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Cover illustration: Schematic representation of the HIV-1 genome. The HIV-1 genome is shown with the various structural features and genes indicated. LTR is long terminal repeat. The genes common to all retrovirus are gag, pol, env. The various auxiliary genes specific for HIV-1 are indicated. Illustration of HIV-1 genome provided by Vicente Planelles, UCLA.

Transacting Functions of Human Retroviruses

Edited by Irvin S.Y. Chen, H. Koprowski, A. Srinivasan, and P.K. Vogt

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Irvin S.Y. Chen
UCLA School of Medicine
Division of Hematology/Oncology, 11–934 Factor
10833 Le Conte Avenue
Los Angeles, CA 90024–1678, USA

Hilary Koprowski
Thomas Jefferson University
Department of Microbiology and Immunology
Head of the Center of Neurovirology
1020 Locust Street
Philadelphia, PA 10107, USA

Alagarsamy Srinivasan
Jefferson Medical College
Department of Microbiology/Immunology
Center for Neurovirology
Rm. 469 Jefferson Alumni Hall
1020 Locust Street
Philadelphia, PA 19107–6799, USA

Peter K. Vogt
The Scripps Research Institute
10666 North Torrey Pines Road
La Jolla, CA 92037, USA

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Preface

The genome of retroviruses contains three major coding regions for virion proteins, *gag*, *pol* and *env*. *Gag* encompasses information for nonglycosylated viral proteins that form the matrix, the capsid and the nucleoprotein structures. From *pol* derive reverse transcriptase and integrase, and *env* codes for the surface glycoproteins of the virion which consist of a transmembrane and a surface domain, linked by disulfide bonds. A viral protease is derived either from the *gag* or from the *pol* coding region, depending on the virus. Simple retroviruses contain only this elementary *gag*, *pol*, and *env* coding information. Once integrated, they are able to multiply efficiently, using the cellular transcriptional and replication machineries without intervention of viral transacting factors. Most oncogenic retroviruses belong in this category.

Complex retroviruses, on the other hand, encode additional nonstructural proteins from multiply spliced messages. These proteins play important regulatory roles in the life cycle of the virus. They function as transacting factors that, in concert with cellular regulatory proteins, control viral gene expression and function and are essential components in the replication of complex retroviruses. To this category belong the lentiviruses, the spumaviruses and a group of oncogenic retroviruses that includes human T cell leukemia virus (HTLV) and bovine leukosis virus(BLV).

The additional layer of regulation found in complex retroviruses is the subject of this volume of *Current Topics in Microbiology and Immunology*. All human retroviruses isolated to date, be they lentiviruses, spumaviruses, or oncogenic retroviruses, have complex genomes. The regulatory mechanisms available to these viruses may enhance their ability to survive and persist in the host. For instance, virus is present in only a small fraction (0.1%–10%) of potential target cells in individuals infected with human immunodeficiency virus (HIV) or with HTLV. Transacting proteins such as Tat of HIV or Tax of HTLV are part of a positive feedback loop that can lead to rapidly increasing rates of viral expression and production of

progeny virus. Interruption of this feedback loop can result in an equally rapid decline of virus production. Thus, in the expression of complex retroviruses bursts of activity may be followed by periods of relative quiescence. This form of regulation may reduce immune recognition of the infected cell and still allow efficient spread of the virus.

Retroviral transacting proteins work through interaction with the cellular regulatory machinery, including various signal transduction, translocation and transcription factors. Several specific biochemical interactions between retroviral transactivating proteins and cellular factors have recently been elucidated. The Tax protein of HTLV has been shown to interact with members of the NF-κB family of transcription factors, and cellular proteins binding to the Tat protein of HIV have also been identified. Thus, the study of viral regulatory mechanisms is providing insights into control elements of the cell.

The interaction of viral factors with the cellular regulatory machinery does not merely facilitate and guide virus reproduction, it inevitably disturbs normal cellular controls. Both the Tax and the Tat proteins are known to affect the levels of cellular growth factors and of transcription factors, and these primary changes can initiate cascades of secondary effects. This interference with cellular regulation appears to play an important role in the pathogenesis of these viruses.

There are at present neither protective vaccines nor curative therapeutic agents available for human retrovirus infections. HIV infections continue to spread, and the suffering and death toll from acquired immunodeficiency syndrome (AIDS) are still on the rise worldwide. Retrovirology is responding to this challenge by concentrating great efforts on the development of a defense against HIV. The transacting proteins of complex retroviruses are attractive targets for therapeutic intervention. They are indispensable for the virus and therefore represent a point of viral vulnerability, and they appear unrelated to cellular proteins allowing, at least theoretically, for highly specific drug-virus interactions without deleterious side effects for the cell. In order to achieve this goal of shutting down a human retrovirus infection by blocking the function of an essential viral protein, a thorough understanding of that viral target will be necessary. It is hoped that this volume, in summarizing the current knowledge in this area, will contribute towards the conquest of disease.

Los Angeles, Philadelphia,
and La Jolla

Irvin S.Y. Chen
Hilary Koprowski
Alagarsamy Srinivasan
Peter K. Vogt

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