Milestone 12

Distinguishing self from non-self

The practice of skin grafting can be traced as far back as antiquity, a time when facial mutilation and wounding were commonplace. The practitioners of these early transplants were well aware that the body did not tolerate foreign tissue for long, although the phenomenon at the heart of graft rejection or acceptance — immunological tolerance — would be recognized only centuries later.

In a short article published in 1945, Ray Owen was the first to observe that dizygotic cattle twins were tolerant to each other's blood. He theorized that blood was shared in utero, enabling haematopoietic cells from one twin to persist in the other well into adulthood. Owen's observation spawned the study of chimerism, but also provided the first conceptual clue on the origins of immunological tolerance.

Frank Macfarlane Burnet at the Walter and Eliza Hall Institute in Melbourne later instilled Owen's seminal work into his research on self/non-self-discrimination. Meanwhile, Peter Medawar initiated his own work on tolerance at University College London after being tasked during the Second World War with uncovering why adult skin does not engraft in genetically disparate individuals. Later, in 1960, Burnet and Medawar would jointly win the Nobel Prize in Physiology and Medicine for their work showing that the ability to distinguish one's own tissue from foreign tissue is imprinted during embryonic development.

This phenomenological work by Burnet and Medawar established that antigen receptors reactive to self are encoded in the germline; however, how such self-reactive receptors are purged from the adult repertoire remained unclear for decades. One predominant hypothesis was that self-reactive T cells are physically eliminated from the host at some point during T cell development. In 1987, John Kappler and Philippa Marrack's group used a monoclonal antibody specific for the $V_\beta17$ segment of the T cell receptor (TCR) to investigate the question. By analysing $V_\beta17$ expression in multiple mouse strains, as well as their heterozygous F_1 progeny, these researchers were able to show that mice lacking the MHC class II molecule IE had a large proportion of $V_\beta17^+$ T cells in the periphery, whereas strains that did express this MHC molecule were devoid of such T cells. Moreover, $V_\beta17^+$ cells were present among immature thymocytes, but not among mature thymocytes, suggesting that IE-reactive T cells are eliminated in the thymus. This idea was formally confirmed when Harald von Boehmer and colleagues at the Basel Institute for Immunology, Switzerland, generated transgenic mice expressing a TCR specific for the male mouse–specific histocompatibility antigen HY. Using this system, they showed that female mice immunized with male splenocytes were enriched for HY-specific T cells, but their male counterparts were not. In the thymus, whereas female mice had increased frequencies of $CD4^-CD8^+$ thymocytes, male mice were depleted of these cells, again demonstrating clonal deletion. Unlike the previous work from Marrack and Kappler, this study also highlighted the fact that TCR specificity and the selecting antigen are essential for clonal deletion.

The 16th century 'Italian method' for nose reconstruction, using autografting of a skin flap from the arm.

The findings from the von Boehmer and Marrack–Kappler groups, however, raised the question of how the thymus could impart the 'knowledge' of what constitutes a self-antigen and what constitutes a foreign one. An important hint came nearly a decade later, when two articles published back-to-back in *Nature Genetics* mapped the genetic basis for autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) to a novel gene, which they named *AIRE*. Although neither of these studies investigated the function of AIRE, both already suggested some involvement in transcriptional regulation.

The first hint about the function of AIRE came with the detection of tissue-specific proteins in a specialized cell subset in the thymic medulla, by Bruno Kyewski's research group at the German Cancer Research Centre in Heidelberg. Soon after, Diane Mathis and Christophe Benoist's group at Harvard Medical School used bone marrow chimaeras to show that these thymic medullary epithelial cells (mTECs) were in control of autoimmunity. Moreover, mTECs from *Aire*-deficient mice lacked expression of a wide spectrum of genes, many of which had tissue-specific expression. Thus, it became clear that AIRE promotes the expression of peripheral tissue antigens in mTECs, enabling these antigens to function as selecting ligands during thymocyte development.

Whereas elimination of self-reactive clones in the thymus was seen as the overarching process that imposes tolerance on the T cell repertoire, other researchers were following the hypothesis that self-reactive T cells are absent from the periphery not because they are purged in the thymus but instead because they are diverted to an alternative lineage. Indeed, this idea proved to be true with the discovery of an anergic T cell subset characterized by the ability to suppress autoimmunity. These cells are now known as regulatory T (T_{reg}) cells and are widely recognized as being essential for the maintenance of tolerance.

It is befitting that decades after Peter Medawar's efforts to understand allograft rejection, T_{reg} cell-based therapeutic strategies are today in trials for kidney transplant rejection (Milestone 6). Therapeutic modalities such as the adoptive transfer of T_{reg} cells and chimeric antigen receptor-expressing T_{reg} cells may bring closer his goal of understanding the physiological process of tissue rejection, but also maintaining lifelong tolerance to organ allografts.

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Milestone study

Kappler, J. W. et al. T cell tolerance by clonal elimination in the thymus. *Cell* **24**, 273–280 (1987)

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