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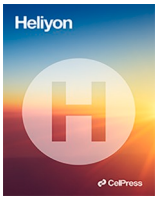

Review article

Crosstalk between macrophages and immunometabolism and their potential roles in tissue repair and regeneration

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ABSTRACT

Immune metabolism is a result of many specific metabolic reactions, such as glycolysis, the tricarboxylic acid (TCA) pathway, the pentose phosphate pathway (PPP), mitochondrial oxidative phosphorylation (OXPHOS), fatty acid oxidation (FAO), fatty acid biosynthesis (FAs) and amino acid pathways, which promote cell proliferation and maintenance with structural and pathological energy to regulate cellular signaling. The metabolism of macrophages produces many metabolic intermediates that play important regulatory roles in tissue repair and regeneration. The metabolic activity of proinflammatory macrophages (M1) mainly depends on glycolysis and the TCA cycle system, but anti-inflammatory macrophages (M2) have intact functions of the TCA cycle, which enhances FAO and is dependent on OXPHOS. However, the metabolic mechanisms of macrophages in tissue repair and regeneration have not been well investigated. Thus, we review how three main metabolic mechanisms of macrophages, glucose metabolism, lipid metabolism, and amino acid metabolism, regulate tissue repair and regeneration.

1. Introduction

Tissue injuries are the result of unexpected organ or tissue damage, which leads to changes in cellular and molecular mechanisms such as lipid metabolism and cell metabolism. Tissue repair after injury is a complex self-protective, metabolic mechanism. After injury, organs or tissues regulate a series of inflammatory and metabolic responses to repair or regenerate necrotic and injured organs or tissues [1]. The innate immune system is a critical component of repair and regeneration processes, especially in terms of macrophage functions [2–5]. Necrotic cells or microbial stimuli promote the production of damage- and pathogen-associated molecular patterns and consequently activate Toll-like receptors (TLRs), NOD-like receptors (NLRs), C-type lectin receptors and inflammasomes, resulting in inflammation and leukocyte recruitment via the production of cytokines and chemokines [6]. Proinflammatory macrophages switch to a reparative phenotype, which formed a permanent scar in the days following injury. The depletion

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or inhibition of macrophages prevents organ repair and regeneration in adults and neonatal animals [2,7].

Tissue-resident macrophages are key mediators that sustain tissue homeostasis, which are derived from the yolk sac, fetal liver, and bone marrow precursor cells and migrate to specific tissues or organs after the end of pregnancy [8]. In Mammals, these cells include Langerhans cells in the skin [9], osteoclasts in bone [10], microglia in the brain [11], Kupffer cells in the liver [12], alveolar

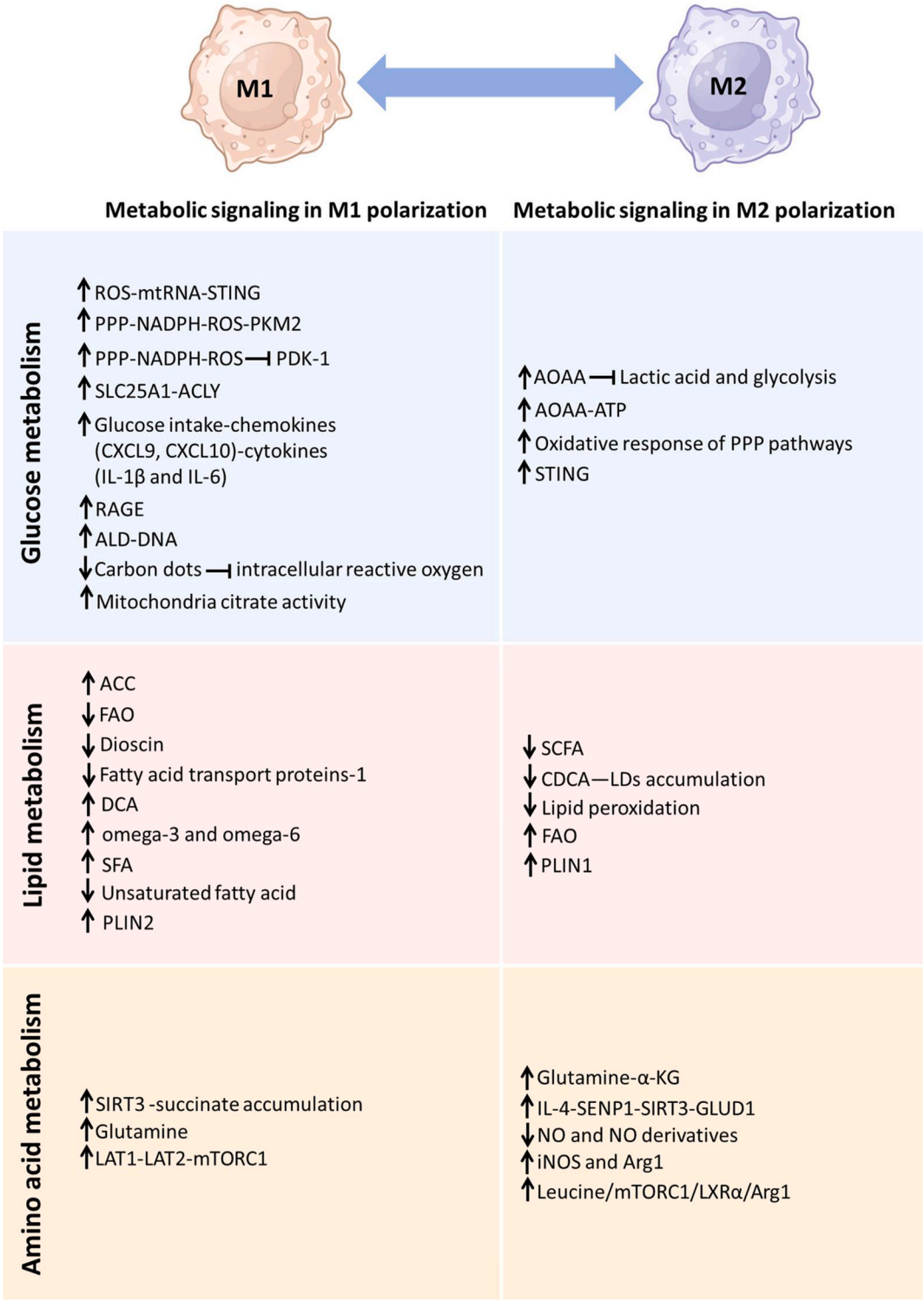

Fig. 1. The potential roles of metabolic pathways in macrophage polarization.

macrophages in the lung [13], cardiac-resident macrophages in the heart [14] and fat-associated macrophages in adipose tissue [15]. Tissue-specific macrophages play different roles in tissue injury and regeneration compared with recruited macrophages, which can interact with specific and systemic tissue responses to produce growth factors, nutrients and waste removal that contribute to tissue regeneration, repair and homeostasis following damage [8,16].

Accumulating studies have demonstrated that cell metabolism is critical for macrophage functions in inflammation and aging [17–19]. As a case in point, blockade of macrophage de novo NAD + synthesis, which is derived from kynurenine pathway metabolism of tryptophan, reduces NAD + levels and impairs macrophage phagocytosis [17]. Lactate hinders the Warburg effect by activating pyruvate kinase M2 (PKM2), which switches macrophages from a proinflammatory phenotype to a reparative phenotype [20]. Additionally, endothelial cell-derived lactate is consumed and oxidized by macrophages, and lactate controls macrophage polarization toward the M2 phenotype after ischemia, promoting muscle regeneration and revascularization in a monocarboxylate transporter 1-dependent fashion [21]. On the other hand, the activation of macrophage retinoic acid-related orphan receptor-α is required for bone regeneration in diabetes mellitus rats [22].

Lipid metabolism also plays a key role in regulating macrophage functions [23–25]. Metabolic differences in fatty acid biosynthesis (FAs) and fatty acid oxidation (FAO) induce polarization from M1-like to M2-like macrophages [24]. Oleic acid supplementation regulated the association between moesin and cofilin to membrane lipid rafts in the sterol regulatory element binding protein (SREBP)-1a deficient-macrophages, thereby enhancing macrophage phagocytosis [26]. Fatty acids also promote IL-4-induced M2-like macrophage activation, including butyrate, fatty acids mixtures (palmitic acid, oleic acid, and stearic acid etc.) and Omega-3 Fatty Acids [27–29]. In addition to FAs, FAO regulates macrophage polarization. FAO is needed for M2-like macrophages and promotes wound healing via IL-4 and IL-13 signaling [30,31].

Mounting evidence has demonstrated that the synthesis of amino acids is essential for multiple cellular mechanisms of immune cell activation, including T-cell differentiation [32,33], dendritic cell functions [34], and macrophage polarization [35]. Amino acid catabolism mediates macrophage activation and maintains the immunosuppressive functions of macrophages, which regulate multiple immune pathways, including mTOR signaling and NO production. Glutamine and arginine control macrophage metabolism via IL-4 stimulation and NO production, preventing the transition of M1-like macrophages to M2-like macrophages [36,37]. Increased arginine intake of macrophages promotes proinflammatory macrophages, which are resistant to *Mycobacterium tuberculosis* infection, by mediating macrophage polarization [37]. In terms of protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK)-deficient M2 macrophages,a significant decrease in the generation of mitochondrial metabolites, histidine/pyrimidine, and several crucial amino acids has been detected. In the context of hepatic ischemia–reperfusion (I/R) injury mouse model, the expression levels of apoptosis related genes (cleaved caspase 3 and cleaved caspase 9) reduced significantly in phosphoserine aminotransferase-1(PSAT1) over-expression-AAV group, which improved liver injury [38]. Moreover, PERK activation upregulates phosphoserine aminotransferase-1 and serine biosynthesis through downstream activating transcription factor 4, promoting immunosuppressive activity in M2 macrophages [18]. Thus, we review how three main metabolisms (glucose, lipid and amino acid metabolism) can be mediated in the immune response of macrophages. We also focused on how macrophage glucose metabolism, lipid metabolism and amino acid metabolism can dynamically change during tissue repair and regeneration.

1.1. Macrophages and metabolic pathways

1.1.1. Glucose metabolism

Glucose metabolism plays a vital role in the energy consumption of the body, transporting glucose to the cell membrane via glucose transporters (GLUT). The glycolysis pathway is a metabolic signaling pathway that produces two pyruvate molecules and two ATP molecules in per unit of glucose [25]. Also, glycolysis pathway provides PPP pathways with glucose-6-phosphate, which contributes to a reduction in nicotinamide adenine dinucleotide phosphate (NADP+) and the production of ribose-5-phosphate [39]. In addition, glucose produces UDP-GlcNAc via the hexosamine biosynthesis pathway (HBP) [39].

In addition, the production of lactic acid by glycolysis is a key mediator of macrophage polarization. Hypoxia and inflammation promote the production of lactic acid under anaerobic and aerobic conditions, which is transported into cells and used as a metabolic substrate to support cell function. Increased levels of lactic acid in macrophages activate hypoxia-inducible factor (HIF)-1α and HIF-2α, promoting M1-like macrophages and M2-like macrophages, respectively [40]. Additionally, high glucose/fructose promoted the secretion of pro-inflammatory cytokines and immune cells infiltration [41,42]. For instance, increased shedding of soluble CD14 resulted in synergistic effects between a high-glucose environment and oxidized low-density lipoprotein, which enhanced the proinflammatory response of human macrophages *in vitro* [41]. Decreased levels of lactic acid and glycolysis and increased levels of ATP were detected in evoked M1 macrophages after aminooxyacetic acid (AOAA) treatment. Additionally, AOAA enhanced the anti-inflammatory phenotype of macrophages, which reduced infarct size and improved cardiac function after myocardial infarction (MI) [43] (Fig. 1). Excessive uptake and breakdown of glucose increase the expression of chemokines (CXCL9, CXCL10), cytokines (IL-1β and IL-6) and PD-L1^{hi} macrophages, which can promote inflammation in coronary artery disease (CAD) [44] (Fig. 1). Moreover, in the context of high glucose treatment, highly expressed reactive oxygen species (ROS) activate stimulation of interferon genes (STING) signaling by transporting mtDNA to the cytoplasm, where it polarizes toward proinflammatory macrophages and produces proinflammatory cytokines [45] (Fig. 1). In a high-fat/fructose/cholesterol (FFC) diet mouse model, the expression level of the receptor for advanced glycation end products (RAGE) in recruited macrophages was upregulated in murine nonalcoholic steatohepatitis (NASH), whereas RAGE inhibitors inhibited macrophages recruitment and proinflammatory macrophage (Fig. 1) [46]. Activated lymphocyte-derived DNA (ALD-DNA) stimulates macrophages, and changes in glucose metabolism subsequently occur, suggesting an increase in lactic acid. However, there was a reduction in the PPP, which resulted in a decrease in the level of NADPH and an increase

in the level of ROS. There is a series of fluctuations in activated lymphocyte-derived DNA-stimulated macrophages, promoting the inflammatory response of macrophages in systemic lupus erythematosus [47] (Fig. 1).

On the other hand, glucose metabolism also contributes to M2-like macrophage polarization. Lactic acid from glycolysis in endothelial cells reversed M2-like macrophage polarization via monocarboxylate transporter-1-dependent signaling [21]. These data showed that macrophage glucose metabolism not only could affect macrophage polarization, but a metabolic paracrine signal from cells surrounding macrophages would regulate macrophage phenotype. Carbon dots, derived from citric acid and glutathione, remove highly efficient intracellular reactive oxygen species to suppress LPS-induced inflammation in macrophages [48] (Fig. 1). Ectopic expression of zinc finger E-box-binding homeobox protein-1 (ZEB-1) generates lactic acid, which induces the expression of M2-like macrophage markers by regulating protein kinase A (PKA)/cyclic-AMP response binding protein (CREB) [49].

PPP and NADPH are responsible for the removal of bacteria by macrophages and the synthesis of antioxidants, such as glutathione and thioredoxin, during respiratory bursts, resulting in limited oxidative damage to cells [50]. The PPP produces NADPH to generate ROS that can kill pathogens by activating PKM2 or inhibiting 3-phosphoinositide-dependent protein kinase-1 (PDK-1) to suppress aerobic glycolysis and LPS-induced M1 macrophage polarization [51,52] (Fig. 1). Additionally, enhancing oxidative response of PPP pathways promotes M2-like phenotype in M1 macrophages, which contributed to tissue repair [53] (Fig. 1). Thus, gene-edited macrophages can promote wound healing via STING, resulting in polarization toward M2 macrophages in macrophage-resident wounds [54,55] (Fig. 1).

The M2 phenotype of macrophages promotes angiogenesis and collagen deposition to improve wound healing [45]. Both TCA cycling and OXPHOS generate ATP in M2 macrophages, but two injury signaling pathways in M1 macrophages (citrate and succinate pathways) contribute to the accumulation of citrate, itaconate and succinate [36,56] (Fig. 1). Mitochondrial citrate export and breakdown stimulate the production of proinflammatory mediators in macrophages [57]. Citrate produces a unit of CoA via citrate carrier (SLC25A1)-ATP citrate lyase (ACLY), promoting a proinflammatory response in macrophages [58] (Fig. 1). Itaconic acid inhibited the activity of isocitratelyase in bacteria, potentially exerting an antibacterial effect [59]. In addition, itaconic acid has an anti-inflammatory effect by inhibiting succinate dehydrogenase, but the overexpression of succinic acid increases the level of IL-1β [57]. Therefore, metabolites associated with glucose metabolism could regulate macrophages to control proinflammatory or anti-inflammatory responses, which could be a potential method for tissue repair and regeneration.

1.1.2. Lipid metabolism

Lipid metabolism, such as FA and mitochondrial FAO, is a key regulator of macrophage functions [23,24]. Upregulated acetyl-CoA carboxylase (ACC), a regulator of fatty acid synthesis and oxidation, controls the immune response of proinflammatory macrophages [60] (Fig. 1). Inhibition or deficiency of ACC inhibited LPS-induced proinflammatory macrophage polarization, and ACC also resulted in the switch to glycolysis under TLR induction [60] (Fig. 1). Additionally, lipid peroxidation products with oxidation-specific epitopes regulate cellular metabolism and inflammation. FAO is a source of ATP when glucose is lacking in the mitochondrial matrix [61] (Fig. 1). FAO not only promoted an anti-inflammatory response but also stimulated inflammasome activation in proinflammatory macrophages [62]. Despite the fact that there was no direct anti-inflammatory phenotype of macrophages *in vitro*, the inhibition of FAO suppressed NLRP-3 activation, resulting in the downregulation of IL-1β expression [63] (Fig. 1). However, perhexiline treatment inhibited FAO, leading to M1 macrophage polarization through increased levels of inducible nitric oxide synthase (iNOS), NO, IL-23, IL-27, and TNF-α [64] (Fig. 1). Dioscin inhibited M1 macrophage polarization, improving DSS-induced ulcerative colitis by promoting FAO [65] (Fig. 1).

Knocking out fatty acid transport protein-1 (FATP1) increased inflammation in adipose tissue, whereas overexpressing FATP1 inhibited the immune response in proinflammatory macrophages [66] (Fig. 1). Fatty acids, which are saturated fatty acids, are internal activators of TLR4 signaling and contribute to macrophage activation [67–69] (Fig. 1).Palmitic acid stimulates Delta-like ligand 4 signaling in macrophages, resulting in senescence of vascular smooth muscle cells [69]. Oral short-chain fatty acids (SCFAs) treatment activated G protein-coupled receptor 43 and enhanced the ability of macrophage phagocytosis to clearance of *Klebsiella pneumoniae* [70] (Fig. 1). Chenodeoxycholic acid (CDCA) contributes to lipid droplets accumulation and lipid peroxidation, inhibiting M2-like macrophage polarization in acute myeloid leukemia [71]. Deoxycholic acid (DCA) increased the expression levels of iNOS, TNF-α and IL-6, which promoted M1 macrophage polarization under high-fat diet conditions [72] (Fig. 1).

Fatty acids included SFAs (Saturated fatty acids), monounsaturated fatty acids, and polyunsaturated fatty acids (PUFAs). SFAs increased the levels of proinflammatory cytokines (IL-1β and IL-6) and chemokines (MCP-1), but unsaturated fatty acids counteracted these trends [73] (Fig. 1). Macrophages treated with omega-3 and omega-6 were reprogrammed to proteins, enhancing the inflammatory response and increasing the level of anti-inflammatory proteins (pleckstrin). omega-3 and omega-6 supplementation increased the levels of lipids associated with the inflammatory response and induced the expression of succinic acid [74] (Fig. 1). Recent studies have shown that PUFAs promote macrophage reprogramming in chronic acute liver failure [75]. Lipid droplets, a source of fatty acids, play a critical role in immune cell metabolism, cellular signaling and tissue protection [23,76–79]. Peripheral lipid droplet (LD) proteins (PLINs) play a different role in macrophage polarization. PLIN2 expression contributed to inflammatory human macrophages, but PLIN1 was associated with anti-inflammatory macrophages in symptomatic stroke patients [80] (Fig. 1).These results suggested that fatty acids affect the metabolic signaling and reprogramming of macrophages in human diseases.

1.1.3. Amino acid metabolism

Glutamine participates in the regulation of metabolic biology in immune cells, such as amino acid and nucleotide synthesis, NADPH production, energy production and cell proliferation. Additionally, glutamine plays a vital role in the regulation of M1 or M2 macrophage function. Glutamine is an important source of carbon and nitrogen in metabolic reprogramming in M1 macrophages,

which contributes to production of glutamic acid and α-ketoglutarate (α-KG) [36,37] (Fig. 1). α-KG is involved in macrophage epigenetic reprogramming through the demethylation of H3K27, resulting in a switch toward the M2 phenotype [81] (Fig. 1). More interestingly, enhanced glutaminolysis and upregulated α-KG activate M2 macrophage polarization by stimulating the IL-4- sentrin-specific protease 1 (SENP1) - SIRT3 - Glutamate Dehydrogenase 1 (GLUD1) pathways [82] (Fig. 1). Another study showed that macrophage-derived glutamine activated mTOR signaling to promote satellite cell proliferation and differentiation *in vitro*, resulting in muscle regeneration after cardiotoxin muscle injury in glutamate dehydrogenase-1-knockout macrophages or the inhibition of glutamate dehydrogenase-1 [83]. Also, SIRT3 deficiency highly acetylizes succinate dehydrogenase to enhance succinate accumulation, resulting in the expression of Kruppel-like factor 4, which activates proinflammatory macrophages [84] (Fig. 1). Glutamine led to M1 macrophage polarization during *Mycobacterium tuberculosis* infection *in vitro* [85] (Fig. 1). Thus, targeting glutamine may modulate macrophage functions in several pathological contexts.

Arginine metabolic signaling controls macrophage phenotypes. The levels of inducible nitric oxide synthase are increased in the presence of LPS, TNF-α and IFN-γ, which produce NO and citrulline by releasing arginine [24]. Activation of the L transporters L-type amino acid transporter-1 (LAT1)and L-type amino acid transporter-2(LAT2) by NOS2-stemed citrulline contributed to the uptake of neutral amino acids and consequently activated the mTORC1 pathway and reprogrammed the metabolism of M1-like macrophages [37] (Fig. 1). NO and NO derivatives enhanced antimicrobial activity and prevented M2-like macrophage polarization [86] (Fig. 1). NO production has biphasic effects on several pathological processes; optimal NO production attenuates bone marrow-derived macrophage (BMDM) damage induced by LPS or IFN-γ generated from NO [87], but increased levels of NO inhibit the proinflammatory response of macrophages by reducing the levels of COX-2 and inducible nitric oxide synthase, which contributes to balancing the immune response during tissue injury [88]. During wound healing, this healing process promoted M2 macrophage polarization by increasing the expression of iNOS and Arginase 1 (Arg1) in periodontal disease [89] (Fig. 1). Additionally, a metabolic change from arginine and ornithine derived from apoptotic cells to putrescine has been detected after injury, which enhances continual macrophage efferocytosis via Arg1 and ornithine decarboxylase (ODC) [90]. Arg1 is expressed in the anti-inflammatory phenotype of M2-like macrophages, supporting the production of ornithine and urea by arginine [25]. Ornithine is translated into polyamines (putrescine, spermidine, and spermine), which promote macrophage proliferation and collagen production in tissue repair [36,50]. Also, M2-like macrophage polarization promoted Arg1 expression, thereby promoting axonal regeneration and structural and functional recovery of the injured spinal cord [91].

Indoleamine 2,3-dioxygenase influences the breakdown of tryptophan, and high levels of indoleamine 2,3-dioxygenase in macrophages deplete extracellular tryptophan, affecting the proliferation and function of T cells [24,92,93]. A lack of amino acids activated general control nonderepessible-2 to regulate cell metabolism to alleviate damage to cells. General control of nondereptic-2 promoted the coordination of injured red blood cells to the macrophage-resident liver to recover iron recycling, which controlled iron metabolism in red blood cells [94]. In addition, another study revealed that leucine promoted M2 macrophage polarization via the mTORC1/LXRα/Arg1 axis pathway, alleviating cytokine storm syndrome in LPS-treated mice [95] (Fig. 1).

1.2. The effects of macrophage immune metabolism on tissue repair and regeneration

1.2.1. Heart

Cardiac resident macrophages (cMacs) play an important role in maintaining myocardial tissue homeostasis [96]. Many macrophages have been found in myocardial tissue and coordinate with cardiomyocytes to regulate heart function [97]. cMacs are divided into two types of macrophages: C-C motif chemokine receptor-2 (CCR2)-cMacs and CCR2+cMacs. CCR2-cMacs are derived from the embryo and self-renew, which contributes to inhibiting the proinflammatory response and monocyte recruitment, and mainly participate in tissue repair, while CCR2+cMacs, which have functions similar to those of M1-type macrophages, recruit and proliferate monocytes to promote the proinflammatory response [98–102].

Enhanced glycolysis promoted signal transducer and activator of transcription-3 (STAT3) phosphorylation via PKM2 dimerization to enhance the proinflammatory response in CAD patients, but a STAT3 inhibitor (Stattic) decreased the levels of *IL-1β* and *IL-6* [103] (Table 1). A recent study in a MI mouse model suggested that there was an increase in glucose oxidation in macrophages of CCR-2 knockout mice, but glycolysis decreased significantly [104] (Table 1). Further data also showed that the expression levels of Ldha and PKM2 were lower in macrophage-CCR2 knockout mice surrounding infarcted areas [104] (Table 1). Thus, these data indicated that changes in glycolytic metabolic reprogramming occurred in monocyte-derived macrophages rather than in cardiac-resident macrophages. Moreover, dichloroacetate treatment significantly reduced pyruvate dehydrogenase phosphorylation of macrophages in the intact remote zone following MI, but there was no change of macrophage phenotype or metabolism in infarct zones [104] (Table 1). Therefore, these data illustrated that cardiac repair or regeneration is associated with the metabolism of different macrophages at different injury sites. Additionally, further studies should evaluate the effects of pyruvate dehydrogenase phosphorylation inhibitors on cardiac repair and regeneration.

cMacs mainly consumed glucose to produce energy that compensated for the reduction in ATP and OXPHOS, resulting in an increase in the survival rate after ischemia in mice [105](Table 1). However, a study involving myeloid-specific deletion (mKO) of the mitochondrial complex I protein in a mouse model suggested that there was impaired efferocytosis of mKO macrophages, which contributed to reducing the production of anti-inflammatory cytokines and tissue repair genes in macrophages by increasing the levels of glycolysis and mitochondrial ROS (mtROS), which promoted cardiac injury through the inhibition of myofibroblast proliferation and activation in infarcted areas [106] (Table 1). These data showed that the mitochondrial complex I protein is a key mediator of macrophage metabolism to maintain or promote cardiac repair after injury. Furthermore, upregulated glucose uptake was also detected in macrophages from patients with CAD. Further study suggested that histone lactylation increased the expression levels of

Table 1
The effects of Macrophage metabolism in cardiac repair and regeneration.

Metabolic types	Macrophages phenotype	Metabolites	Mechanisms	Experimental models	References
Glucose metabolism	Coronary artery disease (CAD) macrophages	Increased glucose uptake	Enhanced Glycolysis promote STAT3 phosphorylation via PKM2 dimerization and STAT3 inhibitor (Stattic) inhibit IL-1β and IL-6 expression	*In vitro*	[103]
	LV infarct macrophages	Dichloroacetate	No change in macrophages glycolysis or OXPHOS, but reduced pyruvate dehydrogenase phosphorylation	*In vitro*	[104]
	CCR2-KO- cardiac macrophages	Decreased glycolysis and increased glucose oxidation	Decreased in Ldha and Pkm2 expression	Showed glycolytic metabolic reprogramming in monocyte-derived macrophages rather than resident macrophages	[104]
	Cardiac macrophages	An increased uptake of glucose	Produced energy to compensate for ATP and OXPHOS defects	Defectively generated ATP and unstable metabolism after depleting cMacs	[105]
	BMDMs	Mitochondrial complex I protein knockout	Increasing levels of glycolysis and mitochondrial ROS (mtROS)	Promoted cardiac injury	[106]
	Monocytes derived macrophages	Sodium lactate	Histone lactylation increased the expression levels of reparative genes (Lrg1, Vegf-a, and IL-10) and H3K18la	Reduced cardiac fibrosis and then improved cardiac repair after MI	[107]
	Monocyte/macrophage	2-DG	Reduced macrophages glycolysis (lactate signal) and inflammatory response (IL-1β) by using 2-DG inhibitor	Improved left ventricular function in rats after MI	[108]
	BMDMs	Glucose-free media or 2-DG	Inhibited TLR4-stimulated MerTK cleavage because of blocking upregulated HIF-1α–mediated glycolysis	Improved cardiac repair in mice after MI.	[109]
	cMac	Dimethyl fumarate(DMF)	Blocked HIF-1α activation Enhanced macrophage OXPHOS but did not affect glycolysis	Promoted collagen deposition and angiogenesis after MI	[110]
	Ly6c2+ monocytes/ macrophages	HIF1A inhibitor	Inhibited an increase of glycolysis in macrophage and reduced $CD4^+$ and $CD8^+$ T cells infiltration	Reduced immune rejection after heart transplantation	[112]
Lipids metabolism	Neonatal macrophages	Upregulated the expression level of PPAR-δ	Elevated fatty acid catabolism	*In vitro*	[114]
	CD68+macrophages	Eicosapentaenoic acid (EPA)	Macrophage M2-like polarization	Enhanced anti-fibrotic effects by M2 polarization	[115]
	Cardiac macrophages	Propionate	Macrophage M2-like polarization and reduced the production of pro-inflammatory cytokines	Reduced cardiac fibrosis and improve cardiac function by inhibiting JNK/P38/NF-κB signaling pathways	[116]
	$CD68^+$ macrophages	Resolvin E1 (RvE1)	M2-type macrophage polarization and inhibited cardiomyocyte apoptosis	Cardiac injury after sepsis-induced cardiomyopathy	[117]
Animo acid metabolism	Cardiac macrophages from zebrafish	Clodronate liposomes	Destroyed ROS homeostasis and energy metabolism in macrophage	Inhibited cardiac repair after MI in zebrafish	[121]
	Cardiac macrophages	Resolvin D1 (RvD1)	Macrophages clearance and shifted towards M2-type macrophages polarization	Reduced collagen content after cardiac injury	[122]

Abbreviations.
BMDMs = Bone marrow–derived macrophages; CCR2 = C-C motif chemokine receptor 2 Gene; H3K18 = histone H3 lysine 18.
HIF = hypoxia-inducible factor.
JNK = c-Jun N-terminal kinase; Ldha = lactate dehydrogenase a.
NF-κB = nuclear factor kappa-B.
OXPHOS = oxidative phosphorylation.
PKM2 = pyruvate kinase M2.
PPAR = peroxisome proliferators-activated receptor.
ROS = reactive oxygen species.
TLR4 = toll-like receptor 4; STAT3 = Signal transducer and activator of transcription 3; 2-DG = 2-deoxyglucose.

reparative genes (*Lrg1, Vegf-a*, and *IL-10*) in monocyte-derived macrophages post-MI *in vitro* [107]. *In vivo* data also illustrated that sodium lactate treatment reduced mouse cardiac fibrosis after MI by increasing the expression of reparative genes and H3K18la in macrophages [107] (Table 1). However, 2-deoxyglucose inhibitors reduce monocyte/macrophage glycolysis (lactate signal) and the inflammatory response (IL-1β) in treated rats after MI injury, thus improving left ventricular function [108] (Table 1). These studies showed that there were different roles for macrophage glycolysis in different models, and subsequent studies should investigate the regulation of glycolysis signaling in different animal models of cardiovascular diseases in cardiac repair and regeneration.

In addition, the findings in bone marrow–derived macrophages (BMDMs) treated with glucose-free media or 2-deoxy-D-glucose (2-DG) suggested that HIF-1α activation increased TLR4-stimulated macrophage glycolysis, but glucose-free media or 2-DG inhibited TLR4-stimulated Mer tyrosine kinase (MerTK) cleavage by blocking upregulated HIF-1α–mediated glycolysis, which improved cardiac repair after MI [109](Table 1). Dimethyl fumarate blocked HIF-1α activation in cMacs and then strengthened cMacs mitochondrial respiration to polarize toward the anti-inflammatory type of macrophages, which contributed to collagen deposition and angiogenesis after MI [110] (Table 1). Moreover, inhibition of HIF-1α and glycolysis decreased the level of the phagocyte receptor MerTK, which is needed for cardiac repair [111]. On the other hand, increased glucose metabolism in macrophages was observed in heart transplantation patients with acute rejection, but HIF-1α inhibitors reduced immune cell infiltration and glycolysis in macrophages, which inhibited proinflammatory macrophages [112] (Table 1). Thus, the regulation of macrophage glycolysis by targeting HIF-1α and MerTK could be a potential therapy for cardiac repair after injury.

Disrupted fatty acid oxidation contributes to hypoxia resistance and promotes cardiomyocyte proliferation, resulting in cardiac regeneration in CPT1b-mutant cardiomyocytes after IR injury [113]. In mammalian neonatal macrophages, fatty acids upregulate the expression of PPAR-δ, which stimulates endothelial progenitor cells and induces cardiovascular myogenesis via paracrine factors [114] (Table 1). Moreover, many fatty acids play a vital role in cardiac repair after injury by regulating macrophage polarization. For instance, eicosapentaenoic acid is a PUFA that promotes M2-type macrophage polarization and increases IL-10 expression, alleviating cardiac fibrosis in hypertension [115] (Table 1). Propionate (a SCFA) promoted macrophage M2-like polarization and reduced the production of proinflammatory cytokines in the infarct zone after MI, which contributed to reducing cardiac fibrosis and improving cardiac function by inhibiting the JNK/P38/nuclear factor kappa-B (NF-κB) signaling pathway after MI [116] (Table 1). Resolvin E1, another PUFA metabolite, regulates M2-type macrophage polarization and inhibits cardiomyocyte apoptosis, which improves cardiac injury after sepsis-induced cardiomyopathy [117] (Table 1). These studies demonstrated that fatty acids could promote macrophage polarization toward the M2 phenotype and an anti-inflammatory response during the process of cardiac injury, but there are fewer concerns about cardiac regeneration. Therefore, further studies should focus on cardiac regeneration by regulating lipid metabolism in cardiac resident macrophages.

Elevated glutamine levels are found in zebrafish and neonatal mouse hearts and are required for heart regeneration [118]. Solute carrier family 1 member 5 gene (SLC1A5) transporter proteins deliver glutamine into macrophages, and glutamine consequently supports macrophage polarization toward the M2 type [119]. Also, glutamine breakdown provided OXPHOS with substrates, increasing the effectiveness of endocytosis. Glutamine, which generates glutamic acid, can also be converted into ornithine, arginine or polyamines. During the process of apoptotic cell degradation, macrophages consume a large amount of arginine and ornithine, which are diverted into putrescine by Arg1 and ornithine decarboxylase (ODC), facilitating apoptotic cell engulfment [111,120]. On the other hand, clodronate liposome treatment delayed the recruitment of macrophages, resulting in prolonged inflammatory gene expression and energy metabolism dysfunction after cardiac injury in zebrafish [121] (Table 1). Resolvin D1 also enhanced macrophage clearance and shifted toward M2-type macrophage polarization without changing the proinflammatory response on day 5 after MI, which contributed to reduced collagen content after cardiac injury [122] (Table 1). However, there are few studies on glutamine-mediated cardiac repair and regeneration after injury.

1.2.2. Brain

Brain macrophages include microglia, border-associated macrophages (BAMs) in the choroid plexus, meningeal and perivascular spaces and monocyte-derived macrophages [123,124]. There are three types of macrophages in BAMs: choroid plexus macrophages (cpMΦs), meningeal MΦs (mMΦs) and perivascular space MΦs (pvMΦs) [125,126]. In the context of ischaemic brain, BAM depletion of rodent brain, which was depleted by CSF1 inhibitors, reduced vascular inflammation in that csf1 expression was required for BAMs self-proliferation [125,127]. pvMΦ inhibited proteins (>10 kDa), promoting blood–brain barrier (BBB) function [123]. A study in zebrafish showed that pvMΦ can repair the injured BBB [126,128]. During lymphocytic pigment meningitis virus infection, infected mMΦ suppressed viral infection of meninges by regulating the interferon response [123]. On the other hand, mMΦ improved learning and memory [123,129]. Monocyte-derived macrophages alleviate brain edema, BBB injury, neuronal apoptosis and cerebral ischemic infarction [123].

In co-culture with microglia after LPS and ATP stimulation, dimethyl itaconate inhibited the production of NLRP3, IL-1β, lactate dehydrogenase (LDH) and gasdermin D (GSDMD) in microglia via Nrf-2/HO-1 signaling in brain nerves [130] (Table 2). Additionally, sodium butyrate reduced the production of IL-1β in microglia following LPS stimulation, which had a protective effect on a brain ischemia model and a spinal cord injury model [131](Table 2). In a five-gene familial Alzheimer's disease mutation (5XFAD) mouse model, H4K12la was increased in microglia in the surrounding Aβ plaques, enhancing glycolytic activity by regulating the promoters of genes involved in glycolysis [132] (Table 2). Further data showed that glycolysis/H4K12la/PKM2 alleviated microglial dysfunction in Alzheimer's disease [132] (Table 2). Rosiglitazone, a diabetes treatment drug, promoted OXPHOS to reduce the proinflammatory response and transferred phagocytosis-enhanced microglia to myelination-associated microglia, facilitating remyelination *in vivo* [131] (Table 2). A study in a cerebral ischemia–reperfusion(I/R) injury of hyperglycemic rat model suggested that blood glucose contributed to M1 microglial polarization but an decrease of microglia in the infarct zone after injury [133] (Table 2). Thus, the

Table 2
The effects of Macrophage metabolism in brain repair and regeneration.

Metabolic types	Macrophages phenotype	Metabolites	Mechanisms	Experimental model	References
Glucose metabolism	BV2 microglia cells	Dimethyl itaconate	Reduced NLRP3, pro-IL-1β and cleaved IL-1β expression levels, but upregulated these gene expression in Nrf-2 knockdown, which had a protective effect of the Nrf-2/HO-1 pathway against inflammation	*In vitro*	[130]
	Microglia	Sodium butyrate	Reduced the production of IL-1β with LPS stimulation in microglia	*In vitro*	[131]
	Microglia	Rosiglitazone	Increased fatty acid and "OXPHOS/FAO'' genes, decreased lipid droplets accumulation and pro-inflammatory cytokine release as well as promoted the production of pro-remyelination factors	*In vitro*	[131]
	5X FAD microglia	Glycolysis/H4K12la/PKM2	Enhanced glycolysis/H4K12la/PKM2, aggravating microglial dysfunction	Strengthen cognitive functions such as learning and memory	[132]
	Microglia	Streptozotocin	Increased the polarization of M1 microglia after cerebral I/R	Increased infarct volume after cerebral I/R	[133]
Lipids metabolism	Microglia RAW 264.7 BMDMs BV2 microglial cell	3-sulfogalactosyl diacylglycerols (SGDG)	Decreased the production of IL-6 and TNF-α with LPS-induction	*In vitro*	[135]
	Microglia	Enhanced cholesterol efflux (GW3965)	Inhibited the expression of pro-inflammatory cytokines, but increased the production of pro-regenerative factors	*In vitro*	[134]
	Microglia	CPT-1a inhibitor(Etomoxir)	Suppressed FAO and OXPHOS, aggravating inflammation	*In vitro*	[134]
	mouse BMDMs mouse microglia human MDMs	myelin	promoted an inflammatory phagocyte phenotype	*In vitro*	[139]
	Microglia	Enhanced TREM2 with monoclonal antibody 4D9	Prevented TREM2 cleavage induced by myelin-debris phagocytosis, and promoted cholesterol efflux genes expression after myelin uptake	*In vitro*	[141]
	Hexokinase 2 (HK2)-KO microglia	HK2 knockout	Promoted microglia phagocytosis, and also increased ATP production by downregulating G-6-P,F-6-P and NADPH in microglia to remove Aβ.	*In vitro*	[143]
	TREM2- KO-microglia	Rosiglitazone	Shifted glycolysis toward OXPHOS/FAO, enhancing cholesterol metabolism	Rosiglitazone treatment facilitated remyelination *in vivo*, which was independent of Trem2	[134]
	Microglia	Enhanced TREM2 with monoclonal antibody 4D9	Reduced foam cells and enhanced remyelination	Regulated TGFβ/TREM2 signalling to improve remyelination after demyelinating injury	[141]
Amino acid metabolism	Microglia	Arginine and ornithine	Transferred apoptotic cell-derived arginine and ornithine into putrescine, contributing to enhance efferocytosis via Rac1 activation	*In vitro*	[89]
	VDR-KO microglia	Vitamin D receptor (VDR) knockout	Produced pro-inflammatory cytokines (TNF-αand IFN-γ), enhanced the releasing of CXCL10 and infiltrated peripheral T lymphocytes	Destroyed the blood brain barrier	[144]

Abbreviations.
Aβ = amyloid β-protein; BMDMs = mouse bone marrow–derived macrophages; CPT-1a = Carnitine palmitoyltransferase-1a; FAD = flavin adenine dinucleotide.
FAO = fatty acid oxidation.
H4K12 = histone H4 lysine 12.
LPS = Lipopolysaccharide.
MDMs = monocyte-derived macrophages; NLRP3 = NOD-like receptor thermal protein domain associated protein 3.
OXPHOS = oxidative phosphorylation.
PKM2 = pyruvate kinase M2.
Trem2 = Triggering receptor expressed on myeloid cells 2.

glucose metabolism of brain-resident macrophages can regulate brain repair and regeneration, but there are few studies in this field, especially regarding regenerative capacity in the brain after injury.

Enhanced cholesterol efflux could inhibit the expression of proinflammatory cytokines by inducing myelin debris and increasing the expression of proregenerative factors, but etomoxir suppressed the expression of FAO and OXPHOS, which aggravated inflammation in microglia [134] (Table 2). The levels of 3-sulfogalactosyl diacylglycerols, which are lipids of the central nervous system, decrease with age and are associated with the formation of the myelin sheath. 3-Sulfogalactosyl diacylglycerols regulate NF-κB signaling pathways to inhibit LPS-induced gene expression and proinflammatory cytokine production in microglia [135] (Table 2). PUFAs also participate in interactions between lipid metabolism and neuroinflammation after injury [136]. A study in a spinal cord injury model suggested that ω-3 PUFAs inhibited NLRP3 inflammasome activation, reactive microgliosis, and ongoing demyelination, which enhanced the anti-inflammatory response [137]. Additionally, ω-3 PUFAs suppressed caspase-1 cleavage and IL-1β secretion, alleviating inflammation after traumatic brain injury [138]. However, there have been few investigations of ω-3 PUFA-mediated effects on microglia in brain repair and regeneration.

Additionally, myelin treatment promoted an inflammatory phagocyte phenotype in microglia and macrophages *in vitro* [139] (Table 2). Triggering receptor expression on myeloid cells-2 affects cholesterol, myelin and phospholipid metabolism in microglia, which promotes a shift toward disease-associated microglia [140]. Increased triggering receptor expression on myeloid cells-2 promoted lipid clearance in phagocytes after injury, resulting in remyelination after injury [141] (Table 2). The impaired clearance of amyloid-β (Aβ) is recognized as the main cause of Alzheimer's disease [142]. Moreover, hexokinase 2 knockout promoted microglial phagocytosis and increased ATP production in microglia to remove Aβ, which alleviated cognitive impairment in male Alzheimer's disease mice [143] (Table 2). Lipid metabolism can regulate microglia to improve tissue repair and regeneration in the brain.

During efferocytosis, the Arg1-ornithine decarboxylase-putrescine pathway enhances continual efferocytosis in macrophages *in vivo,* which promotes the clearance of plaques in atherosclerosis [90] (Table 2). A study in a mouse ischemic stroke model demonstrated that there was an increase in the expression level of vitamin D receptor in microglia surrounding infarction areas [144]. Vitamin D receptor knockout results in a proinflammatory phenotype in microglia, which produces proinflammatory cytokines (TNF-α and IFN-γ) and consequently enhances the release of CXCL10 and destroys the blood–brain barrier [144] (Table 2). Additionally, there was an increase in the number of infiltrated peripheral T lymphocytes [144] (Table 2). Moreover, Arg1 reduced the expression level of Ragulator-Rag complexes, resulting in impaired intracellular degradation of microglia [145]. Thus, these metabolites could be beneficial for tissue repair and regeneration in the brain after injury.

1.2.3. Lung

Lung-resident macrophages include alveolar macrophages (AMs) and interstitial macrophages [146,147]. AMs play a vital role in the immune response of alveoli and airways, but interstitial macrophages have similar functions in the pulmonary vasculature and maintain lung tissue homeostasis, metabolism and repair [148–150]. Glucose metabolism plays a key central role in lung injury diseases and lung tissue homeostasis. In a high-glucose environment, PM2.5 induces the activation of the NLRP3 inflammasome and NF-κB nuclear translocation, promoting the production of IL-1β [151] (Table 3). Low glucose and β-hydroxybutyric acid enhanced the inflammatory response of yak alveolar macrophages via GPR109A/NF-κB signaling [152] (Table 3). These data showed that glucose could enhance the inflammatory response of macrophages, so glucose metabolism could be harmful for repairing lung tissues after injury. However, treatment with FG-4592, a HIF prolyl hydroxylase inhibitor, inhibited TR-AM death and alleviated acute lung injury in mice [153] (Table 3). Additionally, N-phenethyl-5-phenylpicolinamide, another HIF-1α inhibitor, decreased the expression levels of HIF-1a, glycolysis genes (GLUT1 and hexokinase-2), ASIC1a, and proinflammatory genes (IL-1β and IL-6), which alleviated the inflammatory response after acute lung injury [154] (Table 3). α-KG inhibited the expression of M1 marker genes (IL-1β, IL-6, and TNF-α) but increased the expression of M2 marker genes (Arg1), promoting M2 macrophage polarization via the PPAR-γ/mTORC1/p70S6K pathway. Consequently, α-KG treatment improved acute lung injury after LPS induction in a mouse model [155] (Table 3). Thus, these studies suggested that targeting glycolysis in lung macrophages could improve lung injury and that the regulation of macrophage glycolysis was beneficial for repairing lung tissue after injury.

In the context of *in vivo* studies, a study in an LPS-induced endothelial injury model illustrated that the secretion of Rspondin3 from lung endothelial cells stimulated β-catenin signaling, enhancing mitochondrial respiration by utilizing glutaminolysis (Table 3). In turn, the production of α-KG promoted DNA hydroxymethylation, which inhibited inflammation and subsequently improved injured tissue in the lung [156] (Table 3). Thus, metabolites from other cells could also regulate tissue-resident macrophages to control tissue repair and regeneration. On the other hand, AM treatment with 2-DG reduced the expression level of GLUT1 and consequently inhibited HIF-1α expression [157] (Table 3). With silica induction, the expression of IL-1β was decreased, alleviating lung fibrosis and injury [157] (Table 3). Additionally, 2-DG reduced the production of proinflammatory genes (TNF-α, pro-IL-1β, IL-1β, pro-IL-18, NLRP3 and pro-caspase-1) by inhibiting glycolysis in LPS-induced macrophages, which improved acute lung injury in a mouse model [158,159] (Table 3). However, tissue-resident alveolar macrophages (TR-AMs) are dependent on mitochondrial function rather than glycolysis, and hypoxia maintains the production of HIF-1α in TR-AMs, promoting glycolysis [153].

On the other hand, FA oxidation has been regarded as a source of energy in lung macrophages, which supports lung remodeling [160]. For instance, upregulated β-oxidation in lung macrophages increases $Ca2+$ transport by the mitochondrial calcium uniporter (MCU) and PGC-1α activation, which induced tissue fibrosis in the lung [161] (Table 3). Additionally, there was an increase in the expression of MCU in the lung macrophages of both patients with idiopathic pulmonary fibrosis (IPF) and in a bleomycin-induced mouse lung fibrosis model. MCU transports $Ca +$ into the mitochondrial matrix and subsequently activates PGC-1α, which is related to lipid metabolism in mitochondria [161] (Table 3). In high-fat diabetic mice and LPS-induced acute lung injury models, arachidonic acid suppressed the activation of MD2/Toll-like receptor 4 signaling to inhibit the inflammatory response by binding to

Table 3
The effects of Macrophage metabolism in lung repair and regeneration.

Metabolic types	Macrophages phenotype	Metabolites	Mechanisms	Experimental model	References
Glucose metabolism	MH-S	Glucose	Enhanced -PM2.5-induced production of IL-1β and NF-κB nuclear translocation	*In vitro*	[151]
	Yak alveolar macrophages	Low Glucose β-hydroxybutyrate (BHB)	Enhanced pro-inflammatory response by regulating GPR109A/NF-κB signaling pathway	*In vitro*	[152]
	Tissue-resident alveolar macrophages (TR-AMs)	HIF prolyl hydroxylases inhibitor(FG-4592)	Increased glycolytic protein expression and decreased TR-AMs death	*In vitro*	[153]
	RAW264.7 macrophages and primary alveolar macrophages	HIF-1α	Decreased the expression levels of HIF-1a, glycolysis genes(GLUT1 and HK2), ASIC1a, and pro-inflammatory genes (IL-1β, and IL-6)pathway.	*In vitro*	[154]
	MH-S	α-KG	Inhibited M1 marker gene expression (IL-1b, IL-6, and TNF-a) and strengthen M2 marker gene expression (Arg1) by regulating PPAR-γ/mTORC1/p70S6K pathway	*In vitro*	[155]
	BMDMs	Rspondin3	Increased mitochondrial respiration by glutaminolysis and shifted towards an anti-inflammatory phenotype	*In vitro*	[156]
	Mouse alveolar macrophages	2-deoxy-D-glucose	Inhibited glycolysis and reduced the expression levels of GLUT1, HIF-1α and IL-1β	Alleviated in lung fibrosis and injury with silica induction	[157]
	Primary murine macrophages	2-deoxyglucose (2-DG)	Inhibited glycolysis and reduced the expression levels of pro-inflammatory factors (TNF-α, pro-IL-1β, IL-1β, pro-IL-18, NLRP3 and pro-caspase-1) in the following LPS stimulation	Alleviated lipopolysaccharide-induced acute lung injury in a mouse model	[159]
	primary lung interstitial macrophages	Rspondin3	Increased mitochondrial respiration by glutaminolysis and shifted towards an anti-inflammatory phenotype of lung interstitial macrophages transition by activing α-ketoglutarate-TET2 pathway	Promoted resolution of inflammation and tissue repair during inflammatory injury *in vivo*	[152]
Lipids metabolism	Lung -resident macrophages	Upregulated β-oxidation	Increased the ability to Ca + transport of MCU and PGC-1α activation	*In vitro*	[161]
	primary macrophages	Arachidonic acid (AA)	Inhibited inflammatory cell infiltration and cytokine expression (TNF-α and IL-6) via MD2/toll-like receptor 4 signaling	*In vitro*	[162]
	Isolated alveolar macrophages	NO_2-FA	Increased MFG-E8 expression, collagen uptake and degradation	*In vitro*	[163]
	MH-S and IPF lung macrophages	Carnitine palmitoyltransferase 1a (Cpt1a)	Inhibited interaction between Cpt1a and Bcl-2 by Bcl-2 inhibition to attenuate apoptosis, preventing fibrosis after bleomycin induced lung injury	*In vitro*	[164]
	MH-S from MCU ±mice.	MCU deficiency	Reduced macrophages profibrotic polarization	Inhibited pulmonary fibrosis *in vivo*	[161]
	Lung macrophages	fatty acid oxidation	Increased the expression levels of PGC-1α and CPT1A	Promoted fibrotic repair after injury *in vivo*	[165]
	Interstitial macrophage(IMs)	NO2-FA	Decreased the number of interstitial macrophages	Inhibited activation of pro-inflammatory response *In vivo*	[167]
Amino acid metabolism	RAW264.7 cells	FABP5S-glutathionylation	Promoted PPAR-β/δ target genes and suppressed the LPS-induced inflammation in macrophages.	*In vitro*	[169]

Abbreviations.
ASIC1a = acid-sensing ion channel 1a.
Bcl-2 = B-cell lymphoma-2.
CPT = Carnitine palmitoyl transferase.
GLUT1 = glucose transporter 1.
HIF = hypoxia-inducible factor.
LPS = Lipopolysaccharide.
MCU = mitochondrial calcium uniporter.
mTORC1 = mechanistic target of rapamycin complex 1; MFG-E8 = milk fat globule-epidermal growth factor 8.
NLRP3 = NOD-like receptor thermal protein domain associated protein 3.
NF-κB = nuclear factor kappa-B.
PGC-1α = Peroxisome proliferator-activated receptor γ coactivator 1-alpha.
PPAR = peroxisome proliferators-activated receptor.
α-KG = α-ketoglutarate.

myeloid differentiation factor 2 (MD2), which protected lung tissues [162] (Table 3). Thus, these metabolic signals can affect the macrophage inflammatory response to regulate lung repair, but few studies on lung regeneration after injury exist.

Lipid metabolism plays a critical role in lung repair and regeneration after injury. NFAs increase the expression of collagen-targeting factor (milk fat globule-EGF factor 8 [MFG-E8]), which promotes collagen intake and degradation in alveolar macrophages and dedifferentiated myofibroblasts to improve pulmonary fibrosis [163] (Table 3). CPT1 limited the rate-limiting step of FAO. CPT1 interacted with Bcl-2 by binding to the BH3 structure of B-cell lymphoma-2 (Bcl-2) to alleviate cell apoptosis, which was dependent on the activity of CPT1A. Additionally, CPT1A and Bcl-2 are directly correlated in patients with idiopathic pulmonary fibrosis (IPF), but a lack binding between CPT1A and Bcl-2 induces cell apoptosis. For instance, a lack of Bcl-2 in macrophages inhibited lung fibrosis in mice [164] (Table 3). Moreover, upregulated MCU contributed to an increase in the expression levels of PGC-1α and CPT1A, resulting in an increase in fatty acid oxidation to promote fibrotic repair after injury [165,166] (Table 3). Thus, FAs and CPT1A play a protective role in the progression of lung fibrosis after injury and could be potential targets for lung repair and regeneration after injury. Unsaturated fatty acids react with NO and nitrite to form nitro-fatty acids (OA-NO2), which protect the population of alveolar macrophages [167,168] (Table 3). However, this phenotype of macrophages was not detected in lung tissues after acute injury but maintained a non-inflammatory response in the lung [167,168] (Table 3). Additionally, OA-NO2 decreased the expression of macrophage markers (Ly6C and CD206), which inhibited the activation of the proinflammatory response [167] (Table 3). These data suggested that lipid metabolism-regulated macrophages function to promote lung fibrosis after injury.

There are few studies on the effects of amino acid metabolism on macrophages in lung repair and regeneration compared with the effects of the other two metabolic pathways. Oxidative stress-induced FABP5 S-glutathionylation inhibited macrophage inflammation by inducing LPS, which suppressed acute lung injury [169] (Table 3). Additionally, connective tissue growth factor, which promotes lung repair and regeneration, is associated with the metabolism of multiple amino acids, such as histidine metabolism, tyrosine metabolism, arginine biosynthesis and arginine and proline metabolism, after acute lung injury [170]. However, there is no evidence on how regulation of specific metabolites influences lung repair or regeneration.

2. Conclusion and perspectives

Macrophages are required for tissue repair and regeneration, especially vascular repair and regeneration [2,171]. After injury, a great deal of tissue or immune cells die in the surrounding injured areas. On the other hand, many circulating innate immune cells, including infiltrated macrophages and neutrophils, are recruited to the infarct zone [172,173]. Infiltrated innate immune cells interact with dead, apoptotic tissue cells surrounding the infarct zone, leading to the removal of dead cells and necrotic debris, a proinflammatory response, and tissue repair or regeneration after injury [174].

It is well known that macrophage phenotypes are associated with metabolic pathways, such as glucose metabolism, lipid metabolism and amino acid metabolism pathways. The regulation of glucose metabolism in macrophages regulates tissue repair and regeneration via proinflammatory or anti-inflammatory responses, which are associated with macrophage polarization [175,176]. However, the mechanisms of macrophage immune metabolism in tissue repair and regeneration are still unknown. Cardiac repair or regeneration could be associated with the metabolism of different macrophages at different injury sites and in different animal models. The effects of pyruvate dehydrogenase phosphorylation inhibitors, which target HIF-1α and MerTK, fatty acids and glutamine on cardiac repair and regeneration should be further investigated, especially for cardiac regeneration after injury. Additionally, ketone metabolism could be enhanced in heart failure because there was a reduction of glucose oxidation [177]. Oral ketone treatment alleviated cardiac inflammation in MI porcine models [178].More interestingly, ketone metabolism promoted M2-macrophage polarization by STAT6 pathway, reducing inflammatory response in colitis [179]. However, there were little studies to evaluate the effect of macrophage ketone metabolism on tissue repair and regeneration after injury.

In the context of brain injury models, glucose metabolism and lipid metabolism in macrophages have rarely been studied in brain repair and regeneration, although multiple studies have focused on how to alleviate inflammation or inhibit inflammatory markers after injury. There was a similar trend in amino acid metabolism in macrophages during tissue repair and regeneration. Additionally, macrophage glucose metabolism and lipid metabolism are beneficial for lung tissue repair and regeneration, but few studies have investigated the effects of amino acid metabolism on macrophages in lung repair and regeneration. On the other hand, pharmacological interventions, including 2-DG inhibitors, HDAC inhibitors, rosiglitazone, SGDGs, monoclonal antibodies against 4D9, HK2 inhibitors, FG-4592, and α-KG, also contribute to tissue repair and regeneration by targeting macrophage immunometabolism. Thus, the basic mechanism of targeting macrophage metabolism should be further investigated to develop metabolic drugs for tissue repair and regeneration after injury. Clearly, focusing on macrophage immunometabolism in tissue repair and regeneration may provide potential therapeutic targets for tissue repair and regeneration.

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Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Hongbo Ma: Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Limei Gao:** Validation, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Rong Chang:** Validation, Resources, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Lihong Zhai:** Visualization, Validation, Software, Resources, Methodology, Investigation. **Yanli Zhao:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

ACC	acetyl-CoA carboxylase
AMs	alveolar macrophages
Arg1	arginase 1
BAMs	border-associated macrophages
Bcl-2	B-cell lymphoma-2
CAD	coronary artery disease
CCR2	C-C motif chemokine receptor 2
CD	cluster of differentiation
cMac	Cardiac resident macrophages
CPT	Carnitine palmitoyl transferase
CoA	coenzyme A
FAO	fatty acid oxidation
FAs	fatty acid biosynthesis
GLUT	glucose transporter
HIF	Hypoxia-inducible factor
iNOS	inducible nitric oxide sythase
LPS	lipopolysaccharide
MerTK	Mer Tyrosine Kinase
MCU	mitochondrial calcium uniporter
MI	Myocardial infarction
NF-κB	nuclear factor kappa-B
NLRs	NOD-like receptors
OXPHOS	oxidative phosphorylation
PPP	pentose phosphate pathway
PPAR	peroxisome proliferator-activated receptor-γ
PKM2	pyruvate kinase M2
PUFAs	Polyunsaturated fatty acids
PGC-1α	Peroxisome proliferator-activated receptor γ coactivator 1-alpha
ROS	reactive oxygen species
SCFAs	Short-chain fatty acids
SFAs	saturated fatty acids
TCA	tricarboxylic acid
TLRs	toll-like receptors
TR-Ams	tissue-resident alveolar macrophages
α-KG	α-ketoglutarate
2-DG	2-Deoxy-D-glucose

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