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STATE-OF-THE-ART REVIEW

# Immunometabolism at the Heart of Cardiovascular Disease

Matthew DeBerge, PhD,* Rajesh Chaudhary, PhD,* Samantha Schroth, MSTP, Edward B. Thorp, PhD

## HIGHLIGHTS

- **Cardiac leukocytes are regulated by cell-intrinsic shifts in metabolism, which in turn modulate heart function.**
- **Both innate and adaptive cardiac immune cells are uniquely regulated by immunometabolic signaling.**
- **Ischemia and cardiometabolic disease differentially polarize leukocyte immunometabolism, suggesting unique therapeutic strategies.**

## SUMMARY

Immune cell function among the myocardium, now more than ever, is appreciated to regulate cardiac function and pathophysiology. This is the case for both innate immunity, which includes neutrophils, monocytes, dendritic cells, and macrophages, as well as adaptive immunity, which includes T cells and B cells. This function is fueled by cell-intrinsic shifts in metabolism, such as glycolysis and oxidative phosphorylation, as well as metabolite availability, which originates from the surrounding extracellular milieu and varies during ischemia and metabolic syndrome. Immune cell crosstalk with cardiac parenchymal cells, such as cardiomyocytes and fibroblasts, is also regulated by complex cellular metabolic circuits. Although our understanding of immunometabolism has advanced rapidly over the past decade, in part through valuable insights made in cultured cells, there remains much to learn about contributions of in vivo immunometabolism and directly within the myocardium. Insight into such fundamental cell and molecular mechanisms holds potential to inform interventions that shift the balance of immunometabolism from maladaptive to cardioprotective and potentially even regenerative. Herein, we review our current working understanding of immunometabolism, specifically in the settings of sterile ischemic cardiac injury or cardiometabolic disease, both of which contribute to the onset of heart failure. We also discuss current gaps in knowledge in this context and therapeutic implications. (J Am Coll Cardiol Basic Trans Science 2023;8:884-904) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

High leukocyte counts have long been associated with poor clinical outcome, in both the setting of acute myocardial infarction (MI) and heart failure (HF).[1,2] Leukocytes are composed of both innate and adaptive immune cells. Among the innate immune cells, neutrophils are the first to be recruited to the heart after tissue damage. Monocytes follow and differentiate into long-lived, phagocytic macrophages, which consist of these recruited monocyte-derived cells as well as tissue-resident cells established during development. Dendritic cells are also recruited to the heart where they

From the Department of Pathology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA. *Drs DeBerge and Chaudhary contributed equally to this work and are joint first authors.
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acquire cardiac antigen and migrate to lymphoid organs to activate adaptive immune responses consisting of cardiac-specific T cells and B cells. Experimental models have consistently reproduced causal associations between the various leukocyte subsets and heart disease. As such, multiple clinical trials have targeted leukocytes in the setting of cardiovascular disease. However, broad-range strategies have largely failed,[3] in part because various leukocyte subsets also exert cardioprotective functions. Trials such as CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) and others, which more specifically target inflammatory function, have offered promise for reappraising the role of inflammation in HF.[4-6] Yet, the potential of clinical immunomodulation for heart disease remains unfulfilled, partly because of an incomplete understanding of fundamental mechanisms that underly immune cell regulation. One of the more timely and cutting-edge areas of research in this space is immunometabolism, which refers to intracellular metabolic pathways within immune cells and consequences for leukocyte function and surrounding tissue.

## BRIEF OVERVIEW OF IMMUNOMETABOLISM AND ITS RELEVANCE TO CARDIOVASCULAR DISEASE

Cellular metabolism may be conventionally described as a balance between biosynthetic and catabolic reactions, merely indicating the sum of all chemical processes that are necessary for cell function. Yet, a more evolved appreciation is that specific metabolic programs are intricately connected to unique patterns of immune activation. For example, activated or effector lymphocytes develop a thirst for glucose and prioritize glycolysis over mitochondrial metabolism.[7] Glycolysis is a commonly prioritized pathway in immune cells, and although it is not the most efficient path to generate energy, it is supportive of rapid cell proliferation during immune activation.[8] Such metabolite preferences, as elaborated on later, may also interweave with signal transduction networks to calibrate the immune response. These adaptations are greatly affected by the extracellular milieu, which vary significantly during the onset of heart disease. Within the heart, MI depletes local oxygen and nutrient concentrations, and this presents a challenge to metabolically demanding leukocytes that carry out tissue repair. Furthermore, metabolic syndromes that are characterized by high fat and insulin resistance are associated with both the activation of immune cells and cardiac dysfunction.[9,10] From this perspective, it is interesting and relevant to contrast paradigms of immunometabolism in ischemic vs cardiometabolic heart disease (**Central Illustration**). Much of our current insight in this space originates from studies of myocardial ischemia, which is where we begin.

## IMMUNOMETABOLISM OF MYOCARDIAL ISCHEMIA

Myocardial ischemia, as occurs after MI, activates innate and adaptive immune responses and increases risk for heart failure with reduced ejection fraction (HFrEF).[6,11] After MI, both resident as well as recruited immune cells must traffic through a decreasing gradient of oxygen tension and adapt to limited metabolite availability to mediate repair within the infarct and border tissue. Innate immune cells, including neutrophils and monocytes, also experience varying oxygen and metabolite availability as they are released from peripheral sites and traffic to the injured heart. Within the infarct, cardiomyocyte death leads to the release of damage-associated molecular patterns (DAMPs) and self-antigen that trigger metabolic reprogramming of macrophages, dendritic cells (DCs), and T- and B-cell responses. Dying or dead cardiomyocytes must also be cleared, presenting phagocytes with a substantial metabolic burden that requires timely and efficient processing for inflammation resolution and tissue repair. Later we elaborate on how immunometabolism directs these cardioprotective and cardiopathogenic responses after myocardial ischemic injury in humans and experimental models.

## NEUTROPHIL METABOLISM DURING CARDIAC ISCHEMIA

Neutrophils or polymorphonuclear leukocytes are among the first to be recruited from blood after cardiac ischemia. Rapid mobilization of the repair response is critical in the heart because nonregenerative cardiomyocytes die quickly under limiting oxygen and nutrients.[12] Although neutrophils have wound healing functions, elevated neutrophils directly correlate with cardiac damage after acute MI in humans.[13] In experimental animals, neutrophils are implicated in both promoting cardiac injury and facilitating cardiac repair after MI.[14,15] This dichotomy may be explained by an emerging appreciation of the heterogeneity of

## ABBREVIATIONS AND ACRONYMS

**AC** = apoptotic cell

**AMPK** = AMP-activated protein kinase

**APC** = antigen-presenting cell

**ATP** = adenosine triphosphate

**cDC** = conventional dendritic cell

**D2-HG** = D-2-hydroxyglutarate

**DAMP** = damage-associated molecular pattern

**DC** = dendritic cell

**DCM** = dilated cardiomyopathy

**FDG** = fluorodeoxyglucose

**GAPDH** = glyceraldehyde 3-phosphate dehydrogenase

**HF** = heart failure

**HFpEF** = heart failure with preserved ejection fraction

**HFrEF** = heart failure with reduced ejection fraction

**HIF** = hypoxia-inducible factor

**HSPC** = hematopoietic stem and progenitor cell

**IFN** = interferon

**Ig** = immunoglobulin

**IL** = interleukin

**MHCII** = major histocompatibility complex II

**MI** = myocardial infarction

**mTOR** = mammalian target of rapamycin

**NAD** = nicotinamide adenine dinucleotide

**pDC** = plasmacytoid dendritic cell

**PKM2** = pyruvate kinase M2

**ROS** = reactive oxygen species

**SDH** = succinate dehydrogenase

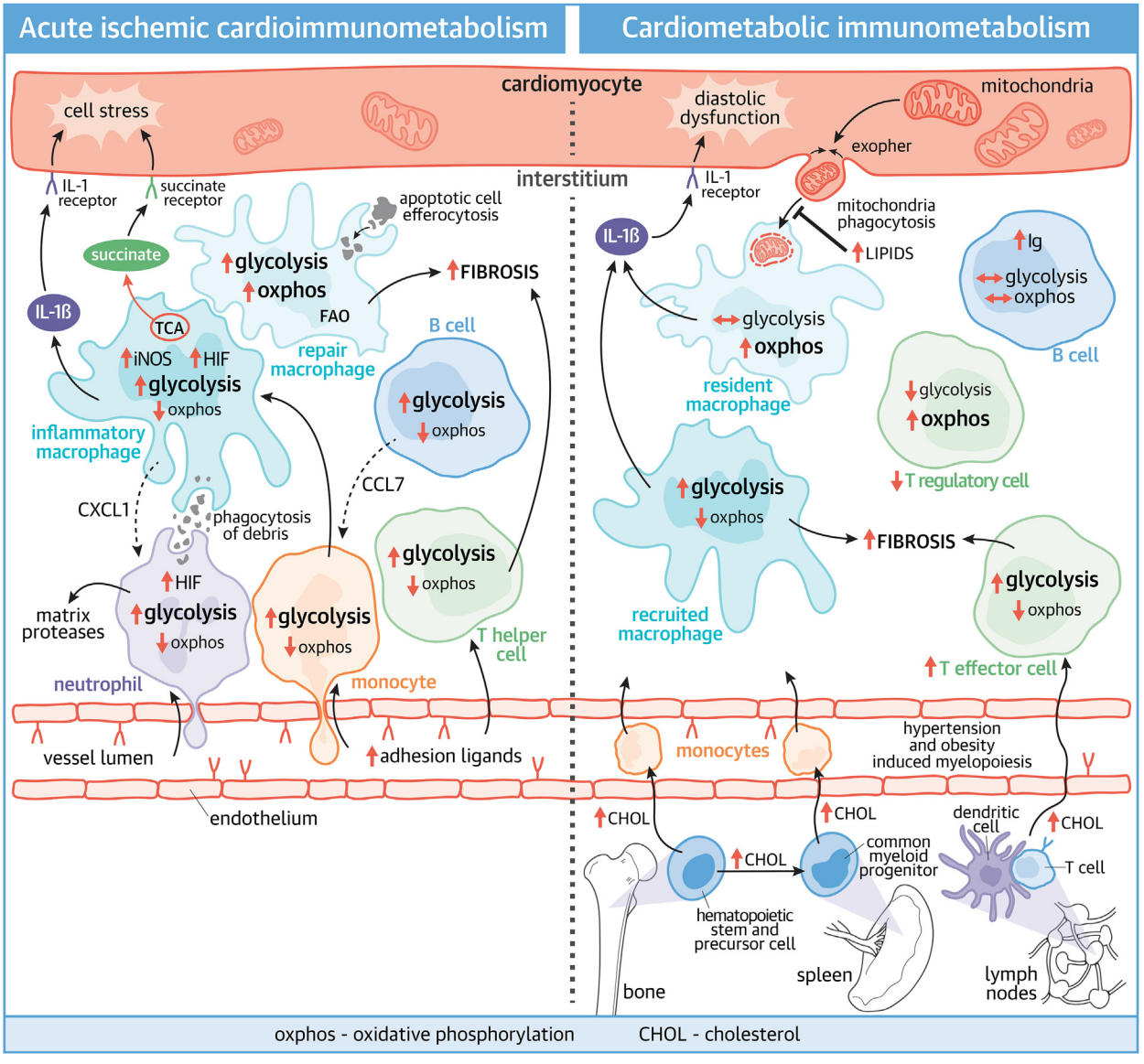
**TCA** = tricarboxylic acid cycle

**Th** = T helper

**TLR** = Toll-like receptor

**TNF** = tumor necrosis factor

**CENTRAL ILLUSTRATION** **Working Model of Cardiac Immunometabolism After Ischemia and Cardiometabolic Disease**

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neutrophil subtypes in the hypoxic heart.[16,17] Within the heart, these "first responders" migrate toward a high front of hypoxia before the onset of compensatory angiogenesis. Hypoxia, a component of ischemia, is often associated with inflammation,[18] and is known to significantly regulate neutrophil function and cellular metabolism.[19] Hypoxia is a transcriptional stimulus that rewires cellular metabolism toward glycolysis.[20,21] Hypoxia activates pretranslated hypoxia-inducible transcription factors (HIFs),[22] including HIF-1α and HIF-2α, which are primed to rapidly transactivate the expression of a number of glycolytic genes.[23] Hypoxia-independent activation of HIF-1α can also occur in neutrophils after the activation of Toll-like receptors (TLRs),[24] which recognize DAMPs released by necrotic cardiomyocytes.[25] The rapid activation of HIFs is coupled to glycolysis, which mobilizes metabolites faster than mitochondrial metabolism.[8] Indeed, neutrophil inflammatory functions rely more on glycolysis and less on mitochondria metabolism. New evidence from metabolic flux assays using

radiolabeled glucose, glutamine, and pyruvate have revealed that this is reinforced in neutrophils by maintaining adequate glycogen stores, both through gluconeogenesis and glycogenesis.[26] Under conditions of limited extracellular glucose availability, neutrophils are also able to derive glutamine from scavenged proteins to fuel gluconeogenesis and generate adenosine triphosphate (ATP).[27] Although critical for neutrophil survival during hypoxia and inflammation, the metabolic switch to glycolysis for ATP production has important roles in neutrophil function beyond cellular bioenergetics. For example, neutrophils release ATP that signals in an autocrine loop through purinergic and adenosine receptors to direct cell migration,[28] neutrophil extracellular trap formation depends on glycolysis,[29] and the diversion of glucose-6-phosphate from glycolysis to the pentose phosphate pathway supports neutrophil oxidative bursts.[30] Relative to other leukocytes, mature neutrophils exhibit reduced numbers of mitochondria.[31] Nevertheless, mitochondrial metabolism may be critical for neutrophil differentiation, migration, and survival. For example, blockade of the electron transport chain can selectively impede neutrophil differentiation from myeloid progenitors,[32] and mitochondrial metabolism has recently been shown to be instrumental for neutrophil migration.[33] Furthermore, neutrophils increase glucose flux through the mitochondrial glycerol 3-phosphate shuttle to increase production of mitochondrial reactive oxygen species (ROS), which further stabilizes HIF-1α and promotes neutrophil survival during hypoxia.[34] Taken together, a working model emerges wherein neutrophil mitochondrial function is necessary for early cell differentiation and migration followed by glycolytic mobilization for neutrophil effector functions and survival. Whether recently implicated cardiac neutrophil subsets have metabolic biases remains unclear.

## MONOCYTE METABOLISM DURING CARDIAC ISCHEMIA

After neutrophil influx, blood-borne monocytes infiltrate the ischemic heart. Like neutrophils, acute inflammatory monocytes are highly glycolytic. This "appetite" for glucose has been leveraged clinically to detect inflammatory monocytes by fluorodeoxyglucose (FDG)-positron emission tomography. After experimental MI, FDG uptake is increased within the infarct and linked to monocyte infiltration.[35] In acute MI patients, peripheral CD14+ monocyte abundance is associated with elevated myocardial FDG uptake, larger infarcts, and worsened systolic function,[36] consistent with monocyte glycolytic function promoting adverse cardiac remodeling in humans. Indeed, monocytes from MI patients are hyperinflammatory with increased glycolytic flux, which leads to nuclear translocation of the glycolytic enzyme pyruvate kinase M2 (PKM2) to promote transcription of inflammatory cytokines interleukin (IL)-6 and IL-1β.[37] Similarly, healthy human CD14+ monocytes activated with an inflammatory TLR4 agonist increase glycolysis and suppress mitochondrial oxidative phosphorylation, in part through down-regulation of genes involved in fatty acid oxidation.[38] Glycolysis was required for both PKM2 signaling and the production of IL-1β because the inhibition of glycolysis in monocytes with 2-deoxyglucose attenuated inflammatory activation.[37,38] However, in cases of glucose deprivation, as may occur within the ischemic infarct, monocytes have the capacity to compensate and rely on oxidative phosphorylation by mobilizing lipid depots in response to inflammation.[39] Even in the presence of sufficient glucose, different TLR agonists exhibit specific patterns of metabolic rewiring because TLR2 stimulation requires monocytic mobilization of both glycolysis and oxidative phosphorylation for inflammatory activation.[38] Within the myocardium, the recruitment of monocytes to the ischemic heart is elevated under hyperlipidemic conditions, and this is associated with impaired infarct healing.[40] This can be explained by a hypercholesterolemic increase in the survival and proliferation of inflammatory monocytes.[41] Advances in single-cell transcriptomic analyses and fate mapping monocytes from myeloid progenitors have begun to reveal the heterogeneity of monocytes after MI in humans and mice, which consists of multiple functional subsets.[42,43] For example, comparisons of the transcriptional profile of peripheral monocytes before and 48 hours after primary angioplasty in patients with acute MI revealed enrichment for genes involved in inflammation and carboxylic acid metabolic processes, the latter of which includes expression of the glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and the gluconeogenesis enzyme aspartate aminotransferase.[42] Single-cell transcriptomics of healthy or infarcted mouse hearts identified 13 populations of monocyte/macrophage populations with inflammatory monocytes giving rise to proinflammatory macrophages as well as noninflammatory *Trem2*$^{hi}$ macrophages, which share a transcriptional signature similar to lipid-associated macrophages found in obese adipose tissue or atherosclerotic lesions.[43] Whether unique immunometabolic programs contribute to distinct monocyte

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subset functions remains to be clarified after cardiac ischemia.

## MACROPHAGE METABOLISM DURING CARDIAC ISCHEMIA

Plasticity is a hallmark of macrophages and refers to their polarization between distinct functional states.[44] Although single-cell transcriptomics have advanced our understanding of cardiac macrophage plasticity beyond the M1/M2 dichotomy,[43,45] the general paradigm that has emerged is one in which inflammatory macrophages prioritize glycolysis, whereas anti-inflammatory macrophages leverage fatty acid oxidation and mitochondrial respiration. MI mobilizes both cardiac resident macrophages and recruited monocyte-derived macrophages to repair the damaged myocardium. Tracking macrophage polarity over the span of 1 week after experimental MI indicated a notable early induction of glycolysis gene transcripts that were congruent with inflammatory cytokine biosynthesis and adaptations to hypoxia.[46] This likely reflects the activity of recruited, monocyte-derived macrophages as macrophages expressing *Ccr2*, indicative of recent differentiation from monocytes, has increased the expression of genes involved in glycolysis and the response to hypoxia compared with resident *Timd4* expressing macrophages.[45] Furthermore, PKM2 directly interacts with HIF-1α in monocyte-derived macrophages to enhance glycolysis and inflammatory activation,[37,47] linking PKM2 signaling in peripheral monocytes to differentiation into inflammatory, glycolytic macrophages within the infarct. The loss of HIF-1α in myeloid cells attenuates inflammation and preserves ventricular function in a model of permanent occlusion MI[48] in which resident macrophages are lost after infarction,[49] implying that HIF-1α–dependent glycolysis in recruited macrophages can be detrimental to cardiac repair. Mechanistically, HIF-1α activation in macrophages led to proteolysis of the phagocytic receptor MerTK, which is necessary for clearing dead myocardial tissue.[50] Importantly, this MerTK proteolysis was blunted by inhibitors of glycolysis. Similarly, genetic deletion or pharmacologic inhibition of PKM2 enhances macrophage clearance of dying cells,[51] demonstrating that glycolytic signaling directly antagonizes cardioprotective responses in addition to supporting inflammatory activation. Macrophage HIF-2α also perpetuates a maladaptive immunometabolic cardiac repair response because loss of HIF-2α in myeloid cells reduced adverse remodeling after experimental MI.[48] In contrast to HIF-1α, HIF-2α indirectly contributes to the glycolytic shift in macrophages by sequestering fatty acids in lipid droplets to "starve" the mitochondria of fuel that is necessary for anti-inflammatory function. Within mitochondria, inflammatory macrophage activation leads to increased levels of the tricarboxylic acid cycle (TCA) metabolite succinate, which is oxidized by succinate dehydrogenase (SDH), increasing mitochondrial membrane potential and mitochondrial ROS production.[52] This is important because mitochondrial ROS activates HIF-1α[53] as well as the production of inflammatory IL-1β.[54] Selective accumulation of succinate is a signature of myocardial ischemia and is associated with the generation of proinflammatory mitochondrial ROS.[55] As such, the inhibition of SDH was demonstrated to reduce the accumulation of mitochondrial ROS and limit reperfusion-associated injury.

In contrast to inflammatory macrophage activation, anti-inflammatory macrophage polarization is correlated to myocardial repair[56] and, separately, macrophage mitochondrial metabolism and metabolites.[57,58] In addition to succinate, inflammatory macrophage activation also leads to increased levels of the TCA intermediate itaconate.[59] Contrary to succinate, itaconate has been shown to have anti-inflammatory effects[60] as well as cardioprotective features after cardiac ischemia. For example, intravenous infusion of dimethyl itaconate during ischemia reduced myocardial infarct size.[61] Likewise, dimethyl itaconate delivered via subcutaneous nanofiber patches also attenuated adverse remodeling after experimental MI, which was associated with increased anti-inflammatory macrophage polarization and cytokines.[62] Itaconate is synthesized by aconitate decarboxylase 1, which is encoded by *Irg1*, and exhibits selective expression in activated immune cells,[63] particularly inflammatory macrophages,[64] supporting its role in feedback inhibition of inflammation. Itaconate suppresses inflammation by antagonizing SDH,[52] which limits mitochondrial ROS generation from complex I of the electron transport chain. Itaconate can also suppress inflammation by alkylating an inhibitor of the key antioxidant protein NRF2[60] as well as inhibit components of the inflammasome, which regulates IL-1β biosynthesis.[65] It remains unknown the degree to which itaconate is produced in cardiac macrophages or if macrophage polarization could enhance itaconate production for a therapeutic effect in the heart. Although succinate and itaconate are 2 of the most well-characterized metabolites regulating macrophage function, roles for additional TCA intermediates are beginning to emerge. For example, TLR4 activation of macrophages leads to late-stage accumulation of TCA cycle

intermediate, D-2-hydroxyglutarate (D2-HG), in part by increased catalysis of α-ketoglutarate.[66] The treatment of macrophages with D2-HG attenuates tumor necrosis factor (TNF)-α production, whereas D2-HG administration during experimental sepsis attenuates systemic inflammation,[66] demonstrating a similar feedback inhibitory role as itaconate. Interestingly, excess D2-HG sourced from myeloid malignancies has been documented to impair contractile function in rodent hearts,[67] but its role in acute MI remains unknown. Together, just how cell metabolism differs in cardiac macrophage subsets, including embryonic-derived resident cardiac macrophages, vs inflammatory-phase recruited and blood-borne monocyte-derived macrophages remains a future area for clarification. The conventional thinking here is that newly recruited macrophages likely are more glycolytic than their resident macrophage counterparts; the latter may leverage mitochondrial metabolism for prorepair functions as discussed later.

## PHAGOCYTIC MACROPHAGE METABOLISM DURING CARDIAC ISCHEMIA

For cardiac repair to proceed after ischemic injury, apoptotic cells (ACs) must first be cleared by the process of efferocytosis. The physical removal of dying cells prevents secondary necrosis limiting infarct expansion, and AC engulfment activates downstream pathways leading to the production of inflammation-resolving mediators.[68] A cardiac macrophage engages in efferocytosis of apoptotic cells larger than itself as well as during multiple rounds of efferocytosis,[69] which increases metabolic load and oxidative stress.[70] For example, continuous efferocytosis increases mitochondrial membrane potential and calcium levels,[71,72] both of which promote ROS production and compromise the survival of the efferocytic macrophage.[70] To adapt to the increases in oxidative stress, continuous efferocytosis mobilizes mitochondrial uncoupling proteins to lower mitochondrial membrane potential[71] and mitochondria fission machinery to shunt calcium into the cytosol and facilitate phagolysosome formation around subsequent ACs.[72] Additionally, efferocytosis initiates transcriptional changes that protect the macrophage against oxidative stress,[73] which may confer a survival advantage to efferocytotic macrophages in the setting of elevated ROS after myocardial ischemia-reperfusion injury. After AC engulfment, macrophages generate proreparative cytokines, including IL-10, by transporting AC-derived lipids into the mitochondria where they are metabolized and contribute to the generation of the metabolic cofactor nicotinamide adenine dinucleotide (NAD).[74] The loss of this pathway in macrophages impairs cardiac repair and leads to ventricular rupture after experimental MI,[74] revealing the requirements of mitochondrial-NAD signaling within macrophages for cardioprotection. Interestingly, peripheral blood mononuclear cells from HFrEF patients exhibit reduced mitochondrial respiration and elevated expression of IL-6 compared with healthy controls, which can be reversed by the administration of nicotinamide riboside, an NAD precursor.[75] Mechanistically, IL-6 reduces mitochondria membrane potential and impairs complex I activity,[75,76] the latter of which leads to NAD/nicotinamide adenine dinucleotide imbalance, HIF-1α activation, and HF.[77,78] NAD restoration increases α-ketoglutarate levels, which favors HIF-1α degradation[78] and promotes anti-inflammatory macrophage polarization,[79] demonstrating the importance of NAD in metabolic reprogramming of myeloid cells. Efferocytosis can also activate glycolysis followed by release of the glycolytic end product lactate, which is recognized by lactate receptors on neighboring macrophages and leads to their anti-inflammatory polarization.[80] Lactate promotes cardioprotective macrophage responses and preserves ventricular function after experimental MI,[81] supporting a putative role for efferocyte-derived lactate in cardioprotection after ischemic injury. To sustain efferocytosis-induced production of proresolving mediators, macrophages convert AC-derived methionine into S-adenosylmethionine, which is used to epigenetically repress negative feedback pathways that impair inflammation resolution.[82] Methionine uptake is increased in the infarcts of patients after acute MI and observed in regions exhibiting reduced glucose uptake,[83] raising the possibility that these changes reflect efferocytic macrophage function. Together, these studies reveal the importance of AC metabolism in proreparative macrophage function and support future studies to determine their role after cardiac injury.

## DC METABOLISM DURING CARDIAC ISCHEMIA

DCs are another phagocytic population of leukocytes that serve as a bridge between the innate and adaptive immune response. DCs can sample antigen at sites of injury and traffic through draining lymphatics or peripheral circulation to regulate the activation state of other myeloid cells and lymphocytes.[84,85] It has become increasingly clear that DC function is calibrated by shifts in metabolism. Homeostatic or

"resting" DCs prioritize fatty acid oxidation and oxidative phosphorylation,[86] as do some vitamin D3-induced tolerogenic, anti-inflammatory DCs.[87] During inflammation mediated by TLR signaling reported to occur in ischemia-reperfusion injury,[88] DCs undergo a rapid phase of metabolic transition from steady-state oxidative phosphorylation to aerobic glycolysis[86] through catabolism of intracellular glycogen stores.[89] This glycolytic polarization leads to elevations in citrate, an intermediate of the TCA cycle, which can be converted to acetyl-CoA and then malonyl-CoA for use in fatty acid synthesis.[90] Such de novo fatty acid synthesis is hypothesized to facilitate increased production of inflammation-induced proteins through membrane expansion of the endoplasmic reticulum and Golgi apparatus. Recognizing these general paradigms of DC metabolism, DCs have been implicated in both protective and pathologic roles after MI. For example, CD11c ablation increases inflammation and Ly6Chi monocyte infiltration, leading to worsened ventricular function and impaired remodeling after MI.[91] However, it is important to note that CD11c is expressed not only on DCs but also subsets of macrophages and monocytes.[92] Relatedly, DCs are highly heterogenous but can be separated into distinct, functionally divergent lineages, namely conventional DCs (cDCs) and plasmacytoid DCs (pDCs).[93] Although our understanding of the unique roles of these populations is currently in its infancy, it is reasonable to surmise these populations participate in specific functional responses to cardiac ischemia. Recently developed genetic tools have begun to provide the opportunity to dissect subset-specific responses at both the functional and the metabolic level.[94] Indeed, targeted depletion of conventional DC subsets led to improved cardiac function and reduced infarct size after MI.[95] In contrast, pDCs were dispensable for remodeling and repair.[95] TLR stimulation of human myeloid DCs (most similar to cDCs) induces glycolysis, whereas it promotes oxidative phosphorylation and glutamine metabolism in pDCs.[96] These profound differences in immunometabolism after equivalent stimulation may explain in part the differential cardiac outcomes after targeting separate DC subpopulations. Additionally, cross presentation of antigen by cDCs, specifically cDC1s, primes anticardiac T cells to exacerbate ischemic cardiac injury.[97,98] These recent subset-specific studies seem to depict a more inflammatory and immunostimulatory role for antigen-presenting cDCs and we hypothesize a glycolytic sourcing of energy during ischemia.

## T-CELL METABOLISM DURING CARDIAC ISCHEMIA

Multiple T-cell subsets have been studied in the setting of cardiac ischemia, with both cardioprotective and detrimental effects documented after MI. For example, myocardial CD4+ T helper (Th) 1 cells are increased after experimental MI, and their depletion in the chronic stage after coronary ligation ameliorates pathological remodeling and ventricular dysfunction.[99] Similarly, depletion of CD8+ T cells after experimental MI reduces inflammation and preserves ventricular function, which is recapitulated in mice lacking the cytotoxic effector molecule granzyme B.[100] CD4+ T-cell activation leads to increased levels of the glucose transporter Glut1,[7] which promotes glycolytic metabolism and Th1 differentiation.[101] Moreover, both elevated Glut1 expression and glycolytic metabolism are required to support CD4+ T-cell production of interferon (IFN)-γ[102] as well as CD8+ T-cell expression of granzyme B.[103] Like Th1 cells, Th17 cells are also elevated after experimental MI,[99] and their differentiation requires glycolytic reprogramming through metabolic sensor mammalian target of rapamycin (mTOR)-dependent HIF-1α activation.[104] In contrast, lymphopenia after percutaneous coronary intervention is associated with poor prognosis,[105] and the activation of $CD4^+$ T cells improves wound healing and survival after experimental MI.[106] This may require regulatory Foxp3+ T cells (Tregs), which attenuate cardiac ventricular remodeling and improve healing after MI.[107,108] Interestingly, cardioprotective Treg responses may be cardiac antigen specific[109] and act through direct communication with cardiomyocytes.[110] Treg migration requires glucokinase-mediated glycolysis,[111] but in contrast to proinflammatory T cells, Tregs have high rates of lipid oxidation and express low levels of Glut1.[7] Moreover, Treg differentiation can be enhanced by the inhibition of mTOR or HIF-1α.[104,112] Indeed, T-cell activation is energetically demanding, and the reduced availability of extracellular amino acids during ischemia may also selectively impair T-cell mobilization or differentiation. This is because activated T cells use extracellular amino acids, such as leucine, which is taken up by amino acid transporters and leads to mTOR-dependent Th1 and Th17 differentiation.[113] Lastly, although the experimental studies described previously imply T-cell recognition of autoantigen after MI, the relevant antigen specificities in humans remain relatively unclear. Recent work has led to the identification of CD4+ T-cell

recognition of epitopes within cardiac α-myosin heavy-chain or adrenergic receptor β1 proteins in patients after MI,[114,115] but whether antigen specificity dictates function is unknown. However, T cells have also been reported to mediate cardioprotection independent of antigen recognition by increasing hydrolysis of extracellular nucleotides such as ATP and NAD released by necrotic tissues to inhibit the production of inflammatory and fibrotic cytokines IFN-γ and IL-17.[116] Together, these studies reveal the key role of metabolic shifts in T-cell differentiation and function, which dictates the extent of adverse remodeling after ischemic cardiac injury.

## B-CELL METABOLISM DURING CARDIAC ISCHEMIA

After experimental MI, polyclonal B cells are recruited to the ischemic myocardium[117] where they impair cardiac function through secreting chemokines (eg, CCL7), which facilitate cardiac recruitment of inflammatory monocytes[118] and support inflammatory macrophage activation.[119] DAMPs released by dying cardiomyocytes also lead to B-cell production of anticardiac immunoglobulin (Ig) G,[120] which is increased in patients with end-stage ischemic HF compared with non-HF controls.[121] Similar to T-cell receptor activation, B-cell receptor ligation can trigger glycolysis[122] to promote B-cell proliferation and antibody production.[123] IgG biosynthesis requires considerable energy, and metabolic tracing experiments suggest that IgG production preferentially favors glucose-derived carbons. These carbons are favorably shunted to the biosynthesis of sugars that are required for IgG glycosylation.[124] Interestingly, the aforementioned CCL7 is a transcriptional target of the glycolysis regulator HIF-1α.[125] Thus, a conservative hypothesis is that glycolytic activation in cardiac B cells during cardiac ischemia contributes to both CCL7-induced monocyte recruitment and anticardiac IgG production and, therefore, the perpetuation of cardiac inflammation. In contrast, IL-10–producing B cells are enriched in pericardial adipose tissue, and B-cell production of IL-10 is required for cardioprotection after experimental MI.[126] The short-chain fatty acid butyrate induces IL-10 production by B cells,[127] which may be mediated in part by butyrate enhancing fatty acid oxidation.[128] Therefore, it is tempting to speculate that elevated B-cell lipid metabolism may generally counteract the production of detrimental anticardiac IgG and favor regulatory function. It should also be noted that long-lived, antibody-secreting plasma cells prioritize fatty acid oxidation over glycolysis for survival.[129] However, plasma B-cell survival vs IgG production may be uncoupled because mTOR inhibition decreases antibody secretion without affecting survival.[130] Together, these studies highlight the emerging role of B cells and their metabolism during ischemic HF.

## METABOLIC BIASES OF IMMUNE CELLS DURING CARDIOMETABOLIC HF

Relative to the immunometabolism of acute ischemia, there is a much larger knowledge gap between immune cell metabolism and nonischemic, cardiometabolic heart disease.[131] Although there is less experimental data to discuss here, we anticipate this to change significantly over the next few years, particularly with the advent of new animal models in this research space.[132] A critical syndrome in this area is heart failure with preserved ejection fraction (HFpEF), which accounts for nearly half of all heart failure[133] and is directly linked to metabolic syndrome. Although heterogeneous in its etiology, inflammation is a common characteristic of patients with HFpEF.[134] In contrast to cardiac ischemia in which the trigger for immune cell activation originates from within the myocardium, cardiometabolic heart failure, such as HFpEF, develops initially from extracardiac stress.[135] Accumulating evidence indicates that cardiometabolic risk factors also track with maladaptive immune responses, which contribute to disease progression.[136] Furthermore, metabolic profiling of HFpEF and HFrEF patients has revealed metabolites that are uniquely elevated in HFpEF patients compared with HFrEF patients.[137-139] This is expected to differentially rewire immune cell metabolism leading to cardiometabolic HF-specific responses as discussed later.

**MYELOPOIESIS AND MONOCYTE METABOLISM IN THE SETTING OF CARDIOMETABOLIC DISEASE.** Monocyte abundance is increased in both the periphery and hearts of HFpEF patients compared with controls.[140,141] Gene expression of monocyte chemoattractant *Ccl2* is also increased in the heart during hypertension,[142] indicating that peripheral monocytes are actively recruited to the heart during cardiometabolic HF. The production of peripheral monocytes during cardiometabolic HF may be fueled by the bone marrow or through splenic extramedullary myelopoiesis, the process by which progenitor cells differentiate into mature myeloid cells.[143] This is compounded by metabolic stress because hypertension and diet-induced obesity have been shown to promote myelopoiesis from hematopoietic stem and progenitor cells (HSPCs).[144,145] The skewing of HSPCs toward mature, inflammatory

monocytes during diet-induced obesity requires monocytic glycolytic reprogramming with a concomitant decrease in oxidative phosphorylation.[146] In support of glycolysis favoring bone marrow myelopoiesis, loss of glucose transporter Glut-1 blunted glucose uptake in HSPCs during hyperlipidemic conditions and reduced myelopoiesis.[147] HSPCs can also be activated during hyperglycemia by neutrophil-derived alarmins, the production of which are similarly dependent on Glut-1-mediated glucose uptake and glycolysis in neutrophils, leading to bone marrow myelopoiesis and monocytosis.[148] Increases in diastolic dysfunction are associated with increased bone marrow and splenic glucose uptake in humans,[142] raising the possibility that glycolytic reprogramming within the bone marrow niche increases the production of inflammatory monocytes to propagate cardiometabolic HF.

Recent work has also shown a direct role for cholesterol because patients with familial hypercholesterolemia exhibit increased gene expression of pathways involved in bone marrow HSPC migration and myelomonocytic proinflammatory differentiation.[149] Importantly, cholesterol-lowering treatment reverted the myelomonocytic differentiation, which may have resulted in part through the restoration of oxidative phosphorylation in HSPCs.[149] Similar findings in animals demonstrate that although cholesterol boosts proinflammatory monocyte production,[41] once in the circulation, metabolic stress directly activates monocyte adhesion and subsequent chemotaxis.[150] In this context, cholesterol accumulation in monocytes may be promoted by the microRNA miR-33a,[151] which suppresses genes involved in cholesterol efflux.[152] Moreover, miR33a is involved in metabolic reprogramming independent of cholesterol homeostasis through the suppression of both mitochondrial respiration and fatty acid oxidation.[153] Within monocyte-derived macrophages, this leads to proinflammatory glycolytic reprogramming because miR33a blocks activation of the energy sensor adenosine monophosphate-activated protein kinase (AMPK) and downstream fatty acid oxidation.[154] AMPK deletion in myelomonocytic cells also leads to excessive inflammation and exacerbates hypertensive organ injury,[155] highlighting the importance of this pathway in metabolic reprogramming of monocytes. Thus, the evidence supports metabolically driven activation of monocytes followed by their targeting to the heart during cardiometabolic HF.[156]

A challenge to targeting metabolic-driven activation of monocytes is that cardiometabolic stress leads to long-term transcriptional changes within myeloid progenitor cells, a phenomenon known as trained immunity. Trained immunity results from stimuli-induced transcriptomic and epigenomic reprogramming of HSPCs and mature myeloid cells, leading to enhanced inflammatory function after restimulation. This is exemplified in familial hypercholesterolemia patients in whom cholesterol-lowering therapy attenuates myelomonocytic skewing of HSPCs, but HSPCs still retain an inflammatory gene signature.[149] Trained immunity is also recapitulated in animal models in which hypercholesterolemia-primed HSPCs retain the propensity to generate inflammatory monocytes, which then differentiate into hyperinflammatory macrophages, even when transferred into normocholesterolemic mice.[157] Cardiometabolic stress, including obesity,[158] hyperglycemia,[159] and diabetes,[160] has also been demonstrated to lead to trained immunity. Metabolically, mTOR- and HIF-1α–mediated aerobic glycolysis are required for trained immunity,[161] with hyperglycemia-driven glycolysis leading to histone methylation and increased chromatin accessibility of inflammatory and glycolytic genes.[159] TCA metabolites succinate and malate are also increased in hyperglycemic cells, which act as antagonists for histone and DNA demethylases to further affect gene expression through epigenetic modifications.[162] Separately, supraphysiological levels of aldosterone, which lead to secondary hypertension, induces trained immunity in human monocyte-derived macrophages independent to changes in glycolysis or oxidative phosphorylation.[163] Instead, aldosterone-dependent increases in transcriptionally permissive histone methylation were dependent on fatty acid synthesis because the treatment of cells with the fatty acid synthesis inhibitor cerulenin abolished aldosterone-induced trained immunity.[163] Together, this demonstrates how cardiometabolic stress leads to long-lasting immunometabolic changes in monocytes and their progenitors to create a state of systemic inflammation.

**MACROPHAGE METABOLISM IN THE SETTING OF CARDIOMETABOLIC DISEASE.** In the case of macrophages, endomyocardial biopsies have revealed increased abundance and activation of macrophages in HFpEF patients compared with controls,[140,156] and the blockade of their recruitment during experimental hypertension ameliorates cardiac fibrosis and diastolic dysfunction.[142] Hyperlipidemia is a risk factor for cardiometabolic HF, and macrophages are well-known for their capacity to metabolize lipids, including cholesterol. Metabolism of cholesterol in macrophages is linked to the attenuation of inflammatory function because the breakdown of

cholesterol by cholesterol ester hydrolase leads to significantly lower levels of proinflammatory cytokines such as IL-1β, IL-6, and CCL2.[164] Conversely, saturated fatty acids, including palmitate, activate HIF-1α in macrophages during diet-induced obesity, leading to glycolytic reprogramming and enhanced production of IL-1β.[165] Thus, the capacity for macrophages to properly metabolize fatty acids and cholesterol may be critical for controlling the degree of cardiac inflammation.

In contrast to the protective role of fatty acid-fueled macrophage production of IL-10 after ischemic cardiac injury, IL-10 may contribute to the pathogenesis of cardiometabolic HF. For example, macrophage deletion of IL-10 attenuates diastolic dysfunction during experimental hypertension.[142] Furthermore, monocytes from healthy donors cultured in the presence of HFpEF serum but not control or hypertensive serum differentiate into IL-10–expressing macrophages,[141] revealing a key role for serum factors in macrophage reprogramming during HFpEF. Compared with the serum from HFrEF patients, HFpEF patients exhibit higher levels of hydroxyproline, alanine, and kynurenine.[137] Higher levels of kynurenine may reflect increased catabolism of tryptophan, which is mediated by indoleamine 2,3-dioxygenase. Both indoleamine 2,3-dioxygenase and kynurenine have been linked to macrophage production of IL-10,[166,167] which may increase *Il10* expression through downstream activation of the aryl hydrocarbon receptor,[168] and manifest as increased plasma levels of IL-10 in HFpEF patients compared with controls.[141] The sustained expression of IL-10 leads to lung fibrosis, which is dependent on the activity of CCR2+ macrophages.[169] Thus, macrophage production of IL-10 is likely a compensatory response to chronic inflammation present during cardiometabolic HF; however, its sustained production may exacerbate cardiac fibrosis and diastolic dysfunction.

Phagocyte cross talk by macrophages with cardiomyocytes may also directly affect macrophage metabolism and cardiac function. For example, deletion of the phagocytic receptor MerTK impairs cardiac macrophage homeostatic removal of dysfunctional cardiomyocyte mitochondria and, in turn, impairs myocyte metabolism, leading to cardiac diastolic dysfunction.[170] Excess dietary lipids also inhibit mitochondria transfer to macrophages,[171] suggesting that cardiometabolic risk factors may similarly impair mitochondria transfer to cardiac macrophages. Mitochondria transfer to macrophages leads to the increased expression of anti-inflammatory genes and the down-regulation of genes involved in antigen presentation.[172] This effect may be mediated in part by increased macrophage oxidative phosphorylation because treatment with the mitochondrial respiration inhibitor oligomycin abrogates the anti-inflammatory effect of mitochondria transfer in macrophages.[173] Together, macrophage metabolic reprogramming likely underlies both inflammatory as well as compensatory anti-inflammatory responses, and additional studies are needed to unravel their respective roles in cardiometabolic HF.

**DC METABOLISM IN THE SETTING OF CARDIOMETABOLIC DISEASE.** Despite the known importance of DCs in regulating the infiltration of inflammatory monocytes and macrophages during cardiac ischemia alongside their role in "educating" the adaptive arm of the immune response as professional antigen-presenting cells (APCs),[91] few studies have assessed DCs specifically within cardiometabolic disease. During diet-induced obesity, cDCs present in visceral adipose tissue rely on Wnt/β-catenin and PPARγ signaling to produce IL-10 and inhibit inflammatory T-cell responses.[174] In contrast, diet-induced obesity increases visceral adipose tissue infiltration of pDCs, and their deletion abrogates weight gain and insulin resistance.[175] Extracellular saturated fatty acids activate TLR4 signaling in cultured DCs leading to increased expression of major histocompatibility complex II (MHCII), costimulatory molecules (CD40, CD80, and CD86), and IL-6 production,[176] which may contribute to pDC-mediated metabolic dysfunction. Obesity also induces increased expression of genes involved in lipid metabolism and fatty acid oxidation in splenic DCs, leading to increased mitochondrial respiration and ROS production.[177] This shift to oxidative phosphorylation during metabolic stress may fuel pathogenic pDCs and antagonize protective cDCs because these cells diverge in their use of mitochondrial metabolism.[96] In contrast to metabolic stress, hypertensive patients exhibit increased abundance of myeloid DCs (similar to cDCs) with a reduction in pDCs compared with healthy controls.[178] Depletion of cDCs blunts hypertensive organ damage, including cardiac hypertrophy, during experimental hypertension,[179] which was associated with reduced effector T-cell accumulation in the kidney.[180] DCs respond directly to increased extracellular sodium chloride during hypertension by increasing sodium uptake via amiloride-sensitive channels, leading to ROS production.[181] This activates DC production and the presentation of immunogenic isolevuglandin protein adducts, which are neoantigens that promote hypertension through T-cell production of IL-17 and IFN-γ.[181] Although T cells are primarily activated by

professional APCs, such as DCs, nonprofessional APCs, including fibroblasts, have also been found to activate T cells during nonischemic HF. During cardiac pressure overload, IFN-γ induces MHCII and CD80 expression on cardiac fibroblasts, leading to cardiac fibrosis and systolic dysfunction.[182] Depletion of cardiac fibroblast MHCII expression attenuates cardiac injury linking antigen presentation by nonprofessional APCs to HF pathogenesis. Metabolically, IFN-γ fuels fibroblast activation by promoting glucose uptake.[183] Increased glucose uptake and utilization by cardiac fibroblasts, mediated in part by HIF-1α-dependent expression of pyruvate dehydrogenase kinase, fuels the production of transforming growth factor-β and leads to cardiac fibrosis during pulmonary arterial hypertension.[184] Thus, metabolic programming in both professional and nonprofessional APCs during cardiometabolic dysfunction has the capacity to regulate the degree of T-lymphocyte activation; the latter is discussed later.

**T-CELL METABOLISM AND POTENTIAL LINKS TO CARDIOMETABOLIC DISEASE.** Both human and experimental HFpEF are characterized by increased T-cell accumulation in the heart. In ventricular biopsies, increased CD3+ T cells were observed in HFpEF patients compared with controls without congestive HF.[185] Similarly, myocardial infiltration of both CD4+ and CD8+ T cells is increased in experimental HFpEF compared with control animals.[186] Increased levels of inflammatory CD4+ T cells expressing TNF-α and IFN-γ have also been observed in the circulation of HFpEF patients compared with HFrEF patients.[187] IFN-γ production by proinflammatory Th1 effector T lymphocytes induces cardiac fibroblast production of profibrotic transforming growth factor-β,[188] suggesting a putative mechanism by which effector CD4+ T cells promote cardiac fibrosis and cardiac dysfunction. During cardiac pressure overload, a nonischemic and noncardiometabolic model of HF, CD4+ T cells promote the transition from compensated cardiac hypertrophy to HF,[189] and interventional blockade of T- cell costimulation ameliorates HF,[190] revealing a pathogenic role for CD4+ T cells in nonischemic HF.

It is unclear whether T-cell metabolism significantly affects nonischemic cardiometabolic HF, either positively or negatively. Evidence from humans and rodents with nonischemic HF supports a critical role for lymphocyte metabolism. In patients with nonischemic HF or dilated cardiomyopathy (DCM), CD4+ T cells exhibit increased adhesion to activated endothelial cells[191] and increased glucose utilization.[192] Glycolysis appears to be important because HF induced by adoptive transfer of activated CD4+ T cells into healthy recipients can be effectively blocked if T-cell glycolysis is inhibited before transfer.[192] These effects may have been mediated in part by the attenuation of CD4+ T-cell accumulation within the heart because reduced glycolytic flux within T cells inhibits proliferation.[193] In contrast, fatty acid oxidation within CD4+ T cells has been shown to support inflammatory Th17 lineage specification over Treg polarization through the expression of the Th17 pioneer transcription factor BATF.[194] Patients with HFpEF exhibit an increase in the frequencies of circulating Th17 cells with a concomitant decrease in Tregs compared with normal controls.[195] Th17 lineage specification also requires polyamine metabolism because inhibition of the rate-limiting enzyme ornithine decarboxylase 1, which converts arginine to ornithine, blocks Th17 induction and favors Treg polarization.[196] In the Framingham Heart Study, ornithine was the top metabolite associated with incident HFpEF,[197] suggesting that changes in T-cell metabolism regulate the balance of pro- and anti-inflammatory subsets and pathogenesis during HFpEF.

Systemic metabolic dysregulation, including obesity alone and as occurs in cardiometabolic HF, can also trigger T-cell activation, leading to inflammatory differentiation and culminating in chronic inflammation.[198] Diets high in saturated fatty acids affect the activation of divergent T-cell subsets because long- and medium-chain fatty acids support Th1 and Th17 cell differentiation, whereas short-chain fatty acids promote the induction of Tregs.[199] This is evident in experimental diet-induced obesity in which CD4+ T cells exhibit increased uptake of medium-chain fatty acids contributing to a hypermetabolic state[200] and increased TNF-α and IFN-γ production.[201] Higher plasma levels of long- and medium-chain fatty acids are observed in HFpEF patients compared with non-HF controls[139] and are associated with worsened disease,[202] which may result from fueling inflammatory CD4+ T-cell responses. Patients with HFpEF also display higher plasma levels of alanine compared with patients with HFrEF.[137] Alanine is required as an extracellular nutrient to support the activation of naïve T cells as well as restimulation of memory T cells.[203] This occurs through increased glucose uptake and carbon metabolism to stimulate protein biosynthesis and the production of inflammatory cytokines, including TNF-a and IFN-g.[203] Together, changes in fatty acid and metabolite availability may favor inflammatory metabolic reprogramming in T cells and contribute to the onset of HFpEF.

Hypertension is a hallmark of both impaired systemic metabolic homeostasis and cardiometabolic HF and is characterized by increased IL-17–producing CD4+ T cells and IFN-γ–producing CD4+ and CD8+ T cells.[204] T cells are required for the onset of hypertension because genetic deletion of T cells[205] or pharmacologic blockade of T cell costimulation[206] ameliorates experimental hypertension. Both Th1 and Th17 cells have been implicated in the pathogenesis of hypertension,[207,208] supporting the involvement of the metabolic pathways required for their activation and differentiation. During hypertension, both glucose uptake[209] and plasma levels of fatty acids[210] are increased, which may favor CD4+ T-cell inflammatory effector function. This culminates in increased ATP production by CD4+ T cells and is dependent on mitochondrial ROS,[211] which may support glycolytic metabolism through HIF-1α activation.[53] In addition to changes in metabolites, T cells may also respond directly to the elevated levels of extracellular sodium chloride during hypertension because expression of the salt-sensing kinase (ie, serum/glucocorticoid-regulated kinase 1) is required for Th17 differentiation and hypertensive end-organ damage.[212] However, not all hypertensive T-cell responses are likely to be pathogenic. Cystathione γ lyase–dependent production of hydrogen sulfide within CD4+ T cells attenuates inflammation during hypertension by activating AMPK and inhibiting mTOR, which promotes Treg differentiation and proliferation.[213] Similar increases in Treg accumulation are observed in HFpEF patients compared with HFrEF patients,[187] implicating a compensatory anti-inflammatory response to restore homeostasis under the chronic inflammatory conditions of both hypertension and HFpEF.

**B-CELL METABOLISM AND POTENTIAL LINKS TO CARDIOMETABOLIC DISEASE.** In contrast to T cells, little is known about how B cells may regulate cardiometabolic HF, let alone with respect to immunometabolic contributions. Increased myocardial infiltration of B cells is observed during nonischemic DCM, and treatment of HF patients with rituximab, which depletes CD20+ B cells, improves ventricular function.[214] Similar to T cells, B-cell depletion has also been demonstrated to improve cardiac function in mice after nonischemic, experimental pressure overload.[215] Patients in the early stages of left ventricular diastolic dysfunction exhibit increased plasma levels of total IgG compared with healthy controls, suggesting a role for B cells in the onset of clinical HFpEF.[216] There is also evidence that B-cell activity in obese patients is dysregulated. For example, in patients with a body mass index >30 kg/m$^2$, B-cell abundance and secretion of IgM are increased compared with nonobese controls.[217] B cells from mice fed a high-fat diet recapitulated these effects with increased production of IgM and IgG in the absence of additional stimulation.[217] B cells from obese mice were also found to secrete elevated levels of IL-6 and were required for the activation of T-cell inflammatory function.[218] B-cell depletion in DCM patients also reduced myocardial T-cell infiltration,[214] highlighting the importance of B- and T-cell cross talk in HF pathogenesis. Moreover, B cells themselves can promote metabolic dysfunction because mice lacking B cells are protected from both diet-induced insulin resistance despite weight gain[219] and hypertensive organ injury.[220] B-cell function is altered by metabolite availability because the production of anti-inflammatory cytokines, including IL-10, requires glutamine-dependent mTOR activation.[221] This is in contrast to T cells where glutamine-dependent mTOR activation favors Th1 differentiation as opposed to Tregs.[222] Myocardial glutamine levels are negatively correlated with ventricular fibrosis in a feline model of HFpEF,[223] indicating that changes in metabolites may link pathogenic or regulatory metabolic reprogramming in B cells to clinical outcomes during HFpEF.

In contrast to the well-characterized link between cardiometabolic stress and myelopoiesis, less is known on how cardiometabolic stress affects lymphopoiesis. An earlier study found that diet-induced obesity increased bone marrow B lymphopoiesis as measured by an increased abundance of premature, immature, and mature B cells,[224] and this was mediated in part by increased levels of leptin.[225] Subsequent studies have found that diet-induced obesity disrupts the bone marrow niche, leading to loss of mechanical support,[226] reduced expression of the B-cell growth factor IL-7,[227] and increased adiposity, which increases bone marrow levels of suppressive adipokines.[228] Together, this suppresses bone marrow B lymphopoiesis to reduce circulating levels of mature B cells. Diet-induced obesity also restricts thymic production of naïve T cells and increases the expansion of effector memory T cells,[229] which exhibit relatively greater metabolic demands. Taken together, there are many more questions than answers with respect to the effects of cardiometabolic disease on lymphopoiesis and B-cell metabolism.

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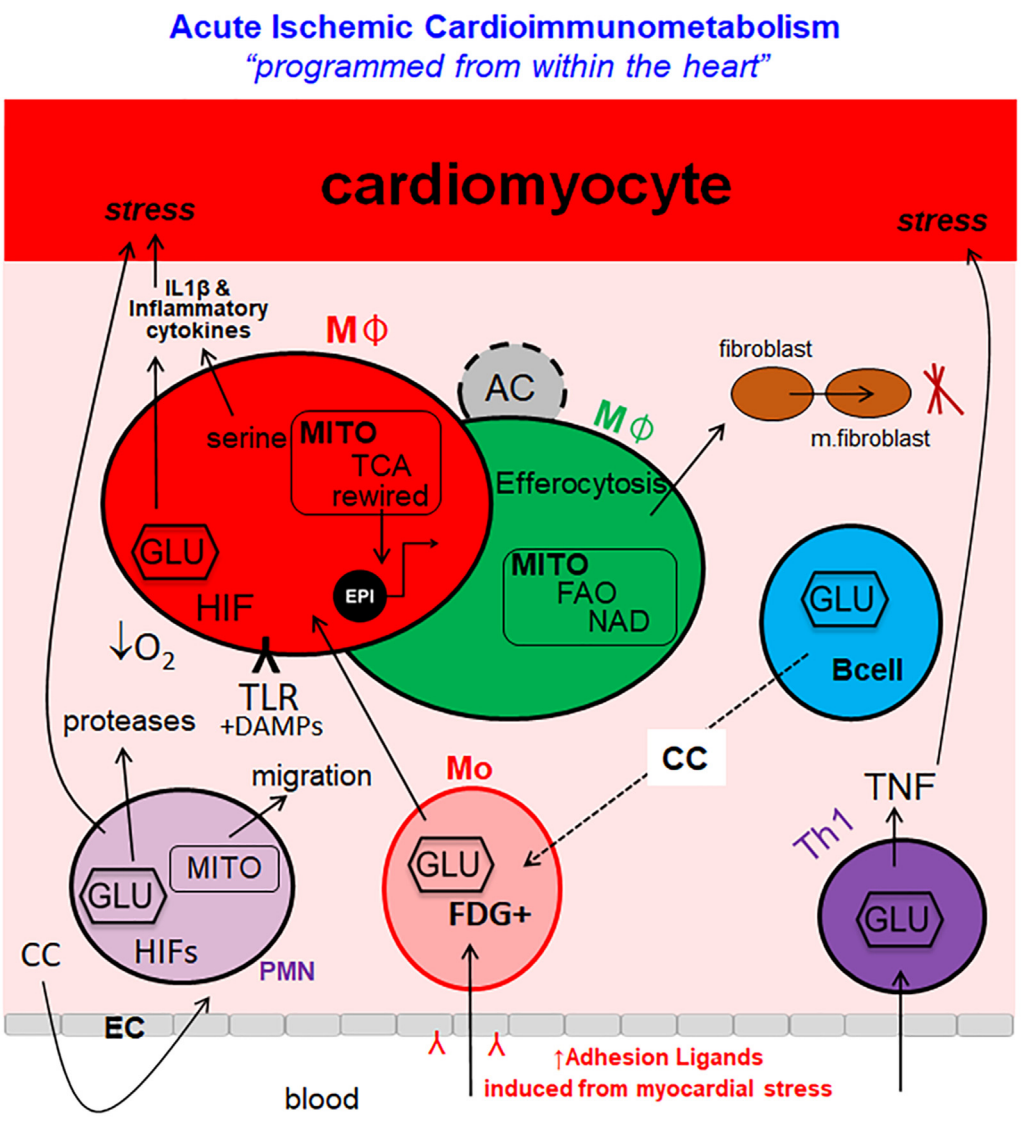
## TARGETING IMMUNOMETABOLISM TO MITIGATE HF

Immunometabolism is central to inflammatory and anti-inflammatory responses during HF, supporting therapeutic targeting of specific metabolites or metabolic enzymes to improve patient outcomes. Because glycolysis has been linked to inflammatory activation, therapeutic efforts targeting these pathways have been explored in experimental models. For glycolysis inhibition, the treatment of mice with the inhibitory glucose analog 2-deoxyglucose attenuated cardiac fibrosis after experimental MI.[230] Separately, the administration of rasagiline, which blocks nuclear translocation of GAPDH,[231] was associated with reduced cardiac fibrosis and preservation of ventricular function after experimental MI[232] as well as reduced cardiac ROS accumulation and improved systolic function during nonischemic HF in rats.[233] GAPDH can also be targeted by dimethyl fumarate, which succinates and inactivates GAPDH in activated macrophages and lymphocytes to block aerobic glycolysis and proinflammatory cytokine production.[234] The treatment of mice with dimethyl fumarate blocked cardiac macrophage HIF-1α activation, leading to increased mitochondrial respiration and anti-inflammatory polarization after MI,[235] and attenuated diastolic dysfunction during experimental HFpEF.[236] Finally, pharmacologic inhibition of PKM2 using TEPP-46 attenuated cardiac inflammation, macrophage accumulation, and ventricular dysfunction during experimental pulmonary arterial hypertension,[237] supporting therapeutic inhibition of glycolysis to attenuate cardiac dysfunction.

Drugs that target metabolism to promote anti-inflammatory phenotypes have also been tested for cardioprotection during ischemic or cardiometabolic heart disease. For example, the antihyperglycemic drug metformin activates AMPK, leading to suppression of fatty acid synthesis and increased fatty acid oxidation.[238] After experimental MI, metformin treatment was associated with AMPK-dependent increases in myocardial mitochondrial respiration[239] and reductions in both macrophage inflammatory responses and infarct size.[240] The administration of metformin was also linked to improved diastolic dysfunction in a mouse model of HFpEF.[241] AMPK is also activated by methotrexate, which inhibits the 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase leading to increased levels of the AMPK activator 5-aminoimidazole-4-carboxamide ribonucleotide.[242] In a mouse model of chronic myocardial vasculopathy, methotrexate treatment led to AMPK-dependent increases in genes protective against oxidative stress and attenuation of cardiac injury.[243] The administration of methotrexate also blunted systemic levels of inflammatory cytokines IL-6 and TNF-α during diet-induced obesity.[244] Separately, the administration of rapamycin, a specific inhibitor of mTOR, reduced inflammatory nuclear factor kappa B signaling and macrophage infiltration in the infarct border zone, leading to the attenuation of adverse cardiac remodeling after experimental MI.[245] In aged mice, rapamycin treatment also improved diastolic function, which was associated with increases in both myocardial expression of mitochondrial complex I proteins and metabolic flux through the TCA cycle.[246] Together, therapeutic targeting of metabolic pathways may be beneficial during cardiovascular disease.

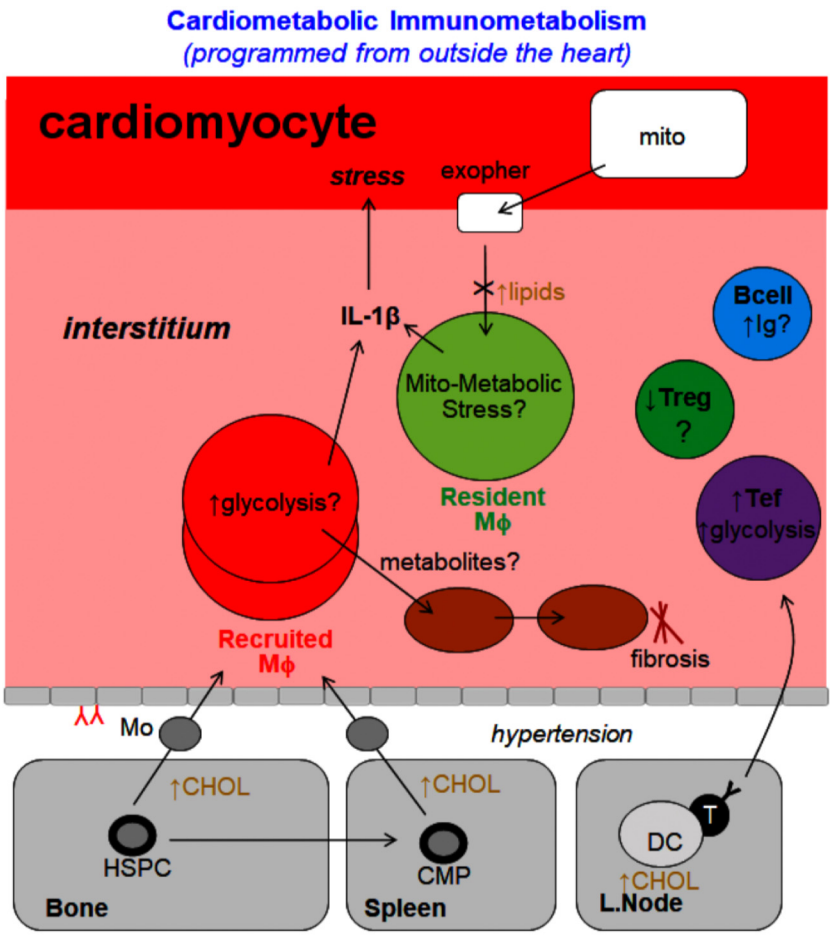
A limitation to many of the experimental studies discussed earlier is that the metabolic interventions were not immune specific, which may explain why these drugs have often failed to confer clinical benefit in humans. For example, retrospective studies have found that metformin and methotrexate protect against HFpEF in diabetic patients and HF in rheumatoid arthritis patients, respectively.[247,248] However, results from clinical trials using either metformin or methotrexate to treat MI patients have produced suboptimal results ranging from no protection to worsened outcomes.[249-251] In the case of methotrexate, both animal and human studies have found that methotrexate doses similar to those administered to MI patients can impair cardiomyocyte contractility and lead to fatal cardiotoxicity,[252,253] suggesting that the adverse effects of methotrexate on cardiomyocytes may negate any beneficial effect in dampening inflammatory responses. In contrast, a clinical trial using rapamycin-eluting stents in acute MI patients preserved reperfusion of the target vessel and improved survival,[254] indicating that the net effect of mTOR inhibition may be cardioprotective. Ultimately, any cardiotoxic effect may be circumvented by targeting these drugs specifically to immune cells. Targeting of myeloid cells with liposomal nanoparticles loaded with cardiac antigen and rapamycin has been demonstrated to induce tolerogenic DCs that promote Treg-mediated cardioprotection after experimental MI.[255] Antitumor drugs have also been specifically delivered to T cells using antibody-targeted nanoparticles,[256] necessitating future studies targeting metabolic interventions to immune cells during ischemic or cardiometabolic heart disease.

**FIGURE 1** **Working Model of Core Pathways in Acute Ischemic Cardioimmunometabolism**




Acute ischemic injury induces altered immune metabolism caused by damage within the myocardium. Depicted in the figure are cardiac leukocytes after acute myocardial infarction and during the initiation of the resolution of cardiac inflammation. "First-responder" recruited polymorphonuclear neutrophils not only rely on rapid glycolysis (activated by hypoxia-inducible factors [HIFs]) but also may use mitochondria during migration to the ischemic area. Infiltrating monocytes (Mo) and activated macrophages (Mϕ) are also highly glycolytic, which fuels pathways that promote the production of inflammatory cytokines that stress cardiomyocytes. Phagocytic clearance of dying apoptotic cells (ACs) initiates mitochondrial metabolism that can promote healing and fibrosis through fatty acid oxidation (FAO) and generation of nicotinamide adenine dinucleotide (NAD). Depicted also are immunometabolic properties of T cells. During inflammation resolution, polymorphonuclear subtypes and clearance of dying cells (ACs) may trigger efferocytic metabolism in resident cardiac Mϕs, which can prioritize mitochondrial-based metabolism. Depicted also are emerging roles for lymphoid cells, which recruit monocytes via chemokines (CC) and produce proinflammatory cytokines driven by glycolysis. DAMP = damage-associated molecular pattern; FDG = fluorodeoxyglucose; GLU = glycolysis; IL = interleukin; MITO = mitochondrial; TCA = tricarboxylic acid cycle; TNF = tumor necrosis factor; TLR = Toll-like receptor.

**FIGURE 2** Working Model of Core Pathways of Cardiometabolic Immunometabolism




Systemic dysregulated systemic metabolism fuels hematopoietic and extramedullary myeloid and lymphoid cell recruitment from the periphery to the heart. Dendritic cell activation also stimulates inflammatory T-cell activation. Within the myocardium, activated immune cell metabolism leads to nonresolving chronic inflammation. This includes impaired homeostatic clearance of spent mitochondria from cardiomyocytes. CHOL = cholesterol; CMP = common myeloid progenitor; DC = dendritic cell; EC = endothelial cell; Ig = immunoglobulin; Mo = monocyte.

## SUMMARY AND FUTURE PROSPECTS

Our appreciation of how immunometabolism affects the myocardial microenvironment, relative to other milieus, such as the tumor microenvironment, is currently at an early stage of research. However, this will change soon as our heightened appreciation of inflammation as a target for myocardial disease converges with substantial current research activity in the field of immunometabolism. It is important to recognize that although the pathologies of ischemic and cardiometabolic heart disease are indisputably unique, overlapping signaling pathways within the immunologic milieu may still exist. However, current paradigms of cardioimmunometabolism have limitations to consider. These include conclusions that are based on static cellular metabolite levels, which are not equivalent to metabolic flux. For example, higher cellular metabolite levels could be indicative of slower metabolite turnover or faster biosynthesis. Also, higher metabolite flux is not always reflected by changes in metabolite levels. Moreover, most metabolic assessments of primary cells still suffer from lengthy tissue extraction methods, which can lead to metabolite loss or metabolic adaptation. Thus, future studies should optimize protocols that limit artifacts caused by tissue extraction procedures, and interpretations should take care to reflect this. Another consideration is our updated appreciation of the considerable

heterogeneity of immune cell subsets in the heart,[257] which have been informed by single-cell sequencing technologies. In this regard, metabolic circuits may also diverge between individual cells. Coupling these technologies with metabolomics will accelerate our resolution of immunometabolism in upcoming years.[258] Regardless, the key concepts discussed herein (**Figures 1 and 2**), rooted in fundamental frameworks of cell and molecular biology and cell metabolism, may serve as a foundation for new strategies that seek to repurpose immunometabolism for enhanced immune-mediated repair, inflammation resolution, and ultimately cardioprotection.

**ADDRESS FOR CORRESPONDENCE:** Dr Edward B. Thorp, Department of Pathology, Northwestern University Feinberg School of Medicine, 303 East Chicago Avenue Ward 4-116, Chicago, Illinois 60611, USA. E-mail: ebthorp@northwestern.edu.

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