Immune recognition

The Nobel prize for the year 1996 in physiology or medicine has been awarded to two immunologists – Peter Doherty and Rolf Zinkernagel for describing the manner in which the virus-infected cells are recognized by the immune system. Their work was published in 1974 from the John Curtin School of Medical Research, Canberra, Australia. Rolf Zinkernagel is now the head of the Institute of Immunology at the University of Zurich, Switzerland while Peter Doherty is an adjunct professor at the University of Tennessee College of Medicine, USA.

Defence reactions against foreign matter and the maintenance of individuality is a trait that has existed from the beginning of evolution and can be observed as incompatibility reactions in hydractinia corals as well as skin graft rejections in annelid worms. Elucidating the defensive role of cell-mediated immune reactions against pathogens began with the discovery by Elie Metchnikoff that macrophages were responsible for protection against foreign bodies in bipinnaria larva of starfish. Ever since, the idea of leukocyte involvement in immunity, has only been confirmed time and time again.

The conceptual need to evoke a distinction between self and non-self became apparent with the proposition of the clonal selection hypothesis by Macfarlane Burnet and David Talmage in 1957. According to this hypothesis, an individual is a mosaic of lymphocyte clones each of which is capable of producing only one type of antibody that is specific to a single antigenic determinant or epitope. Since an individual does not produce immunity against his or her own antigens, clones capable of producing antibodies against antigens normally present within the same individual need to be eliminated in the foetus – a time at which clonal diversification occurs. This is the process of tolerance induction to self molecules and therefore the need to distinguish self from non-self or altered self.

Using inbred strains of mice that they had generated by the 1920s, Ernest Tyzzer and Clarence Little established the presence of genes that controlled tumour rejection and tissue compatibility in general. During his efforts to describe blood groups in these inbred strains, Peter Gorer also observed that a group of genes controlled graft rejection. This gene complex was later termed the Major Histocompatibility Complex (MHC) when a similar set of genes were demonstrated in humans by Jean Dausset. It is now clear that the MHC codes for a set of highly polymorphic antigens known as MHC antigens and that these antigens are unique to each individual member within a species. Expression of these antigens on the tissue cells of one individual causes their recognition by lymphocytes when transplanted to another individual. Such transplants are also known as allografts. Lymphocytes belonging to different individuals recognize the presence of the other's MHC antigen (non-self) and react to it by enhancing their proliferation. It was this ability of lymphocytes to undergo proliferation and blast transformation that was used by Barbara Bain's group as well as Fritz Bach and Kurt Hirschhorn as the principle to develop the Mixed Lymphocyte Reaction (MLR) in 1964. Lymphocytes belonging to one individual termed as the responder are cultured along with irradiated lymphocytes of another termed stimulator cells. Irradiation of the stimulators blocks their proliferation but does not kill them. Hence the proliferating responder population can be followed by measuring the incorporation of tritiated thymidine into its DNA. Such assays along with other antibody-based methods are now used for tissue typing purposes.

The occurrence of cell-mediated cytolysis during graft rejections was also discovered by A. Govaerts at about the same time in 1960 while conducting kidney transplantation experiments in dogs. Lymphocytes from the recipient dog that had already rejected a donor kidney possessed the ability to kill the epithelial cells derived from the donor kidney. This basic observation later led to the perfection of the Cell Mediated Lympholysis (CML) assay.

The CML assay is basically a MLR that is carried out for 5 days. During this culture period, the unirradiated responding lymphocyte population is sensitized to the MHC antigens borne by the stimulator cells. Instead of adding thymidine, the surviving effector (killer) cells are added to lymphocytes or tumour cells matched at the MHC locus with the stimulators. These 'target' cells are labelled with radioactive chromium which will be released when the targets are killed by the activated cells generated during the culture. The use of radioactive chromium enables the quantification of the killing reaction. Thus the assay is based on the recognition of differing MHC antigens on the stimulating population by the responder lymphocytes. However, it soon became clear that CML can occur against many other membrane-bound antigens also.

Rolf Zinkernagel and Peter Doherty showed in their classic paper published in 1974 that Lymphocytic Choriomeningitis Virus (LCMV) would not be recognized by virus-specific cytotoxic T lymphocytes (CTL) if the LCMV-infected target was not matched at the MHC with the CTL effector cell[1,2]. Other target cells expressing MHC molecules different from that of the LCMV-infected stimulator cell were not recognized in spite of being infected with the same virus. In other words, CTL were blind to LCMV if they were not associated with self MHC molecules. This was termed as MHC restriction and was shown by Gene Shearer, Michael Bevan and others to operate for other antigens such as minor histocompatibility antigens, tumour-specific antigens and virus-specific antigens.

We now know that MHC restriction is due to the binding of antigen-derived peptides to the antigen binding cleft formed between the two α helices of the MHC Class I[3,4] or Class II molecule. The recognition of peptide-bound MHC on the surface of an antigen-presenting cell (APC) by the T cell receptor (TCR) makes MHC restriction a universal feature for most T cell interactions. The two subunits of the TCR contain immunoglobulin-like variable and constant domains that fold into a structure resembling the antigen-binding region of antibodies. Recent crystallization studies of the TCR-bound MHC Class I and viral peptide have now confirmed the

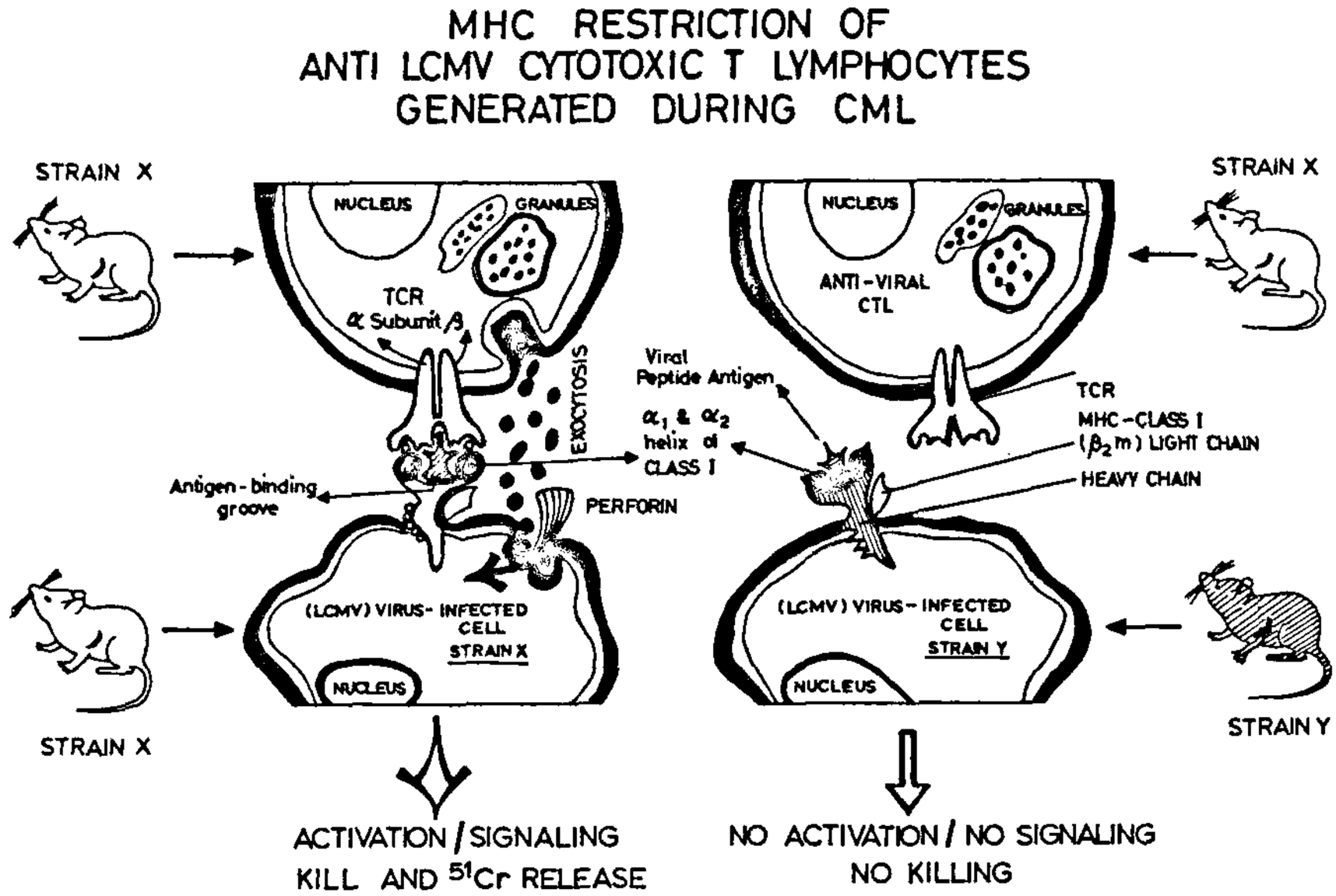

Figure 1.

phenomenon of MHC restriction in three dimensional terms. These papers[5–7] lucidly describe the quaternary structure of the TCR and show that a subunit of the TCR positions itself over the left end of the Class I antigen binding groove while the β subunit covers its right end. The α and β subunits thus make contact with residues in the amino-terminal half and the carboxy-terminal half of the antigenic peptide respectively. Confirmation that antigenic peptide occupies the antigen-binding groove of MHC has come not only from these studies but also from earlier interpretations of the electron density maps that were obtained therefrom[3,4]. The diagonal orientation of the TCR across the antigen-binding groove ensures that the first and second complementarity determining region (CDR) loops of a TCR subunit contact the amino-terminal part of the α_1 helix and the carboxy-terminal part of the α_2 helix of MHC Class I respectively. The TCR β subunit does the same in a complementary fashion, thus enabling the TCR to encompass both MHC and bound peptide in its face.

The affinity of peptide binding to the MHC molecule will be determined by the structural features of the peptide and the MHC allele that it binds to. Different MHC antigens bind different peptides. Thus T cell activation is not only influenced by MHC and peptide but also by the manner in which this complex is recognized by the T cell receptor. It could be speculated that the generation of antigenic peptides by APC could also differ between individuals depending on the manner in which different proteins such as TAP and LMP proteins function during antigen presentation. Therefore the development of most vaccines and therapeutic procedures against infectious as well as autoimmune diseases will be influenced by the discovery of MHC restriction. It is now easy to understand why the award of the Nobel prize to Rolf Zinkernagel Doherty was well deserved.

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