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POSITION PAPER

The crosstalk between immune activation and metabolism in heart failure. A scientific statement of the Heart Failure Association of the ESC

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A better understanding of additional mechanisms of heart failure (HF) progression may allow a different and more complete phenotyping of the disease and identification of novel therapeutic targets. Persistent latent myocardial inflammation/immune activation in HF may represent an attempt to restore tissue homeostasis in the failing heart, where cardiomyocytes and immune cells undergo metabolic reprogramming, which allows them to deal with decreased availability of nutrients and oxygen. This status can trigger a metabolic crosstalk between immune cells and cardiomyocytes which, depending on the outcome, can either perpetuate the maladaptive remodelling of the heart, or determine an adaptive response. Therefore, the interplay between immune activation and metabolism is gaining recognition as a potential therapeutic framework. On these premises, future studies addressing novel HF treatments should attempt to evaluate the potential therapeutic role of direct metabolic and immunological crosstalk modulation. The aim of the present scientific statement from the Heart Failure Association of the ESC is to summarize the current evidence for the connection between inflammatory and immune activation and metabolic adaptation in the onset and progression of HF, in order to promote future strategies for the development of targeted-disease preventive and therapeutic measures.

Keywords Aging • Heart failure • Immunometabolism • Inflammation • Maladaptive • Myocardial Metabolism • Therapy

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[Correction added on 5 July 2025, after first online publication: Sophie Von Linthout has been corrected to Sophie Van Linthout, and two affiliations have been added under her name in this version.]

Introduction

The pathophysiological pathways that initiate and perpetuate heart failure (HF) are complex. Multiple maladaptive and adaptive compensatory mechanisms exist, which span from the subcellular level to organ-to-organ interactions. The contemporary treatments for HF aim at counteracting the haemodynamic impairment and the pathological neurohormonal hyperactivation that characterize the evolution of the syndrome. Nevertheless, increasing evidence shows that other mechanisms, including immunoinflammatory activation and metabolic adaptation, are active part of disease progression, are tightly interconnected to each other, and play a central role in the pathophysiology of HF. Systemic metabolism and the immune system respond in a coordinated manner to stress, such as infection, cancer, or other organ and tissue injuries. Haemodynamic impairment is a trigger for cardiac inflammation and changes in cellular metabolism. Immune cells also play important non-immune functions, including neural development, and modulation of cardiovascular function and metabolism. Experimental and clinical studies on HF pathophysiology have highlighted the role of these factors in the onset and progression of HF, but their comprehension is still partial and a large gap remains in the understanding of their dynamic interplay. The concept of immunometabolism may advance our knowledge of the complex interaction between energetic metabolism pathways and immune cell response.[1]

The aim of the present scientific statement from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) is to summarize current evidence on the connection between inflammatory, immune activation and metabolic adaptation in the development and progression of HF, in order to outline future strategies for the identification of targeted-disease preventive and therapeutic measures.

Metabolic and immune adaptation in heart failure: pathophysiological concepts

Cardiac metabolic changes in heart failure

The heart requires a large amount of adenosine triphosphate (ATP) to sustain contractile function, which is obtained from mitochondrial oxidative phosphorylation and glycolysis. The healthy heart is 'metabolically flexible', and readily shifts between fatty acids, lactate, glucose, ketones, and amino acids as fuel sources to maintain ATP production.[2] In contrast, the failing heart loses its metabolic flexibility and can become energy deficient due to a decrease in ATP production,[3–5] primarily due to a reduced mitochondrial oxidative capacity and impaired mitochondrial creatine kinase energy metabolism.[6–11] These altered mitochondrial dynamics are important contributors to the overall reduction in mitochondrial oxidative capacity and therefore ATP production in HF (*Figure 1*).

Decreased mitochondrial oxidative metabolism in HF leads to the induction of glycolysis in an attempt to compensate for the decrease in mitochondrial ATP production.[3–5] However, this increase in glycolysis is inefficient and not accompanied by enhanced mitochondrial oxidation of pyruvate derived from glycolysis.[12–22] Inhibition of cardiac mitochondrial pyruvate uptake results in the development of HF in mice.[23,24] The reduction in pyruvate utilization may also contribute to adverse left ventricular remodelling.[15,23,25–27]

Heart failure is also associated with alterations in cardiac fatty acid oxidation. It is reported that reductions in mitochondrial fatty acid oxidation occur in HF, but data are not consistent across different studies.[23,26,28–39] Myocardial fatty acid oxidation also increases in response to conditions such as type 2 diabetes (T2D), obesity and insulin resistance.[40–43] Despite the close association, a causal role for increased fatty acid oxidation rates in cardiac dysfunction under obesity or diabetic conditions is less certain. Since cardiac lipid uptake is increased in these models, an imbalance between lipid uptake and oxidation likely contributes to lipotoxicity.

Cardiac ketone oxidation is also altered in the failing hearts. The increase in ketone metabolism is thought to be an adaptive process in HF,[44] and may provide the 'starving' failing heart with an extra source of ATP.

In summary, the failing heart is energy deficient, primarily due to a decrease in mitochondrial oxidative capacity, an increased glycolysis uncoupled with glucose oxidation, and either a decrease or no change in fatty acid oxidation. In contrast, if there is increased fatty acid availability, as occurs in obesity, an increase in cardiac fatty acid oxidation may occur. These energy metabolic changes result in the failing heart becoming less efficient.

Immunological changes in heart failure

The primary role of an inflammatory response is to resolve the source of the disturbance, thereby allowing the involved tissues to ultimately restore their function. In the setting of chronic HF, while some inflammation may be required to repair a short-term injury and therefore be protective, a persistent myocardial and systemic inflammatory state takes place and can contribute to disease progression.[45] The enduring expression of pro-inflammatory cytokines and ongoing inflammation that have been demonstrated in the failing heart indicate a state of ongoing chronic inflammation that is intermediate between normality and acute inflammation.[46] These pro-inflammatory cytokines contribute to the pathogenesis and progression of HF primarily by left ventricular remodelling and dysfunction, and secondarily by interacting with the neurohormonal system and cardiac metabolism.[47] Activation of neurohormonal systems in HF further contributes to maintain systemic and cardiac inflammation.[48] Both the innate and adaptive immune systems have a pro-inflammatory role in HF. The immune response-triggered inflammation mechanism is called immune or sterile inflammation. This intermediate state has also been termed para-inflammation, and does not require overt tissue injury or infection for it to be sustained, but instead represents a sustained inflammatory response aimed at restoring tissue functionality.[49] Since HF is generally characterized by decreased availability of nutrients and oxygen, cardiomyocytes and non-cardiomyocytes, including fibroblasts

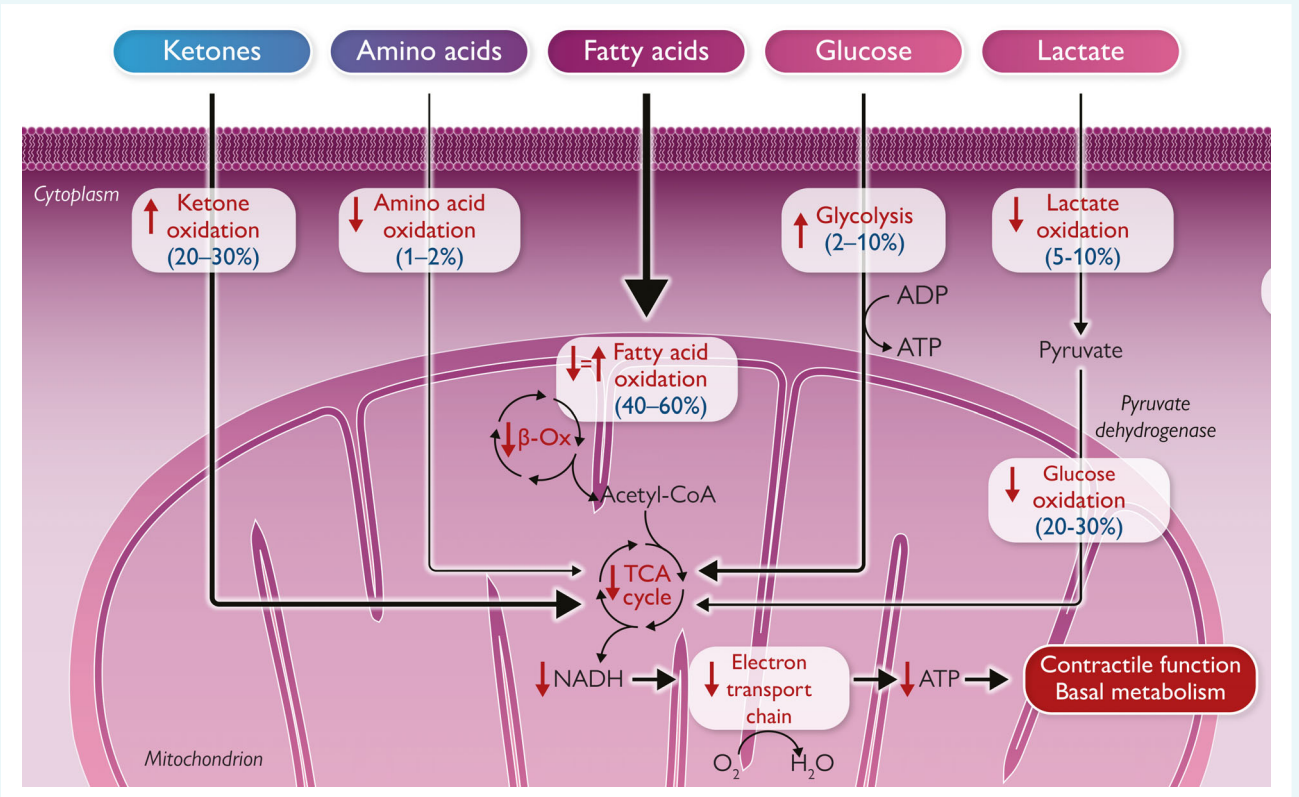

Figure 1 Cardiac energy metabolism in heart failure with reduced ejection fraction (HFrEF). Mitochondrial fatty acid oxidation, glucose oxidation, ketone oxidation, lactate oxidation and amino acid oxidation are the main sources of adenosine triphosphate (ATP) production in the heart. Cytoplasmic glycolysis is also a source of ATP production. In HFrEF, overall mitochondrial oxidative metabolism and ATP production is decreased, with glucose oxidation being markedly impaired. Fatty acid oxidation can also decrease as the severity of heart failure increases, or increase in settings such as obesity. In contrast, both glycolysis and ketone oxidation increase in HFrEF. Red arrows indicate direction of change in HFrEF. Blue text indicates the relative contribution of the various metabolic pathways to ATP production. ADP, adenosine diphosphate; NADH, nicotinamide adenine dinucleotide; TCA, tricarboxylic acid.

and immune cells, undergo metabolic reprogramming in order to adapt to this condition.[50] Competition for nutrients and increased production of signalling metabolites initiate a metabolic crosstalk between immune cells and cardiomyocytes, which is proposed to tip the balance between resolution of inflammation versus adverse cardiac remodelling.[51] With glucose metabolism and ATP generation being deeply involved in immune cell activation, proliferation, trafficking and effector functions, reprogramming of the metabolic status of immune cells leads to changes in their functional properties and supports phenotype switching between different subtypes[52–56] (*Figure 2*).

Diet and HF-associated gut microbiota further affect immune cell metabolism and foster chronic inflammation and ineffective adaptive immunity. This implies that therapeutic modulation of systemic metabolism can re-establish immune cell homeostasis and modulate adverse cardiac remodelling. Caloric excess shortens lifespan, promotes systemic inflammation and increases the risk of cardiometabolic diseases.[57] In contrast, caloric restriction and fasting have been shown to be inversely associated with cardiovascular diseases, and there is now an increasing attention to its therapeutic potential.[58] In HF, and especially in obese patients with a preserved ejection fraction phenotype, caloric restriction or fasting programmes, alone or in association with exercise training, improved peak oxygen uptake at cardiopulmonary excercise testing and quality of life.[59,60]

However, prolonged fasting and reduction in caloric intake can have also negative effects, particularly on immunity regulation. During starvation, organs and systems set a sparing energy process with a survival-driven hierarchy. The production of immune cells slows down relatively early in the process of conserving resources, potentially increasing the infective risk. A recent study has shown that during nutrient scarcity the marrow is a safe haven for monocytes and re-feeding prompts mobilization culminating in monocytosis of chronologically older and transcriptionally distinct monocytes.[61] These shifts could alter the adaptation to external stressors response, outlining that diet, in particular a diet temporal dynamic balance, modulates monocyte lifespan, with consequences on regulating the immune response, inflammation, and tissue repair. An appropriate regulation of immune cells turnover is vital for overall health and immune function, therefore the definition of the optimal balance is necessary to preserve the organism's immunological response.

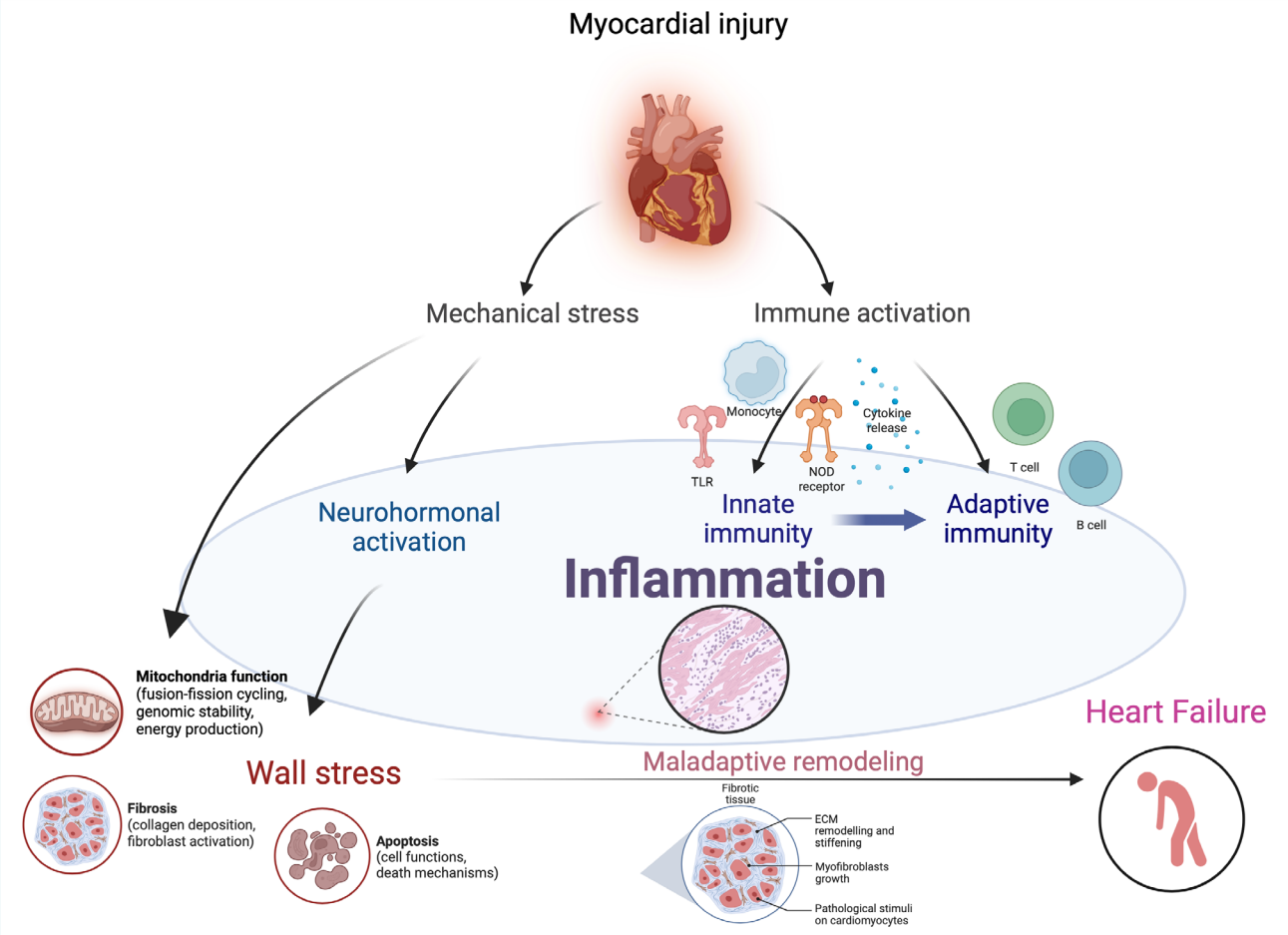

Figure 2 Immunological changes in heart failure. Myocardial injury can trigger the pathological process leading to heart failure involving multiple mechanisms. Indeed, the classical neurohormonal activation mediated by the circulatory and mechanical stress is paired with immunometabolic changes which flow in a state of persistent inflammation. The process is mediated by the activation of both adaptive and innate immunity and their interaction. The maladaptive remodelling of the heart resulting from the negative effects of each of the involved mechanisms is characterized by several alterations in cellular functions and a pro-fibrotic state. ECM, extracellular matrix; NOD, nucleotide-binding oligomerization domain-like; TLR, Toll-like receptor.

Adaptive role of immunity and interplay between metabolism and inflammation

Although immune activation is typically maladaptive in HF, it is crucial to acknowledge that inflammation is a fundamentally adaptive process (*Figure 3*). In response to viral myocarditis for instance, inflammation initially serves an adaptive purpose, but excessive immune cell activation can cause a switch from host defence to injury.[62] In fact, in HF the adaptive immune system is dysregulated, with an exaggerated inflammatory response that contributes to the progression of the disease. Macrophages, neutrophils, T cells, B cells, and humoral immunity all play key roles in driving chronic inflammation, fibrosis, and tissue remodelling. Understanding the complex interactions between these immune cells and pathways is crucial for developing targeted therapies to modulate the immune response and potentially slow the progression of HF.

Macrophages are central to the inflammatory process in HF and play both protective and detrimental roles, depending on their polarization and activation state. In HF, mechanisms of activation are altered, which contributes to chronic inflammation, fibrosis, and adverse cardiac remodelling. M1 macrophages secrete pro-inflammatory cytokines such as tumour necrosis factor-α, interleukin (IL)-1, and IL-6, which exacerbate cardiac inflammation and injury. Increased recruitment and activation of macrophages in the heart tissue may contribute to myocardial inflammation, fibrosis, and remodelling by secreting various cytokines, chemokines, and matrix metalloproteinases.[63]

Neutrophils are part of the innate immune response and are actively involved during acute exacerbations or after myocardial infarction, infiltrating the heart and releasing pro-inflammatory cytokines, reactive oxygen species (ROS) and enzymes that contribute to tissue damage and amplification of inflammation. In chronic HF, sustained neutrophil activation contributes

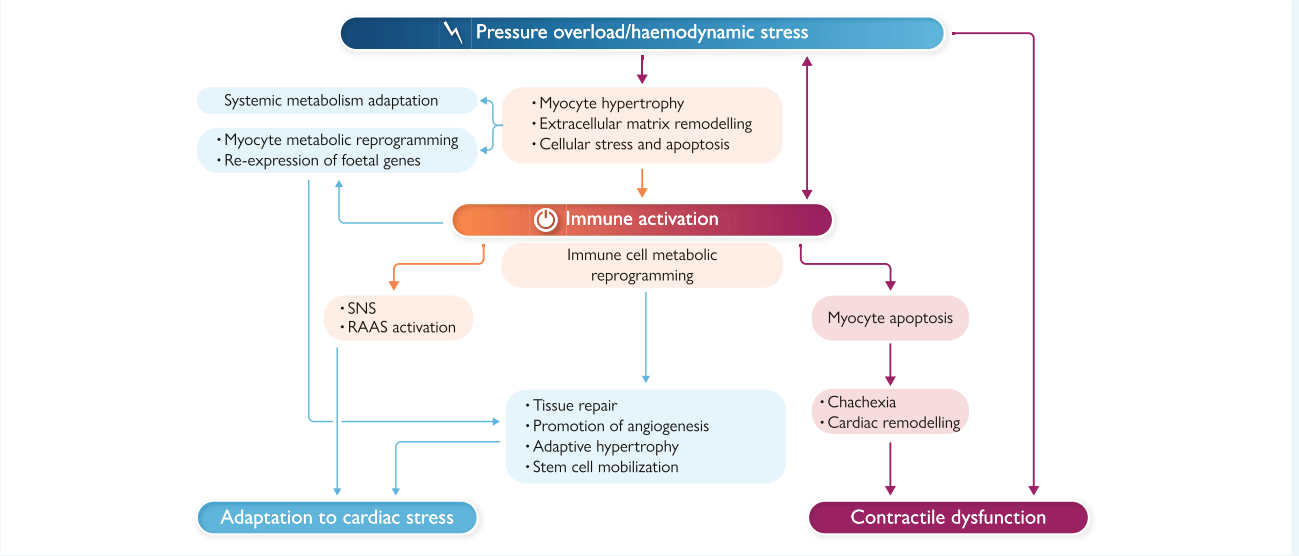

Figure 3 Adaptive role of immunity and interplay between metabolism and inflammation in heart failure. Inflammation plays a significant role in the pathophysiology of heart failure, acting both as a potentially adaptive response (blue lines) and as a contributor to disease progression (violet lines). Heart failure is both driven by and exacerbates a state of chronic inflammation, characterized by elevated levels of inflammatory cytokines, which are involved in recruiting immune cells to sites of injury, helping the removal of dead cells and promoting tissue repair and remodelling. Inflammatory signals can also stimulate angiogenesis. Additionally, inflammation contributes to the structural and functional remodelling of the heart in response to injury or stress by promoting adaptive cardiac hypertrophy. Finally, inflammatory cytokines are involved in remodelling the extracellular matrix of the heart by regulation of matrix metalloproteinases. Activated immune cells, such as macrophages and T cells, shift their metabolism towards glycolysis. This metabolic shift supports rapid proliferation and function of immune cells, promoting their activation and prolonging the adaptive inflammatory response. Inflammatory signals can also contribute to energy metabolism modification in cardiac cells to meet the increased energy demands during stress. This includes a shift from fatty acid oxidation to glucose utilization, which is a more efficient metabolic pathway, especially under ischaemic conditions. Inflammatory cytokines can activate the sympathetic nervous system (SNS) and the renin–angiotensin–aldosterone system (RAAS) which help to maintain blood pressure and perfusion of vital organs. Brown lines represent functions with conflicting or unclear evidence. While inflammation serves adaptive purposes, chronic and excessive inflammation can become maladaptive, contributing to the progression of heart failure. Persistent inflammation can lead to continuous cardiac remodelling, myocyte apoptosis and drive systemic effects contributing to cachexia and worsening overall health.

to ongoing inflammation, oxidative stress, and endothelial dysfunction.[64]

T cells have been found to play both beneficial and harmful roles in HF, contributing to both the adaptive immune response and the chronic inflammation. T helper cells, particularly Th1 and Th17 cells, are associated with increased inflammation and tissue damage in HF with the production of cytokines such as interferon-γ and IL-17, which are promoters of enhanced macrophagic response and inflammatory activation, myocardial fibrosis and adverse remodelling.[65] Regulatory T cells, that typically act as down-modulators of immune activation and inflammation, are down-regulated in HF. There is also evidence suggesting that cytotoxic T cells ($CD8^+$) may contribute to myocardial injury by inducing cell death in the heart tissue, exacerbating the inflammatory milieu and HF progression.[66]

B cells in HF may produce autoantibodies leading to autoimmunity. For example, autoantibodies directed against β-adrenergic receptors have been observed in HF patients.[67] These antibodies can impair receptor function, contributing to cardiac dysfunction. In some forms of HF, particularly in the context of myocarditis or autoimmune diseases, B cells may infiltrate the myocardium and contribute to local inflammation and tissue damage.[68]

Additionally, multiple cardiac cell types, including myocytes, fibroblasts, and vascular cells, actively contribute to inflammation in response to pressure overload, suggesting that cardiac inflammation may also serve initially as an adaptive response to cardiac stress.[69] For example, the NLRP3 inflammasome is the activated downstream of calcium signalling pathways in response to haemodynamic stress, which implies that inflammation is partly driven by cardiac autonomous mechanisms.[70] Furthermore, while inhibition of immune cell activation in HF models decreases disease severity and slows down the progression of cardiac hypertrophy and fibrosis, anti-cytokine therapies have not yet provided significant clinical benefits in patients with HF.[71] Nevertheless, since persistent inflammation can lead to continuous cardiac remodelling and myocyte apoptosis and determine systemic effects contributing to cachexia and worsening overall health, further research into therapeutic anti-inflammatory strategies is warranted.

The interplay between inflammation and metabolism is gaining recognition as a potential underlying factor in HF.[72] Of particular interest are the recent observations relative to the potential harmful role of epicardial adipose tissue via paracrine or vasocrine secretion of pro-inflammatory and pro-fibrotic cytokines, leading

to both local and systemic inflammation.[73] In particular, inflamed epicardial adipose tissue may provide a direct source of cardiac inflammation due to its close proximity to the myocardium.[74] Second, research has revealed that inflammatory cytokines, such as IL-6, can induce pathological cardiomyocyte hypertrophy, which could contribute to the typical metabolic changes observed in HF.[69] Third, cytokines have the ability to directly target metabolic pathways, as evidenced by the insulin resistance and suppression of the metabolic sensor AMPK that was observed following IL-6 infusion in a HF with preserved ejection fraction (HFpEF) model.[75] Finally, the increase in ROS production associated with inflammation can lead to mitochondrial damage and dysfunction, further exacerbating metabolic derangements.[69] A confounding aspect is that the interplay between inflammation and metabolism may differ between HF with reduced ejection fraction (HFrEF) and HFpEF. In general, inflammation is retained to develop during the course of HF as a response to remodelling, haemodynamic impairment and neurohormonal activation in patients with HFrEF, whereas it may be the primary cause of diastolic dysfunction and hypertrophy in HFpEF as a consequence to extra-cardiac conditions such as diabetes, metabolic syndrome, chronic kidney disease.[76] These findings underscore the critical interplay between inflammation and metabolic dysregulation in HF, supporting the need for more in-depth research into the mechanisms.

Metabolically trained immunity

Long-term epigenetic reprogramming of innate immune cells in response to microbes is known as 'trained immunity', and causes prolonged altered cellular functionality to protect from secondary infections.[77] Immune cells, especially macrophages, reprogram their metabolic pathways to support an enhanced inflammatory response. This often involves a shift from oxidative phosphorylation to glycolysis, which supports a robust immune response. In addition to metabolic reprogramming, trained immunity involves epigenetic modifications that alter gene expression. 'Trained' immune cells can provide a stronger response to infections and inflammatory injuries. This has positive effects in terms of effective pathogens' clearance but can also be responsible for a hyper-inflammatory response.

In a recent animal study, a sterile trigger of inflammation such as western diet feeding, has been shown to generate increased proliferation and enhanced innate immune response, with the NLRP3 inflammasome appearing to be critical for this response.[77] Hence, the use of small molecule inhibitors that block the NLRP3 signalling pathway could represent a new therapeutic approach to better modulate the innate immune response following inflammatory triggers and thereby mediate the potentially deleterious effects of trained immunity in chronic inflammatory conditions.

Immunometabolic abnormalities in specific conditions

Ageing

The principal characteristic of cardiac ageing is a decrease of tissue capacity of recovery and regeneration (*Figure 4*). Along with increased development of tissue fibrosis, the number of cardiomyocytes and their turnover declines progressively with ageing.[78,79] As discussed above, the immune system plays an important role in the development of cardiac damage and progression of HF, especially in the elderly.[80] It is well established that the inflammatory system is chronically over activated in patients with HF, and that there is an association with patient outcome.[81] The immune response is also dynamically remodelled with ageing, determining a phenomenon described as 'immunosenescence'.[82,83] This phenomenon increases susceptibility to multiple clinical conditions such as infections, autoimmune disorders, and malignancies, and causes a subclinical chronic pro-inflammatory state also known as 'inflamm-aging'.[84,85] A possible sequence of events could be initiated by cardiac ageing, which is associated with decline in mitochondrial function and accumulation of dysfunctional mitochondria[86,87] producing and accumulating ROS that, in turn, could lead to accumulation of damaged DNA, proteins, and lipids as well as mitochondrial DNA damage and release.[88] In older subjects, ROS could increase the release of mitochondrial DNA from the cellular cytosol,[89] which produces damage-associated molecular patterns, and is considered to be a driver of inflammatory responses.[90] Inflammatory cells release fibrogenic cytokines and growth factors stimulating the reparative process, characterized by fibroblasts undergoing proliferation to replace lost cardiomyocytes and resulting in remodelling and fibrosis.[91] In this context, preservation of mitochondrial morphology, dynamics, and function might be a therapeutic approach to prevent cardiac ageing. There are several potential drugs and nutraceuticals that could potentially improve age-related mitochondrial dysfunction and, thus, attenuate the process of cardiac 'inflamm-aging'.[92–95] Interestingly, physical exercise has also been shown to preserve mitochondrial health and metabolism and, as a consequence, to reduce 'inflamm-aging'.[96,97]

Finally, clonal haematopoiesis of indeterminate potential (CHIP), the clonal expansion of blood stem cells with preleukemic acquired genetic variants, is an age-related condition affecting approximately 10% of individuals aged at least 70 years.[98] Recent work suggests CHIP is also an independent risk factor for incident HF, with experimental models indicating a role for CHIP in the development of cardiac dysfunction through inflammatory dysregulation and fibrotic remodelling.[99] These findings may have implications for the prevention and management of HF in the elderly, including development of targeted therapies.

In conclusion, the balance between adaptive and maladaptive immune activation and metabolism in senescence is crucial for determining the overall impact on health and ageing. Understanding this balance can guide therapeutic strategies to promote healthy ageing and prevent age-related diseases.

Obesity

In obesity, metabolic alterations and immune dysregulation are intertwined.[72,100] Changes in systemic- and tissue-specific metabolism drive immune alterations and vice versa, participating to the pathogenesis of HF in subjects with obesity.[101,102] The crosstalk between immunity and metabolism in concomitant obesity and HF is bidirectional. The perspective of identifying an

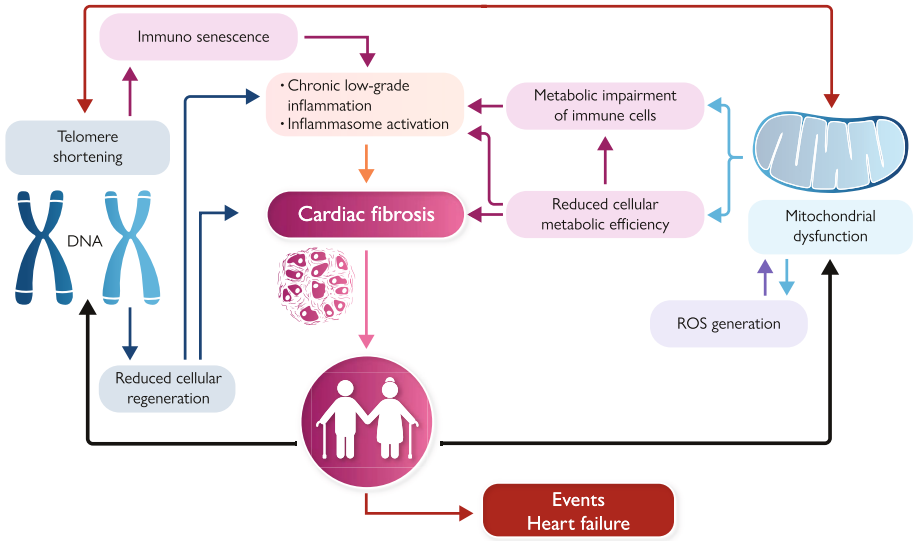

Figure 4 Cardiac ageing. The principal characteristic of cardiac ageing is a decreased tissue capacity for recovery and regeneration, and development of cardiac fibrosis and heart failure. A possible sequence of events could be initiated by a decline in mitochondrial function and accumulation of dysfunctional mitochondria producing and accumulating reactive oxygen species (ROS) that, in turn, could give rise to accumulation of damaged DNA as well as mitochondrial DNA damage and release. Additionally, mitochondrial dysfunction contributes to telomere shortening. The immune system is highly sensitive to shortening of telomeres as its competence depends on cell renewal and clonal expansion of T- and B-cell populations. These effects drive immunosenescence and consequent inflammasome activation. In fact, the vicious circle between mitochondrial dysfunction and DNA damage can lead to a state of chronic low-grade inflammation. Additionally, ROS could increase the release of mitochondrial DNA from the cellular cytosol, becoming a driver of inflammatory responses. In this context, preservation of mitochondrial morphology, dynamics, and function might be a main therapeutic approach to prevent cardiac ageing.

inflammatory signature coupled with alterations of cardiac energy substrate metabolism—a concept which can be encompassed in the term of immunometabolism—in HF is becoming of growing interest.

Obesity-driven changes of both innate and adaptive immunity dysregulate a number of signal pathways which impact on cardiac metabolism in HF. For example, the role of adipose tissue dysfunction and the alterations of its immune compartment in HF pathogenesis are still unclear.[103] Both the metabolic reprogramming of the heart in response to systemic, chronic low-grade inflammation in obesity and the immune phenotype of this condition have not been elucidated in depth.

Metabolic inflammation—that has been specifically termed 'metainflammation'—refers to a systemic, chronic, low-grade inflammation promoted in response to nutrient overload.[104] In obesity, adipose tissue expansion leads to the secretion of chemokines, thereby initiating immune cells recruitment.[105,106] It is known that signals from a particular microenvironment direct immune cell activation as well as macrophage polarization, and T-cell activation. The increase in immune cell infiltration is a hallmark of adipose tissue inflammation in obesity.[107] In this setting, the secretion of systemic pro-inflammatory mediators (e.g. cytokines) has detrimental effects on cardiac function.[50,108] In particular, in HFpEF, this may be mediated by both epicardial adipose tissue and microvascular endothelial dysfunction.[109–113]

Cardiomyocytes have limited capacity to store lipids. When in excess, lipids may enter harmful non-oxidative pathways, yielding the production of toxic intermediates which impacts on immune system function(s).[114] In particular, ceramides are known critical pro-inflammatory molecules and lipotoxic mediators.[115] To contrast toxic lipid spillover, it has been proposed that visceral adipose tissue expansion acts as a buffer and prevents the detrimental effects caused by lipid accumulation in non-adipose tissues.[116] Lipid metabolism and inflammatory pathways are highly integrated, but the contribution of lipotoxicity to metabolic inflammation in HF is still incompletely understood.

Diabetes

Patients with T2D are at increased risk of developing HF, either HFrEF or HFpEF, and the coexistence of T2D and HF is associated with a worse prognosis.[117] Although common causes of HF in patients with T2D are represented by coronary artery disease and/or hypertension, insulin resistance and hyperglycaemia may also have direct effects on the myocardium, and a distinctive cardiac phenotype known as diabetic cardiomyopathy has been described.[118–120] The presence of this distinct entity has been difficult to prove, but several interactions of systemic, myocardial and cellular/molecular manifestations have been demonstrated as contributing mechanisms to T2D-associated HF.[121] Insulin resistance and/or reduced insulin signalling in adipose tissue, liver and

skeletal muscle play a pathophysiological role in T2D-associated HF, but also abnormal cardiac extracellular matrix deposition, metabolic disturbances, oxidative stress and inflammatory pathways may contribute to adverse cardiac remodelling.[122,123] The interplay between cardiomyocytes and non-myocytes in the heart (fibroblasts, vascular cells, autonomic neurons, and immune cells) is crucial.[118] Excessive and sustained local inflammation in response to a persistent stress/trigger such as T2D may be 'maladaptive' and favour cardiac injury. T2D-mediated oxidative stress enhances a pro-inflammatory milieu and promotes the mobilization of leucocytes (neutrophils, monocytes, macrophages and lymphocytes).[118,121] Rather than favouring the polarization of macrophages towards a reparative M2 phenotype, the secretion of pro-inflammatory cytokines by neutrophils alters the macrophage function and promotes an inflammatory M1-like phenotype, further enhancing macrophage-mediated local inflammation and injury.[118,124] Abnormalities in T-cell signalling and regulation have also been described, further contributing to cardiac inflammation, hypertrophy and fibrosis.[118,125–128] Furthermore, cardiac autoimmunity may have a role, especially among patients with type 1 diabetes. In both type 1 and type 2 diabetes, chronic hyperglycaemia causes subclinical myocardial injury with consequent exposure of heart muscle proteins to the immune system, thus a dysregulated adaptive immune system (typical of type 1 diabetes with poor glycaemic control) may overreact, leading to a local pro-inflammatory state and to the development of autoantibodies to cardiac antigens.[129,130]

Gut microbiome

In the presence of HF, low cardiac output and venous fluid overload contribute to a decrease in intestinal perfusion, mucosal ischaemia, and ultimately in a disrupted intestinal mucosa and increased gut permeability.[131,132] By this means, gut microbiome-derived metabolites, like trimethylamine-N-oxide (TMAO), can reach the systemic circulation, fuel metabolic inflammation and HF exacerbations.[133,134] TMAO levels are in fact a strong predictor of clinical outcomes in patients with HF regardless of the underlying aetiology.[135] The HF-associated gut luminal hypoxia and decrease in mucosal pH further alter the microbiota to pathogenic microbiota and lead to loss of microbial diversity or 'gut dysbiosis', which in turn contributes to the raise in gut permeability and systemic inflammation.[136,137] On the other hand, different gut microbiome compositions have varying abilities to generate TMAO, and higher levels of circulating TMAO can be attributable to a TMA-producing microbiome harbouring TMA lyases.[138]

Vice versa, there is accumulating evidence showing that under the influence of certain environmental factors and host genetic susceptibility, interactions between the microbiome and the host immune system contribute to cardiovascular disease and HF.[139] Risk factors of HF, including Western lifestyle with high salt composition, can lead to hypertension and cardiovascular disease involving reduced survival of *Lactobacillus murinus* and increased T_H17 cells.[140] Western diet, characterized by a high intake of fat and a low intake of fiber, decreases the production of short chain fatty acids (SCFAs) by intestinal microbiota, accounting for the altered regulatory T-cell frequency in mesenteric lymph nodes.[141] On the other hand, caloric restriction modulates gut microbiota composition, leading to regulatory T-cell expansion.[142] In obesity, microbiome-mediated tryptophan metabolites modulate white adipose tissue inflammation,[143] fostering low-grade systemic inflammation and HFpEF.[76] In metabolic dysfunction, the gut contains increased numbers of (γδ)T cells, macrophages, dendritic cells, NK cells, CD8+ cells (αß TCR) and Th1 T cells but less T regulatory cells,[144] linked to intestinal barrier dysfunction, and intestinal dysbiosis. Evidence for the specific involvement of gut immune cells in cardiovascular disease and HF comes from integrin β7 (ITGb7) knockout mice, which lack intraepithelial (αβ) and (γδ)T cells, B cells and myeloid cells in the gut.[145] ITGb7, LDLr knockout mice fed with a high cholesterol diet exhibit lower adipose tissue inflammation, reduced numbers of $Ly6C^{high}$ monocytes and smaller aortic lesions.[146] ITGb7 knockout mice are further protected from hypertension, obesity and diabetes and have higher levels of the gut incretin hormone glucagon-like peptide-1 (GLP-1) due to absence of gut immune cells expressing GLP-1 receptor.[146] GLP-1 is increased in HF independent of food intake as an endogenous protective counter-regulatory response.[147] GLP-1 receptor agonists have been shown to decrease hospitalization for HF in T2D patients by 11%.[148,149] Further, prospective randomized controlled clinical trials in patients with HFpEF and obesity, comparing the GLP-1 receptor agonist semaglutide with placebo, have shown a decrease in body weight with an improvement in quality of life and exercise tolerance altogether with a reduction in C-reactive protein and N-terminal pro-B-type natriuretic peptide (NT-proBNP) plasma concentrations, consistent with a reduction in inflammatory activation and an improvement in diastolic function with the study drug.[150,151] A pre-specified pooled analysis of these trials has also shown better outcomes with semaglutide versus placebo.[152]

Besides the abovementioned mutual interplay between HF and microbiota/dysbiosis-induced systemic inflammation and (extra)-intestinal immunity, it has been shown that cardiac myosin-specific T_H17 cells can be generated, imprinted in the intestine by a commensal *Bacteroides* species peptide mimic, promoting progression of myocarditis to lethal heart disease.[153] This is supported by both the successful prevention of lethal disease in mice by antibiotic therapy and the significantly elevated *Bacteroides*-specific $CD4^+$ T-cell and B-cell responses observed in myocarditis patients. Taken together, these findings highlight a strong mutual inter-relation between the gut and the heart, involving metabolism and the immune system.

Gender

The differences between men and women in epidemiology, pathophysiology, outcomes and treatment of HF are very broad.[154] The hormonal background is considered to yield a protective effect on the cardiovascular system in young women. In women, after menopause the loss of the hormonal balance leads to several changes which increase the risk of HF, and in particular HFpEF.[155,156] Metabolic dysregulation and pro-inflammatory state are only two of the multiple mechanisms behind the different pathogenesis and manifestation of HF in the two sexes.

Microvascular dysfunction, together with the hyperactivation of systemic and local inflammation, is a major determinant of HFpEF especially in women, whereas in men the typical atherosclerotic degeneration of the epicardial coronary circulation predominates.[157] Impaired activation of the endothelial nitric oxide pathway and release of pro-angiogenic factors trigger microvascular dysfunction enhanced by the post-menopausal reduction in oestrogens.[156,158] An additional contribution to microvascular alterations in women comes from the immune-mediated predisposition to endothelial inflammation. Adipokines and inflammatory markers such as leptin and C-reactive protein, both central in the pathogenesis of HFpEF, are indeed expressed to a greater extent in women compared with men, regardless of the post-menopausal period.[159] This is linked with the differences in immune response which is enhanced in women, ensuring prompter recovery from infection and higher protection towards cancer, but the increased systemic inflammatory activation and the stimulation of multiple pro-inflammatory pathways mediated by the stronger immune response indirectly expose women to higher risk of HFpEF.[160] It is of interest and worthy of more deep investigations that sex-specific risk factors (i.e. sex hormones, pregnancy and breast cancer therapy) are strongly linked each other and involved in the pathogenesis of sex-specific diseases or sex-prevalent diseases, such as peripartum cardiomyopathy and stress cardiomyopathy. The common pathophysiological mechanisms behind these diseases involve indeed endothelial inflammation and microvascular dysfunction.[161,162]

Dysfunctional tissue and systemic metabolism characterizing HF also presents some discrepancies in women and men. In men, increased afterload leads to more pronounced down-regulation of lipid and energy metabolism related genes and this implies less preservation of mitochondrial function compared with women.[163,164] On the other hand, females show an up-regulation of peroxisome-dependent lipid utilization genes representing an alternative pathway to cover greater energy demand for the myocardium exposed to increased afterload.[165] Oestrogens are important mediators of mitochondrial function, exerting through different mechanisms a protective effect under the influence of detrimental stressors,[166–168] and also stimulate the activation of antioxidative pathways.

Therapeutic approaches to inflammation and metabolism in heart failure

Therapeutic targets

As outlined above, it is evident that normal cellular homeostasis relies on the crosstalk between the immune system and metabolic regulation, and that several diseases are produced and exacerbated by their dysfunction and crosstalk. Apart from primary inflammatory/metabolic/immune diseases, the plausible biological mechanism in most chronic HF phenotypes is primarily a mechanical incompetence which, in turn, determines metabolic adaptation and inflammatory/immune consequences. The targets of the presently available drugs for the treatment of HF are mainly maladaptive neurohormonal activation and, consequently, improving cardiac mechanical function, which ultimately regulates also metabolic and immune adaptations. This precise sequence of events is deduced by the unsuccessful results of clinical trials of anti-inflammatory therapies in HF, despite the fact that the chronic inflammatory state associated with progression and complications of HF had identified this dysregulated immunologic state as a potential additional therapeutic target.[169,170] On the other hand, improvement of metabolic efficiency may limit inflammation by promoting endogenous anti-inflammatory effects, providing strong evidence for the therapeutic potential also in targeting metabolic processes as for controlling immune effector functions and thereby alleviating pathological inflammation,[171] again likely consequent to cardiac mechanical incompetence. Nevertheless, intensive[71] research is still active to define the potential therapeutic role of anti-cytokine therapy in HF. Some studies employing anakinra, canakinumab and colchicine have shown a significant reduction in inflammatory biomarkers along with an improvement in exercise performance and quality of life and a reduction in natriuretic peptides.[172,173] A clinical trial with ziltivekimab is still ongoing.[174]

In the real world, evidence-based treatments for HF may contribute to modulate the metabolic and immunological crosstalk in HF[52,175] (*Table 1*). HF induces neurohormonal and immune activation, which directly and indirectly modify myocardial metabolism. The autonomic nervous system contributes to the regulation of cardiac function. Enhanced sympathetic stimulation induced by cardiac mechanical failure increases myocardial energy metabolic requirements. Additionally, sympathetic hyperactivity is associated with increased production of myeloid immune cells in the bone marrow, resulting in higher numbers of circulating myeloid immune cells.[176] Recent studies have shown that microglia, known as brain-resident immune cells, may play an important role in regulating sympathetic nervous system activities and cardiovascular function by releasing cytokines, chemokines, and growth factors.[176–178] Beta-blockers blunt the cardiovascular response to adrenergic stimulation and, apart from reducing ischaemia and protecting the infarcted myocardium, have also been shown to directly affect myocardial energetics, by reducing circulating levels of free fatty acids (FFA) and, due to substrate competition, inducing a shift of heart energy metabolism towards a greater utilization of carbohydrates[179–181] (*Table 1*). The observed increase in cardiac carbohydrate metabolism after beta-blockade probably results from decreased FFA delivery and oxidation, as well as from augmented arterial glutamate availability.[182–186] Therefore, a higher rate of carbohydrate utilization induced by beta-blockade may result in a greater cardiac energy production at similar levels of oxygen consumption. Interestingly, there are profound differences in the metabolic profile of the non-cardioselective and selective beta-blockers, the former causing significant inhibition of the lipolytic, glycogenolytic and the growth hormone-releasing effects of adrenaline when compared with the cardioselective ones.[187] Additionally, catecholamines play an important role in the regulation of the physiological immune response and, therefore, the efficacy of beta-blockers in HF may also depend by their crucial immunoregulatory role in modifying a dysregulated cytokine

Table 1 Immunometabolic effects of established and potential medical therapies for heart failure

Drug	Metabolic effects
Beta-blockers	• Reduction of peripheral lipolysis • Increased carbohydrate utilization • Improved insulin sensitivity • Immunoregulatory role in modifying a dysregulated cytokine network
RAAS inhibitors	• Improved glucose homeostasis by increased blood flow in skeletal muscle • More efficient insulin release
Partial fatty acid oxidation inhibitors	• Reduction of lipolysis • Anti-inflammatory effect • Enhancement of insulin sensitivity • Increased glucose oxidation
Coenzyme Q10	• Modulation of late sodium current, thereby reducing the accumulation of intracellular Ca^{++} • Attenuation of macrophage infiltration and pro-inflammatory responses in sepsis-induced myocardial dysfunction • Inhibition of the mitochondrial permeability transition pore • Inactivation of apoptotic cascades and the oxidative inactivation of key proteins involved in ATP production
SGLT2i	• Increased bioavailability and myocardial utilization of ketone bodies • Ketone body-mediated anti-inflammatory effects • Inhibition of epicardial adipose tissue accumulation and inflammation
Statins	• Positive influence on pro-inflammatory cytokine production, immune cell migration and T-cell signalling • Inhibition of epicardial adipose tissue accumulation and inflammation
GLP-1 receptor agonists	• Mitigation of inflammation in visceral fat adipocytes • Modulation of the immune system
Adipose triglyceride lipase inhibitors	• Improved adipose tissue storage capacities • Reduced lipolytic activity
Ketone bodies and short-chain fatty acids	• Anti-apoptotic, anti-fibrotic, and anti-inflammatory actions • Alternative fuel sources • Inhibition of NLRP3 inflammasome formation

ATP, adenosine triphosphate; GLP-1, glucagon-like peptide-1; RAAS, renin–angiotensin–aldosterone system; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

network.[188–191] Indeed, in patients with HF, beta-blockers have been shown to reduce the expression of inflammation, regardless of left ventricular functional response.[192]

The renin–angiotensin–aldosterone system (RAAS) is another system that is hyperactivated in presence of cardiac mechanical dysfunction. Apart from regulating blood pressure, angiotensin II is also an important modulator of cardiac energy metabolism and function. Angiotensin II damages mitochondria in the cardiomyocyte by increasing ROS production,[193,194] and affects mitochondrial oxidative phosphorylation, including FFA oxidation.[19,193] There is also evidence that angiotensin II regulates glucose oxidation and that inhibition of angiotensin II may exert beneficial metabolic effects.[195–198] In addition, by decreasing oxidative metabolism, angiotensin II can reduce ATP production.[199] In this context, apart from blood pressure and fluid balance regulation, angiotensin II antagonism represents an attractive therapeutic approach to target metabolic deregulation in HF. Additionally, as for beta-blockers, RAAS antagonism has been shown to yield a significant reduction in markers of inflammation in different cardiological contexts. Angiotensin-converting enzyme inhibitors (ACEi), compared with angiotensin receptor blockers, appear to produce a more robust anti-inflammatory effect.[200] However, the role of ACEi in inflammation is still debated. Intrinsic ACE has been detected in macrophages and neutrophils, where its overexpression results in enhanced immune responses, independent of angiotensin II. In contrast, ACE activity is also elevated in certain autoimmune diseases and its inhibition benefits patient outcome where inflammatory immune cells are overactive. Further research on the potential role of ACEi in modulating immune response are definitely warranted.[201]

Cardiac metabolism in HF can also be beneficially targeted by specific drugs, by improving mitochondrial membrane stability, mainly dependent on cardiolipin and coenzyme Q10.[202,203] Coenzyme Q10 is an obligatory component of the respiratory chain in mitochondria and plays an essential role in ATP formation in most tissues, including the heart. In addition, Q10 has antioxidant properties and protects circulating low-density lipoprotein particles from oxidation. Its inhibition of the mitochondrial permeability transition pore prevents the activation of apoptotic cascades and the oxidative inactivation of key proteins involved in

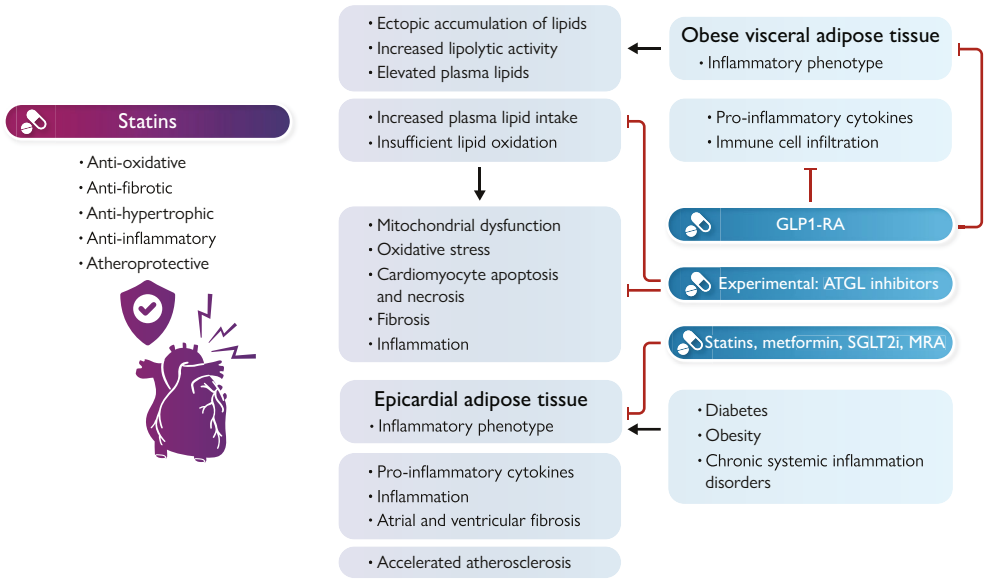

Figure 5 Targeting other sources of inflammation. Statins exert several beneficial pleiotropic effects in the vasculature and cardiac tissue. Obese visceral adipose tissue and epicardial adipose tissue promote pro-inflammatory and lipid-associated pathological effects as well as pro-fibrotic actions, negatively impacting on cardiomyocyte function and survival as well as on cardiac fibrosis. Statins and several other established (in part non-cardiac) and experimental pharmacological treatments inhibit these negative effects, positively influencing immunometabolism of the heart. ATGL, adipose triglyceride lipase; GLP1-RA, glucagon-like peptide-1 receptor agonist; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

ATP production[204] (*Table 1*). Lower levels of coenzyme Q10 are associated with worse HF symptoms, lower ejection fraction and higher NT-proBNP.[205,206] However, association between its values and mortality remains controversial.[207] Coenzyme Q10 supplementation improved HF symptoms and reduced major cardiovascular outcomes in patients with HF in a randomized controlled trial.[208] However, a more recent meta-analysis, due to the low quality of available data, concluded for no convincing evidence supporting the use of coenzyme 10 in patients with HF.[209]

In addition, beneficial effects on cardiac metabolism can be achieved with the direct inhibition of oxidative phosphorylation by shifting energy production from fatty acid to glucose oxidation by selective block of mitochondrial long chain 3-ketoacyl coenzyme A thiolase (3-KAT) activity, the last enzyme involved in beta-oxidation[210] (*Table 1*). This approach has been shown to preserve phosphocreatine and ATP intracellular levels in the failing heart and to exert significant beneficial effects in patients with ischaemic and non-ischaemic left ventricular dysfunction, especially in HF patients who also have diabetes.[211–213] More recently, partial FFA oxidation inhibition with trimetazidine has been shown to attenuate macrophage infiltration and pro-inflammatory responses in sepsis-induced myocardial dysfunction. These effects are achieved by normalizing the inflammatory response pathway in macrophages.[214] Similar anti-inflammatory effects have been observed with ranolazine, another partial FFA oxidation inhibitor, which has also been shown to inhibit the cellular late inward sodium current.[215–217] In particular, the demonstration that functional Na^+ shuttling is required for a full cellular response to inflammation and that inhibition of Na^+–Ca^{2+} exchange during inflammation by ranolazine reduces the inflammatory response in human endothelial cells *in vitro*, in a mouse atherosclerotic disease model and in human patients, opens a new potential immunometabolic therapeutic target.[215]

Moderate caloric restriction could also represent an attractive therapeutic tool targeting the immunometabolic crosstalk in HF. It could improve transcriptional reprogramming in adipose tissue through pathways regulating mitochondrial bioenergetics and anti-inflammatory responsivity,[218,219] possibly by a conveyed reduction of sympathetic activity.[220] Caloric restriction exerts potent anti-inflammatory effects in different pathological conditions by supporting the function of memory T cells and inducing a metabolic switch from glycolysis and fatty acid synthesis to fatty acid oxidation and lipolysis,[221,222] with mechanisms related to increased ketone bodies availability.[27,223–226] Additional studies are warranted to evaluate the clinical role of nutritional intervention in different pathologic conditions, including HF.[227,228]

Targeting other sources of inflammation

Other drugs than evidence-based pharmacotherapy are frequently used in patients with HF due to the frequent coexistence of multiple comorbidities. In randomized controlled trials, statins did not clearly show a prognostic benefit in patients with HFrEF.[229,230] A possible selection bias due to the exclusion of patients with strong primary indication for statins cannot be excluded. Two large observational studies suggested a possible benefit with statins in HFrEF with an ischaemic aetiology, where they are indicated

regardless of HF,[231,232] whereas in HFpEF the observed benefit was independent of the aetiology. It was hypothesized that in HFpEF the underlying effect on systemic inflammation or on microvascular dysfunction might be implicated (*Table 1*, *Figure 5*).[233] Statins are mainly involved in vasculoprotective and anti-atherosclerotic effects; however, they were also shown to mediate direct effects on cardiac tissue, including cardiac endothelium, cardiomyocytes and connective tissue, as for example anti-oxidative, anti-hypertrophic and anti-fibrotic effects, among others through regulating small GTP-binding proteins.[234–236]

White adipose tissue serves as endocrine organ which systemically secretes adipokines and cytokines.[237] Adipokines are involved in metabolic processes and regulate insulin signalling, glucose uptake, FFA oxidation and other energy-producing processes; cytokines mediate regulation of inflammation and adaptive angiogenesis. Lean, healthy adipose tissue secretes anti-inflammatory adipokines and cytokines, whereas obese adipose tissue switches to an inflammatory phenotype, secreting both locally and systemically pro-inflammatory cytokines and chemo-attractants, and is characterized by immune cell infiltration.[237] Obese adipose tissue inflammation negatively impacts remote organ function, including the heart.[103,237] Interestingly, epicardial adipose tissue may be involved in chronic inflammatory disorders, especially those leading to HFpEF, by switching to an inflammatory adipocyte phenotype which, by secreting pro-inflammatory adipokines, may cause atrial and ventricular fibrosis.[108] Thus, epicardial adipose tissue may be a transducer of the adverse effects of systemic inflammation and metabolic disorders on the heart, and may therefore represent an interesting therapeutic target. Drugs such as statins, metformin, sodium–glucose cotransporter 2 inhibitors (SGLT2i) or mineralocorticoid receptor antagonists may inhibit epicardial adipose tissue accumulation and inflammation[108] (*Table 1*, *Figure 5*). GLP-1 receptor agonists mitigate inflammation in visceral fat adipocytes, exert pleiotropic anti-inflammatory properties in different tissues and may modulate the immune system, with potential beneficial effects on cardiac immunometabolism[238,239] (*Table 1*, *Figure 5*).

Neutrophils secrete myeloperoxidase, which has been implicated in the comorbidity-inflammation-microvascular dysfunction paradigm for HFpEF, and inhibition of myeloperoxidase with mitiperstat (AZD4831) appears promising in HFpEF.[110,240]

Low-grade inflammation of adipose tissue promotes the ectopic accumulation of lipids in other organs, including the heart, and catecholamine-derived increased lipolytic activity in adipose tissue results in elevated plasma lipids. Elevated lipid uptake and insufficient lipid oxidation in cardiomyocytes may cause mitochondrial dysfunction and oxidative stress, and consequently cardiac apoptosis, necrosis, fibrosis and inflammation.[241] Novel experimental therapies, such as adipose triglyceride lipase inhibitors, leading to improved adipose tissue storage capacities and reduced lipolytic activity as well as to anti-apoptotic, anti-fibrotic, and anti-inflammatory actions in cardiac tissue, showed promising results on cardiac metabolism and cardiac dysfunction in experimental disease models, and may therefore represent new promising pharmacological tools to treat pathological metabolic phenotypes of HF[241] (*Table 1*, *Figure 5*).

Finally, iron is essential for cardiovascular processes, including bioenergetics, electrical activity, and programmed cell death. Iron deficiency leads to impaired immune function and metabolism, while iron overload causes oxidative stress, chronic inflammation, and increased susceptibility to infections and metabolic disorders.[242] Therefore, maintaining iron homeostasis is crucial for both immune health and overall metabolic balance. Specifically, several studies have shown that a dysregulated systemic iron homeostasis can determine and/or worsen HF.[243] The evidence of the beneficial effects of iron-modulating therapeutics in HF demonstrate the importance of maintaining iron homeostasis in the cardiovascular system.[244]

The role of metabolic substrate availability

Traditionally, metabolic drug development for HF aimed to stimulate glucose oxidation or inhibit FFA oxidation.[2] An alternative approach to restoring cardiac energetics may lie in providing the heart with alternative fuel sources that can bypass the roadblocks in cardiac metabolism that occur in failing cardiomyocytes.[2,245,246]

Ketone bodies are efficient fuel that are easily oxidized by both failing and non-failing hearts.[225,246,247] Failing hearts have a significant capacity to further increase ketone oxidation, suggesting that strategies to increase ketone delivery to the heart may serve as a viable treatment for HF.[225,247–249] SGLT2i have been shown to induce a state of mild ketosis and improve myocardial energetics, and it has been proposed that the beneficial effects of SGLT2i may at least partially depend on enhanced myocardial ketone oxidation.[250–252] Moreover, ketone treatment has also been shown to ameliorate cardiac dysfunction and restore myocardial energetics in small and large animal models of HFpEF and HFrEF.[225,249,253] Short-term ketone infusion or ingestion strategies also resulted in acute improvements in cardiac function in healthy volunteers and patients with HF.[225] In a preliminary small-sized randomized controlled trial, short-term treatment with ketone ester improved rest and exercise haemodynamics in HFrEF.[254] Multiple clinical trials are currently ongoing to determine the effects of acute and chronic ketone treatment strategies on clinical endpoints in HF.[225]

Short-chain fatty acids (SCFA) are another promising alternative energy source for the failing heart due to their ability to bypass the down-regulation of the CPT1 shuttle.[255] Supplementing isolated perfused hearts with the SCFA butyrate resulted in robust improvements in cardiac performance, surpassing the benefits of ketone bodies in this model.[247] The potential of butyrate as a cardiac fuel provides a strong rationale for exploring SCFA as metabolic treatments for HF, although it may be challenging to reach sufficient circulating concentrations to serve as fuels.

Ketone bodies and SCFAs have also been shown to modulate cellular signalling and suppress inflammation through a variety of pathways. Ketone bodies inhibit NLRP3 inflammasome formation and reduced pro-inflammatory cytokine-triggered mitochondrial dysfunction and fibrosis in a murine model of HFpEF.[253] β-hydroxybutyrate also reduces NLRP3 activity in macrophages isolated from diabetic patients.[256] SCFAs, in particular butyrate,

share many of these anti-inflammatory and signalling properties with ketone bodies, but appear to do so at low concentrations.[245,257] This suggests that ketone bodies and SCFAs may offer cardioprotective benefits beyond fuelling the heart by reducing inflammation and fibrosis.

Benefits of exercise

Physical inactivity is linked to the development of many chronic diseases through a chronic low-grade inflammation state.[258] In chronic HF, exercise deprivation has been specifically related to further deterioration of left ventricular remodelling.[259] Exercise elicits a strong anti-inflammatory response and systemic effects on immune function, inflammation, and host metabolism independently of weight loss and can be a useful non-pharmacologic strategy to counteract low-grade inflammation conditions, including HF.[260] Physical exercise inhibits the inflammatory response by various molecular mechanisms.[261,262] Accumulating data from the field of exercise immunology indicate that exercise affects immune function via cellular metabolism.[263] Apart from its role on skeletal and cardiac muscle metabolism, exercise interferes with the regulation and function of leucocyte metabolism.[264] T cells and macrophages show high sensitivity to changes in their metabolic environment, which indirectly or directly affects their central functions.[265] Understanding the interactions between the level of physical activity and the metabolic status of immune cells could be helpful to target the dysregulated immune system in primary and secondary prevention of HF. In these contexts, future research shall eventually dissect out the differential effects of acute exercise and chronic exercise training on immunometabolism, and potential differences in the effects of exercise between immune cell types and subsets.[266]

Conclusions

Heart failure is an ongoing epidemic. Despite remarkable therapeutic progress, hospitalizations for HF remain both frequent and costly. In this context, the complete understanding of alternative mechanisms of disease progression may allow a different and more complete phenotyping of the disease and the identification of novel therapeutic targets. Persistent latent myocardial inflammation in HF probably represents an attempt to restore tissue homeostasis in the failing heart, where cardiomyocytes and immune cells undergo metabolic reprogramming, which allow them to deal with decreased availability of nutrients and oxygen. This status can trigger a metabolic crosstalk between immune cells and cardiomyocytes which can perpetuate the maladaptive remodelling of the heart. Therefore, the interrelation between immune activation and metabolism is gaining recognition as a potential therapeutic framework. The traditional cornerstones of HF treatment are mainly directed at counteracting the neurohormonal activation induced by haemodynamic incompetence and the abnormal metabolic and immune adaptations can be mitigated indirectly as a consequence of reverse remodelling and improved mechanical function. Nevertheless, chronic inflammatory/immune activation remains associated with the progression of HF and indicates that this dysregulated immunologic state is not merely the result of the overall HF process but an active player which could be tackled with specific treatments. On the other hand, improving the metabolic efficiency of the failing circulatory system might itself alleviate the pathological inflammation breaking the vicious circle that contributes to the progression of the syndrome. We are still far from completely understanding the shape and extent of cardiac and systemic metabolic alterations in HF impacting on immune function. However, it is becoming increasingly clear that the investigation of this conundrum—metabolism and immunity—in HF, is emerging as a priority research target for HF pathophysiology and therapeutic strategies. On these premises, future studies addressing novel HF treatments should attempt to evaluate the potential therapeutic role of direct metabolic and immunological crosstalk modulation.

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