## Contents

1 Introduction to Interrelated Biology of Age-Associated Chronic Diseases and Cancer: Chronic Inflammation, a Common Denominator in Morbidity and Mortality ......................... 1

1 Introduction .......................................................................................... 2

2 Neglected Historical Observations, Theories and Discoveries on the Role of Immunity in Controlling Carcinogenesis .................. 5

2.1 Observations by Paul Ehrlich and Ilya Mechinkov in Nineteenth and Twentieth Centuries: Era of Modern Experimental Immunology .................................................. 7

2.2 Contributions of Peyton Rous in 1900s: Era of Tumor Virology. Virus-Causing Cancers .................. 7

2.3 Burnet (1957): Insightful Theory of Immune Surveillance-Controlling Cancer Cells .................. 8

2.4 Biological Cascades Toward Cancer Metastasis: Extension of the Theory of ‘Seed and Soil’ by Paget (1889) .................................................. 13

2.5 Contribution of Dvorak (1986): ‘Tumors Are Wounds that Do Not Heal’ .................................. 13

2.6 ‘Accidental’ Discoveries: Systematic Studies Led to First Evidence on Direct Link Between Inflammation and Tumorogenesis (Khatami et al. 1980s) .................. 14

3 Why War on Cancer Will Not End: False Foundation and Visionless/Reductionist Approaches to Cancer Research and Therapy as Bases for Extremely Slow Progress and Financial Toxicity to Society. Might of Power Over Right of Science! ............................................................... 18

4 Answer to Cancer: A Case for Inflammation as Common Denominator in Induction of Nearly All Age-Associated Chronic Diseases and Site-Specific Cancers .......................... 20
Assessing Claimed ‘Targeted’ Therapies, ‘Personalized’ or ‘Precision’ Medicine for Solid Tumors ............................................. 23
Heavy Economic Burden to Society on Falsely Designed Clinical Trials that Repeatedly Failed: Cancer Financial Toxicity ................................................................. 26
Challenges in Conducting Effective Research and Clinical Trials for Cancer ........................................................................... 27
Concluding Remarks and Proposed Future Directions: Maintenance of Immune Surveillance Key to Healthy Aging ............ 28
References ........................................................................................................................................................................... 31

2 Immune Surveillance in Health and Diseases of Aging: Definitions of Acute and Chronic Inflammation [Yin and Yang] ........................................................................ 37
1 Introduction ................................................................................................................................................................. 38
2 Acute Inflammation: Division of Labor in Programmed Cell Death. Protective, Self-Terminating Property of Immune Surveillance. Balancing Growth-Arrest (Yin) and Growth-Promote (Yang) Arms of Immunity ....................... 41
2.1 Yin Phenomenon: Pro-inflammatory or Initiation Stage: Apoptosis, Program Cell Death, Growth-Arresting or Tumoricidal [DRESSED TO KILL!] ................. 43
2.2 Yang Phenomenon: Post-inflammatory or Termination/Resolution of Acute Inflammation (Wound Healing, Growth-Promoting, Tissue Repair, Tumorigenic). Host Revival! ................................................................. 45
2.3 Contribution of Non-immune Systems in Acute Inflammation in Balancing Yin-Yang ........................................................................ 47
2.4 Mission and Outcomes of Acute Inflammation (Yin-Yang) or Effective Immunity (Immune Surveillance) .... 52
3 Sequence of Events in Immediate Hypersensitivity Reactions............................................................................. 53
4 Molecular Mechanisms of Acute Inflammation .................................................................................................... 54
5 Interrelated Cell Death Categories ....................................................................................................................... 55
6 Chronic Inflammation: ‘Immunological Chaos’ in Host Tissue and Initiation of Disease Process. Not All Immune Disruptors Created Equal! ................................................................. 58
7 Stem Cells; Shared or Special Features in Innate and Adaptive Immune Cell Responses in Health and Age-Associated Chronic Diseases or Cancer ......................................................................... 59
8 Differential Influence of Acute and Chronic Inflammation in Immune-Privileged and Immune-Responsive Tissues and Chronic Diseases .................................................................................. 61
8.1 Immune Surveillance (Protection) in Immune-Responsive Tissues ......................................................................... 62
8.2 Immune Protection (Tolerance) in Immune-Privileged Tissues ............................................................................. 62
9 Clinical and Immunological Features of Immune Deficiencies........... 67
10 Challenges in Understanding Dynamics of Immune Responses and Inflammation ................................................................. 75
11 Concluding Remarks ...................................................................... 76
References ............................................................................................ 78

3 Theories of Aging and Chronic Diseases: Chronic Inflammation an Interdependent ‘Roadmap’ to Age-Associated Illnesses .......... 91
1 Introduction ..................................................................................... 92
2 Principals in Biology of Aging Process ............................................ 95
3 Biological Theories of Aging: Search for Common Link ................. 98
4 Free Radical Concept and Oxidative Stress Theory of Aging:
   Role of Mitochondria .................................................................... 100
5 Genomic Theory of Aging .............................................................. 104
   5.1 Role of Hyperactivation of Suppressor Gene Pathways in Aging ....................................................................... 106
6 Immunosenescence Theory: Connecting the Dots with Oxidative Stress and Skewed Dynamics of Immunity in Aging ................................................................. 107
   6.1 Immune Competency in Aging: Role of Antigen Presenting Cells (APCs) in Immunosenescence ......................... 108
   6.2 Multipotent Hematopoietic Stem Cells ................................... 109
   6.3 Cytokine/Chemokine Dynamics: Role of Decoy Receptors in Control of Acute or Chronic Inflammation in Health and Diseases .............................................. 112
   6.4 Role of Natural Killer Cells in Aging: Skewed Cytotoxicity ............................................................................. 115
   6.5 T Cell Immunity in Aging .......................................................... 116
   6.6 B Cells and Lymphoid Organ Function in Aging .................... 118
   6.7 Germinal Center Dynamics: Antibody-Forming and Memory Cells .................................................................... 119
   6.8 Role of Neutrophils in Remodeling Extracellular Matrix and Angiogenesis ......................................................... 120
   6.9 Mast Cells: Innate Immune Cells Possessing Effector Cell Properties .................................................................. 121
   6.10 Function of Dendritic Cells in Immunity and Aging .................. 125
   6.11 Role of Macrophages in Acute and Chronic Inflammation and Aging ................................................................. 127
7 Cytobiology of Vasculature, Platelets and Complement in Acute or Chronic Inflammatory Diseases ............................... 132
   7.1 Platelets Contributions in Immunity: Shared Features with Innate Immune Cells .................................................. 136
   7.2 Nitric Oxide in Inflammation and Aging ................................. 137
Contents

7 Addressing Additional Major Knowledge Gaps in Cancer Biology .......................................................... 202
8 Types of Allergies and Immune Disorders: Rational for Promotion of Balance Between Yin (Tumoricidal) and Yang (Tumorigenic) Pathways in Immunity for Prevention of Chronic Diseases ........................................ 204
9 Conclusions and Perspectives ............................................................................................................. 205
References............................................................................................................................................. 206

5 Cancer Statistics and Concerns for Safety of Drugs or Vaccines: Increased Population of Drug-Dependent Sick Society! .............................................. 213
1 Introduction........................................................................................................................................ 214
2 Statistical and Epidemiologic Data on Disease Mortality and Morbidity Around the World: Why Americans Health Rank Last?........................................................................................................ 215
2.1 Anatomy of a Sick Care Nation (America): Power of Advertisement-Creation of ‘Magical Reality’ Culture for Selling Drugs and Unhealthy Food Products ...... 217
3 Cancer Global Burden: Statistics on Incidence and Mortality .......................................................... 218
4 Statistical Definitions for Cancer Mortality and Morbidity ............................................................. 220
5 Results and Analyses of Cancer-Related Statistics on Incidence, Mortality and Morbidity ................ 223
6 Cancer Risk Factors: Impact of Aging Process, Chronic Infections, Pathogen-Specific Vaccines, Carcinogens and Chemicals......................................................................................... 238
7 Misrepresented Information and Knowledge Gaps on Cancer Triggers: Viral Oncogene Sub-structures in Vaccines and Sharp Increase in Cancer Incidence or Chronic Neurodegenerative and Autoimmune Diseases ........................................ 243
8 Challenges in Formulation of Accurate Risk Assessment: Immune Disruptor-(Antigen)-Induced Chronic Inflammation as Precancerous State of Tissues......................................................... 246
9 Proposed Future Directions: Risk Reduction and Control of Cancer................................................ 247
10 Author’s Final Comments on Future Perspectives ................................................................. 249
References............................................................................................................................................ 250

6 Cancer Biology: Severe Cumulative Delayed Type Hypersensitivity Reactions .......................................... 261
1 Introduction........................................................................................................................................ 262
2 Highlights of Two Centuries of Cancer Research and Therapies: Neglected Common Sense on Fundamental Observations and Discoveries ........................................................................... 264
3 Forgotten Common Sense to Systematically Study Cancer Science: Bases for Lack of Progress in Therapy or Prevention ...... 269
<table>
<thead>
<tr>
<th>Content</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 American Tragedy of 1955s: Virus-Contaminated</td>
<td>271</td>
</tr>
<tr>
<td>Polio Vaccines and Sharp Increase in Cancer Incidence</td>
<td></td>
</tr>
<tr>
<td>and Mortality and Other Chronic Inflammatory Diseases</td>
<td></td>
</tr>
<tr>
<td>in Baby Boomer Generation: A Sick Drug-Dependent Society</td>
<td></td>
</tr>
<tr>
<td>5 Maintenance of Health: Biological Laws in Policing</td>
<td>272</td>
</tr>
<tr>
<td>Body’s Health. Biphasic/Dual Roles of Yin and Yang</td>
<td></td>
</tr>
<tr>
<td>Pathways in Acute Inflammation</td>
<td></td>
</tr>
<tr>
<td>6 Hypersensitivity Reactions or Biological Terrorists:</td>
<td>275</td>
</tr>
<tr>
<td>Tissue-Specific Immune Disorders or Cancers</td>
<td></td>
</tr>
<tr>
<td>7 Immune Disorders: Common Denominators of ‘Mild’,</td>
<td></td>
</tr>
<tr>
<td>‘Moderate’ or ‘Severe’ Hypersensitivity Responses: Cancer a ‘Severe’</td>
<td></td>
</tr>
<tr>
<td>Cumulative Altered Immune Responses that Destroy Architectural Integrity</td>
<td>281</td>
</tr>
<tr>
<td>of Tissue</td>
<td></td>
</tr>
<tr>
<td>7.1 Histamine a Blue Print? [An Idea Who’s Time Has Come!]</td>
<td>281</td>
</tr>
<tr>
<td>7.2 Interdependent Categories in Age-Associated</td>
<td>283</td>
</tr>
<tr>
<td>Chronic Diseases</td>
<td></td>
</tr>
<tr>
<td>8 Metabolism and Function of Histamine (Catecholamine)</td>
<td>284</td>
</tr>
<tr>
<td>in Acute and Chronic Inflammatory Diseases</td>
<td></td>
</tr>
<tr>
<td>8.1 Spectrum of Anaphylaxis and Inflammatory Diseases</td>
<td></td>
</tr>
<tr>
<td>When Beneficial Biphasic Yin and Yang of Immunity</td>
<td>285</td>
</tr>
<tr>
<td>becomes Health Hazards</td>
<td></td>
</tr>
<tr>
<td>8.2 Allergies and Induction of Diverse Diseases and Cancer</td>
<td>287</td>
</tr>
<tr>
<td>9 The Many Faces of Histamine: Friend and Foe!</td>
<td>288</td>
</tr>
<tr>
<td>9.1 Biological Gaps: Connecting Dots on Diverse Function of Histamine</td>
<td></td>
</tr>
<tr>
<td>under Oxidative Stress and Aging Process</td>
<td>293</td>
</tr>
<tr>
<td>10 Energy-Requiring Activation of Immune Cells in Health or Immune</td>
<td>294</td>
</tr>
<tr>
<td>Disorders: Role of Mitochondrial Oxidative Phosphorylation and Autophagy</td>
<td></td>
</tr>
<tr>
<td>11 Bioenergetics of Mast Cell Exocytosis, Secretory Lysosomes</td>
<td>296</td>
</tr>
<tr>
<td>and Ca(^{2+}) Fluxes in Acute and Chronic Inflammation</td>
<td></td>
</tr>
<tr>
<td>12 Histamine Influence on Tissue Physiology and Function</td>
<td>298</td>
</tr>
<tr>
<td>12.1 Oxidative Stress and Low Level Circulating Histamine:</td>
<td></td>
</tr>
<tr>
<td>Preparing Host for Induction of Tumorigenesis?</td>
<td>300</td>
</tr>
<tr>
<td>12.2 Asthma: Intermediate Inflammatory Responses: Increased Risk of</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>301</td>
</tr>
<tr>
<td>12.3 Mediators of Late Phase Hypersensitivity Responses</td>
<td>302</td>
</tr>
<tr>
<td>13 Pattern Recognition Receptors (PRRs) in Biological Events:</td>
<td></td>
</tr>
<tr>
<td>Constituent (Innate) and Induced (‘Designer’). Crucial Roles in</td>
<td>304</td>
</tr>
<tr>
<td>Circadian Rhythms and Immunity</td>
<td></td>
</tr>
<tr>
<td>13.1 Constituent: Innate and Adoptive Receptors and Surface Molecules</td>
<td>305</td>
</tr>
<tr>
<td>13.2 Induced or Transient Receptors and Surface Molecules: ‘Designer’</td>
<td></td>
</tr>
</tbody>
</table>
13.3 Pattern Recognition Receptors (PRRs) in Health and Immune Disorders: Toll-like Receptors (TLRs) and Inhibitors: Role in Multistep Carcinogenesis ................... 306
13.4 Pattern Recognition for Regulation (Tolerance) of Inflammation by IRAK-M: Special Features of Yin-Yang Events? .......................................................... 307
14 Regulatory Signaling Mechanisms of Soluble Hormones and Tumor Factors in Immune Tolerance: Role of IRAK-M in Violations of Biological Laws and Tumorigenesis! .................. 309
14.1 Receptor Recognition and Function in Autoimmune Diseases .............................................................................. 312
15 Energy-Dependent Differential Role of Mitochondria in Maintenance of Yin and Yang Balance: mTOR/PI3K/AKT Complexes in Health or Immune Disorders and Cancer .......... 313
15.1 Mechanisms of mTOR-Kinase Complexes in Metabolism, Hormonal Regulation, Cell Growth and Immunity .......... 314
15.2 Role of mTOR in Metabolism and Immunity of Adipose Tissue (an Endocrine Organ) ................................................. 315
15.3 Bioenergetics of Chromatin Complexes: Remodeling of Nucleosome .............................................................. 318
15.4 Inflammation-Hypothalamus-Adrenal Axis: Interdependent Acute Phase Response (APR) and Systemic Response ................................................................. 319
15.5 Inflammation- Hepatic Axis in Acute Phase Response (APR) .................................................................................. 320
15.6 Mitochondria and Immune Dysfunction: Activation of Oncogenes ........................................................................ 321
16 Bird’s Eye View of Intrinsic (Innate) and Induced (Adaptive) Response Profiles in Initiation of ‘Mild’, ‘Moderate’ and ‘Severe’ Immune Disorders and Tumorigenesis: Differential Bioenergetics Requirement in Yin and Yang Events ...................... 323
17 Is Cancer a Severe Late Hypersensitivity Reaction (Immune Tsunami) That Destroys Host Tissue for Immortal Life? The Precious Truth!! ........................................................................ 325
17.1 Cancer-Induced Oxidative Stress: Dysfunction of Genomic, Immune Response and Metabolism in Tissue ....... 326
17.2 Tumor Lysis Syndrome and Tissue Metabolism ......... 328
18 Bioenergetics of Host-Immune Dynamics: Contribution of Mitochondria and Oxidative Metabolism .............................................................. 329
18.1 Differential and Parallel Bioenergetics Requirements of Mitochondria and Immune-Surveillance from Fetus Growth, and throughout Life: Features of ‘Mild’, ‘Moderate’ and ‘Severe’ Immunological Disorders and Cancer ......................................................... 329
18.2 Bases for Repeated Failed Cancer Therapeutics: Ignoring Nature of Compensating Biological Events! .......... 331
19 Fundamental Questions for Future Considerations: Influence of Inflammatory Responses in Induction of Chronic Diseases or Cancer ............................................................ 332
20 Concluding Remarks and Future Perspectives .................................................. 334
References ........................................................................................................ 335

Index .................................................................................................................. 377
Inflammation, Aging and Cancer
Biological Injustices to Molecular Village of Immunity
that Guard Health
Khatami, M.
2017, XVI, 389 p. 57 illus., 52 illus. in color., Hardcover
ISBN: 978-3-319-66473-6