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## **Preface**

John D. Mountz and Hui-Chen Hsu

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## **Pathways to a Robust Immune Response in the Elderly**

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and Anders Wikby

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The elderly experience an increased frequency and severity of infectious disease that is caused partly by suboptimal immune function. Innate and humoral immunity seem relatively unaffected by aging, but the T-cell compartment may show marked age-associated alterations. Longitudinal studies suggest that immune parameters can be clustered to yield an immune-risk phenotype (IRP) that is predictive of mortality in the elderly and possibly in younger individuals. Interventions to selectively target changes that are identified as part of the IRP may improve the health and quality of life of the elderly, reduce healthcare costs, and avoid potential unwanted side effects of global intervention approaches, such as triggering or exacerbating autoimmunity and inflammation.

## **Age-Related Inflammatory Cytokines and Disease**

Helle Brüttinggaard and Bente Klarlund Pedersen

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Studies have demonstrated that circulating levels of plasma cytokines are influenced greatly by age and that chronic elevated levels of certain cytokines are associated with chronic diseases. This article discusses the origin of age-associated elevations in circulating levels of cytokines, focusing on the multifunctional tumor necrosis factor  $\alpha$  and interleukin 6 and their possible biologic effects in age-associated diseases. Low-grade elevated levels are strong independent risk factors of morbidity and mortality in the elderly. Exercise and dietary interventions may be possible strategies to decrease inflammatory activity and improve the health status of the elderly.

## **Problems and Solutions to the Development of Vaccines in the Elderly**

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Rita B. Effros

One of the major target populations for vaccination is the ever-increasing cohort of persons aged 65 and older, a group that is characterized by high morbidity and mortality from infections that partly are caused by reduced immune function. Many elderly persons also show suboptimal responses to vaccines that are intended to prevent infection. A new immune biomarker of reduced antibody response to vaccination is the presence of a high proportion of memory CD8 T cells that lack expression of the CD28 costimulatory molecule. This article discusses some of the challenges involved in custom-designing vaccines that account for the remodeled immune system of the elderly.

## **Infectious Disease Risk in the Elderly**

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Bradley S. Bender

Older persons suffer excessively from infectious diseases such as pneumonia and urinary tract infections. This article discusses some of the reasons for this additional morbidity and mortality, including the anatomical and physiological changes with aging, impairment of immune function, presence of co-morbid diseases, and delays in diagnosis and initiation of therapy.

## **Origin of Late-Onset Autoimmune Disease**

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Hui-Chen Hsu and John D. Mountz

Autoimmune disease in the elderly is hypothesized to be caused by an imbalance in T-cell expansion and deletion after an encounter with self-antigens. A decrease in thymic output leads to a decreased pool of naïve T cells in the periphery and to increased oligoclonal expansion of T cells. This expansion may be caused by stimulation with autoantigens that drive high-affinity interactions with self-antigens. Accumulation of presenescent, apoptosis-resistant, and proinflammatory T cells results in the growth of these autoreactive T cells. A decreased T-cell activation response that occurs with age leads to several defects that diminish the immune response.

## **Aging, Immunity, and Tumor Susceptibility**

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Huang-Ge Zhang and William E. Grizzle

The study of aging, susceptibility to tumors, and immunity is at an initial stage, and numerous excellent questions challenge immunologists and tumor biologists. Because unpredicted factors contribute to tumor susceptibility in the human population, the authors feel that the development of an animal model is essential to dissect these complicated issues.

## **Immunologic and Inflammatory Mediators and Cognitive Decline in Alzheimer's Disease**

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Namanjeet Ahluwalia and Bruno Vellas

Local up-regulation of immune mediators is involved as a secondary or tertiary event in the development of Alzheimer's disease (AD); however, the systemic cell-mediated immune response in patients with AD may be impaired. Several factors, including malnutrition, may be involved in the reduced immune response in advanced stages of AD. A better understanding of the immune mediators that are involved in the local and systemic immune response in AD may assist in mediating the development of AD, halting its progression, and treating patients with effective anti-inflammatory drugs and immunization strategies.

## **Atherosclerosis as a Paradigmatic Disease of the Elderly: Role of the Immune System**

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Michael Knoflach, Bruno Mayrl, Christina Mayerl, Roland Sedivy, and Georg Wick

Clinically overt atherosclerosis is considered a paradigmatic disease of the elderly. Postmortem pathohistological evaluation of the arteries of children and young adults who died from noncardiovascular diseases, as well as *in vivo* sonographic assessment of the intima media thickness of young adults clearly show that the first alterations in the arterial wall can already be found at this age. During the past few years the authors have put forward a new immunologic hypothesis for the development of atherosclerosis. In principle, this concept states that the first stage of the disease is of an immunologic-inflammatory nature that is caused by an autoimmune reaction against stress proteins (heat shock protein 60) expressed by arterial endothelial cells as a consequence of the action of stress factors (ie, classical atherosclerosis risk factors). If these risk factors are not eliminated, the progression of atherosclerosis, by way of fatty streaks, to severe plaques occurs.

## **Future Challenges in Analysis and Treatment of Human Immune Senescence**

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Juan Salvador, Erica J. Adams, Rachel Ershler, and William B. Ershler

Immune function declines with normal aging. Immune function also declines in association with a variety of diseases that occur more frequently with age, most notably cancer, diabetes, and atherosclerosis. The consequences of the composite immune deficiency that are observed in many older people is a predisposition to certain infections, a reduced capacity to respond to vaccines, and possibly an increased incidence of cancer. Reconstitution of immune function can be accomplished either selectively or globally in laboratory animals

with cytokines, hormones, transplantation, or nutritional intervention. In older people, however, complexities produced by existing comorbidities and other variables have made it difficult to reach conclusions regarding the mechanisms of any effects produced by immunorestorative approaches. Yet, the benefits of selected interventions, including vaccines, immunoglobulin, nutrition, and exercise are now clearly established. Additional studies are needed to define the most efficient mechanisms to improve immune functions in the typical, frail, elderly patient, in whom the immune deficiency is due to a number of factors, in addition to an inherent aging of the immune system, and the consequences may be life threatening.