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Immunological hurdles of ageing: Indispensable research of the human model

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Abstract

Census reports of many countries indicate continuing trends for the graying of their populations. For the United States alone, persons aged ≥65 years are projected to comprise over 20% of the population by the year 2050. In view of the special medical needs of elders, scientific investigation into the biological aspects of aging is key towards the improvement of geriatric care for the coming decades. This special issue of *Ageing Research Reviews* focuses on advances in research on the immunology of human ageing. Herein are nine articles about the age-related alterations in both the innate and adaptive arms of the immune system, and about continuing hurdles in vaccinology. These articles point to a common theme that the immunological milieu in old age is substantially different from that seen in the young. This suggests that new development and/or innovation of immune-based clinical interventions for the elderly may need to be customized for their age group, rather than the mere adoption of therapies that have been designed for and/or tested for younger persons.

Introduction: Pandemic ageing of human populations

Since the latter half of the 20th century, many countries are witnessing the increased graying of their populations (UN-ESA, 2007). Japan currently has the largest proportion of older adults aged ≥65 years at ~23% that is projected to rise to ~40% by the year 2050 (Japan Statistics Bureau, 2010). For the United States, the current 12% of the population consisting of older adults is projected to also rise to 20% by the year 2050 (NCHS, 2010). Similarly, older adults comprise 21% of the current population of the European Union, with Sweden and Italy having largest numbers of old people (Grant *et al*., 2004). The elderly European population is projected to increase by 2050 at par with that of Japan due to phenomenal steady decline in birth rates for Japan and for the European Union member states (Grant *et al*., 2004; Japan Statistics Bureau, 2010). Demographic shifts towards the increasing numbers of elderly persons are not exclusive to industrialized countries, but it is a global phenomenon (CIA, 2010). Older adults are projected to comprise up to 25% and 15% of the aggregate population of developed and least developed countries, respectively, by 2050 (UN-ESA, 2005). Considering the myriad of age-related physiologic alterations, many of which are associated with age-related clinical syndromes (Stanziano *et al*., 2010), and the

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projected steady rise in the cost of geriatric medical care irrespective of country (Rice and Fineman, 2004; Payne *et al*., 2007; van Elk *et al*., 2010), ageing of the world population is a pandemic that present biomedical, socio-economic, and geopolitical challenges.

Immunity and ageing: Indispensability of human-based research

Immunity is a determinant of individual fitness, and the development of a diverse armamentarium of immune defenses is a *modus operandi* of speciation over millennia of evolution (McDade, 2003; McKean *et al*., 2008; Rosenstiel *et al*., 2009; Flajnik and Kasahara, 2010). In higher chordates, immune defenses, like other physiological systems, undergo dramatic changes over the lifetime of the individual. Human neonates have very distinct immune physiology from that of adults (Zaghouani *et al*., 2009), providing rationale for the traditional customization of immune interventions for infants and adolescents (de Brito *et al*., 2009). It is now clear that the immune system undergoes even more dramatic changes beyond adolescence and sexual maturity. With the increasing numbers of elderly humans, research on the immunology of ageing is paramount more than ever to facilitate efforts for the improvement of the quality of life of elders for the coming decades.

Animal models, principally the various genetic strains of the laboratory mouse, have been advancing knowledge on the immunology of ageing as in many areas of scientific investigation. Mouse models will undoubtedly remain to be useful tools in answering basic questions pertaining to the regulation, or dysregulation as might be the case, of immune processes with age.

However, it is important to emphasize that there are fundamental differences in the basic immunology of mice and humans (Mestas and Hughes, 2004). Such differences range from subtle regulatory controls to the stark species-specific contrast. An example of a subtle difference is the case for regulatory T cells for which mice have constitutive $FOXP3^+$ and FOXP3-inducible subsets, but the human counterpart consists only of FOXP3-inducible cells (Ziegler, 2006). Examples of clear species-specific differences are the unique human (primate) genes encoding for killer cell immunoglobulin-like receptors (Parham *et al*., 2010); the unique subset of human marginal zone B cells (Weill *et al*., 2009); the lack of expression of CD56 on mouse natural killer cells (Hayakawa *et al*., 2006); and the activating versus inhibitory activity of B7-H3 in mouse and human T cells, respectively (Yi and Chen, 2009). And perhaps the best example of species-specific immunologic differences in the context on chronologic ageing is the case for CD28 that is expressed on T cells throughout the life of mice, but is progressively and irreversibly lost with ageing in humans (Vallejo, 2005). Such specific-differences underscore caution in the interpretation of observations from murine studies as to its applicability to human biology (Rosol *et al*., 2003; Downey and Cohen, 2009; Shedlock *et al*., 2009; Bodewes *et al*., 2010; Boudet, 2010).

The experimental setting is also significantly different between murine and human studies. Murine studies are generally conducted within the confines of a sanitized environment, and oftentimes involve the use of highly contrived genetic strains such as transgenics or knockouts. In contrast, the host and the environment in human studies are largely unmodified allowing assessment of “experiments of nature” that truly affect individual health and survival (Casanova and Abel, 2004). Ageing in the human immune system is such an experiment of nature. The nine articles in this special issue of *Ageing Research Reviews* discuss the results of observational immunology that may provide insights into stronger rationale for future translation efforts into the improvement of immune protection of the elderly.

Alterations of innate immune function with ageing

Two articles discuss the impact of age on the innate immune system. The first is by Shaw and colleagues (2010) delving on age-related properties of Toll-like receptors (TLR), the most primitive of the innate defenses. They report that while not all TLR function is adversely affected by age, there is insufficiency of signaling of particular TLRs that appears to be associated with dysregulation of protein trafficking rather than simple block of transcription or translation. Dysregulation of TLR trafficking is consistent with an emerging theme about progressive perturbation of the quality control of protein homeostasis as cells naturally undergo senescence, or more acutely within the context of pathologic states (Buchberger et al., 2010).

The second paper is by Agrawal and Gupta (2010) synthesizing research about age-related changes in dendritic cell (DC) function. Notably, they report diversity of human DC phenotypes, some of which have no obvious counterparts in the mouse. Depending on type of DC, functional deficits of DC function appear to be related to either the loss of DC numbers and/or signaling of particular receptors such DCs express. Considering that DCs serve as bridge between innate and adaptive immunity, ascertaining types and lineages of DC subsets remains a fundamental undertaking towards to the prospects of cell-based immunotherapy (Crozat *et al*., 2010). In the context of ageing, a key question is whether there is (are) particular DC subset(s) that could be harnessed to enhance its innate protective function and/or its capacity to prime cell-mediated immunity.

Age-related alteration in adaptive immune immunity

The paper by Frasca and colleagues (2010) examines the B cell compartment. They report about the increasing trend for the accumulation of functionally exhausted, switched-memory B cells with age. But more importantly, they also report that the proportion of naïve B cells increases with age. This phenomenon is not due to new B cell lymphoiesis, but to alteration in the immunoglobulin (Ig) class switching machinery. It appears that this pool of aged naïve B cells is much increased among centenarians (Colonna-Romano *et al*., 2010). An intriguing question then is whether there is yet an undiscovered role of naïve B cells that might perhaps be beneficial in extreme old age.

In the T cell compartment, age-related functional alterations are highlighted by the insufficiency of signaling. The paper by Larbi and colleagues (2010) synthesizes research on aged T cell signaling. They discuss primary signaling deficits of the T cell receptor (TCR)-CD3 complex, changes in costimulatory signals exemplified by the loss of CD28, altered cytokine signaling, and the impact of increased number of inhibitory receptors. The importance of these signaling studies is underscored by the impetus of translational efforts into intervening against age-related clinical syndromes (D'Antona and Nisoli, 2010; McCubrey *et al*., 2010).

Two papers discuss age-related changes in the T cell repertoire. The first is by Brunner *et al* (2010) summarizing repertoire changes within the context of persistent viral infections. Consistent with the notion of experiment in nature, they report that persistent viruses such as cytomegalovirus (CMV) impose natural pressure towards the accumulation of CMV-specific T cells throughout life. But due to persistent activation, many such antigen-specific T cells have pronounced functional defects and so they may not provide protection against CMV re-infection or re-activation. An important research footnote by the authors is the apparent difference in the pattern of CMV infection between Europe and US elderly populations. Europeans get infected with CMV more slowly and progressively with age, such that CMV seropositivity in old age has been associated with poor health outcomes among elderly Europeans (Wikby *et al*., 2005). In contrast, there is more widespread CMV seroprevalence

within the US population due to CMV exposure at an early age (Bate *et al*., 2010). Hence, it will be of interest to examine whether CMV serology significantly impacts health outcomes of US elders. A curious notion is whether there might be a protective anti-CMV memory response among US seniors.

The second paper on T cell repertoire changes is by Vallejo and colleagues (2010). They summarize studies reporting the unusual increased expression of natural killer (NK) receptors on T cells with advancing age. They postulate that such NK-like T cells may be a compensatory mechanism for the phenomenal age-related contraction of TCR repertoire diversity and for the corresponding functional deficits of classical NK cells. It will therefore be of interest to examine the nature and the extent to which NK-like T cells contribute to protective immunity in old people, particularly in centenarians who appear to have a unique immune physiology (Sansoni *et al*., 2008). A challenge of course is to decipher whether and how a single, or multiple, NK-related receptors elicit T cell-driven protective responses either in a TCR-dependent or TCR-independent manner.

Challenges of vaccinology, and the importance of population-based studies

Considering the myriad changes in immune function with ageing, it is perhaps unsurprising that optimizing vaccine responses in the elderly remain a fundamental challenge. The papers by Lang *et al* (2010) and McElhaney (2010) discuss the continuing hurdles about vaccination against influenza. In the US, 90% of annual influenza-related deaths consist of older adults despite high vaccine coverage (CDC, 2010). Such demographic data underscore the ongoing controversy about the efficacy of flu vaccines, and for the wisdom, or lack thereof, for the public health policy of primarily targeting elderly people for seasonal flu vaccination. Efficacy of flu vaccines could be influenced by intrinsic clinical characteristic of the population receiving the vaccine. Thus, Lang *et al* notes the importance of assessing the health status of elders, and so mortality outcomes alone may not truly be indicative of vaccine efficacy. It might be time therefore for researchers and epidemiologists to better define immunologic and clinical criteria of what constitutes flu vaccine efficacy. McElhaney suggests that the usual measurement of vaccine antibody titers could be complemented with cellular measures of anti-flu responses. Clearly, much research is still needed to improve flu vaccine design for old people.

The paper by Singh and Newman (2010) provides an exhaustive review of population studies of aging. A common theme of these studies is the low-level systemic upregulation of inflammatory cytokines with age, with interleukin-6 being a strong predictor of disease and disability in many elderly populations. An important question then is whether inflammatory cytokines directly cause disability in old people, bearing in mind that young people with chronic inflammatory diseases such as rheumatoid arthritis have even higher magnitudes of systemic cytokine upregulation yet they do not seem to manifest the same forms of disability and clinical syndromes as old people. Considering the pleiotropic effects of cytokines, one thought is that the low-level systemic cytokine upregulation in old age indicates an immunologic environment wherein the quality of immune responses are influenced by the prevailing cytokine milieu.

Conclusion: Steadying the course of human-based research on the immunology of ageing

On the one hand, age clearly imposes drastic changes in immune physiology that contribute to poorer immune responsiveness of old people relative to younger people. On the other

hand, older adults have heterogeneous health and immune phenotypes with increasing numbers of very old people in their 8^{th} to 10^{th} decade of life. Therefore, research on the immunology of ageing needs to go beyond the characterization of age-related immune deficiencies. Arguably, it remains to be examined whether there are unique of immune mechanisms that directly promote healthy ageing and/or maintain immune protection in old age. An interesting question is whether immune competence in old age could be genetically determined. Classical immune interventions such as vaccines may also need to be age-specific, rather than simply adopting intervention regimes used for younger people. Improvements of the quality of life of the growing population of older adults, through research progress on the immunology of ageing and in all biological aspects of ageing, are very much within reach. It may only be stifled by the continuous shrinking trend of funding for ageing research (Wadman, 2010).

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