing CTLs, respectively, but not by the H-2^k-bearing CTLs.

These MHC-restriction experiments did not show the nature of the antigen that the T cells recognized. Earlier experiments had shown B cells could recognize only native antigen, but that T cells could recognize denatured antigen. There were questions in the field about whether MHC restriction involved one or two receptors on T cells; could there be one receptor involved in recognizing the MHC and another one involved in recognizing the antigen? Or was there one T cell antigen receptor that recognized MHC in complex with the antigen? Ultimately, experiments from several labs, including those of Kappler, Marrack, Grey, Unanue and Townsend, showed the single-receptor hypothesis to be correct. Early structural analyses of an MHC complex by Bjorkman, Strominger and others showed a 'density' in the MHC groove that was unclear in initial crystals but was later shown to be processed peptide.

"two different Nobel prizes were awarded for early work that helped to identify the immune functions of the MHC"

Today, it is appreciated that MHC class I and MHC class II restriction of $CD8^+$ T cells and $CD4^+$ T cells, respectively, is central to most aspects of T cell function, including T cell development and tolerance (Milestone 12), T cell activation by antigen-presenting cells (Milestone 10), T cell help for B cells (Milestone 19) and T cell killing of infected or cancerous cells (Milestone 2). Notably, two different Nobel prizes were awarded for early work that helped to identify the immune functions of the MHC: one in 1980 to Snell, Daussett and Benacerraf, and one in 1996 to Doherty and Zinkernagel.

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Milestone studies

Zinkernagel, R. M. & Doherty, P. C. Restriction of in vitro T cell-mediated cytotoxicity in lymphocytic choriomeningitis within a syngeneic or semiallogeneic system. *Nature* **248**, 701 –702 (1974) | Zinkernagel, R. M., Doherty, P. C. Immunological surveillance against altered self components by sensitised T lymphocytes in lymphocytic choriomeningitis. *Nature* **251**, 547– 548 (1974)

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