

Tamas Fulop, Claudio Franceschi
Katsuiku Hirokawa, Graham Pawelec
Editors

Handbook on Immunosenescence

*Basic Understanding and Clinical
Applications*



Springer

Tamas Fulop, Claudio Franceschi
Katsuiku Hirokawa, Graham Pawelec
Editors

Handbook on Immunosenescence

*Basic Understanding and Clinical
Applications*



Springer

Handbook on Immunosenesence

Handbook on Immunosenescence

Basic Understanding and Clinical
Applications

1

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

Editors

Tamas Fulop
Research Center on Aging
Division of Geriatrics
Dept. of Medicine, Faculty of Medicine
1036 Rue Belvedere
Sherbrooke J1H 4C4
Canada
tamas.fulop@usherbrooke.ca

Claudio Franceschi
CIG Interdepartmental Center
“L. Galvani”
University of Bologna
Department of Experimental Pathology
Via San Giacomo 12
40126 Bologna
Italy
claudio.franceschi@unibo.it

Katsuike Hirokawa
Institute for Health and Life Sciences
4-6-22 Kohinato
Tokyo
Bunkyo-ku
112-0006 Japan

Graham Pawelec
University of Tübingen
ZMF - Zentrum Med. Forschung
Abt. Transplant./ Immunologie
Waldhörnlestr. 22
72072 Tübingen
Germany
graham.pawelec@uni-tuebingen.de

ISBN: 978-1-4020-9062-2

e-ISBN: 978-1-4020-9063-9

Library of Congress Control Number: 2008944075

© 2009 Springer Science+Business Media B.V.

No part of this work may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, microfilming, recording or otherwise, without written permission from the Publisher, with the exception of any material supplied specifically for the purpose of being entered and executed on a computer system, for exclusive use by the purchaser of the work.

Printed on acid-free paper

9 8 7 6 5 4 3 2 1

springer.com

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 neuro-endocrine-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 challengingly, 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 to 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
Claudio Franceschi
Katsuiku Hirokawa
Graham Pawelec

Quebec, Canada
Bologna, Italy
Tokyo, Japan
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, Leonarda 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
11. Age-related Changes in Subpopulations of Peripheral Blood Lymphocytes in Healthy Japanese Population	
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
13. T-cell Cycle and Immunosenescence: Role of Aging in the T-cell Proliferative Behaviour and Status Quo Maintenance	
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 Listi, 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-Mediated apoptosis 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