Replication-Competent Viruses for Cancer Therapy
Replication-Competent Viruses for Cancer Therapy

Volume Editors

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18 figures, 1 in color, and 12 tables, 2001
Drug Dosage. The authors and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

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Introduction

Cancer plays a major role in human morbidity and mortality. Unfortunately a considerable proportion of cancer is not amenable to surgery and needs to be treated by chemotherapy and/or irradiation. These approaches are characterized by an extremely narrow therapeutic index and major efforts in medical oncology are dedicated to treating their adverse effects. Viruses provide an alternate biological approach to cancer therapy. Initial attempts at the clinical application of viruses during the middle part of the 20th century were fraught with significant side effects and large variability in antitumor activity, likely due to the use of wild-type virus, passage-attenuated virus or infected cell lysates.

With the increase in our understanding of the molecular underpinnings of malignant cells and viruses it has been possible to exploit viruses for cancer therapy. The malignant behavior of a tumor cell is based on genetic alterations that create an imbalance between growth and growth control. The transformed phenotype provides a permissive environment for some viruses or functions to complement viral mutations. Oncolytic viruses are able to selectively replicate in tumor cells and kill them. A major advantage of such replication-competent viruses is this in situ amplification and subsequent spread within the tumor. However, cytotoxicity must be limited or controlled so that normal tissue is not harmed and pathology is minimized.

This book reviews many of the replication-competent viruses currently being pursued for cancer therapy, including those in clinical trial, and highlights features of viral biology that can be harnessed for therapy. These viruses cover the spectrum of animal viruses from RNA to DNA, single-stranded to double-stranded and enveloped to non-enveloped (table 1). Targeting of herpes simplex
virus (HSV) and vaccinia virus is mainly accomplished by mutating genes required for DNA replication in nondividing cells, such as ribonucleotide reductase and thymidine kinase, or virulence. Mutations in adenovirus E1a and E1b genes create viruses that can replicate in cells lacking Rb and p53 activity, respectively, which are common alterations in cancer cells but not normal cells. Therefore, the transformed phenotype is permissive for these mutants, as it is for reovirus which utilizes an activated Ras pathway, autonomous paroviruses and Newcastle disease virus. Viruses can also be engineered to selectively replicate in tumor cells by transcriptional regulation of essential genes with tumorspecific promoters/enhancers, such as prostate-specific adenovirus and hepatoma-specific HSV. These examples illustrate the variety and complexity of viral strategies for cancer therapy, and how virus–host interactions can be exploited. The field of oncolytic viruses is in its infancy and this monograph provides an overview of those viruses being employed and how this approach is being translated to the clinic.

We would like to thank the authors who have been instrumental in moving the field forward, those patients who have participated in clinical trials in the hope of a better treatment for cancer, and the ‘Frankfurter Stiftung für Krebskranke Kinder’ that has promoted this new approach to cancer therapy by generously sponsoring this book.

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