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SPOTLIGHT REVIEW

Inflammageing, a targetable pathway for preventing cardiovascular diseases

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Inflammageing, characterized by persistent chronic inflammation in older adults, has emerged as a critical factor linked to age-related diseases, such as cardiovascular diseases (CVDs), metabolic disorders, and cognitive decline, which collectively contribute to the leading causes of death globally. Elevated levels of cytokines, chemokines, and other inflammatory mediators characterize inflammageing and serve as indicators of biological age. Among the causes of inflammageing, deterioration of the immune system, mitochondrial dysfunction, dysbiosis, accumulation of DAMPs, together with genetic or epigenetic factors, contribute to inflammageing not only in CVD but also in other age-related conditions. This review examines the causes and consequences of inflammageing, particularly its implications for atherosclerosis and heart failure with preserved ejection fraction and explores potential strategies to mitigate it in the onset of CVD.

Keywords Inflammation • Atherosclerosis • Heart failure • HFpEF • Ageing

This article is part of the Spotlight Issue on Ageing.

1. Introduction

Ageing is defined as the gradual and inevitable process characterized by a progressive decline in functional capacity and heightened susceptibility to diseases, culminating in frailty—a clinical syndrome marked by diminished physiological reserves and increased vulnerability to adverse health outcomes in older adults.[1,2] The complexity of ageing, encompassing factors such as genetic, epigenetic, cellular, and environmental influences, underscores the absence of a definitive cure for ageing. While certain interventions, such as caloric restriction and pharmacological agents, have shown promise in delaying age-related diseases in model organisms, their efficacy and safety in humans are yet to be fully understood.[3] Inflammageing is the persistent chronic inflammation that emerges during ageing and has been coupled with age-related conditions, such as cardiovascular diseases (CVDs), metabolic disorders, non-alcoholic fatty liver disease, chronic kidney disease, and cognitive decline.[4] Altogether, these diseases represent the leading causes of death worldwide. Understanding the causes and consequences of inflammageing and its relationship with age-associated diseases is, therefore, a priority for public health, especially now that the global population is ageing. Inflammageing is now considered a hallmark of ageing[1] because it meets the three criteria: (i) the gradual appearance of changes that occur accompanying the ageing process, (ii) the ability to speed up ageing through experimental intensification of the identified characteristic, and (iii) the potential to slow down, stop, or even reverse ageing through therapeutic interventions targeting the identified hallmark. Furthermore, studies have demonstrated the hallmarks of ageing, including inflammageing, across species, are evolutionary conserved as well as the underlying pathways and mechanisms of this phenomenon, which will be elaborated later on.[5,6]

The circulating concentration of inflammatory mediators, such as cytokines and chemokines, and biomarkers of inflammation, such as C-reactive protein (CRP), increase with age. In fact, biological age can be estimated by measuring inflammatory mediators in the blood.[7] This inflammatory clock of ageing has been called iAge and tracked with multimorbidity, immunosenescence, frailty, and cardiovascular ageing. One of the contributors to iAge is the CXCL9 chemokine, which has been involved in vascular ageing and adverse cardiac remodelling. Among the other cytokines and chemokines that are elevated with ageing, tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) stand out.[8] In fact, high levels of IL-6 are predictive biomarkers of all-cause mortality in ageing human populations. A substantial subset of older individuals shows inflammasome activation leading to caspase-1-mediated maturation of proinflammatory cytokines, such as IL-1β and IL-18.[9] Lastly, the proinflammatory chemokine CCL5 has also been shown to be increased in the bone marrow of aged animals, promoting neutrophil accumulation and bone loss.[10,11] As such, anti-inflammatory agents, lifestyle interventions such as exercise and

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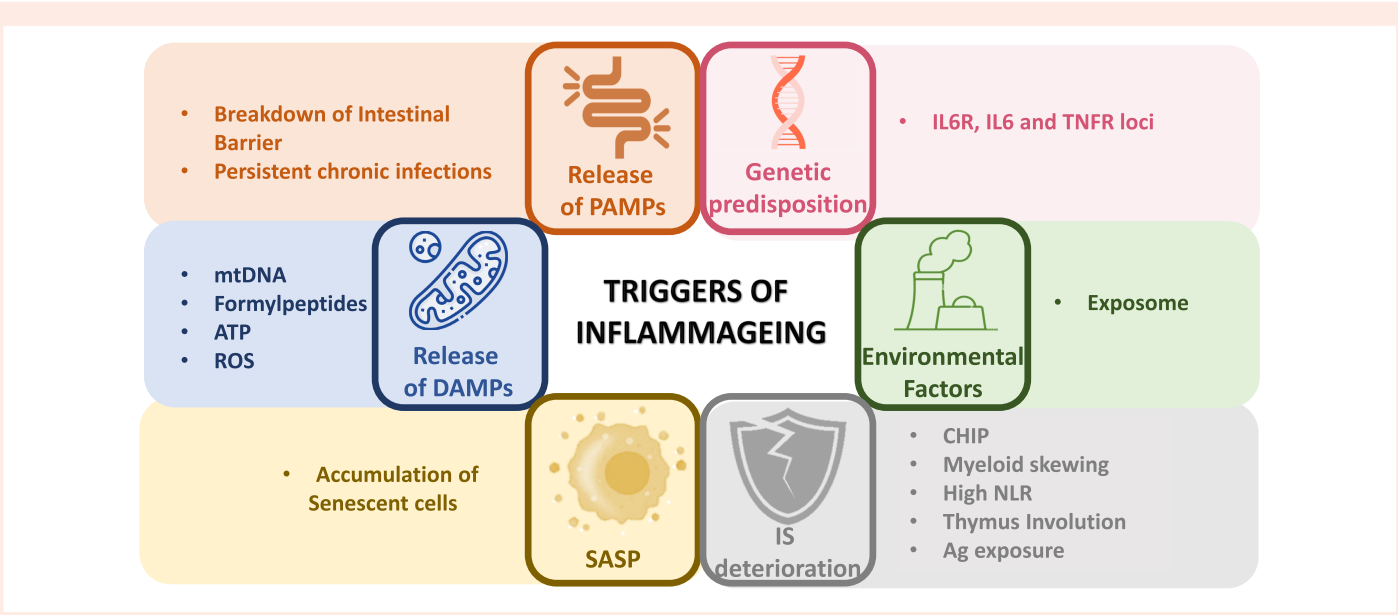

Figure 1 Causes of inflammageing. The presence of PAMPs due to physical rupture of intestinal barrier or persistent chronic infections activate inflammatory pathways in the IS. In addition, cells undergoing stress release DAMPs like mtDNA, formylpeptides, and ROS, and some of them become senescent with the characteristic SASP-secreting inflammatory signals. Of note, release of DAMPs, PAMPs, and SASPs contribute to inflammageing and foster the deterioration of the IS affecting to quality and quantity of immune responses and worsening inflammageing. These factors, together with intrinsic factors that contribute to the deterioration of the IS, like CHIP, myeloid skewing, high NLR, thymus involution, and antigen exposure. PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; mtDNA, mitochondrial DNA; ROS, reactive oxygen species; CHIP, clonal haematopoiesis of indeterminate potential; NLR, neutrophil to lymphocyte ratio; SASP, secretory-associated senescence phenotype.

nutrition, and pharmacological treatments targeting specific inflammatory pathways are among the potential approaches to improve the condition of frail older adults.[2,12]

In this review, we will discuss the current knowledge about the causes of inflammageing and its consequences for CVDs, with a special focus on potential strategies to control inflammageing that could be employed to delay the onset of CVDs.[13]

1.1 Causes behind inflammageing

The causes of inflammageing are complex and involve various factors that contribute to persistent chronic inflammation during ageing. The main feature of inflammageing is that it occurs in the absence of evident aggression to the organism and at the same time, it prevents the effective and specific response to antigen stimulations. Some key factors related to the appearance of inflammageing include immune system (IS) deterioration, the secretory-associated senescence phenotype (SASP) due to accumulated senescent cells, and accumulation of DAMPs driven by a breakdown in mitochondrial endosymbiosis and microbial commensalism or by persistent infections (*Figure 1*, *Table 1*). Additionally, some of the molecular mechanisms and signatures of inflammageing share strong similarities between mouse and human species in terms of immune/inflammatory response, suggesting that it is evolutionarily conserved and, more importantly, that the results obtained in mouse trials could be easily translated to future therapies in humans.[47]

2. Changes in the IS

During ageing, there is a deterioration of IS function. This phenomenon, known as immunosenescence, results in a dysregulated immune function that instead of mounting specific immune responses, engages useless inflammatory responses.

As the ageing process unfolds, intricate alterations manifest in both the adaptive and innate branches of the IS, marked by a reduction in circulating lymphocytes (T and B cells) and an elevation in myeloid cells (mostly neutrophils). This imbalance of immune populations culminates in an increased neutrophil-to-lymphocyte ratio (NLR) in the organismal circulation. A high NLR predicts mortality and poor prognosis in virtually all age-associated diseases as well as during natural ageing. The heightened infiltration of neutrophils into tissues induces damage[17] and triggers tissue senescence[18] during the ageing process and inflammation. The decrease in the frequency of both CD4 and CD8 T cells in circulation is accompanied by significant alterations in the subsets of T lymphocytes. This comprehends a reduction in the naïve pool and an increase in effector/memory T cells with a terminally differentiated phenotype.[48] Effector memory T cells (TEM), exhibiting exhausted, cytotoxic, and senescent features, lose the capacity to migrate to lymph nodes and spleen, acquiring instead the ability to migrate to non-immune tissues. This shift in T-cell population from naïve towards terminally differentiated phenotype compromises immunosurveillance, increases autoimmune diseases, and reduces the repair of biological barriers, altogether fostering inflammageing.[49] Age-associated alteration studies in immune cells led to the identification in mouse organs of a subpopulation of granzyme K (GZMK)-expressing $CD8^+$ T (Taa) distinct from TEM. Interestingly, humans share the proportion of this circulating $GZMK^+$ $CD8^+$ T-cell subset and the transcriptional and epigenetic signature with mouse T cells during ageing, suggesting that inflammageing is a conserved process across species and therefore represents an attractive therapeutic target.[50]

As it is observed in numerous other cell types throughout the body, T cells exhibit a decline in mitochondrial function as they age. Although this failure may be originated primarily in mitochondria, other intracellular compartment defects, such as lysosome and autophagosome, can affect T-cell activation, which in turn lead to an exacerbated and/or incorrect immune response and the loss of homeostasis. Defects in lysosomal acidification through cytokine-inducible SH2-containing protein expression in $CD4^+$ T cells promote release of mitochondrial DNA (mtDNA), which increases inflammatory serum cytokines and reduces antibody production.[51] In fact, mitochondrial insufficiency triggers the functional exhaustion terminal state of T cells through the oxidative stress-HIF-1α (hypoxia inducible factor 1)—metabolic reprogramming pathway.[52] Therefore, targeting mitochondrial and lysosomal dysfunction in T-cell responses may offer a potential approach to mitigate inflammation and enhance immune function in the ageing population.

Table 1 Sources of inflammageing, description, and molecular targets involved

Source	Description	Molecular targets	Refs.
NLRP3 inflammasome activation	Involved in inflammageing and HFpEF pathogenesis	NLRP3, Caspase-1 cleavage, NF-κB, chemokines (CCL5)	14–16
Inmunosenescence	Malfunctioning of IS, unadaptive, or insufficient response	CDXX, KLRG1, TEM, CHIP, myeloid skewing, thymus involution	17–21
Proinflammatory Cytokines	Elevated levels linked to inflammageing and mortality in ageing populations	IL-1β, IL-6, TNF-α	22,23
DAMPs and SASP	Accumulation contributes to chronic inflammation and inflammageing	mtDNAs, succinate, fumarate, *N*-formyl peptides, AGEs, ROS, Cardiolipin, and ATP	24–28
Mitochondria	Dysfunction plays a role in inflammation and cellular ageing	Mutations in mtDNA, ROS, TCA, OXPHOX, PGC-1α, and TFAM	29–38
Genetic/epigenetic factors	Influence inflammageing through gene expression and epigenetic modifications	MiRNAs (CHIP: DNMT3A, TET2, ASXL1), SNPs, DNA methylation, and histone modifications	25,39–43
Intestinal microbiota PAMPs	Dysbiosis impacts systemic inflammation and ageing processes	Calprotectin, LPS, TCA metabolites	44–46

We and others have previously contributed to demonstrate that the deterioration on the IS function with ageing is sufficient to induce organismal ageing and age-related multimorbidity.[19,20] Data from our lab show that T-cell-specific mitochondrial defect by depleting the mitochondrial transcription factor A (TFAM) not only mimics age-associated T-cell mitochondrial dysfunction and recapitulate the main hallmarks of T-cell ageing, but is also sufficient to drive cardiovascular, cognitive, metabolic, and physical ageing coupled to premature inflammageing. The TNF inhibitor etanercept delays this phenotype. These results support that ageing of T cells may drive inflammageing and organismal ageing. In fact, haploinsufficiency of the DNA repair protein ERCC1 in haematopoietic cells is also sufficient to induce senescence of non-lymphoid organs, as well as numerous signs of organ damage coupled to reduced lifespan.[53]

Recently, a new subset of CD4 T lymphocytes with a cytotoxic phenotype characterized by the expression of the EOMES transcription factor producing granzymes and CCL5 has been reported that appears during ageing and is especially abundant in supercentenarians.[14] The results from our lab support that this subset infiltrates the bone marrow during ageing, favouring myeloid skewing and the overproduction of neutrophils.[10]

Most of the changes in immune population frequencies and phenotypes predominantly result from:

(1) *Alterations in bone marrow, myeloid skewing, and clonal haematopoiesis of indeterminate potential* (CHIP; *Figure 2*). Distinct factors contribute to increased levels of neutrophils during ageing, but the most recognized cause is a skewing of haematopoiesis towards the differentiation of myeloid progenitors at the expense of lymphoid progenitors.[52] CHIP is a common age-related condition characterized by the clonal expansion of haematopoietic stem cells bearing mutations in certain genes, especially DNMT3A, TET2, and ASXL1.[39,40] These mutations affect myeloid cells, such as macrophages and neutrophils, leading to increased expression of inflammatory genes, which might account for the increased risk of cardiovascular complications in individuals with CHIP. In fact, TET2-deficient macrophages showed increased IL-6 production and NLRP3 inflammasome activity reflected in IL-1β secretion.[22] Moreover, CHIP driven by TET2 also favours CVD, which is attenuated by treatment with canakinumab, an anti-IL-1β antibody.[23] Similarly, monocytes of heart failure (HF) patients harbouring DNMT3A driver mutations exhibited markedly increased expression of inflammatory genes, including NLRP3 inflammasome.[15,16]

(2) *Thymus involution*. The thymus is the primary immune organ responsible for generating self-tolerant and immunocompetent T cells. However, the thymus gradually involutes during early life resulting in declined naïve T-cell production. Thymic involution has many negative impacts on immune function, including reduced pathogen resistance, high autoimmunity incidence, and attenuated tumour immunosurveillance contributing to inflammageing.[21,54]

(3) *History of antigen recognition.* As we encounter antigens and pathogens over time, the cumulative effect on our IS can accelerate immunosenescence, potentially leading to increased susceptibility to infections and decreased ability to mount robust immune responses.[55] Altogether, these alterations in immune cellular subsets and function contribute to inflammageing.

3. Accumulation of senescent cells in tissues

As cells undergo the process of ageing, they may transition into a state of senescence, wherein they halt their division yet maintain metabolic activity. Senescent cells exhibit arrested cellular cycle, resistance to apoptosis, and are characterized by an SASP.[24] The accumulation of senescent cells producing elevated amounts of proinflammatory cytokines and SASP cell extrinsic factors favours inflammageing driving the decline in immunological protection as we age, thereby targeting these cells might be a strategy to delay inflammageing. A very recent study has found conserved epigenetic clocks in memory T cells both in murine and in human species, as shown by DNA methylation profiles of replicative senescence-associated genes in this cell population.[25] Although the IS is prepared to recognize and eliminate senescent cells in a physiological way, the age-associated deterioration of the IS or the expression of immunosuppressive ligands, such as PD-L1 and PD-L2 by senescence cells could favour the accumulation of senescence cells in the tissues.[26]

Senolytics are a class of drugs and natural products that deplete senescence cells through apoptosis. In a preclinical trial with middle-aged non-human primates, 6 months of intermittent treatment with a senolytic combination of dasatinib and quercetin delayed inflammageing probably via immune benefits and improved intestinal barrier function.[56] Same senolytics also prevent mtDNA induced inflammageing in older organs.[57] In addition, other compounds named senomorphics inhibit senescence-associated secretory phenotype by targeting pathways related to SASP expression, such as the p38MAPK, PI3k/Akt, mTOR, and JAK/STAT pathways and transcription factors, such as nuclear factor kappa B (NF-κB), C/EBP-β, and STAT3, therefore reducing systemic inflammation. Metformin is an example of senomorphic with anti-inflammageing properties[58] and therapeutic potential as a treatment for CVD.[59]

4. Mitochondrial dysfunction and break in mitochondrial endosymbiosis

With ageing, the function of mitochondria declines due to multiple interlaced mechanisms including the accumulation of mtDNA mutations and

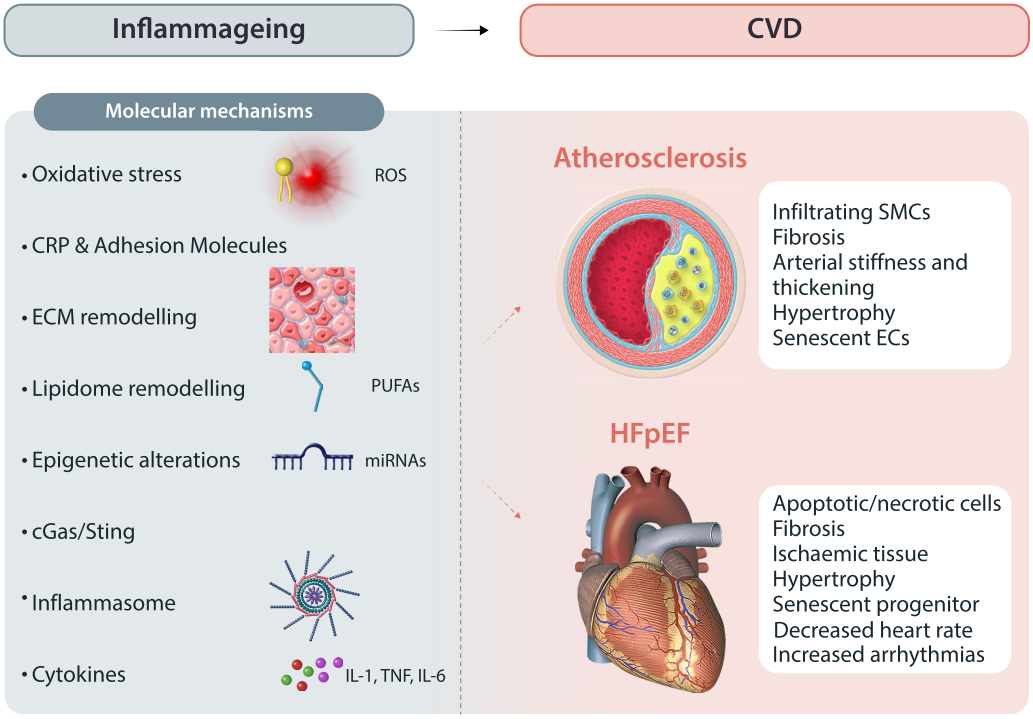

Figure 2 Molecular mechanisms of inflammageing. In the heart and the vasculature, inflammageing promotes oxidative stress and increases inflammatory mediators such as CRP and adhesion molecules that result in ECM and lipidome remodelling. Additional factors, such as epigenetic changes, including oscillations in levels of several miRNAs, has been shown to contribute to the sustained inflammation that lead to endothelial dysfunction, atherosclerosis, vascular injury, and heart failure. CVD, cardiovascular disease; HFpEF, heart failure preserved ejection fraction; CRP, C-reactive protein; ECM, extracellular matrix; PUFA, polyunsaturated fatty acids; miRNA, microRNA; IL-1, interleukin-1; IL-6, interleukin-6; TNF, tumour necrosis factor.

deletions, reduced turnover of the organelle, and changes in mitochondrial dynamics. The deterioration in mitochondria function not only compromises the cellular bioenergetics state, but also can contribute to inflammageing. Mitochondria constitute a latent trigger of inflammation due to their endosymbiotic origin.[29] Mitochondria retain many bacterial remnants that can act as damage-associated molecular patterns (DAMPs). Under stress conditions, mitochondrion-derived molecules, such as mtDNAs, succinate, fumarate, *N*-formyl peptides, reactive oxygen species (ROS), cardiolipin, and ATP, are released from mitochondria and activate several inflammatory pathways.[30–32] MtDNA present in many copies within mitochondria is not methylated at CpG and is more susceptible to oxidative damage due to its location and its limited repair capability. The mtDNA release to the cytosol can trigger a cascade of inflammatory innate responses, such as cGAS stimulator of interferon (IFN) gene expression, Toll-like receptor 9 (TLR9) pathway activation, and cytosolic inflammasome formation.[33] Circulating mtDNA appears to increase gradually with age after the fifth decade of life, and the abundance of unhoused mtDNA is associated with accelerated ageing.[34] The 13 polypeptides translated within mitochondria are all initiated with an *N*-formyl methionine. These mitochondrial proteins, including *N*-formyl peptides, primarily induce inflammation through binding to formyl peptide receptor-1.[35] On the other hand, after the formation of double-strand breaks in the mtDNA, herniation mediated by BAX and BAK releases mitochondrial RNA (mtRNA) into the cytoplasm stimulating NF-κB through RIG-I and mitochondrial antiviral-signalling protein. Consequently, this leads to activation of Type I IFN response.[36]

In addition to mtDNA, mtRNA, formyl peptides, and ROS, mitochondrial dysfunction releases tricarboxylic acid cycle (TCA) intermediate metabolites into the cytosol with inflammatory effects[37] such as fumarate or succinate. Fumarate inhibits lysine-specific demethylase 5 A (KDM5) histone demethylase activity and inhibition of KDM5 increases the levels of H3K4me3, a marker of active gene transcription at the promoters of TNF-α and IL-6 cytokine.[38] Furthermore, elevated levels of succinate, resulting from mitochondrial dysfunction, may contribute to chronic inflammation by activating the HIF-1α pathway through stabilization of the hypoxic transcription factor HIF-1α. Succinate inhibits prolyl hydroxylases, enzymes responsible for the degradation of HIF-1α thus stabilizing HIF-1α that translocates into the nucleus and initiates the transcription of inflammatory cytokines, such as IL-1β.[60]

5. Dysbiosis, intestinal barrier dysfunction, and leaky gut

The integrity of the intestinal barrier is essential for the health of the organism throughout life. Intestinal barrier dysfunction is an evolutionarily conserved feature of aged organisms, as it has been reported in worms, flies, fish, rodents, and primates.[61] Pioneers studies come from the drosophila model using a non-absorbable blue food approach to monitor intestinal barrier function in living flies.[62–64] In these assays, the presence of the dye outside of the digestive tract throughout the body is an indicator of intestinal barrier dysfunction which is called Smurf phenotype. By separating Smurf flies by chronological age, the authors showed that intestinal barrier dysfunction is a better predictor of mortality than chronological age. Moreover, this study also reported that intestinal barrier dysfunction was associated with additional markers of health decline, including markers of inflammageing.[63] The disrupted intestinal barrier is the cause of changes in microbiota composition, known as a gut dysbiosis and can also be affected by the deterioration of the IS.[44] Changes in permeability allow some bacteria and their molecules, PAMPs, to enter the circulatory system enhancing inflammageing. Faecal calprotectin is a general marker of gut

inflammation that consist in a heterodimer of S100 calcium-binding proteins that is primarily expressed in immune cells and can be released from the cytosol of activated neutrophils. Recent studies have shown that levels of faecal calprotectin are associated with advanced age and Alzheimer's disease[45] and with acute HF.[65] The lipopolysaccharide (LPS)-binding protein, which is known as a marker of clinical endotoxaemia, and the soluble form of CD14 (sCD14), co-receptor for LPS, are both also used as markers of gut permeability and bacterial translocation.[46]

6. Accumulation of DAMPs

As state before, the age-related rupture of both mitochondrial endosymbiosis and intestinal barrier constitutes an immense source of DAMPs and PAMPs. Additionally, even though the human body is provided of complex and well-regulated mechanisms to repair or eliminate degraded cellular material, during age-associated diseases, there is an accumulation over time of diverse biological debris.[27] These metabolites also include advanced glycation endproducts (AGEs), oxLDL, high mobility group protein B1, ATP, and many others. Our IS recognize them and is activated constantly due to inability to be eliminated by other mechanisms. Ultimately, the sustained activation of innate and adaptive immunity branches by DAMPs triggers the hyper-responsiveness of myeloid and lymphoid cells contributing to chronic inflammation.[28]

6.1 Genetic predisposition, chronic infections, endocrine changes, and environmental factors

Other causes that contribute to heterogeneity of inflammageing are related to each individual and include genetic predisposition, chronic infections, endocrine changes, and environmental factors. Over the past decades, studies with human populations demonstrated the link of genetic variants with the proinflammatory profile found in the blood biomarkers.[66] The most relevant genetic associations are those related to SNP, such as IL1RN minor alleles, multiple SNP in CRP gene or in the promoter region of IL-6.[41–43] However, a large divergence has been observed during ageing in the inflammatory markers in twins for many of these genetic variants, suggesting that the influence of environmental factors is also remarkable. In many other cases, there are strong evidence that inflammageing is powered by the relative abundance of micro RNAs (miRNAs) in circulating cells or plasma during ageing as we will explain latter in this review.[67] The response of the IS to some persistent infections may become dysregulated with age, such as cytomegalovirus (CMV) and HIV or bacterial infections. The reactivation episodes against these viruses can contribute to chronic inflammation over time, but the mechanism behind this is still unclear. One hypothesis in the case of human-persistent CMV infection is that it accelerates inmunosenescence of memory T-cell compartment in older individuals. In fact, a new population of $CD57^{+}CD28^{-}CD8^{+}$ T cells, which are enriched in individuals with HIV and CMV chronic infections, are associated with immunosenescence, suggesting a link to chronic viral infections and immune dysregulation.[68] Ageing is associated also with physiological changes in the endocrine system. Hormone levels can impact the IS and contribute to maintain an inflammatory state due to excessive or deregulated trophic signals resulting in activation of GH/IGF1/Pi3K/AKT/mTORC1 signalling pathways.[69] For example, adiponectin and leptin are affected in adipocytes in several fat depots during obesity and ageing, and together with the circulating proinflammatory signals of chemokines/cytokines foster inflammageing. A recent study using a mouse model has linked the altered nutrient sensing through mTOR signalling with senescence and myeloid inflammation and neutrophil infiltration in tissues reducing lifespan.[70] Sex hormones, specifically androgens and oestrogens, can modulate inflammatory responses. Whereas oestrogens can exhibit either anti-inflammatory (at high concentrations) or proinflammatory (at low concentrations) effect, androgens shown anti-inflammatory effects both *in vivo* and *in vitro*.[71] Accordingly, sex/gender differences in inflammageing are shown during immune ageing when sex hormones decline. While older women have higher adaptive immune activity, older men show higher activity for monocytes and inflammation, indicating greater inflammageing in men.[72–74] Moreover, the X chromosome contains several genes encoding immune and inflammatory molecules, including FOXP3, essential for regulatory T-cell development, or the TLR7, essential receptor for PAMPs and DAMPs that has been associated with CVD, including atherosclerotic plaque formation.[75] Finally, some environmental factors, such as pollution and chemotoxicity, can be intertwined with all the above and worsening inflammation.

Understanding these contributing factors is essential for developing strategies to mitigate inflammageing and its associated health risks. Ongoing research aims to unravel the complex interplay of these factors and identify potential interventions to promote healthy ageing.

6.2 Inflammageing and atherosclerosis: causes and consequences of inflammageing for atherosclerosis and treatments based on inflammageing

As individuals age, they become increasingly susceptible to cardiometabolic pathologies due to a combination of biological, physiological, and lifestyle factors.[76,77] Among the most studied ones, inflammageing has emerged as a key pathophysiological process driving this relationship, with significant relevance in the context of atherosclerosis. Indeed, ageing is a major risk factor for atherosclerosis, presumably due to inflammageing.[78]

6.3 Definition of atherosclerosis: hints on inflammageing

Atherosclerosis is an intricate vascular condition marked by the gradual build-up of lipids, inflammatory cells, and fibrous material within the subendothelial space of large arteries.[79] Despite advancements in prevention and treatment, it continues to be the foremost cause of death in developed nations.[80] Atherosclerotic lesions typically develop in branching regions of disturbed blood flow, which damage vascular endothelial cells and triggers inflammatory pathways, heightened permeability, oxidative stress, NF-κB activity, and followed by the expression of receptors and cytokines that attract leucocytes. Compromised endothelial integrity also enables the accumulation and oxidation of cholesterol-laden LDL particles within the arterial wall which increasingly contributes to the later events such as monocyte differentiation to macrophages and transition to foam cells.[81] The NLRP3 inflammasome activation in macrophages, cells responsible of clearance of cholesterol excess in the plaque through efflux, prompts the release of IL-1β, IL-18 together with other proinflammatory cytokines, serving as chemoattractant for T and B cells, which play critical roles in the atherogenesis. Evolved atheroma encompasses a necrotic core enriched in apoptosis and senescent cells expressing p16INK4A and the tumour suppressor ARF, characterized by SASP that fosters inflammation and provokes the destabilization of the atherosclerotic plaque.[12] This intricate progression contributes significantly to the vulnerability and rupture of the plaque, the formation of thrombus, and the onset of acute vascular occlusion that might later result in a myocardial infarction or stroke.[79]

6.4 Inflammageing contributing to atherosclerosis

Inflammageing not only contributes to atherosclerosis itself but also interacts with conventional cardiovascular risk factors, such as obesity, hypertension, and Type 2 diabetes mellitus, amplifying their adverse cardiovascular effects. The origins of inflammageing and its interconnection to other health outcomes are not fully understood. An ongoing debate centres around whether elevated levels of proinflammatory compounds found in circulation and tissues are causally contributing to associated pathological conditions or if inflammation merely serves as a reactive marker to the underlying pathology. Both possibilities are believed to be feasible as these mechanisms are highly interconnected.[12] This is particularly true for atherosclerosis, where early damage occurring during inflammation

Table 2 Main clinical trials of anti-inflammatory therapy in CVD

Clinical trial	Drug/ compound	Molecular target	Outcome/observations
Anakinra trials[100,101]	Anakinra	IL-1R	Reduced systemic inflammatory status and decreased CRP levels in HFpEF patients
CANTOS trial[102]	Canakinumab	IL-1β	Demonstrated effectiveness in reducing recurrent fatal and non-fatal cardiovascular events
CIRT trial[103]	Methotrexate	Purinergic signalling	International study exploring anti-inflammatory approaches against CVD, outcome not successful
COLCOT trial[104–106]	Colchicine	Inflammatory pathways	Included in ESC recommendations for prevention in high-risk CVD patients
DELIVER study[107]	Dapagliflozin	SGLT2	Reduced combined risk of worsening HF or CV death among HFpEF patients
EMPEROR preserved[108]	Empagliflozin	SGLT2	Reduced cardiovascular death or hospitalization for HF in HFpEF patients
LoDoCo trial[104]	Colchicine	Microtubule assembly	Reduced risk of CVD events in patients with post-myocardial infarction
LoDoCo trial 2[103,109]	Colchicine	Microtubule assembly	Lowered risk of CVD events in individuals with chronic coronary disease
MEASURE study[98,99]	Tocilizumab	IL-6R	Targeting specific inflammatory pathways in HFpEF
PARAGON trial[110]	LCZ696	Angiotensin-nepresylin	No significant improvement in inflammation level in HFpEF patients
STABILITY trial[104,111]	Darapladib	Lp-PLA2	Investigated inhibition of Lp-PLA2, outcome not successful
STEP-HFpEF trial[100,112]	Semaglutide	GLP-1R	Reduced inflammation in obese HFpEF patients
VISTA-16 trial[111]	sPLA2	sPLA2	Inhibition of lipid inflammatory mediator, outcome not successful

of vascular endothelial cells triggers the development of the atherosclerotic lesions, while atherosclerosis itself generates antigens and perpetuates the inflammatory response. Adding to the complexity, the crosstalk between chronic inflammation and other hallmarks of ageing such as senescence or telomere shortening during atherosclerosis, results in a vicious cycle that exacerbates the decline in cellular functions and promotes ageing.[78] Furthermore, important aspects associated with the deterioration of IS linked to ageing have been directly related to atherosclerosis. As such, mutations leading to CHIP contribute to the increased inflammation seen in ageing and partially explain the age-related risk of CVD.[39] Moreover, the high NLR, a marker of systemic inflammation increased during ageing, represents an independent prognostic factor for coronary artery disease and is a strong predictor of atherosclerotic carotid plaques in older adults.[82] Additionally, recent studies in humans have shown inflammatory transcriptional reprogramming and myeloid skewing in patients with atherosclerosis.[83] Also, it has been reported that clonally expanded memory $CD8^+$ T cells accumulate in atherosclerotic plaques and are proatherogenic in aged mice.[84] Vascular extrinsic mechanisms are reviewed in detail elsewhere.[85]

Noteworthy, chronic inflammation can accelerate telomere dysfunction and cell senescence in HIV-infected population. Emerging data indicate that, even under strict control of the traditional cardiovascular risk factors, HIV infection increases rates of atherosclerosis-related disease, mostly due to chronic arterial inflammation, which, in turn, promotes atherosclerosis. In fact, young HIV-infected adults show premature biological ageing with accentuated immune activation. Chronic inflammation with excessive T-cell activation could be associated with telomere shortening, premature ageing, and subclinical atherosclerosis in young HIV-infected adults.[86] All in all, this evidence strongly suggests that atherosclerosis shares several common pathologic mechanisms with ageing and inflammageing.[87]

With the aim of simplifying the complex phenomena currently describing the mechanisms and consequences of atherosclerosis, inflammageing can be seen from a cellular or systemic level perspective (*Figure 2*). In this sense, several circulating proinflammatory markers of inflammageing, such as IL-1β, IL-6, CRP, and TNF-α, are considered as predicted risk factors of CVD in an ageing setting.[88–90] High TNF-α levels in centenarians are associated with a low ankle-brachial arterial pressure index, indicating peripheral atherosclerosis.[91,92] In agreement, genome-wide association studies (GWASs) conducted with centenarian populations from Italy and China have pinpointed polymorphisms within the IL-6 gene locus as key determinants of longevity, explaining up to 1% of lifespan variance.[93–95] In the Italian centenarian population (InCHIANTI study), circulating levels of IL-6 and soluble TNFR1 emerged as robust predictors of inflammatory risk, with an inflammation index score proving to be a strong predictor of 10-year all-cause mortality in older individuals.[96] Notably, recent GWASs have implicated the IL-6 locus in calcific aortic valve stenosis, suggesting a link between inflammageing and this age-related CV condition.[97] Moreover, works from Ridker and others have shown that IL-6, together with IL-1, well-known contributors to the pathophysiology of atherosclerosis, represent potential therapeutic targets for the disease.[88] In line with this, impaired IL-6 signalling due to polymorphisms or the inhibition of the IL-6 receptor (IL-6R) by tocilizumab (TCZ), a blocker monoclonal antibody to treat rheumatoid arthritis, have shown significant decreased odds of coronary heart disease events in large cohorts of patients[98,99] potentially due to reduced proinflammatory HDL-associated serum amyloid A[42] (*Table 2*). The therapeutic outcome of this strategy has been further explored. A small study TOCRIVAR, for instance, demonstrated that abnormalities in the lipid profile in TCZ-treated patients correlated to levels of proprotein convertase subtilisin/kexin-9 (PCSK9), but reduced Lp(a) serum concentration and increased cholesterol efflux capacity, reinforcing a favourable effect on lipid metabolism, and consequently on cardiovascular risk.[113] Aligned with the inflammatory characteristics of ageing, atherosclerosis and its acute manifestations, individuals with chronic extracardiac inflammatory conditions like rheumatoid arthritis or psoriatic arthritis exhibit an increased CVD-related mortality compared with the general population.[113] Aside from IL-6, the primary circulating form of IL-1, IL-1β, triggers atherogenic events, including smooth muscle cell (SMC) proliferation, recruitment of inflammatory cells followed by leucocyte adhesion, production of IL-6, and exerts a procoagulant activity.[114] Indeed, the large canakinumab anti-inflammatory thrombosis outcomes study (CANTOS trial) published in 2017 in a large cohort consisting of >10 000 patients with previous myocardial infarction and high CRP has shown demonstrable effectiveness of anti-inflammatory therapy using a monoclonal antibody targeting IL-1β and reducing recurrent fatal and non-fatal cardiovascular events[102] (*Table 2*). Some other anti-inflammatory therapeutic approaches against CVD explored have failed, like the international study with methotrexate (CIRT trial)[103] or the VISTA-16 and the STABILITY trials that investigated the inhibition of lipid inflammatory mediator sPLA2 or Lp-PLA2, respectively.[111] Nevertheless, clinical approaches testing other compounds have shown promising effectiveness. This applies for colchicine, a drug that down-regulates several inflammatory pathways and reduces neutrophil function and migration through the vascular endothelium, both proatherogenic events linked to unstable coronary disease.[104] In the LoDoCo and LoDoCo Trial 2, colchicine treatment resulted in lowering the risk of CDV events in patients who have experienced a recent myocardial infarction and in individuals diagnosed with chronic coronary

disease, respectively.[103,109] More recently, conclusions from COLCOT trial have led the European Society of Cardiology to include colchicine as a recommendation for prevention in high-risk patients of CVD[105,106] (*Table 2*).

From a more experimental standpoint, a significant number of studies have highlighted the impact of inflammageing on key molecular and cellular mechanisms occurring or contributing to atherogenesis. That is the case for hypertension in older individuals, where inflammatory mediators contribute to the dysfunction of vascular endothelial cells (ECs) and vascular smooth muscle cells (VSMCs). In experimental hypertension, the presence of inflammatory cells such as dendritic cells, NK cells, and macrophages is typical.[115] Monocytes expressing receptors for Angiotensin II and mineralocorticoids drive hypertension by promoting inflammatory polarization and increasing ROS production.[116] The context of inflammageing amplifies these effects, with macrophages in the vessel wall generating higher ROS levels, which leads to reduced nitric oxide (NO) availability, increased adhesion molecule expression, VSMC hypertrophy, and activation of MMPs, contributing to vascular remodelling and dysfunction.[117] Mice with functionally deficient macrophages exhibit reduced vascular oxidative stress, improved endothelial function, and resistance to hypertension.[118] Mediators of inflammageing, including TNF, IL-1β, Caspase 1, and components of NLRP3 inflammasome, are potential targets for age-related hypertension that hastens the formation of atherosclerotic plaque.[119] In addition, cholesterol crystals activate the NLRP3 inflammasome in macrophages, leading to the release of proinflammatory cytokines, further fuelling the inflammatory response associated with atherosclerosis. In this line, lipid intermediates, such as cholesterol, play a pivotal role in connecting inflammageing and atherosclerosis and related events orchestrated by immune cells like macrophages and lymphocytes within the atherosclerotic plaque. As indicated before, the accumulation of LDL-cholesterol within arterial walls represents a key event during atherogenesis, which triggers inflammation, engaging T cells, and promoting the formation of atherosclerotic plaques. A recent study provides additional clues regarding the existing crosstalk between lipid pathways, inflammageing, and atherosclerosis. The Westerterp group's demonstrated that T-cell-specific deficiency in cholesterol efflux transporters Abca1 and Abcg1 led to increased T-cell activation, apoptosis, and premature ageing, ultimately contributing to increased atherogenesis in middle-aged mice.[120] These findings shed light on the role of the adaptive IS and lipid pathways in age-related inflammation and atherosclerosis, potentially offering new insights for therapeutic interventions in ageing individuals. In agreement with this, the lipidome changes associated with ageing might be relevant as they can reflect the progressive deterioration of metabolic health and contribute to age-related pathologies. Hornburg *et al.*,[121] reported changes in >800 lipid species in human plasma, many of which are associated with health-to-disease transitions in diabetes, ageing and inflammation, as well as cytokine–lipidome networks. The researchers observed a shift in the physicochemical properties of lipids, including increased levels of saturated fatty acids and monounsaturated fatty acids and reduced levels of polyunsaturated fatty acids (PUFAs). This pattern has been associated with dyslipidaemia and inflammation, indicating progressive deterioration of cardiometabolic health during ageing.[122] Additionally, depleted levels of beneficial omega-3 fatty acids, such as docosahexaenoic acid and eicosapentaenoic acid, were observed with ageing. Some other specialized mediators derived from PUFAs, proresolvins, have gained increasing interest as a potential therapeutic target for inflammageing and its associated pathologies. Although bibliography has not provided specific findings in the context of age-related CVD, significant reduced levels of resolvin D1 have been found in vulnerable regions of atherosclerotic plaques, particularly where macrophages express 5-lipooxygenase. This enzyme converts arachidonic acid to proinflammatory leukotrienes, suggesting a potential role in promoting plaque rupture.[123] Nevertheless, the discovery of factors that integrate synergistic effects contributing to atherosclerosis, such as inflammatory and lipid metabolic factors or biomechanical effects, will help to better understand the linking between atherosclerosis and ageing. Caveolin-1 (Cav-1) for instance, a structural protein cholesterol-enriched membrane rafts known as caveolae,[124] is known to be necessary for the development of atherogenesis by enhancing LDL transcytosis, EC vascular inflammation, and modulation of ECM remodelling.[79] Interestingly, Cav-1 has been shown to play a critical role in vascular ageing *in vivo*, regulating dyslipidaemia and disturbed flow and promoting endothelial stiffening induced by oxidized-LDL *in vitro*.[125] Moreover, Cav-1 deficiency also enhances autophagy in the aortic endothelium, a recognized age-associated mechanism thereby mitigating vascular ageing and atherosclerosis.[81] Altogether, previous studies suggest a therapeutic avenue for managing several aspects of vascular ageing and atherosclerosis through modulation of Cav-1 expression.

6.5 miRNAs in atherosclerosis and inflammageing

Epigenetic alterations, encompassing DNA methylation, modifications to histones, and post-transcriptional regulators, such as miRNAs or RNA-binding proteins, are associated with the control of inflammatory pathways and processes related to ageing (*Figure 2*). A growing number of reports have shown the capacity of miRNAs to target effectors of longevity or stem cell behavior[1,126] or other aspects closely associated with age-related CVD, such as lipid metabolism and inflammation.[127,128] Although our understanding of their involvement in atherosclerosis and cardiovascular metabolism is more comprehensive,[129] further research is required to precisely elucidate how these post-transcriptional regulators synergistically contribute to both inflammageing and atherosclerosis. MiRNAs have emerged as direct modulators of inflammatory pathways, including NF-κB, mTOR, Sirt, TGF-β, and differential patterns of miRNA signatures are linked to age-related diseases, including atherosclerosis.[130,131] Conducted research showed up-regulated miRNAs such miR-21-5p and miR-126-3p during ageing while others like miR-25-3p, miR-92a-3p, miR-93-5p, miR-101-3p, miR-106b-5p, miR-142-5p, miR-151a-3p, and miR-181a-5p are reduced levels in age individuals. Some other up-regulated miRNAs present in circulating plasma and extracellular vesicles, such as miR-29a-3p, miR-29c-3p 3, miR-155-5p, miR-184-3p, or miR-300-3p, have been lately described as systemic regulators of ageing. Despite the available information, the promiscuous nature of the regulation of gene expression by miRNAs makes it necessary to explore direct actions on specific pathways or targets involved in inflammation in the context of age-induced atherosclerosis. For instance, miR-21-5p levels are higher in patients with CVD than in age-matched controls and inversely correlate to circulating inflammatory markers of CVD, such as CRP or fibrinogen.[132] Another example is miR-34, which has emerged a key gero-miRNA, increasing with age and promoting senescence and inflammation in vascular cells. Indeed, various risk factors of CVD modulate miR-34a expression, exacerbating vascular dysfunction or promoting VSMC proliferation during disease progression.[107] To add further intricacy to the field, patterns of molecular changes in miRNAs during ageing seems to be tissue- and cell-type specific,[131,133] that, summed to the complex multicellularity of the atherosclerotic process, makes these studies very challenging. Nevertheless, approaches as experimental heterochronic parabiosis have been able to partially reverse the age-related increase in miR-29c-3p, a miRNA that targets ECM and secretion pathways which could potentially impact inflammageing and CVD.[131] Related to the inflammatory nature of miRNAs during ageing, studies analysing whole-blood human samples suggest that the miRNAs showing an increase with age primarily originated from immune cells, including B cells, monocytes, NK cells, and cytotoxic T cells. Moreover, analysis of large cohort of patients uncovered pan-disease and disease-specific alterations in ageing miRNA profiles. Specifically, miRNAs, such as miR-191-5p and miR-16-5p, were highlighted as dysregulated in the context of cardiovascular disorders, suggesting their potential involvement in the underlying molecular mechanisms.[131]

These findings provide insights into the complex dynamics of miRNA changes during ageing and their potential implications for understanding age-related cardiovascular disorders and developing specific disease biomarkers. In summary, the identification of disease biomarker sets in ageing profiles has the potential to revolutionize the diagnosis, treatment, and management of age-related diseases, ultimately improving the quality of life for older patients.

The acknowledgement of the interconnected relationship between ageing, inflammation, and CVD has garnered significant new mechanistic insights, as

outlined in this section. Several innovative therapeutic possibilities have arisen from these advancements in basic science. Utilizing biomarkers to evaluate the heightened activity of specific proinflammatory pathways could aid in tailoring therapies and improving the personalization of medical interventions, particularly in the expanding aged population.

6.6 Heart failure with preserved ejection fraction and inflammageing

The molecular mechanisms of inflammageing in cardiac and vascular ageing involve several key pathways and processes including the NLRP3 inflammasome activation and the interaction with TFG-β1 axis, telomere shortening, oxidative stress, and endothelial dysfunction among others (*Figure 2*).[134] These altered inflammation processes impact in CVDs other than atherosclerosis such as HF disease, hypertension, and degenerative aortic aneurysm. HF with preserved ejection fraction (HFpEF) is a condition that affects over 50% of HF patients where the heart is unable to pump blood effectively, leading to a range of symptoms, such as fatigue, shortness of breath, and fluid retention. Despite in HFpEF, the ejection fraction is preserved, meaning that the heart's pumping function is still relatively normal, patients with HFpEF display abnormal diastolic fraction.[135] This results in elevated pressures within the heart, leading to symptoms of HF. There are several risk factors for HFpEF but compared with HF-reduced ejection fraction (HFrEF), in which the ejection fraction is reduced, HFpEF is more often associated with conditions such as hypertension, obesity, diabetes, insulin resistance, and ageing.[135,136] In fact, available evidence suggests that the severity of HFpEF increases more rapidly with age than HFrEF but also the prevalence of HFpEF at any given age is higher in women compared with men, suggesting a close interplay between ageing, gender, and age-related HFpEF progression compared with HFrEF.[137] Moreover, metabolic dysfunction is a feature of ageing, and a large proportion of HFpEF individuals is overweight or obese and display metabolic cardiomyopathy. Clinical and preclinical studies have linked adiposity with deteriorating cardio-pulmonary parameters in HFpEF.[138]

In this section of the review, we explore the molecular and pathological settings by which inflammageing may be both a risk factor and a pathogenic mechanism of HFpEF and identifies potential targets, specifically those that are based on anti-inflammageing strategies. Inflammageing plays a causative role in the development of HFpEF which is disproportionately found in older individuals. Several key inflammatory pathways are involved in HFpEF, including chronic low-grade systemic inflammation, activation of the renin–angiotensin–aldosterone system, oxidative stress, and activation of the IS. These pathways can contribute to the development and progression of HFpEF and its associated comorbidities. Inflammageing may also induce changes in the vasculature of the heart.[139] Specifically, by reducing availability of NO, an important vasodilator and regulator of protein kinase G activity causing hypertrophic changes and endothelial production of E-selectin. This results in an increase of lymphocytes recruitment which in turn release TFG-β1, encouraging fibrosis and thus ventricular stiffening, all of which can worsen diastolic function. Activation of the renin–angiotensin–aldosterone system can also contribute to fibrosis and hypertrophy of the heart, while oxidative stress can lead to metabolic heart disease. Recent evidence shows that PCSK9 has emerged as a new regulator of cardiometabolic ageing as their levels are increased in older people and is an independent predictor of left ventricle diastolic dysfunction.[140] On the other hand, cardiac ageing increases cardiomyocyte senescence that affects normal function of heart resembling HFpEF manifestations.[108] It has been suggested that HFpEF merely represents an acceleration of a normal ageing process. In fact, senile systemic amyloid deposition as part of the degenerative ageing process is emerging as an prominent and underdiagnosed contributor to HFpEF with age (*Figure 2*). Lately, activation of the IS by all these stressors and other events, such as previous infections, particularly with CMV and HIV can also contribute to the development progression and perpetuation of HFpEF and its associated comorbidities through inflammageing. In this context, due to the chronic or persistent antigen stimulation, T-cell responses are compromised during ageing at least partially owed to inmunosenescence and inflammation as hypothesized by Sansoni *et al.*[141]

Managing HFpEF typically involves addressing underlying conditions, lifestyle modifications, and medications to alleviate symptoms and improve the overall function of the heart.[142,143] Efficacy of common HF therapeutics has turned unsatisfactory in HFpEF so far. Specific therapeutic strategies for HFpEF treatment include drug repurposing, targeting metabolic-induced inflammation, and ongoing clinical trials testing various pharmacological therapies with immunomodulatory actions for CVD and diverse HF. Regarding available targeted metabolic dysfunction interventions, which are the most, some of them have beneficial effects in inflammatory status of HFpEF. Clinical trials testing other targets and device-based approaches in HFpEF are also being explored. Among them, direct targeting of inflammageing offers a new therapeutic opportunity for HFpEF patients.

6.7 Targeting low chronic inflammation for HFpEF treatment

Different inflammatory pathways converge in the onset of inflammageing as discussed above; therefore, attenuation of inflammatory burden during ageing may attenuate the severity of symptoms observed in HFpEF patients, which in turn can enhance the quality of life and life expectancy. Immunomodulatory therapies, such as monoclonal antibodies targeting proinflammatory cytokines, are the most used. The activation of NLRP3 inflammasome signalling in HFpEF remains circumstantial and requires further investigations. In contrast to other CVD events, such as atherosclerosis, canakinumab has not been tested in HFpEF patients yet.[102] However, several trials aiming to inhibit cardiac proinflammatory pathways in HFpEF, by blockade of IL-1R with anakinra, a recombinant IL-1 receptor antagonist, resulted in reduced systemic inflammatory status and decreased CRP levels.[100,101] Because of elevated levels of systemic IL-6 and TNF-α in HFpEF patients, targeting these specific inflammatory pathways with anti-IL-6 therapy (TCZ) and anti-TNF-α, respectively, represents the best examples of immunomodulatory strategies[144] (*Table 2*). These cytokines, together with CRP, have also proved useful as robust biomarkers to identify patients who may benefit from anti-inflammatory treatments. The potential benefits of TNF-α antagonism in rescuing the effects of ageing on stroke are shown in a study that offers exciting perspectives for targeting inflammageing and improving stroke outcomes and other HF diseases.[145] In another study, treatment with a DC-SIGN ligand (DCSL1, dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin ligand 1) reduced macrophage polarization and diastolic dysfunction during ageing, but in a gender-specific manner.[146] The reduction in proinflammatory macrophage polarization was accompanied by a decrease in fibrosis, suggesting that the anti-inflammatory effects of DCSL1 may have contributed to the improvement in diastolic function in female mice. On the other hand, colchicine has been shown to have anti-inflammatory properties in a high salt diet rat model of HFpEF, attenuating cardiac dysfunction and fibrosis and modulating the inflammasome NLRP3 and NF-κB pathways.[147] Several clinical trials have been conducted on colchicine in reducing cardiovascular events in diverse heart disease and CVD, including atherosclerosis; however, despite the promising results of colchicine in animal models, its use in humans should be carefully considered because of certain side effects. Even so, low doses in humans are only recommended to high CVD-risk patients.[105,106]

Since there is a strong correlation between HFpEF and metabolic syndrome, T2D, and obesity, available therapeutic strategies for these diseases are now being evaluated to prevent or manage diverse pathological aspects of heart disease and specifically HFpEF. Some of these metabolic interventions using inhibitors with indirect beneficial effects on the inflammatory status of HFpEF, include trials testing sodium-glucose cotransporter 2 inhibitors (SGLT2 inhibitors), a monoamine oxidase inhibitor,[148] a xanthine oxidase inhibitor,[149] and an inhibitor of the uric acid transporter URAT1.[150] While the empagliflozin SGLT2 inhibitor has turned out to be beneficial and showed significant changes in cognitive impairments and frailty,[151] it has not been tested yet for inflammageing in HFpEF disease.[94] However, another SGLT2 inhibitor, dapagliflozin, also used in the treatment of T2D, resulted in improvement of HFpEF as indicated by

reduced hospitalizations and cardiovascular death[152] (*Table 2*). In this line, a recent study provides new clues about the metabolic stress-dependent activation of cardiac macrophages in a model of dyslipidaemia-induced diastolic dysfunction, putting the IS back in the spotlight as a target for treatment HFpEF. In this study, the authors suggest the use of SLTG2 inhibitors as potential agents in the therapy of this specific phenotype of HFpEF. Other pharmacological treatments mainly used for non-alcoholic fatty liver disease, including statins, thiazolidinediones, GLP-1R agonists, and metformin, have shown beneficial effects on HFpEF progression but whether this mechanism involves reduction of inflammageing has not been addressed yet. Recently, semaglutide has gained increasing interest in targeting diabetes and other metabolic dysfunction. This GLP-1R agonist is approved in obese HFpEF patients' treatment and may reduce inflammation at the systemic level by measuring CRP levels as shown in the STEP-HFpEF trial.[112,153]

The use of angiotensin receptor neprilysin inhibitors may exert its therapeutic effects in HFpEF by targeting multiple pathological mechanisms involved in the pathogenesis and progression of the condition, including inflammation, hypertrophy, and fibrosis. One of them, sacubitril/valsartan reduces myocardial inflammation[154] while LCZ696 inhibitor used in other trial (PARAGON) for HFpEF patients,[110] did not show any significant improvement at the inflammation level, except in some specific cases of HFpEF. The use of different angiotensin inhibitor therapeutic agents has revealed heterogeneity in the symptoms of this disease. Therefore, more evidence is needed to clarify the exact mechanism by which some individual respond better than others.

Other evidence suggests that stimulators of the NO-sensitive soluble guanylyl cyclase could be a potential therapeutic option for humans with HFpEF. A study shows that using the NO-independent stimulator BAY 41-8543 in a double-transgenic rat model of HFpEF can drastically improve survival rates, reduce cardiac fibrosis and inflammation, and improve cardiac function and hemodynamics.[155] Thus, future studies are necessary to determine the interplay between senescence mechanisms and metabolic-induced inflammation for the HFpEF pathogenesis.

Finally, another interesting strategy is based on targeting the mitochondria-inflammation circuit to mitigate HFpEF. By increasing circulating β-hydroxybutyrate abundance, it ameliorates HFpEF phenotypes by abrogating the vicious circuit of mitochondrial damage and inflammation. The study investigates metabolic mechanisms and tests therapeutic interventions of HFpEF by revealing new mechanisms between mitochondrial dysfunction and activation of NLRP3 inflammasome as a key driver in the pathogenesis of HFpEF.[156]

6.8 Nutritional and lifestyle-based interventions with reduced inflammageing

There is ample evidence that western lifestyle in the developed world in combination with environmental triggers increases cardiovascular risk of the world's population as it age. A sedentary lifestyle, hypercaloric diets or stress may accelerate or worsen the symptoms of CVD.[157] For example, recent evidence showed association of non-regular sleep and subclinical markers of CVD, with special impact on atherosclerosis.[158] There is a variety of lifestyle modifications based on reduced dietary intake, and their pharmacological mimics, that delay the onset of age-related diseases and expand life expectancy. Nutrient sensors, such as mTOR and its downstream mediator Syntaxin 13 (Syx13), are linked to lysosome morphology and regulate inflammageing as shown in a recent study.[159] Of note, rapamycin treatment reduced inflammageing and immunosenescence. Therefore, distinct interventions other than the use of medications are being developed to mitigate inflammageing and therefore the onset and progression of its associated diseases. The role of nutrition is a key on inflammageing status as described by many authors and it is clear that specific modifications in dietary patterns that affects inflammageing have become in a powerful strategy for healthy ageing.[160,161] Additionally, natural non-drug intervention based on regular exercise are now being explored in several trials to test whether inflammatory markers are reduced. As shown in this recent work,[162] in addition to positive impact delaying the onset of age-related diseases, exercise has been shown to enhance proteostasis, stress response, and epigenetic stability, while reducing inflammation and metabolic dysregulation. Previous studies have demonstrated higher levels of proinflammatory eicosanoids in HF, including prostaglandins PGI2 and PGE2, suggesting their involvement in the inflammatory processes underlying HFpEF.[163] Some of these lipids act as ideal biomarkers of HFpEF status and exercise manifestations in the disease. Therefore, targeting these bioactive lipid mediators could be a therapeutic strategy to modulate inflammation in the physiopathology of HFpEF.[164]

Malandish and Gulati investigated the effects of exercise interventions on serum or plasma levels of specific inflammageing markers (TNF-α, IL-6, IL-1β, IL-8, and high-sensitivity CRP, hs-CRP) in overweight and obese patients with HFpEF. The study revealed significant differences in the effects of aerobic, resistance, and concurrent exercises on inflammageing markers in overweight/obesity patients with HF, specifically improving inflammageing markers such as TNF-α, IL-6, and hs-CRP. In addition, the analysis of subgroups by age, body mass index (BMI), type, intensity, duration of exercise, and mean left ventricular ejection fraction revealed specific reductions in TNF-α, IL-6, and hs-CRP for different exercise modalities and patient's characteristics. Furthermore, the meta-analysis highlighted that aerobic and concurrent interventions with moderate and high exercise intensities, as well as short, long, and very long-term follow-ups, may downregulate the inflammageing process in HF patients. These findings suggest that the type and intensity of exercise interventions, as well as the duration of follow-up, play a significant role in modifying inflammageing markers in overweight/obesity patients with HF.[165] These findings have several potential implications for the development of exercise interventions for patients with HF and related conditions including tailored exercise prescription and the anti-inflammageing effect of the exercise prescription, which may have clinical benefits for patients with HF. The findings call for further research to explore how exercise interventions, ageing, and BMI modify the inflammageing process in individuals with HF. Overall, the data described in this review provide new approaches on how to treat CVD and present strategies to prevent atherosclerosis and HF, both based in modifying inflammageing markers and improving clinical outcomes for patients with HF and obesity. Lastly, all these analyses can help to improve or even delay the ageing process.

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