Contents

Contributors xiii
Preface xv

1. **An Overview of the Innate Immune Response to Infectious and Noninfectious Stressors**
Stefania Gallucci

Introduction 1
Recognition 2
PRRs and PAMPs 3
Toll-Like Receptors 5
C-Type Lectin Receptors 6
The RIG-I-Like Receptors 7
NLRs and the Inflammasome 8
AIM2-Like Receptors 9
C-GAS and Other DNA Sensors 10
RAGE 10
Soluble PRRs 11
PRR Localization 11
DAMPs 12
Nucleic Acids 12
ATP 13
Uric Acid 14
Heat-Shock Proteins 15
Mitochondrial Danger Signals 15
HMGB1 16
Degradation Products of the Extracellular Matrix 17
Secondary Endogenous Danger Signals 18
Emerging and Homeostatic Danger Signals 18
Conclusions 19
References 20

2. Homeostatic Inflammation as Environmental-Adaptation Strategy
Kensuke Miyake, Ryutaro Fukui

Introduction 25
Innate Immune Sensors Recognize Various Endogenous Ligands Including Metabolites 25
Modulation of Metabolites Recognized by Extracellular Sensors 27
Modification of Nucleic Acid-Sensing Receptors 28
DNA and RNA are Modified to be Recognized or not by Innate Immune Sensors 31
Priming Effect of Noninfectious Inflammation on Immune Response 33
Correlation with Inflammatory and Autoimmune Diseases in Adipose Tissue 35
Excessive Activation of Nucleic Acid-Sensing Sensors Induces Autoimmune Diseases 37
Regulation of Homeostatic Inflammation and Innate Immune Sensors for Controlling Immune System and Homeostasis 39
References 40

3. The Molecular Basis of the Immune Response to Stressed Cells and Tissues
Segundo González, Carlos López-Larrea, Alejandro López-Soto

Innate Immune Responses: Receptors and Ligands 54
Stress-Mediated Regulation of Immune Receptors and Ligands: An Overview 54
Transcriptional Regulation of NK-Cell Activating Ligands Modulated by Stress Responses 57
Posttranscriptional Regulation of Stress-Controlled NK-Cell Activating Ligands 58
Translational and Posttranslational Regulation of Stress-Modulated NK-Cell Activating Ligands 59
Different Forms of Stress Regulate Innate Immunity 61
Osmotic Stress 61
Thermal Stress 62
Genotoxic Stress 63
Oxidative Stress 65
Endoplasmic Reticulum Stress 66
Stress-Induced Senescence 67
Immunogenic Cell Death: Putting all the Things Together 68
References 70

4. Modulation of Innate Immunity by Hypoxia
Elena Riboldi, Antonio Sica

Hypoxia 81
Hypoxia Sensing 82
Hypoxia-Inducible Factors 83
Nuclear Factor κB 85
Hypoxia Effects on Leukocytes 86
Myeloid Cells 86
Lymphoid Cells 91
Hypoxia, Myeloid Cells, and Diseases 92
Pulmonary Hypertension (PH) 92
Rheumatoid Arthritis 92
Inflammatory Bowel Disease 93
Atherosclerosis 93
Ischemia 94
Preeclampsia 94
Allergy 94
Cancer 94
Therapeutic Targeting of Hypoxic Signaling 95
HIF Activators 95
HIF Inhibitors 96
References 97

5. Metabolic Stress, Heat Shock Proteins, and Innate Immune Response
Nicola Lacetera

Introduction 107
Metabolic Stress Conditions 107
Metabolic Stress and Innate Immunity 110
Metabolic Stress, Oxidative Stress, and Heat Shock Proteins 113
Heat-Shock Proteins and Innate Immune Response 118
Conclusions 123
References 123

6. Innate Immune Responses and Cancer Metastasis
Yoshiro Maru

Clinical Information on Metastasis 133
Elements that Constitute Metastasis 134
Definition and Understanding 134
Triangle 136
Angiogenesis Promotes Coagulation and Induces Inflammation 136
Coagulation Promotes Angiogenesis and Inflammation 138
Inflammation Participates in Both Angiogenesis and Coagulation 143

Lung Homeostasis 145
Interphase 145
Cell Mobilization 146
Mimicry 148
Premetastasis 148
An Idea of Premetastasis 148
Isolated Lung Perfusion 149
Molecular Biology of Premetastatic Lungs 151
Defective Conservation of SAA3 152
Homeostatic Inflammation and Therapeutic Targeting 153
References 157

7. Innate Immune Response and Psychotic Disorders
Jaana Suvisaari, Outi Mantere

Introduction 165
Psychotic Disorders: Neurodevelopmental Disorders with a Neuroprogressive Component 168
Pre- and Perinatal Exposures 169
Childhood and Adolescence Exposures 170
Genetic Evidence of the Contribution of Immunological Factors to Psychotic Disorders 171
Innate Immunity Disturbances in People with Psychotic Disorders 171
Microglia in Psychotic Disorders 175
Neuronal Autoantibodies and Psychosis 176
Microbiome and Inflammation in Psychotic Disorders 176
An Immune-Mediated Two-Hit Model for Psychosis 177
Confounders 178
Psychosis as Compared to Autoimmune Disorders 179
Anti-Inflammatory Drugs as Adjunctive Medication in Psychotic Disorders 179
Future Directions 180
References 182

8. Modulation of the Interferon Response by Environmental, Noninfectious Stressors
Elisabetta Razzuoli, Cinzia Zanotti, Massimo Amadori

Introduction 191
Biological Functions 192
Constitutive Expression 194
Stress, Tissue Damage, and IFN Responses 196
Human Models 197

Animal Models 199
Weaning Stress 199
Transportation Stress 199
Exposure to Mycotoxins 200
Pregnancy 201
Conclusions 202
References 202

9. **Disease-Predicting and Prognostic Potential of Innate Immune Responses to Noninfectious Stressors: Human and Animal Models**
Erminio Trevisi, Livia Moscati, Massimo Amadori

Introduction 209
Health and Disease 209
Innate Immunity and Inflammation 210
Mediators of Inflammation: Local and Systemic Effects 210
Possible Causes of Dysregulated Inflammatory Response 213
Inflammation and Disease 214
Human Models 214
Animal Models: The Periparturient Dairy Cow 217
Disease Occurrence in Periparturient Dairy Cows 217
Causes of the Inflammatory Response in Periparturient Dairy Cows 217
Blood Indexes to Assess the Inflammatory Response in Dairy Cows 218
Aggregate Indices of the Inflammatory Response After Calving Allow Early Diagnosis and/or Prognosis of Disease Conditions 219
Blood Indices in Late Pregnancy Allow to Predict Disease Occurrence After Calving 223
Animal Models: The Farmed Pig 225
Disease Occurrence in Farmed Pigs 225
Lean Type Pig: Borderline Animal 226
Case 1: Innate Immunity Parameters as Prognostic and Diagnostic Tools 227
Case 2: Human–Animal Relationship in Pig Production: Influence on Innate Immunity 227
Case 3: Innate Immune Response to Thermal Stress 228
References 229

Subject Index 237