

CONTENTS

Contributors	v
<i>Chapter 1</i>	
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
<i>Chapter 2</i>	
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
 <i>Chapter 3</i>	
Regulatory Pathways for Fibrocyte Differentiation	37
<i>Darrell Pilling and Richard H. Gomer</i>	
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
 <i>Chapter 4</i>	
Hematopoietic Origin of Fibrocytes	61
<i>Amanda C. LaRue and Makio Ogawa</i>	
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	75
<i>JianFei Wang, Yaujiong Wu, Abelardo Medina, Paul. G. Scott and Edward E. Tredget</i>	
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	143
<i>Brigitte N. Gomperts and Robert M. Strieter</i>	
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	163
<i>Norihiko Sakai, Takashi Wada, Kouji Matsushima and Shuichi Kaneko</i>	
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
 <i>Chapter 10</i>	
Role of Fibrocytes in Atherogenesis	175
<i>Heather Medbury</i>	
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
 <i>Chapter 11</i>	
Nephrogenic Systemic Fibrosis: A Prototype Fibrocyte Disease	195
<i>Cynthia L. Kucher and Shawn E. Cowper</i>	
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