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The current status of viral immunology

Carol S. Reiss and Barry T. Rouse

Many aspects of viral immunity, ranging from the molecular and cellular studies of the interaction between viruses and host cells in vitro and the crystalline structures of the MHC and peptides, to the regulation of pathogenesis in experimental animals and humans were discussed at a recent meeting. The question 'How does the host defend itself against reovirus?' was answered by Skip Virgin (St Louis) who emphasized the importance of both cellular and humoral immunity. He also examined the post-binding effects of antibody to viral surface proteins (binding, processing, proteolysis, membrane penetration and replication), and has also initiated studies of virulence factors for the infection of SCID mice.

The interaction between poliovirus and its receptor was detailed by Elisabeth Colston (New York) in studies of tissue tropism and peripheral muscle to CNS spread of virus in the mouse. Gillian Air (Birmingham, USA) described the ultrastructural investigations of complexes of the influenza N9 neuraminidase (NA) and a mAb, NC41, and determined the effect of alterations in NA-Ab contact residues on binding, mAb minimal number and kinetics and mechanisms of neutralization of picornaviruses (such as the polio PV1 and the neuroviruses HR14) were discussed by Roland Rueckert (Madison) who noted observations of the binding of viruses to the intercellular adhesion molecules, (ICAM's).

New strategies

Among the new strategies for understanding the molecular viral pathogenesis is the use of mice whose individual genes can be selectively knocked out. The response of a B2-microglobulin deficient mouse has been explored by Jeff Frelinger (Chapel Hill) using experimental challenge with LCMV and Listeria monocytogenes. CD4+ cells are actively recruited and there are also gender effects in susceptibility to lethal infection. Cytokines, especially interleukin 2 (IL-2), IL-12, interferon gamma (IFN-γ) and transforming growth factor β (TGF-β) tightly regulate both T-cell and natural-killer cell activity. Additionally IFNs derived from NK cells are involved in the regulation of virus replication and inhibition of viral spread. The role of IFN-α and IFN-γ in viral infection has been investigated by David Knipe (Bethesda) who discussed the effect of these cytokines on viral replication and the induction of antiviral state in infected cells. The interaction between the virus and its receptor was also highlighted by Carol Reiss (New York) who emphasized the importance of interactions between viruses and host cells in the regulation of immune response.

The program began with a joint session devoted to antigen processing and presentation. Jack Bennink (Bethesda) discussed the central role of peptide transporters, TAP1 and TAP2, in the sensitization of experimental animals and humans to viral antigens. The importance of antigen presentation was highlighted by Gary Winslow (Denver) who spoke on the role of viral superantigens. Interestingly, the influenza virus-specific p35 expressing T-cells were described in the H-2d mouse but were not found to be essential for recovery. However, Peter Doherty (Nashville) demonstrated that, in αβ mutant mice, delayed recovery from viral infection occurs. He concluded that TCR availability in Vβ1.1, Vβ2.3 and Vβ2 transgenic mice was not limiting; in contrast, the ability of peptides to interact with the MHC was critical. The response to superantigens, the mouse mammary tumor virus Sag gene (Mls-1) in association with the deletion of Vβ6 or Vβ7 or 9 was attributed to a 14 amino acid peptide from the C terminal LTR by Brigitte Huber (Boston). In addition to describing the production of the first mAb to an Mls antigen, she demonstrated the essential role of T cells in transmitting mouse mammary tumor virus (MMTV) infection.

Hans Hengartner (Zurich) focused on the TCR specificity for the epitope 33–41 of the glycoprotein (Vor, Vb10), the selection of viral escape mutants and the effector mechanisms in lymphotrophic choriomeningitis virus (LCMV) infection of H-2b mice. In collaboration with Kagi and Lederman (Sandoz A.G.) they have observed that perforin knockout mice have a dramatically reduced ability to clear the virus.

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cells and induced by infection or by poly-IC result in the leucocyte redistribution and are associated with control of LCMV and MCMV infections (Christine Biron, Providence). Doris Moster (La Jolla), when using the SCID HU mouse, investigated the pathogenesis and cell tropism of HIV-1 and HIV-2 infection using recent clinical isolates and concluded that viral load or in vitro viral tropism may not be an accurate predictor of disease progression.

Analysis of the human immune response to another clinically relevant agent, varicella zoster virus, was described by Ann Arvin (Stanford) who concluded that the vaccine under investigation evoked similar responses when compared to natural infection, both specific for IE62 and GP1.

Marc Jenkins (Minneapolis) described a critical role of cell division in the induction of T-cell anergy in Trl clones, stressing the roles of IL-2, IL-2R, CD28, and its ligand B7 (Ref. 7). Rari Ahmed (Los Angeles) spoke about long-lived virus-specific T-cell memory and suppression, terming it 'life and death by viruses'; he provided evidence that the memory cells reside in lymphoid organs and are in cycle, in the absence of residual antigen. The mechanisms by which IL-10 regulates Trl cells and macrophage activation, and a new cytokine, T2-derived P600 (also known as IL-13), were the focus of Tim Mosmann's (Edmonton) presentation. Barry Rouse (Knoxville) discussed the role of a factor in the pathogenesis of hepatitis B virus (HBV) persistence as a consequence of T-cell tolerance induction in both murine and human studies was described by David Milich (La Jolla). Jim Allison's (Berkeley) lecture was on the topic of costimulation by B7 in tumor immunotherapy. He provided convincing evidence that, in the presence of costimulators, tumors are readily rejected.

Viral pathogenesis

Several speakers dealt with the issue of viral pathogenesis. Michael Buchmeier (La Jolla) discussed the pathogenesis of a neurovirulent mutant of mouse hepatitis virus, a coronavirus; the neurovirulence was associated with the spike protein characteristics and viral clearance is due both to CD4 and CD8 expressing T cells. Frank Chisari (La Jolla) described the mechanism by which persistent HBV causes acute disease and leads to chronicity. Chronic immunopathological phase was mediated by CD8+ T cells and at least three strategies of pathology were evident and subject to modulation. Barry Rouse (Knoxville) discussed the pathology of the corneal stroma caused by herpes simplex virus (HSV); T1 and CD4+ cells caused the lesion through toxic nitric oxide radicals (Science "molecule of the year" for 1993). An immunopathological role for CD4+ cells was also shown for mice immunized with formalin inactivated respiratory syncytial virus and later challenged with infectious virus (Brian Murphy, Bethesda). For effective immunity against rous sarcoma virus (RSV), CD8+ cells are essential. In another system, murine cytomegalovirus (CMV) infection, CD8+ cells specific for an I-E gene product were also shown by Uli Koszinowski (Ulm) to be responsible for clearance of CMV from all tissues except the salivary gland; in the absence of CD8+ cells, CD4+ cells effectively compensated [as has been seen in LCMV (Frelinger), VSV (Reiss) and influenza (Doherty)]. In the salivary gland, few cells express MHC thus requiring TNF- and IFN-induction associated with CD4+ cells for viral clearance.

Several presentations focused on HIV infection. Gene Shearer (Bethesda) presented evidence that the interaction of T1 and T2 CD4+ cells in infected individuals may affect the ability of the host to cope with other infections. As the disease progresses, T1 cells are functionally lost, thus inhibiting delayed-type hypersensitivity (DTH), proliferative responses and antigen processing by macrophages. Sandy Morse (Benedict) described his studies of MAIDS including the genetics of susceptibility, and the role of T12 cells in resistance from the lymphoproliferative disease. Jay Levy (San Francisco) emphasized the protective role of CD8+ cells against systemic HIV infection and discussed the role of a factor produced by CD8+ cells which suppresses HSV replication in CD4+ cells. AIDS dementia seems to be the result of an indirect effect on neurons of toxic factors released by HIV-infected cells or other amplifying cells (Richard Price, Minneapolis). Jay Nelson (Portland) discussed an important coinfection often seen in AIDS and CMV and he presented evidence that viral gene expression is upregulated in infected peripheral blood cells. The infection of the male genital-urinary tract mucosa was the focus of Deborah Anderson's (Boston) presentation; she described the immunology of the urethra, and emphasized that vaccines for STDs should target local immunity in the mucosa of the male and female genito-urinary systems. She observed that CTLs may not be beneficial at this site, but that secretory immunity could be protective.

Viruses may be endowed with certain gene products which counteract the host's protective immunity. Linda Gooding (Atlanta) described at least three evasive mechanisms adenoviruses have developed to protect from, for example TNF- mediated target cell lysis. Kees Melief (Netherlands) also discussed adenovirus, specifically CT1 recognition of the E1a proteins and the role of CT1 in eradication of infection. Alan Robinson (Birmingham, UK) dealt briefly with an IL-10 homologue of the Epstein-Barr virus. He focused most of his presentation on CTL epitope and their interaction with MHC class I, and the selection of virus mutant in New Guinea which has a single a change in the predominant HLA-A11 restricting peptide of the EBNA-3 of Type 1 virus.

Vaccine vehicles and immunity at local sites of infection

Jay Berzofsky (Bethesda) described the function of different residues in a peptide with a view toward improving immunogenicity. A chimeric peptide was described that generated broadly crossreactive CTLs in mouse and man. Hans-Georg Rammensee (Max-Plank Inst) discussed in detail the anatomy of allele-specific motifs for class II MHC molecules; he indicated that potent CT1 responses against soluble proteins might be induced by boiling or autoclaving of the antigen before immunization.
The cytokine has pleiotropic effects characterized. Interleukin 12 (IL-12, including: induction of transcription on natural killer (NK) and T cells, accessory cells, bacterial products, or parasites) has been discovered. Here, Giorgio Trinchieri reports on one of these, Interleukin 12, and discusses the significance of the cytokine to the generation of CD8+ T cells, from the Peyer's Patch responses in mucosal gut immunity to reovirus. Diane Griffin (Baltimore) reviewed the immune response to Sindbis, an alphavirus. She showed the importance of antibody specific for the E2 spike protein to viral clearance in the CNS. It appears that the antibody may act intracellularly (as was also seen in Virgin's reovirus studies). Antibody-secreting cells are persistent in the brains of infected mice, and are critical for prevention of relapse. Robert Coffman (DNAX) provided a flow chart of the interaction among cells of the immune system with cytokine products up- or down-regulating the equilibrium; he describe archetypal infections which were biased in one mode or the other, and analysed the outcomes of infection based on the flow chart.

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Interleukin-12 and its role in the generation of T<sub>H1</sub> cells
Giorgio Trinchieri

Over the past few years a growing number of new cytokines have been discovered. Here, Giorgio Trinchieri reports on one of these, Interleukin 12, and discusses the significance of the cytokine to the generation of T<sub>H1</sub> cells.

The importance of cytokine networks in determining physiological responses in immunity and inflammation and their alteration in pathology is becoming more and more evident as new members of the cytokine family are identified and characterized. Interleukin 12 (IL-12, also known as natural killer cell stimulatory factor) is a heterodimeric cytokine produced by monocyte-macrophages, B cells, and other accessory cells, in response to bacteria, bacterial products, or parasites. The cytokine has pleiotropic effects on natural killer (NK) and T cells, including induction of transcription and secretion of cytokines; enhancement of cytotoxic activity; and induction of proliferation of T and NK cells that are activated by other stimuli.

The IL-12 heterodimer is composed of two covalently linked glycosylated chains, p40 and p35, encoded by separate genes. The light chain, p35, has limited homology with IL-6 and G-CSF, and has, like most other cytokines, an o-helix-rich structure. Unexpectedly, the p40 heavy chain is not homologous to other cytokines, but belongs to the hemopoietin receptor family and most resembles the IL-6 receptor and the ciliary neurotrophic factor (CNTF) receptor. This similarity with IL-6R and CNTF-R is interesting, since most of all transmembrane cytokine receptors can be secreted by cells in a soluble form, either by proteolysis of the membrane form or by translation of a soluble form from an alternatively spliced message. These