Review

*Discovery Medicine* 2024; 36(188): 1772–1779
https://doi.org/10.24976/Discov.Med.202436188.163

# Inflammaging, Epigenetic Damage, Mitochondrial Dysfunctions, and Macrophage Alterations are the Main Missing Pieces in the Complex Mosaic of Stem Cell Physiology

Marco Tatullo[1,*], Sandro Rengo[2], Gilberto Sammartino[2], Michele Simeone[2], Alessandra Valletta[2,†], Roberta Gasparro[2,†]

[1]Department of Translational Biomedicine and Neuroscience - DiBraiN, University of Bari "Aldo Moro", 70124 Bari, Italy
[2]Department of Neuroscience, Reproductive and Odontostomatological Sciences, University of Naples "Federico II", 80131 Naples, Italy
*Correspondence: marco.tatullo@uniba.it (Marco Tatullo)
[†]These authors contributed equally.
Published: 20 September 2024

**Aging is frequently associated with a progressive increase in chronic low-grade inflammation, known as "inflammaging". Numerous studies have shown that inflammaging is closely linked to the development of several age-related diseases. However, the underlying mechanism and its causal role are still not fully understood despite this association. In the complex context of aging, mesenchymal stem cells (MSCs) undergo changes in behavior and functionality. This narrative topical review examines the recent advances in aging research, specifically focusing on the role of inflammaging and related mechanisms that contribute to age-related chronic diseases. The authors critically investigated whether and how inflammaging, epigenetic damage, mitochondrial changes, and macrophage alterations may influence stem cell behavior, highlighting the interplay between these factors and their potential therapeutic implications. By elucidating the mechanisms underlying these processes, we can gain valuable insights into the maintenance and regeneration of stem cell populations, providing the basis for novel therapeutic strategies targeting age-related decline and disease progression.**

**Keywords:** aging; inflammaging; mesenchymal stem cells; epigenetic damage; mitochondrial dynamics; macrophage alterations

## Introduction

Aging is a complex biological process characterized by a gradual decline in various physiological functions and pathways, leading to increased susceptibility to age-related diseases and, ultimately, death [1]. This decline affects the functionality of numerous organs and systems, significantly increasing the risk of developing age-related diseases [2], such as neurodegenerative diseases, cardiovascular diseases, infectious diseases, diabetes mellitus (DM), autoimmune diseases, and cancer [3]. As we age, cellular and molecular changes occur: in fact, cells become less efficient in repairing damage and renewing themselves, while the immune and endocrine systems show reduced efficiency. This progressive deterioration leads to a general weakening of the body's defenses, increasing its vulnerability to several pathologies [2].

The aging process is a meticulously orchestrated symphony of multiple factors, including genetic instability, epigenetic changes, metabolic dysfunction, telomere attrition, mitochondrial alterations, impaired intracellular communication, and chronic inflammation [4]. Interestingly, the gut microbiota, a vast community of trillions of microorganisms residing in the human intestine, has been demonstrated to significantly contribute to the aging process. Metabolites produced by gut bacteria during food digestion and fermentation, including short-chain fatty acids (SCFAs), hormones, neurotransmitters, phenols, ammonia, and endotoxins, can enter the bloodstream and indirectly impact various cell types, including mesenchymal stem cells (MSCs). This complex interplay suggests that the gut microbiota may influence the conditions leading to cellular senescence and aging [5].

A notable *hallmark* of aging is undoubtedly the phenomenon termed "inflammaging", which involves a state of persistent immune system activation. This condition is characterized by elevated levels of inflammatory markers and activated immune cells circulating in the bloodstream. Therefore, understanding the molecular and cellular mechanisms driving the onset of inflammaging may be critical to counteract its overall detrimental effects on cells and organ function. In this scenario, a comprehensive understanding of aging is strategic for the development of effective preventative and therapeutic approaches to improve the health

Copyright: © 2024 The Author(s). Published by Discovery Medicine. This is an open access article under the CC BY 4.0 license.
Note: *Discovery Medicine* stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

and quality of life of the elderly population. Therefore, unraveling the complex interplay of factors contributing to age-related diseases is critical to achieving this goal.

The intricate relationship between aging and stem cell physiology, particularly the impact of inflammaging, epigenetic modifications, mitochondrial dysfunction, and macrophage alterations, has garnered significant attention in recent research. This review delves into the multifaceted nature of aging, exploring the interplay between these factors and their implications for stem cell behavior and therapeutic interventions. By better understanding the mechanisms underlying these processes, we can gain valuable insights into the maintenance and regeneration of stem cell populations, paving the way for novel therapeutic strategies targeting age-related decline and disease progression.

## Role of Aging in Stem Cell Physiology

Stem cells play a vital role in tissue regeneration and repair; attracting growing interest in the research community working on aging. Stem cell impairment may depend on several co-factors: aging is certainly one of the most impacting conditions, able to profoundly influence strategic physiological processes, such as tissue healing. This aging-related decline in regenerative capacity increases the susceptibility of individuals to various diseases, also reducing the overall regenerative and reparative capabilities [1]. Understanding how aging impacts stem cell physiology can pave the way for therapeutic strategies aimed at improving or restoring stem cell function, mainly in elder individuals.

A particularly dynamic area of research focuses on how aging impacts the proliferation, differentiation, and functionality of MSCs [6]; in the last decades, MSCs have been largely investigated and used as therapeutic support in several clinical applications [7], such as rheumatoid arthritis [8], DM [9], bone repair [10], vascular diseases [11], muscle repair [12], neurodegenerative diseases [13], and many others.

Accumulating evidence suggests that MSCs actively participate in a complex network of intracellular signaling pathways, essential for maintaining tissue homeostasis. Conversely, a decrease in either the number or function of MSCs is linked to several inflammatory and degenerative diseases, including DM, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) [14]. This qualitative and quantitative age-related decline in stem cell function, known as “stem cell exhaustion”, is considered a key factor in the aging process [15]. During aging, MSCs undergo morphological changes, reduced proliferative and differentiation potential, and encounter qualitative/quantitative changes in their composition [5]. For example, aged MSCs exhibit a progressive shift towards senescent cell behavior, showing a preference for adipogenic differentiation while their osteogenic capacity decreases [16]: this process is well-recognized, as an example, in the aetiopathogenesis of osteoporosis [14]. Recent studies have highlighted a close link between chronic inflammation and MSC impairment, contributing significantly to the onset of various age-related diseases. The underlying molecular mechanism involves the secretion of inflammatory molecules (cytokines) by MSCs, which in turn activate immune cells. This chain reaction leads to tissue damage, metabolic dysfunction, and compromised cell function [5].

Despite these challenges, aged MSCs still hold promise for therapeutic applications, particularly when their secretome and extracellular vesicles (EVs) are considered. Recently, a growing number of researchers have proposed MSCs as a target or pivotal factor in tissue repair and regeneration. The MSC secretome and related MSC-EVs play a key role in the biological modulation of inflammation, resulting in extremely important in neuroinflammation [17], autoimmune diseases [18], and bone repair [19], among others.

In addition, numerous studies have investigated the release of EVs by senescent cells, revealing that senescent EVs have a distinct biochemical composition, and can deliver signals to neighboring cells [20]. Among these investigations, the EVs released by gingival-derived mesenchymal stem cells (GMSCs) have attracted attention. In aged mice, GMSC-EVs appear to counteract some aging-related processes by reducing oxidative stress and lowering levels of aging markers, such as p21, mammalian target of rapamycin (mTOR), interleukin 6 (IL-6), and tumor necrosis factor $\alpha$ (TNF-$\alpha$) [21]. Furthermore, MSC-derived exosomes hold great promise for cell-free therapies due to their ability to mitigate the risk of transplant rejection. These exosomes actively promote an anti-inflammatory phenotype in regulatory macrophages by down-regulating the expression of the pro-inflammatory cytokines IL-22 and IL-23 [22], making them excellent candidates for safe and effective treatments.

Therefore, studying the underlying stem cell aging is crucial to gaining a deeper understanding of the pathophysiological processes related to aging and to developing new regenerative therapies aimed at preserving or restoring stem cell functions in the elderly. This approach holds great promise for promoting healthy aging and mitigating age-related tissue degeneration [23,24]. By elucidating the pathways and factors that contribute to MSC aging, researchers can identify targeted interventions to enhance MSC functionality, opening new avenues for regenerative medicine and the treatment of age-related diseases.

## Inflammaging: an Impaired Environment Creating Dysfunction and Pathogenesis

Inflammaging, a chronic low-grade inflammatory state, was first described by Franceschi *et al.* [25] in 2000; it is considered a key aspect of the aging process, as this phenomenon is driven by multiple factors, including mito-

chondrial dysfunction, genetic factors, persistent infections, obesity, chronic dysbiosis [26], and it is typically sustained by an imbalanced immune system. Interestingly, the immune system has a pivotal role in driving inflammaging, as it increases this process by releasing pro-inflammatory factors. Pro-inflammatory cytokines are well-known to be involved in the transition from acute to chronic inflammation, and the early onset of inflammaging [27]. Recently, animal studies have demonstrated the involvement of various cytokines, such as IL-1$\beta$, IL-4, IL-10, IL-17, Interferon-$\gamma$ (IFN-$\gamma$), nuclear factor $\kappa$B (NF-$\kappa$B), and TNF-$\alpha$ in the progression of chronic inflammation progression [28]. This aligns with the observation of elevated levels of inflammatory cytokines (e.g., IL-1, IL-6, IL-18, and TNF-$\alpha$), and markers (e.g., C-reactive protein—CRP), in the bloodstream of elderly individuals, compared to younger subjects [29].

Based on these preliminary findings, inflammaging seems to be a major contributor to various age-related diseases [30,31]. At the cellular level, the inflammatory condition is closely linked to an impairment of MSCs influencing their ability to differentiate into different cell types and regenerate tissues [2].

Despite extensive research efforts, the exact molecular mechanisms driving inflammaging and the related MSCs impairment, remain unclear. Nonetheless, various lifestyle and pharmacological intervention strategies have been proposed over time to counteract this age-related inflammatory state [32]. Mainly, those lifestyles improving the dietary intake of calories have shown promising effects in facing inflammaging-related conditions. Moreover, the strategies aimed at reducing calories [33,34] by intermittent fasting, or a healthier adherence to the Mediterranean diet [35], supplemented with specific nutrients (zinc, omega-3 polyunsaturated fatty acids, vitamins C, D, and E) have obtained interesting results in this field [36–38].

## Inflammaging and Mitochondria Alterations

Mitochondria are known to act as maestros orchestrating numerous biological processes, including ionic homeostasis, redox balance, cell growth, and intercellular signaling [39]. The biological pathways linking low-grade inflammation and aging seem to be directly correlated to specific mitochondria alterations [40], although the specific mechanisms are still poorly understood. In addition, mitochondria serve as a reservoir for damage-associated molecular patterns (DAMPs), that can amplify the inflammatory response [41]. In this context, a growing body of research, suggests that the mitochondrial genome may also play a key role in the aging process [42]. Specifically, dysfunctions and alterations in the mitochondrial genome can lead to a decrease in adenosine triphosphate (ATP) synthesis and an increase in the generation of reactive oxygen species (ROS), both variously associated with age-related diseases [43]. Furthermore, the critical role of mitochondria in the complex interplay between infection and inflammation has attracted interest in their potential role as targets for therapeutic intervention. Undoubtedly, the key mitochondrial mechanisms, such as mitophagy, ROS production, and inflammasome activation [44] are deeply investigated to understand how mitochondria may impact inflammaging. In particular, the Nod-Like Receptor Protein 3 (NLRP3) inflammasome, a multi-protein complex involved in the innate immune response, has gained significant attention in the context of aging and age-related diseases [45]. Over time, the dysregulation of the NLRP3 inflammasome has been associated with various diseases, including metabolic syndrome [46], atherosclerosis, type II diabetes, and Alzheimer's disease [47].

Recently, the mitochondrial calcium uniporter complex (MCUC) has been investigated as a strategic molecular pathway able to merge tissue aging and systemic macrophage-mediated age-associated inflammation; this intriguing finding may lead to speculate about novel treatments for inflammaging, based on the restoration of mitochondrial calcium (mCa2+) uptake capacity in macrophages [48].

From the clinical point of view, taking diabetes as an example, previous studies [49,50] have demonstrated that high-glucose levels can progressively reduce the survival rate of MSCs, down-regulating the mitochondrial complexes I, IV, and V in high glucose conditions [51]. Thus, mechanistically, preserving the mitochondrial complexes from alterations may help the overall MSCs survival rate in patients with hyperglycaemia (HG) [52].

In the last decades, various strategies have been explored to optimize the mitochondrial functions occurring in inflammaging-related conditions. These strategies basically focus on three key aspects: (i) increasing mitochondrial abundance, (ii) enhancing mitochondrial morphology and environment, and (iii) boosting the basal mitochondrial activity [53]. In this context, the use of mitochondria-targeted antioxidants to counteract oxidative damage and interventions that promote mitochondrial biogenesis and mitophagy (the selective removal of dysfunctional mitochondria) are considered promising. Nonetheless, the modulation of NLRP3 inflammasome activity has shown a discrete potential in mitigating chronic inflammation, consequently enhancing the therapeutic outcomes in several inflammatory age-related diseases.

Similar considerations can be also extended to MSCs: in fact, maintaining a balanced mitochondrial behavior may be helpful in reducing cellular senescence, thus improving the MSC longevity and performance in the field of regenerative medicine [54–58].

## Crosstalk among Stem Cell Functions and Macrophage Alterations

During inflammaging, macrophages can turn against the body, releasing inflammatory cytokines and ROS, which can damage tissues and amplify the inflammatory response. Scientists are even more interested in understanding the intricate interaction between macrophages and MSCs [59]. These two cell types communicate in a two-way feedback loop, influencing each other's behavior and functions. MSCs act like maestros, regulating how macrophages perform their tasks: polarization, phagocytosis, and metabolism. In turn, macrophages can influence MSCs behavior, affecting their differentiation, migration, apoptosis, and immunomodulatory functions. This bidirectional interplay is crucial for various physiological and pathological processes, from tissue repair and inflammation control to even cancer prevention [60]. Although the field is still young, research on MSCs-macrophages interaction is extremely promising in the treatment of various diseases. For example, MSCs can be used to treat liver diseases (such as acute liver injury and liver fibrosis) by inhibiting proinflammatory macrophages (M1) and stimulating anti-inflammatory macrophages (M2), thereby promoting the resolution of inflammation [61]. Similarly, a study suggests their potential in the treatment of diabetes by modulating macrophage polarization and promoting an anti-inflammatory M2 phenotype, thereby improving insulin sensitivity [62]. Based on these considerations, by exploring the complexities of this cellular communication network (MSCs-macrophages) researchers can develop innovative regenerative and immunomodulatory therapies.

## Epigenetic Damage Impact on Limited Stem Cells Functionality

The aging of stem cells is likely controlled by a multifactorial network in which epigenetics plays a pivotal role. In the field of modern aging research, there is an increasing focus on the development of epigenetic "aging clocks", which involve the comprehensive mapping of DNA changes across various human tissues [63]. Over time, several epigenetic clocks have been developed, such as the "PhenoAge" of Levine [64], showing a strong correlation with gene expression related to damage and repair mechanisms [65]. An acceleration of "PhenoAge" has been shown to be linked to chronic inflammation, reduced response to DNA damage, and even mitochondrial dysfunction [64].

In this scenario, epigenetic studies reveal a complex interplay orchestrated by an ensemble of enzymes [66]. Key enzymes, such as DNA methyltransferases, histone acetylases and deacetylases, methylases, and demethylases, work synergistically to establish and maintain the epigenetic patterns that regulate gene expression. Protein complexes are also crucial for chromatin remodeling and the synthesis and maturation of non-coding RNA (nc-RNA) [2]. Furthermore, changes in gene expression and epigenetic modifications contribute to the aging of MSCs [67,68]. Therefore, understanding and potentially preserving the epigenetic state of MSCs is essential for maintaining their regenerative potential throughout life.

In the therapeutic context, where the use of certain MSCs lineages, such as adipose-derived mesenchymal stem cells (Ad-MSCs), faces numerous challenges, recent studies have shed light on the epigenetic mechanisms linking, for instance, DM with hypermethylation of Ad-MSCs triggered by specific hypermethylated gene promoters [67]. Furthermore, remaining in the context of diabetes, Alicka *et al*. [69] have elucidated the detrimental effects of type II diabetes on Ad-MSCs, revealing impaired functions such as proliferation, viability, mitochondrial dynamics, antioxidant defenses, and secretory capacity, thus reducing their therapeutic efficacy. Specifically, the authors identified significant alterations in the expression of miRNAs that regulate cell proliferation (miR-16-5p, miR-146a-5p, and miR-145-5p), as well as key miRNAs and genes involved in glucose homeostasis and insulin sensitivity (miR-24-3p, 140-3p, miR-17-5p, SIRT1, HIF-1$\alpha$, LIN28, FOXO1, and TGF$\beta$) [69].

These findings highlight the urgent need for strategies aimed at modulating epigenetic modulations and enhancing the functionality of MSCs, opening new perspectives for the development of effective therapeutic approaches to aging and age-related diseases.

## Discussion

Within the field of aging research, the concept of "inflammaging" has emerged as a pivotal area of exploration [70]. While the topic of aging has captured growing interest, it undoubtedly presents numerous complex challenges. Unraveling the complex control mechanisms governing aging is a main challenge: in fact, researchers are investigating a novel strategy aiming at targeting specific molecules that have a pivotal role in orchestrating the homeostasis of aging-related processes. This strategy highlights the importance of effective preventive strategies and treatments, given the expanding global geriatric population [71]. Collectively, these conditions represent both a challenge and an opportunity to face a unique therapeutic strategy for some severe human diseases. In this review, the authors explore an intriguing perspective: inflammaging, epigenetic damage, mitochondrial dysfunction, and macrophage deficit contribute, like discordant notes, to the progressive alteration of the perfect symphony played by human cells, anticipating the further decline of the overall regenerative/reparative capabilities of the human body. The close interactions among inflammation, aging, mitochondria, and macrophages, represent a complex mosaic that slightly the

multi-level feedback between immunology, inflammaging, and stem cell physiology: understanding these challenging pathways means a step forward towards highly personalized medicine [72], performing customized treatments, based on patients' characteristics and clinical needs. In our review, we have also described several concepts of basic medicine that shed light on a number of potential clinical issues. Specifically, one of the most useful applications of understanding aging mechanisms is the early identification of biomarkers associated with inflammaging and stem cell dysfunction. By pinpointing these biomarkers, healthcare providers could diagnose age-related diseases at an earlier stage, potentially delaying or preventing their onset and allowing for interventions before significant disease progression occurs [73].

Targeted therapies represent another promising avenue, focusing on the development of treatments that directly address the specific mechanisms involved in aging processes. For instance, targeting inflammaging could aid in developing therapies that mitigate inflammatory responses at the cellular and multi-organ levels. Similarly, addressing mitochondrial dysfunction can lead to the most effective energy production and reduced oxidative stress; these effects might inspire therapies aimed at enhancing mitochondrial efficiency or reducing oxidative damage, both severe issues in several clinical diseases. Moreover, understanding and manipulating the onset of epigenetic changes, which involve modifications in gene expression without altering the DNA sequence, could provide insights into reversing or slowing aging processes. Finally, alterations in macrophage function, which play a crucial role in immune response, could also be targeted to maintain immune system efficiency over time [74].

An important factor in aging-related diseases is related to the reduced stem cell function. As stem cells are pivotal for tissue repair and regeneration, improving their function could reroute the current approach to organ repair in the elderly. From the clinical point of view, this could lead to breakthroughs in treating conditions like degenerative joint diseases, cardiovascular diseases, and neurodegenerative disorders, significantly enhancing quality of life and lifespan [11].

Finally, the overarching goal of these interventions is to promote healthy aging, ultimately improving the quality of life for the elderly population. By addressing and potentially reversing the underlying mechanisms of aging, these strategies could lead to increased health span and reduced incidence of age-related diseases, allowing older adults to enjoy more active lives well into their later years.

## Conclusions

In our review, we have comprehensively investigated the intricate relationship between aging and the most impacting co-factors, such as inflammation, organelles dysfunction and stem cell behavior. Overall, we can summarize the core points into 3 major factors able to influence the aging process:

- Factors related to inflammation: in this field, ma main role is played by the inflammaging, the chronic, low-grade inflammation, closely linked to the decline of stem cell function and the development of age-related diseases.

- Factors related to functional alterations: here, we can list all such functional impairments involving mitochondria and macrophages, contributing to the increase of oxidative stress and releasing inflammatory signals.

- Factors related to stem cell behavior: the combined effects of inflammaging, mitochondrial dysfunction, and immunological alterations, leading to a decline in stem cell function, and contributing to age-related degenerations and diseases. Alterations in the epigenome, and some chemical modifications of specific genes, seem to have also impact on stem cell behavior and contribute to aging.

The relentless progression of aging is thus driven by a chronic low-grade inflammation, known as "inflammaging"; nonetheless, several other important co-factors may influence the quality and severity of the aging process as well. Recent research has widely and undoubtedly confirmed the crucial role of epigenetic changes, mitochondrial dysfunction, and macrophage alteration: these factors, like discordant notes in a once-perfect symphony, gradually diminish the body's ability to regenerate and repair itself. Understanding the complex interplay between inflammaging, epigenetics, mitochondria, and macrophages harbors significant promise. Deciphering these complex pathways sets the stage for highly personalized medical approaches, enabling tailored treatments in line with the patient's individual characteristics and clinical requirements.

Future research efforts should prioritize identifying the key drivers of chronic inflammation; in fact, a deeper understanding of the molecular mechanisms underlying inflammaging could lead to the identification of novel strategic therapeutic targets. Once key targets are identified, the development of targeted interventions, such as specific drugs or modifications of lifestyle, could help to mitigate the effects of inflammaging and may improve the overall stem cell activity. In this landscape, investigating the individual variations in inflammaging and stem cell aging could pave the way for personalized medicine approaches, tailoring treatments to the specific needs of each patient.

Of course, future efforts should include the design of longitudinal clinical studies able to track changes in aging development over time, providing valuable insights into the possibility of promoting early intervention on specific risk factors.

## Availability of Data and Materials

Not applicable.

## Author Contributions

MT, SR, GS, MS, AV, and RG collected and analyzed the literature. MT, SR and GS provided help and advice on the structure and content of the paper. All authors were involved in the drafting and critical revision of the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.

## Acknowledgment

Not applicable.

## Funding

This research received no external funding.

## Conflict of Interest

The authors declare no conflict of interest.

## References

[1] Tatullo M. Entropy Meets Physiology: Should We Translate Aging as Disorder? Stem Cells. 2024; 42: 91–97.

[2] López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: An expanding universe. Cell. 2023; 186: 243–278.

[3] Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nature Reviews Endocrinology. 2018; 14: 576–590.

[4] Moustakli E, Zikopoulos A, Sakaloglou P, Bouba I, Sofikitis N, Georgiou I. Functional association between telomeres, oxidation and mitochondria. Frontiers in Reproductive Health. 2023; 5: 1107215.

[5] Lyamina S, Baranovskii D, Kozhevnikova E, Ivanova T, Kalish S, Sadekov T, *et al*. Mesenchymal Stromal Cells as a Driver of Inflammaging. International Journal of Molecular Sciences. 2023; 24: 6372.

[6] Tatullo M. Editorial: Coordinated regulation of the balance between stem cell self-renewal and differentiation. Frontiers in Cell and Developmental Biology. 2024; 12: 1391626.

[7] Qin L, Liu N, Bao CLM, Yang DZ, Ma GX, Yi WH, *et al*. Mesenchymal stem cells in fibrotic diseases-the two sides of the same coin. Acta Pharmacologica Sinica. 2023; 44: 268–287.

[8] Lopez-Santalla M, Fernandez-Perez R, Garin MI. Mesenchymal Stem/Stromal Cells for Rheumatoid Arthritis Treatment: An Update on Clinical Applications. Cells. 2020; 9: 1852.

[9] Cho J, D'Antuono M, Glicksman M, Wang J, Jonklaas J. A review of clinical trials: mesenchymal stem cell transplant therapy in type 1 and type 2 diabetes mellitus. American Journal of Stem Cells. 2018; 7: 82–93.

[10] Tatullo M, Piattelli A, Zavan B. Regenerative Medicine: Role of Stem Cells and Innovative Biomaterials 2.0. International Journal of Molecular Sciences. 2022; 23: 4199.

[11] Gardin C, Bosco G, Ferroni L, Quartesan S, Rizzato A, Tatullo M, *et al*. Hyperbaric Oxygen Therapy Improves the Osteogenic and Vasculogenic Properties of Mesenchymal Stem Cells in the Presence of Inflammation In Vitro. International Journal of Molecular Sciences. 2020; 21: 1452.

[12] Perniconi B, Coletti D, Aulino P, Costa A, Aprile P, Santacroce L, *et al*. Muscle acellular scaffold as a biomaterial: effects on C2C12 cell differentiation and interaction with the murine host environment. Frontiers in Physiology. 2014; 5: 354.

[13] Staff NP, Jones DT, Singer W. Mesenchymal Stromal Cell Therapies for Neurodegenerative Diseases. Mayo Clinic Proceedings. 2019; 94: 892–905.

[14] Fraile M, Eiro N, Costa LA, Martín A, Vizoso FJ. Aging and Mesenchymal Stem Cells: Basic Concepts, Challenges and Strategies. Biology. 2022; 11: 1678.

[15] Maldonado E, Morales-Pison S, Urbina F, Solari A. Aging Hallmarks and the Role of Oxidative Stress. Antioxidants. 2023; 12: 651.

[16] Infante A, Rodríguez CI. Osteogenesis and aging: lessons from mesenchymal stem cells. Stem Cell Research & Therapy. 2018; 9: 244.

[17] Zupan J, Strazar K, Kocijan R, Nau T, Grillari J, Marolt Presen D. Age-related alterations and senescence of mesenchymal stromal cells: Implications for regenerative treatments of bones and joints. Mechanisms of Ageing and Development. 2021; 198: 111539.

[18] Dabrowska S, Andrzejewska A, Strzemecki D, Muraca M, Janowski M, Lukomska B. Human bone marrow mesenchymal stem cell-derived extracellular vesicles attenuate neuroinflammation evoked by focal brain injury in rats. Journal of Neuroinflammation. 2019; 16: 216.

[19] Sharma J, Hampton JM, Valiente GR, Wada T, Steigelman H, Young MC, *et al*. Therapeutic Development of Mesenchymal Stem Cells or Their Extracellular Vesicles to Inhibit Autoimmune-Mediated Inflammatory Processes in Systemic Lupus Erythematosus. Frontiers in Immunology. 2017; 8: 526.

[20] Manni G, Buratta S, Pallotta MT, Chiasserini D, Di Michele A, Emiliani C, *et al*. Extracellular Vesicles in Aging: An Emerging Hallmark? Cells. 2023; 12: 527.

[21] Shi HZ, Zeng JC, Shi SH, Giannakopoulos H, Zhang QZ, Le AD. Extracellular Vesicles of GMSCs Alleviate Aging-Related Cell Senescence. Journal of Dental Research. 2021; 100: 283–292.

[22] Duong L, Radley HG, Lee B, Dye DE, Pixley FJ, Grounds MD, *et al*. Macrophage function in the elderly and impact on injury repair and cancer. Immunity & Ageing. 2021; 18: 4.

[23] Brunet A, Goodell MA, Rando TA. Ageing and rejuvenation of tissue stem cells and their niches. Nature Reviews Molecular Cell Biology. 2023; 24: 45–62.

[24] Kapadia CD, Goodell MA. Tissue mosaicism following stem cell aging: blood as an exemplar. Nature Aging. 2024; 4: 295–308.

[25] 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.

[26] Routy B, Gopalakrishnan V, Daillère R, Zitvogel L, Wargo JA, Kroemer G. The gut microbiota influences anticancer immunosurveillance and general health. Nature Reviews Clinical Oncology. 2018; 15: 382–396.

[27] Rea IM, Gibson DS, McGilligan V, McNerlan SE, Alexander HD, Ross OA. Age and Age-Related Diseases: Role of Inflammation Triggers and Cytokines. Frontiers in Immunology. 2018; 9: 586.

[28] Dabravolski SA, Nikiforov NG, Zhuravlev AD, Orekhov NA, Grechko AV, Orekhov AN. Role of the mtDNA Mutations and

Mitophagy in Inflammaging. International Journal of Molecular Sciences. 2022; 23: 1323.

[29] Sebastian-Valverde M, Pasinetti GM. The NLRP3 Inflammasome as a Critical Actor in the Inflammaging Process. Cells. 2020; 9: 1552.

[30] Dugan B, Conway J, Duggal NA. Inflammaging as a target for healthy ageing. Age and Ageing. 2023; 52: afac328.

[31] Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nature Reviews Cardiology. 2018; 15: 505–522.

[32] Flynn MG, Markofski MM, Carrillo AE. Elevated Inflammatory Status and Increased Risk of Chronic Disease in Chronological Aging: Inflamm-aging or *Inflamm-inactivity*? Aging and Disease. 2019; 10: 147–156.

[33] Ma S, Sun S, Geng L, Song M, Wang W, Ye Y, *et al*. Caloric Restriction Reprograms the Single-Cell Transcriptional Landscape of Rattus Norvegicus Aging. Cell. 2020; 180: 984–1001.e22.

[34] Zhou RH, Wang Q, Hu XM, Liu M, Zhang AR. The influence of fasting and caloric restriction on inflammation levels in humans: A protocol for systematic review and meta analysis. Medicine. 2021; 100: e25509.

[35] Nani A, Murtaza B, Sayed Khan A, Khan NA, Hichami A. Antioxidant and Anti-Inflammatory Potential of Polyphenols Contained in Mediterranean Diet in Obesity: Molecular Mechanisms. Molecules. 2021; 26: 985.

[36] Nunes CDR, Barreto Arantes M, Menezes de Faria Pereira S, Leandro da Cruz L, de Souza Passos M, Pereira de Moraes L, *et al*. Plants as Sources of Anti-Inflammatory Agents. Molecules. 2020; 25: 3726.

[37] Zheng G, Qiu P, Xia R, Lin H, Ye B, Tao J, *et al*. Effect of Aerobic Exercise on Inflammatory Markers in Healthy Middle-Aged and Older Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Frontiers in Aging Neuroscience. 2019; 11: 98.

[38] Conway J, A Duggal N. Ageing of the gut microbiome: Potential influences on immune senescence and inflammageing. Ageing Research Reviews. 2021; 68: 101323.

[39] Javadov S, Kozlov AV, Camara AKS. Mitochondria in Health and Diseases. Cells. 2020; 9: 1177.

[40] Miwa S, Kashyap S, Chini E, von Zglinicki T. Mitochondrial dysfunction in cell senescence and aging. The Journal of Clinical Investigation. 2022; 132: e158447.

[41] Vringer E, Tait SWG. Mitochondria and cell death-associated inflammation. Cell Death and Differentiation. 2023; 30: 304–312.

[42] Calabrese EJ, Osakabe N, Di Paola R, Siracusa R, Fusco R, D'Amico R, *et al*. Hormesis defines the limits of lifespan. Ageing Research Reviews. 2023; 91: 102074.

[43] Guo Y, Guan T, Shafiq K, Yu Q, Jiao X, Na D, *et al*. Mitochondrial dysfunction in aging. Ageing Research Reviews. 2023; 88: 101955.

[44] Yuk JM, Silwal P, Jo EK. Inflammasome and Mitophagy Connection in Health and Disease. International Journal of Molecular Sciences. 2020; 21: 4714.

[45] Alcocer-Gómez E, Castejón-Vega B, López-Sánchez M, Cordero MD. Inflammasomes in Clinical Practice: A Brief Introduction. Experientia Supplementum (2012). 2018; 108: 1–8.

[46] Mastrocola R, Aragno M, Alloatti G, Collino M, Penna C, Pagliaro P. Metaflammation: Tissue-Specific Alterations of the NLRP3 Inflammasome Platform in Metabolic Syndrome. Current Medicinal Chemistry. 2018; 25: 1294–1310.

[47] Walker KA, Basisty N, Wilson DM, 3rd, Ferrucci L. Connecting aging biology and inflammation in the omics era. The Journal of Clinical Investigation. 2022; 132: e158448.

[48] Seegren PV, Harper LR, Downs TK, Zhao XY, Viswanathan SB, Stremska ME, *et al*. Reduced mitochondrial calcium uptake in macrophages is a major driver of inflammaging. Nature Aging. 2023; 3: 796–812.

[49] Khasawneh RR, Al Sharie AH, Abu-El Rub E, Serhan AO, Obeidat HN. Addressing the impact of different fetal bovine serum percentages on mesenchymal stem cells biological performance. Molecular Biology Reports. 2019; 46: 4437–4441.

[50] Al-Qarakhli AMA, Yusop N, Waddington RJ, Moseley R. Effects of high glucose conditions on the expansion and differentiation capabilities of mesenchymal stromal cells derived from rat endosteal niche. BMC Molecular and Cell Biology. 2019; 20: 51.

[51] Abu-El-Rub E, Almahasneh F, Khasawneh RR, Alzu'bi A, Ghorab D, Almazari R, *et al*. Human mesenchymal stem cells exhibit altered mitochondrial dynamics and poor survival in high glucose microenvironment. World Journal of Stem Cells. 2023; 15: 1093–1103.

[52] Zhang Y, Li Q, Niu Y, Wei K, Wang X, Niu B, *et al*. Research progress on aging mechanism and drugs and the role of stem cells in anti-aging process. Experimental Gerontology. 2023; 179: 112248.

[53] Yao L, Liang X, Qiao Y, Chen B, Wang P, Liu Z. Mitochondrial dysfunction in diabetic tubulopathy. Metabolism: Clinical and Experimental. 2022; 131: 155195.

[54] Lee HJ, Chae CW, Han HJ. Enhancing the therapeutic efficacy of mesenchymal stem cell transplantation in diabetes: Amelioration of mitochondrial dysfunction-induced senescence. Biomedicine & Pharmacotherapy. 2023; 168: 115759.

[55] Mosser DM, Hamidzadeh K, Goncalves R. Macrophages and the maintenance of homeostasis. Cellular & Molecular Immunology. 2021; 18: 579–587.

[56] Wculek SK, Dunphy G, Heras-Murillo I, Mastrangelo A, Sancho D. Metabolism of tissue macrophages in homeostasis and pathology. Cellular & Molecular Immunology. 2022; 19: 384–408.

[57] Molawi K, Wolf Y, Kandalla PK, Favret J, Hagemeyer N, Frenzel K, *et al*. Progressive replacement of embryo-derived cardiac macrophages with age. The Journal of Experimental Medicine. 2014; 211: 2151–2158.

[58] Keshavarz-Bahaghighat H, Darwesh AM, Sosnowski DK, Seubert JM. Mitochondrial Dysfunction and Inflammaging in Heart Failure: Novel Roles of CYP-Derived Epoxylipids. Cells. 2020; 9: 1565.

[59] Arabpour M, Saghazadeh A, Rezaei N. Anti-inflammatory and M2 macrophage polarization-promoting effect of mesenchymal stem cell-derived exosomes. International Immunopharmacology. 2021; 97: 107823.

[60] Lu D, Xu Y, Liu Q, Zhang Q. Mesenchymal Stem Cell-Macrophage Crosstalk and Maintenance of Inflammatory Microenvironment Homeostasis. Frontiers in Cell and Developmental Biology. 2021; 9: 681171.

[61] Wang J, Liu Y, Ding H, Shi X, Ren H. Mesenchymal stem cell-secreted prostaglandin $E_2$ ameliorates acute liver failure via attenuation of cell death and regulation of macrophage polarization. Stem Cell Research & Therapy. 2021; 12: 15.

[62] Gao J, Cheng Y, Hao H, Yin Y, Xue J, Zhang Q, *et al*. Decitabine assists umbilical cord-derived mesenchymal stem cells in improving glucose homeostasis by modulating macrophage polarization in type 2 diabetic mice. Stem Cell Research & Therapy. 2019; 10: 259.

[63] Baechle JJ, Chen N, Makhijani P, Winer S, Furman D, Winer DA. Chronic inflammation and the hallmarks of aging. Molecular Metabolism. 2023; 74: 101755.

[64] Levine ME, Lu AT, Quach A, Chen BH, Assimes TL, Bandinelli S, *et al*. An epigenetic biomarker of aging for lifespan and healthspan. Aging. 2018; 10: 573–591.

[65] Pamplona R, Jové M, Gómez J, Barja G. Whole organism aging: Parabiosis, inflammaging, epigenetics, and peripheral and central aging clocks. The ARS of aging. Experimental Gerontology. 2023; 174: 112137.

[66] Wang K, Liu H, Hu Q, Wang L, Liu J, Zheng Z, *et al*. Epigenetic regulation of aging: implications for interventions of aging and diseases. Signal Transduction and Targeted Therapy. 2022; 7: 374.

[67] Pepin ME, Infante T, Benincasa G, Schiano C, Miceli M, Ceccarelli S, *et al*. Differential DNA Methylation Encodes Proliferation and Senescence Programs in Human Adipose-Derived Mesenchymal Stem Cells. Frontiers in Genetics. 2020; 11: 346.

[68] Wagner A, Schosserer M. The epitranscriptome in ageing and stress resistance: A systematic review. Ageing Research Reviews. 2022; 81: 101700.

[69] Alicka M, Major P, Wysocki M, Marycz K. Adipose-Derived Mesenchymal Stem Cells Isolated from Patients with Type 2 Diabetes Show Reduced "Stemness" through an Altered Secretome Profile, Impaired Anti-Oxidative Protection, and Mitochondrial Dynamics Deterioration. Journal of Clinical Medicine. 2019; 8: 765.

[70] Li Y, Berliocchi L, Li Z, Rasmussen LJ. Interactions between mitochondrial dysfunction and other hallmarks of aging: Paving a path toward interventions that promote healthy old age. Aging Cell. 2024; 23: e13942.

[71] Liu B, Qu J, Zhang W, Izpisua Belmonte JC, Liu GH. A stem cell aging framework, from mechanisms to interventions. Cell Reports. 2022; 41: 111451.

[72] Sugandh F, Chandio M, Raveena F, Kumar L, Karishma F, Khuwaja S, *et al*. Advances in the Management of Diabetes Mellitus: A Focus on Personalized Medicine. Cureus. 2023; 15: e43697.

[73] Yeo GEC, Ng MH, Nordin FB, Law JX. Potential of Mesenchymal Stem Cells in the Rejuvenation of the Aging Immune System. International Journal of Molecular Sciences. 2021; 22: 5749.

[74] Lei Y, Liao F, Tian Y, Wang Y, Xia F, Wang J. Investigating the crosstalk between chronic stress and immune cells: implications for enhanced cancer therapy. Frontiers in Neuroscience. 2023; 17: 1321176.