

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

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	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
Sabrina Mattoli and Matthias Schmidt
 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
Arnold E. Postlethwaite
 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
Brigitte N. Gomperts and Robert M. Strieter

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
*Norihiko Sakai, Takashi Wada, Kouji Matsushima
 and Shuichi Kaneko*

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
<i>Peter J Barth</i>	
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