FASTING AND DIETARY RESTRICTION IMPACT ON IMMUNE SYSTEM IN AGING POPULATION: A NARRATIVE REVIEW

Luh Gede Laksmi Rahayu Handayani[1], Fitriana Nur Rahmawati[2], Dianita Susilo Saputri[2*]

[1]Idaman Hospital, Banjarbaru, Indonesia;
[2]Research Institute for Microbial Diseases (RIMD), Osaka University, Suita, Japan

Corresponding Author:

Name	: Dianita Susilo Saputri
Email	: dianitasusilosaputri@gmail.com
Mailing address	: Department of Genome Informatics, RIMD, Osaka University Yamadaoka 3-1, Suita, Osaka, Japan 562-0031
Telephone	: +81 9074793376 / +62 85782195295
Fax	: -
ORCID ID	: 000-0002-5538-0499

Abstract

Dietary habits and nutrition metabolism are strongly associated with human physiology. Overnutrition or calorie excess has been shown to have many deleterious effects. At the same time, the impact of fasting as part of dietary restriction (DR) remains elusive, especially on the immune system during the aging process. Here, we describe current updates of fasting and DR impact on the immune system and host responses in the aging population. Generally, fasting causes alteration in immune cell distribution by increasing the homing of peripheral cells to the bone marrow. In the aging population, fasting reduces the inflammatory response and promotes cell regeneration. Additionally, fasting is associated with the B cell clonal expansions important to counter infection. This review offers new perspectives and enhances our understanding of immunosenescence as a key to healthy aging.

Keywords

Aging, Dietary Restriction, Fasting, Immunosenescence

Introduction

During aging, the immune system typically experiences functional dysregulation, leading to an increased susceptibility to viral and bacterial infection. This, in turn, results in a higher incidence of cancer and age-related disease. This phenomenon is referred to as immunosenescence. In the elderly population (those aged over 65 years), the accumulation of aging-related factors, such as the acquisition of senescence-associated secretory phenotype cells, macrophage activation, oxidative stress, adiposity, and gut dysbiosis, promotes a chronic inflammation that contributes to immunosenescence (Figure 1).[1] Age-related impairments in hematopoietic stem cells (HSC) lead to a skewed differentiation toward a myeloid lineage, thereby decreasing common lymphoid progenitors, T- and B-cell lymphogenesis, and regenerative capacity. The reduction in naive lymphocytes and the expansion of late-differentiated and exhausted lymphocytes further impair immune function and may contribute to cancer and autoimmune disease.[2]

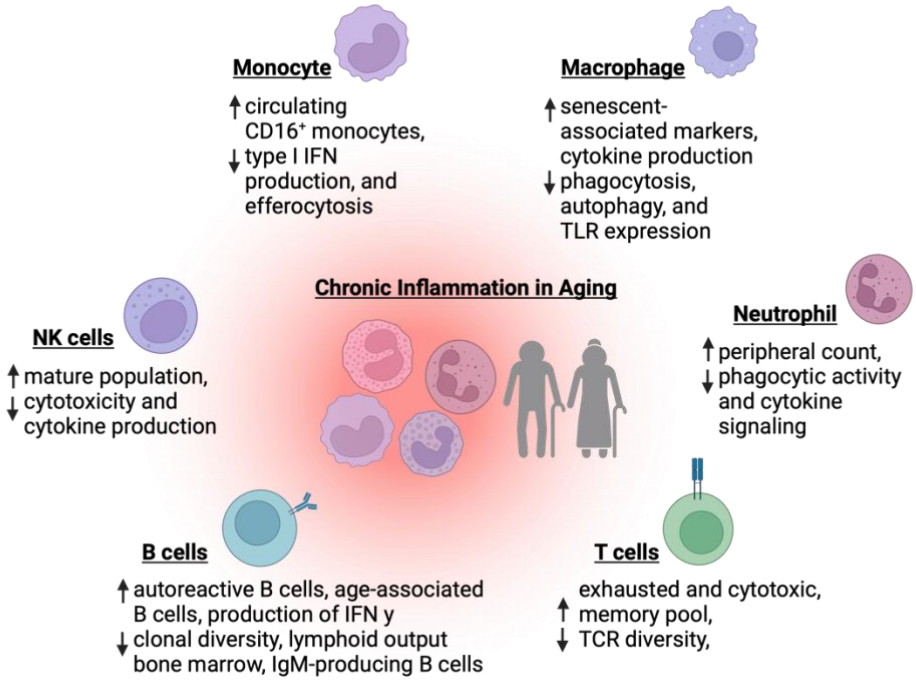

Figure 1. Age-related changes in various immune cells.
Aging induces chronic inflammation responses due to the accumulation of immune dysfunction in the innate and adaptive immune systems.[3–7]

Among the various factors associated with aging, nutrition has been shown to significantly impact the immune system.[8] Dietary restriction (DR), a 20-40% reduction in daily calorie intake without causing malnutrition, both in the short term (less than four weeks) and the long-term (more than six months), is known to play a crucial role in extending life span and delaying many aging-related diseases, such as

diabetes, atherosclerosis, cardiovascular disease, kidney disease, autoimmune disease and neurodegenerative conditions like Parkinson's and Alzheimer disease. The prevention of many aging-related diseases by DR and fasting has been linked to immune responses, including its anti-inflammatory qualities, reduction in reactive oxygen species, slowing of thymic involution, and decreased production of lymphocytes.[9]

In this review, we discuss the effect of nutritional interventions, especially fasting and DR, on immunosenescence in the context of innate and adaptive immunity. To explore the clinical and molecular aspects of the topic, we have not limited our resources to human studies alone but have also included studies on animal models. This study broadens our perspectives and enhances our understanding of immunosenescence as a cornerstone for successful aging.

Effect of fasting or DR on innate immunity during aging

Innate immunity, which encompasses the body's initial defense mechanism such as the skin, mucosal layer, and non-lymphocyte immune cells, plays a crucial role in mounting a rapid response to immune disturbances.[10] In this section, we will focus on the effects of DR and fasting on age-related changes in innate immune cells, which are closely linked to inflammatory response.

As individuals age, the innate immune system activates an inflammatory network, and DR has been shown to reduce this response effectively.[11] A small-scale clinical study conducted by Walrand et al.[12] examined changes in peripheral blood and observed that fasting and subsequent refeeding increased the total blood neutrophil and white blood count, regardless of age. However, fasting decreased the neutrophil chemotaxis index in both young adults and elderly populations, and the migration capacity was restored by refeeding only in young adults but not in the elderly.[12]

Ma et al. used a mouse model to perform single-cell analyses, which revealed a notable increase in neutrophils in multiple tissues, except bone marrow, during aging. These neutrophil numbers decreased with DR. In the aging population, neutrophils may migrate from the bone marrow to infiltrate peripheral tissues such as brown adipose tissue (BAT), white adipose tissue (WAT), liver, and kidney tissues. DR may reverse this migration. Increased pro-inflammatory macrophage infiltration was observed in various aged tissues, but DR reversed this, mitigating chronic inflammation associated with aging-associated conditions.[13] Similarly, Rasa et al. demonstrated that DR inhibits the age-induced dysregulation of pro-inflammatory cytokines, such as interferon (IFN) and tumor necrotizing factors (TNF).[11]

Janssen et al. used animal models to comprehensively analyze the distribution of immune cells during fasting, focusing not exclusively on aging. Fasting leads to the reorganization of the leucocyte landscape across various organs. They observed the

reentry of monocytes into bone marrow during fasting. Refeeding after prolonged fasting results in a surge of monocytes in circulation, which alters the immune response to bacterial infections.[14]

Another study by Tao Si et al.[15] reported that DR significantly corrects the imbalance in the HSC pool in older mice (15-18 months of age, equivalent to 50-60 years in humans), particularly the myeloid-biased HSCs ($CD150^{high}$ HSC and $CD41^{+}$ HSC) which subsequently develop into non-specific immune cells (neutrophil, monocytes, macrophages). In contrast, the lymphoid-biased HSCs ($CD150^{low}$ HSC and $CD41^{-}$ HSC) which later develop into the adaptive immune system (B and T cell lymphocytes), remain unaltered. HSC from DR mice exhibited increased quiescence, preventing the accumulation of DNA damage and functional decline in HSC. Long-term DR restored the expression of mitochondrial Unfolded Protein Response (UPRmt) genes (C1pP, HSP10, and HSP60) in aging HSC, along with the UPRmt upstream suppressor Sirtuin 7 (SIRT7) and the SIRT2-NLRP3-caspase 1 axis to levels comparable to young HSCs. Targeting the SIRT2-NLRP3-caspase 1 axis is known to be able to reverse the age-related functional deterioration of HSC.[16]

Another population of innate immune cells influenced by fasting and aging is natural killer (NK) cells, the predominant innate lymphocytes mediating antitumor and antiviral responses.[17] A study by White et al.[18] demonstrated an association between DR and the accumulation of immature/early-stage NK cells. They also reported reduced expression of Ly49 receptors in calorie-restricted mice, which is related to self-antigen recognition by NK cells. There was a tendency for increased NK proliferation in response to IL12/IL18 in calorie-restricted mice. However, the functional effect of calorie restriction on NK physiology is yet to be fully elucidated.

The adaptive immune response of the aging population during fasting or DR

The adaptive immune system, which includes the B and T cells (lymphocytes) activation, works synergistically with innate immunity to defend against immune perturbations. Adaptive immune cells provide a specific memory capacity for rapid pathogen elimination during secondary infection.[10]

B cells development occurs in the bone marrow, where lymphoid progenitor cells begin to differentiate from pro-B cells, pre-B cells, immature B cells, to ultimately recirculating mature B cells. As previously mentioned, the decreased lymphopoiesis in the bone marrow during aging, particularly that of B cells, was not rescued by DR.[15] Sushimita et al.[9] reported that both DR and fasting in mice led to a significant reduction in the population of pro-B, pre-B, and immature-B cells in the bone marrow, accompanied by a significant increase in circulating mature B cells. Evidently, dietary changes prompt the bone marrow to conserve energy by inhibiting the generation of additional B cells while prioritizing energy preservation to manage metabolic

imbalances. Fasting and DR also induced a depletion of immature transitional B cells ($CD19^+B220^+IgM^+IgD^-$) and mature B cell populations ($CD19^+B220^+IgM^+IgD^+$) in the spleen. Furthermore, fasting caused a significant depletion of the marginal zone and follicular B cells.

During aging, naive B cells are predominantly replaced by memory B cells, resulting in limited diversity of the B cell receptor repertoire and reduced antigen specificity. This lack of diversity is associated with a diminished capacity for antigen recognition in infections and vaccinations.[19] The reduction in repertoire diversity is a direct consequence of clonal expansion among B cells.[20]

DR initiated in mid-life mice (at 16 months of age) was sufficient to maintain both B cell receptor (BCR) repertoire diversity (evaluated using Shannon and Simpson diversity measures) and reduce clonal expansions in the spleen. DR mice exhibited an increased abundance of both IgM and IgG, a characteristic of a healthier BCR repertoire. Notably, there is an age-related increase in the production of autoantibodies, including IgG glycans, and the heightened IgG is essential for countering this phenomenon. Likewise, the rise in IgM levels may indicate an enhanced capacity for HSC regeneration and increased repertoire responsiveness.[20]

Clonal diversity is crucial for effective antigen recognition. Upon encountering antigens in a T cell-dependent manner, naive B cells are prompted to enter germinal centers to generate high-affinity antibodies. This affinity maturation of B cells is achieved through class switch recombination (CSR) and somatic hypermutation (SHM). SHM introduces mutation into the BCR, resulting in increased affinity for antigens. Unlike the spleen, the BCR repertoire of the ileum showed only minor changes with aging and in response to DR. However, an increase in SHM suggests an enhanced capacity for antigen binding.[20]

When it comes to T cells, White MJ et al. [18] found no significant age-related changes in the proportion of $CD4^+$, $CD8^+$, or T regulatory among C57BL/6 mice in the spleen, lung, liver, and lymph nodes. However, DR significantly increased the proportion of $CD8^+$ cells, leading to a corresponding decline in the CD4/CD8 ratio. Asami T et al.[21] observed age-associated decreases in the proportions of $CD4^+$ and $CD8^+$ T cells, which were attenuated by long-term DR.

Aging reduces the proportion of naive ($CD44^-CD11a^-$) $CD4^+$ and $CD8^+$ cells, leading to a skewing of the T cell phenotype toward memory T cells. Remarkably, long-term DR significantly delayed the transition from a naive to effector T cell phenotype in aged mice, resulting in a distribution of naive/effector T cells that resembled that of young mice.[18,21]

Furthermore, during aging, there is a decline in the generation of T cell cytokines such as interleukin (IL)-2, interferon, (IFN)-γ and granzyme B, all of which play pivotal roles in coordinating both innate and adaptive immune system responses. Long-term DR significantly increased the numbers of $CD4^+$ T cells

producing IL-2 and IFN-γ, as well as granzyme B-producing CD4+ and CD8+ T cells. However, it had no impact on the production of these cytokines by $CD8^+$ T cells.[21] Additionally, DR significantly reduced the transcription factors NR4A1 and TOX, leading to a decrease in exhausted T cells marked by KLRG1 and Tim3.[18,21] Together, the effects of fasting and DR on the immune system in aging are illustrated in Figure 2.

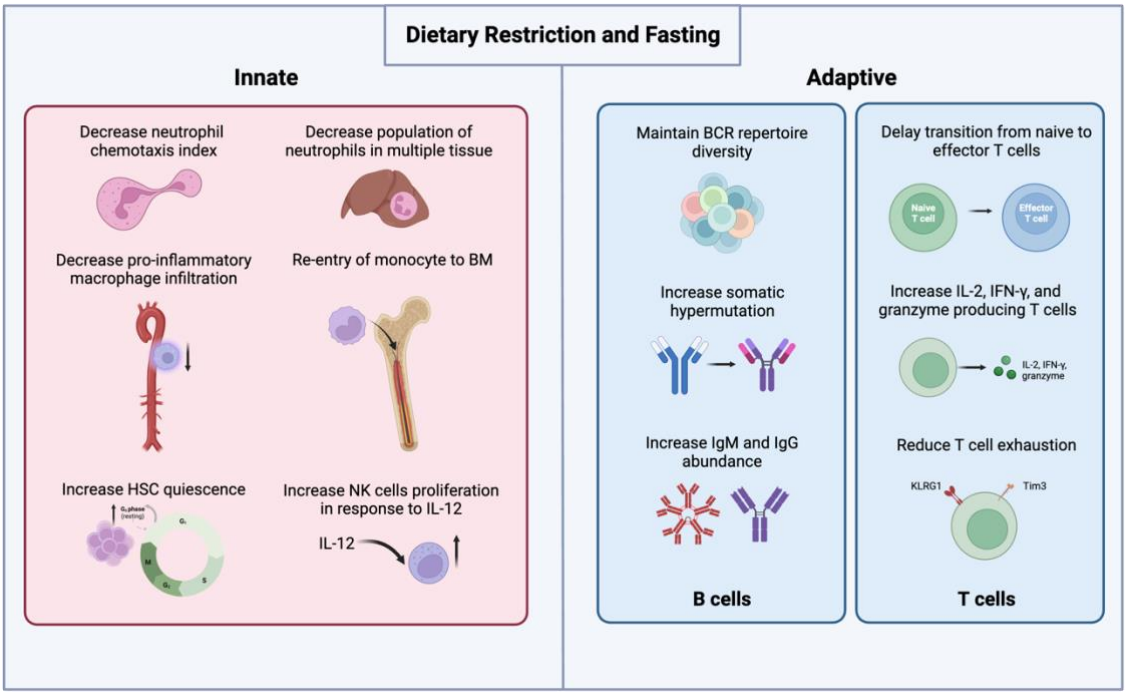

Figure 2. Effect of fasting and DR in the immunosenescence.
Fasting alters the distribution of immune cell and decrease inflammation in aging.

Conclusion

Dietary interventions have been proven to be effective in reducing major inflammatory disturbances associated with aging-related immune perturbations and in suppressing organ damage and inflammation. In summary, fasting and DR can alter immune cell distribution. However, further studies, including humans, are needed to gain a more comprehensive understanding of the molecular mechanism and clinical impact of fasting to immunosenescence in humans.

Conflict of Interests

The authors declare no conflict of interest.

Acknowledgment

Illustrations in Figure 1 and 2 were created using Biorender.com. This article was presented at the 8th International Conference and Exhibition on Indonesian Medical Education and Research Institute (8th ICE on IMERI) 2023, Faculty of Medicine, Universitas Indonesia. We are grateful for the outstanding assistance provided by the committee of the 8th ICE on IMERI 2023 throughout the preparation of the manuscript and the peer-review process.

References

1. Longo VD, Cortellino S. Fasting, dietary restriction, and immunosenescence. Journal of Allergy and Clinical Immunology [Internet]. 2020 Nov 1;146(5):1002–4. Available from: https://doi.org/10.1016/j.jaci.2020.07.035
2. Longo VD, Di Tano M, Mattson MP, Guidi N. Intermittent and periodic fasting, longevity and disease. Nat Aging. 2021 Jan 14;1(1):47–59.
3. Mittelbrunn M, Kroemer G. Hallmarks of T cell aging. Nat Immunol. 2021 Jun 13;22(6):687–98.
4. de Mol J, Kuiper J, Tsiantoulas D, Foks AC. The Dynamics of B Cell Aging in Health and Disease. Front Immunol. 2021 Oct 5;12.
5. Van Avondt K, Strecker J, Tulotta C, Minnerup J, Schulz C, Soehnlein O. Neutrophils in aging and aging-related pathologies. Immunol Rev. 2023 Mar 31;314(1):357–75.
6. Qi C, Liu Q. Natural killer cells in aging and age-related diseases. Neurobiol Dis. 2023 Jul;183:106156.
7. De Maeyer RPH, Chambers ES. The impact of ageing on monocytes and macrophages. Immunol Lett. 2021 Feb;230:1–10.
8. Pahlavani MA. Influence of caloric restriction on aging immune system. J Nutr Health Aging. 2004;8(1):38–47.
9. Shushimita S, de Bruijn MJW, de Bruin RWF, IJzermans JNM, Hendriks RW, Dor FJMF. Dietary Restriction and Fasting Arrest B and T Cell Development and Increase Mature B and T Cell Numbers in Bone Marrow. PLoS One. 2014 Feb 4;9(2):e87772.
10. Marshall JS, Warrington R, Watson W, Kim HL. An introduction to immunology and immunopathology. Allergy Asthma Clin Immunol. 2018;14(Suppl 2):49.
11. Rasa SMM, Annunziata F, Krepelova A, Nunna S, Omrani O, Gebert N, Adam L, Käppel S, Höhn S, Donati G, Jurkowski TP, Rudolph KL, Ori A, Neri F. Inflammaging is driven by upregulation of innate immune receptors and systemic interferon signaling and is ameliorated by dietary restriction. Cell Rep. 2022 Jun;39(13):111017.
12. Walrand S, Moreau K, Caldefie F, Tridon A, Chassagne J, Portefaix G, Cynober L, Beaufrère B, Vasson MP, Boirie Y. Specific and nonspecific immune responses to fasting and refeeding differ in healthy young adult and elderly persons. Am J Clin Nutr. 2001 Nov;74(5):670–8.
13. Ma S, Sun S, Geng L, Song M, Wang W, Ye Y, Ji Q, Zou Z, Wang S, He X, Li W, Esteban CR, Long X, Guo G, Chan P, Zhou Q, Belmonte JCI, Zhang W, Qu J, Liu GH. Caloric Restriction Reprograms the Single-Cell Transcriptional Landscape of Rattus Norvegicus Aging. Cell. 2020 Mar;180(5):984-1001.e22.

14. Janssen H, Kahles F, Liu D, Downey J, Koekkoek LL, Roudko V, D'Souza D, McAlpine CS, Halle L, Poller WC, Chan CT, He S, Mindur JE, Kiss MG, Singh S, Anzai A, Iwamoto Y, Kohler RH, Chetal K, Sadreyev RI, Weissleder R, Kim-Schulze S, Merad M, Nahrendorf M, Swirski FK. Monocytes re-enter the bone marrow during fasting and alter the host response to infection. Immunity. 2023 Apr;56(4):783-796.e7.
15. Tao S, Wang Y, Wu J, Zeng T, Cui H, Tao Z, Lei L, Yu L, Liu A, Wang H, Zhang L, Tang D. Long-term mid-onset dietary restriction rejuvenates hematopoietic stem cells and improves regeneration capacity of total bone marrow from aged mice. Aging Cell. 2020 Oct 15;19(10).
16. Luo H, Mu WC, Karki R, Chiang HH, Mohrin M, Shin JJ, Ohkubo R, Ito K, Kanneganti TD, Chen D. Mitochondrial Stress-Initiated Aberrant Activation of the NLRP3 Inflammasome Regulates the Functional Deterioration of Hematopoietic Stem Cell Aging. Cell Rep. 2019 Jan 22;26(4):945-954.e4.
17. Abel AM, Yang C, Thakar MS, Malarkannan S. Natural Killer Cells: Development, Maturation, and Clinical Utilization. Front Immunol. 2018;9:1869.
18. White MJ, Beaver CM, Goodier MR, Bottomley C, Nielsen CM, Wolf ASFM, Boldrin L, Whitmore C, Morgan J, Pearce DJ, Riley EM. Calorie Restriction Attenuates Terminal Differentiation of Immune Cells. Front Immunol. 2017 Jan 12;7.
19. Ademokun A, Wu YC, Dunn-Walters D. The ageing B cell population: Composition and function. Biogerontology. 2010 Apr 25;11(2):125–37.
20. Monzó C, Gkioni L, Beyer A, Valenzano DR, Grönke S, Partridge L. Dietary restriction mitigates the age-associated decline in mouse B cell receptor repertoire diversity. Cell Rep. 2023 Jul;42(7):112722.
21. Asami T, Endo K, Matsui R, Sawa T, Tanaka Y, Saiki T, Tanba N, Haga H, Tanaka S. Long-term caloric restriction ameliorates T cell immunosenescence in mice. Mech Ageing Dev. 2022 Sep;206:111710.