FIBROCYTES

New Insights into
Tissue Repair and Systemic Fibrosis

This page intentionally left blank

FIBROCYTES

New Insights into
Tissue Repair and Systemic Fibrosis

Editor

Richard Bucala

Yale University, USA

World Scientific

NEW JERSEY • LONDON • SINGAPORE • BEIJING • SHANGHAI • HONG KONG • TAIPEI • CHENNAI

Published by

World Scientific Publishing Co. Pte. Ltd.

5 Toh Tuck Link, Singapore 596224

USA office: 27 Warren Street, Suite 401-402, Hackensack, NJ 07601

UK office: 57 Shelton Street, Covent Garden, London WC2H 9HE

Library of Congress Cataloging-in-Publication Data

Fibrocytes : new insights into tissue repair and systemic fibroses / editor,

Richard Bucala.

p. cm.

Includes bibliographical references and index.

ISBN-13 978-981-256-869-4 -- ISBN-10 981-256-869-7

1. Fibroblasts. 2. Fibroblasts--pathology. 3. Fibroblasts--physiology.
4. Fibroses--physiopathology. 5. Wound Healing--physiology. I. Bucala, Richard.

QP88.23 .F53 2006

612.7'5--dc22

2006051165

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library.

Copyright © 2007 by World Scientific Publishing Co. Pte. Ltd.

All rights reserved. This book, or parts thereof, may not be reproduced in any form or by any means, electronic or mechanical, including photocopying, recording or any information storage and retrieval system now known or to be invented, without written permission from the Publisher.

For photocopying of material in this volume, please pay a copying fee through the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, USA. In this case permission to photocopy is not required from the publisher.

Typeset by Stallion Press

Email: enquiries@stallionpress.com

Printed in Singapore.

CONTRIBUTORS

Peter J. Barth, MD

Institute of Pathology
University Hospital Giessen and Marburg GmbH
Location Marburg
Medical Faculty of Philipps — University Marburg
Baldingerstraße, 35043 Marburg
Germany

Rick Bucala, MD, PhD

Yale University School of Medicine
The Anlyan Center, S525
PO Box 208031
300 Cedar Street
New Haven, CT 06520-8031
USA

Jason A. Chesney, MD, PhD

J.G. Brown Cancer Center
University of Louisville
Delia Baxter Research Bldg., Rm. 204E
508 So. Preston Street
Louisville, KY 40202
USA

Shawn E. Cowper, MD

Department of Dermatology and Pathology
Yale University School of Medicine
P.O. Box 208059
15 York St. LMP 5032
New Haven, CT 06520-8059
USA

Richard Gomer, PhD

Department of Biochemistry and Cell Biology
MS-140, Rice University
Houston, TX 77005-1892
USA

Brigitte N. Gomperts, MD

Department of Pediatrics
Division of Hematology and Oncology
University of Washington
School of Medicine in St. Louis
660 S. Euclid Avenue, Campus Box 8116
St. Louis, MO 63110
USA

Shuichi Kaneko, MD, PhD

Department of Gastroenterology and Nephrology
Kanazawa University
Graduate School of Medical Science
Takara-Machi 13-1
Kanazawa 920-8641,
Japan

Cynthia L. Kucher, MD

Greenwich Hospital — Pathology Department
5 Perryridge Road
Greenwich, CT 06830
USA

Amanda C. LaRue, PhD

Department of Veterans Affairs Medical Center
Division of Experimental Hematology
Department of Medicine
Medical University of South Carolina
Charleston, SC 29401
USA

Kouji Matsushima, MD, PhD

Department of Molecular Preventive Medicine
Graduate School of Medicine and
Faculty of Medicine
University of Tokyo
7-3-1, Hongo, Bunkyo-ku,
Tokyo, 113-0033
Japan

Sabrina Mattoli, MD, PhD

Avail Biomedical Research Institute, Basel, Switzerland
Avail GmbH
PO Box 110, CH-4003 Basel
Switzerland

Heather Medbury, PhD

Senior Scientist
Department of Surgery
University of Sydney
Westmead Hospital
Westmead 2145
Australia

Abelardo Medina

UBC Experimental Medicine
344A Jack Bell Research Centre
2660 Oak Street
Vancouver, BC
Canada

Makio Ogawa, MD, PhD

Department of Veterans Affairs Medical Center
Division of Experimental Hematology
Department of Medicine
Medical University of South Carolina
Charleston, SC 29401
USA

Darrell Pilling, PhD

Department of Biochemistry and Cell Biology
MS-140
Rice University
Houston, TX 77005-1892
USA

Arnold Postlethwaite, MD

Division of Rheumatology
Department of Medicine
University of Tennessee Health Science Center
956 Court Avenue
Coleman Building, G326
Memphis, Tennessee 38163
USA

Norihiko Sakai, MD, PhD

Department of Gastroenterology and Nephrology
Kanazawa University Graduate School of Medical Science
Ishikawa
Japan

Matthias Schmidt

Avail Biomedical Research Institute, Basel, Switzerland
Avail GmbH
PO Box 110, CH-4003 Basel
Switzerland

Paul G. Scott

Department of Surgery
2D3. 81 WMSHC
8440-112 Street
University of Alberta
Edmonton, Alberta
Canada

Robert M. Strieter, MD

Department of Internal Medicine
University of Virginia
School of Medicine
P.O. Box 800466, VA 22908-0466
USA

Edward E. Tredget, MD

Department of Surgery
2D3. 81 WMSHC
8440-112 Street
University of Alberta
Edmonton, Alberta
Canada

Takashi Wada, MD, PhD

Department of Gastroenterology and Nephrology
Kanazawa University Graduate School of Medical Science
13-1 Takara-machi
Kanazawa 920-8641
Japan

JianFei Wang

Department of Surgery
2D3.81 WMSHC
8440-112 Street
University of Alberta
Edmonton, Alberta
Canada

Yaojiong Wu

Department of Surgery
2D3. 81 WMSHC
8440-112 Street
University of Alberta
Edmonton, Alberta
Canada

CONTENTS

Contributors	v
-------------------------------	----------

Chapter 1

Fibrocytes: Discovery of a Circulating Connective Tissue Cell Progenitor	1
<i>Richard Bucala</i>	
Introduction	2
Phenotypic Properties	4
Functional Roles in Wound Repair	6
Role in Health and Disease	7
Wound Repair	8
Tumor Biology	9
Immunostimulatory Properties	9
Infectious Diseases	10
Scleroderma	10
Nephrogenic Systemic Fibrosis (NSF)	11
Asthma, Acute Lung Injury, and Pulmonary Fibrosis	12
Conclusions	12
Acknowledgments	14
References	15

Chapter 2

Fibrocytes: Immunologic Features	19
<i>Jason Chesney</i>	
Introduction	19
Requirement of T Cells for the Development of Fibrosis	20

T Cell-mediated Fibrosis in Human Disease 21

Fibrocytes 22

Fibrocytes are Potent Antigen Presenting Cells 24

Fibrocytes Secrete Type I Collagen and
Inflammatory Cytokines 28

Conclusion 31

References 32

Chapter 3

Regulatory Pathways for Fibrocyte Differentiation 37

Darrell Pilling and Richard H. Gomer

Introduction 37

Biology of the Monocyte-Macrophage System 39

Differentiation of Monocytes into Cell Types Other than
Macrophages 40

Peripheral Blood Mononuclear Cells can also Differentiate into
Fibroblast/Stromal Cells 41

Soluble Factors that Regulate Fibrocyte Differentiation 42

Regulation of Fibrocytes by Glucose and Insulin 44

Regulation of Fibrocyte Differentiation by SAP and
Aggregated IgG 45

Regulation of Fibrocyte Differentiation by T cells and
Extracellular Matrix 50

Summary 51

Acknowledgments 52

References 52

Chapter 4

Hematopoietic Origin of Fibrocytes 61

Amanda C. LaRue and Makio Ogawa

Introduction 61

Fibroblast Precursors 62

Clonal Transplantation 63

HSC Origin of Fibroblasts	65
Perspectives	67
Acknowledgments	69
References	69

Chapter 5

The Role of Fibrocytes in Post-burn Hypertrophic Scarring <i>JianFei Wang, Yaujiong Wu, Abelardo Medina, Paul. G. Scott and Edward E. Tredget</i>	75
Introduction	75
Altered Structure and Composition of the Extracellular Matrix of Hypertrophic Scars	77
A Th2 Polarized Immune Response in Hypertrophic Scar . . .	79
Dysregulated Apoptosis in Hypertrophic Scar	81
Apoptosis in the Resolution of Inflammation	81
Delayed Fibroblast and Myofibroblast Apoptosis in Hypertrophic Scar	82
Increased Levels of the Profibrotic Growth Factors TGF- β and CTGF in Hypertrophic Scar	84
Hypertrophic Scarring is Associated with Blood Borne Fibrocytes	86
Increased Numbers of Fibrocytes can be Cultured from the Blood of Burn Patients	87
Establishment of LSP-1 as a Fibrocyte Marker	88
Increased Numbers of Fibrocytes in Post-burn Hypertrophic Scar	91
Potential Interaction of Fibrocytes and Endothelial Cells . . .	92
Possible Interactions of Fibrocytes and Fibroblasts	93
Elevated TGF- β and CTGF mRNA Levels in Burn Patient Fibrocytes	93
Fibrocytes may Contribute to the Myofibroblast Population . .	94
Possible Role of Fibrocytes in the Polarized Th2 Immune Response	95
Proposed Role of Fibrocytes in Hypertrophic Scar Formation .	96

Summary and Prospects for Future Work	97
Acknowledgments	97
References	97

Chapter 6

Role in Asthmatic Lung Disease	105
<i>Sabrina Mattoli and Matthias Schmidt</i>	
Introduction	106
Phenotypic and Functional Characteristics of Fibrocytes	107
Differentiation of Fibrocytes at the Tissue Sites	109
Fibrocytes in Asthma	110
Fibrocytes in Asthma Models	113
Potential Fibrocyte Chemoattractants in Asthma	115
Conclusions	117
References	119

Chapter 7

Fibrocytes and Other Fibroblast/Myofibroblast Progenitors in Systemic Sclerosis	125
<i>Arnold E. Postlethwaite</i>	
Systemic Sclerosis Clinical Characteristics	126
The Vasculature in SSc	126
The Immune System in SSc	127
The Fibroblast Phenotype in SSc	128
Accumulation of T cells, Monocytes and Mast Cells in Clinically Involved Skin in SSc	129
Relationship of Autoimmunity, Vascular Abnormalities and Fibrosis in SSc (the Old Paradigm)	129
Possible Alternative Sources of Fibroblasts in SSc	130
Resident Fibroblast Progenitors	130
Fibroblast Progenitors from the Circulation in Patients with SSc and Related Fibrotic Conditions	131
Circulating Fibrocytes and other Progenitors of Fibroblast-like Cells (FLC)	132
Overall Hypothetical Scheme for Pathogenesis of SSc	134

New Treatment Strategies for SSc based on Circulating Fibroblast Progenitors	136
References	137

Chapter 8

Fibrocytes in Interstitial Lung Disease <i>Brigitte N. Gomperts and Robert M. Strieter</i>	143
Introduction	144
The Fibrocyte is a Unique Cell Population that has been Implicated in Wound Repair	144
Fibrocyte Trafficking	145
The Fibrocyte Demonstrates Plasticity Compatible with the Concept of an Adult Stem Cell/Progenitor Cell . . .	148
Fibrocytes in Pulmonary Fibrosis	149
Pulmonary Fibrosis	149
The Origin of the Fibroblast/Myofibroblast: A Pivotal Cell in Mediating Fibroproliferation in Pulmonary Fibrosis .	150
Fibrocytes in Asthma	157
Repair and Remodeling of the Airway in Asthma	157
Fibrocytes in Airway Remodeling in Asthma	158
Fibrocytes in Pulmonary Vascular Remodeling	159
Conclusions	160
References	160

Chapter 9

Role of Fibrocytes in Renal Fibrosis <i>Norihiko Sakai, Takashi Wada, Kouji Matsushima and Shuichi Kaneko</i>	163
Introduction	164
Fibrocytes in an Experimental Renal Fibrosis Model	165
1) Presence of fibrocytes in fibrotic kidneys	165
2) CCL21/CCR7 signaling regulates fibrocyte infiltration and renal fibrosis	165
3) Infiltration routes of fibrocytes to fibrotic kidneys	167

4) Effect of blockade of CCL21/CCR7 signaling on
expression of renal monocyte chemoattractant protein-1
(MCP-1/CCL2) and infiltration of F4/80-positive
macrophages 169

Fibrocytes in Human Renal Diseases 169

Concluding Remarks 170

References 170

Chapter 10

Role of Fibrocytes in Atherogenesis 175

Heather Medbury

Introduction 175

Atherosclerosis: The Perpetual Wound 177

 Inflammation: Fatty Core Development 177

 Tissue Formation/Remodeling: Development
 of the Fibrous Cap 178

 Plaque Rupture 183

 TGF- β : The Key Factor 184

Fibrocytes: Friend or Foe in Atherosclerosis 185

 Monocytes: A Source of Fibrocytes 186

Intimal Hyperplasia 187

Conclusion 188

References 188

Chapter 11

Nephrogenic Systemic Fibrosis: A Prototype Fibrocyte
Disease 195

Cynthia L. Kucher and Shawn E. Cowper

Introduction 195

Historical Context 196

The Affected Population 197

 Renal Disease 197

 Dialysis 198

 Renal transplantation 199

Other Comorbidities 200

Hypercoagulability, thrombosis, and endothelial injury	200
Other systemic processes	202
Presentation	203
Signs, Symptoms and Progression	203
Diagnosis	205
Laboratory investigation	205
Biopsy and histopathology	207
Ancillary studies	210
Treatment	213
Renal transplantation	213
Extracorporeal photopheresis (ECP)	213
Plasmapheresis	214
Other considerations	214
Discussion	215
Circulating Fibrocytes	215
A basic conceptual model and possible triggers	216
The newest suspect: Endothelin-1	217
Fibrosis via accretion — a proposal	219
Fibrosis via exogenous substances — an alternate hypothesis	219
Acknowledgment	221
References	221

Chapter 12

CD34⁺ Fibrocytes in Normal and Neoplastic Human

Tissues 227

Peter J Barth

Introduction	227
Normal CD34 ⁺ Fibrocytes — Morphology	228
CD34 ⁺ Fibrocytes in the Carcinoma-associated Stroma	232
Pathogenesis of CD34 ⁺ Fibrocyte Loss	235
Diagnostic Significance of CD34 ⁺ Fibrocytes	237
Tumors Histogenetically Linked to CD34 ⁺ Fibrocytes	238
Solitary Fibrous Tumor (SFT)	238
Dermatofibrosarcoma Protuberans (DFSP)	239

Stromal Tumors of the Breast 239

 Lipomatous Tumors 239

 Miscellaneous Tumors 240

 Gastrointestinal Stromal Tumors 240

Concluding Remarks and Future Perspectives 240

References 241

Index 247