Allergy and Immunology

AIMS Allergy and Immunology, 10(1): 16–20.
DOI: 10.3934/Allergy.2026002
Received: 05 January 2026
Revised: 05 January 2026
Accepted: 06 January 2026
Published: 06 January 2026

https://www.aimspress.com/journal/Allergy

Editorial

Aging and immunity

Ken S. Rosenthal*

Professor of Immunology, Augusta University/University of Georgia Medical Partnership, Athens GA; Adjunct Professor, Department of Infectious Diseases, College of Veterinary Medicine, University of Georgia, Athens, GA; Emeritus Professor, Northeast Ohio Medical University, Rootstown, OH

* **Correspondence:** E-mail: Kenneth.Rosenthal@uga.edu.

The changes in the immune system with aging start at birth, not just after 50 years of age. As such, it is important to view the consequences of these changes over the lifespan. In addition to changes in antimicrobial protections, these changes also have a great influence on the aging of tissues, organs and functions of the human body and a person's immune-resilience is linked with longevity. Aging of the immune system is the topic of the reviews in this journal [1,2] and many other reviews and studies, some of which are listed herein. *Many questions remain to be answered regarding the changes that occur over the course of a lifetime and their consequences. Some of these questions are raised in this editorial.*

Like a computer, some components of the immune system are hard wired and immediately functional, like the innate components, but other components must learn the programs and develop memory for the antigen-specific adaptive components. In the womb, maternal protections allow the system to develop with minimal need for surveillance or reactivity to challenge. Rapid growth and turnover of cells is tolerated. At birth, the immune system switches from innate and more regulatory actions to more active and reactive responses to take over from maternal protections. The system becomes trained/educated by microbial exposures. The timing and nature of the microbial training is a major determinant of the balance or predilection towards either Th2 helper responses that favor antibody, mucosal and eosinophilic responses or proinflammatory Th17 and Th1 responses that support antibody and epithelial, neutrophil, macrophage and other cell mediated protections. Ultimately, the goal is to develop a balance between the effector functions and the maintenance and regulatory functions without compromising protection from microbial attack or tumor surveillance. *What influences do vaccination, diet, exercise and pre-birth health and activities play on the development of the fetal and child's immune system. What role does exposure to maternal microbiota upon traversing the birth canal or breast feeding have on the system? Can timing and microbial exposure be*

manipulated to optimize immune balance and function? What are the consequences of disrupting the mother's or newborn's microbiota with antibiotics on the development of the immune system?

Maturation from infancy and childhood into teen and adult years comes with a shift towards more inflammatory responses to infection causing more significant immunopathogenesis and disease upon challenge. The emphasis shifts from innate and potent but controlled adaptive protections to more inflammatory mechanisms and more severe disease presentations. For example, in adults, varicella zoster elicits pneumonia at the site of acquisition and then progresses to chicken pox and loss of an early differentiated NK cell and the type of CD8 T cell response of a child leads to more serious EBV infectious mononucleosis [3]. *What triggers these changes in the immune system? Why do they occur? What is gained? Lost? If aberrant, what are the consequences for personal health? Once identified, can they be manipulated when necessary?*

Women's immune systems age differently from men primarily due to hormonal differences but also due to XX and XY. Estrogen has a large influence on the immune system and levels change as women progress into and through menarche and then to menopause [4–6]. Testosterone also has its effects on the immune system but the consequences of decreases in function with age are less apparent. *The differences between men and women and the influence of women's hormonal status with age require more attention, especially in studies of immunological diseases, supplements, vaccines, and therapies.*

Some consequences of aging are inevitable. Like many adult bodies, the thymus also turns fatty with age and its involution reduces the generation of new T cells [7,8]. Responsivity of the T cell population becomes dependent upon previously developed naïve T cells and memory T cells. In addition, a large amount of memory T cells may be dedicated to controlling or responding to latent-recurrent herpesvirus infections, especially CMV, or driven into senescence [9]. NK cell function is also diminished with reduced surveillance of virus infections, tumors and senescent cells [10]. B cell generation from the bone marrow may continue but overall, there is a predilection towards myeloid rather than lymphoid cell development [11].

The changes that aging brings to the immune system can compromise normal functions that maintain skin and mucosal epithelium, regulate the microbiota of the GI tract, provide surveillance of cancers and latent herpes and other infections, regulate inflammatory and autoimmune diseases and even promote hair production. T cell deficits particularly affect the gut, where helper T cells and their cytokines are important for maintaining mucoepithelium and GI tissue function and microbiota homeostasis. Hair production depends upon Treg production of TGF-β [12]. These immune functions are crucial for overall health during aging. *Why does the system age at different rates in some individuals and ultimately can anything be done to limit the negative changes. Can lymphocyte production be maintained in the older adult? For me, a big question is how to stimulate the relevant T regs to promote hair growth?*

In the older adult, the immune system has accumulated weapons and components (antibodies and T cells) dedicated to previously encountered enemies, but is less capable of developing weapons against newer ones and controlling responses to life's challenges. This makes it more difficult to maintain the balance between effector/inflammatory and regulatory/suppressive functions. The ability to promote immune protections (immunocompetence) and control inflammation, termed immune-resilience, is an important indicator of personal health and potentially, longevity [13]. *CD4:CD8 T cell ratios and gene expression profiles have been linked to immune-resilience but are there other indicators and genes of relevance [14]? Can manipulation of these genes make a difference in immune-resilience? Should measures of immune-resilience be tied to evaluations of vaccines, immunotherapies and the study of immunodiseases?*

Responses to microbial infection are reduced in the older adult [15,16]. Multi-omic profiling of immune cells indicate a bias towards Th2 memory responses in the older adult that can compromise antiviral and antitumor responses [17]. Loss of immune memory increases risk for varicella zoster recurrence as zoster, requiring a vaccine boost to keep the virus in latency. Response to vaccines is reduced requiring higher potency or adjuvanted vaccines. For influenza, this appears to be due to less induction of cell mediated immune responses [18,19]. There are many other examples. *With the dominance of memory T cells to CMV in the older adult, could vaccines to CMV, EBV and other herpesviruses allow expansion of the repertoire of memory T cells beyond these dominant antigens in the older adult? Why are the responses diminished with aging for some but not all vaccines? Which ones? What other changes will be identified by multi-omic analysis? How can this knowledge help to design better vaccines and immunotherapies? Will we see a shift towards vaccine induced T cell responses, especially for the adults?*

The bodies and immune systems of older adults reflect the consequences and reactions to life's challenges, stresses, good and bad habits, environmental and infectious challenges and the buildup of molecular errors and losses. B and T cells adopt more pro-inflammatory and autoaggressive characteristics with aging. There are increases in systemic inflammation, termed inflammaging, and immune organs and cells undergo immunosenescence and cease to function or function aberrantly [20–22]. Systemic inflammation lowers the threshold for many inflammatory diseases, including inflammatory bowel disease and neurological diseases. Inflammation can compromise the blood brain barrier and enhance the potential for inappropriate inflammatory responses of microglial cells increasing risk for neurological diseases, including Alzheimer's and Parkinson's diseases. In addition, inflammaging and immunosensescence can lead to more aches and pains, loss of hair, increased incidence of cancer and inflammatory autoimmune diseases, susceptibility to infectious disease and other problems. *How can inflammaging and immunosenescence be slowed or corrected?*

The changes to the immune system with aging are inevitable [20–24] but the rate and extent of change is individualistic. Manipulation of lifestyle, stress, sleep hygiene, diet, obesity, and exercise have been suggested as ways to slow the aging related changes to the immune system. The microbiome has been attributed with large influences on inflammaging and immune function and its manipulation suggested as an intervention. Studies have suggested that changes in metabolism with metformin or mTOR (target of rapamycin) inhibitors can slow aging, in part due to their positive effects on the immune system. In mice, administration of rapamycin starting in mid-life extended the lifespan of mice by 9%–14% [25]. Anti-inflammatory interventions to reduce inflammaging and targeted therapies have also been suggested. Blocking the action of the proinflammatory cytokine, IL11, extended mouse health and lifespan possibly by reducing inflammaging [26]. Elimination of senescent immune cells with small molecular drugs (anti-senolytics) or CAR-T cells has also been suggested [27]. *What insights into the mechanisms and means for attenuating or preventing the detrimental changes to the immune system and even links to extending lifespan be provided by study of the immune systems of individuals who age faster or slower, and superagers including centenarians?*

Longevity depends upon a healthy immune system. As such, identifying the changes that occur with aging can facilitate development of interventions and more effective therapies for infectious diseases, cancer, autoimmune and inflammatory diseases. Recent advances may have provided the tools for cataloguing the changes and new approaches for targeted interventions of the aging immune system.

Use of AI tools declaration

The author declares He has not used Artificial Intelligence (AI) tools in the creation of this article.

Conflicts of interest

Ken S. Rosenthal is a member of the editorial board of the *Allergy and Immunology* and was not involved in the editorial review or the decision to publish this article. The author declares no conflict of interest.

References

1. Rosenthal KS, Baker JB (2022) The immune system through the ages. *AIMS Allergy Immunol* 6: 170–187. https://doi.org/10.3934/Allergy.2022013
2. Arachchige AS (2023) Aging and immunity: Unraveling the complex relationship. *AIMS Allergy Immunol* 7: 213–221. https://doi.org/10.3934/Allergy.2023015
3. Azzi T, Lünemann A, Murer A, et al. (2014) Role for early-differentiated natural killer cells in infectious mononucleosis. *Blood* 16: 2533–2543. https://doi.org/10.1182/blood-2014-01-553024
4. Johnson C, Baldwin A, Bruner LP, et al. (2024) Sex, gender, and other factors that influence infections for men and women. *Infect Dis Clin Pract* 32: 1405. https://doi.org/10.1097/IPC.0000000000001405
5. Sharma S, Gibbons A, Ollmann Saphire E (2025) Sex differences in tissue-specific immunity and immunology. *Science* 389: 599–603. https://doi.org/10.1126/science.adx4381
6. Forsyth KS, Jiwrajka N, Lovell CD, et al. (2024) The conneXion between sex and immune responses. *Nat Rev Immunol* 24: 487–502. https://doi.org/10.1038/s41577-024-00996-9
7. Sandstedt M, Chung R, Skoglund C, et al. (2023) Complete fatty degeneration of thymus associates with male sex, obesity and loss of circulating naïve $CD8^+$ T cells in a Swedish middle-aged population. *Immun Ageing* 20: 45. https://doi.org/10.1186/s12979-023-00371-7
8. Elyahu Y, Monsonego A (2021) Thymus involution sets the clock of the aging T-cell landscape: Implications for declined immunity and tissue repair. *Ageing Res Rev* 65: 101231. https://doi.org/10.1016/j.arr.2020.101231
9. Khan N, Shariff N, Cobbold M, et al. (2002) Cytomegalovirus seropositivity drives the CD8 T cell repertoire toward greater clonality in healthy elderly individuals. *J Immunol* 169: 1984–1992. https://doi.org/10.4049/jimmunol.169.4.1984
10. Brauning A, Rae M, Zhu G, et al. (2022) Aging of the immune system: Focus on natural killer cells phenotype and functions. *Cells* 11: 1017. https://doi.org/10.3390/cells11061017
11. Su TY, Hauenstein J, Somuncular E, et al. (2024) Aging is associated with functional and molecular changes in distinct hematopoietic stem cell subsets. *Nat Commun* 15: 7966. https://doi.org/10.1038/s41467-024-52318-1
12. Liu Z, Hu X, Liang Y, et al. (2022) Glucocorticoid signaling and regulatory T cells cooperate to maintain the hair-follicle stem-cell niche. *Nat Immunol* 23: 1086–1097. https://doi.org/10.1038/s41590-022-01244-9

13. Ahuja SK, Manoharan MS, Lee GC, et al. (2023) Immune resilience despite inflammatory stress promotes longevity and favorable health outcomes including resistance to infection. *Nat Commun* 14: 3286. https://doi.org/10.1038/s41467-023-38238-6
14. Ganesan A, Moore AR, Zheng H, et al. (2025) A conserved immune dysregulation signature is associated with infection severity, risk factors prior to infection, and treatment response. *Immunity* 58: 2104–2119.e5. https://doi.org/10.1016/j.immuni.2025.05.020
15. Scott D, Bond M, Manning TH, et al. (2023) How are older adults different than other adults for infections? *Infect Dis Clin Pract* 31: e119. https://doi.org/10.1097/IPC.0000000000001197
16. Quiros-Roldan E, Sottini A, Natali PG, et al. (2024) The impact of immune system aging on infectious diseases. *Microorganisms* 12: 775. https://doi.org/10.3390/microorganisms12040775
17. Gong Q, Sharma M, Glass MC, et al. (2025) Multi-omic profiling reveals age-related immune dynamics in healthy adults. *Nature* 648: 696–706. https://doi.org/10.1038/s41586-025-09686-5
18. Gustafson CE, Kim C, Weyand CM, et al. (2020) Influence of immune aging on vaccine responses. *J Allergy Clin Immunol* 145: 1309–1321. https://doi.org/10.1016/j.jaci.2020.03.017
19. Silva-Moraes V, Reis LR, Ross TM (2025) Comparative analysis of cellular immune responses to four seasonal inactivated influenza vaccines in younger and older adults. *J Immunol* 2025: vkaf286. https://doi.org/10.1093/jimmun/vkaf286
20. Wrona MV, Ghosh R, Coll K, et al. (2024) The 3 I's of immunity and aging: immunosenescence, inflammaging, and immune resilience. *Front Aging* 5: 1490302. https://doi.org/10.3389/fragi.2024.1490302
21. Monti D, Ostan R, Borelli V, et al. (2017) Inflammaging and human longevity in the omics era. *Mech Ageing Dev* 165: 129–138. https://doi.org/10.1016/j.mad.2016.12.008
22. García-Domínguez M (2025) Pathological and inflammatory consequences of aging. *Biomolecules* 15: 404. https://doi.org/10.3390/biom15030404
23. Yu W, Yu Y, Sun S, et al. (2024) Immune alterations with aging: Mechanisms and intervention strategies. *Nutrients* 16: 3830. https://doi.org/10.3390/nu16223830
24. Ayoub M, Abou Jaoude C, Ayoub M, et al. (2026) The immune system and cellular senescence: A complex interplay in aging and disease. *Immunology* 177: 149–169. https://doi.org/10.1111/imm.70036
25. Roark KM, Iffland PH (2025) Rapamycin for longevity: The pros, the cons, and future perspectives. *Front Aging* 6: 1628187. https://doi.org/10.3389/fragi.2025.1628187
26. Widjaja AA, Lim WW, Viswanathan S, et al. (2024) Inhibition of IL-11 signalling extends mammalian healthspan and lifespan. *Nature* 632: 157–165. https://doi.org/10.1038/s41586-024-07701-9
27. Amor C, Fernández-Maestre I, Chowdhury S, et al. (2024) Prophylactic and long-lasting efficacy of senolytic CAR T cells against age-related metabolic dysfunction. *Nat Aging* 4: 336–349. https://doi.org/10.1038/s43587-023-00560-5

AIMS Press