

Contents

Preface.....	xi
Acknowledgments.....	xiii
Authors.....	xv

Chapter 1 Composition and Function of the Interstitial Fluid	1
1.1 Definition of Interstitial Fluid.....	1
1.2 Extravasation	12
1.3 Cell Secretion in Interstitial Space.....	16
1.4 Connectivity of Interstitial Fluid and Other Extravascular Fluids	17
1.5 Relationship of Interstitial Fluid to Lymph	18
1.6 Structure of Interstitium	18
1.6.1 Heterogeneity in Interstitium	19
1.7 Methods for Obtaining Interstitial Fluid and Some Diagnostic Applications	20
1.8 Transport of Drugs and Biologicals in Interstitial Fluid	22
1.8.1 Transport of Drugs in Interstitial Space.....	23
1.8.2 Transport of Biologicals in Interstitial Space.....	25
1.9 Tumor Interstitial Fluid	27
References	28

Chapter 2 The Extracellular Matrix, Basement Membrane, and Glycocalyx	43
2.1 Matrices that Modulate Interstitial Fluid Composition	43
2.2 Extracellular Matrix	44
2.3 Basement Membrane	58
2.4 Glycocalyx.....	59
References	59

Chapter 3 The Biochemistry of Hyaluronan in the Interstitial Space.....	67
3.1 Hyaluronan	67
3.1.1 Introduction to Hyaluronan	67
3.1.2 Physical Characteristics of Hyaluronan	67
3.1.2.1 Effect of Protein on Hyaluronan Conformation.....	68
3.1.3 Solvent and Hyaluronan	69
3.2 Hyaluronan in Interstitial Space.....	70
3.3 Effect of Hyaluronan on Enzyme Activity.....	72
3.4 Specific Interaction of Hyaluronan with Receptors (Hyaladherins)	73

3.4.1	CD44	73
3.4.2	RHAMM	74
3.4.3	Other Cell Surface Receptors for Hyaluronan	74
3.4.4	Hyaluronan Binding to Other Hyaladherins	75
3.5	Low-Molecular-Weight Hyaluronan	76
3.6	Hyaluronan as a Therapeutic	78
3.7	Hyaluronidase and Drug Delivery in Interstitial Space	78
	References	81
Chapter 4	Proteolysis in the Interstitium	91
4.1	Proteolytic Enzymes in Interstitial Space	91
4.2	ADAM Proteases	111
4.3	ADAMTS Proteases	114
4.4	Comment on Proteolytic Enzymes in Interstitial Space	115
	References	115
Chapter 5	The Fibrinolytic System in the Interstitial Space	123
5.1	Components of Fibrinolytic System	123
5.2	Fibrinolytic System in Interstitial Space	123
5.2.1	Origin of Components of Fibrinolytic System Found in Interstitium	130
5.2.2	Effect of Hyaluronan on Components of Fibrinolytic System	131
5.3	Urokinase-Type Plasminogen Activator	132
5.4	Urokinase-Type Plasminogen Activator Receptor (CD87) ...	135
5.5	Activation of Plasminogen on Bacterial Surfaces	136
5.6	Plasminogen Receptors on Eukaryotic Cells	136
5.7	Plasminogen and Plasmin	137
5.8	Vitronectin	139
5.9	Plasminogen Activator Inhibitor 1 (Serpine1)	140
5.10	Plasminogen Activator Inhibitor 2 (Serpine2)	140
5.11	Plasminogen Activator Inhibitor 3	140
5.12	α_2 -Plasmin Inhibitor (Serpine2)	141
	References	141
Chapter 6	Kallikrein in the Interstitial Space	151
6.1	Kallikrein	151
6.2	Plasma Kallikrein	151
6.3	Tissue Kallikrein and Kallikrein-Related Peptidases	165
6.3.1	Miscellaneous Observations on Kallikreins and Other Kinin-Forming Enzymes in Interstitial Space	168
6.3.2	Hyaluronan and Tissue Kallikrein	169

6.4	Kinins	169
	References	171

Chapter 7 Matrix Metalloproteinases in the Interstitial Space..... 183

7.1	Matrix Metalloproteinases	183
7.2	Activation of Matrix Metalloproteinases	185
7.3	Membrane-Type Matrix Metalloproteinases	188
7.4	Matrix Metalloproteinases and Regulatory Proteolysis	189
7.5	Matrix Metalloproteinases as Biopharmaceuticals	191
7.6	Development of Inhibitors of Matrix Metalloproteinases for Therapeutic Use	192
7.6.1	Substrate Specificity of Matrix Metalloproteinases.....	192
7.6.2	Tissue Inhibitors of Metalloproteinases	195
7.6.3	Chelation of Zinc Ions and Inhibition of Matrix Metalloproteinases	195
7.7	Compartmentalization and Regulation of Matrix Metalloproteinases	196
	References	196

Chapter 8 Coagulation Factors in the Interstitial Space 233

8.1	Coagulation Factors and Their Regulation in Interstitial Space.....	233
8.2	Coagulation Factors in Lymph and Interstitial Fluid	234
8.3	Prothrombin.....	237
8.4	Fibrinogen.....	238
8.4.1	Fibrinogen and Hyaluronan.....	238
8.5	Factor VII, Factor VIIa, and Tissue Factor	239
8.5.1	Regulation of Tissue Factor in Interstitial Space and Cryptic Tissue Factor	241
8.5.2	Activity of Tissue Factor, Factor VII/VIIa, and Tissue Factor–Factor VIIa Not Related to Blood Coagulation	241
8.5.3	Factor VII and VIIa in Interstitial Space	243
8.5.4	Tissue Factor–Factor VIIa and Interstitial Pathology	243
8.5.4.1	Tissue Factor–Factor VIIa and Tumor Development	243
8.6	Intrinsic Coagulation Pathway in Interstitium.....	244
8.6.1	Factor IX	245
8.6.2	Factor VIII and von Willebrand Factor.....	245
8.7	Thrombin.....	246
8.7.1	Formation of Thrombin in Interstitial Space	246

8.7.2	Factors Influencing Activity of Thrombin in Interstitial Space.....	250
8.7.2.1	Effect of Hyaluronan on Thrombin Activity	251
8.7.3	Substrates for Thrombin in Interstitial Space	252
8.7.4	Role of Thrombin in Interstitial Fibrosis.....	252
	References	256
Chapter 9	Protease Inhibitors in the Interstitial Space	271
9.1	Proteolytic Regulation in Interstitial Space.....	271
9.2	Antithrombin	271
9.3	Latent Antithrombin	277
9.4	Plasminogen Activator Inhibitor 1	279
9.5	α_1 -Antitrypsin	279
9.6	Heparin Cofactor II	280
9.7	α_2 -Macroglobulin	280
9.8	Tissue Inhibitors of Metalloproteinases	283
	References	283
Index		291