Milestone 6

T cells in transplantation: ready and willing to reject

Transplantation is one of the great breakthroughs of medical science, and in the context of a graft that is derived from a non-identical donor, it requires breaking a central tenet of immunology – the recognition of self and non-self. The Nobel Prize winning work of Peter Medawar and others laid the foundations of transplant immunology; that non-self is rejected unless immunological tolerance is established. This groundbreaking work predated our understanding of the thymus and recognition of B and T cells (Milestone 1), and subsequently dawned the topic of transplant immunology.

The human leukocyte antigen (HLA) confers diversity in the histocompatibility antigens expressed, which results in diverse arrays of major histocompatibility complex (MHC) expression between members of the same species. The MHC is central to the activation of T cells (Milestone 4), and MHC differences between individuals is central to T cell activation during allogenic transplantation and recognition of non-self MHC. Recognition of non-self MHC rapidly activates T cells, which results in the destruction of donor tissue that we term rejection. These adaptive immune responses are enhanced by the physical conditions of transplant surgery including surgical trauma, ischemia and reperfusion.

T cell-mediated recognition of non-self MHC on transplant tissues is a major barrier to successful transplantation and engraftment, which currently requires substantial immunosuppressive therapy. The discovery and description of the pathways of allorecognition were pivotal milestones in transplant immunology.

In vitro, the co-culture of leukocytes from genetically disparate individuals reported by Bain et al. modelled the activation of leukocytes in an early incarnation of what we refer to as the mixed lymphocyte reaction (MLR). In 1977, Lindahl and Wilson incorporated radioactively labelled allogeneic antigen presenting cells (APCs) and determined that 0.7–1.2% cells were cytolytically active during experimental MLR. The size of the responding T cell population is orders of magnitude above the size of antigen-specific T cell populations. Impressively, their estimation of the alloreactive T cell pool in this manner is still in line with present day measures, which supports the rapid activation of large numbers of T cells that is seen in allogeneic transplant settings. While not established at the time, this represented what became the 'direct pathway' of allorecognition: the direct response of T cells to non-self MHC molecules, which is a pivotal pathway and a major challenge during acute rejection.

"T cell-mediated recognition of non-self MHC on transplant tissues is a major barrier to successful transplantation and engraftment"

In 1982, subsequent work from Lechler and Batchelor using the depletion of passenger leukocytes in rat models of allograft kidney transplantation suggested a further mechanism of rejection that functioned during chronic rejection. Their work established the 'indirect pathway' of allorecognition: donor MHC molecules that are derived from the graft, and processed and presented by recipient APCs, which results in T cell reactivity against MHC alloantigens that functions during rejection.

More recently, Lechler and colleagues defined a third mechanism of allorecognition, the 'semi-direct pathway'. Recipient APCs acquire allo-MHC–peptide donor-derived complexes via trogocytosis in conjunction with indirect presentation of allopeptide in the context of self MHC.

Taken together, these pivotal studies establish the three pathways of allorecognition and the role of T cells in alloreactivity, which in conjunction with the role of the accompanying antibody response, form the major hurdles of acute and chronic graft rejection.

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Milestone study

Lindahl, K. F. & Wilson, D. B. Histocompatibility antigen-activated cytotoxic T lymphocytes. I. Estimates of the absolute frequency of killer cells generated in vitro. *J. Exp. Med.* **145**, 500–507 (1977)

Further reading

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