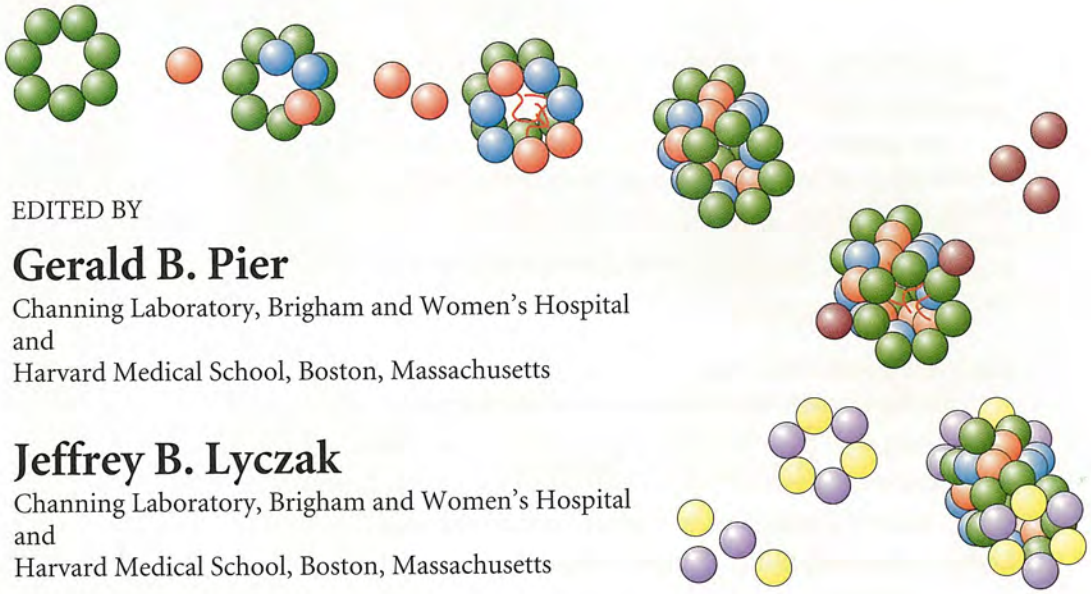
Immunology, Infection, and Immunity



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ASM PRESS
WASHINGTON, D.C.

Genome & Co. v. Univ. of Chicago
PGR2019-00002
UNIV. CHICAGO EX. 2024

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Phone: (800) 546-2416 or (703) 661-1593
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E-mail: books@asmusa.org
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American Society for Microbiology
1752 N St. NW
Washington, DC 20036-2904

Library of Congress Cataloging-in-Publication Data

Immunology, infection, and immunity / edited by Gerald B. Pier, Jeffrey B. Lyczak, Lee M. Wetzler.
p. ; cm.
Includes bibliographical references and index.
ISBN 1-55581-246-5 (hardcover)
1. Immunology. 2. Infection.
[DNLM: 1. Immune System. 2. Immunity, Cellular. 3. Immunologic Diseases. 4. Infection. QW 504 I333 2004] I. Pier, Gerald Bryan. II. Lyczak, Jeffrey B. III. Wetzler, Lee M. IV. Title.
QR181.I443 2004
616.07'9—dc21

2003002554

10 9 8 7 6 5 4 3 2 1

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chapter 24

Cancer and the Immune System

Lisa H. Butterfield, Stephen P. Schoenberger, and Jeffrey B. Lyczak

topics covered

- Genetic and physiological aspects of tumorigenesis
- Immune recognition of tumors: tumor antigens
- Immune cell types that respond to tumors
- Cancer immunotherapies

Cancer can be considered as a disease resulting from the progressive cellular expansion of a single cell whose progeny have escaped from normal regulatory mechanisms controlling cell division and homeostasis. At first glance, cancer appears to be a vast and bewildering array of diseases, with as many different types of cancer as there are types of cells in the body (Table 24.1). There are, in fact, over 100 different types of cancer known, and subtypes of these disease states can be found within specific organs. As methods for the treatment and prevention of infectious and cardiovascular diseases improve, cancer is emerging as the leading cause of death in industrialized countries (Fig. 24.1). Although conventional cancer treatments such as surgery, chemotherapy, and radiation have greatly enhanced patient survival, manipulation of the immune response to cancer cells to promote their destruction remains an important and increasingly realistic goal for physicians. Immunological control of cancers could conceivably play a role in the eradication of primary tumors and disseminated metastases as well as the residual cancer cells that remain after conventional treatment regimens. The ideal result of immunotherapy would be the specific eradication of cancer cells with minimal damage to normal host cells. However, almost by definition a tumor cell has escaped immunologic recognition and progressed to cancer because the affected patient's immune system did not control tumor growth. Attainment of the goal of effective immunotherapy for tumors requires an understanding of how the immune system both fails to respond to cancer cells and has the potential to respond and the ways in which this response can be strategically manipulated.

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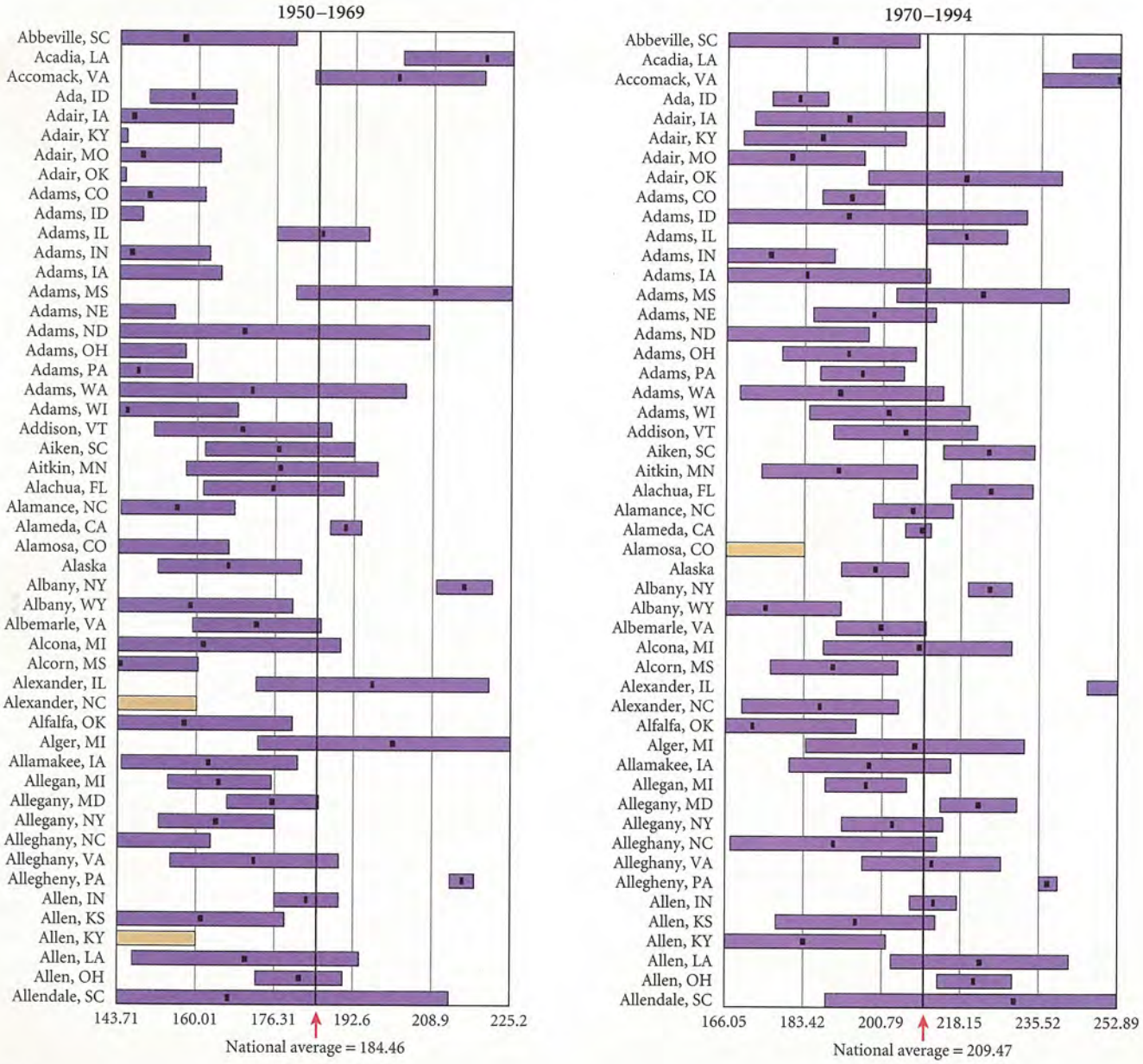
Table 24.1 Nomenclature of several types of cancer

Normal tissue	Benign tumor[a]	Malignant tumor[b]
Blood vessels	Angioma	Angiosarcoma
Bone	Osteoma	Osteosarcoma
Cartilage	Chondroma	Chondrosarcoma
Epithelium	Papilloma	Carcinoma
Glandular epithelium	Adenoma	Adenocarcinoma
Liver hepatocytes	Hepatoma	Hepatocarcinoma
Skeletal muscle	Rhabdomyoma	Rhabdomyosarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma

[a]Benign tumors are anatomically restricted to their original tissue site.
[b]Malignant tumors are capable of spreading (metastasis) to distant sites.

Figure 24.1 Cancer deaths in the United States, comparing the period from 1950 to 1969 with the period from 1970 to 1994. Data are for white males of all ages, are grouped according to county, and are expressed as the number of cancer-related deaths per 100,000 person-years. The vertical black bar in the center of each graph shows the nationwide average of cancer-related deaths. Data are from the National Cancer Institute's Atlas of Cancer Mortality, which can be viewed at http://www3.cancer.gov/atlasplus/.



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Cancer Is a Disease of Genes

Through intensive research efforts over the past 25 years, cancer is now understood as a series of defects in the molecular machinery that governs proliferation and homeostasis in nearly all cell types. Normal cellular growth within an organism is kept in balance by various regulatory circuits that govern the rate at which cells divide, differentiate, and die. Some of these regulatory circuits are intrinsic to the cell whereas others are coupled to the signals that cells receive from their surrounding microenvironment (Fig. 24.2). Cancer arises through a process termed *neoplastic transformation* that occurs when a cell undergoes a series of genetic alterations and acquires the capability to escape these regulatory mechanisms. This process is thought to occur in a discrete stepwise process involving the age-related incidence of four to seven stochastic events that drive the transformation of a normal cell into highly malignant clonal derivatives (Fig. 24.3). This process is similar to a Darwinian model of evolution, in that each genetic change confers a growth advantage that leads to overrepresentation of the altered cell. The successive and heritable nature of cellular transformation events is supported by histological analyses of precancerous lesions revealing cells that appear to represent intermediate steps in the pathway between normal and transformed cells.

Another known situation that establishes a genetic basis for cancer comes from studies that have identified certain mutant forms of normal genes that predispose individuals to be at a greater risk for a given type of cancer. For example, women have a 10% lifetime risk for developing breast cancer, but among these patients are a small percentage with mutations in one of two genes, *BRCA1* and *BRCA2*, that greatly increase the risk of developing breast cancer. However, even carrying a high-risk mutation in the *BRCA* genes does not inevitably lead to breast cancer as 20 to 30% of women with mutant genes never develop this disease. Thus there are clearly modifier genes that can counteract the negative effects of the mutant genes. Other genetic predispositions to cancer include colon cancer associated with the adenomatous polyposis coli gene on chromosome 5; hereditary nonpolyposis colon cancer associated with DNA mismatch repair genes on chromosomes 2, 3, and 7; melanoma associated with the

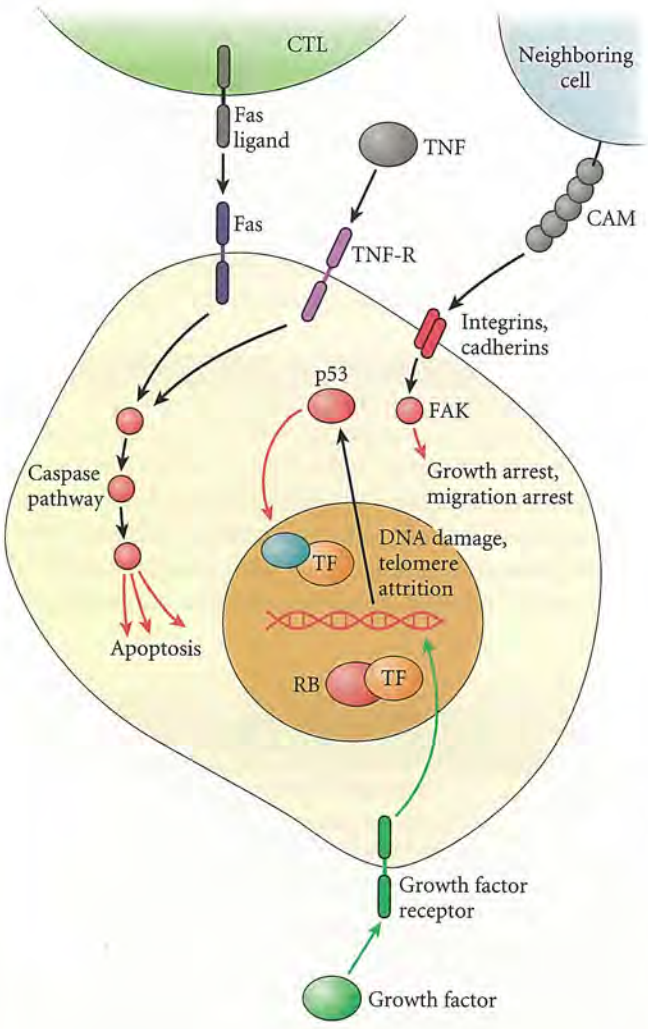

Figure 24.2 Schematic diagram of a typical eukaryotic cell showing the factors or conditions that regulate its growth. Exogenous factors, stimuli, or cues are shown in black type. Growth inhibitory factors and events are shown with red arrows. Growth stimulatory factors and events are shown with green arrows. TNF-R, tumor necrosis factor receptor; CAM, cell adhesion molecule; FAK, focal adhesion kinase; RB, retinoblastoma tumor suppressor protein; TF, transcription factor.

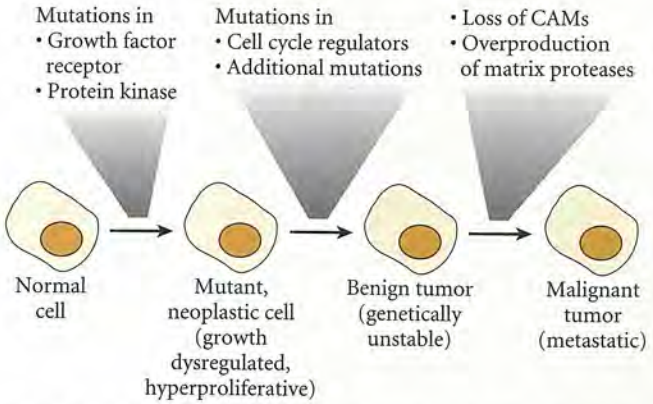

Figure 24.3 The multistep process of tumorigenesis. The cell, which is originally normal (at the left), undergoes several genetic changes in a stepwise fashion. Each genetic change results in a phenotypic alteration that favors unregulated growth, exemption from apoptotic signals, genetic instability, and metastasis (ability to spread from its original tissue site to other remote tissues of the host).

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