Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Immunology

Review

The immunometabolic roots of aging

Pierpaolo Ginefra[1,*], Helen C Hope[1,*], Girieca Lorusso[2,*], Patrizia D'Amelio[2] and Nicola Vannini[1]

Aging is one of the greatest risk factors for several chronic diseases and is accompanied by a progressive decline of cellular and organ function. Recent studies have highlighted the changes in metabolism as one of the main drivers of organism dysfunctions during aging and how that strongly deteriorate immune cell performance and function. Indeed, a dysfunctional immune system has been shown to have a pleiotropic impact on the organism, accelerating the overall aging process of an individual.

Intrinsic and extrinsic factors are responsible for such metabolic alterations. Understanding the contribution, regulation, and connection of these different factors is fundamental to comprehend the process of aging and develop approaches to mitigate age-related immune decline. Here, we describe metabolic perturbations occurring at cellular and systemic levels. Particularly, we emphasize the interplay between metabolism and immunosenescence and describe novel interventions to protect immune function and promote health span.

Addresses
[1] Department of Oncology, Ludwig Institute for Cancer Research, University of Lausanne, Epalinges, Switzerland
[2] Service of Geriatric Medicine, Department of Internal Medicine, CHUV University Hospital of Lausanne, University of Lausanne, Lausanne, Switzerland

Corresponding authors: D'Amelio, Patrizia (patrizia.damelio@chuv.ch), Vannini, Nicola (nicola.vannini@unil.ch).
[*] These authors contributed equally to this work.

Current Opinion in Immunology 2024, **91**:102498

This review comes from a themed issue on **Immunometabolism**

Edited by **Hongbo Chi** and **Ping-Chi Ho**

For complete overview of the section, please refer to the article collection, "Immunometabolism (2024)"

Available online 26 October 2024

https://doi.org/10.1016/j.coi.2024.102498

Introduction

Several chronic diseases are direct consequences of the natural process of aging. In this context, 12 age-associated hallmarks and their complex interconnections have been identified and suggested as the main drivers of the aging process [1]. Within those, an important factor contributing to systemic aging is the metabolic dysfunction occurring in immune cells, which has been shown to profoundly impact the aging process at organism level [2,3]. Metabolic defects drive the acquisition of senescence phenotype in immune cells, which in turn promote premature senescence and consequent multi-organs morbidity and accelerated aging.

In this review, we will explore the intrinsic metabolic changes occurring within aged immune cells, including alterations in mitochondrial function, autophagy, and redox homeostasis, which collectively impair immune cell functionality. In addition, we will examine environmental and systemic modifications, hereafter referred as extrinsic factors, such as inflammaging and the senescence-associated secretory phenotype (SASP), which contribute to metabolic dysfunction in immune cells. Finally, we will integrate human data and clinical insights to address how a healthy lifestyle, including exercise and nutrition, can positively impact the aging immune system.

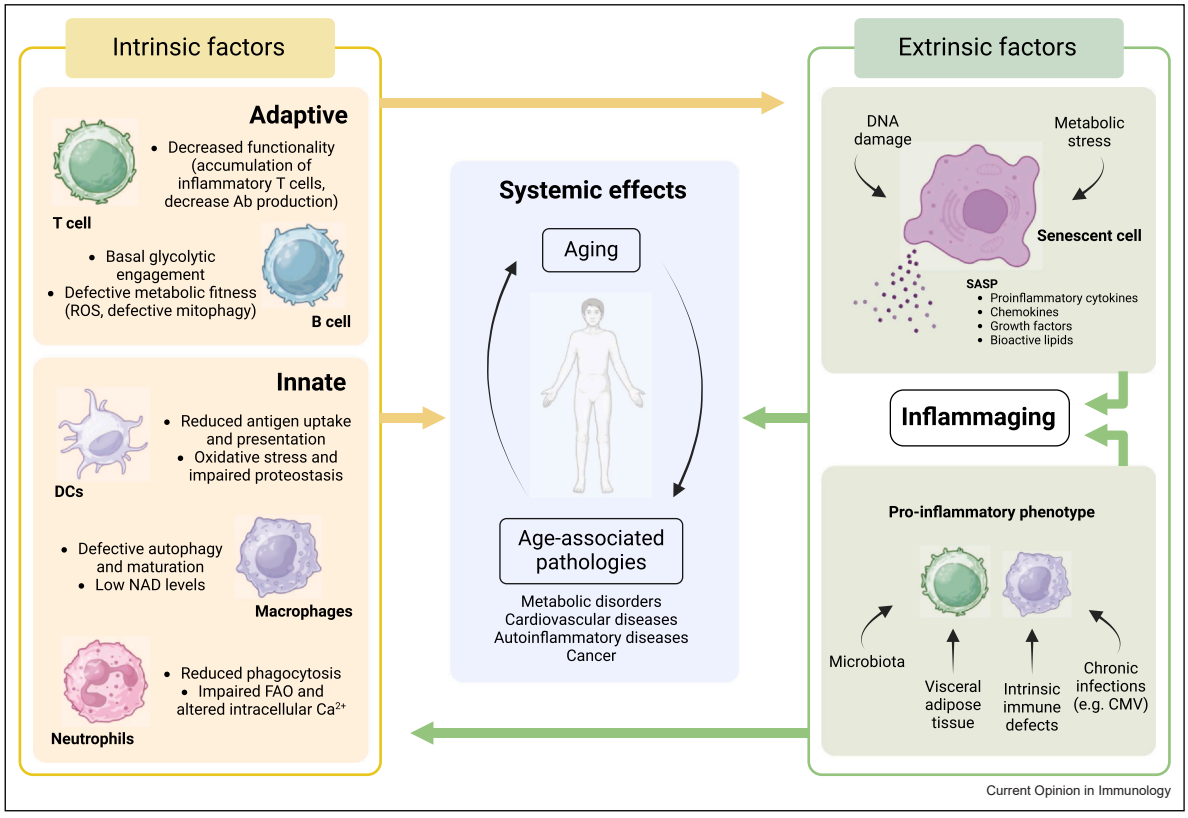
Overall, we intend to provide an overview of the metabolic roots of immune aging, highlighting the interplay between metabolism and immunosenescence and suggesting potential therapeutic strategies for mitigating age-related immune decline.

Intrinsic factors

Immune cells rapidly switch their metabolic programs in response to activating stimuli and to support fate commitment. Increasing evidence has demonstrated the pivotal role of cellular metabolism as a central regulator of immune function and how factors such as aging can alter metabolism of immune cells and thus their overall functionality. In fact, aging impairs both the innate and the adaptive immune cells, making older adults more susceptible to infections, autoimmune diseases, cancer, as well as less responsive to vaccines.

Age-associated changes in metabolism have been described especially in innate immune cells (Figure 1). Indeed, macrophages are considered as sentinel of the body, dedicated both to fighting infection and healing wound. Macrophages derived from aged mice are characterized by dysfunctional nicotinamide adenine dinucleotide (NAD) metabolism and cellular quality control processes such as mitophagy and autophagy. Old

Figure 1



Immunometabolic reprogramming during aging and age-associated pathologies. During aging, both adaptive and innate immune cells acquire metabolic deficiencies that lead to impaired functionality. T and B lymphocytes engage a basal glycolytic metabolism and present defective mitochondria, leading to an inflammatory phenotype and decreased Ab production, respectively. On the other hand, DCs, macrophages, and neutrophils accumulate oxidative stress, low NAD levels, or impaired FAO, which leads to poor antigen presentation and phagocytic properties. Moreover, due to several stress stimuli, such as DNA damage or metabolic stress, aged cells can enter a state of senescence, which is linked to a pro-inflammatory phenotype known as SASP. This pro-inflammatory phenotype can also be acquired by a chronic activation of innate cells due to chronic infections, visceral adipose tissue, microbiota changes, or intrinsic immune defects per se. Altogether, this drives a chronic and systemic inflammation that, together with the intrinsic immune defects, accelerate aging processes and promote the appearance of age-associated pathologies.

macrophages have reduced NAD levels due to the downregulation of the expression of genes encoding for enzymes of the *de novo* synthesis pathway [4], which actuates NAD synthesis from dietary tryptophan through the kynurenine pathway. Low NAD level triggers mitochondrial dysfunction and increases inflammatory phenotype. These phenomena are exacerbated in old macrophages, where the lack of an efficient mitophagy machinery leads to the accumulation of damaged mitochondria and decline of metabolic capacity. In fact, old macrophages fail to promote mitochondria ubiquitination [5] and downregulate the expression of autophagy proteins, such as autophagy-related 5 (ATG5) and microtubule-associated proteins 1A/1B light chain 3 B [6,7]. These metabolic alterations lead to defective maturation and functionality, and together with an increased release of pro-inflammatory cytokines, contribute to the systemic chronic sterile inflammation found in older individuals.

Similarly, monocytes contribute to chronic inflammation in older individuals [6,8] by downregulating two key genes, *PLA2G4B* and *ALOX15B*, encoding for enzymes involved in the conversion of phosphatidylcholine to anti-inflammatory lipoxins [9]. These features are accompanied by increased oxidative stress and higher abundance of reactive oxygen species (ROS) [10] triggered by nicotinamide adenine dinucleotide phosphate oxidase hyperactivation [11].

Neutrophils are the most abundant immune cells in human blood and act as first-line defense against micro-

organisms. In healthy aged blood donors, neutrophils also bear metabolic and cellular dysfunctions characterized by decreased fatty acid oxidation capacity and altered calcium homeostasis, which lead to reduced phagocytic and antimicrobial activities [12,13].

Aging impacts also professional antigen-presenting cells, such as dendritic cells (DCs), thus profoundly perturbing adaptive immune response. In fact, aging impairs metabolic pathways, such as PI3K-Akt, which governs key functions of DCs, including antigen uptake, antigen presentation, and release of antiviral cytokines [14]. Together with an increased oxidative stress due to the defective activity of nicotinamide adenine dinucleotide phosphate oxidase and ROS scavenger enzymes, old DCs carry major mitochondrial dysfunction due to an abnormal mitochondrial depolarization and impaired proteostasis [11,15,16]. Altogether, aging perturbs DCs metabolism at several levels, which in turn reduces their capacity to efficiently present antigens and secrete antiviral cytokines, hindering a proper activation of adaptive immunity [17].

How aging influences the metabolism of less represented innate cells, such as basophils and eosinophils, is poorly investigated. Few studies have evidenced an expansion of these cells in old mice but with reduced degranulation and cytokines production capacity [18,19].

Metabolism is an important regulator of survival, differentiation, and function of adaptive immune cells (Figure 1). Therefore, age-related metabolic changes are often responsible for defective proliferative response, activation, and survival of T cells. During aging, mitochondrial mass has been shown to increase in both CD4 and CD8 T cells derived from human subjects [20–22]. However, the higher mitochondrial mass does not result in improved mitochondrial activity. Instead, the accumulation of dysfunctional mitochondria leads to an overall increase in mitochondrial content with much lower metabolic capacity and higher production of ROS [22]. Importantly, this accumulation of damaged mitochondria derives from inefficient cellular quality control processes, such as autophagy and mitophagy [23–25], which are deeply impaired during aging. Indeed, few recent studies have suggested that reduced level of spermidine and FOXO1 activity in old animals impair mitophagy and autophagy processes and lysosome activity [26,27], describing a novel molecular mechanism orchestrating metabolic dysfunction in old T cells. Moreover, the elevated ROS and mitochondrial dysfunction reprogram T cells' fate toward an effector/pro-inflammatory phenotype [28]. Interestingly, old T cells display an increased basal glycolytic rate due to higher activation of the mammalian target of rapamycin (mTOR) and mitogen activated protein kinase signaling [29,30]. However, old murine T cells fail to engage a proper and efficient glycolysis upon stimulation [31], reducing their capacity to fully mount an appropriate adaptive immune response. Interestingly, the deletion of the transcription factor TFAM, master regulator of mitochondrial function and biogenesis, in young T cells accelerates T cell aging by recapitulating the metabolic defects observed in old T cells and contributing to inflammaging and organism-wide premature aging [2].

On the contrary of T cells, to date, few studies have described the impact of aging on B cell metabolism and function. Similar to old T cells, old B cells have higher basal rate of glycolysis and higher expression of glucose transporters, such as GLUT-1 [32,33]. Moreover, old B cells have also higher mitochondrial mass; however, the limited detoxification machineries lead to increased ROS generation and reduces mitochondrial energy production [34].

In conclusion, aging drastically affects the metabolic efficiency of both innate and adaptive immune cells, impairing their fate commitment and function. A deeper analysis of the metabolic processes governing the age-driven immune dysfunction will help in the future to develop intervention to rejuvenate immune cell function and, consequently, mitigate the ravages of aging in the older population.

Extrinsic factors

Besides the cell-intrinsic defects described above, a low-grade, chronic, and sterile systemic inflammation emerges in aged individuals [35,36]. This phenomenon, known as 'inflammaging', is the consequence of two main phenomena: the accumulation of senescent cells and the chronic activation of the innate immune system (Figure 1).

Cellular senescence is a state of irreversible cell cycle arrest triggered by stress stimuli to prevent cellular damage. Among these stress stimuli, DNA damage and metabolic burden are the main drivers of this process, particularly during aging, where, together with a reduced clearance capacity of the immune system, they lead to an aberrant accumulation of senescent cells. In addition to the cell cycle arrest induced by p53-p21 and p16-pRb pathways, senescent cells become moderately resistant to cell death and acquire a peculiar SASP characterized by the increased production of pro-inflammatory cytokines (e.g. interleukin [IL]-1β, IL-6, or IL-8), chemokines (e.g. CCL2, CCL5), growth factors (e.g. tumor growth factor beta, TGFβ) or bioactive lipids (prostaglandins and leukotrienes), which sustain 'inflammaging' [37].

In this context, mitochondria play a central role in the regulation of senescence and age-associated diseases. Mitochondrial dysfunction can be driven during aging by mitochondrial DNA mutations, loss of sirtuin activity, disruptions of the electron transport chain, mitophagy defects, or production of ROS, overall leading to the so-called mitochondrial dysfunction–associated senescence (MiDAS) phenotype [38]. Mechanistically, cells presenting

mitochondrial dysfunction release damage-associated molecular patterns that trigger the NLRP3 inflammasome and the production of pro-inflammatory cytokines.

Another factor bridging mitochondrial dysfunction and senescence is NAD^+ metabolism. Indeed, MiDAS is characterized by a lowered NAD/NADH ratio that restricts glycolytic activity and ATP production, promoting 5' adenosine monophosphate-activated protein kinase (AMPK) activation and cell cycle arrest [38]. NAD decline has been observed across multiple tissues during aging, such as liver, white adipose tissue, or skeletal muscle [39]. However, whether NAD depletion is a driver or a consequence of senescence is still unclear. Some investigations have reported that NAD decline with age is caused by the upregulation of the NAD-cyclase degrading enzyme CD38 [39]. CD38 is upregulated via nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) in response to SASP-associated factors and is part of the biosynthetic pathway of the immunomodulatory molecule adenosine, suggesting NAD decline as a downstream effect of CD38 activity [40]. Similarly, Poly (ADP-ribose) polymerase activation in response to DNA damage has been shown to rapidly deplete NAD cellular levels [41,42]. Moreover, low NAD levels further disrupt mitochondrial fitness, generating a positive feedback loop that accelerates cellular senescence. Restoration of NAD levels through nutritional supplementation with NAD precursors or CD38 depletion has been shown to maintain mitochondrial fitness and prevent age-related pathologies in murine models, highlighting the key role of NAD homeostasis in the regulation of senescence and aging [39].

Senescent cells also undergo a metabolic reprogramming that copes with lack of proliferation while actively synthesizing SASP factors. Specifically, senescent cells significantly alter their lipid metabolism. They increase the expression of enzymes involved in β-oxidation or fatty acid synthesis (e.g. fatty acid synthase), which are required for energy production [43,44]. Moreover, senescent cells activate phospholipase A2 and produce high levels of free polyunsaturated fatty acids (PUFAs), such as arachidonic acid or docosahexaenoic acid, which are incorporated into triglycerides and stored as lipid droplets. Alternatively, free PUFAs are converted in oxylipin via cyclooxygenase-2, which can be secreted and imported by neighboring cells or in an autocrine manner, leading to the activation of RAS-p53 and promoting cell cycle arrest [45,46]. In addition, cell cycle is further hindered in senescent cells by a decreased levels of deoxynucleotides triphosphates required for DNA biosynthesis and deterioration of autophagy and lysosomal function [47,48].

Together with the accumulation of senescent cells, the age-driven chronic activation of the innate immune cells strongly contributes to 'inflammaging'. The triggering causes of innate immune system activation are varied, including the accumulation of visceral adipose tissue, microbiota dysbiosis, chronic infections, and intrinsic immune defects, are the most studied. In this context, the hematopoietic stem cell myeloid bias and the restricted naïve T cell pool imposed by aging together with the presence of chronic viral infections, such as cytomegalovirus or HIV, lead to a pro-inflammatory phenotype in both myeloid and lymphoid compartments, contributing to 'inflammaging'.

Altogether, 'inflammaging' is often the main responsible for the development of chronic age-associated diseases, including metabolic syndrome, osteoarthritis, type 2 diabetes mellitus, cardiovascular diseases, autoimmune diseases, or cancer. However, the specific cellular and molecular mechanisms triggered by 'inflammaging' are context dependent. For example, pro-inflammatory cytokines can promote bone resorption leading to osteoporosis, while Janus kinase (JAK) activation via toll-like receptor 4 can induce the phosphorylation of the insulin receptor, contributing to insulin resistance [49]. Overall, 'inflammaging' is an important risk factor for multimorbidity, accelerating an unhealthy aging process, driving frail syndrome, and increasing disease susceptibility in older subjects (Figure 1).

Clinical studies for therapeutic targeting immune and metabolic pathways in age-related diseases

Cellular senescence is one of the fundamental biological processes driving aging and, as described above, responsible for multiple age-related diseases. Hence, over the past years, an increased number of studies have been focused on developing novel therapeutic interventions to counteract the aging process, thus increasing health span and preventing the social and economic impact of a progressively older population. Geroprotector strategies were conceived with the aim of targeting immunosenescence and other hallmarks of aging, rather than individual age-related diseases, often concurrent in multimorbidity and risk of mortality in the older population [50]. Senolytics have been developed to specifically target and induce apoptosis of senescent cells undergoing SASP, both locally and systemically [51].

Importantly, as a result of promising preclinical studies conducted in 2016, quercetin, a natural senolytic agent, was tested in combination with dasatinib, a Src/tyrosine kinase inhibitor, (D+Q) in the first-in-human trial in 2018 for the treatment of a fatal senescence-associated disease, idiopathic pulmonary fibrosis. Indeed, quercetin together with fisentin were the first discovered senolytics with demonstrated capacity to induce apoptosis of senescent cells through inhibition of BCL2/BAX and PI3K/AKT pathways [52].

This first-in-human, proof-of-concept trial paved the way to further development and testing of D+Q, as well as alternative strategies with other senolytics, such as fisetin (F)

and luteolin (L), in numerous clinical trials for various age-related diseases, including Alzheimer's disease, chronic kidney disease, physical frailty, and, more recently, coronavirus disease 2019 COVID-19 (from severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) in older subjects [53].

As an alternative, complementary strategies inhibiting SASP with specific inhibitors called senomorphics have been developed and shown to potently reduce inflammaging. Several senomorphic approaches have been developed by targeting different intracellular signal transduction pathways such as JAK-STAT [54], NF-kB transcription factor, mediating cell response to inflammation [55], mTOR, via treatment with rapamycin (sirolimus) and its analog 'rapalog' (everolimus) [56], and AMPk, via treatment with the antidiabetic drug metformin [57]. The first-in-human clinical trial testing Torc 1 inhibition (mTOR pathway) proved its efficacy in enhancing immune functions and improving vaccine protection against influenza viral infection in older subjects [58]. Moreover, AMPk inhibition ameliorated T_h17 T cell subset performance by enhancing autophagy and improving mitochondrial bioenergetics of peripheral blood mononuclear cells derived from the older subjects treated with metformin [28]. NAD^+ precursors as nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) are capable to counteract the age-associated NAD decline guided by CD38 NAD-degrading enzyme [39]. Many studies on both precursors have been conducted on preclinical models showing geroprotective effects. Although NR and NMN supplements are easily accessible on the market, further clinical studies are needed to prove their efficacy, coupled with their already tested capacity to increase NAD levels in humans [59], as effective geroprotectors.

Prospectively, larger, randomized, controlled, and rigorous trials are required to develop and improve the clinical safety and efficacy of senolytics and, more in general, geroprotectors. Novel senolytics and geroprotectors might additionally be tested for the prevention of organ dysfunction (heart, muscle, brain, bone, for example) and age-related diseases in older individuals. The proven effectiveness from novel clinical studies of these agents on aged immune system and dysfunctional metabolism, and their combination with disease-specific interventions would possibly lead to a more successful translation into the clinic, improving health span and delay the onsets of age-related diseases.

Human data from healthy lifestyles (diet and exercise) and centenarians as paradigm of successful healthy aging

Regular training exercise has been demonstrated to have a geroprotective effect, with improvement of quality of life and increase in lifespan of older population. Among the beneficial effects of regular exercise, the most relevant are the enhancement of muscle mass and strength, improvement of cardiovascular and musculoskeletal functions, as well as a preventive protective effect in the younger population by delaying and reducing the risk of physical frailty with aging [60]. Although the molecular mechanisms underlying the protective effect of exercise against age-related diseases are still not fully covered, an increased number of ongoing studies are trying to better understand the geroprotective role of this healthy habit. The beneficial stress of regular exercise promotes tissue regeneration in various organs (as myogenesis, osteogenesis, neurogenesis, and synaptic plasticity) by calcium-mediated mechanotransduction signaling, and intracellularly mitochondria biogenesis via AMPK /SIRT1 PGC1α-mediated pathway and ROS detoxification [61].

Proper nutrition has been associated with reduction of the risk of all types of chronic disease and increased health span and lifespan. Although is difficult to conduct rigorous human studies that compare different diets avoiding bias and confounding variables (e.g. geographic location, traditions, and culture), it is widely accepted that diets excluding or minimizing processed foods, preferentially plant-based, avoiding overeating and fat, and low alcohol consumption reduce chronic disease risk and favor health span and longevity (as Mediterranean diet, Okinawa diet) [62,63]. In recent years, the field of nutrition has expanded with exciting results on health preventive and curative benefits of intermitted fasting [64], fasting-mimicking diets [65] and time-restricted eating (TRE) [66], limiting the eating window in a 24-hour period.

Since the early 2000s, centenarians have been studied as a model to address the biological basis of successful healthy aging and a paradigm of longevity [67]. Despite a globally increasing aging population, the ratio of centenarians (CR) in economically developed countries is strongly influenced by social factors, with approximately 1:5000, 1:10 000, with the highest demographic peak registered in Japan [68]. Centenarians offer a remarkable paradigm of successful, healthy aging, exhibiting resistance to many age-related diseases, such as cancer and autoimmune disorders, and maintaining robust immune responses well into advanced age. Surprisingly, the incidence of autoimmune diseases among centenarians is low despite the age-related decline in immune function typically observed in the general population [69]. Similarly, cancer in centenarians is a relatively uncommon disease, with a decreased incidence and mortality, and displaying a less aggressive and more indolent behavior. This paradox may be explained by unique immunometabolic profiles that allow centenarians to maintain immune homeostasis. For instance, centenarians have been shown to mount effective immune responses to

viral infections, such as severe acute respiratory syndrome cronavirus 2, with favorable outcomes.

Interesting studies aimed to understand the successful aging of centenarians; among these, one showed that $CD34^+$ hematopoietic progenitors are still circulating in the peripheral blood of centenarians and display a stem cell function comparable to the $CD34^+$ cells derived from young donors when cultured *ex vivo* [70]. Being the decline of hematopoietic function one of the drivers of immunosenescence, the maintenance of functional $CD34^+$ progenitor cells in centenarians could in part explain their protections against aging.

Overall, the studies on centenarians have helped identifying key biological features of healthy aging and longevity and their association to specific immune profiles [71]. A whole genome sequencing study on centenarians of extreme longevity (105–110 years/old) demonstrated that centenarians display an unique transcriptional profile associated with efficient DNA repair mechanisms and reduced clonal hematopoiesis, both supporting cellular homeostasis and protecting against cardiovascular diseases [72]. In the future, the increasing insights derived from human studies on older individuals will pave the way for developing immune-targeting preventive strategies to limit age-associated pathologies toward a successful healthy aging.

Conclusion

In conclusion, the intricate relationship between metabolic dysfunction and immunosenescence underscores the complexity of the aging process and its effects on health. This review highlights the pivotal role of intrinsic metabolic alterations in aged immune cells, including mitochondrial dysfunction, impaired autophagy, and disrupted redox balance, which collectively compromise immune function and fitness. Additionally, extrinsic factors such as 'inflammaging' and the SASP further exacerbate metabolic dysfunction in immune cells. By integrating human data and clinical insights, we have underscored the importance of a healthy lifestyle, particularly exercise and nutrition, in positively mitigating immune aging. This capacity to preserve or restore immune functions that promote disease resistance and control inflammation in infectious diseases as well as other inflammatory-related diseases is known as immune resilience [73]. The optimal immunocompetence–inflammation balance associated with immune resilience leads to a favorable immune and overall health outcome, contrasting sharply with the concept of immunosenescence, which describes the gradual deterioration of the immune system with age, leading to increased susceptibility to disease.

Ultimately, understanding the metabolic underpinnings of immunosenescence paves the way for developing therapeutic strategies aimed at preserving immune health and counteracting age-related diseases toward improved health and life spans.

Author Contributions

PG, HCH, and GL performed the primary literature search and wrote part of the manuscript. PDA and NV wrote part of the manuscript. PDA and NV defined the topic and guided during the writing. All the authors agreed on the current version of the paper.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

NV laboratory is supported by Fondazione San Salvatore, Switzerland, Emma Muschamp, Switzerlan, and Leukemia and Lymphoma Society, USA.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- •• of outstanding interest

1. López-Otín C, *et al.*: **Hallmarks of aging: an expanding universe**. *Cell* 2023, **186**:243-278.

2. •• Desdín-Micó G, *et al.*: **T cells with dysfunctional mitochondria induce multimorbidity and premature senescence**. *Science* 2020, **368**:1371-1376.
This paper shows how deterioration in mitochondrial function in T cells have systemic effect and accelerate the senescene phenotype at systemic level.

3. Yousefzadeh MJ, *et al.*: **An aged immune system drives senescence and ageing of solid organs**. *Nature* 2021, **594**:100-105.

4. •• Minhas PS, *et al.*: **Macrophage de novo NAD(+) synthesis specifies immune function in aging and inflammation**. *Nat Immunol* 2019, **20**:50-63.
This study underlines the importance of the *de novo* NAD+ synthesis pathway in immune function. Importantly, decline in the NAD+ levels is associated with innate immune dysfucntion in aging.

5. Zhong W, *et al.*: **Defective mitophagy in aged macrophages promotes mitochondrial DNA cytosolic leakage to activate STING signaling during liver sterile inflammation**. *Aging Cell* 2022, **21**:e13622.

6. Stahl EC, *et al.*: **Macrophages in the aging liver and age-related liver disease**. *Front Immunol* 2018, **9**:2795.

7. Khalil H, *et al.*: **Aging is associated with hypermethylation of autophagy genes in macrophages**. *Epigenetics* 2016, **11**:381-388.

8. De Maeyer RPH, Chambers ES: **The impact of ageing on monocytes and macrophages**. *Immunol Lett* 2021, **230**:1-10.

9. Saare M, *et al.*: **Monocytes present age-related changes in phospholipid concentration and decreased energy metabolism**. *Aging Cell* 2020, **19**:e13127.

10. Pence BD, Yarbro JR: **Aging impairs mitochondrial respiratory capacity in classical monocytes**. *Exp Gerontol* 2018, **108**:112-117.

11. Linton PJ, Thoman ML: **Immunosenescence in monocytes, macrophages, and dendritic cells: lessons learned from the lung and heart**. *Immunol Lett* 2014, **162**:290-297.

12. Richer BC, *et al*.: **Changes in neutrophil metabolism upon activation and aging**. *Inflammation* 2018, **41**:710-721.

13. Immler R, Simon SI, Sperandio M: **Calcium signalling and related ion channels in neutrophil recruitment and function**. *Eur J Clin Invest* 2018, **48 Suppl 2**:e12964.

14. Li G, *et al*.: **Age-associated alterations in CD8α+ dendritic cells impair CD8 T-cell expansion in response to an intracellular bacterium**. *Aging Cell* 2012, **11**:968-977.

15. Chougnet CA, *et al*.: **Loss of phagocytic and antigen cross-presenting capacity in aging dendritic cells is associated with mitochondrial dysfunction**. *J Immunol* 2015, **195**:2624-2632.

16. Cannizzo ES, *et al*.: **Age-related oxidative stress compromises endosomal proteostasis**. *Cell Rep* 2012, **2**:136-149.

17. Gardner JK, *et al*.: **Modulation of dendritic cell and T cell cross-talk during aging: the potential role of checkpoint inhibitory molecules**. *Ageing Res Rev* 2017, **38**:40-51.

18. van Beek AA, *et al*.: **Aged mice display altered numbers and phenotype of basophils, and bone marrow-derived basophil activation, with a limited role for aging-associated microbiota**. *Immun Ageing* 2018, **15**:32.

19. Busse PJ, *et al*.: **Effect of ageing on pulmonary inflammation, airway hyperresponsiveness and T and B cell responses in antigen-sensitized and -challenged mice**. *Clin Exp Allergy* 2007, **37**:1392-1403.

20. Bektas A, *et al*.: **Age-associated changes in human CD4(+) T cells point to mitochondrial dysfunction consequent to impaired autophagy**. *Aging* 2019, **11**:9234-9263.

21. Nicoli F, *et al*.: **Altered basal lipid metabolism underlies the functional impairment of naive CD8(+) T cells in elderly humans**. *J Immunol* 2022, **208**:562-570.

22. Sanderson SL, Simon AK: **In aged primary T cells, mitochondrial stress contributes to telomere attrition measured by a novel imaging flow cytometry assay**. *Aging Cell* 2017, **16**:1234-1243.

23. Callender LA, *et al*.: **Mitochondrial mass governs the extent of human T cell senescence**. *Aging Cell* 2020, **19**:e13067.

24. Phadwal K, *et al*.: **A novel method for autophagy detection in primary cells: impaired levels of macroautophagy in immunosenescent T cells**. *Autophagy* 2012, **8**:677-689.

25. Vaena S, *et al*.: **Aging-dependent mitochondrial dysfunction mediated by ceramide signaling inhibits antitumor T cell response**. *Cell Rep* 2021, **35**:109076.

26. Alsaleh G, *et al*.: **Autophagy in T cells from aged donors is maintained by spermidine and correlates with function and vaccine responses**. *Elife* 2020, **9**:e57950.

27. •• Jin J, *et al*.: **FOXO1 deficiency impairs proteostasis in aged T cells**. *Sci Adv* 2020, **6**:eaba1808.
This paper demonstrated how FOXO1 promotes lysosome function and formation in T cells. During aging, sustained FOXO1 repression induces senescent-like defect in protein homeostasis altering T cells function.

28. Bharath LP, *et al*.: **Metformin enhances autophagy and normalizes mitochondrial function to alleviate aging-associated inflammation**. *Cell Metab* 2020, **32**:44-55 e6..

29. Lanna A, *et al*.: **A sestrin-dependent Erk–Jnk–p38 MAPK activation complex inhibits immunity during aging**. *Nat Immunol* 2017, **18**:354-363.

30. Lanna A, *et al*.: **The kinase p38 activated by the metabolic regulator AMPK and scaffold TAB1 drives the senescence of human T cells**. *Nat Immunol* 2014, **15**:965-972.

31. Ron-Harel N, *et al*.: **Defective respiration and one-carbon metabolism contribute to impaired naïve T cell activation in aged mice**. *Proc Natl Acad Sci USA* 2018, **115**:13347-13352.

32. Frasca D, *et al*.: **Metformin enhances B cell function and antibody responses of elderly individuals with type-2 diabetes mellitus**. *Front Aging* 2021, **2**:715981.

33. Frasca D, *et al*.: **Hyper-metabolic B cells in the spleens of old mice make antibodies with autoimmune specificities**. *Immun Ageing* 2021, **18**:9.

34. Kurupati RK, *et al*.: **Age-related changes in B cell metabolism**. *Aging* 2019, **11**:4367-4381.

35. Franceschi C, *et al*.: **Inflammaging: a new immune–metabolic viewpoint for age-related diseases**. *Nat Rev Endocrinol* 2018, **14**:576-590.

36. Fulop T, *et al*.: **The integration of inflammaging in age-related diseases**. *Semin Immunol* 2018, **40**:17-35.

37. Wiley CD, Campisi J: **The metabolic roots of senescence: mechanisms and opportunities for intervention**. *Nat Metab* 2021, **3**:1290-1301.

38. •• Wiley CD, *et al*.: **Mitochondrial dysfunction induces senescence with a distinct secretory phenotype**. *Cell Metab* 2016, **23**:303-314.
This paper shows that mitochondrial dysfunction triggers an specific senescence phenotype, known as MiDAS, characterized by a modified SASP and altered NAD/NADH ratios.

39. Camacho-Pereira J, *et al*.: **CD38 dictates age-related NAD decline and mitochondrial dysfunction through an SIRT3-dependent mechanism**. *Cell Metab* 2016, **23**:1127-1139.

40. •• Covarrubias AJ, *et al*.: **Senescent cells promote tissue NAD(+) decline during ageing via the activation of CD38(+) macrophages**. *Nat Metab* 2020, **2**:1265-1283.
This paper highlights the importance of CD38 upregulation in immune cells as key contributor to NAD decline and subsequent acquisition of senescent properties across several tissues.

41. Liu L, *et al*.: **Quantitative analysis of NAD synthesis-breakdown fluxes**. *Cell Metab* 2018, **27**:1067-1080 e5.

42. Mouchiroud L, *et al*.: **The NAD(+)/sirtuin pathway modulates longevity through activation of mitochondrial UPR and FOXO signaling**. *Cell* 2013, **154**:430-441.

43. Quijano C, *et al*.: **Oncogene-induced senescence results in marked metabolic and bioenergetic alterations**. *Cell Cycle* 2012, **11**:1383-1392.

44. Fafián-Labora J, *et al*.: **FASN activity is important for the initial stages of the induction of senescence**. *Cell Death Dis* 2019, **10**:318.

45. •• Wiley CD, *et al*.: **Oxylipin biosynthesis reinforces cellular senescence and allows detection of senolysis**. *Cell Metab* 2021, **33**:1124-1136 e5.
This paper elucidates a novel mechanism by which senescent cells can maintain an active secretory phenotype while being in cell cycle arrest. Here, the authors show that senescent cells rewire their metabolism to activate the biosynthesis of oxylipins and activate RAS signaling.

46. Wiley CW, *et al*.: **Secretion of leukotrienes by senescent lung fibroblasts promotes pulmonary fibrosis**. *JCI Insight* 2019, **4**:e130056.

47. Kang C, Elledge SJ: **How autophagy both activates and inhibits cellular senescence**. *Autophagy* 2016, **12**:898-899.

48. Aird KM, *et al*.: **Suppression of nucleotide metabolism underlies the establishment and maintenance of oncogene-induced senescence**. *Cell Rep* 2013, **3**:1252-1265.

49. Ferrucci L, Fabbri E: **Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty**. *Nat Rev Cardiol* 2018, **15**:505-522.

50. Campisi J, *et al*.: **From discoveries in ageing research to therapeutics for healthy ageing**. *Nature* 2019, **571**:183-192.

51. Zhu Y, *et al*.: **The Achilles' heel of senescent cells: from transcriptome to senolytic drugs**. *Aging Cell* 2015, **14**:644-658.

52. Justice JN, *et al*.: **Senolytics in idiopathic pulmonary fibrosis: results from a first-in-human, open-label, pilot study**. *EBioMedicine* 2019, **40**:554-563.

53. •• Chaib S, Tchkonia T, Kirkland JL: **Cellular senescence and senolytics: the path to the clinic**. *Nat Med* 2022, **28**:1556-1568.
The authors discuss cellular senescence as a fundamental aging process contributing to many disorders and age-related diseases. The discovery of senolytic drugs that selectively eliminate senescent cells offers promising therapeutic strategies for treating various age-related conditions. The review outlines the rationale for targeting senescent cells and discusses the most promising clinical trials for translating these interventions into clinical practice.

54. Xu M, *et al*.: **JAK inhibition alleviates the cellular senescence-associated secretory phenotype and frailty in old age**. *Proc Natl Acad Sci USA* 2015, **112**:E6301-E6310.

55. Tilstra JS, *et al*.: **NF-kappaB inhibition delays DNA damage-induced senescence and aging in mice**. *J Clin Invest* 2012, **122**:2601-2612.

56. Lamming DW, *et al*.: **Rapalogs and mTOR inhibitors as anti-aging therapeutics**. *J Clin Invest* 2013, **123**:980-989.

57. Moiseeva O, *et al*.: **Metformin inhibits the senescence-associated secretory phenotype by interfering with IKK/NF-kappaB activation**. *Aging Cell* 2013, **12**:489-498.

58. Mannick JB, *et al*.: **TORC1 inhibition enhances immune function and reduces infections in the elderly**. *Sci Transl Med* 2018, **10**:eaaq1564.

59. Martens CR, *et al*.: **Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD(+) in healthy middle-aged and older adults**. *Nat Commun* 2018, **9**:1286.

60. Lee DC, *et al*.: **Running as a key lifestyle medicine for longevity**. *Prog Cardiovasc Dis* 2017, **60**:45-55.

61. Chen J, *et al*.: **Molecular mechanisms of exercise contributing to tissue regeneration**. *Signal Transduct Target Ther* 2022, **7**:383.

62. Willett W, *et al*.: **Food in the Anthropocene: the EAT-Lancet Commission on healthy diets from sustainable food systems**. *Lancet* 2019, **393**:447-492.

63. Adler A, Saksena R: **Live to eat and eat to live longer**. *Nat Food* 2023, **4**:1029-1030.

64. Longo VD, Mattson MP: **Fasting: molecular mechanisms and clinical applications**. *Cell Metab* 2014, **19**:181-192.

65. •• Brandhorst S, *et al*.: **A periodic diet that mimics fasting promotes multi-system regeneration, enhanced cognitive performance, and healthspan**. *Cell Metab* 2015, **22**:86-99.
The authors review the adaptive cellular responses to fasting, highlighting its benefits in reducing oxidative damage and inflammation, optimizing energy metabolism, and enhancing cellular protection. Human studies show fasting aids in reducing obesity, hypertension, asthma, and rheumatoid arthritis, indicating its potential to delay aging and mitigate various diseases while avoiding the side effects of chronic dietary interventions.

66. Hatori M, *et al*.: **Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet**. *Cell Metab* 2012, **15**:848-860.

67. Franceschi C, Bonafe M: **Centenarians as a model for healthy aging**. *Biochem Soc Trans* 2003, **31**:457-461.

68. Kim JI: **Social factors associated with centenarian rate (CR) in 32 OECD countries**. *BMC Int Health Hum Rights* 2013, **13**:16.

69. Anaya JM, *et al*.: **Autoimmunity in centenarians. A paradox**. *J Transl Autoimmun* 2024, **8**:100237.

70. Bagnara GP, *et al*.: **Hemopoiesis in healthy old people and centenarians: well-maintained responsiveness of CD34+ cells to hemopoietic growth factors and remodeling of cytokine network**. *J Gerontol A Biol Sci Med Sci* 2000, **55**:B61-B66 discussion B67-70.

71. Karagiannis TT, *et al*.: **Multi-modal profiling of peripheral blood cells across the human lifespan reveals distinct immune cell signatures of aging and longevity**. *EBioMedicine* 2023, **90**:104514.

72. •• Garagnani P, *et al*.: **Whole-genome sequencing analysis of semi-supercentenarians**. *Elife* 2021, **10**:e57849.
In this study, the authors explore the immune profiles of centenarians to uncover patterns associated with aging and exceptional longevity. Using single-cell RNA sequencing and flow cytometry, they discovered unique shifts in immune cell populations. These findings suggest that centenarians possess highly adaptive immune systems, potentially contributing to their extended lifespans and delayed onset of age-related diseases.

73. Ahuja SK, *et al*.: **Immune resilience despite inflammatory stress promotes longevity and favorable health outcomes including resistance to infection**. *Nat Commun* 2023, **14**:3286.