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Review

Macrophage Metabolic Reprogramming and Its Role in Heart Diseases

Xingkai Huang [1,†], Gangjie Zhu [2,†], Shenghang Liu [3,†], Yigang Zhong [2,*],
and Hanwen Zhang [3,4,*]

[1] Department of Clinical Medicine, Nanjing Medical University, Nanjing 211166, China
[2] Department of Cardiology, Affiliated Hangzhou First People's Hospital, School of Medicine, Westlake University, Hangzhou 310000, China
[3] Department of Pathophysiology, Nanjing Medical University, Nanjing 211166, China
[4] Key Laboratory of Jiangsu Province on Targeted Intervention of Cardiovascular Diseases, Nanjing Medical University, Nanjing 211166, China
* Correspondence: zhongyigangly@163.com (Y.Z.); hanwenzhang@njmu.edu.cn (H.Z.)
† These authors contributed equally to this work.

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Abstract: Cardiovascular diseases, particularly heart failure, remain the leading cause of death. Pathological cardiac remodeling, driven by chronic inflammation and metabolic dysfunction, is a key underlying mechanism. Macrophages, central regulators of cardiac inflammation, exhibit remarkable functional plasticity shaped by metabolic reprogramming. This review synthesizes current evidence on how metabolic shifts—glycolysis, fatty acid oxidation, and amino acid metabolism—dictate macrophage phenotypes in ischemic and non-ischemic heart diseases. In myocardial infarction, hypoxia-induced glycolytic reprogramming fuels pro-inflammatory CCR2$^+$ macrophages, while oxidative metabolism supports reparative subsets. In non-ischemic conditions like HFpEF, metabolic stress from obesity or diabetes skews macrophages toward a dysfunctional, pro-fibrotic state. Key regulatory pathways (e.g., HIF-1α, PPARγ, AMPK) and metabolite-driven epigenetic modifications (e.g., lactylation, succinylation) further link metabolism to macrophage-mediated remodeling. Therapeutic strategies targeting glycolysis (e.g., PFKFB3 inhibition) or promoting oxidative metabolism (e.g., PPARγ agonists) show preclinical promise but face challenge in specificity. Future directions emphasize spatial-temporal mapping of macrophage metabolism and precision-targeted interventions to resolve inflammation and restore cardiac homeostasis.

Keywords: heart diseases; inflammation; macrophage; metabolism; metabolic reprogramming; cardiac remodeling

1. Introduction

Cardiovascular diseases, particularly heart diseases, remain the leading cause of death globally [1]. Ultimately, all forms of heart disease lead to heart failure (HF), a condition characterized by the heart's inability to pump blood effectively, resulting in symptoms such as shortness of breath, fatigue, fluid retention, and exercise intolerance [2]. Heart diseases leading to heart failure can be broadly categorized into ischemic and non-ischemic types. Although the incidence of ischemic heart disease (IHD) has decreased in recent years due to advances in health education and a reduction in risk factors such as smoking and high blood cholesterol, post-myocardial infarction (MI) heart failure continues to pose a significant health challenge [3]. In parallel, the incidence of non-ischemic heart failure, particularly heart failure with preserved ejection fraction (HFpEF), has been steadily increasing due to rising risk factors such as obesity, diabetes, hypertension, and lack of exercise [4]. In the treatment of heart failure, while percutaneous coronary intervention (PCI) and pharmacological therapies aimed at cell protection have significantly reduced mortality in the acute phase of MI, many survivors experience long-term complications that eventually progress to heart failure [5]. For non-ischemic heart failure, especially HFpEF, effective diagnostic and therapeutic options remain limited, making it one of the major unmet challenges in cardiovascular disease today [6]. Particularly, effective therapies for pathological remodeling during heart failure remain scarce. Current treatments often fail to adequately address cardiac remodeling induced by metabolic diseases, as these therapies tend to focus on symptom management rather than on targeting the underlying mechanisms [7]. Therefore, gaining a deeper understanding of the molecular mechanisms of pathological remodeling has become an emerging area of research. Exploration in this field is expected to provide potential targets for developing novel therapeutic strategies.

Both ischemic and non-ischemic cardiac pathological remodeling are associated with systemic or local metabolic changes triggered by factors such as ischemia, obesity, and diabetes [8]. These metabolic alterations, including disruptions in lipid, glucose, and amino acid metabolism, affect both systemic and cardiac metabolism [9]. For instance, in obesity and diabetes, the balance between fatty acid oxidation and glucose metabolism is disturbed, leading to an accumulation of fatty acids and enhanced glycolysis in the systemic circulation and the heart [10]. In ischemic heart disease, oxidative phosphorylation is impaired, and a switch to glycolysis occurs to compensate for energy shortages [11]. These metabolic changes induce metabolic reprogramming in cardiac parenchymal cells, particularly cardiomyocytes, leading to cell death and reduced contractility [12]. In the early stages of myocardial infarction, cardiomyocytes shift from oxidative phosphorylation to glycolysis to generate ATP under conditions of oxygen deprivation [13]. Similarly, in diabetic cardiomyopathy, the imbalance between fatty acid oxidation and glucose metabolism in cardiomyocytes contributes to cardiac dysfunction [14]. These metabolic alterations also trigger inflammatory responses, both systemically and within the heart [15]. Metabolic byproducts such as lactate and fatty acids activate specific inflammatory pathways, which exacerbate cardiac pathological remodeling [16]. For example, lactate accumulation enhances glycolysis and stimulates immune cell recruitment, amplifying local inflammation [17]. In diabetic models, fatty acids modulate immune cell activity, leading to increased cardiac inflammation and fibrosis [18]. Furthermore, in ischemic heart disease, the interaction between metabolic reprogramming and inflammation worsens myocardial injury [19]. Current research on targeting inflammation in cardiac remodeling has focused on cytokines like IL-1β, IL-6, and TNF-α. The CANTOS trial showed promise in reducing inflammation and improving outcomes [16]. However, challenges remain, such as unclear targets, significant side effects, and uncertain long-term benefits [20]. Consequently, metabolic reprogramming-induced inflammatory responses may represent a novel therapeutic target, providing new opportunities for intervening in heart disease through the modulation of metabolic pathways and inflammation.

Macrophages are key regulators of cardiac inflammation, exhibiting remarkable heterogeneity and functional plasticity. Rather than fitting into a binary M1/M2 framework, cardiac macrophages span a spectrum from pro-inflammatory to anti-inflammatory and reparative states. Single-cell transcriptomic analyses have identified distinct subsets such as $TIMD4^+$ (homeostatic), $LYVE1^+$ (perivascular and reparative), $FOLR2^+$ (anti-inflammatory), and $CCR2^+$ (monocyte-derived, pro-inflammatory) macrophages, each with specific spatial localization and roles in cardiac remodeling [21]. These cells modulate inflammation through cytokine and chemokine secretion, matrix remodeling, and efferocytosis. Clinical and experimental data—such as the CANTOS trial and studies targeting $CCR2^+$ macrophages—underscore their central role in disease progression. However, therapeutic translation remains limited due to the complexity of inflammatory networks, redundant signaling pathways, and the lack of disease-specific, functionally precise targets. These limitations highlight the need to identify upstream regulatory mechanisms—such as metabolic reprogramming—that govern macrophage function in a context-dependent manner.

Macrophage function in the heart is closely regulated by cellular metabolism [10]. Pro-inflammatory macrophages predominantly rely on glycolysis, whereas anti-inflammatory and reparative subsets utilize oxidative phosphorylation and fatty acid oxidation [22]. These metabolic programs are not merely byproducts of activation but active drivers of macrophage phenotype, modulated by intermediates such as succinate and α-ketoglutarate, and signaling pathways including HIF-1α, PPARγ, and AMPK [23]. In cardiac injury, shifts in macrophage metabolism determine the balance between inflammation and repair—dysregulation of these pathways can prolong inflammation and promote pathological remodeling [10]. Despite increasing recognition of the importance of immunometabolism, our understanding of how metabolic reprogramming shapes macrophage function in heart disease remains incomplete. This review summarizes current knowledge on macrophage metabolism in the context of cardiac inflammation and remodeling, with the goal of identifying potential metabolic targets for therapeutic intervention.

2. The Immunometabolic Landscape of Cardiac Macrophages

Cardiac macrophages are essential immune cells involved in tissue homeostasis, inflammation, and repair [24]. They originate from two major sources: embryonic progenitors from the yolk sack or fetal liver that give rise to self-renewing resident macrophages, and circulating monocytes that are recruited to the myocardium during steady state, stress, or injury [25]. These two populations exhibit distinct transcriptional and functional profiles, contributing differently to cardiac remodeling [26].

Advancements in single-cell RNA sequencing have uncovered the remarkable heterogeneity of cardiac macrophages beyond the classical M1/M2 polarization model [27]. Specific subsets with unique gene signatures and spatial localizations have been identified [13]. TIMD4$^+$ macrophages represent a population of long-lived, tissue-resident cells involved in immune surveillance and anti-inflammatory responses [14]. LYVE1$^+$ macrophages are predominantly found in perivascular regions and contribute to vascular integrity and repair [15]. FOLR2$^+$ macrophages exhibit anti-inflammatory transcriptional programs, while CCR2$^+$ macrophages are derived from circulating monocytes and are highly pro-inflammatory, playing key roles in fibrosis and adverse cardiac remodeling following injury [10].

The functional identity of these macrophage subsets is tightly linked to their metabolic state [5]. Pro-inflammatory macrophages tend to rely on glycolysis, a rapid but inefficient metabolic pathway that supports the production of cytokines and reactive oxygen species [28]. In contrast, anti-inflammatory and reparative macrophages preferentially rely on mitochondrial oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO), which provide sustained energy for tissue maintenance and repair [29]. These metabolic programs are not fixed but dynamically regulated by local cues such as hypoxia, nutrient availability, lipid accumulation, and redox stress—features commonly found in diseased cardiac tissue.

Moreover, specific metabolic pathways are closely tied to macrophage longevity, plasticity, and effector function. For instance, tissue-resident TIMD4$^+$ macrophages demonstrate mitochondrial enrichment and oxidative metabolism, supporting their long-term survival and immunoregulatory roles [30]. In contrast, recruited CCR2$^+$ macrophages after cardiac injury often exhibit a glycolytic bias, aligning with their short-lived, pro-inflammatory activity during acute injury [7]. These distinctions underscore the importance of understanding not only macrophage origin and phenotype but also their metabolic configuration within the cardiac microenvironment. The immunometabolic framework lays the foundation for understanding how metabolic reprogramming shapes macrophage behavior in different stages of cardiac disease and why targeting macrophage metabolism represents a promising therapeutic approach.

3. The Crosstalk between Macrophages and Other Immune Cells

3.1. Interactions between Macrophages and Neutrophils

Neutrophils are among the earliest immune cells recruited to sites of cardiac injury, where they remove pathogens and necrotic debris through the release of ROS, proteases, and neutrophil extracellular traps (NETs) [31]. The interplay between macrophages and neutrophils is particularly critical during the acute inflammatory phase. Pro-inflammatory macrophages secrete chemokines such as CXCL8/IL-8 and CCL2 to recruit neutrophils, while cytokines, including TNF-α and GM-CSF, enhance neutrophil activation and survival. During the resolution phase, macrophages contribute to the termination of inflammation by engulfing apoptotic neutrophils through efferocytosis, a process that not only clears dying cells but also reprograms macrophages toward an anti-inflammatory phenotype via lipid mediator signaling (e.g., resolvins) [32]. This bidirectional interaction ensures efficient clearance of tissue debris while preventing excessive inflammation and collateral tissue damage.

3.2. Interactions between Macrophages and Dendritic Cells

Dendritic cells (DCs) are professional antigen-presenting cells that bridge innate and adaptive immunity [33]. Macrophages promote DC maturation by releasing cytokines such as IL-12 and IL-18 and by engaging pattern recognition receptors (PRRs). In the context of cardiac injury, macrophage-derived signals enhance DC activation, leading to increased expression of co-stimulatory molecules (CD80, CD86) and MHC class II, thereby amplifying antigen presentation and subsequent T cell priming. Conversely, activated DCs can influence macrophage polarization through the secretion of IL-23 and type I interferons. This reciprocal communication between macrophages and DCs plays an important role in shaping adaptive immune responses and may contribute to the persistence of inflammation in chronic cardiac diseases [34].

3.3. Interactions between Macrophages and B Cells

Macrophages also interact with B cells through both antigen presentation and cytokine signaling. Acting as antigen-presenting cells, macrophages facilitate B cell activation and differentiation into antibody-producing plasma cells. Following myocardial infarction, macrophage-derived IL-6 and BAFF (B cell activating factor) enhance B cell proliferation and antibody generation [35]. These antibodies may form immune complexes that further activate Fcγ receptor signaling on macrophages, reinforcing inflammatory cascades. Additionally, macrophages regulate immunoglobulin class switching via cytokines such as IL-10 and TGF-β, which may fine-tune the balance between pro-inflammatory and regulatory antibody responses. Dysregulated macrophage–B cell crosstalk has been implicated in promoting maladaptive remodeling and autoimmunity-like features in failing hearts [36].

3.4. Interactions between Macrophages and T Cells

Macrophages are central regulators of T cell responses through cytokine and antigen-dependent mechanisms. In ischemic heart disease, $CCR2^+$ pro-inflammatory macrophages release IL-1β, IL-6, and TNF-α, which drive differentiation of $CD4^+$ T cells into Th1 and Th17 subsets, thereby amplifying tissue inflammation [37]. In contrast, reparative macrophage subsets (e.g., $LYVE1^+$ and $TIMD4^+$ cells) secrete IL-10 and TGF-β, promoting the expansion of regulatory T cells (Tregs) that suppress excessive immune responses and facilitate tissue repair [38]. Moreover, co-stimulatory and co-inhibitory molecules expressed on macrophages (e.g., CD80/CD86 and PD-L1) directly modulate T cell activation thresholds. This dynamic macrophage–T cell crosstalk is a key determinant of whether the post-injury environment evolves toward resolution and healing or toward chronic inflammation and fibrosis.

Taken together, macrophages engage in multifaceted interactions with neutrophils, dendritic cells, B cells, and T cells, orchestrating the transition from acute inflammation to tissue repair. Dysregulation of these intercellular communications contributes to persistent inflammation, adverse remodeling, and progression to heart failure.

4. Core Metabolic Pathways in Macrophage Reprogramming

Functional transition of macrophage is not solely governed by external stimuli such as cytokines or pathogens, but is fundamentally shaped by intrinsic metabolic programs. These pathways determine the availability of energy and biosynthetic intermediates required for immune functions and actively modulate gene expression, signaling, and epigenetic states. In the context of heart failure, shifts in glycolysis, fatty acid oxidation, and amino acid metabolism play central roles in dictating macrophage phenotypes during injury and remodeling [12].

4.1. Glycolysis and Pro-Inflammatory Activation

Glycolysis is rapidly upregulated in macrophages in response to ischemic injury or damage-associated signals [13]. This metabolic switch is essential for supporting the biosynthetic demands of cytokine production, ROS generation, and cell migration [14]. Key regulators such as hypoxia-inducible factor 1-alpha (HIF-1α) and mTOR drive this glycolytic reprogramming, promoting the expression of glucose transporters (e.g., GLUT1) and glycolytic enzymes (e.g., HK2, PFKFB3) [15]. In hypoxic or inflamed cardiac tissue, glycolysis dominates due to impaired mitochondrial respiration, aligning with the predominance of pro-inflammatory macrophages such as $CCR2^+$ monocyte-derived cells [39]. Notably, the accumulation of succinate under these conditions stabilizes HIF-1α and further amplifies the inflammatory response [40].

4.2. Fatty Acid Oxidation and Reparative Macrophages

In contrast, macrophages involved in resolution and repair preferentially rely on fatty acid oxidation (FAO) and oxidative phosphorylation (OXPHOS) [28]. This shift supports sustained ATP generation and redox balance and is characteristic of anti-inflammatory or tissue-reparative macrophages, including subsets such as $LYVE1^+$ and $TIMD4^+$ cells [29]. FAO is regulated by pathways such as PPARγ and AMPK, which enhance mitochondrial function and suppress glycolytic flux [30]. During the subacute and chronic phases of myocardial infarction, the reprogramming of macrophages toward FAO is essential for suppressing inflammation and promoting tissue healing [7].

4.3. Amino Acid Metabolism: Glutamine, Arginine, and Tryptophan

Amino acid metabolism provides additional layers of macrophage function regulation. Glutaminolysis supports both inflammatory and reparative macrophage states by fueling the TCA cycle and producing α-ketoglutarate, a metabolite with known epigenetic and anti-inflammatory effects. Arginine metabolism bifurcates into two competing pathways: iNOS-mediated nitric oxide (NO) production in pro-inflammatory cells and arginase-mediated urea and polyamine synthesis in reparative cells [14]. Tryptophan metabolism, via the kynurenine pathway and IDO1 enzyme, is associated with immune regulation and tolerance, particularly during tissue repair and fibrosis [15].

5. Regulatory Pathways and Transcriptional Control

5.1. Upstream Regulatory Network

Meanwhile, the metabolic routes are also coordinated or interact closely with upstream regulatory networks. For example, mTOR integrates nutrient and growth factor signals to promote glycolytic activation, while AMPK senses energy stress and enhances FAO and autophagy [10]. HIF-1α and PPARγ act as metabolic transcription factors that enforce pro-inflammatory or anti-inflammatory programs, respectively [40]. In addition, changes in $NAD^+/NADH$ ratio, ROS levels, and acetyl-CoA availability provide feedback that links chromatin remodeling and transcriptional metabolic state to cell fate decisions [28].

5.2. Metabolite-Derived Modifications

Beyond their role in energy production, metabolites also function as critical regulators of macrophage behavior through post-translational and epigenetic modifications [30]. A prime example is histone lactylation, a recently discovered mechanism by which the glycolytic byproduct lactate modifies lysine residues on histones, promoting the transcription of genes associated with tissue repair and resolution-phase macrophage functions [7]. This process provides a metabolic-epigenetic link, whereby lactate not only reflects the glycolytic state but also drives macrophages toward an anti-inflammatory phenotype during the resolution phase of inflammation.

Similarly, succinate, accumulated during pro-inflammatory activation, stabilizes HIF-1α and can mediate lysine succinylation, which alters protein function and gene expression patterns in macrophages [13]. Other metabolites such as acetyl-CoA promote histone acetylation, while α-ketoglutarate and S-adenosylmethionine (SAM) serve as co-factors for DNA/histone demethylation and methylation, respectively, affecting transcriptional programs related to inflammation, metabolism, and repair [14]. However, the primary proteins in macrophages that can be affected by post-translational modification, such as lactylation or acetylation, and their dynamics during different heart failure contexts are still unknown. These modification pathways represent an emerging regulatory axis in immunometabolism, where cellular metabolism not only reflects but also actively instructs macrophage identity and function.

Understanding these core metabolic pathways not only clarifies how macrophages respond to different phases of cardiac injury but also identifies potential intervention points for reprogramming macrophage behavior toward beneficial phenotypes.

6. Macrophage Metabolic Reprogramming in Specific Cardiac Diseases

The role of macrophage metabolic reprogramming in heart disease is highly context-dependent, varying across disease types and stages [15]. In ischemic injury, metabolic shifts support acute inflammation and tissue clearance, whereas in chronic non-ischemic conditions, persistent metabolic stress may sustain inflammation and drive maladaptive remodeling [30].

6.1. Ischemic Heart Disease and Myocardial Infarction

During acute ischemic injury, macrophages undergo a glycolytic-driven activation state, marked by elevated expression and secretion of pro-inflammatory mediators including IL-1β, TNF-α, and IL-6, alongside increased reactive oxygen species (ROS) generation and upregulation of glycolytic enzymes and glucose transporters [41]. These changes facilitate efficient clearance of necrotic cells and debris. However, if this pro-inflammatory activation fails to transition into a reparative phenotype in a timely manner, it can perpetuate tissue injury and drive adverse cardiac remodeling [42].

As oxygenation improves during the subacute/reparative phase due to angiogenesis or revasculation, macrophages shift toward enhanced mitochondrial oxidative metabolism, including fatty acid oxidation (FAO), mitochondrial biogenesis, and increased expression of oxidative phosphorylation (OXPHOS) genes [43]. They also increase secretion of anti-inflammatory and pro-repair factors such as IL-10, TGF-β, and growth factors. Disruption of this metabolic transition—for example, by impaired AMPK signaling, insulin resistance, or lipid overload—leads to mitochondrial dysfunction, defective efferocytosis, sustained inflammation, and eventual fibrosis with impaired ventricular recovery [44].

6.2. Non-Ischemic Heart Disease: HFpEF and Diabetic Cardiomyopathy

In non-ischemic heart diseases such as HFpEF or diabetic cardiomyopathy, metabolic stress is chronic rather than acute. Macrophages are persistently exposed to hyperglycemia, elevated free fatty acids, lipotoxic intermediates, and low-grade systemic and local inflammation [39]. Moreover, microvascular rarefaction and impaired myocardial perfusion in these conditions give rise to localized hypoxic niches, further shaping macrophage activation and metabolic reprogramming [45]. Under these conditions, macrophages may exhibit metabolic inflexibility characterized by co-activation of glycolysis, accumulation of intracellular lipids (lipid droplets, ceramides), mitochondrial ROS generation, endoplasmic reticulum (ER) stress, and impaired FAO/OXPHOS [46]. Signaling pathways such as HIF-1α, TLR4/NF-κB, and impaired AMPK/SIRT activity have been implicated [47]. These changes sustain a state of chronic low-grade inflammation, which contributes to interstitial fibrosis and diastolic dysfunction [48].

Taken together, the patterns of macrophage metabolic reprogramming differ fundamentally between ischemic and non-ischemic heart diseases, reflecting distinct pathophysiological drivers. In ischemic heart disease, metabolic adaptation is largely driven by acute hypoxia and nutrient deprivation, which induce a glycolytic shift that supports rapid pro-inflammatory activation but must subsequently transition toward oxidative metabolism for tissue repair. In contrast, non-ischemic heart diseases such as HFpEF and diabetic cardiomyopathy are characterized by persistent systemic and myocardial metabolic stress—including hyperglycemia, excess fatty acids, and low-grade inflammation—which impose chronic metabolic inflexibility and mitochondrial dysfunction on macrophages [38]. These divergent contexts highlight that therapeutic strategies aimed at reprogramming macrophage metabolism should be disease-specific, with ischemic settings requiring timely facilitation of the glycolysis-to-FAO/OXPHOS transition, whereas non-ischemic conditions may benefit from interventions that restore metabolic flexibility and alleviate lipotoxic or oxidative stress [49].

6.3. Heart Failure Progression

In both HFrEF and HFpEF, chronic heart failure is marked by a failure to resolve inflammation [15]. Macrophages in this setting often remain in an energetically compromised state, with persistent glycolytic bias, impaired mitochondrial function, and altered NAD^+/NADH homeostasis [30]. This metabolic profile limits their ability to switch to a reparative phenotype, perpetuating cytokine release, extracellular matrix remodeling, and myocyte dysfunction [7]. Notably, metabolic signatures of macrophages isolated from failing hearts often correlate with disease severity, suggesting potential use as biomarkers or therapeutic targets.

6.4. Questions Remain in Macrophage Metabolic Reprogramming in Different Heart Failure

Despite growing insights, macrophage metabolic reprogramming in cardiac diseases remains incompletely understood. In the chronic phase of ischemic heart disease, for example, the metabolic state and functional role of specific macrophage clusters such as $CD206^+$ cells are still unclear, as they have been implicated in promoting late-stage fibrosis despite being considered reparative [13]. In non-ischemic conditions like hypertension, diabetes, and obesity, it remains elusive how distinct systemic metabolic stressors converge to shape macrophage metabolism and inflammatory activation in the heart. Moreover, emerging paradoxes—such as glycolysis driving inflammation while its byproduct, lactate, exerts anti-inflammatory effects—suggest the existence of complex feedback mechanisms, spatial heterogeneity, or stage-specific roles [14]. Clarifying these open questions will require integrated approaches combining spatial profiling, metabolic flux analysis, and disease-specific models to map how macrophage metabolism dynamically contributes to cardiac pathology.

Together, these disease models highlight the dynamic interplay between metabolic cues and macrophage function in the heart. They underscore the therapeutic potential of modulating macrophage metabolism in a stage- and disease-specific manner.

7. Therapeutic Targeting of Macrophage Metabolism in Cardiac Disease

As the immunometabolic regulation of macrophages becomes increasingly well-defined, targeting their metabolic pathways has emerged as a promising therapeutic approach for modulating inflammation and promoting repair in heart disease. Several preclinical and clinical studies have investigated how pharmacological or genetic manipulation of key metabolic regulators can influence macrophage behavior and cardiac outcomes.

7.1. Targeting Glycolysis and HIF-1α Signaling

Given the pivotal role of glycolysis in promoting pro-inflammatory macrophage activity, inhibiting this pathway has shown therapeutic benefit in preclinical models of myocardial infarction and heart failure. Suppression of HIF-1α or glycolytic enzymes such as PFKFB3 reduces inflammatory cytokine production and limits adverse remodeling. Experimental studies have shown that inhibiting glycolysis—using agents such as dichloroacetate (a PDK inhibitor) or LDH inhibitors—can suppress IL-1β production and reduce macrophage-mediated inflammation in cardiovascular disease models, providing mechanistic evidence for targeting glycolysis-driven immune activation.

7.2. Promoting Oxidative Metabolism and FAO

Conversely, enhancing mitochondrial function and fatty acid oxidation (FAO) in macrophages can promote a reparative phenotype and support the resolution of inflammation. Pharmacological activators of PPARγ, such as pioglitazone or rosiglitazone, have been shown to induce FAO-related gene expression and reduce macrophage-driven fibrosis in animal models. AMPK activators, including metformin and AICAR, have demonstrated anti-inflammatory and cardioprotective effects by promoting FAO and autophagy in cardiac immune cells. While these agents are not macrophage-specific, their systemic metabolic effects may contribute to immunomodulation in the heart [30].

7.3. Indirect Modulation by Metabolic and Anti-Diabetic Drugs

SGLT2 inhibitors (e.g., empagliflozin), originally developed for glycemic control, have shown unexpected cardiovascular benefits in both HFrEF and HFpEF. Recent studies suggest that these drugs can modulate cardiac immune cell metabolism and inflammatory tone, possibly through ketone body utilization, reduction of ROS, and improvement of NAD^+ balance. Similarly, statins and GLP-1 receptor agonists may indirectly influence macrophage metabolic states and inflammatory profiles [7].

7.4. Challenges and Opportunities

Despite these advances, several challenges remain. Many metabolic pathways are shared across cell types, raising concerns about off-target effects and systemic toxicity. Moreover, macrophage metabolic phenotypes are context- and stage-specific—intervening too early or too broadly may disrupt essential immune functions. Current tools often lack the precision to selectively reprogram macrophages within the heart without affecting other organs or immune populations. Emerging strategies such as nanoparticle-based delivery systems, metabolic imaging, and single-cell transcriptomic profiling may help overcome these limitations by enabling spatial and temporal targeting of macrophage subsets.

In sum, immunometabolic targeting holds strong potential for cardiovascular therapy but requires further refinement to balance efficacy with specificity and safety [13].

8. Conclusions and Future Directions

Macrophage metabolism plays a central role in regulating cardiac inflammation and remodeling. Distinct metabolic programs—such as glycolysis, fatty acid oxidation, and amino acid metabolism—govern macrophage polarization, cytokine production, and reparative capacity in a context-dependent manner. In both ischemic and non-ischemic heart diseases, dysregulated metabolic reprogramming of macrophages contributes to chronic inflammation, fibrosis, and progressive cardiac dysfunction.

Recent advances in single-cell transcriptomics and immunometabolism have revealed unprecedented heterogeneity within cardiac macrophage populations and established clear links between their metabolic state and functional phenotype. These insights open new opportunities for therapeutic intervention, especially in conditions like heart failure with preserved ejection fraction (HFpEF), where current treatments are limited.

However, major challenges remain. The metabolic environment of the heart is complex and dynamic, making it difficult to precisely target macrophage subsets without affecting other cells. Furthermore, most metabolic drugs lack cell-type specificity, and their effects can vary depending on disease stage and systemic conditions. Understanding the spatiotemporal dynamics of macrophage metabolism—and developing tools to modulate it selectively—will be critical for translating these insights into effective therapies.

Future research should focus on integrating metabolic profiling with spatial transcriptomics and in vivo imaging to map functional macrophage states across time and disease context. Targeted delivery systems, such as nanoparticles or cell-specific prodrugs, may offer more precise control over macrophage metabolism. Ultimately, a better understanding of immunometabolic reprogramming may enable the development of next-generation therapies for heart disease—ones that go beyond symptomatic control to actively reshape the inflammatory and reparative landscape of the heart.

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