Editorial

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Immunity Holds the Key to Anti-Ageing Interventions

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Ageing is a well-known risk factor for several chronic conditions, such as heart diseases, diabetes, cancer, chronic kidney disease, non-alcoholic fatty liver disease (NAFLD), and neurodegenerative and autoimmune conditions that negatively impact health and overall survival rate [1]. A hallmark of ageing is the occurrence of low-grade systemic chronic inflammation (SCI), commonly known as 'inflammaging', which not only emerges with advancing age but also serves as an predictor of age-related pathologies [2]. While the significance of the immune system in maintaining human health and well-being has been recognized for over a century, the chronic inflammatory features of the immune system as an integrated part of ageing have only been acknowledged in recent decades [3].

Understanding the underlying causes of chronic inflammation needs a deeper investigation of the immune system, which undergoes substantial alterations during the ageing process, even before the onset of disease. Various immune components, including cellular frequencies and functional capacity across innate and adaptive arms, are changed with age, leading to an impeded immune responsiveness and a mild rise in circulating inflammatory mediators [4]. Contrary to the acute inflammatory response, characterized by a temporary elevated and tightly regulated immune response to infection, chronic and systemic inflammation is deemed to be elicited by persistent endogenous danger signals, such as 'damage-associated molecular patterns' (DAMPs) triggered by cellular stress or injury [5]. This shift from a transient to a persistent immune response disrupts normal cellular homeostasis, compromises immune tolerance, and elevates the risk of developing various chronic diseases.

Driven by the connection between the immune system and numerous age-related diseases, studies have identified immune-related indicators capable of predicting an individual's risk for age-associated diseases [4,5]. Based on the immune patterns associated with age-related inflammation, a study assessing blood immune profiles from a large population cohort aged 8 to 96 years reported the inflammatory clock of ageing (iAge). This mechanism has shown a strong correlation with multimorbidity [6], considered the gold standard in ageing research. Interestingly, consistent with the immunological shift observed during ageing, iAge demonstrated specific peripheral immune subtypes as predictors of multimorbidity. The positive predictors include effector CD8+ T cells, central memory T cells, and monocytes, while total CD8+ T cells, transitional B cells, and plasmablasts were observed as negative predictors. Furthermore, immune responses to cytokine stimuli also demonstrated an association with iAge, where responses from T cells and B cells were negatively correlated, while monocyte responses were substantially linked to iAge [6].

Aligned with the global shift in immune homeostasis observed with ageing, an age-related rise in type 2/interleukin (IL)-4-expressing memory T cell sub-populations and pro-inflammatory CD8 T cells were observed in a population cohort aged 25 to 85 years [7]. Moreover, immune cell subtypes are crucial in epigenetic ageing, as measured by DNA methylation-based epigenetic clocks, which have emerged as valuable tools for assessing chronological age. Particularly, the epigenetic age accelerator (EAA) has been correlated with morbidity and disease outcomes. Peripheral immune cell composition strongly correlates with EAA in human blood and with epigenetic ageing [8], highlighting the intricate relationship between immunity and ageing.

Identifying biomarkers of ageing warrants a deeper understanding of the widespread implication of the immune system during the ageing process. Age-related chronic inflammation differs significantly from infection-induced (acute) inflammation, particularly regarding their respective markers. For example, classical indicators of acute inflammation, such as IL-6 and tumour necrosis factor-α (TNF-α), are not prominent markers of age-related chronic inflammation [6]. Interestingly, the strongest contributor to the iAge is the chemokine (C-X-C motif) ligand 9 (CXCL9), an interferon-related chemokine. Under normal homeostatic conditions, CXCL9 is expressed at low levels but is substantially upregulated and secreted by monocytes, fibroblasts, endothelial cells (ECs), and cancer cells in response to interferon (IFN)-γ. CXCL9 acts as a chemoattractant for immune cells that express its receptor, C-X-C motif chemokine receptor type 3 (CXCR3), on their surface, including several types of innate and adaptive immune cells [9]. Notably, CXCL9 expression in ECs elevates with ageing and is associated with EC dysfunction and cellular

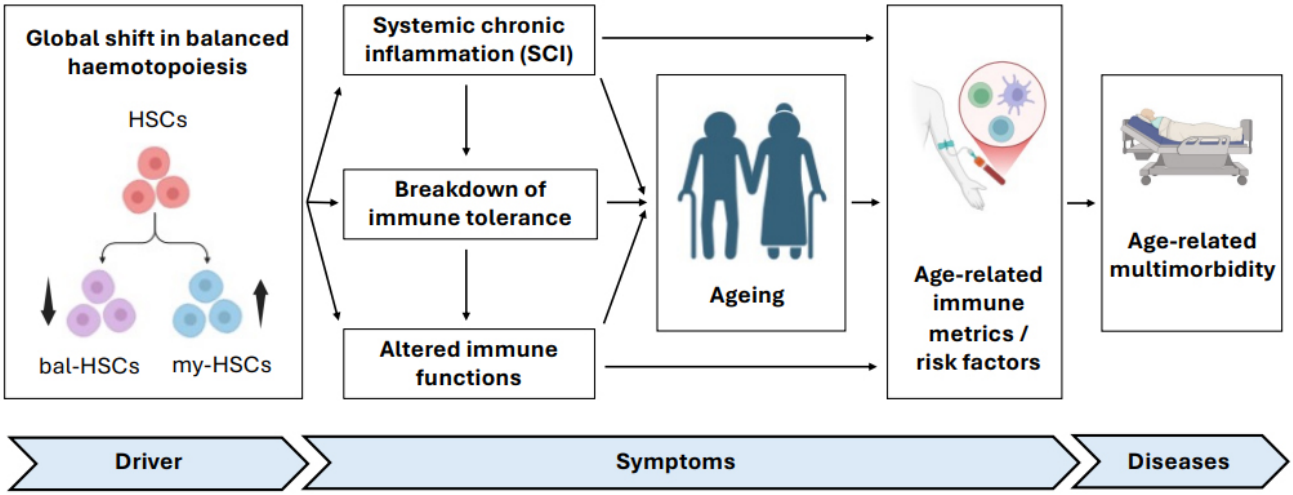

Fig. 1. Immune alterations driving ageing and age-related multimorbidity. A global shift in balanced haematopoiesis, characterized by decreased bal-HSCs and increased my-HSCs, drives immune alterations. Immune alterations manifest chronic inflammation, compromised immune tolerance, and altered immune functions – collectively facilitating ageing process and associated immune metrics (risk factors) for age-related multimorbidity. HSCs, haematopoietic stem cells; bal-HSCs, balanced haematopoietic stem cells maintaining both lymphoid and myeloid cells; my-HSC, myeloid-biased haematopoietic stem cells giving rise to myeloid cells only. Each arrow indicates the direction. The drawing of this figure was completed using the Microsoft PowerPoint software (version 16.89.1).

senescence, facilitating the ageing process [6]. This age-related increase in CXCL9 highlights its crucial role in immune system alterations and chronic inflammation during ageing.

A comprehensive understanding of the ageing process and developing pre-clinical proof-of-concept approaches for anti-ageing interventions require an assessment of the global shift in balanced haematopoiesis (Fig. 1). This shift is characterised by an alleviation in lymphopoiesis and adaptive immunity accompanied by an elevated myelopoiesis which leads to chronic inflammation and myeloid-driven pathologies [10]. Furthermore, haematopoietic stem cells (HSCs), responsible for maintaining immune cell populations and the stem cell pool, undergo an age-related shift from 'bal-HSCs' which facilitate balanced production of lymphoid and myeloid cells, to 'my-HSCs' predominantly producing myeloid cells [11,12]. In aged mice, the antibody-mediated depletion of my-HSCs rebalanced the haematopoietic system, restoring immune homeostasis by increasing lymphocyte progenitor levels, improving adaptive immunity, and enhancing adaptive responses to viral infection [13]. Given the impact of systemic inhibition of Rho family GTPases (RhoGTPase) cell division control protein 42 (Cdc42) activity on the increased regenerative potential of aged HSCs, transplantation of aged HSCs after a short systemic treatment with a specific inhibitor of Cdc42 had the same life-extending effects in aged immunocompromised mice that hadn't received the treatment [14]. Many age-related organ damages can also be repaired by rejuvenating the immune system, at least in mice. Transplantation of immune cells from the spleen of young mice reversed senescence and multiple organ damage in mice induced by the deletion of a DNA-repair enzyme in the immune system [15].

Despite significant progress in uncovering the intricate role of immunity in ageing (Fig. 1), a precise and quantitative measure of ageing that accounts for immune dysfunction are essential. Such measures are crucial for assessing the efficacy of rejuvenation therapies. Advancing therapeutic interventions for ageing requires further investigations into the underlying causes of immune imbalance, particularly the molecular cues driving impaired adaptive immune responses, elevated inflammatory myeloid output, and detrimental cross-talk between HSC subsets.

Author Contributions

AUA single-handedly performed all literature search, conceived the draft outlines, drafted the manuscript, revised the manuscript and prepared Fig. 1. The author contributed significantly to editorial changes of important content. The author read and approved the final manuscript. The author has participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

Afsar U. Ahmed is an employee of Aeterna Health Services Pty Ltd.

References

[1] Li Z, Zhang Z, Ren Y, Wang Y, Fang J, Yue H, *et al*. Aging and age-related diseases: from mechanisms to therapeutic strategies. Biogerontology. 2021; 22: 165–187.

[2] Franceschi C, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E, *et al*. Inflamm-aging. An evolutionary perspective on immunosenescence. Annals of the New York Academy of Sciences. 2000; 908: 244–254.

[3] Kotas ME, Medzhitov R. Homeostasis, inflammation, and disease susceptibility. Cell. 2015; 160: 816–827.

[4] Alpert A, Pickman Y, Leipold M, Rosenberg-Hasson Y, Ji X, Gaujoux R, *et al*. A clinically meaningful metric of immune age derived from high-dimensional longitudinal monitoring. Nature Medicine. 2019; 25: 487–495.

[5] Goldberg EL, Dixit VD. Drivers of age-related inflammation and strategies for healthspan extension. Immunological Reviews. 2015; 265: 63–74.

[6] Sayed N, Huang Y, Nguyen K, Krejciova-Rajaniemi Z, Grawe AP, Gao T, *et al*. An inflammatory aging clock (iAge) based on deep learning tracks multimorbidity, immunosenescence, frailty and cardiovascular aging. Nature Aging. 2021; 1: 598–615.

[7] Terekhova M, Swain A, Bohacova P, Aladyeva E, Arthur L, Laha A, *et al*. Single-cell atlas of healthy human blood unveils age-related loss of NKG2C^{+}GZMB^{-}CD8^{+} memory T cells and accumulation of type 2 memory T cells. Immunity. 2023; 56: 2836–2854.e9.

[8] Zhang Z, Reynolds SR, Stolrow HG, Chen JQ, Christensen BC, Salas LA. Deciphering the role of immune cell composition in epigenetic age acceleration: Insights from cell-type deconvolution applied to human blood epigenetic clocks. Aging Cell. 2024; 23: e14071.

[9] Tokunaga R, Zhang W, Naseem M, Puccini A, Berger MD, Soni S, *et al*. CXCL9, CXCL10, CXCL11/CXCR3 axis for immune activation - A target for novel cancer therapy. Cancer Treatment Reviews. 2018; 63: 40–47.

[10] Rossi DJ, Jamieson CHM, Weissman IL. Stems cells and the pathways to aging and cancer. Cell. 2008; 132: 681–696.

[11] Dykstra B, Kent D, Bowie M, McCaffrey L, Hamilton M, Lyons K, *et al*. Long-term propagation of distinct hematopoietic differentiation programs in vivo. Cell Stem Cell. 2007; 1: 218–229.

[12] Dykstra B, Olthof S, Schreuder J, Ritsema M, de Haan G. Clonal analysis reveals multiple functional defects of aged murine hematopoietic stem cells. The Journal of Experimental Medicine. 2011; 208: 2691–2703.

[13] Ross JB, Myers LM, Noh JJ, Collins MM, Carmody AB, Messer RJ, *et al*. Depleting myeloid-biased haematopoietic stem cells rejuvenates aged immunity. Nature. 2024; 628: 162–170.

[14] Florian MC, Leins H, Gobs M, Han Y, Marka G, Soller K, *et al*. Inhibition of Cdc42 activity extends lifespan and decreases circulating inflammatory cytokines in aged female C57BL/6 mice. Aging Cell. 2020; 19: e13208.

[15] Yousefzadeh MJ, Flores RR, Zhu Y, Schmiechen ZC, Brooks RW, Trussoni CE, *et al*. An aged immune system drives senescence and ageing of solid organs. Nature. 2021; 594: 100–105.