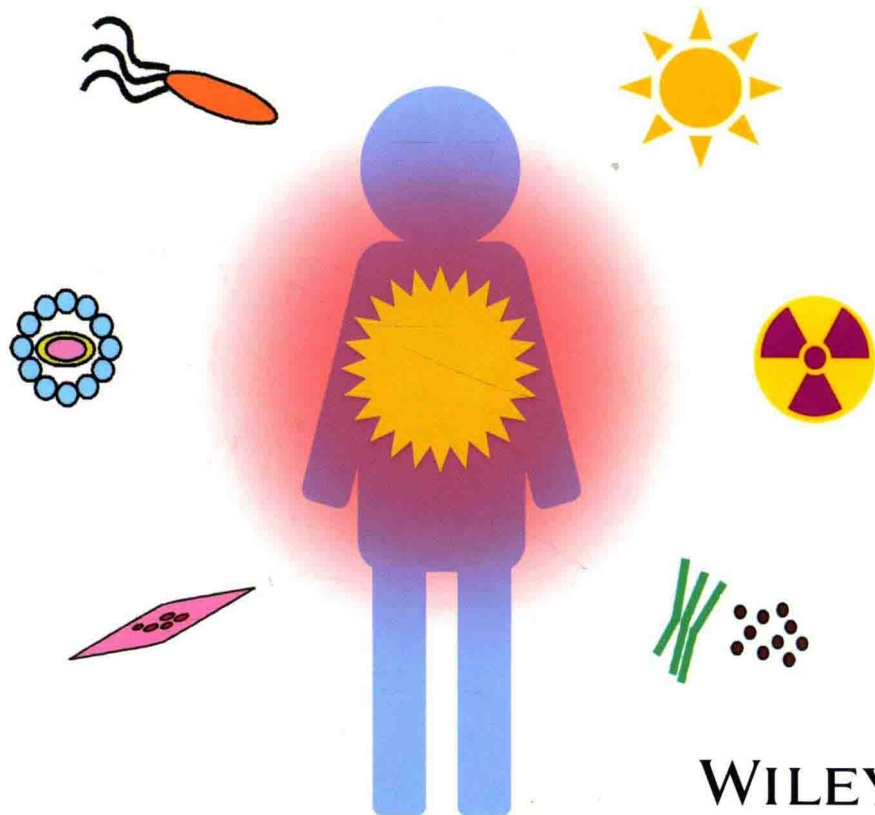


Cancer and Inflammation Mechanisms

Chemical, Biological, and Clinical Aspects

Edited by

Yusuke Hiraku, Shosuke Kawanishi, Hiroshi Ohshima



WILEY

CANCER AND INFLAMMATION MECHANISMS

Chemical, Biological, and Clinical Aspects

Edited by

YUSUKE HIRAKU

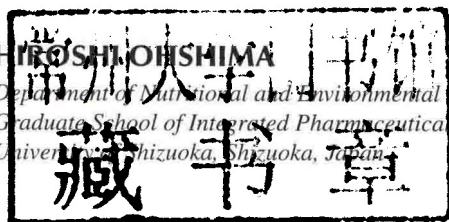
*Department of Environmental and Molecular Medicine
Mie University Graduate School of Medicine, Tsu, Mie, Japan*

SHOSUKE KAWANISHI

*Faculty of Pharmaceutical Sciences
Suzuka University of Medical Science, Suzuka, Mie, Japan*

HIROSHI OHSHIMA

*Department of Nutritional and Environmental Sciences
Graduate School of Integrated Pharmaceutical and Nutritional Sciences
University of Shizuoka, Shizuoka, Japan*



WILEY

Copyright © 2014 by John Wiley & Sons, Inc. All rights reserved.

Published by John Wiley & Sons, Inc., Hoboken, New Jersey.

Published simultaneously in Canada.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning, or otherwise, except as permitted under Section 107 or 108 of the 1976 United States Copyright Act, without either the prior written permission of the Publisher, or authorization through payment of the appropriate per-copy fee to the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, (978) 750-8400, fax (978) 750-4470, or on the web at www.copyright.com. Requests to the Publisher for permission should be addressed to the Permissions Department, John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, (201) 748-6011, fax (201) 748-6008, or online at <http://www.wiley.com/go/permission>.

Limit of Liability/Disclaimer of Warranty: While the publisher and author have used their best efforts in preparing this book, they make no representations or warranties with respect to the accuracy or completeness of the contents of this book and specifically disclaim any implied warranties of merchantability or fitness for a particular purpose. No warranty may be created or extended by sales representatives or written sales materials. The advice and strategies contained herein may not be suitable for your situation. You should consult with a professional where appropriate. Neither the publisher nor author shall be liable for any loss of profit or any other commercial damages, including but not limited to special, incidental, consequential, or other damages.

For general information on our other products and services or for technical support, please contact our Customer Care Department within the United States at (800) 762-2974, outside the United States at (317) 572-3993 or fax (317) 572-4002.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic formats. For more information about Wiley products, visit our web site at www.wiley.com.

Library of Congress Cataloging-in-Publication Data:

Cancer and inflammation mechanisms : chemical, biological, and clinical aspects /

edited by Dr. Yusuke Hiraku, Dr. Shosuke Kawanishi, Dr. Hiroshi Ohshima.

1 online resource.

Includes index.

ISBN 978-1-118-82655-3 (ePub) – ISBN 978-1-118-82667-6 (Adobe PDF)

– ISBN 978-1-118-16030-5 (cloth) 1. Carcinogenesis. 2. Inflammation—Mediators.

3. Inflammation—Immunological aspects. 4. Cancer—Immunological aspects.

I. Hiraku, Yusuke, editor of compilation. II. Kawanishi, Shosuke, 1942– editor of compilation.

III. Ohshima, Hiroshi, 1949– editor of compilation.

RC268.5

616.99'401–dc23

2013039801

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

*CANCER AND INFLAMMATION
MECHANISMS*

CONTRIBUTORS

Helmut Bartsch Division of Toxicology and Cancer Risk Factors, German Cancer Research Center, Heidelberg, Germany

Michele Carbone University of Hawai'i Cancer Center, University of Hawai'i, Honolulu, HI, United States

Department of Pathology, John. A. Burns School of Medicine, University of Hawai'i, Honolulu, HI, United States

Fu Chen Department of Radiation Oncology, Eye Ear Nose & Throat Hospital of Fudan University, Shanghai, China

Kaiwen W. Chen Institute for Molecular Bioscience, The University of Queensland, St Lucia, Australia

Tsutomu Chiba Department of Gastroenterology and Hepatology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Pei-Hsin Chou Department of Environmental Engineering, National Cheng Kung University, Tainan, Taiwan

Kyung-Soo Chun College of Pharmacy, Keimyung University, Daegu, South Korea

Jonas Fuxe Department of Medical Biochemistry and Biophysics, Division of Vascular Biology, Karolinska Institute, Stockholm, Sweden

Giovanni Gaudino University of Hawai'i Cancer Center, University of Hawai'i, Honolulu, HI, United States

Alexandros G. Georgakilas Physics Department, School of Applied Mathematical and Physical Sciences, National Technical University of Athens, Zografou Campus, Athens, Greece

Zhaojian Gong Hunan Key Laboratory of Nonresolving Inflammation and Cancer, Disease Genome Research Center, The Third Xiangya Hospital, Central South University, Changsha, China

Cancer Research Institute, Key Laboratory of Carcinogenesis of Ministry of Health, Key Laboratory of Carcinogenesis and Cancer Invasion of Ministry of Education, Central South University, Changsha, China

Department of Stomatology, The Second Xiangya Hospital, Central South University, Changsha, China

Yusuke Hiraku Department of Environmental and Molecular Medicine, Mie University Graduate School of Medicine, Tsu, Mie, Japan

Lorne J. Hofseth Department of Pharmaceutical and Biomedical Sciences, South Carolina College of Pharmacy, University of South Carolina, Columbia, SC, United States

Tingting Huang Department of Radiation Oncology, First Affiliated Hospital of Guangxi Medical University, Nanning, China

Sandro Jube University of Hawai'i Cancer Center, University of Hawai'i, Honolulu, HI, United States

Mikael C. I. Karlsson Department of Medicine, Translational Immunology Unit, Karolinska Institutet, Karolinska Hospital, Stockholm, Sweden

Shosuke Kawanishi Faculty of Pharmaceutical Sciences, Suzuka University of Medical Science, Suzuka, Mie, Japan

Ching-Lung Lai Department of Medicine, the University of Hong Kong, Queen Mary Hospital, Hong Kong

State Key Laboratory for Liver Research, the University of Hong Kong, Queen Mary Hospital, Hong Kong

Danae A. Laskaratou Physics Department, School of Applied Mathematical and Physical Sciences, National Technical University of Athens, Zografou Campus, Athens, Greece

Guiyuan Li Hunan Key Laboratory of Nonresolving Inflammation and Cancer, Disease Genome Research Center, the Third Xiangya Hospital, Central South University, Changsha, China

Cancer Research Institute, Key Laboratory of Carcinogenesis of Ministry of Health, Key Laboratory of Carcinogenesis and Cancer Invasion of Ministry of Education, Central South University, Changsha, China

Xiaoling Li Hunan Key Laboratory of Nonresolving Inflammation and Cancer, Disease Genome Research Center, The Third Xiangya Hospital, Central South University, Changsha, China

Cancer Research Institute, Key Laboratory of Carcinogenesis of Ministry of Health, Key Laboratory of Carcinogenesis and Cancer Invasion of Ministry of Education, Central South University, Changsha, China

Xiayu Li Hunan Key Laboratory of Nonresolving Inflammation and Cancer, Disease Genome Research Center, the Third Xiangya Hospital, Central South University, Changsha, China

Cancer Research Institute, Key Laboratory of Carcinogenesis of Ministry of Health, Key Laboratory of Carcinogenesis and Cancer Invasion of Ministry of Education, Central South University, Changsha, China

Yong Li Department of Biochemistry and Molecular Biology, Center for Genetics and Molecular Medicine, School of Medicine, University of Louisville, Louisville, KY, United States

Jian Ma Hunan Key Laboratory of Nonresolving Inflammation and Cancer, Disease Genome Research Center, The Third Xiangya Hospital, Central South University, Changsha, China

Cancer Research Institute, Key Laboratory of Carcinogenesis of Ministry of Health, Key Laboratory of Carcinogenesis and Cancer Invasion of Ministry of Education, Central South University, Changsha, China

Hiroyuki Marusawa Department of Gastroenterology and Hepatology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Tomonari Matsuda Research Center for Environmental Quality Management, Kyoto University, Otsu, Shiga, Japan

William Matsui Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, United States

Ifigeneia V. Mavragani Physics Department, School of Applied Mathematical and Physical Sciences, National Technical University of Athens, Zografou Campus, Athens, Greece

Pranab Behari Mazumder Department of Biochemistry and Molecular Biology, Center for Genetics and Molecular Medicine, School of Medicine, University of Louisville, Louisville, KY, United States

Noriyuki Miyoshi Department of Nutritional and Environmental Sciences, Graduate School of Integrated Pharmaceutical and Nutritional Sciences, University of Shizuoka, Shizuoka, Japan

Yiqun Mo Department of Environmental and Occupational Health Sciences, School of Public Health and Information Sciences, University of Louisville, Louisville, KY, United States

Akira Murakami Division of Food Science and Biotechnology, Graduate School of Agriculture, Kyoto University, Kyoto, Japan

Michihiro Mutoh Division of Cancer Prevention Research, National Cancer Center Research Institute, Tokyo, Japan

Urmila Jagadeesan Nair Division of Toxicology and Cancer Risk Factors, German Cancer Research Center, Heidelberg, Germany

Unit of Cancer Prevention and WHO Collaborating Center, German Cancer Research Center, Heidelberg, Germany

Andrea Napolitano University of Hawai'i Cancer Center, University of Hawai'i, Honolulu, HI, United States

Department of Molecular Biosciences and Bioengineering, University of Hawai'i, Honolulu, HI, United States

Chikako Nishigori Division of Dermatology, Department of Internal Related, Kobe University Graduate School of Medicine, Kobe, Japan

Hiroshi Ohshima Department of Nutritional and Environmental Sciences, Graduate School of Integrated Pharmaceutical and Nutritional Sciences, University of Shizuoka, Shizuoka, Japan

Futoshi Okada Division of Pathological Biochemistry, Tottori University Faculty of Medicine, Yonago, Tottori, Japan

Chromosome Engineering Research Center, Tottori University, Yonago, Tottori, Japan

Harvey I. Pass Department of Cardiothoracic Surgery, NYU Langone Medical Center, New York, NY, United States

Angela Poehlmann Department of Pathology, Otto-von-Guericke University Magdeburg, Magdeburg, Germany

Deepak Poudyal Department of Pharmaceutical and Biomedical Sciences, South Carolina College of Pharmacy, University of South Carolina, Columbia, SC, United States

Ayanthi A. Richards Institute for Molecular Bioscience, The University of Queensland, St Lucia, Australia

Albert Roessner Department of Pathology, Otto-von-Guericke University Magdeburg, Magdeburg, Germany

Kurt J. Sales Institute of Infectious Disease and Molecular Medicine and Division of Medical Biochemistry, University of Cape Town Faculty of Health Sciences, Observatory, Cape Town, South Africa

Kate Schroder Institute for Molecular Bioscience, The University of Queensland, St Lucia, Australia

Australian Infectious Disease Research Centre, The University of Queensland, St Lucia, Australia

Wai-Kay Seto Department of Medicine, the University of Hong Kong, Queen Mary Hospital, Hong Kong

Haruhiko Sugimura Department of Pathology, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka, Japan

Young-Joon Surh Tumor Microenvironment Global Core Research Center, College of Pharmacy, Seoul National University, Seoul, South Korea

Mami Takahashi Central Animal Division, National Cancer Center Research Institute, Tokyo, Japan

Osamu Takeuchi Laboratory of Infection and Prevention, Institute for Virus Research Centre, Kyoto University, Kyoto, Japan

Toshihiko Tanno Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, United States

Sarang Tartey Laboratory of Infection and Prevention, Institute for Virus Research Centre, Kyoto University, Kyoto, Japan

Department of Host Defense, WPI Immunology Frontier Research Centre, Osaka University, Suita, Osaka, Japan

David J. Tollerud Department of Environmental and Occupational Health Sciences, School of Public Health and Information Sciences, University of Louisville, Louisville, KY, United States

Susumu Tomono Department of Nutritional and Environmental Sciences, Graduate School of Integrated Pharmaceutical and Nutritional Sciences, University of Shizuoka, Shizuoka, Japan

Keiji Wakabayashi Division of Nutritional and Environmental Sciences, University of Shizuoka, Shizuoka, Japan

Rong Wan Department of Environmental and Occupational Health Sciences, School of Public Health and Information Sciences, University of Louisville, Louisville, KY, United States

Xue Xiao Department of Otolaryngology-Head & Neck Surgery, First Affiliated Hospital of Guangxi Medical University, Nanning, China

Wei Xiong Hunan Key Laboratory of Nonresolving Inflammation and Cancer, Disease Genome Research Center, The Third Xiangya Hospital, Central South University, Changsha, China

Cancer Research Institute, Key Laboratory of Carcinogenesis of Ministry of Health, Key Laboratory of Carcinogenesis and Cancer Invasion of Ministry of Education, Central South University, Changsha, China

Haining Yang University of Hawai'i Cancer Center, University of Hawai'i, Honolulu, HI, United States

Department of Pathology, John. A. Burns School of Medicine, University of Hawai'i, Honolulu, HI, United States

Man-Fung Yuen Department of Medicine, the University of Hong Kong, Queen Mary Hospital, Hong Kong

State Key Laboratory for Liver Research, the University of Hong Kong, Queen Mary Hospital, Hong Kong

Alina Zamoshnikova Institute for Molecular Bioscience, The University of Queensland, St Lucia, Australia

Zhaoyang Zeng Hunan Key Laboratory of Nonresolving Inflammation and Cancer, Disease Genome Research Center, The Third Xiangya Hospital, Central South University, Changsha, China

Cancer Research Institute, Key Laboratory of Carcinogenesis of Ministry of Health, Key Laboratory of Carcinogenesis and Cancer Invasion of Ministry of Education, Central South University, Changsha, China

Qunwei Zhang Department of Environmental and Occupational Health Sciences, School of Public Health and Information Sciences, University of Louisville, Louisville, KY, United States

Zhe Zhang Department of Otolaryngology-Head & Neck Surgery, First Affiliated Hospital of Guangxi Medical University, Nanning, China

Ming Zhou Hunan Key Laboratory of Nonresolving Inflammation and Cancer, Disease Genome Research Center, The Third Xiangya Hospital, Central South University, Changsha, China

Cancer Research Institute, Key Laboratory of Carcinogenesis of Ministry of Health, Key Laboratory of Carcinogenesis and Cancer Invasion of Ministry of Education, Central South University, Changsha, China

Xiaoying Zhou Department of Otolaryngology-Head & Neck Surgery, First Affiliated Hospital of Guangxi Medical University, Nanning, China

PREFACE

Cancer is a life-threatening human disease, and it is estimated that approximately 25% of cancer cases worldwide are attributed to chronic inflammation. In the nineteenth century, Rudolf Virchow noted leucocytes in neoplastic tissues and suggested that the “lymphoreticular infiltrate” reflected the origin of cancer at sites of chronic inflammation. Since then, numerous epidemiological and experimental studies have provided evidence of linkage between inflammation and cancer. Chronic inflammation can be induced by a wide variety of environmental factors, such as infectious agents, inflammatory diseases, and physicochemical factors.

The aim of this book is to review current knowledge on the linkage between chronic inflammation and cancer, and to discuss comprehensively the mechanisms of carcinogenesis in terms of its chemical, biological, and clinical aspects. Future perspectives of chemoprevention of inflammation-related cancer are included. The book consists of the following sections:

Section I: General overview of inflammation-related cancer. The book begins with a general overview of the mechanisms of carcinogenesis mediated by chronic infection and inflammation. This is followed by topics in emerging fields of cancer biology, such as stem cell theory and epithelial–mesenchymal transition, and their roles in inflammation-related carcinogenesis are discussed.

Section II: Biochemistry in inflammation-related cancer. During chronic inflammation, reactive oxygen and nitrogen species are generated in biological systems and attack various biomolecules, including DNA. In this section the role of DNA damage mediated by reactive species in inflammation-related carcinogenesis and a comprehensive analytical method for DNA adducts (the “adductome” approach) are discussed.

Section III: Molecular biology in inflammation-related cancer. The main topics in this section are current knowledge on inflammation-related molecules, such as Toll-like receptors, inflammasome, activation-induced cytidine deaminase, and microRNAs, and their roles in carcinogenesis. An experimental animal model to investigate the role of inflammation in tumor progression is also reviewed.

Section IV: Inflammation-related cancer induced by specific causes. This section covers the mechanism of carcinogenesis mediated by oncogenic viruses such as human papillomavirus, hepatitis viruses, and Epstein–Barr virus, and inflammatory diseases such as Barrett’s esophagus. Also covered are the mechanisms of carcinogenesis induced by physicochemical factors such as asbestos, nanomaterials, ultraviolet light, and ionizing radiation.

Section V: Prevention of inflammation-related carcinogenesis. While the first four sections deal primarily with the mechanisms of inflammation-related

carcinogenesis, this section includes a perspective and strategy of cancer chemoprevention using anti-inflammatory agents and natural components.

The target audience for this book includes researchers in the fields of medical, biological, and pharmacological sciences and clinical medicine. We also expect undergraduate and postgraduate students of these fields to be interested in the book. We are extremely grateful to all authors who contributed to the book. Finally, we thank Jonathan Rose and Amanda Amanullah for providing us with the opportunity to edit this book and for helpful advice throughout the editorial process.

YUSUKE HIRAKU
SHOSUKE KAWANISHI
HIROSHI OHSHIMA

CONTENTS

CONTRIBUTORS	ix
--------------	----

PREFACE	xv
---------	----

SECTION I *GENERAL OVERVIEW OF INFLAMMATION-RELATED CANCER*

CHAPTER 1	<i>INFECTION, INFLAMMATION, AND CANCER: OVERVIEW</i>	1
	Hiroshi Ohshima, Noriyuki Miyoshi, and Susumu Tomono	

CHAPTER 2	<i>STEM CELL THEORY AND INFLAMMATION-RELATED CANCER</i>	9
	Toshihiko Tanno and William Matsui	

CHAPTER 3	<i>EPITHELIAL-MESENCHYMAL TRANSITION: A LINK BETWEEN CANCER AND INFLAMMATION</i>	23
	Jonas Fuxe and Mikael C. I. Karlsson	

SECTION II *BIOCHEMISTRY IN INFLAMMATION-RELATED CANCER*

CHAPTER 4	<i>ROLE OF NITRATIVE DNA DAMAGE IN INFLAMMATION- RELATED CARCINOGENESIS</i>	41
	Yusuke Hiraku and Shosuke Kawanishi	

CHAPTER 5	<i>LIPID PEROXIDATION-DERIVED DNA ADDUCTS AND THE ROLE IN INFLAMMATION-RELATED CARCINOGENESIS</i>	61
	Helmut Bartsch and Urmila Jagadeesan Nair	

CHAPTER 6	<i>LEVEL OF INFLAMMATION-RELATED DNA ADDUCTS IN HUMAN TISSUES</i>	75
	Tomonari Matsuda, Pei-Hsin Chou, and Haruhiko Sugimura	

SECTION III <i>MOLECULAR BIOLOGY IN INFLAMMATION-RELATED CANCER</i>		
CHAPTER 7	<i>TOLL-LIKE RECEPTORS: ROLE IN INFLAMMATION AND CANCER</i> Sarang Tartey and Osamu Takeuchi	83
CHAPTER 8	<i>INFLAMMASOMES AND INFLAMMATION</i> Kaiwen W. Chen, Ayanthi A. Richards, Alina Zamoshnikova, and Kate Schroder	103
CHAPTER 9	<i>ACTIVATION-INDUCED CYTIDINE DEAMINASE: AN INTRINSIC GENOME MODULATOR IN INFLAMMATION-ASSOCIATED CANCER DEVELOPMENT</i> Hiroyuki Marusawa and Tsutomu Chiba	119
CHAPTER 10	<i>MicroRNA AND INFLAMMATION-RELATED CANCER</i> Zhaojian Gong, Zhaoyang Zeng, Pranab Behari Mazumder, Jian Ma, Ming Zhou, Xiayu Li, Xiaoling Li, Wei Xiong, Yong Li, and Guiyuan Li	131
CHAPTER 11	<i>INFLAMMATION AS A NICHE FOR TUMOR PROGRESSION</i> Futoshi Okada	149
SECTION IV <i>INFLAMMATION-RELATED CANCER INDUCED BY SPECIFIC CAUSES</i>		
CHAPTER 12	<i>HUMAN PAPILLOMAVIRUS AND CERVICAL CANCER</i> Kurt J. Sales	165
CHAPTER 13	<i>HEPATITIS VIRUSES AND HEPATOCELLULAR CARCINOMA</i> Wai-Kay Seto, Ching-Lung Lai, and Man-Fung Yuen	181
CHAPTER 14	<i>EPSTEIN-BARR VIRUS AND NASOPHARYNGEAL CARCINOMA</i> Xiaoying Zhou, Xue Xiao, Fu Chen, Tingting Huang, and Zhe Zhang	193
CHAPTER 15	<i>BARRETT'S ESOPHAGUS AND ESOPHAGEAL CANCER</i> Albert Roessner and Angela Poehlmann	213

CHAPTER 16	<i>ASBESTOS-INDUCED CHRONIC INFLAMMATION AND CANCER</i> Andrea Napolitano, Sandro Jube, Giovanni Gaudino, Harvey I. Pass, Michele Carbone, and Haining Yang	223
CHAPTER 17	<i>NANOMATERIALS</i> Yiqun Mo, Rong Wan, David J. Tollerud, and Qunwei Zhang	235
CHAPTER 18	<i>INFLAMMATORY PATHWAYS OF RADIATION-INDUCED TISSUE INJURY</i> Danae A. Laskaratou, Ifigeneia V. Mavragani, and Alexandros G. Georgakilas	249
CHAPTER 19	<i>PHOTOCARCINOGENESIS AND INFLAMMATION</i> Chikako Nishigori	271
SECTION V. PREVENTION OF INFLAMMATION-RELATED CARCINOGENESIS		
CHAPTER 20	<i>CHEMOPREVENTION OF COLORECTAL CANCER BY ANTI-INFLAMMATORY AGENTS</i> Michihiro Mutoh, Mami Takahashi, and Keiji Wakabayashi	285
CHAPTER 21	<i>NUTRACEUTICALS AND COLON CANCER PREVENTION</i> Deepak Poudyal and Lorne J. Hofseth	301
CHAPTER 22	<i>CANCER CHEMOPREVENTION BY TARGETING COX-2 USING DIETARY PHYTOCHEMICALS</i> Kyung-Soo Chun and Young-Joon Surh	339
CHAPTER 23	<i>REGULATION OF INFLAMMATION-ASSOCIATED INTESTINAL DISEASES WITH PHYTOCHEMICALS</i> Akira Murakami	355
	<i>INDEX</i>	371

INFECTION, INFLAMMATION, AND CANCER: OVERVIEW

Hiroshi Ohshima, Noriyuki Miyoshi, and Susumu Tomono

It has been estimated that about 2 million (16.1%) of the total 12.7 million new cancer cases in 2008 were attributable to infections (1). This percentage was higher in less-developed (22.9%) than in more-developed (7.4%) countries, and varied 10-fold by region from 3.3% in Australia and New Zealand to 32.7% in sub-Saharan Africa. Four major infections with *Helicobacter pylori*, hepatitis B and C viruses, and human papillomavirus are estimated to be responsible for 1.9 million cases of gastric, liver, and cervical cancer. Cervical cancer accounts for about half of the infection-related burden of cancer in women, and in men liver and gastric cancers account for over 80%. In addition, as shown in Table 1.1, chronic infection by a variety of viruses, bacteria, or parasites and tissue inflammation such as gastritis and hepatitis, which are often caused by chronic infection, are recognized risk factors for human cancers at various sites. Furthermore, the chronic inflammation induced by chemical and physical agents such as tobacco smoke and asbestos is also associated with an increased risk of cancer. Thus, chronic bronchitis and emphysema lead to increased risks of lung cancer. Inhalation of asbestos causes chronic lung and pleural inflammation and increases the risk of mesothelioma. Gastroesophageal reflux disease and Barrett's esophagus, which are caused by abdominal obesity, gastroesophageal reflux, and cigarette smoking, induce chronic inflammation and increase the risk of esophageal adenocarcinoma. Autoimmune and inflammatory diseases of uncertain etiology are also associated with an increased risk of cancer. For example, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis are associated with an increased risk of colon cancer. There is an increased risk of pancreatic cancer in chronic pancreatitis. Thus, a significant fraction of the global cancer burden is attributable to chronic infection and inflammation. It is estimated that there would be about 21% fewer cases of cancer in developing countries and 9% fewer cases in developed countries if these known infectious diseases were prevented (2).

TABLE 1.1 Infection and Inflammatory Conditions as Risk Factors for Human Cancers

Cancer site	Infection/inflammation
Breast	Inflammatory breast cancer
Cervix	Human papillomaviruses, herpes simplex virus
Esophagus	Barrett's esophagitis, gastroesophageal reflux
Gallbladder and extrahepatic biliary ducts	Stone/cholecystitis, <i>Salmonera typhimurium</i>
Kaposi's sarcoma	Human immunodeficiency viruses
Large intestine (colon/rectum)	Inflammatory bowel diseases, <i>Schistosomiasis japonicum</i>
Leukemia/lymphoma	Human T-cell leukemia virus, Epstein–Barr virus, malaria
Liver /intrahepatic biliary ducts	Hepatitis viruses B and C, cirrhosis, <i>Opistorchis viverrini</i> , <i>Clonorchis sinensis</i> , <i>Schistosomiasis japonicum</i>
Lung	Cigarette smoke, particles (asbestos, silica dust, nanomaterials, etc.)
Nasopharynx	Epstein–Barr virus
Oral cavity	Leukoplakia
Pancreas	Pancreatitis
Pleura (mesothelioma)	Asbestos
Prostate	Proliferative inflammatory atrophy
Skin	Ultraviolet radiation, sunburn, human papillomaviruses
Stomach	<i>Helicobacter pylori</i> , chronic atrophic gastritis, Epstein–Barr virus
Thyroid	Thyroiditis
Urinary bladder	Stones, bacterial infections, <i>Schistosomiasis haematobium</i>

INFECTION, INFLAMMATION, AND CANCER: POSSIBLE MECHANISMS

Although various mechanisms have been proposed for infection- and inflammation-associated carcinogenesis, at many sites carcinogenic mechanisms associated with infection and inflammation have not been fully elucidated. Both direct and indirect mechanisms may be involved in carcinogenesis associated with infection. Direct mechanisms include integration of viral DNA into the human genome, which often results in alterations of host DNA (insertion, deletion, translocation, and amplification). Products of integrated viral DNA (e.g., the X protein of hepatitis B virus and the E6 and E7 proteins of human papillomavirus) interact with tumor suppressor gene products such as pRB, p53, and Bax, inactivating these proteins in host cells (see Chapters 12 and 13). Viral products such as the E6 and E7 proteins of human papillomavirus may also immortalize infected cells (e.g., human genital keratinocytes) and interact with transcription factors of host genes (e.g., activation of c-myc by the X protein of hepatitis B virus), deregulating the cell cycle, or cell growth and death. In contrast, indirect mechanisms include inflammation-related cellular and genetic alterations and viral-infection-induced immunosuppression (e.g., human immunodeficiency virus), which can increase the risks of some types of malignancy (e.g., Kaposi's sarcoma). It is likely that both direct (integration of viral DNA into