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The Aging Immune System: Challenges for the 21st Century

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The demographics of our planet have taken a turn towards rapid growth of older adult population. Predictions for 2050 indicate that 2 billion people on earth will be older than 60–65, the age at or near which most countries classify their citizens as seniors. With that population boom looming, it is incumbent upon societies to deal with issues and problems of older age, including increasing costs of health care.

While the precise molecular and cellular causes of aging remain elusive and often misnamed [1], it is clear that aging can be significantly postponed by several manipulations that affect nutrient sensing and cellular metabolism in a wide variety of model organisms, from yeast, worms and flies to rodents and perhaps primates [1–3]. These include nutritional manipulations (caloric restriction), pharmacological inhibition of the (mammalian) target of rapamycin (TOR/mTOR) or genetic attenuation or abrogation of growth factor (particularly insulin growth factor – IGF) pathways. Strikingly, these manipulations also seem to improve "Healthspan", defined as reduced morbidity and mortality due to major age-related diseases, and ostensibly improved quality of life in older ages – at least under laboratory-controlled conditions. Henceforth emerge two key implications. First, it is likely that the fundamental cause of cellular aging lies, at least in part, in metabolic alterations. Second, successful intervention at the level of global Healthspan extension (the Holy Grail of gerontology) seems within reach for biomedical scientists studying the biology of aging.

Until this goal is reached, however, it falls to individual biomedical disciplines to improve the quality of life for older adults by alleviating or mitigating the most frequent adverse effects of aging and age-related diseases. In that context, infectious diseases remain a serious threat to older adults, taking a massive toll in morbidity and mortality in that population [4, 5]. In particular, the situation is dismal with regard to vaccine-preventable diseases, which are up to 1,000 times more likely to kill an older adult compared to vaccine-aged children [6].

Several mechanisms are likely to participate in this age-related increase in susceptibility to infection and reduced response to vaccination, including, but not limited to, impaired function of body barriers, and changes in microbial colonization. However, the age-related decline of function of the immune system itself, also called immunosenescence, is undoubtedly the principal component of poor vaccine responses, and is likely a prominent participant in the increased susceptibility with age to infection. Intense studies are underway

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to understand how and why the immune system ages, and how aging of specific elements of the immune system contribute to decreased immune protection. Numerous defects have been described in vitro and in vivo, affecting most, if not all, of the components examined. Nonetheless, to this day we still do not possess a comprehensive picture of immune aging. This is particularly true of the changes occurring with aging in innate immunity, [see the accompanying article by Solana and colleagues].

Aging of the immune system affects development of lymphocytes, starting with hematopoietic stem cells and their pluripotent progeny that will give rise to lymphocytes. It has long been known that lymphopoiesis declines with aging much more rapidly than myelopoeisis. While it is an oversimplification to say that myelopoiesis is maintained with aging at the expense of lymphopoiesis, over a lifetime, T and B cell precursors do not develop as robustly as they did in young age. In the case of T cells, this decline occurs very early after birth due to thymic involution. Dorshkind and colleagues present a compelling review and argument that cell-intrinsic age-related defects impair development of T and B cells. However, lymphopoiesis critically depends upon specialized microenvironments in the bone marrow and the thymus, and both undergo dramatic age-related changes, with thymic involution still representing both the earliest and the most radical age-related change in the immune system that may potentially set afoot many of the manifestations seen in T cells as a consequence of aging, particulary as related to T cell turnover and homeostatic disturbances. To that end, the discussion of lymphopoiesis in the context of aging is rounded out in the review by Sempowski Manley et al., discussing the age-related erosion of lymphopoietic niches. That work also contains an informative overview of efforts to rejuvenate the thymus, which has been receiving increased amounts of critical appraisal in the literature [7].

As mentioned above, some of the most exciting advances in the biology of aging were made with the discoveries that signaling pathways affecting metabolism and nutrient sensing can profoundly influence aging. This topic, in the context of immune aging, is expertly reviewed by Dixit, with particular focus upon adipose tissue signaling and the impact of adipose transdifferentiation upon thymic involution and overall T cell immunity.

The largest underserved area of research on immunosenescence relates to the age-related defects of the innate immune system. While we are rapidly discovering different changes and alterations, there are still relatively few studies evaluating the in vivo impact of these newly characterized defects. Solana and colleagues cover our state of knowledge on innate immune aging while devoting particular attention to NK cells, dendritic cells (DC) and their aging.

In following the course of the immune response itself, immunologists have explored the communication between adaptive and innate immunity with aging. This area continues yielding new information on immune aging almost on a weekly basis, yet we still have a lot to learn. The topic per se does not have a devoted article in this issue. Rather, it is addressed by at least three reviews; that by Solana et al. addressing innate immunity, by Haynes and Swain on CD4 T cells, and the one by our group on CD8 T cells. It is possible, and even likely, that the main breakthroughs in the immunology of aging, and specifically in manipulating an old immune response to improve protective immunity, may occur precisely

at the interface between innate and adaptive immunity. Two reviews in the issue deal with T-cell aging – one by Haynes and Swain covering primarily CD4 cells, and another by our group, dominantly focusing on CD8 T cells. These reviews address, to varying degree, defects in both primary and memory responses, and also touch upon partners of T cells in initiating or regulating T cell responses. There is remarkable concordance in such defects across different infections, yet clearly many rules are not the same for CD4 and CD8 cells, and therefore one must resist the urge to lump them together in considering mechanisms of immune aging.

B cell functions decline with aging and the expert group of John Cambier, Mike Cancro and their collaborators address age-related changes in B cell development and repertoire formation, maintenance and function, highlighting B cell-autonomous defects that exist clearly and undoubtedly outside of other defects in immune aging.

As lymphocytes age, their signaling characteristics change, and that is underlying at least in part the altered primary and memory T cell responses. Jorg Goronzy and colleagues provide an incisive review of signaling steps affected by the process of aging and the impact of manipulating these steps, primarily in human T cells.

Finally, the volume concludes with the review of translational immunology and aging by High et al., with highlights of strengths and weaknesses of current models to study immunity and aging. Mice, humans and other models are considered, evaluated and criticized, and pitfalls in our current approaches and funding policies with regard to grant proposals are linked to gaps in our knowledge. There is even a balanced call to action at the end, highlighting the complexity in the aging process and inviting the NIH and other funding agencies to embrace it in their support mechanisms.

For the first 20–25 years of its existence, the immunology of aging has enjoyed an unusual and curious history as a discipline that, for a long period of time and with the exception of a handful of investigators, did not deal very profoundly or mechanistically with either immunology or aging. Vast literature of unclear relevance exists that abounds with nomenclature identifying cells as “senescent” or “replicatively arrested” based upon a single or a handful of markers without functional or operational validation in immune protection. Tremendous advances in each of the disciplines have now paved way for a qualitatively and quantitatively more rigorous approach, where incisive studies can marry the advances in understanding the aging process with cutting edge immunological studies. Reviews in this volume make a strong step in that direction. However, it remains incumbent upon us to persist on this pathway. Aging and immunity are each incredibly complex disciplines and we must simultaneously study them both in order to understand how and why the immune system ages, and what we can do to improve and prolong its function. Moreover, we must do so with utmost rigor and ensure that processes and cells are functionally and operationally defined in our research, preferably using in vivo criteria relevant for immune protection.

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