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The Role of Innate Immune Cells in Cardiac Injury and Repair: A Metabolic Perspective

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Abstract

Purpose of Review Recent technological advances have identified distinct subpopulations and roles of the cardiac innate immune cells, specifically macrophages and neutrophils. Studies on distinct metabolic pathways of macrophage and neutrophil in cardiac injury are expanding. Here, we elaborate on the roles of cardiac macrophages and neutrophils in concomitance with their metabolism in normal and diseased hearts.

Recent Findings Single-cell techniques combined with fate mapping have identified the clusters of innate immune cell subpopulations present in the resting and diseased hearts. We are beginning to know about the presence of cardiac resident macrophages and their functions.

Summary Resident macrophages perform cardiac homeostatic roles, whereas infiltrating neutrophils and macrophages contribute to tissue damage during cardiac injury with eventual role in repair. Prior studies show that metabolic pathways regulate the phenotypes of the macrophages and neutrophils during cardiac injury. Profiling the metabolism of the innate immune cells, especially of resident macrophages during chronic and acute cardiac diseases, can further the understanding of cardiac immunometabolism.

Keywords Cardiac homeostasis · Inflammation · Immunometabolism · Macrophage · Neutrophil · Cardiac injury

Introduction

Immune cells make up to 5–10% of total cells in the adult myocardium with myeloid cells (granulocytes, monocytes, macrophages, and dendritic cells) being 80% of these cardiac immune cells and the rest being non-myeloid/lymphoid cells (B cells and T cells) [1, 2]. Cardiac immune cells can either be residing cells of embryonic origin, such as macrophage, or infiltrating cells from circulation, such as T cells, B cells, neutrophils, mast cells, monocytes, and macrophages [2, 3•, 4–6]. Both normal and diseased hearts contain immune cells, but the quantity and types of immune cells change drastically depending on different (patho)physiological conditions [7•, 8, 9]. Technology advances that improved resolution of immune cell subpopulations within myocardium and vascular spaces have substantially increased the knowledge of cardiac immunology. This review will focus on innate immune cell subpopulations, specifically neutrophils and macrophages, and their role in cardiac homeostasis and disease.

In the last decade, there has been a paradigm shift in macrophage research. Tissue macrophages, including cardiac macrophage, have been shown to have two distinct origins. Majority of resident macrophages in normal adult hearts derives from yolk sac or fetal liver, and they are maintained throughout adulthood by self-renewal [10–13]. A smaller fraction of cardiac macrophage is monocyte derived under normal conditions, but this fraction can increase substantially during injury [4, 14–16]. The two populations of cardiac macrophages can be distinguished by the expression of C–C chemokine receptor 2 (CCR2). Macrophages derived from monocytes are $CCR2^{+}Ly6C^{hi}$ while macrophages of embryonic origin are $CCR2^{-}$ and express low level of Ly6C [10].

Neutrophils are originated from bone marrow. Immature neutrophils in humans show surface markers of $CD15^{+}CD11b^{+}CD16^{+}CD10^{+}$ while mature, circulating neutrophils are classified as $CD16^{hi}CXCR2^{hi}CXCR4^{lo}CD62L^{hi}$. Mouse neutrophils have distinct markers from humans

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characterized by $CD11b^{+}CD45^{+}Ly6G^{+}F4/80^{-}/CD115^{-}$ with alterable CD62L expression [17–20]. Minimum neutrophils are found in normal adult hearts, although one study reported actively infiltrate neutrophil in naïve heart [21, 22]. Some reports have shown the presence of other resident innate immune cells in human hearts and healthy mice, such as dendritic cells (DCs) [23, 24]. Neutrophil infiltration is an important response to cardiac injury. After myocardial infarction, infiltration of pro-inflammatory N1 neutrophil occurs in the initial stages, whereas at the later stage of resolution and tissue repair, the N2 phenotype is more dominant [25, 26].

It is known that activation of immune cells is associated with marked metabolic changes [27, 28]. The role of metabolism in modulating cardiac immune cell function has been emerging. Metabolic alterations in the cardiomyocytes during various cardiac diseases have been widely implicated [29]. Metabolism of non-myocyte is also increasingly recognized to modulate cardiac repair and remodeling [30]. While adult cardiomyocytes can switch from fatty acid oxidation to utilization of other substrates based on their availability and ATP demand, immune cells reprogram their metabolism to switch phenotypes [28, 31, 32]. In the present review, we discuss recent advances in understanding metabolic programs in the innate immune cells, in particular neutrophils and macrophages, in conjunction with their role in the healthy and diseased heart.

The Role of Innate Immune Cells in Cardiac Homeostasis

Recent studies revealed novel functions of resident macrophages, somewhat unexpected from immune cells, in healthy hearts. Cardiac macrophages contribute to electrical conduction, angiogenesis, and vascular development, and maintain mitochondrial homeostasis [3•, 33, 34] (Fig. 1). Primitive embryonic $CCR2^{-}$ macrophages participate coronary maturation, and they are required for coronary plexus remodeling [35]. In developing hearts, resident macrophages are found adhering to newly developed blood and lymphatic vessels and expressing genes that promote angiogenesis, lymphangiogenesis, and ECM remodeling [34]. In adult hearts under stress, cardiac resident macrophage promotes angiogenesis as an adaptive response [13, 36, 37].

Abundant cardiac resident macrophages were also found in the conduction system facilitating cardiac electrical conduction through the distal atrioventricular (AV) node, via the connexin 43 expressed by elongated macrophages in contact with myocytes, both in human and mice [33]. Amphiregulin (AREG) produced by cardiac macrophages has been recently shown to regulate cardiac impulse conduction and may be a potential therapeutic target in sudden death from severe arrhythmias [38].

A recent study showed that cardiac resident macrophages took up ejected mitochondria in double layered vesicles called "exophers," derived from cardiomyocytes, in healthy hearts. This likely provided a mechanism for maintaining mitochondrial homeostasis in cardiomyocytes. Depletion of resident macrophages led to accumulation of defective mitochondria inside cardiomyocytes leading to inflammasome activation, metabolic dysregulation, and cardiac dysfunction [3•].

Metabolism of innate immune cells is mostly studied using bone marrow derived primary cells or cell lines [39–41]. Metabolism of cardiac resident macrophages is poorly understood. It is unknown whether they are metabolically distinct although they possess unique functions compared to bone marrow derived macrophages. With increasing knowledge of the genetic identify of cardiac resident macrophages, targeting metabolism in this specific cell population becomes feasible, which should provide valuable information to the field.

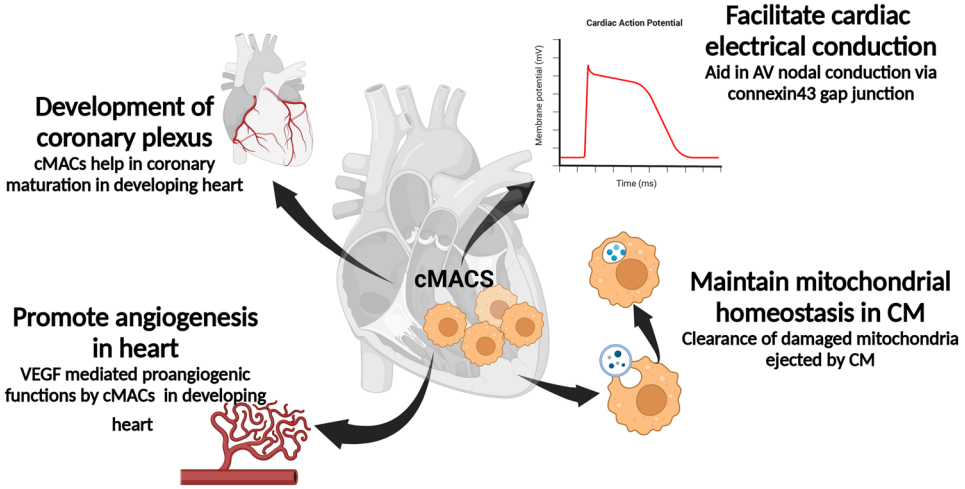

Fig. 1 Function of cardiac resident macrophages in the steady-state heart. Cardiac resident macrophages or cMACs are mostly embryonic in origin and perform homeostatic functions in the resting heart. CM cardiomyocyte, cMAC cardiac macrophage, AV atrioventricular. Created with BioRender.com

Metabolism and Function of Innate Immune Cell During Acute Cardiac Injury

Neutrophils

In the blood, neutrophils are the most abundant leukocytes and the first responders to infection, injury, and cellular stress-induced inflammation [42–44]. During tissue damage or injury such as viral myocarditis and myocardial infarction, pathogens and necrotic tissue resident cells release the pathogen-associated molecular patterns (PAMPS) or damage-associated molecular patterns (DAMPs) and cytokines (such as TNFα, produced by dying cardiomyocytes) and chemokines like CXCL1/IL8, CXCL2, and CCL2 to recruit neutrophils through their surface receptors, i.e., CXCR2 and CCR2 [45–47]. Infiltrating neutrophils clear dead cell debris via phagocytosis and at same time releasing ROS, granular components, proteolytic enzymes, and inflammatory mediators [25, 48–50]. Neutrophils undergo apoptosis shortly after infiltration and lose their IL6 receptors, thereby augmenting the inflammatory signal by stimulating endothelial cells to recruit more inflammatory immune cells [42, 47, 51]. Formation of neutrophil extracellular trap (NETosis), a network of decondensed chromatin or DNA released from activated or dying neutrophils, contributes to inflammation and thrombosis [52, 53]. However, studies also show that neutrophils exert anti-inflammatory, pro-angiogenic, and pro-reparative effects and promote tissue repair post-myocardial infarction by polarizing macrophages towards their reparative phenotype and depletion of neutrophils worsens heart failure pathologies [54–56]. Timely cell death of neutrophil by apoptosis and NETosis have also shown benefit in tissue repair post-MI by scavenging chemokines and cytokines [57].

Immature neutrophils show robust oxidative metabolism during differentiation and are rich in mitochondria compared to mature neutrophils [58–60]. Fatty acid oxidation (FAO) and mitochondrial respiration regulate neutrophil differentiation [59, 60]. On the other hand, mature and active neutrophils have fewer mitochondria and prefer glycolysis for energy production [39, 61, 62]. Activated neutrophils primarily depend on glycolysis for phagocytic functions and in the formation of NET [61]. While not a major player in ATP production, mitochondrial release of proapoptotic factors is an important mechanism regulating apoptosis in neutrophil [62, 63]. A recent study has also shown that neutrophils can use the mitochondrial network for ROS production to stabilize HIF-1α during hypoxia. This study showed that neutrophils shuttled electrons generated from glycolysis via glycerol 3-phosphate pathway to fuel mitochondrial membrane potential for ROS production [64].

Apart from ROS production, mitochondrial function regulates chemotaxis and mTOR signaling [65, 66]. ATP release and mitochondrial purinergic signaling via P2Y2 receptor-mediated mTOR signaling are essential for neutrophil chemotaxis [67, 68]. During acute inflammation, activated neutrophils stimulate mTOR, which then phosphorylates HIF and NF-κB, enhancing the production and release of the inflammatory cytokines such as TNFα and IL6. Cytokine release further promotes accumulation of neutrophil in the injured tissue and enlarge the tissue damage [69, 70]. Migration of neutrophils also has been shown significantly impaired in severe sepsis, which was attributed to activation of PPAR-gamma [71, 72]. Furthermore, sepsis-induced cardiac dysfunction was significantly attenuated by administration of 2-deoxyglucose (2-DG), a glucose analogue that cannot be metabolized via glycolysis, suggesting a contribution of glycolytic metabolism to cardiac dysfunction in sepsis [73].

Monocytes/Macrophages

After acute myocardial infarction (MI), a majority of resident macrophages in the infarct zone die. The injury site is populated with infiltrating neutrophils and macrophages derived from circulating myeloid cells. Ly6C^{hi} monocytes infiltrate the infarct tissue as early as 30 min after coronary ligation in animal studies, and they polarize to CCR2^{+} pro-inflammatory macrophages [74, 75]. The infiltrating CCR2^{+} macrophages can recruit more monocytes to the injured heart through a myeloid differentiation primary response 88 (MYD88)-dependent pathway [12]. In 3–5 days after MI in mice, a shift to Ly6C^{lo} dominant macrophage population and decrease in neutrophil number in the infarcted area marks the transition to resolving phase after tissue injury. During this phase, macrophages engulf dead cells in their surroundings via a process call "efferocytosis" and producing anti-inflammatory and reparative factors such as IL10, vascular endothelial growth factor C (VEGFC), and transforming growth factor beta (TGFβ) [76, 77]. These factors are critical for tissue repair and angiogenesis at the injury site. Depletion of reparative macrophages is associated with left ventricular contractile dysfunction, impaired tissue repair, infarct enlargement, and increased inflammation in the infarct zone [78–80]. A study using inducible deletion strategy to specifically target self-renewing CCR2^{-} resident macrophage found that the loss of this macrophage population resulted in adverse remodeling of the peri-infarcted zone and exacerbate cardiac dysfunction post-MI [81]. While MI sharply reduces cardiac resident macrophages, this population recovers within 1 week after MI in mouse hearts [82]. Together, these studies suggest that cardiac resident macrophages have cardioprotective function nonredundant of reparative macrophages recruited from circulation.

Viral infections and autoimmune diseases can trigger myocarditis and recruitment of Ly6C^{hi}CCR2^{+} monocytes differentiating into MHC-II^{hi}CCR2^{+} macrophages in the heart [83, 84]. Clodronate-mediated depletion of monocytes and macrophages have been shown to increase mortality in viral myocarditis, whereas improves cardiac function in experimental autoimmune myocarditis [85–87]. In a cardiomyocyte-macrophage coculture system, it was found that macrophages induced ROS and apoptosis in after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposure [88]. Recently, a subpopulation of cardiac resident macrophages identified as CD163^{+}RETNLA^{+} (Mac1) with high TREM2 expression was reported to undergo self-renewal and scavenge ejected mitochondria from cardiomyocytes in septic hearts. This subpopulation, when injected into pericardial space, could improve cardiac function of septic hearts [89•]. These observations highlight the functional heterogeneity and divergent roles of monocytes and macrophages in different models of myocarditis. Therefore, future immunotherapy for myocarditis requires better understanding of subpopulation-specific function of immune cells.

Macrophage phenotypes are closely linked to their metabolic profile. Pro-inflammatory macrophages, often referred to as M1 macrophages, are glycolytic, while pro-reparative M2 macrophages rely on oxidative metabolism and fatty acid oxidation [27, 32, 90, 91]. Gene expression profiling showed a shift from highly glycolytic to increased expression of mitochondrial oxidative genes in cardiac macrophages isolated from infarcted region which coincided with the transition from pro-inflammation to reparative phase after MI [92]. Upregulation of glycolysis activates the pentose phosphate pathway (PPP), which increases NADPH-oxidase production of ROS (hydrogen peroxide and superoxide); thus, apart from ATP production, glycolysis also generates ROS in M1 macrophages [93–95]. Glycolytic metabolism also fuels cytoskeletal remodeling allowing macrophage migration to injury sites [96]. Macrophages (CD11b^{+}Ly6G^{-}) isolated from the infarcted region of the myocardium show significant upregulation of glycolytic, pro-inflammatory, and hypoxia-related (HIF-1α) genes as early as 1 day after MI [92, 97]. In vitro studies showed that macrophages lacking glucose transporter, GLUT1, or PDK1 (pyruvate dehydrogenase kinase 1) presented with decreased glycolysis and a phenotypic shift towards pro-resolving M2 macrophages [98, 99]. Using hyperpolarized magnetic resonance, it was shown that inhibiting glycolysis by 2-DG administration could reduce cardiac macrophage glycolysis and inflammation, improving LV function in a rat model of MI [100].

Macrophages upregulate its fatty acid oxidation upon efferocytosis, which is necessary to dispose engulfed lipid cargo as well as to produce anti-inflammatory and pro-resolving mediators [101, 102]. Mitochondrial dysfunction in macrophages impairs efferocytosis or fatty acid oxidation resulting in poor wound healing after MI [103]. Potential mechanisms linking mitochondrial function to efferocytosis response include oxidative stress, calcium homeostasis, and redox imbalance [103, 104].

A new study reports that during MI, HIF2α could suppress mitochondrial metabolism of anti-inflammatory macrophage, while HIF1α caused macrophage glycolytic reprogramming and suppressed cardio-protection [105]. In addition, involvement of mitochondrial function in macrophage activation via production of mitochondrial ROS during MI has been studied [97]. Also, the role of metabolites in the metabolic and thereafter, functional rewiring of macrophages in response to inflammatory stimuli have been widely studied [106–109].

Contribution of Macrophage to Cardiac Regeneration

It has been shown that cardiac macrophages are required for the regeneration of mammalian neonatal hearts [110]. Furthermore, immune cells respond differently in neonatal versus adult mouse hearts. Resident MHCII^{lo}CCR2^{-} macrophages expand in neonatal hearts after injury whereas, the adult heart selectively recruits the MHCII^{hi}CCR2^{+} monocyte-derived macrophages [4]. Similarly, zebrafish, which can regenerate its heart, shows distinct macrophage dynamics after cardiac injury compared to medaka, another teleost which is incapable of cardiac regeneration [111]. A study reported improvement of cardiac repair when murine neonatal cardiac macrophages were transplanted to injured adult hearts [112]. These findings indicate a novel role of macrophage in cardiac regeneration which can be harnessed for therapy.

Mechanisms by which macrophages promote cardiac regeneration are not fully understood. One potential mechanism is neovascularization as the role of cardiac resident macrophages in coronary development and angiogenesis has been documented [34, 35]. Regenerative macrophages have a unique polarization phenotype and secrete numerous soluble factors that may facilitate the formation of new myocardium [110]. Drivers of such phenotype are not revealed. It is hypothesized that macrophage metabolism can be a contributing factor to their regenerative and proliferative potential [113]. The links between macrophage metabolism and cardiac regeneration are prospective; future studies are required.

Macrophages and Neutrophils in Chronic Cardiac Remodeling

Although prior studies of innate immune cells in the heart focused on acute injury, more recent studies showed an important role of these cell in chronic remodeling and

heart failure. Furthermore, it is now recognized that resident macrophages play distinct roles compared to infiltrating macrophages in hearts under chronic stress. Activation of cardiac resident macrophages led to increased expression of pro-angiogenesis and pro-cardiac growth factors [11, 13, 114•]. A study identified CCR2^{-} cardiac resident macrophage as a source of IGF-1(insulin-like growth factor-1) in response to hypertension in mice and in hypertensive human failing hearts [115]. Depletion of resident macrophages led to reduced cardiac contractility, impaired cardiac remodeling, and accelerated mortality in the setting of dilated cardiomyopathy [11]. Pressure overload by transverse aortic constriction (TAC) in mice triggered early expansion of CCR2^{-} resident macrophages or Ly6C^{lo} macrophages that peaked at 1 week [13, 114•, 116]. Depletion of cardiac resident macrophages decreased angiogenesis and enhanced fibrosis after pressure overload and aggravated pathological remodeling [13, 114•]. These observations collectively indicate an adaptive role of cardiac resident macrophage during chronic stress.

Increased proliferation of CCR2^{-} cardiac resident macrophages has been observed at early stage of pathological hypertrophy, but the triggering mechanism are poorly understood [13, 114•]. In mice with dilated cardiomyopathy, resident CCR2^{-} cardiac macrophages were activated by the mechanic stretch through a transient receptor potential vanilloid 4 (TRPV4) dependent pathways [11]. Another study found that class A1 scavenger receptor (SR-A1) was required for proliferation of cardiac resident macrophage in doxorubicin-induced cardiomyopathy [117]. Ligands of SR-A1 under this condition are unknown.

In contrast to resident macrophages, infiltrating macrophages recruited from circulation appeared to be pro-inflammatory and contributed to adverse remodeling of the heart. A study showed that CCR2^{+}Ly6C^{hi} macrophages, derived from infiltrating monocytes, began to increase in the heart one week following pressure overload, and this M1-like macrophage population activated T-cells, recruited more inflammatory macrophages, and upregulated TNFα and TGFβ expression leading to late-stage left ventricular remodeling and dysfunction and transition to heart failure [118]. Increased infiltration of MHC-II^{hi}CCR2^{+} macrophages in mouse hearts was shown to exacerbate cardiac remodeling [119]. Blockade of the infiltrating macrophages post-TAC could improve myocardial angiogenesis, prevent fibrosis, and preserve cardiac function [13]. Single-cell analysis demonstrated that

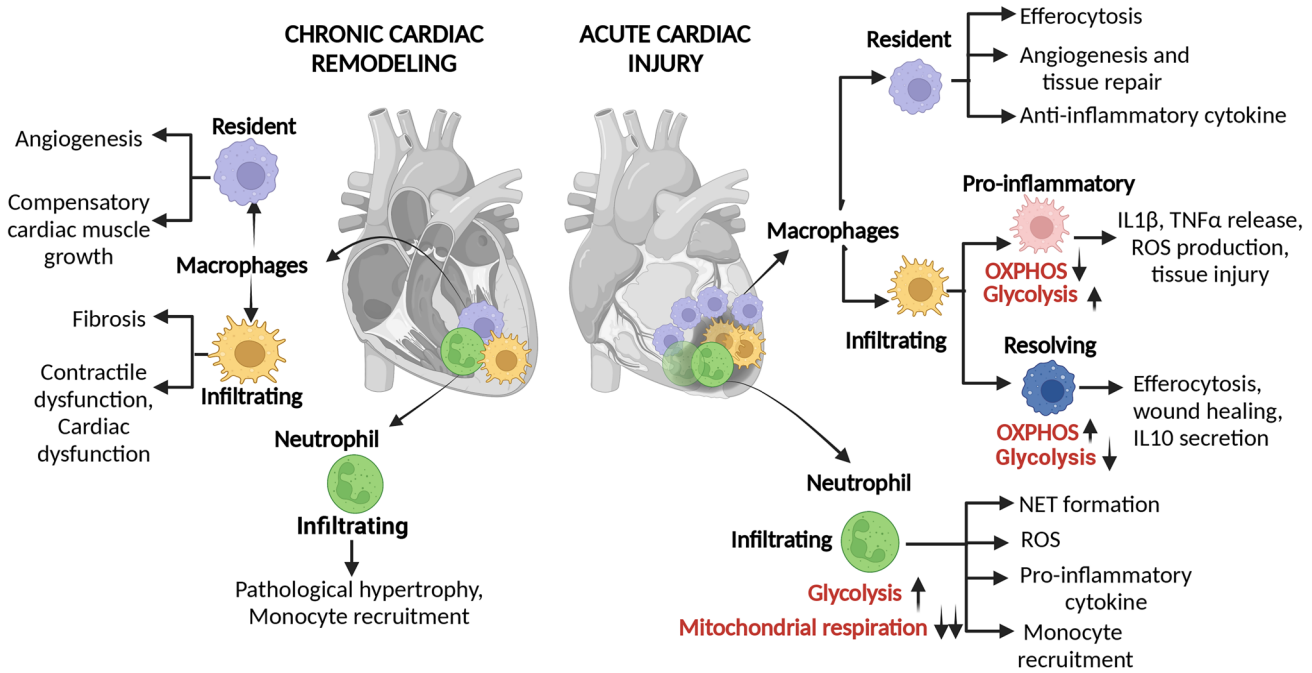

Fig. 2 Function and metabolism of macrophages and neutrophils in diseased hearts. During acute cardiac injury, neutrophils infiltrate as first responders and recruit monocytes causing further inflammation in heart. Infiltrating macrophages are pro-inflammatory at early-stage cardiac injury and cause further inflammatory cell recruitment while at later stage perform inflammation resolving functions. Resident macrophages are anti-inflammatory and carry out reparative functions after cardiac injury. Infiltrating neutrophils induce monocyte recruitment during chronic cardiac remodeling. Resident macrophages preserve cardiac function during chronic cardiac remodeling and promote angiogenesis while infiltrating macrophages cause fibrosis and cardiac dysfunction. While the infiltrating neutrophils and pro-inflammatory macrophages are glycolytic in the setting of acute cardiac injury, the resolving macrophages depend on mitochondrial oxidative phosphorylation or OXPHOS. Created with BioRender.com

macrophage activation and subtype switching was closely correlated with cardiac function and fibrosis which can be targeted in mouse models of heart failure models by pharmacological treatment [7•].

In spite the growing knowledge of differential gene expression and phenotypic profiles in cardiac resident macrophages versus infiltrating macrophages [7•], their respective metabolic profiles have not been defined. Thus, further studies connecting the role of immunometabolism among the various cardiac diseases with specific roles of macrophage subpopulations are needed. So far, studies focusing on the role of macrophage metabolism in cardiac remodeling or cardiac metabolic role in modulating macrophage phenotype during the development of heart failure are lacking.

There are emerging pieces of evidence that neutrophil contributes to cardiac hypertrophy, dysfunction, and development of heart failure in mice through NET formation [120, 121]. In mice with pressure overload, Wnt5a-mediated neutrophil infiltration worsened pathological hypertrophy, inflammation, and cardiac dysfunction. Furthermore, neutrophil depletion could reverse the aggravated pathological hypertrophy by Wnt5a overexpression in pressure overload mouse hearts [122]. Neutrophils were also found to promote thrombosis in small myocardial vessels in response to angiotensin II stimulation via KLF2/NETosis pathway leading to myocardial hypoxia, cell death, and pathological hypertrophy [120]. Metabolic status of infiltrating neutrophils in the chronically remodeled heart is unknown. NET formation in cultured neutrophil is dependent on glycolysis and PPP [123–125]. Further studies are required to determine the relationship between neutrophil metabolism and its function in the failing heart.

Conclusion

Macrophages contribute to cardiac development, homeostasis, repair and regeneration after injury, and cardiac remodeling during chronic stress (Fig. 2). While barely present in normal hearts, neutrophil infiltration causes inflammation and tissue damage in diseased hearts but also contributes to the eventual healing after cardiac injury. Prior studies have identified important metabolic mechanisms in regulating macrophage and neutrophil function in cardiac injury and repair which provided potential therapeutic targets. Recent advances in the heterogeneity of cardiac macrophages, especially the distinct roles of resident and infiltrating macrophages in myocardium in normal and diseased myocardium, have opened newer study avenues. Metabolic profile of resident macrophages performing homeostatic or cardioprotective functions are yet to be defined. Filling this knowledge gap will advance cardioimmunology and guide future metabolic interventions.

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Compliance with Ethical Standards

The figures were created with BioRender.com.

Conflict of Interest The authors confirm that there is no conflict of interest between them.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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