Growth Regulation of Cancer

Editor

Marc E. Lippman

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Volume 72
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Volume 73
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Volume 74
Growth Regulation of Cancer, Marc E. Lippman, *Editor*

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Growth Regulation of Cancer

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Preface

Enormous progress has been made during the past few years toward understanding the growth regulation of human cancer. A remarkable synthesis of somewhat diverse fields, including cell biology, endocrinology, molecular virology, and molecular genetics, has provided confluent results that have enhanced understanding of fundamental events that control both neoplastic cell growth and the malignant process as characterized by invasion and metastasis.

This volume represents critical contributions presented at the Ortho-UCLA Symposium on Growth Regulation of Cancer held in Park City, Utah, January 17–23, 1987. Presentations at this meeting were geared toward synthesizing the varied disciplines at work in the study of growth regulation of cancer. Particular emphasis was placed on the cellular and molecular biology of growth factors and their receptors, which contribute to mitogenesis. Mechanisms of signal transduction by which those receptors evoke phenotypic effects were also explored. Specific aspects of the malignant process, including angiogenesis and critical host interactions regulating the metastatic process, were also given substantial attention, as the communications between normal and malignant tissue are critical for neoplastic progression. Other presentations described the role of oncogenes in the malignant process, with particular attention to those oncogenes that are, or interact with, growth factors and their receptors.

An alternative view of malignant progression reflects the loss of negative or repressive influences. This area was also explored in depth, with major focus on the areas of transforming growth factor beta and tumor necrosis factor and the interferons.

Finally, the role of steroid hormones as critical regulatory molecules of hormone-dependent neoplasia was examined. Work was presented on systems stimulated by steroids, as in human breast cancer, and systems in which steroid hormones function as negative regulators of cell proliferation, as in the leukemias and lymphomas.

We wish to thank the Ortho Pharmaceutical Corporation for generous sponsorship of this meeting. We also gratefully acknowledge gifts from Stuart Pharmaceuticals, Division of ICI Americas, Inc.; Pfizer Central Research, Pfizer, Inc.; and Meloy Laboratories. Additional financial support was received from USHHS grant R13 CA44065-01.

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Marc E. Lippman

Contents

Contributors xiii

Preface
Marc E. Lippman xvii

I. GROWTH FACTORS AS REGULATORS OF NEOPLASTIC CELL GROWTH

Growth Regulation of Human Breast Carcinoma Occurs Through Regulated Growth Factor Secretion
Marc E. Lippman, Robert B. Dickson, Edward P. Gelmann, Neal Rosen, Cornelius Knabbe, Susan Bates, Diane Bronzert, Karen Huff, and Attan Kasid . . . 1

Estrogen-Induced Lysosomal Proteases Secreted by Breast Cancer Cells: A Role in Carcinogenesis?
Henri Rochefort, Françoise Capony, Marcel Garcia, Vincent Cavaillès, Gilles Freiss, Monique Chambon, Muriel Morisset, and Françoise Vignon 17

Effect of Mutations Affecting Na^+:H^+ Antiport Activity on Tumorigenic Potential of Hamster Lung Fibroblasts
Alain E. Lagarde, Arlette J. Franchi, Sonia Paris, and Jacques M. Pouysségur . . . 97

Assessment of Biological Activity of Synthetic Fragments of Transforming Growth Factor-Alpha
Krzysztof Darlak, Glen Franklin, Philip Woost, Elaine Sonnenfeld, Daniel Twardzik, Arno Spatola, and Gregory Schultz 109

Melanoma Growth Stimulatory Activity: Isolation From Human Melanoma Tumors and Characterization of Tissue Distribution
Ann Richmond and H. Greg Thomas 71

Swiss 3T3 Mouse Embryo Fibroblasts Transfected With a Human Prepro-GRP Gene Synthesize and Secrete Pro-GRP Rather Than GRP
Anne-Marie Lebacq-Verheyden, Shoshana Segal, Frank Cuttitta, and James F. Battey . . . . . .

Tissue Organization and Cancer: Role of Autocrine Growth Factors in Extracellular Matrix Biosynthesis
W.R. Kidwell, S. Mohanam, B. Sanfilippo, and D.S. Salomon 145

II. GROWTH FACTOR RECEPTORS AND KINASES

Interactions Between Growth Factor Receptors and Corresponding Monoclonal Antibodies in Human Tumors
Ulrich Rodeck, Meenhard Herlyn, and Hilary Koprowski 65

Expression and Function of the PDGF Receptor in Normal and Transformed Cells
Lewis T. Williams, Jaime A. Escobedo, Shaun R. Coughlin, and Mark T. Keating 151

Epidermal Growth Factor Receptor: Structure and Regulation by Self-Phosphorylation
Paul J. Bertics, Laura Hubler, William S. Chen, Cliff D. Carpenter, Michael G. Rosenfeld, and Gordon N. Gill 157

Epidermal Growth Factor Receptors as Potential Targets for Antitumor Therapy With Monoclonal Antibodies
John Mendelsohn 169

III. ONCOGENES AND GROWTH FACTORS

Analysis of pp60$^{c\text{-}src}$ Tyrosine Kinase Activity and Phosphotyrosyl Phosphatase Activity in Human Colon Carcinoma and Normal Human Colon Mucosal Cells
Virginia DeSeau, Neal Rosen, and Joseph B. Bolen 39

Cloning and Characterization of the Human PIM-1 Gene: A Putative Oncogene Related to the Protein Kinases
Timothy C. Meeker, Lalitha Nagarajan, Abbas ar-Rushdi, and Carlo M. Croce . . . 31

Product and Transcription of the *Fos* Gene
J.R. Barber, P. Sassone-Corsi, and I.M. Verma 175

Oncogenic Potential of the *erb*B-2 Gene: Frequent Overexpression in Human Mammary Adenocarcinomas and Induction of Transformation In Vitro
C.R. King, P.P. Di Fiore, J.H. Pierce, O. Segatto, M.H. Kraus, and S.A. Aaronson 189

Proto-Oncogenes as Mediators of Growth and Development: Discussion Summary
Mark A. Israel 201

IV. ANGIOGENESIS AND HOST INTERACTIONS AND METASTASIS

Invasive Activity and Chemotactic Response to Growth Factors by Kaposi's Sarcoma Cells
Adriana Albini, Charles D. Mitchell, Erik W. Thompson, Ruth Seeman, George R. Martin, Alec E. Wittek, and Gerald V. Quinnan 137

Host Microenvironment Determinants in Cancer Metastasis
Isaiah J. Fidler and Janet E. Price 205

V. NEGATIVE SIGNALS

Characterization of a Hepatic Proliferation Inhibitor (HPI): Effect of HPI on the Growth of Normal Liver Cells—Comparison With Transforming Growth Factor Beta
Anthony C. Huggett, Henry C. Krutzsch, and Snorri S. Thorgeirsson 55

Human Cytokines, Tumor Necrosis Factor, and Interferons: Gene Cloning, Animal Studies, and Clinical Trials
Arthur P. Bollon, Susan L. Berent, Richard M. Torczynski, Norwood O. Hill, Yuri Lemeshev, Joseph M. Hill, Feng Lan Jia, Anwar Joher, Sathit Pichyangkul, and Amanullah Khan 121

VI. STEROIDS AND REGULATION OF CANCER

Repression of Glucocorticoid Hormone-Dependent Transcription of the Mouse Mammary Tumor Virus LTR by the P37 V-MOS Oncogene Product
Bernd Groner, Robert R. Friis, Alexandra Schläfli, and Rolf Jaggi 213

Molecular Genetic Analysis of Glucocorticoid Actions in Human Leukemic Cells
E.B. Thompson, Y.-S. Yuh, J. Ashraf, B. Gametchu, M. Linder, and J.M. Harmon 221

Index 239

Journal of Cellular Biochemistry 35:1–16 (1987)
Growth Regulation of Cancer 1–16

Growth Regulation of Human Breast Carcinoma Occurs Through Regulated Growth Factor Secretion

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We describe studies on human breast cancer in which it is shown that specific growth factors (IGF-I, TGFα, PDGF) are secreted by human breast cancer cells and likely to be involved in tumor growth and progression. These activities are regulated by estradiol in hormone-dependent breast cancer and secreted constitutively by hormone-independent cells. These growth factor activities can induce the growth of hormone-dependent cells in vivo in athymic nude mice. Hormone-dependent breast cancer cells also secrete TGFβ, a growth-inhibitory substance, when treated with antiestrogens. TGFβ functions as a negative autocrine growth regulator and is responsible for some of the growth-inhibitory effects of antiestrogens.

Key words: breast cancer, growth factors, estrogen, IGF-I, TGF, PDGF

Estrogens play a central role in growth regulation of both normal and neoplastic breast tissue. At puberty and throughout menstrual life including pregnancy-lactation, estrogen exerts mitogenic, anabolic, and secretory effects on mammary epithelium. Estrogen treatment of males will induce breast development at any age. Breast cancer occurs in women who have never had functional ovaries with only 1% of the frequency of that in women with intact ovaries. Thus estrogens play a critical role, at least initially, in nearly all breast cancers. Metastatic breast cancer growth is strongly regulated in about one-third of clinical cases by therapies which alter concentrations or activities of estrogens [1]. This hormonal component of growth control appears to be a remnant of the normal control of epithelial proliferation. While estrogen is a proximate mitogen for either normal or malignant breast epithelium, the hypothalamus-pituitary axis is indirectly in control of ovarian estrogen secretion by virtue of GnRH and gonadotropin stimulation [2]. In addition, the pituitary gland (or other

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