Introduction

Rolf M. Zinkernagel, Hans Hengartner

Institute of Experimental Immunology, Department of Pathology, University of Zürich,
Schmelzbergstrasse 12, CH-8091 Zürich, Switzerland

Viruses and the immune system have coevolved to reach a balance. This equilibrium can be demonstrated in many individual infectious disease models; the maintenance is obviously very complicated and regulated by a multiplicity of infectious agents. Viruses are only one group participating in shaping the overall balance. Because specific immunity seems critical in protecting vertebrate hosts against virus infections, it is not surprising that studies on protection against virus infections by vaccination were in many ways the starting point of immunology.

Because viruses and the immune system have coevolved, they represent two complementary sides of one critical biological system, which cannot be monitored by assessing any measurable parameter, but only by measuring what is critically important for survival: to understand antibody specificity is to understand the rules of distinct virus serotypes, assessed by neutralizing protective antibodies, not by measuring antibodies against viral internal antigens such as nucleo- or matrix protein. To understand immunological memory is to understand the kinetics of cross-reactions, of cross-protection and of the critical immunological factors that can protect against reinfection via natural routes and subsequently protect against the consequences of systemic infection.

Whereas immune protection against cytopathic (harmful) viruses is essential for host survival, this is not necessarily the case for infections with noncytopathic (harmless) viruses. In the latter infections, danger to the host arises not from direct toxicity to cells caused by virus infections, but from immunologically mediated damage to infected host cells, particularly by cytotoxic CD8⁺ T cells. The two extremes are: (1) the rapid and efficient immunological elimination of cytopathic viruses, mostly via interleukin-releasing T cells and antibodies during a primary infection, and virtually exclusively by high-level antibodies against reinfection; and (2) elimination by rapid CD8⁺ T-cell-mediated lysis of a few infected cells, preventing extensive cytotoxic T-cell-mediated immunopathology caused by widespread noncytopathic virus infec-

tions. Between these two extremes many intermediate conditions can be found that cause various forms, extents and severities of disease. These various model infections, causing disease directly by the virus and/or indirectly by the varying qualities of the immune response, are the subject of this collection of reviews.

Each virus-host pair reveals some, but never all, facets of the delicate interplay between viruses and host immunity. There is virtually nothing immunological that viruses have not probed, initiated, exploited or avoided in one way or another. Some viruses hide in neurons or in the central nervous system, as summarized by D. Griffin for arboviruses, which coexist in a special way with intracellular antibodies; others may cause chronic demyelinating disease, as exemplified by corona virus infections in mice, reviewed by H. Wege. Several viruses, such as hepatitis B virus, may induce potent antibody responses because of special antigen-patterns, or prevent generation of antibody responses, as documented by D. Milich and coworkers. Other viruses coexist with neutralizing antibodies (sometimes associated with immune complex disease), but exhaust the cytotoxic T-cell response, for example, the lactate-dehydrogenase-elevating virus (LDV) reviewed by P. Plagemann and coworkers. In contrast, antibodies against respiratory syncytial virus (RSV) may enhance the pathogenicity of subsequent infections by T-cell-mediated immunopathology, as discussed by P. Openshaw. Epstein-Barr virus (EBV) does just about everything one may imagine, including inducing autoimmunity, as reviewed by J. Vaughan. Similarly, the retrovirus combination that causes murine AIDS in mice (reviewed by H. Morse and coworkers), the model infection with lymphocytic choriomeningitis virus (LCMV) in mice (reviewed by R. Ahmed et al.), or hepatitis B virus in humans (reviewed by F. Chisari and coworkers) initiates disease as a result of subtle imbalances between virus and host T-cell immune responses. All these examples not only show how much we have learned, but also how little we still know; they encourage further studies not only of genes, proteins, receptors, ligands and signals, but also of the complex pathophysiology resulting from the interactions between the immune system and various viruses.

Our appreciation and sincere thanks go to the authors for their efforts in preparing these reviews and for sharing their results and concepts.