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Age-Associated Declines in Immune System Development and Function:

Causes, Consequences, and Reversal

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Understanding why we age and how that process can be delayed or reversed are topics that have engaged both researchers and the general public [1]. From a scientific perspective, aging is a fascinating biologic question, and knowledge of this process will undoubtedly provide insights into fundamental cellular mechanisms. The subject also intrigues us all because aging affects everyone. If we can find strategies to improve the health of the aged, it would have enormous societal implications, since meeting the medical needs of the growing population of elderly is a huge challenge.

Aging affects multiple organs, but its effects on the immune system are among the best studied. One reason for this is that developing and mature lymphoid cells are easily isolated and manipulated in developmental and functional assays in comparison to cells from other tissues. Furthermore, as pointed out by Liu and Sharpless, lymphoid cells persist for extended periods and thus are particularly susceptible to environmental insults that may lead to age-associated defects. These are being increasingly defined. For example, there is a general consensus that declines in immune function with age make the elderly more susceptible to infectious agents, such as influenza, with increasing morbidity and mortality. Furthermore, as reviewed by McElhaney and Effros, vaccination is less efficient in aged individuals. Thus, a better understanding of age-induced immune senescence may lead to the development of strategies to circumvent impaired immunity and other limitations of aging and to improve human health-span.

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About the Editors

Kenneth Dorshkind: Kenneth Dorshkind received his Ph.D. from the University of Washington and completed postdoctoral training at the Ontario Cancer Institute. His laboratory has a long-standing interest in the differentiation of lymphocytes from hematopoietic stem cells and how that process is regulated by systemic and microenvironmental factors. He is Professor and Vice-Chair (Research) of Pathology and Laboratory Medicine, Director of the Hematopoietic Malignancies Program in the Jonsson Comprehensive Cancer Center, and Academic Associate Director of the Broad Stem Cell Research Center at the David Geffen School of Medicine at the University of California Los Angeles (UCLA), USA.

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The chapters in this volume of *Current Opinion in Immunology* provide a broad perspective on the effects of aging on the immune system. As a result, individuals familiar with this area will obtain the latest information from experts in the field, while readers new to the discipline will gain a perspective on how aging affects lymphocyte production and function. In the following sections we highlight some of the questions addressed in the various chapters and issues in need of further investigation.

Does Immune System Aging Reflect Changes in Hematopoietic Cells or the Hematopoietic Microenvironment?

There are numerous studies documenting that aging negatively affects the function of hematopoietic stem and progenitor cells. For example, as described by Waterstrat and Van Zant, gene profiling studies demonstrate that the genomic integrity of aged hematopoietic stem cells is different from that in their young counterparts. Transplantation studies also indicate functional declines of old stem cells in humans [2].

One question is to what degree these changes are secondary to declines in the hematopoietic support potential of an aging microenvironment (Waterstrat and Van Zant)? In this regard, blood cell development in the bone marrow and T cell differentiation in the thymus are both known to be critically dependent upon a network of supporting stromal cells that regulate the growth, differentiation, and survival of developing cells through the secretion of various soluble mediators and direct cell contact. Although there have been some intriguing data regarding the effect of aging on the hematopoietic microenvironment [3,4], there is still much to be learned. Similarly, mature B and T cells in secondary lymphoid organs interact with stromal and dendritic cells, and more information is needed about the effects of aging on these populations. An understanding of how changes in the microenvironment affect the function of hematopoietic cells is of clinical relevance, particularly in the transplant setting.

What are the Effects of Aging on T and B Cell Function?

The contributions from all the authors reiterate the consistent and reproducible loss of optimum function that occurs in lymphocytes as they age. The functional defects in T cells, particularly in the naïve populations (Haynes, McElhaney and Effros), and B lymphocytes (Blomberg) are broad. For example, age-associated changes in B cells include reduced antibody production. A key facet of T cell immunodeficiency is reduced proliferation in response to antigen. However, expansion in the number of antigen responsive T cells does not cease entirely, indicating that most cells are not fully “senescent” (Liu and Sharpless) or that the population is heterogeneous and composed of both functioning and senescent cells. The ability of inflammatory cytokines and IL-2 to restore some function (Haynes) suggests caution in applying the term “immunosenescence” to reduced T cell function with age.

While the effects of aging on T and B cell function are increasingly well defined, it will be important to translate the changes documented primarily in rodent models to additional species, and most importantly to the human as discussed in several of the chapters (McElhaney and Effros, Derhovanessian et al., and Liu and Sharpless). It will also be important to do additional studies to learn more about the effects of aging on the innate immune system. We did not include a review of changes in innate cells, because this remains an understudied area.

What Genetic Changes Underlie the Aging of Hematopoietic and Immune Cells?

Aging must be under genetic control, because various species exhibit distinctly different life spans ranging from a day to hundreds of years. However, the current challenge is to determine

why differences in life-span, and the decline in immunity, occur in individuals within the same species. The chapters by Fraga, Liu and Sharpless, and Waterstrat and Van Zant address these issues and provide a succinct review of the genetic/epigenetic changes that occur in aging cells and the hereditary, environmental, and stochastic factors that impact upon them. Liu and Sharpless develop the cancer-aging hypothesis, which suggests that activation of tumor suppressor mechanisms prevent cancer but simultaneously promote aging. A tenet of this model is that age-associated defects are the price we pay for prevention of cancer. Particular attention has focused on the p16^{Ink4a} and Arf genes, both of which are production of the *Cdkn2a* locus, which are discussed in depth. The mechanisms and pathways that lead to changes in expression of tumor suppressor genes are unclear and require further analysis, but DNA damage may be one likely trigger.

Most efforts to define the genetic changes that occur in aging have focused on developing hematopoietic progenitors and mature B and T cells, in part because lymphocytes can be isolated in sufficient purity and number for further study. However, as noted above, aging in the microenvironment is clearly involved at some level. Thus, an area for future study is to identify genetic changes in the hematopoietic microenvironment that affect immune cell development and function. A particular challenge will be to identify the specific stromal cell population(s) to be characterized.

What Cells of the Aging Immune System Need to Be Rejuvenated to Restore Immunity?

CD4 and CD8 T cells and B cells are all needed for optimum immune response against pathogens. The reports herein describe age-associated defects in each of these cell types. It is of interest that not all cells are affected similarly by aging. For instance memory CD4 T cells that develop early in life in mice retain function indefinitely while naïve CD4 T cells lose activity (Haynes). Age-associated defects develop in T cells steadily over time (Haynes), but the pace of this development is not as well studied in B cells or in non-lymphocytes, including cells of the innate immune system and stromal elements.

The consistent and early defects in T cells are likely to be due to thymic involution and the loss of new thymic emigrants. Although this process may accelerate at puberty, there is evidence that it actually initiates in infants [5]. In any case, as discussed below, there may be a unique opportunity to target T cell defects by reversing the decline of thymopoiesis (Holland and van den Brink). On the other hand, strategies for restoring B cell function are not yet well-studied (Blomberg), but this may also be possible and deserves further exploration.

How Can Immune System Declines Be Reversed?

Once the key targets of immune system rejuvenation have been identified, a significant challenge is to discover what treatments improve function. As reviewed by Haynes, aging has profound effects on T cell function, and because the integrity of the immune system is dependent upon CD4 T cells in particular, there has been considerable interest in reversing thymic involution.

Despite the age-associated loss of some stem cell and progenitor potential, studies in the mouse (Haynes) and experience with humans (Holland and van den Brink) indicate that at least for T cells, rejuvenation of the thymus leads to production of new naïve T cells that function as well as young cells and better than those from the aged (Haynes). This suggests that strategies to utilize the potential of the hematopoietic stem cells to regenerate lymphocytes could be very promising (Haynes, Holland and van den Brink).

The chapter by Holland and van den Brink reviews strategies for thymus rejuvenation through the use of various factors such as IL-7, growth hormone, and keratinocyte growth factor. Many of these agents are already available in clinical grade preparations and are either in or being evaluated for clinical trials. What is not clear is if they all restore thymopoiesis to comparable degrees and the how the duration of the response compares. These are important issues, because the minimum rejuvenation of the thymus needed to observe a meaningful clinical response needs to be determined.

Another strategy for stimulating thymopoiesis in the elderly is the manipulation of peripheral T cells. Removal of these cells stimulates production of new naïve T cells that seem functionally competent (Haynes). The exact cells that need to be depleted have yet to be defined and the mechanisms by which this homeostasis works are not known. Niches provided by stromal elements may play a role in regulating how many T cells of distinct types can survive in the immune system.

The use of adjuvants to enhance the response of sluggish aged T and B cells is another potential approach to reverse the age-associated decline in vaccine efficacy (McElhaney and Effros and Haynes). It will be important to establish whether such approaches actually “rejuvenate” the “defective” naïve cells or if they simply increase their response without permanent correction of aging defects. The extent to which different approaches reverse the poor ability of the aged to respond to vaccination will need to be carefully quantified.

Another issue is whether various research developments that have piqued the interest of the media and general population will be of clinical value in reversing the effects of aging in the immune system. In particular, there is tremendous interest in resveratrol, the compound found in red wine [6]. However, it is too early to predict what if any effect its administration to aging humans will have.

Finally, medical economics dictate that treatments be applied to those who will truly benefit from them. Thus, there needs to be a way to identify these individuals. As discussed by Derhovanessian et al., there are an increasing number of biomarkers (mostly phenotypic) that correlate well with age-associated changes. Further studies should be designed to identify whether and how each marker is linked to functional defects. In addition there is new hope that epigenetic changes may also be very useful in identifying age associated changes.

Future Directions

As indicated above, the chapters in this volume of *Current Opinion in Immunology* provide a comprehensive review of how aging affects the development and function of the immune system. Much of this information, particularly with regards to the identification of molecular pathways and genes involved in immune system senescence, has been obtained in the last decade. The acquisition of these mechanistic data suggests that we are on the path to discovering the ultimate cause of age-associated declines in immune system development and function. If the factors regulating the expression of age-associated changes can be identified, it may in turn provide us with better insights into what environmental factors cause cells to become less responsive and provide clues for how to intervene in the process.

As more investigators, including physician-scientists, focus their attention on this discipline, the reasonable expectation is that the pace at which new discoveries are made and their translation to the clinic will accelerate. This will hopefully allow the effects of aging on the immune system to be reversed.

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Figure 1.

The figure depicts the effects of aging on lymphocyte production and function and strategies to reverse that process. The points noted are discussed in more detail in the various chapters of this issue of *Current Opinion in Immunology*.