Tumor-Associated Fibroblasts and their Matrix
The Tumor Microenvironment

Series Editor: Isaac P. Witz

For further volumes:
http://www.springer.com/series/7529
Margareta M. Mueller • Norbert E. Fusenig
Editors

Tumor-Associated Fibroblasts and their Matrix
Preface

During the last century cancer research was mainly focussed on the tumor cells alone which could be easily propagated in cell culture. During this time many important findings were obtained clearly demonstrating that cancer is a genetic disease, controlled by the activation and/or inactivation of critical control genes.

However during the last two decades it has become increasingly clear that genetic alterations alone are not the sole driving force behind tumor development but that tumor growth and progression are rather intimately controlled by the microenvironment. One could almost speak of are “rediscovery” of the tumor as a highly complex tissue composed of carcinoma cells and surrounding stroma. Studies in different areas of biology including tumour biology have demonstrated that tissue structure, function and dysfunction are highly intertwined with the microenvironment and that during the development of cancer tissue biology and host physiology are subverted to drive malignant progression. It is now clear that the context is crucial and that the status of the cellular microenvironment plays a significant role in determining whether cells within a tissue retain their normal architecture or undergo tumor progression.

The tumor stroma or microenvironment is made up of multiple non-malignant cell populations, including fibroblasts, adipocytes, endothelial and inflammatory cells that are embedded in a tumour specific extracellular matrix (ECM). Nowadays, there is a huge interest in tumor stroma research, and in understanding the contributions of the different stromal cell types to tumor growth and progression. One of the key components of the tumor microenvironment in carcinomas are activated fibroblasts termed cancer associated fibroblasts (CAFs). In the meantime our knowledge of CAFs has changed from being viewed as a passive bystander to becoming an important co-mediator of cancer progression.

In response to cancer growth, host stromal fibroblasts undergo a dramatic morphologic and biochemical transition to form “reactive stroma” in a desmoplastic reaction much like the granulation tissues found at the site of wound healing. While the malignant cells activate fibroblasts in the tumor stroma by various stimuli, including growth factors and cytokines, cancer associated fibroblasts secrete growth factors and build a permissive soil in which the cancer cells thrive. CAFs are responsible for the elaboration of most of the connective tissue and ECM components
as well as, proteolytic enzymes and their inhibitors. The composition and structure of the ECM in the tumor microenvironment is essential for promoting tumor development and metastasis. The constituents of the ECM include collagens, laminins, fibronectin and several proteoglycans. They provide mechanical support for cells, facilitate cell communication and serve as substrates for cell migration. Changes in the composition or architecture of the extracellular matrix within tumors can alter integrin expression and function and promote metastatic progression, angiogenesis and lymphangiogenesis.

In this unique textbook world leading experts of the area of tumor microenvironment review the most recent knowledge of the still growing complexity of the tumor microenvironment focusing on tumor associated stromal cells and the most important extracellular matrix components and summarize the role of these players in tumor progression. Moreover, novel therapeutic targets are discussed that have been discovered in the tumor microenvironment and are increasingly used in experimental and clinical tumor therapy. The message from their contributions is clear: the tumor microenvironment and its components are important and essential players in tumor progression and interesting targets for novel therapeutic strategies. However there are still many white areas on the map and we are just beginning to understand the complex interplay between tumor and stromal cells.

We express our deepest gratitude to all our colleagues who have made this book the first comprehensive anthology covering all major aspects of the role of the tumor microenvironment and its extracellular matrix components.

Heidelberg

Margareta M. Mueller and Norbert E. Fusenig
## Contents

### Part I  The Tumor Microenvironment

1. **Critical Roles of Stromal Fibroblasts in the Cancer Microenvironments** ................................................................. 3  
   Leland W. K. Chung

### Part II  Stromal Cell Diversity

2. **Functional Diversity of Fibroblasts** .......................................................... 23  
   H. Peter Rodemann and Hans-Oliver Rennekampff

3. **The Role of the Myofibroblast in Fibrosis and Cancer Progression** .... 37  
   Boris Hinz, Ian A. Darby, Giulio Gabbiani and Alexis Desmoulière

4. **The Role of Myofibroblasts in Communicating Tumor Ecosystems** .... 75  
   Olivier De Wever, Astrid De Boeck, Pieter Demetter, Marc Mareel and Marc Bracke

5. **Tumor Vessel Associated-Pericytes** .......................................................... 91  
   Arne Bartol, Anna M. Laib and Hellmut G. Augustin

6. **The Role of Cancer-Associated Adipocytes (CAA) in the Dynamic Interaction Between the Tumor and the Host** ................. 111  
   Marie-Christine Rio

### Part III  The Tumor ECM

7. **Hyaluronan: A Key Microenvironmental Mediator of Tumor-Stromal Cell Interactions** ............................................. 127  
   Naoki Itano

8. **Function of Tenascins in the Tumor Stroma** ........................................ 145  
   Florence Brellier and Ruth Chiquet-Ehrismann
Fibulins and Their Role in the ECM ........................................... 159
Helen C. M. Cooney and William M. Gallagher

Tumor Fibroblast-Associated Metalloproteases ......................... 175
Julie Lecomte, Anne Masset, Dylan R. Edwards and Agnès Noël

Part IV  Tumor Modulating-Fibroblast Interactions

Multiple Fibroblast Phenotypes in Cancer Patients:
Heterogeneity in Expression of Migration Stimulating Factor ........ 197
Ana M. Schor and Seth L. Schor

TGF-β Signaling in Fibroblasts Regulates Tumor Initiation
and Progression in Adjacent Epithelia ........................................... 223
Brian R. Berie and Harold L. Moses

The SDF-1-Rich Tumour Microenvironment Provides
a Niche for Carcinoma Cells ...................................................... 245
Masayuki Shimoda, Kieran Mellody and Akira Orimo

Role of PDGF in Tumor-Stroma Interactions ............................... 257
Carina Hellberg and Carl-Henrik Heldin

Radiation-Induced Microenvironments and Their Role
in Carcinogenesis ........................................................................ 267
Mary Helen Barcellos-Hoff and David H. Nguyen

Part V  Tumor-Modulating ECM Interactions

The Extracellular Matrix as a Multivalent Signaling
Scaffold that Orchestrates Tissue Organization and Function .......... 285
Jamie L. Inman, Joni D. Mott and Mina J. Bissell

SPARC and the Tumor Microenvironment ................................. 301
Stacey L. Thomas and Sandra A. Rempel

Integrin-Extracellular Matrix Interactions ................................. 347
Christie J. Avraamides and Judith A. Varner

The Multifaceted Role of Cancer Associated Fibroblasts
in Tumor Progression .................................................................. 361
Hans Petter Eikesdal and Raghu Kalluri
Part VI  Therapeutic Application/Targeting

20  Cancer Associated Fibroblasts as Therapeutic Targets  ..................  383  
Christian Rupp, Helmut Dolznig, Christian Haslinger, Norbert Schweifer and Pilar Garin-Chesa

21  Targeting Tumor Associated Fibroblasts and Chemotherapy  ..........  403  
Debbie Liao and Ralph A. Reisfeld

22  Antibody-Based Targeting of Tumor Vasculature and Stroma  .......  419  
Katharina Frey and Dario Neri

Index  ............................................................  451
Contributors

Hellmut G. Augustin  Vascular Oncology and Metastasis, German Cancer Research Center (DKFZ-ZMBH Alliance), 69120 Heidelberg, Germany
Medical Faculty Mannheim, Vascular Biology and Tumor Angiogenesis, Heidelberg University, 68167 Mannheim, Germany

Christie J. Avraamides  Moores UCSD Cancer Center, University of California, San Diego, 3855 Health Sciences Drive #0819, La Jolla, CA 92093-0819, USA
e-mail: jvarner@ucsd.edu

Mary Helen Barcellos-Hoff  Departments of Radiation Oncology and Cell Biology, NYU Langone Medical Center, 566 First Avenue, 10016 New York, USA
e-mail: mhbarcellos-hoff@nyumc.org

Arne Bartol  Vascular Oncology and Metastasis, German Cancer Research Center (DKFZ-ZMBH Alliance), 69120 Heidelberg, Germany
Medical Faculty Mannheim, Vascular Biology and Tumor Angiogenesis, Heidelberg University, 68167 Mannheim, Germany
e-mail: bartol@angiogenese.de

Brian R. Bierie  Department of Cancer Biology, Vanderbilt-Ingram Cancer Center, 691 Preston Research Building 2220 Pierce Ave., Nashville, TN 37232-6838, USA
e-mail: bierie@wi.mit.edu

Mina J. Bissell  Life Science Division, Lawrence Berkeley National Laboratory, One Cyclotron Rd, Berkeley, CA 94720, USA
e-mail: mjbissell@lbl.gov

Astrid De Boeck  Laboratory of Experimental Cancer Research, Department of Radiotherapy and Experimental Cancer Research, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium

Marc Bracke  Laboratory of Experimental Cancer Research, Department of Radiotherapy and Experimental Cancer Research, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium
Florence Brellier  Friedrich Miescher Institute for Biomedical Research, Novartis Research Foundation, Maulbeerstrasse 66, 4058 Basel, Switzerland

Ruth Chiquet-Ehrismann  Friedrich Miescher Institute for Biomedical Research, Novartis Research Foundation, Maulbeerstrasse 66, 4058 Basel, Switzerland  
e-mail: ruth.chiquet@fmi.ch

Leland W. K. Chung  Uro-Oncology Research Program, Departments of Medicine and Surgery, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center and the University of California, Los Angeles, CA 90048, USA 
e-mail: leland.chung@cshs.org

Helen C. M. Cooney  73 Nutley Lane, Donnybrook, Dublin 4, Ireland 
e-mail: helen.cooney@ucd.ie

Ian A. Darby  Cancer and Tissue Repair Laboratory, School of Medical Sciences, RMIT University, Bundoora, VIC 3083, Australia

Pieter Demetter  Department of Pathology, Erasme University Hospital, Université Libre de Bruxelles (ULB), Brussels, Belgium

Alexis Desmoulière  Faculty of Pharmacy, Cellular Homeostasy and Pathologies (EA 3842) and Department of Physiology, IFR 145, University of Limoges, 87025 Limoges, France

Helmut Dolznig  Institute of Pathology, Medical University of Vienna, Waehringer Guertel 18–20, 1090 Vienna, Austria

Institute of Medical Genetics, Centre of Pathobiology and Genetics, Medical University of Vienna, Waehringer Strasse 10, 1090 Vienna, Austria  
e-mail: helmut.dolznigt@meduniwien.ac.at

Dylan R. Edwards  School of Biological Sciences, University of East Anglia, Norwich, NR4 7TJ, UK

Hans Petter Eikesdal  Department of Oncology, Haukeland University Hospital, 5021 Bergen, Norway

Katharina Frey  Department of Chemistry and Applied Biosciences, ETH Zurich, Wolfgang-Pauli-Str. 10, 8093 Zurich, Switzerland 
e-mail: katharina.frey@pharma.ethz.ch

Giulio Gabbiani  Department of Pathology and Immunology, CMU, University of Geneva, Rue Michel-Servet 1, 1211 Geneva 4, Switzerland  
e-mail: giulio.gabbiani@unige.ch

William M. Gallagher  UCD School of Biomolecular and Biomedical Science, UCD Conway Institute, University College Dublin, Dublin 4, Ireland 
e-mail: william.gallagher@ucd.ie

Pilar Garin-Chesa  Institute of Pathology, Medical University of Vienna, Waehringer Guertel 18–20, 1090 Vienna, Austria
Contributors

Boehringer Ingelheim RCV GmbH & Co KG, Dr. Boehringer-Gasse 5–11, 1130 Vienna, Austria

Christian Haslinger  Boehringer Ingelheim RCV GmbH & Co KG, Dr. Boehringer-Gasse 5–11, 1130 Vienna, Austria

Carl-Henrik Heldin  Ludwig Institute for Cancer Research, Uppsala University, Box 595, SE 751 24 Uppsala, Sweden
e-mail: c-h.heldin@licr.uu.se

Carina Hellberg  Ludwig Institute for Cancer Research, Uppsala University, Box 595, SE 751 24 Uppsala, Sweden
e-mail: carina.hellberg@licr.uu.se

Boris Hinz  Faculty of Dentistry, Laboratory of Tissue Repair and Regeneration, Matrix Dynamics Group, University of Toronto, Toronto, ON M5S 3E2, Canada

Jamie Inman  Life Science Division, Lawrence Berkeley National Laboratory, One Cyclotron Rd, Berkeley, CA 94720, USA

Naoki Itano  Department of Molecular Oncology, Division of Molecular and Cellular Biology, Institute on Aging and Adaptation, Shinshu University Graduate School of Medicine, Matsumoto, Nagano 390-8621, Japan
e-mail: itano@shinshu-u.ac.jp

Raghu Kalluri  Division of Matrix Biology, Department of Medicine, Beth Israel Deaconess Medical Center & Harvard Medical School, 330 Brookline Ave, E/CLS Room #11-090, Center for Life Sciences, 02115 Boston, MA, USA
Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA, USA
Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA, USA
e-mail: rkalluri@bidmc.harvard.edu

Anna M. Laib  Vascular Oncology and Metastasis, German Cancer Research Center (DKFZ-ZMBH Alliance), 69120 Heidelberg, Germany

Julie Lecomte  Laboratory of Tumor and Development Biology, Groupe Interdisciplinaire de Génoprotéomique Appliqué-Cancer (GIGA-Cancer), University of Liège, 4000 Liège, Belgium

Debbie Liao  Department of Immunology and Microbial Sciences, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

Marc Mareel  Laboratory of Experimental Cancer Research, Department of Radiotherapy and Experimental Cancer Research, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium

Anne Masset  Laboratory of Tumor and Development Biology, Groupe Interdisciplinaire de Génoprotéomique Appliqué-Cancer (GIGA-Cancer), University of Liège, 4000 Liège, Belgium


Ana M. Schor  Unit of Cell and Molecular Biology, The Dental School, University of Dundee, Dundee DD1 4HR, UK
e-mail: a.m.schor@dundee.ac.uk

Seth L. Schor  Unit of Cell and Molecular Biology, The Dental School, University of Dundee, Dundee DD1 4HR, UK
e-mail: s.l.schor@dundee.ac.uk

Norbert Schweifer  Boehringer Ingelheim RCV GmbH & Co KG, Dr. Boehringer-Gasse 5–11, 1130 Vienna, Austria

Masayuki Shimoda  Department of Pathology, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

CR-UK Stromal-Tumour Interaction Group, Paterson Institute for Cancer Research, The University of Manchester, Wilmslow Road, Manchester, M20 4BX, UK

Stacey L. Thomas  Department of Neurosurgery, Hermelin Brain Tumor Center, Henry Ford Hospital, Detroit, MI 48202, USA
e-mail: nsslt@neuro.hfh.edu

Judith A. Varner  Moores UCSD Cancer Center, University of California, San Diego, 3855 Health Sciences Drive #0819, La Jolla, CA 92093-0819, USA
Department of Medicine, University of California, San Diego, La Jolla, CA, 92093-0819, USA
e-mail: jvarner@ucsd.edu

Olivier De Wever  Laboratory of Experimental Cancer Research, Department of Radiotherapy and Experimental Cancer Research, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium
e-mail: olivier.dewever@ugent.be