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REVIEW

Immuno-metabolic interfaces in cardiac disease and failure

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Abstract The interplay between the cardiovascular system, metabolism, and inflammation plays a central role in the pathophysiology of a wide spectrum of cardiovascular diseases, including heart failure. Here, we provide an overview of the fundamental aspects of the interrelation between inflammation and metabolism, ranging from the role of metabolism in immune cell function to the processes how inflammation modulates systemic and cardiac metabolism. Furthermore, we discuss how disruption of this immuno-metabolic interface is involved in the development and progression of cardiovascular disease, with a special focus on heart failure. Finally, we present new technologies and therapeutic approaches that have recently emerged and hold promise for the future of cardiovascular medicine.

Keywords Cardiac disease • Metabolism • Inflammation • Heart failure

1. The clinical problem

Cardiovascular (CV) diseases are the leading cause of death worldwide. Heart failure (HF) is the end result of most CV diseases, with a prevalence between 2% and 4% in Europe, USA, and Canada.[1] The increasing burden of risk factors and comorbidities has an important impact on the development and clinical course of HF.[2] Therefore, HF can no longer be viewed as an isolated organ disease, but rather as a systemic disease that requires cross-disciplinary approaches towards basic research, diagnostics, and treatment. For a systemic approach towards CV diseases, it is important to understand the biological 'languages' by which the heart communicates with other organs. Neuroendocrine activation, inflammation, and metabolism represent major interfaces between the CV system and other organs (*Figure 1*). While most CV drugs rely primarily on targeting neuroendocrine activation, more recent developments indicate that targeting inflammation and metabolism may provide substantial benefit beyond neuroendocrine blockade. In patients after myocardial infarction (MI), treatment with the interleukin (IL)-1β antibody canakinumab reduced the risk of major CV events and hospitalization for HF,[3] and similar results were obtained more recently with colchicine.[4,5] Furthermore, the growing understanding of the interplay between diabetes and HF[6] and the recently uncovered efficacy of sodium/glucose cotransporter (SGLT)2-inhibitors in patients with diabetes at CV risk and/or with HF[7,8] sparked new enthusiasm in metabolic therapies for patients with CV diseases. Therefore, moving ahead beyond neuroendocrine blockade towards targeting inflammation, metabolism or both is an important field of basic, translational, and clinical CV research.

In this review, we outline the tight interrelation of inflammation and metabolism on several levels, with a special focus on the role of metabolism in immune cells and the impact of inflammation on the pathophysiology of cardiac disease and failure. Furthermore, we discuss how novel treatment options targeting inflammation or metabolism impact on these systems and finally, we highlight how technological advances can further improve our understanding of the pathophysiology of CV diseases and HF on a systemic level.

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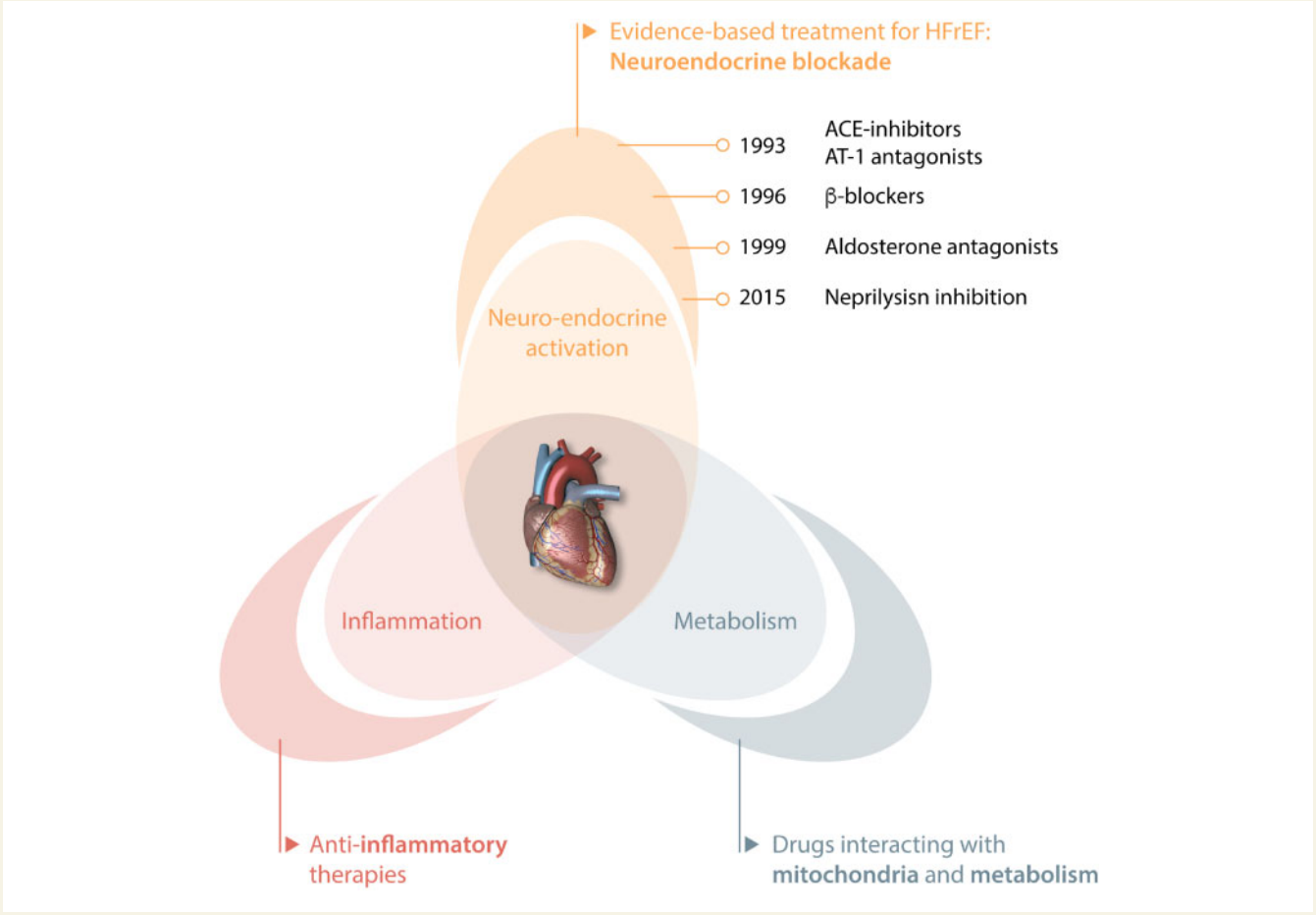

Figure 1 Moving beyond neuroendocrine blockade to treat heart failure. Neuroendocrine blockade remains the cornerstone of HF therapy, while new approaches targeting metabolic remodelling and inflammation are emerging as promising therapeutic options. ACE, angiotensin-converting enzyme; AT1, angiotensin receptor type 1; SGLT2, sodium/glucose transporter 2.

2. Inflammation and immune cell metabolism

2.1 Mitochondria and metabolism in immune cells

Mitochondria are pivotal to immune cell function. They are not only the central hub of oxidative metabolism, but also a platform for intracellular signalling molecules, including the NLRP3 (NACHT, LRR, and PYD domain-containing protein 3) inflammasome.[9] Furthermore, the processes of mitochondrial fission and fusion regulate important aspects of immune cell activation and cell death.[10] Finally, recent studies demonstrated that Krebs cycle intermediates, such as succinate, have a signalling role and can modulate immune cell activity.[11]

In immune cells, glucose oxidation is a dominant source of energy.[12] Glucose is oxidized to pyruvate via the glycolytic pathway. In turn, pyruvate can be reduced to lactate or transported into mitochondria and further oxidized via the Krebs cycle. The enzymatic reactions of the Krebs cycle catalyse the complete oxidation of the two-carbon units of acetyl-CoA (Ac-CoA) into carbon dioxide and represent a major source of intermediates for the biosynthesis of lipids and amino acids (*Figure 2*). The efflux of Krebs cycle intermediates is compensated by several anaplerotic reactions, a prominent example being the conversion of glutamine to α-ketoglutarate. The reducing equivalents NADH and succinate produced by the Krebs cycle sustain oxidative phosphorylation (OxPhos), which is substantially more efficient than glycolysis with respect to ATP production. Furthermore, glycolysis provides substrates for the synthesis of ribose via the pentose phosphate pathway (PPP), required for nucleotide synthesis, and amino acids via the serine biosynthetic pathway. Therefore, glycolysis plays a pivotal role in rapidly proliferating cells.

Fatty acids (FAs) represent another important substrate for ATP production upon β-oxidation (β-ox) in mitochondria. While short-chain FAs can diffuse through mitochondrial membranes, medium- and long-chain FAs need to be actively transported through the inner mitochondrial membrane (*Figure 2*). FAs undergo several cycles of oxidation that ultimately yield $FADH_2$ and NADH as electron donors. A mismatch between cellular FA uptake and the rate of their oxidation in mitochondria results in cytosolic accumulation of FAs, which functions as a pro-inflammatory signal.[13] For instance, unsaturated FAs stimulate the production of IL-1α in macrophages by uncoupling mitochondrial respiration, thereby contributing to vascular inflammation.[14]

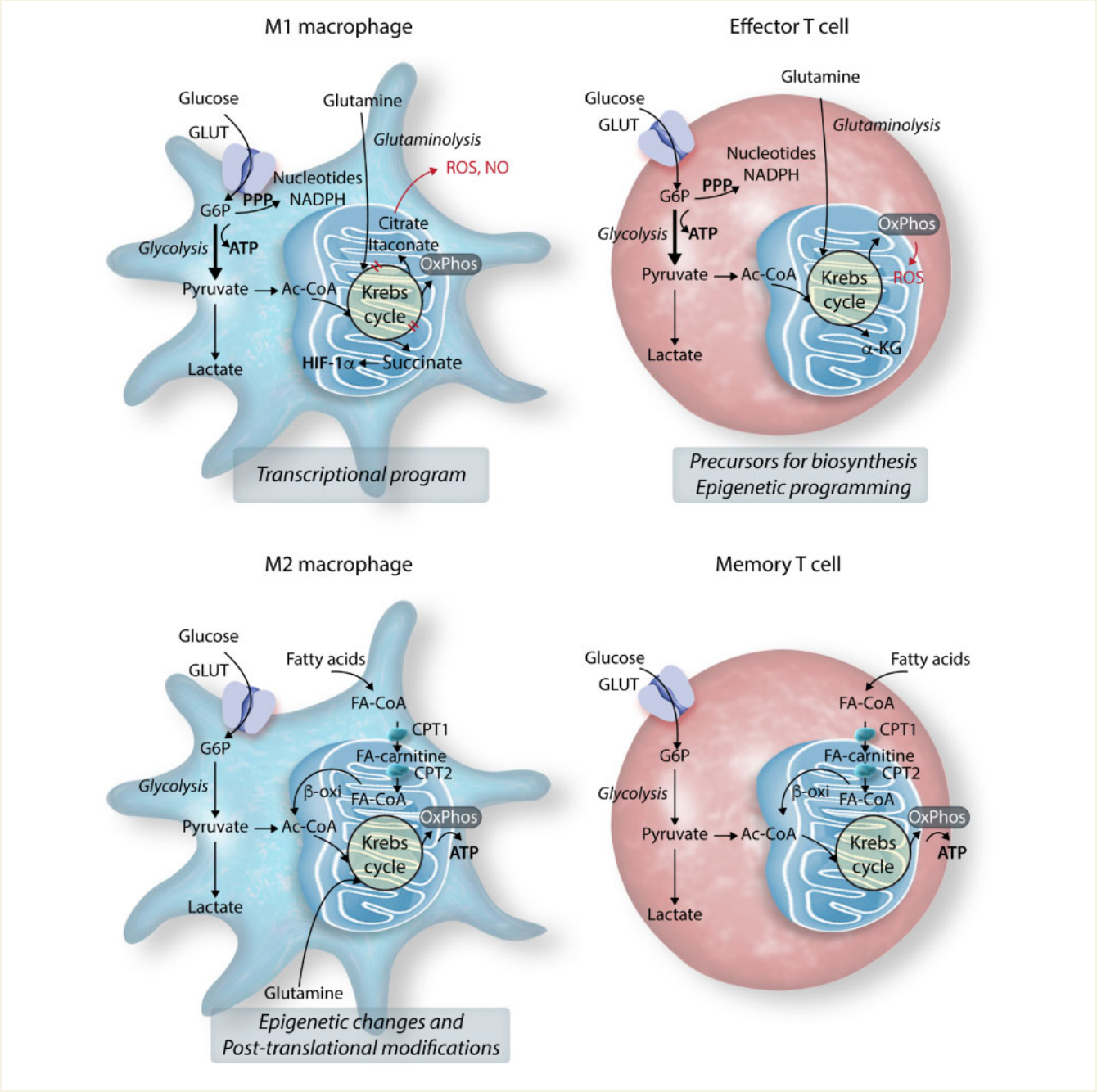

Figure 2 Key metabolic pathways in macrophages and T-cells. Immune cells can use different substrates to support ATP production, proliferation, and changes in their function. Glucose-6-phosphate (G6P) can be oxidized to pyruvate via glycolysis or channelled through the PPP, which produces the reduced form of NADPH as well as ribose for DNA synthesis. Pyruvate can be converted to lactate or further oxidized via the Krebs cycle in mitochondria. The Krebs cycle can be also fuelled by Ac-CoA produced by β-ox of FAs. Reducing equivalents (NADH and $FADH_2$) produced by these processes support OxPhos for ATP production. Importantly, both glycolysis and the Krebs cycle provide intermediates that can serve as precursors for biosynthetic processes or for post-translational modifications of proteins having profound influences on immune cell function. CPT, carnitine palmitoyltransferase; FA-CoA, fatty acyl-coenzyme A; FFA, free fatty acids; NO, nitric oxide; ROS, reactive oxygen species.

2.2 Metabolic control of inflammatory cell differentiation

2.2.1 Macrophages

Changes in immune cell function are accompanied by extensive rewiring of cellular metabolism. During the activation of innate and adaptive immune cells, their metabolism switches from a quiescent to a highly activated state. In fact, activated leucocytes dramatically increase nutrient uptake and flux through several metabolic pathways to support the production of ATP and anabolic intermediates required for the biosynthesis of lipids, proteins, and nucleotides.[15] Furthermore, changes in flux through specific metabolic pathways are key drivers for differentiation of immune cells and for their effector functions. A hallmark of

pro-inflammatory immune cells is the increase in glucose uptake and utilization.[12] In pro-inflammatory (referred to as M1) macrophages, pyruvate is largely reduced to lactate to recycle NAD^+.[16] The switch towards aerobic glycolysis in macrophages is controlled by the hypoxia-inducible factor 1α (HIF-1α), which up-regulates the glucose transporter (GLUT)1 and lactate dehydrogenase (LDH), while down-regulating the pyruvate dehydrogenase complex (*Figure 3*).[17] Metabolic changes play a pivotal role in controlling macrophage effector functions: pharmacological or genetic interventions that inhibit glycolysis also impair macrophage pro-inflammatory activity, whereas GLUT1 overexpression boosts glycolysis and promotes a pro-inflammatory phenotype.[18,19]

In pro-inflammatory M1 macrophages, the Krebs cycle is interrupted at several steps, a situation referred to as 'broken' Krebs cycle (*Figure 4*). Down-regulation of isocitrate dehydrogenase leads to citrate accumulation, which then serves as intermediate for the biosynthesis of lipids and signalling molecules like prostaglandins. Citrate is also converted to itaconate, which exerts an antibacterial activity by inhibiting the bacterial glyoxylate cycle, an important anaplerotic pathway in bacteria and plants. In mammals, however, itaconate is a potent inhibitor of succinate dehydrogenase.[20] Succinate dehydrogenase inhibition causes accumulation of succinate, which contributes to HIF-1α stabilization by inhibiting its negative regulator prolyl hydroxylase.[21] The aspartate–argininosuccinate shunt (AASS) replenishes the Krebs cycle at fumarate, after the break point caused by succinate dehydrogenase inhibition, and links the Krebs cycle to nitric oxide (NO) synthesis (*Figure 4*).[22] Specifically, mitochondrial oxaloacetate can be converted to either fumarate or aspartate and, as part of the urea cycle, aspartate is further converted to arginine, which is a substrate for inducible NO synthase (iNOS). NO production through iNOS is a hallmark of M1 macrophages and is an important antibacterial defence mechanism but may also contribute to the progression of atherosclerosis.[23]

Macrophages regulate immunity by adopting an anti-inflammatory, immune-suppressive phenotype (referred to as M2), which is associated with a metabolic shift towards oxidative metabolism and reduced glycolytic flux. In contrast to M1, M2 macrophages maintain an intact Krebs cycle and display a high production of α-ketoglutarate via glutaminolysis, which induces Jumonji domain-containing protein D 3-mediated epigenetic reprogramming of anti-inflammatory genes.[24] IL-4 is one of the key drivers of M2 macrophage polarization, and achieves its effect by activating peroxisome proliferator-activated receptor (PPAR)-γ coactivator-1β (PGC-1β), a transcriptional regulator that, together with PPARs,[25] induces mitochondrial biogenesis and FA oxidative metabolism (*Figure 3*).[26] In turn, FA oxidation is a major source of Ac-CoA, which is used for histone acetylation and transcriptional induction of IL-4-inducible genes.[26] The transcriptional and epigenetic regulation of macrophage differentiation is very complex and involves other transcriptional regulators like NCoR, SMRT, and LXR, which have been reviewed elsewhere.[27,28]

Mitochondria undergo substantial morphological changes during immune cell activation and differentiation. The structural remodelling of mitochondrial cristae also involves rearrangements of the mitochondrial respiratory chain. In this context, enhanced iNOS-mediated NO production modulates electron transport chain and Krebs cycle activity.[29] Activation of the NADPH oxidase–SRC kinase axis reduces the assembly of complex I into respirasomes, while promoting complex II-dependent respiration.[30] This shifts the NADH to ubiquinone ratio and allows reverse electron transport, whereby electrons from complex II are transduced in reverse flux through complex I, promoting reactive oxygen species (ROS) production. An increase in ROS production is

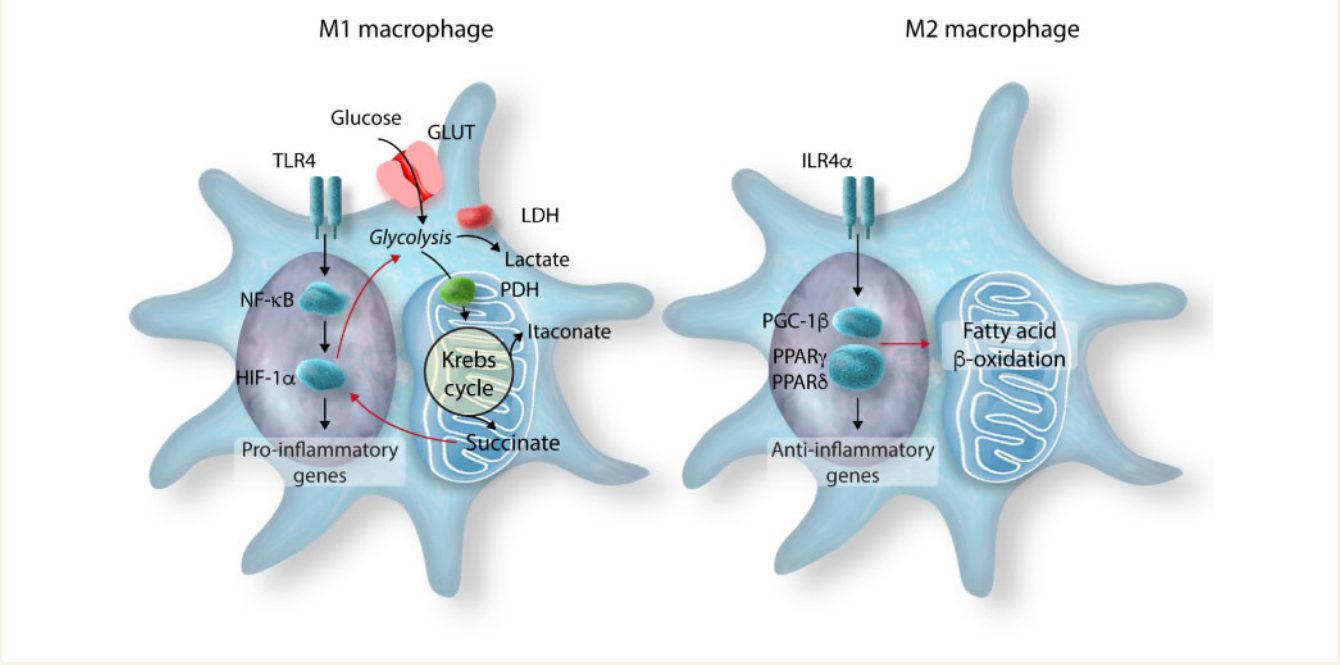

Figure 3 Transcription factors driving metabolic remodelling in macrophages. In pro-inflammatory M1 macrophages, activation of HIF-1α stimulates glycolytic metabolism by up-regulating GLUT1 and LDH, while down-regulating pyruvate dehydrogenase gene expression. In anti-inflammatory M2 macrophages, activation of PPAR-γ and -δ and its coactivator PGC-1β up-regulates genes coding for enzymes of FA β-oxidation. IL4Rα, interleukin-4 receptor α; TLR4, toll-like receptor 4.

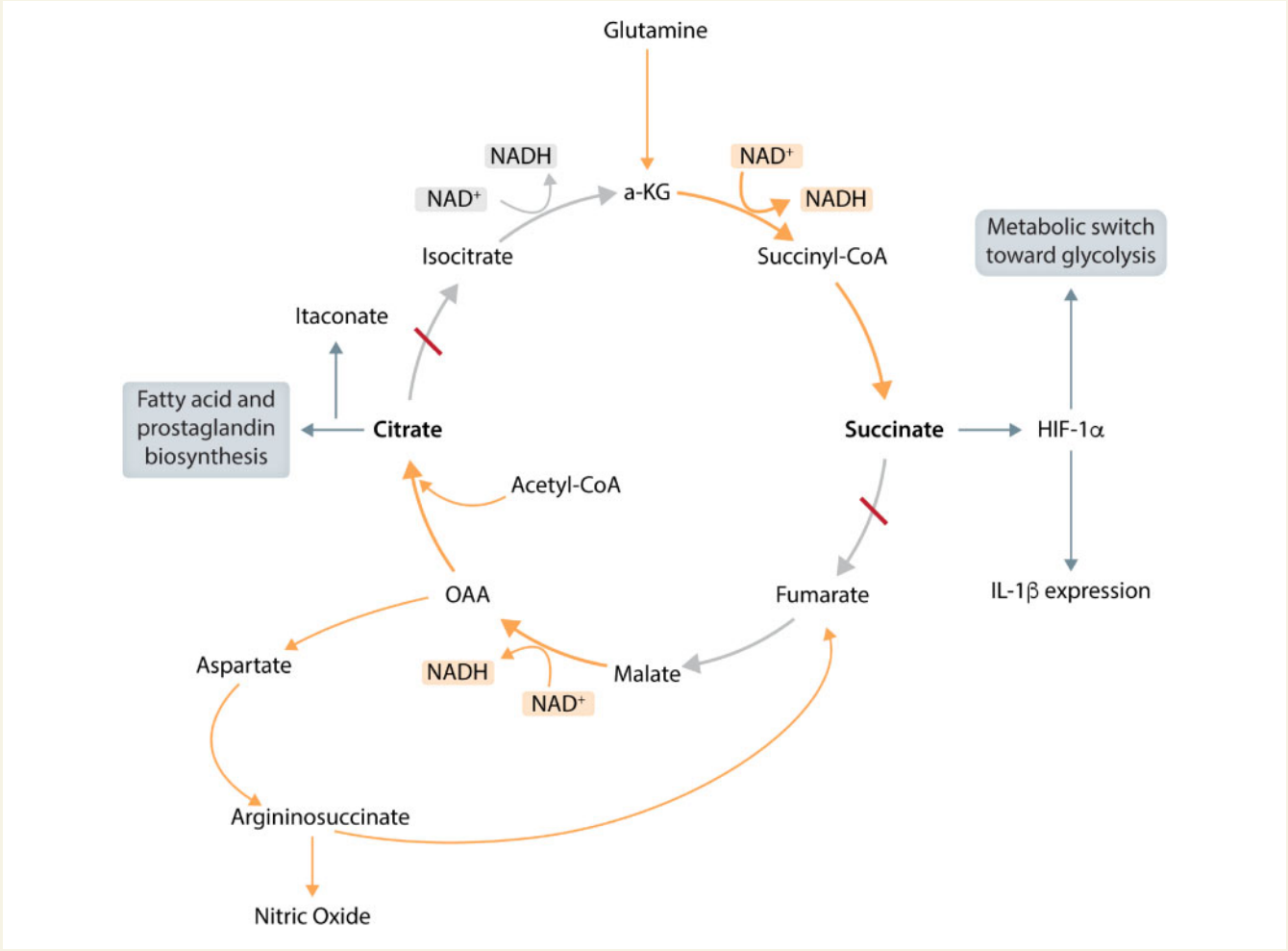

Figure 4 The broken Krebs cycle in pro-inflammatory macrophages. Macrophage polarization towards a pro-inflammatory phenotype is associated with metabolic changes, such as remodelling of the Krebs cycle. This leads to accumulation of citrate, which serves as a precursor of FA and prostaglandin biosynthesis, and succinate, which prevents degradation of the HIF-1α. The Krebs cycle is replenished by an increased flux through the AASS. α-KG, α-ketoglutarate; OAA, oxaloacetate.

also mediated by activation of the complex I assembly factor ECSIT, which depends on lipopolysaccharide (LPS) and toll-like receptor signalling via TRAF6.[31] Altogether, these structural rearrangements redirect the function of the electron transport chain from respiration towards ROS production. Increased ROS signalling from the respiratory chain stabilizes HIF-1α to up-regulate IL-1β gene expression.[32] Accordingly, inhibition of complex I with rotenone or the anti-diabetic drug metformin impairs LPS-induced ROS and IL-1β production and antagonizes the inflammatory function of macrophages.[33]

In summary, changes in metabolism in immune cells represent a major driving force for functional differentiation, and this concept stands as a general characteristic of macrophages. It is important to note that the widely employed pro-inflammatory M1/anti-inflammatory M2 dichotomy, while useful for *in vitro* studies and investigating metabolic activity of macrophages with artificially induced pro/anti-inflammatory polarized states, does not represent the true diversity of macrophages observed in the healthy or diseased heart,[34] and little is known on metabolism of cardiac-specific macrophage subpopulations in health and disease.

2.2.2 T-cells

Similar to macrophages, naïve T-cells exhibit minimal metabolic activity characterized by low glycolytic rate and a preference for FA oxidation.[35] Upon T-cell receptor and CD28 coreceptor stimulation, T-cells undergo a glycolytic switch that supports clonal expansion and differentiation into various effector subtypes. These changes are—at least in part—dependent on calcium (Ca^{2+}) and calcineurin signalling events controlling the activation of the nuclear factor of activated T-cell (NFAT) transcription factor family.[36,37] Inhibition of Ca^{2+} signalling either genetically (e.g. by deleting *Stim1* and *Stim2* genes) or pharmacologically abolishes the up-regulation of GLUTs and glycolytic enzymes. Although Ca^{2+}-mediated NFAT signalling is central for the glycolytic switch in T-cells, many of these events are not mediated directly by NFAT. Instead, NFAT modulates the expression of metabolic master regulators, such as IRF4, HIF-1α, and c-Myc in T-cells.[36,37] Besides Ca^{2+}/calcineurin/NFAT signalling, other pathways contribute critically to the metabolic adaptation of T-cells in response to antigen stimulation. For instance, expression of c-Myc is induced by the PI3K/Akt/mTOR pathway and AMPK signalling, resulting in GLUT1 up-regulation and enhanced glycolysis.[38] Limiting

glucose metabolism suppresses the activation and proliferation of T-cells, whereas GLUT1 overexpression promotes T-cell activation.[39] Activated T-cells also strongly increase glutamine metabolism for anaplerosis of Krebs cycle intermediates.[40] A tight connection exists between production of certain metabolic intermediates and regulation of gene expression. For example, glutamine and glucose metabolism fuel the synthesis of UDP-*N*-acetylglucosamine (GlcNAc) required for the modification of c-Myc with GlcNAc to regulate its transcriptional activity and—in turn—the metabolic activity of T-cells.[41]

Similar to the metabolic switch observed in macrophages, specific energetic programs also dictate the fate and function of T-cells. While inflammatory (effector) T-cells are highly glycolytic, T regulatory cells (Treg) are characterized by reduced glycolytic activity and increased FA oxidation. In line with their metabolic preferences, T-cells exposed to exogenous FAs show enhanced Treg generation and impaired effector function, whereas genetic or pharmacological inhibition of glycolysis promotes Treg differentiation and abrogates the generation of inflammatory subsets. This indicates that oxidative metabolism is an important regulator of Treg and effector T-cell differentiation, although this paradigm has been challenged recently.[42] Similar to Treg cells, memory T-cells have a pronounced oxidative phenotype that is associated with a large mitochondrial respiratory capacity and an augmented FA oxidation.[43] An important cytokine to generate memory T-cells is IL-15, which promotes mitochondrial biogenesis and the expression of carnitine palmitoyl transferase 1A (CPT1A), required for FA transport into mitochondria.[44] Interestingly, enforced expression of CPT1A in T-cells is sufficient to differentiate memory T-cells, suggesting that metabolic changes in T-cells can directly influence the phenotype and function of lymphocytes.

In conclusion, metabolic adaptation of innate and adaptive immune cells is not just a consequence of their activation and differentiation, but is in fact a central prerequisite to support and direct immune cell differentiation, maintenance, and function.

3. Inflammation modulates systemic and cardiac metabolism

Systemic metabolism and the immune system are tightly integrated and respond in a coordinated manner to stress situations, such as infections or tissue injury. From an evolutionary perspective, this interconnection is advantageous because it allows to quickly reallocate energy resources when they are required to mount an immune response.[45] Inflammatory mediators, allied to the activity of the hypothalamic–pituitary–adrenal axis, play a key role in directing metabolism towards a catabolic program, characterized by lipolysis, reduced glucose utilization by skeletal muscle and adipose tissue, along with increased insulin and leptin resistance.[46] As the contribution of the immune system to metabolic disorders emerged, components of the inflammatory response and their respective impact on metabolism were progressively discovered. In particular, the prototypic inflammatory cytokine tumour necrosis factor (TNF) modulates systemic metabolism by inducing free FA release through lipolysis and decreasing insulin secretion by pancreatic β-cells.[47] Similarly, IL-6 also modulates FA metabolism by inducing hepatic triglyceride secretion in response to infections and fasting.[48]

The inflammasome is a key mediator of changes in metabolism driven by inflammation. Caspase-1, a central component of the inflammasome pathway, modulates systemic lipid metabolism. In fact, caspase-1-deficient mice exhibit lower plasma triglycerides and accelerated lipid clearance from plasma after high-fat feeding, independent of IL-1β or IL-18 activity.[49] Moreover, inflammasome activation exerts a multitude of effects on metabolism that depend on cytokine activity, particularly IL-1β.[50] Mice lacking the endogenous IL-1 receptor antagonist (IL-1Ra) show impaired fat accumulation, while hypothalamic released factors and energy expenditure are unaltered.[51] Genetic deletion of IL-1Ra prevents weight gain in mice fed with glutamate or high-fat diet. Interestingly, insulin levels remained low in the presence of excessive IL-1β signalling.[51] In that scenario, IL-1β may directly control glucose metabolism and thereby contribute to the development of type 2 diabetes mellitus (T2DM). IL-1β also causes pancreatic β-cell apoptosis and is up-regulated by β-cells following high glucose stimulation *in vitro*.[52] This cytokine was also detected in pancreatic sections from T2DM patients.[52] In fact, blocking IL-1β activity with anakinra improves glycaemia and β-cell secretory function and reduces systemic inflammatory markers in patients with T2DM, supporting a detrimental role for IL-1β in T2DM progression.[53]

Although pro-inflammatory cytokines clearly play a detrimental role in the context of metabolic syndrome, immune control of systemic metabolism maintains cardiac homeostasis in response to acute inflammatory stress.[54] During sepsis, growth differentiation factor 15 (GDF15) stimulates hepatic triglyceride export via β-adrenergic signalling. Maintenance of FA availability mediated by GDF15 sustains cardiac function, whereas GDF15 inhibition increases troponin levels and reduces cardiac output in both bacterial and viral infections.[55] The pleiotropic cytokine IL-6 also controls cardiac FA metabolism. IL-6 deficiency increases circulating levels of triglycerides, resulting in myocardial lipid accumulation and lipotoxicity.[56,57] While IL-6$^{-/-}$ mice fail to develop obesity when fed a high-fat diet, they develop cardiac dysfunction characterized by myocardial lipid accumulation, fibrosis, and inflammation.[56] Besides the systemic effects on lipid metabolism, IL-6 controls the expression of cardiac FA transporters: IL-6 deficiency increased expression of CD36 and accumulation of toxic lipid species (diacylglycerol and ceramide) in the heart.[57] Strikingly, treatment with tocilizumab, a monoclonal antibody directed against the IL-6 receptor, prevents aerobic exercise-induced cardiac fat loss in humans. Although IL-6 signalling is associated with pathologic cardiac hypertrophy, it appears necessary also for physiological (exercise-induced) hypertrophy and lowering of myocardial lipid content.[58]

Cytokines produced during the resolution phase of inflammation also modulate cardiac metabolism. Amit and co-authors observed a down-regulation of IL-13 receptor in myocardial samples from HF patients. Moreover, ablation of IL-13 signalling in mice results in myocardial dysfunction and dyssynchrony.[59] Bioinformatic analyses demonstrated that cardiac glucose metabolism is impaired in IL-13 receptor-deficient mice, with accumulation of advanced glycosylation end products promoting vascular damage.[59] It is currently unknown whether cytokines produced by cardiac fibroblasts and endothelial cells also contribute to cardiac metabolic remodelling. Existing evidence indicates that cell types other than leucocytes respond to and are a source of cytokine signalling but their contribution in this context has not been investigated.[60] In conclusion, the immune system contributes to homeostatic metabolic functions, but can also fuel metabolic syndromes and tissue dysfunction, a dichotomy that must be considered in designing future therapeutic approaches.

4. The immune system in cardiac physiology and disease

4.1 Immune cells in cardiac homeostasis

Cardiac myocytes represent only one-third of the cells composing the adult heart. In addition to fibroblasts, endothelial cells, and pericytes, the

myocardium harbours all major types of immune cells.[61,62] Macrophages represent the major leucocyte population in the heart. Yolk-sac derived macrophages infiltrate the heart during embryogenesis and modulate coronary maturation, most likely by regulating endothelial cells migration via release of insulin-like growth factor 1 and 2.[63] The adult heart hosts distinct subsets of macrophages, some of which derive from embryonic progenitors and are capable of self-renewal, while others [characterized by the expression of the chemokine receptor type 2 (CCR2)] arise from circulating monocytes.[64] Macrophages are particularly abundant in the cardiac conduction system, where they directly interact with cardiac myocytes via gap junctions formed by connexin 43.[65] Macrophages in the atrioventricular node are electrically coupled with and modulate the electrical properties of adjacent cardiac myocytes.[65] Ablation of resident cardiac macrophages induces atrioventricular block, demonstrating that macrophages are required for normal electrical conduction in the adult mouse heart.[65] In addition, the interaction between resident macrophages and myocytes plays an important homeostatic role in the myocardium, where they remove damaged mitochondria emitted by cardiac myocytes.[66]

4.2 Inflammation in ischaemic heart disease

Cardiac injury following MI triggers a process of tissue repair, where dead cardiac myocytes are ultimately replaced by a fibrous scar.[67] Similar to other wound healing processes, post-MI cardiac repair depends on the sterile inflammatory response developing in the infarcted area,[67] which is characterized by a first wave of neutrophil infiltration, followed by inflammatory monocytes that locally differentiate into macrophages.[67] T- and B-cells also infiltrate the infarcted heart, albeit in lower amounts.[67] In the ischemic heart, inflammatory cells perform a variety of functions promoting both tissue repair and damage. Thus, a fine tuning of the amplitude, timing (i.e. initiation and resolution), and functional quality of the post-MI inflammatory response is a crucial determinant of cardiac repair.

Neutrophils and macrophages promote cardiac healing via phagocytosis, pro-angiogenic activity, active resolution of inflammation, matrix remodelling, and fibroblast activation required for scar formation, but can also promote tissue damage and adverse remodelling via excess proteolysis, interstitial fibrosis, inflammatory cytokines, and ROS production.[67] The healthy and infarcted heart contains distinct monocyte/macrophage populations endowed with specific functions and diverse roles in post-MI cardiac repair.[34,68] This heterogeneity is highly dynamic, with substantial shifts in monocyte/macrophage subsets, gene expression, and functional capacities over the post-MI time continuum.[69–71] Similarly, heterogeneous neutrophil populations are found in the ischemic heart, and time-dependent shifts in neutrophil proteome and transcriptome may also underlie modulation of functions relevant for tissue repair.[72] To date, little is known about the metabolic control of neutrophil and monocyte/macrophage function during the various phases of post-MI cardiac repair. Nevertheless, extrapolation of the vast knowledge gathered in other settings places metabolic pathways as potential central regulators of innate immune cell-mediated cardiac repair (reviewed in References73). A recent report notably showed that metabolic reprogramming of macrophages underlies their switch towards a pro-tissue repair phenotype upon efferocytosis.[74] Metabolic reprogramming and pro-inflammatory priming associated with trained innate immunity may also poise myeloid cells towards pathogenic functions in ischemic heart repair.[75] Finally, macrophages may globally control cardiac metabolic function in stress conditions via their recently proposed role in mitochondrial homeostasis of cardiac myocytes.[66]

T- and B-cells also have important protective and pathogenic functions in post-MI inflammation. B-cells are mostly thought to be pathogenic via pro-inflammatory functions[76] and antibody production.[77] Failure to activate antigen-dependent $CD4^+$ T helper cell response hampers post-MI cardiac repair, indicating an overall protective role of T-cells.[78] However, similar to the situation in atherosclerosis, T-cell polarization is crucial: Treg have a protective role[79,80] while the prototypical Th17 cytokine IL-17A is pathogenic.[81] How metabolic control of T-cell polarization[82] impacts post-MI cardiac repair remains to be investigated.

4.3 Inflammation in pathological cardiac hypertrophy

Cardiac hypertrophy is an adaptive response that can be induced by different physiological and pathological stressors. Pathological hypertrophy most commonly results from pressure or volume overload, often associated with neurohormonal activation. Common aetiologies include systemic hypertension, valvular disease, and maladaptive remodelling following MI.[83] Although a variety of pathological stressors can be involved, and the molecular mechanisms downstream can be manifold, the development of cardiac hypertrophy constantly involves the activation of myocardial resident and peripherally recruited immune cells.[84]

Our understanding of the mechanisms underlying pathological cardiac hypertrophy derives primarily from mouse models of pressure overload, usually induced by aortic constriction (TAC) or treatment with angiotensin II. Early after TAC, an inflammatory response in the heart is orchestrated by release of ILs and chemokines, which mediate the infiltration of the myocardium by macrophages, T-lymphocytes, and other inflammatory cells.[85–89] Importantly, many of the studies that suggest a causal role of macrophage and/or T-cell infiltration for myocardial fibrosis, LV dilation, and dysfunction after TAC were performed in C57BL/6J mice,[85–89] which carry a loss-of-function mutation of the mitochondrial nicotinamide nucleotide transhydrogenase (NNT). In the pressure-overloaded heart, reversal of the NNT reaction oxidizes NADPH, thereby 'stealing' reducing equivalents from mitochondrial antioxidant systems.[90] Therefore, studies in which TAC was performed in the C57BL/6J strain might have underestimated the degree of mitochondrial ROS production[90] and inflammation.

Animal studies have exemplified how overexpression or administration of TNF-α, IL-1β, or IL-6 is sufficient to induce cardiac dysfunction, whereas their genetic ablation is protective in various pathological contexts, including pressure overload-induced hypertrophy (reviewed in References[84]). More recent studies elucidated the role of resident and peripherally recruited myeloid cells in the progression of cardiac hypertrophy towards decompensated HF. Expansion of resident cardiac macrophages and recruitment of circulating monocytes are early events in the development of angiotensin II-induced cardiac hypertrophy.[64] Furthermore, angiotensin II induces inflammasome activation in the $CCR2^+$ (peripheral monocytes-derived) subset of cardiac macrophages, thus inducing IL-1β release.[64] In fact, neurohormonal activation, and in particular mineralocorticoid receptor signalling, promotes polarization of cardiac macrophages towards the pro-inflammatory M1 phenotype.[91]

Pathological cardiac hypertrophy also involves the activation of the adaptive immune response. T-cell infiltration was observed in the left ventricular myocardium of patients with aortic stenosis, one of the most common causes of chronic pressure overload in humans.[92] In mice,

B- and T-cell depletion (by genetic deletion of *Rag1* or *Rag2*) prevents hypertrophy.[89] Among T-cell populations, $CD4^+$ T-cells appear to play the most important role in modulating hypertrophic remodelling.[89] In particular, Tregs protect from hypertrophic remodelling and fibrosis in mice treated with angiotensin II.[93] In conclusion, there is now extensive evidence implicating the innate and adaptive branches of the immune response into the progression of pathological cardiac hypertrophy to overt HF.

4.4 Inflammation in the pathophysiology of diastolic dysfunction

HF with preserved ejection fraction (HFpEF) accounts for already more than 50% of HF cases. The hallmark of HFpEF is diastolic dysfunction, i.e. elevated myocardial stiffness causing an increase in ventricular filling pressures at rest and/or during exercise. Epidemiological studies indicate that HFpEF patients are more often female, of advanced age, and frequently have multiple comorbidities, such as obesity and metabolic syndrome, systemic hypertension, T2DM, and chronic kidney disease.[94] It has been proposed that these comorbidities and in particular, metabolic disorders are in fact primary causes of cardiac dysfunction and drive the structural and functional abnormalities observed in HFpEF by inducing a chronic inflammatory state.[95,96]

HFpEF-related comorbidities, and especially metabolic conditions, are associated with a systemic inflammatory state, which is reflected by elevated circulating levels of pro-inflammatory cytokines. One of the models explaining the pathogenesis of HFpEF holds that this inflammatory milieu induces coronary microvascular endothelial dysfunction, and this in turn hinders myocardial relaxation by altering the elastic properties of the extracellular matrix (ECM) and of cardiac myocytes (*Figure 5*).[96] Recently, Schiattarella et al.[97] developed a mouse model of HFpEF by combining metabolic and hypertensive stress. Specifically, they demonstrated that the combination of high-fat diet and NOS inhibition induces a systemic inflammatory state that increases cardiac expression of iNOS. Elevated iNOS activity promotes S-nitrosylation of proteins, inducing the activation of an evolutionary conserved branch of the unfolded protein response.[97] Overall, this study established a new mouse model of HFpEF and revealed a mechanism how metabolic stress and inflammation induce diastolic dysfunction in rodents and humans.

In conclusion, several cardiac and peripheral abnormalities underlie the clinical syndrome of HFpEF, and the heterogeneity of these factors contributes to the complexity of its pathophysiology. Chronic inflammation, and especially the pro-inflammatory milieu associated with obesity and metabolic disorders, might represent the common denominator for many of these pathogenic factors.[95]

4.5 Inflammation in the pathophysiology of atrial fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with the development of potentially severe complications, including stroke and HF. It has long been known that AF itself induces progressive electrical and structural remodelling of the atria that favour the perpetuation of the arrhythmia (the 'AF begets AF' paradigm), and inflammation is emerging as one major contributor to this vicious cycle.[98]

Levels of inflammatory biomarkers, such as C-reactive protein, IL-6, and TNF are elevated in patients with AF and predict the risk of AF development.[99] In addition to systemic inflammatory processes, expansion and inflammation of epicardial adipose tissue has also been associated with AF.[100,101] In turn, the fibrillating atrium is a source of inflammation: in fact, levels of inflammatory markers decline after ablation of long-standing persistent AF.[102] Preclinical studies have shed light on multiple mechanisms linking cytokines and other inflammatory mediators to AF development. First, some of these mediators can induce structural remodelling of the atria. For instance, cardiac-specific TNF or tissue growth factor (TGF)-β1 overexpression induces atrial fibrosis and thereby increases AF susceptibility in mice.[103] In addition, inflammatory mediators can directly affect the electrophysiological properties of cardiac myocytes by activating the NLRP3 inflammasome. Two recent studies demonstrated that constitutive activation of the NLRP3 inflammasome elicits atrial ectopic activity and enhances AF inducibility in mice.[104,105] Accordingly, AF patients exhibit increased expression of the NLRP3 inflammasome components compared with individuals in sinus rhythm.[104,105]

Overall, there is substantial evidence that inflammatory signalling is involved in the development of AF. An important and, thus far, overlooked question concerns the role of specific immune cell populations in this context. In fact, an increased infiltration of inflammatory cells in the atrial myocardium of patients with AF has been documented, but their pathophysiological role is unclear.[106] The above-mentioned studies implicating cardiac macrophages in electrical conduction suggest that resident and peripherally recruited immune cells might also contribute to arrhythmogenesis.

4.6 Inflammation in the pathophysiology of hereditary cardiomyopathies

Inherited cardiomyopathies are characterized by broad genetic heterogeneity, with mutations in more than 70 genes encoding proteins expressed in a wide variety of sub-cellular systems.[107] However, the cardiomyopathy phenotype is ultimately determined by complex interactions between genes, environment, the immune system, and acquired disorders.[108–110]

Chronic myocardial inflammation can be observed in most forms of genetic cardiomyopathies, including arrhythmogenic and dilated cardiomyopathy (ACM and DCM, respectively), and to a lesser extent in hypertrophic cardiomyopathy. Clinical presentations consistent with acute myocarditis were observed in families with ACM due to mutations in desmosomal proteins, in particular in the intermediate filament protein desmoplakin.[111–113] Elevated plasma troponin levels and signs of inflammation documented by cardiac magnetic resonance and ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging indicate the presence of an inflammatory process in patients with confirmed ACM.[114–116] This is in agreement with histology studies that documented the presence of inflammatory cells in the myocardium of ACM patients. However, it is unclear if immune cells are resident or recruited from the circulation.[117,118] Mouse models of inherited ACM and DCM demonstrated that sterile myocardial inflammation characterized by infiltration of macrophages and $CD4^+$ T-cells is a key feature even at early stages of the disease. Hypothetically, early myocardial damage may enhance inflammation and promote fibrosis and fibrofatty replacement, and in parallel the immune system may produce auto-antibodies directed against myocardial antigens. A recent study demonstrated anti-heart auto-antibodies in the majority of familial and in almost half of sporadic ACM probands, indicating the development of an autoimmune response.[119] Earlier studies on familial DCM also showed that anti-heart auto-antibodies play a role in familial DCM.[120] Further, viral infections can exacerbate the progression of DCM, e.g. in Duchenne muscular

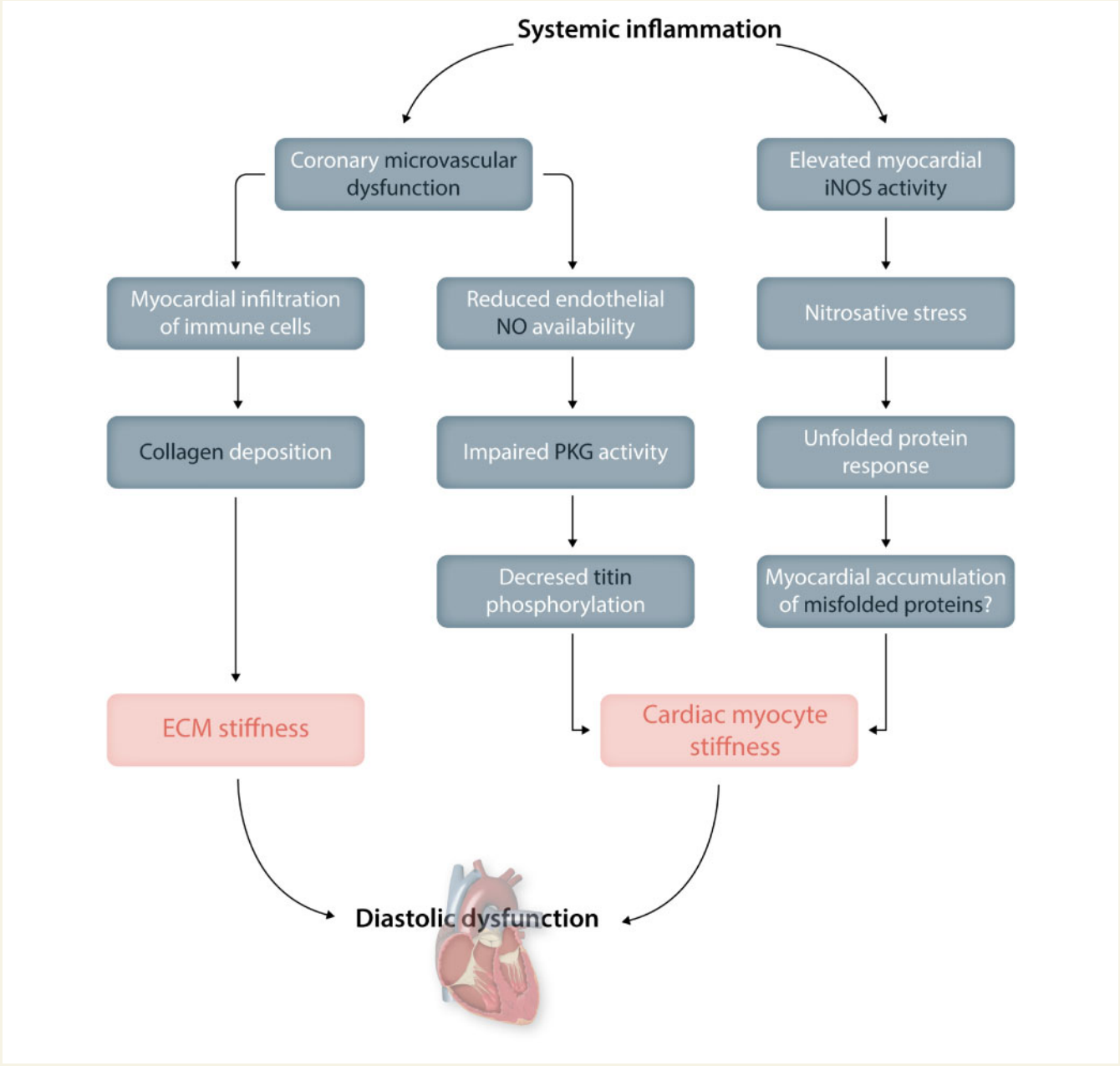

Figure 5 Inflammation in the pathophysiology of diastolic dysfunction. Multiple mechanisms link systemic inflammation to diastolic dysfunction. Inflammation induces coronary microvascular dysfunction and enhances myocardial activity of the iNOS, triggering a cascade of events that ultimately affect the stiffness of both the ECM and cardiac myocytes. PKG, protein kinase G.

dystrophy, due to an interaction between viral proteases and cytoskeletal proteins.[121]

In conclusion, the mechanistic links between genetic cardiomyopathy and inflammatory processes remain unclear. It needs to be investigated whether the mutation *per se* is sufficient to cause inflammation and activate the immune system, or the innate immune response maintains low-grade chronic cardiac inflammation and triggers factors, such as viral infections, toxic stimuli, or autoimmune disease in genetically predisposed individuals.[108] Even more important, it must be clarified whether inflammation is directly affecting sub-cellular structures involved in the progression of cardiomyopathy, such as cell–cell contacts in ACM or cytoskeletal proteins in DCM, or is just a bystander.

5. Novel therapeutic horizons

5.1 Anti-inflammatory medications in CV disease

A large body of preclinical evidence indicates that therapeutic interventions blocking excessive inflammation reduce the risk of MI and consequent progression to HF. However, the tightly controlled balance

between pro- and anti-inflammatory mechanisms is essential for wound healing after MI. Therefore, inflammation cannot be simply regarded as a maladaptive process, especially in the early stages after MI. Key questions on timing, duration, and on the identification of patients that would benefit from an immuno-therapeutic intervention are still open and cannot be properly addressed in the standard rodent models of MI. Therefore, we currently face huge translational roadblocks, which have slowed the advancement of the field for a long time.

Biopsy-proven non-infectious or virus-negative inflammatory cardiomyopathy seems to be the most reasonable target for immuno-modulatory therapy. However, the mainstay of treatment remains standard therapy of HF with reduced ejection fraction (HFrEF), while the use of immuno-modulatory treatments has long been considered controversial, especially for conditions other than sarcoidosis, eosinophilic, or giant cell myocarditis. Steroids and azathioprine have been tested in patients with virus-negative inflammatory cardiomyopathy in the prospective randomized TIMIC[122] and several subsequent observational clinical trials. Based on these results, steroids and azathioprine represent the only immuno-modulatory therapy of choice. Evidence for a potential clinical benefit of other immuno-suppressants in virus-negative myocarditis is almost anecdotal.[123]

Recently, the CANTOS trial showed that pharmacological blockade of IL-1β reduces the risk of recurrent vascular events, HF hospitalization, and mortality in patients with prior MI,[124] lending renewed support to the hypothesis that inflammation is a promising therapeutic target in patients after MI. However, the CANTOS trial was primarily designed to test the hypothesis that anti-IL-1β treatment reduces the incidence of vascular events in patients with a recent MI,[3] and the data on HF are derived from a secondary endpoint analysis. Therefore, the patient cohort was not properly characterized with respect to the prevalence and aetiology of baseline and incident HF. There is a limited number of clinical trials specifically designed to study the impact of drugs interfering with inflammation on HF-related endpoints (reviewed in References[125,126]). Of note, none of these trials showed a convincing benefit leading to translation of the related approach into the standard HF treatment algorithm. Moreover, most of these trials were conducted more than a decade ago and comprised only a small number of patients.

Preclinical studies have raised hopes for new immuno-modulatory approaches that target very different components of the immune system relevant for both atherosclerosis and ischemic HF. However, our understanding of the therapeutic potential of immuno-modulation in non-ischemic HF and especially in inherited cardiomyopathies is still rudimentary. Considering the resources needed to conduct an early clinical trial or even a HF outcome trial, it is currently a major challenge to select promising approaches as advanced translational data, e.g. from large animal experiments, are currently widely lacking. The innate immune system offers a plethora of therapeutic targets, including soluble mediators like chemokines and cytokines, upstream activation pathways like pattern recognition receptors and inflammasomes, and regulators of leucocyte migration that merit further translational studies. Besides these targeted approaches, broader anti-inflammatory interventions include drugs like adenosine receptor agonists and methotrexate that modulate the activity of leucocytes and non-leucocytes. Of note, compounds approved for clinical application are available for many of these targets, as they have been developed for other indications. However, only a minority of these were tested in advanced preclinical or early clinical trials. For instance, a variety of drugs modulating adaptive immunity by targeting T- and B-cells is available for clinical use. The ongoing RITA-MI trial tests the safety of B-cell depletion after MI using rituximab, a well-established anti-CD20 antibody. A safety trial on the use of IL-2 in post-MI patients was just completed.[127] Another interesting approach is the interference with lymphocyte migration by pharmacological agonists of the sphingosine-1-phosphate receptor 1, which are approved for treatment of multiple sclerosis. The largest body of evidence exists for the compound fingolimod, which exerts direct cardioprotective effects beyond it activity on leucocytes.[128]

5.2 Targeting metabolism to modulate inflammation

For a long time, treating patients with diabetes was a therapeutic dilemma because before 2015, hardly any improvement of CV endpoints could be achieved, and even an increased risk of HF was observed that was traced to the effects of glitazones.[129] Meanwhile, we learned that also insulin is associated with worse outcome in patients with HF.[130,131] A major breakthrough in the treatment of diabetes was achieved with SGLT2 inhibitors, which substantially reduce HF hospitalization and CV mortality in patients with diabetes[132] and more recently, even in patients with HFrEF with or without diabetes.[7,8] The modes of action how SGLT2 inhibitors improve outcome in patients with HF but without diabetes are presently incompletely resolved, but may involve off-target effects on cardiac ion handling and/or substrate utilization.[133] SGLT2 inhibitors increase circulating ketones in patients with diabetes, and some studies suggest that this may optimize cardiac fuel utilization and/or efficiency.[134,135] Interestingly, ketones inhibit inflammasome activation independent of their property as a metabolic fuel.[136] On the other hand, SGLT2 inhibition ameliorates NLPR3 inflammasome activation independent of alterations of ketone levels in a HFrEF model.[137] While canagliflozin lowers circulating IL-1β in bone marrow-derived macrophages,[138] empagliflozin boosts antioxidative defence systems in leucocytes in patients with diabetes, which is associated with increased plasma levels of IL-10, but lower C-reactive protein and myeloperoxidase levels.[139] And finally, also other anti-diabetic drugs, such as dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 analogs, exert anti-inflammatory effects.[6] Taken together, it is likely that targeting metabolism may at least to some extent exert protective effects on the CV system by ameliorating maladaptive inflammation.

6. Technological advances to monitor inflammation and metabolism

6.1 Single-cell analysis in CV inflammation

Fast-paced advances in single-cell genomics technologies now allow to analyse genome, epigenome, transcriptome, and cell surface proteome of individual cells, and some of these features can be even assessed simultaneously with specific multimodal methods (e.g. genome and transcriptome, cell surface proteome and transcriptome).[140,141] These novel methods constitute invaluable tools to investigate gene expression and its regulation, intercellular communication, and dynamics of cell differentiation and activation in health and disease with unprecedented resolution. Integration of single-cell genomics analysis with spatially resolved transcriptomic methods[142] further enables to precisely localize where specific cellular processes occur within the tissue anatomy.[140]

The use of single-cell technologies in CV research is still at its infancy, and has been mostly limited to single-cell RNA-seq (scRNA-seq) transcriptome analysis. Nevertheless, numerous scRNA-seq studies have

already greatly improved our understanding of immune cell states and inflammatory dynamics in atherosclerosis and HF.[143] Single-cell analysis has refined our knowledge of macrophage heterogeneity in the steady state and infarcted heart, revealing discrete tissue resident and monocyte-derived macrophage subsets with potentially distinct functional capacities and impact on post-MI tissue repair.[34,68,144,145] Recent scRNA-seq studies have further characterized the precise gene expression dynamics in monocytes, macrophages, and neutrophils over the post-MI time continuum.[70,146] scRNA-seq has also been used to uncover immune activation patterns in pressure overload-induced HF.[147] In humans, scRNA-seq analyses of immune and non-immune cells extracted from the healthy or diseased heart[148] have been performed, but are so far limited to a small number of patients and analysed cells.

Recently developed single-cell technologies appear especially attractive to investigate inflammatory cell states and dynamics in CV disease in clinical studies and experimental models. Single-nucleus RNA-seq allows measurement of transcript levels in nuclei extracted from frozen tissues, and is thus particularly suited to analyse biobank-archived patient tissues.[149] Lineage tracing at the single-cell level in experimental models[150] and humans[151] could enable to reconstruct immune cell differentiation and activation trajectories in CV disease. Single-cell transcriptomic analysis with simultaneous detection of cell surface epitopes using e.g. CITE-seq[152] allows precise characterization of leucocytes in patients and experimental models, and complements other high-dimensional immune profiling approaches, such as cytometry by time-of-flight.[153] Together with the development of cost-effective methods to analyse large cell numbers, and new computational tools allowing integration of single-cell gene expression data across technologies and independent studies,[140] advances in single-cell technologies will undoubtedly play a crucial role in the systematic and detailed unravelling of inflammatory processes in CV diseases.

6.2 Metabolomics

Multiple targeted approaches are available to assess metabolism of immune cells, such as fluorescently labelled glucose and FAs, radioactively labelled metabolites, and analysis of oxygen consumption and extracellular acidification as a measure of respiration and glycolysis, respectively.[154] Novel metabolic signatures are typically identified using unbiased metabolic analyses based on mass-spectrometry approaches. These techniques were instrumental to reveal the accumulation of succinate and itaconate and the role of these metabolites in inducing the pro-inflammatory activation of macrophages.[20,32] To assess metabolic rates and direction of fluxes in immune cells, mass spectrometry has been used to evaluate the metabolic turnover of stable isotope-labelled metabolites. These targeted approaches allow assessment of acetate, serine, glutamine, arginine, or glucose.[155–158] Furthermore, new approaches obtain accurate measurement of cellular metabolism in high-throughput processes at a single-cell resolution.[159] Current methods include profiling, in which a single metabolic signature is collected from each cell, and imaging methods that visualize metabolite distributions within a cell or tissue.[160] Single-cell metabolomics has been used to characterize changes in host cell metabolic pathways upon virus interaction.[161] These technological advancements pave the way to obtaining metabolic profiles of infiltrating immune cells in patient samples or cardiac tissue of animal models in single-cell resolution. Characterizing cellular metabolism across heterogeneous cell populations under homeostatic and pathological conditions will help understanding the impact of metabolic changes in human disease.

6.3 Nuclear imaging of inflammation and metabolism

Advanced nuclear cardiology imaging with targeted radionuclide tracers is another important technology in CV precision medicine. Beyond conventional imaging techniques detecting morphological contrasts, molecular imaging using radionuclide tracers visualizes physiological and pathological processes at cellular and sub-cellular levels within intact living organisms, from animal disease models to humans. Single-photon emission computed tomography (SPECT) and PET are widely used for both research and clinical purposes. Recent advances in engineering enabled high-resolution imaging also in the heart of small rodents. Furthermore, state-of-the-art clinical PET systems with digital photomultipliers and fast electronics with time-of-flight reconstruction offer investigation of 4-dimensional (3-dimensional + time sequence) cardiac biology and physiology with significantly improved imaging quality and accuracy compared to SPECT.[162] Another essential component is the introduction of tracers with high binding affinity, specificity to the target molecule, and high *in vivo* metabolic stability.

The development of radionuclide imaging probes that are sensitive and robust enough to detect size and severity of cardiac inflammatory lesions still remains challenging. Many tracers have been tested for imaging inflammation, but only few agents are available in the clinical arena. The most commonly used is the glucose analogue PET tracer FDG. Enhanced FDG uptake in the inflamed tissue is secondary to increased glucose metabolism from inflammatory cells, such as macrophages, and increased metabolic activity of resident cells in response to inflammation.[163] The presence of physiological background activity from myocytes is the major disadvantage for the cardiac application of FDG. Several other promising probes targeting specific cardiac inflammatory processes, such as infiltration of neutrophils, macrophages, and fibroblasts, as wells as angiogenesis and exposure of ECM have been reported, but remain mostly at an experimental stage and need further clinical evaluation.[164]

Radionuclide imaging of energy substrate metabolism is relatively well-established and enables assessment of FA metabolism, glucose metabolism, and myocardial oxygen consumption using distinct tracers (for recent reviews see References[165,166]). Among those tracers,[121] I-beta-methyl-p-iodophenyl-methylpentadecanoic acid (BMIPP) is one of the most established SPECT tracers for measurement of myocardial FA uptake. The alkyl branching structure of BMIPP is designed to inhibit β-ox, thereby increasing tracer retention into the lipid pool of myocytes and improving signals from the heart. In a recent clinical study, patients with HFpEF underwent BMIPP SPECT imaging and were assessed with summed defect score based on the number of segments and degree of tracer uptake in the heart.[167] A positive correlation between defect score and major adverse cardiac events was observed, suggesting that defective BMIPP uptake might represent a negative prognostic marker in patients with HFpEF. The potential use of BMIPP in risk stratification of HF patients was assessed in a small number of clinical trials.[167] More recently, a promising new class of FA PET tracers specifically targeting β-ox was introduced, i.e. 18-^{18}F-fluoro-4-thia-oleate and its analogues.[168] They are structurally modified FA analogues with sulphur heteroatom substitutions in order to undergo metabolic trapping subsequent to β-ox in mitochondria, while non-oxidative retention of radioactivity in lipid storage is very low. These novel specific ^{18}F-labelled PET tracers, which inherited all advantages of high sensitivity PET imaging and the cost-effectiveness/protocol flexibility of ^{18}F radionuclide, might open

a door for reliable quantification of FA oxidation in basic research and clinical practice.

7. Conclusions

Taken together, after nearly three decades of considerable advancements on how to improve outcome of patients with CV diseases by targeting neuroendocrine activation, we are currently entering a new era of treatments in which we are at the doorstep to revealing how to best target inflammation and/or metabolism. Advanced *in vitro* and *in vivo* technologies have broadened our understanding of these emerging fields and brought to light novel treatment concepts. Ongoing and future research should therefore be directed towards elucidating this exiting interface between inflammation and metabolism, further emphasizing the requirement of interdisciplinary research efforts not only for basic, but also clinical and translational concepts.

Authors' contributions

All authors gave substantial contributions to the work by drafting the manuscript or revising it critically for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work.

Conflict of interest: C.M. received speaker honoraria from AstraZeneca, Bayer, Berlin Chemie, Boehringer Ingelheim, Novartis, Servier and served as an advisor to Amgen, Boehringer Ingelheim, NovoNordisk and Servier. S.F. received speaker honoraria and served as an advisor for Novartis. U.H. received speaker honoraria from AstraZeneca and Boehringer Ingelheim. The other authors have no conflicts of interest.

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