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REGENERATIVE MEDICINE (SM WU, SECTION EDITOR)

# 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.

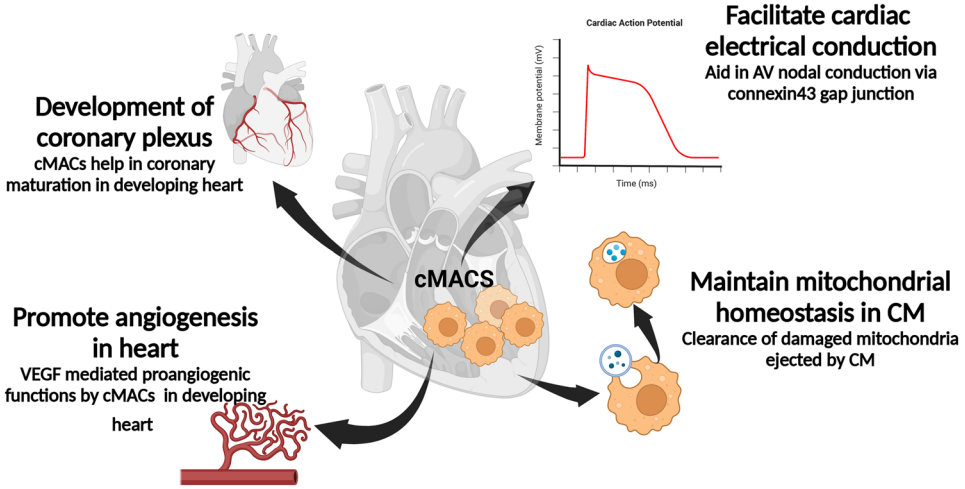


**Fig. 1** Function of cardiac resident macrophages in the steady-state heart. Cardiac resident macrophages or cMACs are mostly embryonic in origin and perform homeostatic functions in the resting heart. CM cardiomyocyte, cMAC cardiac macrophage, AV atrioventricular. Created with BioRender.com

## 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

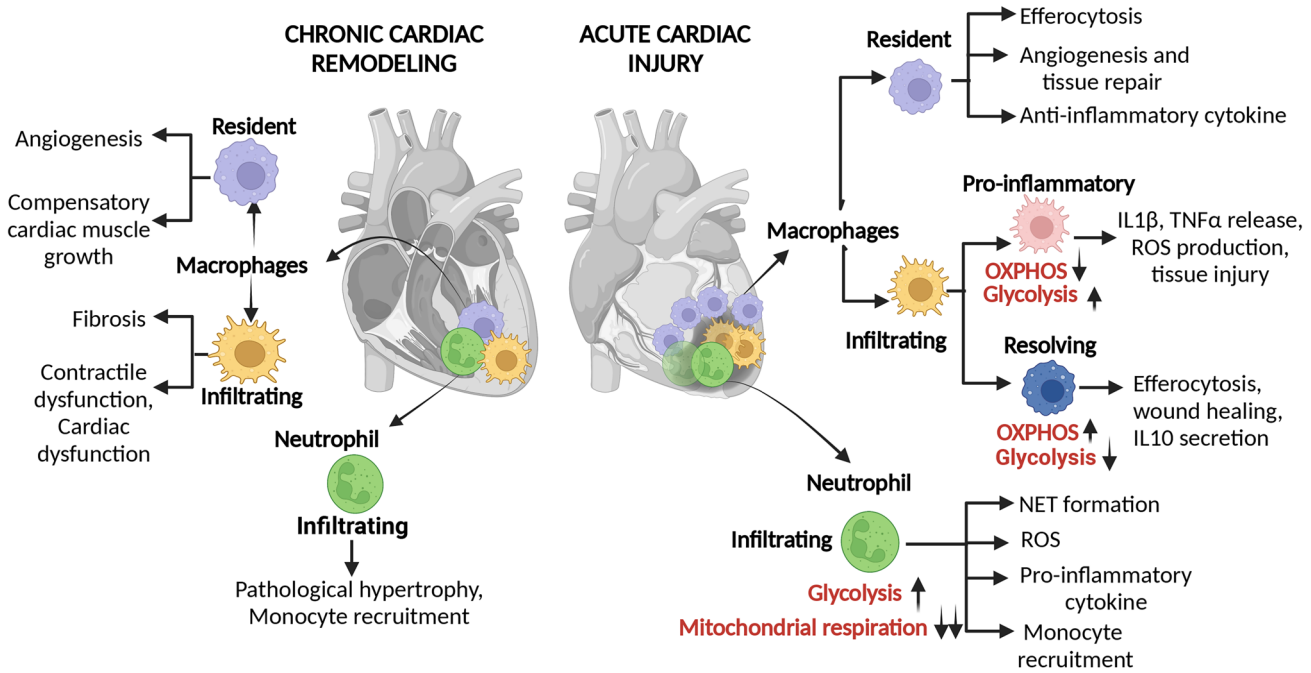


**Fig. 2** Function and metabolism of macrophages and neutrophils in diseased hearts. During acute cardiac injury, neutrophils infiltrate as first responders and recruit monocytes causing further inflammation in heart. Infiltrating macrophages are pro-inflammatory at early-stage cardiac injury and cause 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.

## References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Tallquist MD. Revisiting cardiac cellular composition. Circulation Research, CIRCRESAHA. 2015;115.
2. Swirski FK, Nahrendorf M. Cardioimmunology: the immune system in cardiac homeostasis and disease. Nat Rev Immunol. 2018;18(12):733–44.
3.• Nicolás-Ávila JA, Lechuga-Vieco AV, Esteban-Martínez L, Sánchez-Díaz M, Díaz-García E, Santiago DJ, Rubio-Ponce A, Li JL, Balachander A, Quintana JA, Martínez-de-Mena R. A network of macrophages supports mitochondrial homeostasis in the heart. Cell. 2020;183(1):94–109. **This study showed that cardiac resident macrophages perform homeostatic functions by clearing damaged mitochondria ejected by cardiomyocytes**.
4. Lavine KJ, Epelman S, Uchida K, Weber KJ, Nichols CG, Schilling JD, Ornitz DM, Randolph GJ, Mann DL. Distinct macrophage lineages contribute to disparate patterns of cardiac recovery and remodeling in the neonatal and adult heart. Proc Natl Acad Sci. 2014;111(45):16029–34.
5. Schiattarella GG, Alcaide P, Condorelli G, Gillette TG, Heymans S, Jones EA, Kallikourdis M, Lichtman A, Marelli-Berg F, Shah SJ, Thorp EB. Immunometabolic mechanisms of heart failure with preserved ejection fraction. Nature cardiovascular research. 2022;1(3):211–22.
6. Steffens S, Nahrendorf M, Madonna R. Immune cells in cardiac homeostasis and disease: emerging insights from novel technologies. Eur Heart J. 2022;43(16):1533–41.
7.• Ren Z, Yu P, Li D, Li Z, Liao Y, Wang Y, Zhou B, Wang L. Single-cell reconstruction of progression trajectory reveals intervention principles in pathological cardiac hypertrophy. Circulation. 2020;141(21):1704–19. **This study showed time- and stage-specific change in macrophage subtype during the progression of pathological hypertrophy and its therapeutic importance**.
8. Blanton RM, Carrillo-Salinas FJ, Alcaide P. T-cell recruitment to the heart: friendly guests or unwelcome visitors? Am J Physiol-Heart Circ Physiol. 2019;317(1):H124–40.
9. Strassheim D, Dempsey EC, Gerasimovskaya E, Stenmark K, Karoor V. Role of inflammatory cell subtypes in heart failure. J Immunol Res. 2019;2:2019.
10. Epelman S, Lavine KJ, Beaudin AE, Sojka DK, Carrero JA, Calderon B, Brija T, Gautier EL, Ivanov S, Satpathy AT,

Schilling JD. Embryonic and adult-derived resident cardiac macrophages are maintained through distinct mechanisms at steady state and during inflammation. Immunity. 2014;40(1):91–104.
11. Wong NR, Mohan J, Kopecky BJ, Guo S, Du L, Leid J, Feng G, Lokshina I, Dmytrenko O, Luehmann H, Bajpai G. Resident cardiac macrophages mediate adaptive myocardial remodeling. Immunity. 2021;54(9):2072–88.
12. Bajpai G, Bredemeyer A, Li W, Zaitsev K, Koenig AL, Lokshina I, Mohan J, Ivey B, Hsiao HM, Weinheimer C, Kovacs A. Tissue resident CCR2− and CCR2+ cardiac macrophages differentially orchestrate monocyte recruitment and fate specification following myocardial injury. Circ Res. 2019;124(2):263–78.
13. Liao X, Shen Y, Zhang R, Sugi K, Vasudevan NT, Alaiti MA, Sweet DR, Zhou L, Qing Y, Gerson SL, Fu C. Distinct roles of resident and nonresident macrophages in nonischemic cardiomyopathy. Proc Natl Acad Sci. 2018;115(20):E4661–9.
14. Hashimoto D, Chow A, Noizat C, Teo P, Beasley MB, Leboeuf M, Becker CD, See P, Price J, Lucas D, Greter M. Tissue-resident macrophages self-maintain locally throughout adult life with minimal contribution from circulating monocytes. Immunity. 2013;38(4):792–804.
15. Hoeffel G, Wang Y, Greter M, See P, Teo P, Malleret B, Leboeuf M, Low D, Oller G, Almeida F, Choy SH. Adult Langerhans cells derive predominantly from embryonic fetal liver monocytes with a minor contribution of yolk sac–derived macrophages. J Exp Med. 2012;209(6):1167–81.
16. Ginhoux F, Greter M, Leboeuf M, Nandi S, See P, Gokhan S, Mehler MF, Conway SJ, Ng LG, Stanley ER, Samokhvalov IM. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. Science. 2010;330(6005):841–5.
17. Cottam DR, Schaefer PA, Fahmy D, Shaftan GW, Angus LD. The effect of obesity on neutrophil Fc receptors and adhesion molecules (CD16, CD11b, CD62L). Obes Surg. 2002;12(2):230–5.
18. Parackova Z, Zentsova I, Horvath R, Malcova H, Cebecauerova D, Sediva A, Klocperk A. Immunomodulation of neutrophils and platelets by TNF blockage in patients with juvenile idiopathic arthritis. Clin Immunol. 2022;1(245): 109170.
19. Kologrivova I, Shtatolkina M, Suslova T, Ryabov V. Cells of the immune system in cardiac remodeling: main players in resolution of inflammation and repair after myocardial infarction. Front Immunol. 2021;2(12): 664457.
20. Pillay J, Kamp VM, Van Hoffen E, Visser T, Tak T, Lammers JW, Ulfman LH, Leenen LP, Pickkers P, Koenderman L. A subset of neutrophils in human systemic inflammation inhibits T cell responses through Mac-1. J Clin Investig. 2012;122(1):327–36.
21. Casanova-Acebes M, Nicolas-Avila JA, Li JL, García-Silva S, Balachander A, Rubio-Ponce A, Weiss LA, Adrover JM, Burrows K, A-González N, Ballesteros I. Neutrophils instruct homeostatic and pathological states in naive tissues. J Exp Med. 2018;215(11):2778–95.
22. Hulsmans M, Sam F, Nahrendorf M. Monocyte and macrophage contributions to cardiac remodeling. J Mol Cell Cardiol. 2016;1(93):149–55.
23. Hart DN, Fabre JW. Demonstration and characterization of Ia-positive dendritic cells in the interstitial connective tissues of rat heart and other tissues, but not brain. J Exp Med. 1981;154(2):347–61.
24. Christ A, Temmerman L, Legein B, Daemen MJ, Biessen EA. Dendritic cells in cardiovascular diseases: epiphenomenon, contributor, or therapeutic opportunity. Circulation. 2013;128(24):2603–13.
25. Daseke MJ II, Chalise U, Becirovic-Agic M, Salomon JD, Cook LM, Case AJ, Lindsey ML. Neutrophil signaling during myocardial infarction wound repair. Cell Signal. 2021;1(77): 109816.
26. Mihaila AC, Ciortan L, Macarie RD, Vadana M, Cecoltan S, Preda MB, Hudita A, Gan AM, Jakobsson G, Tucureanu MM, Barbu E. Transcriptional profiling and functional analysis of N1/N2 neutrophils reveal an immunomodulatory effect of S100A9-blockade on the pro-inflammatory N1 subpopulation. Front Immunol. 2021;10(12): 708770.
27. Sack MN. Mitochondrial fidelity and metabolic agility control immune cell fate and function. J Clin Investig. 2018;128(9):3651–61.
28. Caligiuri G, Norata GD. Fuel for thought: immunometabolism is a paradigm shift in understanding immunity in cardiovascular disease. Cardiovasc Res. 2019;115(9):1383–4.
29. Kolwicz SC Jr, Purohit S, Tian R. Cardiac metabolism and its interactions with contraction, growth, and survival of cardiomyocytes. Circ Res. 2013;113(5):603–16.
30. Mouton AJ, Hall JE. Novel roles of immunometabolism and nonmyocyte metabolism in cardiac remodeling and injury. Am J Physiol-Regul Integr Comp Physiol. 2020;319(4):R476–84.
31. Ritterhoff J, Tian R. Metabolism in cardiomyopathy: every substrate matters. Cardiovasc Res. 2017;113(4):411–21.
32. Zhang S, Bories G, Lantz C, Emmons R, Becker A, Liu E, Abecassis MM, Yvan-Charvet L, Thorp EB. Immunometabolism of phagocytes and relationships to cardiac repair. Frontiers in Cardiovascular Medicine. 2019;11(6):42.
33. Hulsmans M, Clauss S, Xiao L, Aguirre AD, King KR, Hanley A, Hucker WJ, Wülfers EM, Seemann G, Courties G, Iwamoto Y. Macrophages facilitate electrical conduction in the heart. Cell. 2017;169(3):510–22.
34. Gula G, Rumiński S, Niderla-Bielińska J, Jasińska A, Kiernozek E, Jankowska-Steifer E, Flaht-Zabost A, Ratajska A. Potential functions of embryonic cardiac macrophages in angiogenesis, lymphangiogenesis and extracellular matrix remodeling. Histochem Cell Biol. 2021;155(1):117–32.
35. Leid J, Carrelha J, Boukarabila H, Epelman S, Jacobsen SE, Lavine KJ. Primitive embryonic macrophages are required for coronary development and maturation. Circ Res. 2016;118(10):1498–511.
36. Bajpai G, Schneider C, Wong N, Bredemeyer A, Hulsmans M, Nahrendorf M, Epelman S, Kreisel D, Liu Y, Itoh A, Shankar TS. The human heart contains distinct macrophage subsets with divergent origins and functions. Nat Med. 2018;24(8):1234–45.
37. Peet C, Ivetic A, Bromage DI, Shah AM. Cardiac monocytes and macrophages after myocardial infarction. Cardiovasc Res. 2020;116(6):1101–12.
38. Sugita J, Fujiu K, Nakayama Y, Matsubara T, Matsuda J, Oshima T, Liu Y, Maru Y, Hasumi E, Kojima T, Seno H. Cardiac macrophages prevent sudden death during heart stress. Nat Commun. 2021;12(1):1910.
39. Kumar S, Dikshit M. Metabolic insight of neutrophils in health and disease. Front Immunol. 2019;20(10):2099.
40. Viola A, Munari F, Sánchez-Rodríguez R, Scolaro T, Castegna A. The metabolic signature of macrophage responses. Front Immunol. 2019;3(10):1462.
41. Sun L, Yang X, Yuan Z, Wang H. Metabolic reprogramming in immune response and tissue inflammation. Arterioscler Thromb Vasc Biol. 2020;40(9):1990–2001.
42. Silvestre-Roig C, Braster Q, Ortega-Gomez A, Soehnlein O. Neutrophils as regulators of cardiovascular inflammation. Nat Rev Cardiol. 2020;17(6):327–40.
43. Vafadarnejad E, Rizzo G, Krampert L, Arampatzi P, Arias-Loza AP, Nazzal Y, Rizakou A, Knochenhauer T, Bandi SR, Nugroho VA, Schulz DJ. Dynamics of cardiac neutrophil diversity in murine myocardial infarction. Circ Res. 2020;127(9):e232–49.
44. Fine N, Tasevski N, McCulloch CA, Tenenbaum HC, Glogauer M. The neutrophil: constant defender and first responder. Front Immunol. 2020;24(11): 571085.

45. Akasaka Y, Morimoto N, Ishikawa Y, Fujita K, Ito K, Kimura-Matsumoto M, Ishiguro S, Morita H, Kobayashi Y, Ishii T. Myocardial apoptosis associated with the expression of proinflammatory cytokines during the course of myocardial infarction. Mod Pathol. 2006;19(4):588–98.
46. Koudela B, Vitovec J, Štěrba J. Concurrent infection of enterocytes with Eimeria scabra and other enteropathogens in swine. Vet Parasitol. 1990;35(1–2):71–7.
47. Puhl SL, Steffens S. Neutrophils in post-myocardial infarction inflammation: damage vs. resolution? Front Cardiovasc Med. 2019;6:25.
48. Frangogiannis NG. The inflammatory response in myocardial injury, repair, and remodelling. Nat Rev Cardiol. 2014;11(5):255–65.
49. Sreejit G, Abdel-Latif A, Athmanathan B, Annabathula R, Dhyani A, Noothi SK, Quaife-Ryan GA, Al-Sharea A, Pernes G, Dragoljevic D, Lal H. Neutrophil-derived S100A8/A9 amplify granulopoiesis after myocardial infarction. Circulation. 2020;141(13):1080–94.
50. Marinković G, Koenis DS, de Camp L, Jablonowski R, Graber N, de Waard V, de Vries CJ, Goncalves I, Nilsson J, Jovinge S, Schiopu A. S100A9 links inflammation and repair in myocardial infarction. Circ Res. 2020;127(5):664–76.
51. Modur V, Li Y, Zimmerman GA, Prescott SM, McIntyre TM. Retrograde inflammatory signaling from neutrophils to endothelial cells by soluble interleukin-6 receptor alpha. J Clin Investig. 1997;100(11):2752–6.
52. Nagareddy PR, Sreejit G, Abo-Aly M, Jaggers RM, Chelvarajan L, Johnson J, Pernes G, Athmanathan B, Abdel-Latif A, Murphy AJ. NETosis is required for S100A8/A9-induced granulopoiesis after myocardial infarction. Arterioscler Thromb Vasc Biol. 2020;40(11):2805–7.
53. Döring Y, Libby P, Soehnlein O. Neutrophil extracellular traps participate in cardiovascular diseases: recent experimental and clinical insights. Circ Res. 2020;126(9):1228–41.
54. Horckmans M, Ring L, Duchene J, Santovito D, Schloss MJ, Drechsler M, Weber C, Soehnlein O, Steffens S. Neutrophils orchestrate post-myocardial infarction healing by polarizing macrophages towards a reparative phenotype. Eur Heart J. 2017;38(3):187–97.
55. Wei X, Zou S, Xie Z, Wang Z, Huang N, Cen Z, Hao Y, Zhang C, Chen Z, Zhao F, Hu Z. EDIL3 deficiency ameliorates adverse cardiac remodelling by neutrophil extracellular traps (NET)-mediated macrophage polarization. Cardiovasc Res. 2022;118(9):2179–95.
56. Daseke MJ II, Tenkorang-Impraim MA, Ma Y, Chalise U, Konfrst SR, Garrett MR, DeLeon-Pennell KY, Lindsey ML. Exogenous IL-4 shuts off pro-inflammation in neutrophils while stimulating anti-inflammation in macrophages to induce neutrophil phagocytosis following myocardial infarction. J Mol Cell Cardiol. 2020;1(145):112–21.
57. Farrera C, Fadeel B. Macrophage clearance of neutrophil extracellular traps is a silent process. J Immunol. 2013;191(5):2647–56.
58. Bainton DF, Ullyot JL, Farquhar MG. The development of neutrophilic polymorphonuclear leukocytes in human bone marrow: origin and content of azurophil and specific granules. J Exp Med. 1971;134(4):907–34.
59. Rice CM, Davies LC, Subleski JJ, Maio N, Gonzalez-Cotto M, Andrews C, Patel NL, Palmieri EM, Weiss JM, Lee JM, Annunziata CM. Tumour-elicited neutrophils engage mitochondrial metabolism to circumvent nutrient limitations and maintain immune suppression. Nat Commun. 2018;9(1):5099.
60. Riffelmacher T, Clarke A, Richter FC, Stranks A, Pandey S, Danielli S, Hublitz P, Yu Z, Johnson E, Schwerd T, McCullagh J. Autophagy-dependent generation of free fatty acids is critical for normal neutrophil differentiation. Immunity. 2017;47(3):466–80.
61. Jeon JH, Hong CW, Kim EY, Lee JM. Current understanding on the metabolism of neutrophils. Immune Network. 2020;20(6).
62. Maianski NA, Geissler J, Srinivasula SM, Alnemri ES, Roos D, Kuijpers TW. Functional characterization of mitochondria in neutrophils: a role restricted to apoptosis. Cell Death Differ. 2004;11(2):143–53.
63. Maianski NA, Mul FP, van Buul JD, Roos D, Kuijpers TW. Granulocyte colony-stimulating factor inhibits the mitochondria-dependent activation of caspase-3 in neutrophils. Blood J Am Soc Hematol. 2002;99(2):672–9.
64. Willson JA, Arienti S, Sadiku P, Reyes L, Coelho P, Morrison T, Rinaldi G, Dockrell DH, Whyte MK, Walmsley SR. Neutrophil HIF-1α stabilization is augmented by mitochondrial ROS produced via the glycerol 3-phosphate shuttle. Blood. 2022;139(2):281–6.
65. Fossati G, Moulding DA, Spiller DG, Moots RJ, White MR, Edwards SW. The mitochondrial network of human neutrophils: role in chemotaxis, phagocytosis, respiratory burst activation, and commitment to apoptosis. J Immunol. 2003;170(4):1964–72.
66. Piccolo EB, Thorp EB, Sumagin R. Functional implications of neutrophil metabolism during ischemic tissue repair. Curr Opin Pharmacol. 2022;1(63): 102191.
67. Chen Y, Yao Y, Sumi Y, Li A, To UK, Elkhal A, Inoue Y, Woehrle T, Zhang Q, Hauser C, Junger WG. Purinergic signaling: a fundamental mechanism in neutrophil activation. Sci Signal. 2010;3(125):ra45-.
68. Bao Y, Ledderose C, Graf AF, Brix B, Birsak T, Lee A, Zhang J, Junger WG. mTOR and differential activation of mitochondria orchestrate neutrophil chemotaxis. J Cell Biol. 2015;210(7):1153–64.
69. Lorne E, Zhao X, Zmijewski JW, Liu G, Park YJ, Tsuruta Y, Abraham E. Participation of mammalian target of rapamycin complex 1 in toll-like receptor 2–and 4–induced neutrophil activation and acute lung injury. Am J Respir Cell Mol Biol. 2009;41(2):237–45.
70. Cramer T, Yamanishi Y, Clausen BE, Förster I, Pawlinski R, Mackman N, Haase VH, Jaenisch R, Corr M, Nizet V, Firestein GS. HIF-1α is essential for myeloid cell-mediated inflammation. Cell. 2003;112(5):645–57.
71. V Lerman Y, Kim M. Neutrophil migration under normal and sepsis conditions. Cardiovascular & Haematological Disorders-Drug Targets (Formerly Current Drug Targets-Cardiovascular & Hematological Disorders). 2015;15(1):19–28.
72. Reddy RC, Narala VR, Keshamouni VG, Milam JE, Newstead MW, Standiford TJ. Sepsis-induced inhibition of neutrophil chemotaxis is mediated by activation of peroxisome proliferator-activated receptor-γ. Blood J Am Soc Hematol. 2008;112(10):4250–8.
73. Zheng Z, Ma H, Zhang X, Tu F, Wang X, Ha T, Fan M, Liu L, Xu J, Yu K, Wang R. Enhanced glycolytic metabolism contributes to cardiac dysfunction in polymicrobial sepsis. J Infect Dis. 2017;215(9):1396–406.
74. Jung K, Kim P, Leuschner F, Gorbatov R, Kim JK, Ueno T, Nahrendorf M, Yun SH. Endoscopic time-lapse imaging of immune cells in infarcted mouse hearts. Circ Res. 2013;112(6):891–9.
75. Frantz S, Nahrendorf M. Cardiac macrophages and their role in ischaemic heart disease. Cardiovasc Res. 2014;102(2):240–8.
76. Glinton KE, Ma W, Lantz C, Grigoryeva LS, DeBerge M, Liu X, Febbraio M, Kahn M, Oliver G, Thorp EB. Macrophage-produced VEGFC is induced by efferocytosis to ameliorate cardiac injury and inflammation. J Clin Investig. 2022;132(9).
77. Zhao M, Wang DD, Liu X, Tian R. Metabolic modulation of macrophage function post myocardial infarction. Front Physiol. 2020;30(11):674.
78. Leblond AL, Klinkert K, Martin K, Turner EC, Kumar AH, Browne T, Caplice NM. Systemic and cardiac depletion of

M2 macrophage through CSF-1R signaling inhibition alters cardiac function post myocardial infarction. PLoS ONE. 2015;10(9): e0137515.
79. Koh TJ, DiPietro LA. Inflammation and wound healing: the role of the macrophage. Expert Rev Mol Med. 2011;13: e23.
80. Falkenham A, de Antueno R, Rosin N, Betsch D, Lee TD, Duncan R, Légaré JF. Nonclassical resident macrophages are important determinants in the development of myocardial fibrosis. Am J Pathol. 2015;185(4):927–42.
81. Dick SA, Macklin JA, Nejat S, Momen A, Clemente-Casares X, Althagafi MG, Chen J, Kantores C, Hosseinzadeh S, Aronoff L, Wong A. Self-renewing resident cardiac macrophages limit adverse remodeling following myocardial infarction. Nat Immunol. 2019;20(1):29–39.
82. Heidt T, Courties G, Dutta P, Sager HB, Sebas M, Iwamoto Y, Sun Y, Da Silva N, Panizzi P, van der Laan AM, Swirski FK. Differential contribution of monocytes to heart macrophages in steady-state and after myocardial infarction. Circ Res. 2014;115(2):284–95.
83. Luo Y, Zhang H, Yu J, Wei L, Li M, Xu W. Stem cell factor/mast cell/CCL2/monocyte/macrophage axis promotes Coxsackievirus B3 myocarditis and cardiac fibrosis by increasing Ly6Chigh monocyte influx and fibrogenic mediators production. Immunology. 2022;167(4):590–605.
84. Jahandideh A, Uotila S, Ståhle M, Virta J, Li XG, Kytö V, Marjamäki P, Liljenbäck H, Taimen P, Oikonen V, Lehtonen J. Folate receptor β–targeted PET imaging of macrophages in autoimmune myocarditis. J Nucl Med. 2020;61(11):1643–9.
85. McCartney SA, Vermi W, Lonardi S, Rossini C, Otero K, Calderon B, Gilfillan S, Diamond MS, Unanue ER, Colonna M. RNA sensor–induced type I IFN prevents diabetes caused by a β cell–tropic virus in mice. J Clin Investig. 2011;121(4):1497–507.
86. De Giusti CJ, Ure AE, Rivadeneyra L, Schattner M, Gomez RM. Macrophages and galectin 3 play critical roles in CVB3-induced murine acute myocarditis and chronic fibrosis. J Mol Cell Cardiol. 2015;1(85):58–70.
87. Wu L, Ong S, Talor MV, Barin JG, Baldeviano GC, Kass DA, Bedja D, Zhang H, Sheikh A, Margolick JB, Iwakura Y. Cardiac fibroblasts mediate IL-17A–driven inflammatory dilated cardiomyopathy. J Exp Med. 2014;211(7):1449–64.
88. Yang L, Han Y, Jaffre F, Nilsson-Payant BE, Bram Y, Wang P, Zhu J, Zhang T, Redmond D, Houghton S, Uhl S. An immunocardiac model for macrophage-mediated inflammation in COVID-19 hearts. Circ Res. 2021;129(1):33–46.
89.• Zhang K, Wang Y, Chen S, Mao J, Jin Y, Ye H, Zhang Y, Liu X, Gong C, Cheng X, Huang X. TREM2$^{hi}$ resident macrophages protect the septic heart by maintaining cardiomyocyte homeostasis. Nat Metab. 2023:1–8. **This study showed the role of cardiac-resident macrophages in septic heart in clearing vesicle bound damaged mitochondria ejected by cardiomyocytes**.
90. Mouton AJ, Li X, Hall ME, Hall JE. Obesity, hypertension, and cardiac dysfunction: novel roles of immunometabolism in macrophage activation and inflammation. Circ Res. 2020;126(6):789–806.
91. Pearce EL, Pearce EJ. Metabolic pathways in immune cell activation and quiescence. Immunity. 2013;38(4):633–43.
92. Mouton AJ, DeLeon-Pennell KY, Rivera Gonzalez OJ, Flynn ER, Freeman TC, Saucerman JJ, Garrett MR, Ma Y, Harmancey R, Lindsey ML. Mapping macrophage polarization over the myocardial infarction time continuum. Basic Res Cardiol. 2018;113:1–8.
93. Mills EL, Kelly B, O'Neill LA. Mitochondria are the powerhouses of immunity. Nat Immunol. 2017;18(5):488–98.
94. Erlich JR, To EE, Luong R, Liong F, Liong S, Oseghale O, Miles MA, Bozinovski S, Brooks RD, Vlahos R, Chan S. Glycolysis and the pentose phosphate pathway promote LPS-induced NOX2 oxidase-and IFN-β-Dependent inflammation in macrophages. Antioxidants. 2022;11(8):1488.
95. Rodríguez-Prados JC, Través PG, Cuenca J, Rico D, Aragonés J, Martín-Sanz P, Cascante M, Boscá L. Substrate fate in activated macrophages: a comparison between innate, classic, and alternative activation. J Immunol. 2010;185(1):605–14.
96. Semba H, Takeda N, Isagawa T, Sugiura Y, Honda K, Wake M, Miyazawa H, Yamaguchi Y, Miura M, Jenkins DM, Choi H. HIF-1α-PDK1 axis-induced active glycolysis plays an essential role in macrophage migratory capacity. Nat Commun. 2016;7(1):11635.
97. Cai S, Zhao M, Zhou B, Yoshii A, Bugg D, Villet O, Sahu A, Olson GS, Davis J, Tian R. Mitochondrial dysfunction in macrophages promotes inflammation and suppresses repair after myocardial infarction. J Clinical Investig. 202315;133(4).
98. Freemerman AJ, Zhao L, Pingili AK, Teng B, Cozzo AJ, Fuller AM, Johnson AR, Milner JJ, Lim MF, Galanko JA, Beck MA. Myeloid Slc2a1-deficient murine model revealed macrophage activation and metabolic phenotype are fueled by GLUT1. J Immunol. 2019;202(4):1265–86.
99. Tan Z, Xie N, Cui H, Moellering DR, Abraham E, Thannickal VJ, Liu G. Pyruvate dehydrogenase kinase 1 participates in macrophage polarization via regulating glucose metabolism. J Immunol. 2015;194(12):6082–9.
100. Lewis AJ, Miller JJ, Lau AZ, Curtis MK, Rider OJ, Choudhury RP, Neubauer S, Cunningham CH, Carr CA, Tyler DJ. Noninvasive immunometabolic cardiac inflammation imaging using hyperpolarized magnetic resonance. Circ Res. 2018;122(8):1084–93.
101. Doran AC, Yurdagul A Jr, Tabas I. Efferocytosis in health and disease. Nat Rev Immunol. 2020;20(4):254–67.
102. Trzeciak A, Wang YT, Perry JS. First we eat, then we do everything else: The dynamic metabolic regulation of efferocytosis. Cell Metab. 2021;33(11):2126–41.
103. Zhang S, Weinberg S, DeBerge M, Gainullina A, Schipma M, Kinchen JM, Ben-Sahra I, Gius DR, Yvan-Charvet L, Chandel NS, Schumacker PT. Efferocytosis fuels requirements of fatty acid oxidation and the electron transport chain to polarize macrophages for tissue repair. Cell Metab. 2019;29(2):443–56.
104. Wang Y, Subramanian M, Yurdagul A, Barbosa-Lorenzi VC, Cai B, de Juan-Sanz J, Ryan TA, Nomura M, Maxfield FR, Tabas I. Mitochondrial fission promotes the continued clearance of apoptotic cells by macrophages. cell. 2017;171(2):331–45.
105. DeBerge M, Lantz C, Dehn S, Sullivan DP, van der Laan AM, Niessen HW, Flanagan ME, Brat DJ, Feinstein MJ, Kaushal S, Wilsbacher LD. Hypoxia-inducible factors individually facilitate inflammatory myeloid metabolism and inefficient cardiac repair. J Exp Med. 2021;218(9): e20200667.
106. Ryan DG, O'Neill LA. Krebs cycle rewired for macrophage and dendritic cell effector functions. FEBS Lett. 2017;591(19):2992–3006.
107. Mills EL, Kelly B, Logan A, Costa AS, Varma M, Bryant CE, Tourlomousis P, Däbritz JH, Gottlieb E, Latorre I, Corr SC. Succinate dehydrogenase supports metabolic repurposing of mitochondria to drive inflammatory macrophages. Cell. 2016;167(2):457–70.
108. Jha AK, Huang SC, Sergushichev A, Lampropoulou V, Ivanova Y, Loginicheva E, Chmielewski K, Stewart KM, Ashall J, Everts B, Pearce EJ. Network integration of parallel metabolic and transcriptional data reveals metabolic modules that regulate macrophage polarization. Immunity. 2015;42(3):419–30.
109. Forman HJ, Torres M. Redox signaling in macrophages. Mol Aspects Med. 2001;22(4–5):189–216.
110. Aurora AB, Porrello ER, Tan W, Mahmoud AI, Hill JA, Bassel-Duby R, Sadek HA, Olson EN. Macrophages are

required for neonatal heart regeneration. J Clin Investig. 2014;124(3):1382–92.
111. Lai SL, Marín-Juez R, Moura PL, Kuenne C, Lai JK, Tsedeke AT, Guenther S, Looso M, Stainier DY. Reciprocal analyses in zebrafish and medaka reveal that harnessing the immune response promotes cardiac regeneration. Elife. 2017;20(6): e25605.
112. Li Y, Li H, Pei J, Hu S, Nie Y. Transplantation of murine neonatal cardiac macrophage improves adult cardiac repair. Cell Mol Immunol. 2021;18(2):492–4.
113. Lantz C, Becker A, Thorp EB. Can polarization of macrophage metabolism enhance cardiac regeneration? J Mol Cell Cardiol. 2021;1(160):87–96.
114.• Revelo XS, Parthiban P, Chen C, Barrow F, Fredrickson G, Wang H, Yücel D, Herman A, van Berlo JH. Cardiac resident macrophages prevent fibrosis and stimulate angiogenesis. Circ Res. 2021;129(12):1086–101. **This study reported that the cardiac resident macrophages prevent fibrosis and cardiac dysfunction during pathological hypertrophy**.
115. Zaman R, Hamidzada H, Kantores C, Wong A, Dick SA, Wang Y, Momen A, Aronoff L, Lin J, Razani B, Mital S. Selective loss of resident macrophage-derived insulin-like growth factor-1 abolishes adaptive cardiac growth to stress. Immunity. 2021;54(9):2057–71.
116. Weisheit C, Zhang Y, Faron A, Köpke O, Weisheit G, Steinsträsser A, Frede S, Meyer R, Boehm O, Hoeft A, Kurts C. Ly6Clow and not Ly6Chigh macrophages accumulate first in the heart in a model of murine pressure-overload. PLoS ONE. 2014;9(11): e112710.
117. Zhang H, Xu A, Sun X, Yang Y, Zhang L, Bai H, Ben J, Zhu X, Li X, Yang Q, Wang Z. Self-maintenance of cardiac resident reparative macrophages attenuates doxorubicin-induced cardiomyopathy through the SR-A1-c-Myc axis. Circ Res. 2020;127(5):610–27.
118. Patel B, Bansal SS, Ismahil MA, Hamid T, Rokosh G, Mack M, Prabhu SD. CCR2+ monocyte-derived infiltrating macrophages are required for adverse cardiac remodeling during pressure overload. JACC: Basic Transl Sci. 2018;3(2):230–44.
119. Jia D, Chen S, Bai P, Luo C, Liu J, Sun A, Ge J. Cardiac resident macrophage-derived legumain improves cardiac repair by promoting clearance and degradation of apoptotic cardiomyocytes after myocardial infarction. Circulation. 2022;145(20):1542–56.
120. Tang X, Wang P, Zhang R, Watanabe I, Chang E, Vinayachandran V, Nayak L, Lapping S, Liao S, Madera A, Sweet DR. KLF2 regulates neutrophil activation and thrombosis in cardiac hypertrophy and heart failure progression. J Clin Investig. 2022;132(3).
121. Bai B, Yang W, Fu Y, Foon HL, Tay WT, Yang K, Luo C, Gunaratne J, Lee P, Zile MR, Xu A. Seipin knockout mice develop heart failure with preserved ejection fraction. JACC: Basic Transl Sci. 2019;4(8):924–37.
122. Wang Y, Sano S, Oshima K, Sano M, Watanabe Y, Katanasaka Y, Yura Y, Jung C, Anzai A, Swirski FK, Gokce N. Wnt5a-mediated neutrophil recruitment has an obligatory role in pressure overload–induced cardiac dysfunction. Circulation. 2019;140(6):487–99.
123. Alarcón P, Manosalva C, Conejeros I, Carretta MD, Muñoz-Caro T, Silva LM, Taubert A, Hermosilla C, Hidalgo MA, Burgos RA. d (−) lactic acid-induced adhesion of bovine neutrophils onto endothelial cells is dependent on neutrophils extracellular traps formation and CD11b expression. Front Immunol. 2017;15(8):975.
124. Rodríguez-Espinosa O, Rojas-Espinosa O, Moreno-Altamirano MM, López-Villegas EO, Sánchez-García FJ. Metabolic requirements for neutrophil extracellular traps formation. Immunology. 2015;145(2):213–24.
125. Azevedo EP, Rochael NC, Guimarães-Costa AB, de Souza-Vieira TS, Ganilho J, Saraiva EM, Palhano FL, Foguel D. A metabolic shift toward pentose phosphate pathway is necessary for amyloid fibril-and phorbol 12-myristate 13-acetate-induced neutrophil extracellular trap (NET) formation. J Biol Chem. 2015;290(36):22174–83.