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Human Retroviral Infections

Immunological and Therapeutic Control

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Preface to the Series

The mechanisms of disease production by infectious agents are presently the focus of an unprecedented flowering of studies. The field has undoubtedly received impetus from the considerable advances recently made in the understanding of the structure, biochemistry, and biology of viruses, bacteria, fungi, and other parasites. Another contributing factor is our improved knowledge of immune responses and other adaptive or constitutive mechanisms by which hosts react to infection. Furthermore, recombinant DNA technology, monoclonal antibodies, and other, newer methodologies have provided the technical tools for examining questions previously considered too complex to be successfully tackled. The most important incentive of all is probably the regenerated idea that infection might be the initiating event in many clinical entities presently classified as idiopathic or of uncertain origin.

Infectious pathogenesis research holds great promise. As more information is uncovered, it is becoming increasingly apparent that our present knowledge of the pathogenic potential of infectious agents is often limited to the most noticeable effects, which sometimes represent only the tip of the iceberg. For example, it is now well appreciated that pathologic processes caused by infectious agents may emerge clinically after an incubation of decades and may result from genetic, immunologic, and other indirect routes more than from the infecting agent in itself. Thus, there is a general expectation that continued investigation will lead to the isolation of new agents of infection, the identification of hitherto unsuspected etiologic correlations, and, eventually, more effective approaches to prevention and therapy.

Studies on the mechanisms of disease caused by infectious agents demand a breadth of understanding across many specialized areas, as well as

much cooperation between clinicians and experimentalists. The series Infectious Agents and Pathogenesis is intended not only to document the state of the art in this fascinating and challenging field, but also to help lay bridges among diverse areas and people.

M. Bendinelli
H. Friedman

Preface

The discovery of the human T cell leukemia virus type I in the late 1970s heralded a new era in retrovirology. For the first time, it was demonstrated that a retrovirus could play a role in the development of a human disease, in this case adult T cell leukemia (ATL). Several years later, the acquired immunodeficiency syndrome (AIDS) epidemic began, and it was demonstrated that a retrovirus, originally designated the human T cell lymphotropic virus type 3, was the causal agent of this syndrome. This virus, later named the human immunodeficiency virus type 1 (HIV-1), has since been extensively studied in terms of its pathogenesis as well as its ability to elicit immune responses. In that time, a tremendous amount of information has been obtained about the virus. Although recent drug regimens have been useful in significantly lowering viral loads and perhaps maintaining an asymptomatic state among individuals infected with HIV-1, an established "cure" for AIDS eludes us. In addition, the effective drug therapies are very expensive, and are not available to infected people in the third world, where greater than 90% of new infections occur. Furthermore, the development of viral resistance against the drug therapies is an additional concern.

Despite extensive study, no effective vaccine has been developed. One of the problems in developing an effective vaccine against HIV-1 is the ability of the virus, particularly in the immunogenic envelop glycoprotein, to undergo amino acid hypervariability. Therefore, vaccines generated against one envelop glycoprotein are ineffective against other viruses with more hypervariable envelopes.

Although the rate of new HIV-1 infections in the United States has slowed and appears to have reached a plateau, nearly 16,000 people per day worldwide become newly infected with this devastating virus. Ominously, it is predicted that at the turn of the century, over 40 million people across the globe will be infected. Clearly, the development of new effective drug therapies, as well as immune prophylactic and therapeutic regimens against

HIV and AIDS is warranted. The chapters in this volume, written by experts in the field of human retroviral pathogenesis, vaccine development, and the clinical treatment of AIDS, summarize the current status of work in these areas as well as future directions for research and therapeutic development.

The first chapter, by Dr. Bristow, deals with the important descriptions of the two principal viremias of HIV-1, sexual (heterologous) transmission and autologous transmission of viruses between cells within the same host. This information is relevant for the development of methods to limit the spread of HIV-1 infection. Drs. Gentile and Loughran then describe evidence for the role of the human T cell leukemia viruses (HTLV) in the etiology and pathogenesis of disorders other than ATL. This is an interesting and important area because of evidence suggesting that the HTLVs may have a role in a number of autoimmune diseases. Next, Dr. Cianciolo discusses the evidence for the immunomodulatory and immunosuppressive activity for a number of HIV-1 proteins including gp120 and gp41 as well as the regulatory proteins Tat and Nef. Dr. Kieber-Emmons describes the importance of carbohydrate moieties and glycosylation patterns in HIV-1 and their role in masking potentially immunogenic and therapeutically important epitopes. Drs. Bennett and Agadjanyan summarize some of the immunologic and molecular aspects of HTLV-I and HTLV-II infection, emphasizing the role of adhesion molecules in the binding of these two viruses to infectible target cells.

The next set of chapters deals with issues concerning the development of immunologic interventions against HTLV, HIV-2, and HIV-1, including vaccine development and passive immunotherapies. Dr. Franchini and colleagues describe the current status of efforts to develop a vaccine against HTLV-I, a retrovirus that infects 10–20 million people worldwide. Dr. Björling discusses immune responses against HIV-2 and how these responses are important for the development of vaccine strategies against this retrovirus, which primarily infects individuals in West Africa. Drs. Staats and McGhee deal with the important need to develop vaccine strategies against HIV-1 which will protect against mucosal infection. Since HIV-1 is transmitted primarily by mucosal routes, this is a very timely and important issue in the area of HIV-1 vaccinology. In terms of novel vaccine strategies against HIV-1, Dr. Boyer and colleagues describe the nucleic acid (DNA) vaccination technology. This approach, which appears to mimic live, attenuated viral vaccines without major safety concerns, elicits both humoral and cytotoxic T cell responses against HIV-1, and is currently in several human clinical trials. Drs. Cotropia and Ugen describe the current status of passive immunotherapy and immunoprophylaxis against HIV-1, including the use of human polyclonal HIV immunoglobulins and specific neutralizing human monoclonal antibodies. The set of chapters dealing with immunologic interven-

tions ends with the description by Dr. Ayyavoo and colleagues of efforts to target the accessory genes of HIV-1 for vaccine development and immunotherapy.

The final set of chapters deals with developments in therapeutic interventions against HIV-1 infection and AIDS using drugs or gene therapy. Drs. Doranz and Doms discuss the role of chemokine receptors in mediating entry of HIV-1 into cells as well as the design of new antiviral therapeutics that may prevent HIV from using these receptors. Dr. Goodenow and colleagues then summarize the activities of the therapeutically important protease inhibitors and, in particular, describe the role of genetic variability of the HIV-1 protease in modulating the response to these drugs in pediatric patients. Drs. Dornburg and Pomerantz follow with a chapter that describes current ideas and implementations of gene therapeutic regimens against HIV-1, as well as future possibilities of such an approach. The volume concludes with a chapter by Dr. Nelson and colleagues on the current status of the clinical use of antiretroviral therapy against pediatric HIV, the relative effectiveness of this therapy, and the need for the development of new therapies.

It is anticipated by the editors as well as by the authors of the individual chapters that this volume will provide a useful summary of the current status of immunologic and therapeutic interventions against human retroviral infections, most notably HIV-1. It is hoped that the need is made apparent for the development of efficacious vaccines against both HIV-1 and HTLV-I, as well as for the development of novel drug therapies and regimens such as gene therapy against HIV-1. The editors thank Ilona Friedman for excellent editorial assistance in coordinating and assisting in the preparation of the manuscripts for this volume.

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