

Contents

Preface.....	xxi
Editors.....	xxiii
Contributors	xxv

SECTION I Systems Biology of Inflammation and Regulatory Mechanisms

Chapter 1 At the Interface between Acute and Chronic Inflammation: Insights from Computational Modeling.....	3
<i>Yoram Vodovotz</i>	
1.1 Inflammation in Health and Disease: A Robust, Adaptive, Multiscale System	3
1.2 Inflammation Is a Complex System with Context-Dependent Regulation: Insights from Computational Modeling	5
1.2.1 Modeling Inflammation in Trauma, Hemorrhage, and Sepsis.....	6
1.2.2 Modeling Inflammation in Wound Healing.....	8
1.3 From Wound Healing to Cancer: Modeling Interrelationships among Acute Inflammation, Chronic Inflammation, and Cancer.....	10
1.4 From Modeling to Rational Reprogramming of Inflammation	11
1.5 Summary: Clinical and Basic Science Perspectives	11
1.6 Conclusions and Future Directions	12
Take-Home Messages.....	12
Acknowledgments	13
References	13
Chapter 2 The Cellular Component of Chronic Inflammation.....	21
<i>Julie M. Roda and Tim D. Eubank</i>	
2.1 What Is Chronic Inflammation?	21
2.2 The Cellular Component of Chronic Inflammation	22
2.2.1 Monocytes and Macrophages.....	22
2.2.2 Neutrophils.....	24
2.2.3 Dendritic Cells	25
2.2.4 Fibrocytes	27
2.2.5 T Cells	27
Take-Home Messages.....	30
References	31
Chapter 3 Mast Cells in Chronic Inflammation.....	35
<i>Traci A. Wilgus and Brian C. Wulff</i>	
3.1 Mast Cell Biology	35
3.1.1 Development, Maturation, and Distribution.....	35

3.1.2 Phenotypes	36
3.1.3 Activation	37
3.1.4 Mediators.....	37
3.2 Physiological Functions	39
3.2.1 Homeostasis.....	39
3.2.2 Innate and Adaptive Immunity	39
3.2.3 Wound Healing.....	40
3.3 Pathological Role in Chronic Inflammatory Diseases	41
3.3.1 Cancer	41
3.3.2 Atherosclerosis	43
3.3.3 Fibrosis	44
3.4 Conclusions and Future Directions	45
Take-Home Messages.....	45
References	46
Chapter 4 Hypoxia and Hypoxia-Inducible Factor in Inflammation	51
<i>Kiichi Hirota</i>	
4.1 Inflammation	51
4.2 Interaction between Hypoxic Environment and Inflammation	52
4.2.1 Hypoxia-Induced Inflammation	52
4.2.2 Inflammation-Induced Hypoxia	52
4.3 Canonical Signaling Pathway to Hypoxia-Inducible Factor Activation	54
4.3.1 Induction of HIF Activation by Continuous Hypoxia.....	54
4.3.2 Induction of HIF by Intermittent Hypoxia.....	55
4.4 Oxygen Tension-Independent Activation of HIF.....	55
4.4.1 Pro-Inflammatory Cytokines and Chemokines and HIF.....	55
4.5 Cross Talk between NF- κ B and HIF	56
4.6 Immunocompetent Cells and HIF	56
4.6.1 Macrophages and Dendritic Cells	56
4.6.2 Neutrophils	57
4.6.3 T Lymphocytes.....	58
4.6.4 B Lymphocytes.....	59
4.6.5 Mast Cells.....	59
4.7 Impact of Anti-Inflammatory Drugs on HIF Activity	59
4.8 Inflammatory Disorders and HIF.....	59
4.8.1 Infection	59
4.8.2 Sepsis.....	60
4.8.3 Wound Healing.....	61
4.9 Conclusions and Future Directions	61
Take-Home Messages.....	62
References	63
Chapter 5 Bioactive Phospholipid Mediators of Inflammation.....	67
<i>Sainath R. Kotha, Jordan D. Secor, Smitha Malireddy, Gowrishankar Gnanasekaran, and Narasimham L. Parinandi</i>	
5.1 Salient Features of Inflammation	67
5.1.1 Disorders and Diseases and Inflammation.....	68
5.2 Mediators of Inflammation.....	69
5.2.1 Non-Lipid Mediators of Inflammation.....	69

5.2.2	Lipid Mediators of Inflammation.....	70
5.3	Phosphatidic Acid (PA) as a Bioactive Phospholipid Mediator of Inflammation	70
5.4	Lysophosphatidic Acid (LPA) as a Bioactive Phospholipid Mediator of Inflammation	71
5.5	Conclusions and Future Directions	73
	Take-Home Messages.....	73
	Acknowledgment.....	74
	References	74
Chapter 6	Hematopoietic Stem Cells in Atherosclerotic Development and Resolution	77
	<i>Reeva Aggarwal, Vincent J. Pompili, and Hiranmoy Das</i>	
6.1	Introduction	77
6.2	HSC Regulation of Self-Renewal	79
6.3	Differentiation of HSCs.....	79
6.3.1	Lymphoid Differentiation.....	79
6.3.2	Myeloid Differentiation	80
6.4	Development of Atherosclerosis	80
6.4.1	Role of Stem Cells and Progenitor Cells in Atherosclerosis	81
6.4.1.1	Vascular Stem Cells.....	81
6.4.1.2	HSC Progenitors and Differentiated Immune Cells	82
6.4.2	Role of Chemokines, Cytokines, and Interleukins in Development and Progression of Atherosclerosis	83
6.5	Therapies for Atherosclerosis	84
6.6	Development of Ischemia and Therapy	87
6.7	Conclusions and Perspectives.....	87
	Take-Home Messages.....	89
	Acknowledgments	89
	References	89
Chapter 7	Inflammation as a Confounding Factor in Regenerative Medicine	93
	<i>Myron Allukian and Kenneth W. Liechty</i>	
7.1	Inflammation	93
7.2	Cells.....	95
7.2.1	Platelets	95
7.2.2	Mast Cells.....	97
7.2.3	Neutrophils	97
7.2.4	Macrophages	98
7.2.5	Mediators of Inflammation (Cytokines, Chemokines, and Growth Factors).....	99
7.3	Extracellular Matrix	100
7.4	Conclusions and Future Directions	101
	Take-Home Messages.....	102
	References	102
Chapter 8	NOX in the CNS: Inflammation and Beyond.....	107
	<i>Annadora J. Bruce-Keller</i>	
8.1	NOX History and Structure.....	107

8.2	Cell Type Specific Expression and Function in Brain.....	109
8.2.1	Microglia.....	109
8.2.2	Astrocytes.....	110
8.2.3	Oligodendrocytes	110
8.2.4	Neurons	110
8.2.4.1	Neuronal Differentiation.....	110
8.2.4.2	Synaptic Physiology.....	111
8.2.4.3	Neuronal Death.....	111
8.2.5	Cerebrovascular Cells	111
8.3	Physiologic Mechanisms of NOX Signaling	111
8.3.1	Oxidative Burst: Direct Antimicrobial Activity in Immune Cells	111
8.3.2	Regulation of pH and Ion Concentration	112
8.3.3	Redox Modulation of Protein Function.....	112
8.4	Conclusions and Unanswered Questions.....	113
	Take-Home Messages.....	114
	References	114
Chapter 9	Resolution of Inflammation.....	119
	<i>Amitava Das and Sashwati Roy</i>	
9.1	Introduction	119
9.2	Cascades of Wound Healing.....	119
9.3	Resolution of Inflammation.....	120
9.3.1	Macrophage Phenotype	121
9.3.2	Dead Cell Clearance.....	122
9.3.3	Lipid Mediators	123
9.3.3.1	Cyclopentenone Prostaglandins.....	124
9.3.3.2	Lipoxins.....	124
9.3.3.3	Resolvins and Protectins.....	124
9.3.3.4	Maresins.....	124
9.4	Role of MicroRNAs in Inflammation.....	125
9.5	Linking MicroRNAs and Lipid Mediators in Resolution of Inflammation ..	125
	Take-Home Messages.....	125
	References	126
Chapter 10	H₂S in Inflammation	129
	<i>Hyun-Ock Pae and Hun-Taeg Chung</i>	
10.1	Introduction	129
10.2	Dynamic Interplay of H ₂ S with NO and CO in Inflammatory Conditions	130
10.3	Janus Face of H ₂ S: Its Pro-Inflammatory and Anti-Inflammatory Effects	132
10.4	Perspectives	133
10.4.1	Clinical Science.....	133
10.4.2	Basic Science.....	133
	Take-Home Messages.....	133
	Acknowledgments	134
	References	134

SECTION II Pathologies Associated with Inflammation

Chapter 11	Is There a Connection between Inflammation and Oxidative Stress?	139
<i>Chandrakala Aluganti Narasimhulu, Xuetong Jiang, Zhaohui Yang, Krithika Selvarajan, and Sampath Parthasarathy</i>		
11.1	Introduction	139
11.2	Atherosclerosis	139
11.3	Oxidative Stress and Atherosclerosis	141
11.4	Inflammation and Atherosclerosis.....	142
11.5	Would Anti-Inflammatories and Antioxidants Prevent Atherosclerosis?	144
11.6	Conclusions.....	146
	Take-Home Messages.....	146
	Acknowledgment.....	146
	References	146
Chapter 12	Chronic Inflammation and Cancer: A Matter of Lifestyle.....	153
<i>Subash C. Gupta, Ji Hye Kim, Sahdeo Prasad, and Bharat B. Aggarwal</i>		
12.1	What Is Inflammation?	153
12.2	Regulation of Inflammation at the Molecular Level	154
12.3	Lifestyle Factors That Activate Inflammation.....	155
12.4	How Inflammation Causes Cancer.....	156
12.4.1	Role of Inflammatory Molecules in Cellular Transformation.....	156
12.4.2	Role of Inflammatory Molecules in Tumor Cell Survival	157
12.4.3	Role of Inflammatory Molecules in Tumor Cell Proliferation.....	157
12.4.4	Role of Inflammatory Molecules in Tumor Cell Invasion, Angiogenesis, and Metastasis.....	158
12.5	Controlling Inflammation and Cancer	159
12.6	Conclusion and Future Directions	163
	Take-Home Messages.....	163
	Acknowledgments	164
	References	164
Chapter 13	Chronic Wounds and Inflammation	173
<i>Jaideep Banerjee and Chandan K. Sen</i>		
13.1	Introduction	173
13.2	Most Common Types of Chronic Wounds	174
13.2.1	Diabetic Foot Ulcer	174
13.2.2	Venous Ulcer	174
13.2.3	Arterial Ulcer	174
13.2.4	Pressure Ulcers.....	174
13.3	Phases of Healing	174
13.3.1	Hemostasis.....	174
13.3.2	Inflammation	175
13.3.3	Proliferation.....	175
13.3.4	Remodeling	176
13.4	Wound Inflammatory Response	176
13.4.1	The Inflammatory Cells	176
13.4.2	Cytokines	177

13.4.3 Lipid Mediators	178
13.4.4 Mechanisms of Inflammatory Resolution	178
13.5 Excess Inflammation Is Associated with Impaired Wound Healing	178
13.6 MicroRNAs in Chronic Inflammation	180
13.7 Biofilm and Chronic Wound Inflammation.....	180
13.8 Conclusions and Future Directions	181
Take-Home Messages.....	182
References	183
Chapter 14 Multiphasic Roles for TGF-Beta in Scarring: Implications for Therapeutic Intervention	187
<i>Praveen R. Arany, George X. Huang, and Woo Seob Kim</i>	
14.1 Introduction	187
14.2 Etiopathogenesis of Scar Generation.....	190
14.2.1 Scar Triggers	191
14.2.2 Scar Modulators	191
14.2.3 Scar Effectors	192
14.3 TGF- β 1 as a Plausible Link.....	192
14.4 Targeting TGF- β 1 in Scar Management.....	194
14.5 Conclusions and Future Directions	195
Take-Home Messages.....	195
References	195
Chapter 15 Natural Vitamin E Tocotrienol against Neuroinflammation and Oxidative Stress	199
<i>Cameron Rink and Savita Khanna</i>	
15.1 Central Nervous System Immunology	199
15.1.1 Defining Neuroinflammation	200
15.1.2 PUFA Oxidation and Neuroinflammation	201
15.2 Tocotrienol Vitamin E	201
15.3 Arachidonic Acid Cascade in Neuroinflammatory Disease	203
15.3.1 Phospholipase A ₂	204
15.3.2 Nonenzymatic Oxidative Metabolism of Arachidonic Acid.....	204
15.3.3 Enzymatic Oxidative Metabolism of Arachidonic Acid.....	205
15.3.3.1 Cyclooxygenase	205
15.3.3.2 Epoxygenase	205
15.3.3.3 Lipoxygenase	206
15.4 Conclusion and Future Directions	206
Take-Home Messages.....	207
References	207
Chapter 16 Inflammatory Cascades in Autoimmune Disease.....	213
<i>Amita Aggarwal and Arpita Myles</i>	
16.1 Introduction	213
16.2 Rheumatoid Arthritis	214
16.2.1 Adhesion.....	214
16.2.2 Migration.....	215
16.2.3 Leukocyte Adhesion and Migration and RA	215

16.2.4	Role of Chemokines and Their Receptors in Adhesion and Migration.....	216
16.2.5	Local Inflammation.....	216
16.2.6	Tissue Damage	218
16.2.6.1	Matrix Metalloproteinases.....	219
16.2.6.2	Wnt Pathway	219
16.2.6.3	RANK Pathway	219
16.3	Systemic Lupus Erythematosus (SLE).....	220
16.3.1	How Do These Autoantibodies Cause Inflammation and Tissue Damage?.....	220
16.3.2	Immune Complex Mediated Inflammation.....	221
16.3.3	Activation of the Innate Immune System.....	221
16.3.4	Activation of B Cells	222
16.3.5	Role of Local Factors	222
16.3.6	Cytokines	222
16.3.7	Role of T Cells in SLE	223
	Take-Home Messages.....	224
	References	224
Chapter 17	Shear Stress and Vascular Inflammation: A Study in the Lung.....	229
	<i>John Noel and Shampa Chatterjee</i>	
17.1	Introduction	229
17.2	Hemodynamic Forces and the Quiescent and Activated Endothelium	230
17.3	Disturbed Flow and Inflammatory Responses of Endothelial Cells	231
17.3.1	Effects of Laminar and Disturbed Flow on Endothelial Signaling and Function	231
17.3.2	Effects of Disturbed Flow on Endothelial-Leukocyte Interactions	232
17.3.3	Effects of Disturbed Flow In Vivo	232
17.4	Inflammation in the Pulmonary Endothelium	233
17.4.1	Effect on Neutrophil Recruitment and on Pulmonary Vascular Permeability	233
17.4.2	Interaction of Platelets with Endothelial Cells and Leukocytes	234
17.4.3	Inflammation in Pulmonary Hypertension	234
17.5	The Pulmonary Endothelium as a Therapeutic Target.....	234
17.6	Conclusions.....	235
	Take-Home Messages.....	235
	References	235
Chapter 18	NGF and Its Receptor System in Inflammatory Diseases.....	241
	<i>Anupam Mitra, Smriti K. Raychaudhuri, and Siba P. Raychaudhuri</i>	
18.1	Neurogenic Inflammation.....	241
18.2	NGF and Its Receptor	242
18.3	NGF and Its Role in Inflammatory Cascade	243
18.3.1	NGF and Immunocompetent Cells	243
18.3.1.1	Mast Cells	243
18.3.1.2	Basophils.....	244
18.3.1.3	Eosinophils	244
18.3.1.4	Neutrophils	244

18.3.1.5 Monocytes/Macrophages.....	244
18.3.1.6 Lymphocytes.....	245
18.3.1.7 Other Cells.....	245
18.3.2 NGF and Cytokines.....	245
18.4 Role of NGF in Different Inflammatory Diseases	246
18.4.1 Multiple Sclerosis	246
18.4.2 Rheumatoid Arthritis	247
18.4.3 Psoriasis.....	247
18.4.4 Psoriatic Arthritis.....	248
18.4.5 Osteoarthritis.....	248
18.4.6 Progressive Systemic Sclerosis.....	248
18.4.7 Systemic Lupus Erythematosus	248
18.4.8 Vasculitic Syndromes	248
18.4.9 Allergic Inflammatory Disease of Airways	248
18.4.10 Inflammatory Bowel Disease.....	249
18.4.11 NGF/TrkA Interaction: Potential New Drug Target	249
18.5 Conclusions.....	250
Take-Home Messages.....	250
References	251

SECTION III Nutrition & Therapeutics for Inflammatory Diseases

Chapter 19 Inflammation, Oxidative Stress, and Antioxidants	259
--	-----

*Naveen Kaushal, Vivek Narayan, Ujjawal H. Gandhi, Shakira M. Nelson,
Anil Kumar Kotha, and K. Sandeep Prabhu*

19.1 Introduction	259
19.2 ROS Mediated Oxidative Stress as a Source of Inflammation	261
19.3 Antioxidants as Anti-Inflammatory Agents	263
19.4 Trace Elements as Antioxidants	265
19.4.1 Selenium.....	265
19.4.1.1 Se and Its Role in Inflammation: Modulation of Lipid Metabolites as Key Regulators of Inflammation	266
19.4.2 Zinc.....	267
19.4.3 Copper	268
19.5 Summary and Future Directives	268
Acknowledgments	270
Take-Home Messages.....	270
References	271

Chapter 20 Lipid Biomarkers of Inflammation.....	275
---	-----

Ginger L. Milne

20.1 Introduction	275
20.2 Prostaglandins and Inflammation.....	275
20.2.1 PGE ₂	276
20.2.1.1 Quantification of PGE ₂ Production In Vivo in Humans: Clinical Perspectives	276

20.2.2 PGD ₂	278
20.2.2.1 Quantification of PGD ₂ Production In Vivo in Humans: Clinical Perspectives.....	278
20.3 Leukotrienes and Inflammation	280
20.3.1 Quantification of LT Production In Vivo in Humans: Clinical Perspectives	280
20.4 Nonenzymatic Lipid Peroxidation: The Isoprostanes	282
20.4.1 Quantification of F ₂ -Isoprostanes in Humans: Clinical Perspectives	282
20.5 Conclusions and Future Directions	283
Take-Home Messages.....	283
References	283
Chapter 21 Physical Activity and Inflammation: An Overview	287
<i>Edite Teixeira de Lemos and Flávio Reis</i>	
21.1 The State of Low-Grade Inflammation—Healthy Significance	287
21.1.1 The Inflammatory Response and Its Mechanisms.....	287
21.1.2 Inflammation as a Cause of Chronic Disease	289
21.2 The Anti-Inflammatory Nature of Physical Activity	290
21.2.1 Physical Activity and Myokines.....	290
21.2.2 The Adipose Tissue—Innate Immune System Hypothesis	292
21.2.3 Type and Intensity of Exercise versus Anti- or Pro-Inflammatory Response	293
21.3 Exercise-Induced Inflammation	294
21.3.1 Exercise-Induced Muscle Damage and Inflammation	294
21.3.2 The Paradox of IL-6 in Physical Activity and Inflammation.....	295
21.4 Physical Activity for the Treatment of Low-Grade Inflammation in Cardiometabolic Disorders: Focus on Type 2 Diabetes Mellitus	295
21.4.1 Effect of Physical Exercise in Type 2 Diabetes.....	296
21.4.2 Beyond the Anti-Inflammatory Effect of Physical Activity in T2DM: Pleiotropic Effects of Regular Exercise	298
21.5 Conclusions and Future Directions	299
Take-Home Messages.....	299
References	300
Chapter 22 Omega-6 and Omega-3 Polyunsaturated Fatty Acids and Inflammatory Processes	305
<i>Philip C. Calder</i>	
22.1 Omega-6 and Omega-3 Polyunsaturated Fatty Acids—Naming, Biosynthesis, Sources, and Intakes.....	306
22.2 Omega-6 and Omega-6 Polyunsaturated Fatty Acids in Cells Involved in Inflammation	307
22.3 Arachidonic Acid Is a Precursor of Eicosanoid Mediators Involved in Inflammation	308
22.4 Omega-3 Fatty Acids and Lipid Mediators	309
22.4.1 Omega-3 Fatty Acids Decrease Production of Eicosanoids from Arachidonic Acid	309
22.4.2 EPA Gives Rise to Alternative Eicosanoids	310
22.4.3 EPA and DHA Give Rise to Anti-Inflammatory and Inflammation Resolving Mediators Called Resolvins and Protectins	310

22.5	Omega-3 Fatty Acids Decrease NF κ B-Mediated Inflammatory Signaling	311
22.5.1	The NF κ B System.....	311
22.5.2	EPA and DHA Inhibit NF κ B Activation and Induction of NF κ B Targets	311
22.5.3	EPA and DHA May Promote an Anti-Inflammatory Interaction between PPAR- γ and NF κ B	311
22.5.4	EPA and DHA May Act through a Cell Surface Receptor That Inhibits NF κ B Activation.....	312
22.6	Effects of EPA and DHA on T Cells	312
22.7	Omega-3 Fatty Acids as a Therapeutic Option for Chronic Inflammation	312
22.7.1	General Comments.....	312
22.7.2	Rheumatoid Arthritis	313
22.7.2.1	Introduction	313
22.7.2.2	Omega-3 PUFAs and Animal Models of RA	313
22.7.2.3	Trials of ω -3 PUFAs in RA	313
22.7.2.4	Meta-Analyses of Trials of ω -3 PUFAs in RA.....	314
22.7.3	Inflammatory Bowel Diseases	314
22.7.3.1	Introduction	314
22.7.3.2	Omega-3 PUFAs and Animal Models of IBD.....	314
22.7.3.3	Trials of ω -3 PUFAs in IBD	315
22.7.3.4	Meta-Analyses of Trials of ω -3 PUFAs in RA.....	315
22.8	Conclusions.....	315
	Take-Home Messages.....	316
	References	317
Chapter 23	Anti-Inflammatory Phytochemicals, Obesity, and Diabetes: An Overview	323
	<i>Srujana Rayalam, MaryAnne Della-Fera, and Clifton A. Baile</i>	
23.1	Introduction	323
23.2	Obesity and Diabetes as Major Public Health Issues	324
23.3	Adipose Tissue as a Secretory Organ.....	324
23.4	Relationship between Obesity, Diabetes, and Inflammation.....	325
23.5	Complications of Obesity and Diabetes	326
23.6	Phytochemicals in Obesity and Diabetes	326
23.6.1	Curcumin.....	327
23.6.1.1	Rodent Studies	327
23.6.1.2	Human Clinical Trials	328
23.6.2	Resveratrol.....	328
23.6.2.1	Rodent Studies	329
23.6.2.2	Human Clinical Trials	329
23.6.3	Epigallocatechin-3-Gallate.....	329
23.6.3.1	Rodent Studies	330
23.6.3.2	Human Clinical Trials	330
23.6.4	Genistein	330
23.6.4.1	Rodent Studies	331
23.6.4.2	Human Clinical Trials	331
23.7	Perspectives	331
23.8	Conclusions and Future Directions	332
	Take-Home Messages.....	332
	References	333

Chapter 24	Anti-Inflammatory Nutraceuticals and Herbal Medicines for the Management of Metabolic Syndrome	337
<i>George Q. Li, Ka H. Wong, Antony Kam, Xian Zhou, Eshaifol A. Omar, Ali Alqahtani, Kong M. Li, Valentina Razmovski-Naumovski, and Kelvin Chan</i>		
24.1	Introduction	338
24.2	Treatment of Metabolic Syndrome in Traditional Chinese Medicine.....	338
24.2.1	Obesity.....	340
24.2.2	Prediabetes	340
24.2.3	Hypertension	340
24.2.4	Hyperlipidemia.....	341
24.3	Heat Clearing Chinese Herbs for Metabolic Syndrome.....	341
24.3.1	Baical Skullcap.....	341
24.3.2	Goldthread.....	342
24.4	Anti-Inflammatory Food and Tea.....	343
24.4.1	Pomegranate	343
24.4.2	Green Tea	344
24.5	Anti-Inflammatory Effects of Polyunsaturated Fatty Acids in the Management of Metabolic Syndrome	344
24.6	Discussion and Summary	345
	Take-Home Messages.....	346
	Acknowledgments	347
	References	347
Chapter 25	Epigenetics and Nutriepigenomics in Chronic Inflammatory Lung Diseases: Nutritional and Therapeutic Interventions	351
<i>Saravanan Rajendrasozhan, Isaac K. Sundar, and Irfan Rahman</i>		
25.1	Lung Inflammation and Pathogenesis of Chronic Lung Diseases (Asthma and Chronic Obstructive Pulmonary Disease)	352
25.2	Epigenetic/Epigenomic Changes.....	352
25.2.1	Epigenetic Changes in COPD	353
25.2.2	Epigenetic Changes in Asthma	354
25.3	Molecular Epigenomic Targets for Therapeutic Interventions.....	354
25.3.1	Histone Acetyltransferases	355
25.3.2	Histone Deacetylases	355
25.3.3	Histone Methyltransferases	356
25.3.4	Histone Demethylases	356
25.3.5	NF- κ B	357
25.3.6	MicroRNAs	357
25.4	Nutriepigenomics.....	358
25.4.1	Curcumin.....	359
25.4.2	Resveratrol.....	360
25.4.3	Catechins.....	361
25.4.4	Garcinol	361
25.4.5	Anacardic Acid.....	361
25.5	Perspectives	361
25.5.1	Clinical	362
25.5.2	Basic Sciences	362
25.6	Conclusions and Future Directions	362
	Take-Home Messages.....	362

Acknowledgments	364
References	364
Chapter 26 Biologics: Molecular Medicine from Bench to Bedside	369
<i>Ananya Datta Mitra, Debasis Bagchi, Siba P. Raychaudhuri, and Smriti K. Raychaudhuri</i>	
26.1 Introduction	370
26.2 Interplay of the Immune System in the Development of Autoimmune Disease.....	370
26.2.1 T Cells in Autoimmunity	370
26.2.2 B Cells in Autoimmunity	371
26.2.3 Cytokines in Autoimmunity.....	371
26.3 Targets for Biologics.....	372
26.3.1 Anti-Cytokine Therapy	373
26.3.1.1 Targeting Tumor Necrosis Factor- α	373
26.3.1.2 Adverse Effects Associated with Anti-TNF Agents.....	376
26.3.1.3 Targeting IL-1	378
26.3.1.4 Targeting IL-6.....	378
26.3.1.5 Other Interleukin Antagonists	378
26.3.2 Targeting T Cells.....	379
26.3.3 Targeting B Cells in the Treatment of Systemic and Cutaneous Autoimmune Diseases.....	382
26.3.3.1 Anti-CD20 Therapies	382
26.3.3.2 Targeting B-Cell Activating Factor and a Proliferation-Inducing Ligand	383
26.3.4 Angiogenesis Factor	383
26.3.5 Drugs That Inhibit Leukocyte Adhesion.....	383
26.3.6 Targeting Nerve Growth Factor	384
26.4 Conclusions.....	384
Take-Home Messages.....	384
References	385
Chapter 27 Disease Modifying Anti-Rheumatic Drugs	391
<i>Nigil Haroon and Vinod Chandran</i>	
27.1 Introduction	392
27.2 Methotrexate.....	392
27.2.1 Mechanism of Action	392
27.2.2 Dose.....	393
27.2.3 Use in Rheumatic Diseases	393
27.2.4 Adverse Effects of Methotrexate.....	394
27.3 Leflunomide.....	395
27.3.1 Mechanism of Action	395
27.3.2 Dose.....	395
27.3.3 Use in Rheumatic Diseases	395
27.3.3.1 Rheumatoid Arthritis.....	395
27.3.3.2 Psoriatic Arthritis	396
27.3.3.3 Other Rheumatic Diseases	396
27.3.4 Adverse Effects of Leflunomide.....	396

27.4	Sulfasalazine.....	397
27.4.1	Mechanism of Action	397
27.4.2	Dose.....	397
27.4.3	Use in Rheumatic Diseases	397
27.4.4	Adverse Effects	398
27.5	Antimalarials.....	398
27.5.1	Mechanism of Action	398
27.5.2	Dose.....	398
27.5.3	Use in Rheumatic Diseases	398
27.5.4	Adverse Effects	399
27.6	Azathioprine.....	399
27.6.1	Mechanism of Action	399
27.6.2	Dose.....	399
27.6.3	Use in Rheumatic Diseases	400
27.6.4	Adverse Effects	400
27.7	Cyclosporin A.....	400
27.7.1	Mechanism of Action	401
27.7.2	Dose.....	401
27.7.3	Use in Rheumatic Diseases	401
27.7.4	Adverse Effects	402
27.8	Other DMARDs	402
27.9	Conclusions.....	402
	Take-Home Messages.....	403
	References	403
Chapter 28	Nonsteroidal Anti-Inflammatory Drugs.....	407
	<i>Alakendu Ghosh and Pradyot Sinhamahapatra</i>	
28.1	Introduction	408
28.2	History	408
28.3	Mechanism of Action	408
28.4	Classification	409
28.5	Pharmacokinetics	409
28.6	Pharmacodynamics	409
28.7	Clinical Uses of NSAIDs	410
28.7.1	Osteoarthritis.....	410
28.7.2	Other Inflammatory Arthropathies.....	411
28.7.3	Other Roles of NSAIDs.....	411
28.8	How to Guide Therapy	411
28.9	Adverse Reactions and Toxicities of NSAIDs.....	412
28.10	Choice of NSAIDs.....	412
28.11	Precautions for Use of NSAIDs.....	412
28.11.1	Anemia	412
28.11.2	Hypersensitivity Reactions: Asthma	412
28.11.3	Delayed Hypersensitivity	413
28.11.4	Pregnancy	413
28.11.5	Elderly	413
28.11.6	Surgery	413
28.12	Drug Interactions.....	413
28.13	Special Situations and Toxicities	414
28.13.1	NSAID-Induced Gastrointestinal Toxicity.....	414

28.13.2 Hepatotoxicity	415
28.13.3 NSAID-Induced Cardiovascular Toxicity	415
28.13.3.1 Patients on Low-Dose Aspirin.....	416
28.13.4 NSAID-Induced Renal Toxicity.....	416
28.13.5 Topical NSAIDs	417
28.14 Treatment Options for Patients with Gastrointestinal and Cardiovascular Risk	417
Take-Home Messages.....	418
Web Sites.....	418
General Resources.....	418
References	419
Index.....	423