Handbook on Immunosenescence

Basic Understanding and Clinical Applications

Editors

Tamas Fulop
University of Sherbrooke, Quebec, Canada

Claudio Franceschi
University of Bologna, Bologna, Italy

Katsuiku Hirokawa
Institute for Health and Life Sciences, Tokyo, Japan

Graham Pawelec
University of Tübingen, Tübingen, Germany

Springer
Preface

What is Immunosenescence?

The number of elderly people is steadily increasing in most countries. Concomitantly, the number of age-related diseases is unfortunately also increasing. One of the leading causes of death in the very elderly is infection, with cardio-vascular diseases and cancer less prevalent than in younger elderly. All three major pathologies are to some extent related to the immune system due to its well-known but still imperfectly investigated deregulation during aging.

Thus, the large amount of data accumulated during the last decade or more has allowed a better but still incomplete understanding of all the complex alterations affecting the immune system with aging. Although we do not know everything, we feel that it is important for the scientific community to become more acquainted with the corpus of knowledge recently generated in this domain, presented in a manner providing a critical evaluation of the current status of research. Many accepted ideas have changed during the last decade, such as the effect of aging on the innate immune system, antigen presentation, the cytokine imbalance and low grade inflammation. If not exactly a paradigm shift, the time seems ripe to present this critical evaluation and update of the state-of-the-art in these different areas. We perceive a great need to assemble this current knowledge in one volume by collecting contributions from the most eminent researchers in the field from all around the world. In this way, we aim to facilitate a synthesis of the different aspects of the disparate disciplines in ageing research to focus on immunosenescence for the first time (basic and clinical, molecular, cellular, biochemical, genetics). We hope this multidisciplinary approach from the aging, immunity and inflammation community will also be important for future innovative research in this domain.

Thus, this book will have as its main themes Aging, Immunity and Inflammation, with an emphasis on studies in humans. However, as data are not always available in this species, work in experimental animals will be also treated as appropriate. A large number of colleagues responded enthusiastically to our proposal and contributed with very high quality chapters. We begin with a description of Methods and models for studying immunosenescence. We continue with Cellular immunosenescence, treating most specifically T cells, B cells, neutrophils, antigen presenting cells
and NK cells. We then proceed to mechanisms. In this context, receptor signaling, the role of mitochondrial activity, the proteasome, cytokine status and the neuroendocrine-immune network are treated. The important but very challenging area of the Clinical relevance of immunosenescence for disease states is covered next by the individual treatment of infections, autoimmunity, cancer, metabolic syndrome, neurodegeneration and frailty. Finally, and even more challengingy, the last part of the book is devoted to possibilities for eventual intervention and modulation. We particularly emphasise nutritional aspects, lipids and experimental interventions. In this way we feel that we cover the whole range of areas from models, through basic molecular mechanisms to the clinical relevance and finally eventual modulation.

One of the main objectives of this book is to present in a systematic way our current knowledge in the field of the immunology related to aging. So do we now know what immunosenescence is? It is still difficult at answer this question, but we hope even the most specialist investigator in the field will find concepts and ideas within the book which will help him or her to approach an answer to this important question more closely than before. We would therefore sincerely like to hope that we have created an authoritative, innovative and thought-provoking book dedicated for the first time to this topic alone. We also like to hope that this volume will help to attract a new generation of researchers to the field of immunosenescence as an expanding and vital research arena.

Tamas Fulop Quebec, Canada
Claudio Franceschi Bologna, Italy
Katsuiku Hirokawa Tokyo, Japan
Graham Pawelec Tübingen, Germany
Contents

Part I: Methods and Models for Studying Immunosenescence

1. The Immune Risk Profile and Associated Parameters in Late Life: Lessons from the OCTO and NONA Longitudinal Studies
   Anders Wikby, Jan Strindhall and Boo Johansson ......................... 3

2. Lymphocytes Sub-Types and Functions in Centenarians as Models for Successful Ageing
   Enrico Lugli, Leonardo Troiano, Marcello Pinti, Milena Nasi,
   Erika Roat, Roberta Ferraresi, Linda Bertoncelli, Lara Gibellini,
   Elisa Nemes and Andrea Cossarizza .................................... 29

3. Mouse Models and Genetics of Immunosenescence
   Qing Yu, Jyoti Misra Sen and Dennis Taub ............................... 63

4. Insect Models of Immunosenescence
   Jeff Leips ................................................................. 87

5. Clonal Culture Models of T-cell Senescence
   Graham Pawelec, Jürgen Kempf and Anis Larbi ......................... 107

6. Mouse Models of Influenza
   Ian C. Brett and Bert E. Johansson ..................................... 117

7. A Transgenic Dwarf Rat Strain as a Tool for the Study of Immunosenescence in Aging Rats and the Effect of Calorie Restriction
   Isao Shimokawa, Masanori Utsuyama, Toshimitsu Komatsu,
   Haruyoshi Yamaza and Takuya Chiba .................................. 131
8. Mathematical Modeling of Immunosenescence: Scenarios, Processes and Limitations
   A. A. Romanyukha, S. G. Rudnev, T. A. Sannikova and A. I. Yashin . . . 145

Part II: Cellular Immunosenescence - T Cells

9. Age, T-cell Homeostasis, and T-cell Diversity in Humans
   David L. Lamar, Cornelia M. Weyand and Jörg J. Goronzy .............. 167

10. The Role of T-regulatory Cells in Immune Senescence
    Paul Moss .......................................................... 193

    Masanori Utsuyama, Yuko Kikuchi, Masanobu Kitagawa and Katsuiku Hirokawa ........................................ 203

12. Age-associated T-cell Clonal Expansions (TCE) in vivo—Implications for Pathogen Resistance: Cellular Immunosenescence – T cells
    Janko Nikolich-Zugich and Anna Lang ............................... 219

    Jacek M. Witkowski .................................................. 235

14. Mismatch Repair System and Aging: Microsatellite Instability in Peripheral Blood Cells of the Elderly and in the T-cell Clone Longitudinal Model
    Simona Neri and Erminia Mariani .................................. 257

15. Activation-Induced Cell Death of T-Cells in Elderly
    Ewa Sikora and Agnieszka Brzezińska ................................. 277

16. CD8 Clonal Expansions in Mice: An Age-associated Alteration of CD8 Memory T-cells
    Eric T. Clambey, John W. Kappler and Philippa Marrack ............ 291

17. Generation and Gene Expression of CD28-CD8 T-cells in Human
    Nan-ping Weng ...................................................... 327

18. Role of Regulatory Subsets During Aging
    Piotr Trzonkowski .................................................. 343
Cellular Immunosenescence - B Cells

19. Transcription Factors in Mature B-Cells During Aging
   Daniela Frasca, Richard L. Riley and Bonnie B. Blomberg . . . . . . . . . . . 381

20. B-Cell Repertoire Changes in Mouse Models of Aging
   Jean L. Scholz, William J. Quinn III and Michael P. Cancro . . . . . . . . . . 393

21. B-Cells and Antibodies in Old Humans
   Kate L. Gibson and Deborah K. Dunn-Walters . . . . . . . . . . . . . . . . . . . 415

Cellular Immunosenescence - Neutrophils

22. Neutrophil Granulocyte Functions in the Elderly
   Peter Uciechowski and Lothar Rink . . . . . . . . . . . . . . . . . . . . . . . . . . . . 439

23. Signal Transduction Changes in fMLP, TLRs, TREM-1
    and GM-CSF Receptors in PMN with Aging
   Carl F. Fortin, Anis Larbi, Gilles Dupuis and Tamas Fulop . . . . . . . . . . . .457

24. Synergistic Effects of Ageing and Stress on Neutrophil
    Function
   Janet M. Lord, Anna C. Phillips and Wiebke Arlt. . . . . . . . . . . . . . . . . . . 475

Cellular Immunosenescence - Antigen Presenting Cells

25. Role of Dendritic Cells in Aging
   Anshu Agrawal, Sudhanshu Agrawal and Sudhir Gupta . . . . . . . . . . . . . 499

26. Phenotypic and Functional Changes of Circulating
    Monocytes in Elderly
   Lia Ginaldi and Massimo De Martinis . . . . . . . . . . . . . . . . . . . . . . . . . . 511

Cellular Immunosenescence - NK and NKT Cells

27. NK Cells in Human Ageing
   Raquel Tarazona, Inmaculada Gayoso, Corona Alonso,
   M. Luisa Pita, Esther Peralbo, Javier G. Casado,
   Beatriz Sánchez-Correa, Sara Morgado and Rafael Solana . . . . . . . . . . . . . 529

28. Natural Killer Cells and Human Longevity
   Hideto Tamura and Kiyoyuki Ogata . . . . . . . . . . . . . . . . . . . . . . . . . . . . 545
29. The Effects of Age on CD1d-restricted NKT-cells and Their Contribution to Peripheral T-cell Immunity
   Douglas E. Faunce and Jessica L. Palmer .......................... 561

Cellular Immunosenescence - Stem Cells

30. Lympho-Hematopoietic Stem Cells and Their Aging
    Hartmut Geiger and Gary Van Zant ......................... 573

31. Implications of Developmental Switches for Hematopoietic Stem Cell Aging
    Jens M. Nygren and David Bryder ......................... 589

Cellular Immunosenescence - Genetics

32. Associations of Cytokine Polymorphisms with Immunosenescence
    Elissaveta Naumova and Milena Ivanova ..................... 615

33. Cytokine Polymorphisms and Immunosenescence
    Owen A. Ross, Kelly M. Hinkle and I. Maeve Rea .......... 631

34. Role of TLR Polymorphisms in Immunosenescence
    Carmela Rita Balistreri, Giuseppina Candore, Giuseppina Colonna-Romano, Maria Paola Grimaldi, Domenico Lio, Florinda Listì, Sonya Vasto, Letizia Scola and Calogero Caruso 659

Part III: Mechanisms - Receptors and Signal Transduction

35. Signal Transduction Changes in T-cells with Aging
    Tamas Fulop, Gilles Dupuis, Carl Fortin and Anis Larbi .......... 675

36. Molecular Signaling of CD95- and TNFR-Mediatedapoptosis in Naïve and Various Memory Subsets of T-Cells
    Sudhir Gupta and Ankmalika Gupta ....................... 695

Mechanisms - Mitochondria

37. Mitochondria and Immunosenescence
    Pazit Beckerman and Arie Ben Yehuda .................... 713

Mechanism - Proteasome

38. Proteasome Activity and Immunosenescence
    Bertrand Friguet .......................................... 729
Mechanisms - Cytokines

39. Age-Related Changes in Type 1 and Type 2 Cytokine Production in Humans
   Elizabeth M. Gardner and Donna M. Murasko 753

40. Cytokine Expression and Production Changes in Very Old Age
   Susan E. McNerlan, Marilyn Armstrong, Owen A. Ross and I. Maeve Rea 771

Mechanisms - Neuro-Endocrine-Immune Network

41. Neuro-Endocrine-Immune Network and its Age-Related Changes
   K. Hirokawa and M. Utsuyama 785

42. Sex Hormones and Immunosenescence
   Christian R. Gomez, Vanessa Nomellini and Elizabeth J. Kovacs 799

43. Glucocorticoids and DHEA: Do They Have a Role in Immunosenescence?
   Moisés E. Bauer, Cristina M. Moriguchi Jeckel, Cristina Bonorino, Flávia Ribeiro and Clarice Luz 833

Mechanisms - Thymus

44. Thymic Involution and Thymic Renewal
   Frances T. Hakim 865

Mechanisms - Inflammation

45. Inflamm-Aging
   L. Bucci, R. Ostan, M. Capri, S. Salvioli, E. Cevenini, L. Celani, D. Monti and C. Franceschi 893

46. Molecular and Cellular Aspects of Macrophage Aging
   Carlos Sebastián, Jorge Lloberas and Antonio Celada 919

Part IV: Clinical Relevance in Disease States-Infection

47. Aging and HIV Disease: Synergistic Immunological Effects?
   Rita B. Effros 949
48. Role of Immunosenescence in Infections and Sepsis in the Elderly
   Tamas Fulop, Steven Castle, Anis Larbi, Carl Fortin, Olivier Lesur and Graham Pawelec ................................. 965

49. Beneficial and Detrimental Manifestations of Age on CD8+ T-Cell Memory to Respiratory Pathogens
   Jacob E. Kohlmeier, Kenneth H. Ely, Alan D. Roberts, Eric J. Yager, Marcia A. Blackman and David L. Woodland .... 979

50. HIV Infection as a Model of Accelerated Immunosenescence
   Victor Appay and Delphine Sauce ......................................................... 997

Clinical Relevance in Disease States- Autoimmunity

51. Autoimmunity and Autoimmune Diseases in the Elderly
   Ewa Bryl and Jacek M. Witkowski .................................................... 1029

52. Autoimmunity—Aging Mouse Model for Autoimmune Diseases
   Yoshio Hayashi and Naozumi Ishimaru .............................................. 1053

53. Atherosclerosis—An Age-dependent Autoimmune Disease
   B. Henderson, A. Rossmann, Ch. Mayerl, M. Wick and G. Wick .... 1063

54. Immuno-Inflammatory Athero-Arteriosclerosis Induced by Elastin Peptides. Effect of Age
   L. Robert and A. M. Robert ................................................................. 1089

Clinical Relevance in Disease States- Cancer

55. Aging, Immunity and Cancer
   Claude Sportès and Frances T. Hakim ................................................. 1119

56. Breast Cancer and Immunosenescence
   Mauro Provinciali, Alessia Donnini, Arianna Smorlesi and Cristina Gatti ..................................................... 1139

57. Aging, Cancer and Apoptosis in Animal Models and Clinical Settings
   Masanobu Kitagawa and Katsuiku Hirokawa ....................................... 1165

58. Her-2/neu Transgenic Mice for Evaluation of Immune and Antitumor Responses Against Self-Tumor Antigens in the Young and the Old
   Joseph Lustgarten and Noweeda Mirza ............................................. 1189
59. **Cancer Immunotherapy and Aging: Lessons From the Mouse**  
Claudia Gravekamp. ..................................................... 1217

**Clinical Relevance in Disease States- Metabolic Syndrome**

60. **Insulin Resistance, Chronic Inflammation and the Link with Immunosenescence**  
Dawn J. Mazzatti, Kavita Karnik, Radu C. Oita  
and Jonathan R. Powell. ............................................. 1247

**Clinical Relevance in Disease States- Neurodegenerative Diseases**

61. **Decline of Immune Responsiveness: A Pathogenetic Factor in Alzheimer’s Disease?**  
Elke Richartz-Salzburger and Niklas Koehler .......................... 1275

**Clinical Relevance in Disease States- Frailty**

62. **Inflammatory Markers and Frailty**  
Sean X. Leng and Linda P. Fried ................................. 1293

63. **CMV Infection and Frailty: Immunologic Consequences and Disease Pathogenesis**  
George C. Wang and Jeremy Walston. ............................... 1305

**Clinical Relevance in Disease States- Osteoporosis**

64. **Osteoporosis, Inflammation and Ageing**  
Lia Ginaldi, Lucia P. Mengoli and Massimo De Martinis  ............. 1329

**Part V: Modulation- Nutrition**

65. **Protein-Energy Malnutrition as a Determinant for Immuno-Senescence**  
Anis Larbi, Bruno Lesourd and Tamas Fulop.......................... 1355

66. **Role of Zinc and Selenium in Oxidative Stress and Immunosenescence: Implications for Healthy Ageing and Longevity**  
Eugenio Mocchegiani and Marco Malavolta .......................... 1367

**Modulation- Lipids**

67. **Immunomodulation by Polyunsaturated Fatty Acids: Impact on T-cell Functions and Signaling**  
Maximilian Zeyda and Thomas M. Stulnig ......................... 1399
68. Omega-3 Polyunsaturated Fatty Acids and Immunosenescence
   Christopher A. Jolly and Sirisha Karri .............................. 1423

69. Effect of Intrinsic and Extrinsic Lipids on T-cell Signalling
   Anis Larbi, Emilie Combet, Graham Pawelec and Tamas Fulop ...... 1437

Modulation - Vaccination

70. Effect of Anti-influenza Vaccination on Immune System in the Elderly
   Piotr Trzonkowski ..................................................... 1455

71. Immunosenescence Modulation by Vaccination
   Janet E. McElhaney and Allan M. McGavin ......................... 1487

Modulation - Can Interventions to Influence Immunosenescence Succeed?

72. Interleukin -7 and Immunorejuvenation
   Wayne A. Mitchell and Richard Aspinall ............................ 1515

73. Assessment of Age-related Decline of Immunological Function and Possible Methods for Immunological Restoration in Elderly
   Katsuiku Hirokawa, Masanori Utsuyama, Yuko Kikuchi and Masanobu Kitagawa ........................................ 1547

74. Thymic Regeneration in Mice and Humans Following Sex Steroid Ablation
   Anne Fletcher, Jessica Reiseger, Katerina Vlahos, Natalie Seach, Jarrod Dudakov, Ann Chidgey and Richard Boyd .......... 1571

75. Nutraceuticals and Immune Restoration in the Elderly
   Barry W. Ritz and Elizabeth M. Gardner ............................ 1611

76. Gene Therapy and Immune Senescence
   Jian Chen, Hui-Chen Hsu and John D. Mountz ...................... 1629

77. Perspectives: Is Immunosenescence Clinically Relevant?
   Tamas Fulop, Claudio Franceschi, Katsuiku Hirokawa and Graham Pawelec ........................................... 1647

Subject Index .......................................................... 1649