The Nobel Prize In Physiology or Medicine

How Do T-Lymphocytes Recognize their Immune Targets?

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Of the Nobel prizes declared a few months ago for 1996, the one in Physiology or Medicine went to Peter Doherty, now at the St Jude's Children's Research Hospital in Memphis, USA, and Rolf Zinkernagel, now at the University Hospital in Zurich, Switzerland, for their contribution to our understanding of 'The Specificity of Cell-Mediated Immune Defence'. Both are in their fifties now. They carried out the work cited for the Nobel award as young scientists at the John Curtin School for Medical Research of the Australian National University in Canberra, Australia, in 1973-75. So what on earth is 'cell-mediated immune defence', why does it need specificity, how is it achieved, and of course, what were these brilliant experiments that Zinkernagel and Doherty did, – what did they achieve to deserve a Nobel prize?

Twenty years ago, the concepts of immunology were far more primitive than those of today. People knew that the immune system was needed for the fight against infections. They also knew that vaccines could boost the ability of the body to fight infections, since some infections, such as smallpox, were already being controlled with the help of vaccines. Infectious diseases were [then as now] the bane of the developing world, and vaccines seemed [then as now] the ideal solutions for the future. But not much was known about how vaccines worked at the cellular and molecular levels. Although people knew something about proteins called 'antibodies' produced by B lymphocytes that could help in 'neutralizing' bacteria or viruses, the exact functions of most other cell types in the immune system were not well understood.

And yet, these are the main components of the immune defence against invading parasites, and one must understand their functions to discover useful means of interventions during infections. To begin with, where can parasites live once they gain access to the host body? Using the nutrients present, they may live in the blood stream and in the fluid that bathes the cells of the body. In such situations the immune system can use antibodies that would bind to specific targets on the infecting pathogens and either damage them directly or mark them for disposal. Then cells that can eat and digest particulate material, or 'phagocytes' can recognize and destroy them. This basic notion was already known by the early seventies. But some pathogens manage to get inside phagocytes, or even non-phagocytic cells, and survive there by avoiding or neutralizing the normal disposal machinery in these cells. No antibodies can get at them, nor would antibodies be very useful even if they did. In order to counter this parasite strategy of hiding inside host cells, the immune system must spot those cells that are infected, and either prod them into getting rid of these intracellular parasites despite their evasive strategies, or at least kill these

infected cells before the invaders mature and proceed to infect another cell. With such drastic surgery as in the latter instance, the invasion would be nipped in the bud. The problem is, if the infection is lurking inside intact host cells, how do immune cells dealing with this problem ever recognize its presence?

In the early seventies, based on genetic experiments, there was an idea floating around that T lymphocytes handled such situations but nobody had any notion of how they recognized an infected cell from the outside. The one thing known about them was that they could kill target cells. But that was based on their ability to kill cells bearing a different set of MHC (Major Histocompatibility Complex) proteins than themselves. These MHC proteins are highly variable in most natural populations; therefore one person's T cells could recognize another person's cells as different and kill them. This could also be demonstrated in inbred mouse strains that had by then been in use for many years. T cells from one mouse strain could kill target cells from an 'MHC-disparate' strain. But this is not a natural situation. Ordinarily, one individual's T cells hardly ever come into contact with another individual's cells. Besides the inbred mouse experiment has nothing to do with infection, although it is of much relevance to transplantation. So what did T cells recognize in real life? The first, and astonishingly comprehensive, set of clues came from Zinkernagel and Doherty's work. They had both been trained in medicine, Doherty in veterinary and Zinkernagel in human medicine; and both were interested in how the body deals with those ultimate intracellular parasites – the viruses. So, when Zinkernagel came to Canberra where Doherty was already working, the two together began to investigate what T cells did to virus-infected targets. They used inbred mouse strains and a virus called lymphocytic choriomeningitis virus or LCMV that can infect mice. The experiments they reported in two papers in *Nature* in 1974 are elegant, simple and need no knowledge of the properties of the virus itself. In essence, they took inbred mice with one set of MHC proteins or one MHC 'type', infected them with non-lethal doses of LCMV, took out their T cells and put them together with either normal or LCMV-infected cells of the same mouse strain. The normal cells did not die, but the virus-infected cells did. Clearly, T cells could indeed kill virus-infected cells, and 'cell-mediated immune defence' was occurring. But what were they recognizing? If cells from the same mouse strain were infected with another virus, and used as target cells, for these T lymphocytes, they did not die. Therefore killing by LCMV-specific T cells needed some component on the surface of infected cells that only LCMV could provide, and the 'cell-mediated immune defence' was 'specific' (*Figure 1*). In other words, a specific 'foreign' component was needed by the T cell recognition molecule, or receptor. However, when Zinkernagel and Doherty infected cells from a mouse strain of a different MHC type than the first one with LCMV, the anti-LCMV T cells could not kill them. This clearly showed that these anti-LCMV T cells from the original mouse have to 'see'

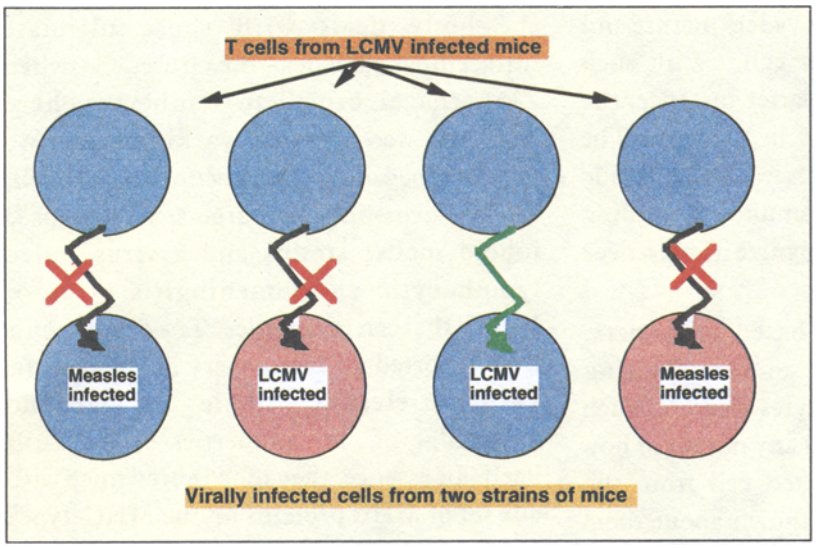

Figure 1 LCMV-specific T cells can recognise only LCMB-infected cells from the same MHC background.

both the LCMV as well as MHC before they can kill, and further, that they can only recognize the 'right' MHC, meaning their own kind. At last we saw what the T cells need for recognition. They see both the target parasite and MHC before recognition is effective, and the MHC has to be of their own type.

Explosively, in the span of a few short years, the complexity was solved. It made sense for T cells to recognize, or rather, to be 'restricted' by, their own MHC, since otherwise they would be useless to the body. This process of 'positive selection' of the developing T cells in the thymus has been the focus of intense interest and work over the past decade. Doherty and Zinkernagel proposed two models to explain the recognition rules they observed. Either T cells had two separate receptor molecules for the virus and the MHC, or they recognized MHC that had been modified in some fashion by the virus. However, having separate receptors would open up the possibility of killing neighbouring, normal cells simply because the MHC receptor was engaged by an MHC molecule on that cell rather than on the infected cell itself, and time has shown that the 'single receptor' theory is correct. T cells do not see the whole parasite but they see chewed-up bits of it bound to MHC molecules. This concept led to an entirely new area of how digested bits or peptides are generated from various microbes and how they tie onto MHC molecules. The seeming paradox that even antibody production was based on a helping hand from T cells was also explained by the fact that B cells 'presented' antigens they recognized to T cells as fragments bound to MHC, and thereby invited T cell help for their own maturation. Zinkernagel and Doherty's work also enabled identification of the T cell receptor by providing a detection system for it. It is a fitting coincidence that their Nobel prize

should come in the same year that the trimolecular complex of the T cell receptor, the MHC and the peptide have been crystallised together and the structure of the composite complex finally analysed at the atomic level. The structure shows that the peptide takes the place of the filling in a sandwich formed by the MHC and the T cell receptor.

Apart from such matters of immediate academic interest, there was much practical interest too in the Zinkernagel and Doherty discovery. Today we know enough about its implications to be able to talk meaningfully at least of peptide based vaccines. It became clear that simple transfer of the immune serum from one individual to another could not work to counter intracellular infections. Also, T cells were necessary, T cells could not be transferred from one individual to the other since, apart from anything else, they would work only with the right MHC. It also led to hypotheses about why some diseases show family predispositions because members of a family would share MHC proteins and the presence or absence of these could predispose the carriers to some diseases. This concept has given great impetus to the understanding of infectious diseases, autoimmune diseases, cancer and problems of tissue transplantation. Relatively simple experiments done in the seventies thus told us a lot about the specificity of cell-mediated immune defence, and much of the current, complex understanding of immunology is based on what we might call a 'simple' notion today. Surely the elegant demonstration of simplicity at the heart of complexity deserves a Nobel prize.

Suggested Reading

- R M Zinkernagel and P C Doherty. Restriction of in vitro T cell-mediated cytotoxicity in lymphocytic choriomeningitis within a syngenic and semiallogeneic system. *Nature.* Vol.248.p.701, 1974.
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