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Mini-review

# Metabolic reprogramming of macrophages during infections and cancer

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ABSTRACT

In response to different microenvironmental stimuli, macrophages are polarized into two populations, M1 macrophages which are classically activated by interferon (IFN)-γ with lipopolysaccharides (LPSs) and M2 macrophages which are alternatively activated by interleukin-4 (IL-4), to perform specific roles in innate immune responses. Accordingly, macrophages occupy distinct metabolic profiles, regulated by orchestrated factors and signaling pathways, including the PI3K-AKT, HIF, c-Myc, AMPK, and PPARs pathways. These factors and pathways play pivotal roles not only in metabolic regulation but also in macrophage polarization. After activation, classically activated M1 macrophages and alternatively activated M2 macrophages display distinct patterns in glucose, lipid, amino acid and iron metabolism. Here, we summarized recently discovered metabolism-related inflammatory signaling factors, along with reprogrammed metabolism, after the activation of macrophages under conditions related to immunity and cancer. Additionally, macrophage regulatory roles in infectious diseases, cancer progression and anti-cancer immunotherapy are discussed in terms of metabolic profiles, providing insight into the prevention and treatment of immune-associated diseases.

## 1. Introduction

The innate immune system consists of different populations of cells, including macrophages, neutrophils, monocytes, eosinophils, basophils, and natural killer cells, which are responsible for innate immunity against pathogens to maintain homeostasis of the host. Macrophages, a key population of innate immune cells, were first described as phagocytic cells by Elie Metchnikoff in the 19th century [1]. Macrophages act as scavengers with phagocytic capability. Additionally, macrophages function as antigen-presenting cells (APCs) with various receptors on cell surfaces. In addition, macrophages are regulators of other innate or adaptive immune cells because they can secrete diverse cytokines.

During activation, macrophages switch from quiescence to an activated state. Activated macrophages are polarized into two populations, M1 (classically activated) and M2 (alternatively activated) [2]. The broad phenotype of macrophages is regulated by various signaling cascades, many of which have been well studied and reviewed elsewhere (Fig. 1) [3]. Research on macrophage metabolic changes began in the 1970s, when the activation of macrophages was first described as the phenotype change induced by interferon (IFN)γ [4]. It provided evidence that during the activation of murine peritoneal macrophages, there is a concurrent higher level of glycolysis, as well as a lower level of oxygen consumption [5]. Researchers, in the late 1980s, also found that the enzymatic activity of glucose metabolism-related enzymes was correlated with the activation of macrophages, intertwining the immune responses with glucose and glutamine metabolism [6]. In the late 1990s, a bacterial lipopolysaccharide (LPS), an agonist of Toll-like receptor (TLR) 4, similar to IFNγ, was found to be a stimulus to promote the generation of M1 macrophages [7]. While LPSs associated with IFNγ were known as classical stimuli for M1 macrophages, another type of activated macrophage induced by interleukin (IL)-4, the alternatively activated M2 subtype, was described [8].

M1 markers include IL-1β, IL-12, tumor necrosis factor (TNF) α and other upregulated pro-inflammatory products. Among them, inducible nitric oxide synthase (iNOS) plays a bactericidal role and promotes the catabolism of arginine [9]. M2 macrophages, on the other hand, have upregulated arginase 1 (Arg1), which functions in the urea cycle by catalyzing the transformation from L-arginine to L-orthinine, as well as other anti-inflammatory products [10]. M2 macrophages also play pivotal roles in tissue repair and anti-parasitic responses [11]. Further

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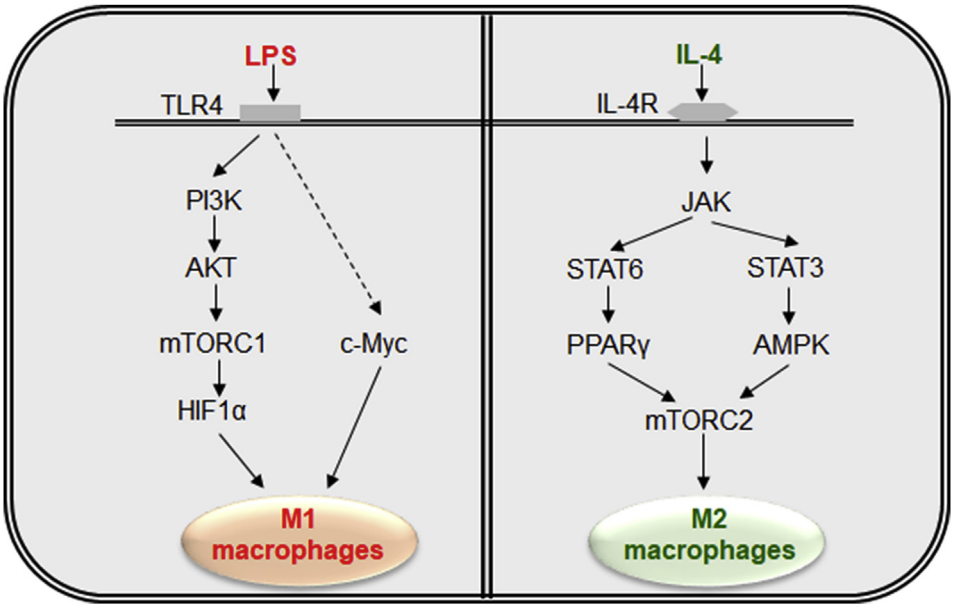


**Fig. 1.** Typical metabolism-related signaling pathways in polarized macrophages. M1 macrophages classically activated in response to IFNγ and LPSs are mediated by the PI3K-AKT-mTOR-HIF-1α signaling cascade pathway. M2 macrophages alternatively activated in response to IL-4 are mediated by JNK-STAT axes.

studies have provided more examples for distinct metabolic profiles of immune cells during various immune responses. Certain metabolic characteristics are suggested as key features of activated macrophages under specific scenarios, such as infection, immunosuppression, cancer-related angiogenesis and autoimmunity [12,13]. In these activated macrophages, reprogramming of energy metabolism, lipid metabolism and iron metabolism is also observed [14].

Taken together, the metabolic reprogramming of macrophage activation during immune responses is an issue worthy of interest. Here, we focus on metabolism-associated signaling pathways that cast effects on macrophage polarization. We also summarize the reprogrammed metabolic profiles of these regulated macrophages in terms of their glucose metabolism, lipid metabolism, amino acid metabolism, iron metabolism, energy metabolism and biosynthesis patterns. Immune-associated diseases relevant to the metabolic reprogramming of macrophages are also discussed and are mainly centered on infection, cancer progression and anti-cancer immunotherapy.

## 2. Metabolism-related signaling pathways in macrophage polarization

Functional control of macrophages largely occurs at the transcriptional level. Genes specifically up- or downregulated in M1 or M2 status have been described in the previous reviews [15–17]. Numerous signaling pathways that are essential to promoting functional differentiation of macrophages have been identified over the years [3]. Metabolic profiles, regulated by various signals and pathways, including the PI3K-AKT, HIF, c-Myc, AMPK, and PPAR pathways, have great influence on macrophage polarization. Among those regulatory factors involved in metabolic regulation, some also play pivotal roles in macrophage functional differentiation (Fig. 1 and Table 1).

### 2.1. PI3K-AKT pathway

To meet the enormous biosynthetic and bioenergetic needs of rapid inflammatory responses of the innate immune system, M1 macrophages switch in a highly glycolytic mode. LPSs induce the activation of M1 macrophages *via* TLR-mediated pathways, such as the PI3K-AKT pathway. Additionally, PI3K in M1 macrophages is considered to upregulate the expression of glucose transporter 1 (Glut1), key enzymes of glycolysis such as hexokinase 2 (HK2) and phosphofructokinase 2 (PFK2) [18]. The signaling *via* TLR, G protein coupled receptors (GPCR) and receptor tyrosine kinase all activate the PI3K-AKT pathway, leading the inflammation infiltrating M1 macrophages to a glycolytic mode and enhancing cancer-related inflammation in tumor-associated macrophages (TAMs) [19]. This evidence indicates that changes in the PI3K-AKT pathway affect macrophage activation (Table 1).

### 2.2. mTOR signaling

The TSC/mTOR pathway, activated by inflammatory stimuli, is a downstream effector of the PI3K/Akt pathway, which is a key sensor of the cell trophic state, playing an important role in coordinating metabolic and inflammatory signals and helping to determine the phenotype of macrophages. Mammalian target of rapamycin (mTOR) is an atypical serine/threonine kinase composed of two scaffolding complexes: mTOR complex 1 (mTORC1, RAPTOR) and mTOR complex 2 (mTORC2, RICTOR) [20,21]. mTOR is considered another important regulator of metabolism in activated macrophages because it couples nutrient sensing with glucose metabolism, lipid metabolism and biosynthesis.

mTORC1 enhances the expression of its downstream signals, such as HIF-1α, which contributes to enhancing aerobic glycolysis. This is defined as the Warburg effect. Similarly, in terms of glycolysis occurring in an anaerobic way, regulation cast by the mTORC1-HIF-1α axis is worthy of interest [22,23]. *Mycobacterium tuberculosis* induces AKT activation *via* TLR2-dependent signaling, which is greatly enhanced when mTOR signaling is blocked by rapamycin [24]. In LPS-induced M1 macrophages, mTORC1 is necessary for nitric oxide (NO) production *via* IFNβ, an NO production-related autocrine co-factor [25]. The mTORC1 pathway is also observed to promote lipid biosynthesis and inhibit autophagy [26]. It is now known that in T cells, mTORC2 is activated by PI3K signaling to regulate metabolism and apoptosis and is also associated with cytoskeletal organization [20]. In innate immunity, mTORC2 is an M2 macrophage marker. Conditional knockout of the myeloid-specific RITOR subunit results in a gain of M1 phenotype [27]. mTORC2 is an upstream signal of interferon regulatory factor 4 (IRF4) in response to IL-4 bypassing the IL-4-signal transducers and activators of the transcription 6 (STAT6) axis [28].

Constitutive activation of mTOR is found to be immunosuppressive and likely introduces a tissue repair-supportive M2 phenotype in

**Table 1**
Identified molecules that regulating the metabolic switch of macrophages in both infection and cancer settings.

| Signaling pathway | Signaling component | Effect of metabolic process | Effects on macrophage polarization | Role in immune-associated diseases |
|---|---|---|---|---|
| Phosphatidylinositol 3-kinase (PI3K) | AKT, Glut1, HK2, PFK2, GPCR and receptor tyrosine kinase | Upregulate glycolysis | M1 macrophages | Host defense |
| Mammalian target of rapamycin (mTOR) complex 1 (mTORC1, RAPTOR) | AKT, NO production via IFNβ, TSC1 and TSC2 or AMPK | Enhance the aerobic glycolysis, promote lipid biosynthesis and inhibit autophagy | M1 macrophages | Host defense |
| mTOR complex 2 (mTORC2, RICTOR) | IRF4, STAT6 | Lipid metabolism and biosynthesis | M2 macrophages | Tissue repair and regeneration |
| Hypoxia-induced factor (Hif)-1α | LDHA, PDK, $NAD^+$, Glut1, HK2, PFKFB3, PKM2, PGK1 | Glycolysis, a crucial player in deciding the ways cells convert pyruvate to lactate | M1 macrophages | Host defense, macrophage-mediated infections, *M. tuberculosis* infection, against tumors |
| Hif-2α | Induced by Vascular niche IL-6, IL-1β production and growth factors in relate to tumor angiogenesis | Relate to tumor angiogenesis | tumorgenic behavior in tumor-associated macrophages (TAMs) | Enhance tumor-related inflammation, glioblastoma |
| c-Myc | LDHA and PDK1, TGF-β, VEGF | Enhance the glycolytic activity, glutaminolysis | M1 macrophages<br>M2 macrophage polarization and tumor promotion of TAMs | Host defense, macrophage-mediated infections, Leishmania, against tumors |
| Adenosine 5′-monophosphate-activated protein kinase (AMPK) | IL-10 and STAT3 | OXPHOS | M2 macrohages | Tissue repair and regeneration |
| Peroxisome proliferator-activated receptors (PPARs) | PPARγ STAT6, IL-10<br>PPARδ<br>PPARα/β | Key sensors for lipids, clearing apoptotic cells | M2 macrophages | Obesity and insulin resistance<br>Buildup of tumor<br>Regulating macrophage biology |
| Carbohydrated kinase-like protein (CARKL) | sedoheptulose-7-phosphate (S7P), NADPH, ROS | Pentose phosphate pathway (PPP) | M1 macrophages | Host defense |
| Isocitrate dehydrogenase (IDH) | α-KG, citrate | Tricarboxylic acid cycle (Krebs cycle, TCA), lipid biosynthesis | M1 macrophages | Host defense against microbes |
| succinate oxidation | Fumarate and malate, enhance the expression of pro-inflammatory IL-1β via Hif-1α | Krebs cycle | M1 macrophages | Host defense |
| PFKFB1 | L-PFK2, fructose-2,6-bisphosphate, STAT6, PGC-1β, NRF-1, estrogen-related receptor-α | Mitochondrial respiration and oxidative phosphorylation | M2 macrophages | Tissue repair and regeneration |
| Triacylglycerol | PPAR and liver X receptor (LXR), IL4-STAT6 axis-triggered PGC-1β | Fatty acid oxidation (FAO) | M2 macrophages | Tissue repair and regeneration |
| arachidonic acid | Higher level of COX2, lower level of COX1 and mPGEs | Arachidonic acid metabolism | M1 macrophages | Host defense |
| | Lower level of COX2, higher level of COX1 and mPGEs | Arachidonic acid metabolism | M2 macrophages | Tissue repair and regeneration |
| L-arginine | iNOS | Urea cycle | M1 macrophages | Host defense |
| | Arg1 | Polyamine synthesis | M2 macrophages | Tissue repair and regeneration |
| Glutamine | GPT2、α-KG、UDP-GlcNAc | Glutamine metabolism, TCA, UDP-GlcNAc synthesis | M2 macrophages | Antigen presentation, phagocytosis and cytokine secretion |
| Iron | less ferroportin and higher levels of H-ferritin | Iron homeostasis | M1 macrophages | Tissue repair and regeneration |
| | Higher ferroportin and less levels of H-ferritin, HO-1, IL-10, Lipocalin (LCN) | Heme catabolism | M2 macrophages | Tissue repair and regeneration, pro-tumor in 4T1 mammary carcinoma model |
| Lactic acid | Arg1, angiogenesis factors and anti-inflammatory factors | OXPHOS | Immunosuppressive TAMs | Tumor promoting |
| Arginine-derived polyamines | Arg1, GLUL | Amino acid metabolism | Immunosuppressive TAMs | Tissue repair and cell proliferation, occur in stable stage of tumor progression |

circumstances such as an established tumor microenvironment. However, this promotion of the immunosuppressive phenotype leads to inhibition of itself by negative feedback through the PI3K pathway [29].

There are also some negative regulators of mTOR activity. In T cells, tuberous sclerosis 1 (TSC1) and TSC2 have been documented to inhibit mTORC1 signaling. Much of the upstream regulation is cast on mTORC1 *via* the TSC1/2 complex, which is inactivated *via* the PI3K-AKT pathway by direct phosphorylation of the TSC1/2 complex, or activated *via* the adenosine monophosphate-activated protein kinase (AMPK) pathway [20]. Similarly, in macrophages, TSC1 deficiency promotes the activation of mTORC1 and c-Jun N-terminal kinase 1/2 (JNK1/2), as well as upregulates the NO production and secretion of pro-inflammatory cytokines [21]. Whether this regulation is also implemented by the upstream signaling pathway PI3K-AKT-TSC1/2 is worthy of discussion.

### 2.3. HIF

The hypoxia-induced factor (HIF) is a key factor in metabolic regulation, especially in glycolysis. Responses of mammalian cells to low oxygen conditions (hypoxia) are introduced by HIF. However, HIF is not only induced by hypoxia but also by TLR agonists and cytokines, especially those pro-inflammatory ones such as TNFα and IL-1β [30]. Cytokine-induced HIF-1α is known to be a crucial player in deciding how cells convert pyruvate to lactate. In the presence of oxygen, cells utilize pyruvate by glycolysis to produce lactate. Additionally, HIF-1α can promote cells to utilize acetyl-CoA by promoting the expression of lactate dehydrogenase (LDHA) and pyruvate dehydrogenase kinase (PDK), which converts pyruvate to lactate and inhibits pyruvate dehydrogenase, respectively [31,32].

$NAD^+$ generated by NADH is necessary to maintain the flux of glycolysis. When the oxidative phosphorylation (OXPHOS) pathway is available, the conversion from pyruvate to lactate in cells is executed by the malate-aspartate shuttle. However, if OXPHOS is inhibited by signals upstream of HIF, cells utilize acetyl-CoA, rather than pyruvate, to generate $NAD^+$ even in the presence of oxygen [33]. Therefore, the HIF isoforms induced by pro-inflammatory cytokines, while OXPHOS inhibited, promote aerobic glycolysis in macrophages and dendritic cells (DCs) [34,35], performing the Warburg effect. On the other hand, HIF-1α, as a key transcription factor, directly regulates the expression of glycolysis-related enzymes such as glucose transporter 1 (Glut1), hexokinase 2 (HK2), and fructose-2,6-bisphosphatase 3 (PFKFB3) [36].

HIF-1α-dependent glycolysis is tightly associated with the M1 phenotype of macrophages since HIF-1α is induced by pro-inflammatory cytokines. However, studies have shown that HIF-1α can upregulate pro-inflammatory cytokines in LPS-treated glycolytic macrophages as well [22]. It also introduces a 'trained immunity' in β-glucan-treated glycolytic macrophages [37]. In response to bacterial or fungal infection, HIF-1α is reported to be critical for pro-inflammatory macrophage differentiation *in vitro* and *in vivo*, accompanied by changes in glycolytic activity [38]. Our previous studies also showed that HIF-1α-dependent glycolysis controls the functional differentiation of other immune cells [39,40].

However, HIF-1α, as well as HIF-2α, are reported to enhance tumor-related inflammation *via* IL-1β production and growth factors in relation to tumor angiogenesis [41,42] and drive tumorigenic behavior in tumor-associated macrophages (TAMs) exposed to hypoxia. HIF-1α likely upregulates glycolysis in TAMs and enhances pro-inflammatory effects in rapidly growing tumors, whereas it skews the tumor into an immunosuppressed state by inducing angiogenesis and immunosuppression *via* factors such as programmed death-1 (PD-L1), as occurred in myeloid-derived suppressor cells (MDSC) [43].

There is a plasticity displayed by HIF-1α-regulated immune cells in their immune responses, which is especially obvious over the course of tumor progression. This provides an interesting point for further exploration; the regulatory effects of HIF-1α on macrophages might also vary dynamically under other conditions.

### 2.4. c-Myc

In combination with HIF, c-Myc, the oncogenic transcription factor, contributes to the production of LDHA and PDK1, which enhance glycolytic activity, as stated above. In amino acid metabolism, c-Myc also plays an important role by upregulating the expression of glutamine transporters and glutamines, which function chiefly in glutaminolysis [44,45]. In addition to its important role in metabolic regulation, c-Myc is also involved in M2 macrophage polarization and tumor promotion of TAMs, as it can regulate pro-tumor factors such as transforming growth factor-β (TGF-β) and vascular endothelial growth factor (VEGF) [46,47]. c-Myc has effects on many metabolic pathways. Nevertheless, the detailed effects of c-Myc on the metabolism of TAMs are far from revealed.

### 2.5. AMPK

IL-4-induced M2 macrophage glucose metabolism mainly through OXPHOS rather than glycolysis. Adenosine 5′-monophosphate-activated protein kinase (AMPK), a key factor regulating OXPHOS, is activated by adenosine, its substrates, and some anti-inflammatory factors, skewing the macrophages to an immunosuppressive state with a metabolism pattern that emphasizes OXPHOS [48]. On the other hand, LPS-induced M1 macrophages display suppressed activation of AMPK and prefer glycolysis as their major glucose metabolism pathway [49].

### 2.6. PPAR

Peroxisome proliferator-activated receptors (PPARs) are key sensors for lipids. As nuclear receptors and transcription factors, they directly initiate or suppress the expression of many target genes. Induced by IL-4 and IL-13, PPARγ is involved in M2 macrophage polarization, in combination with some corepressors to repress the expression of pro-inflammatory factors, such as histone deacetylase-3. IL-4-induced phosphorylated STAT6 also appears to be in crosstalk with PPARγ [50,51]. PPARγ deficiency leads to inhibited M2 macrophage polarization. Additionally, PPARγ deficiency results in obesity and insulin resistance when treated with a high fat diet [52]. PPARδ, another member of the PPAR family, plays a scavenging role in clearing apoptotic cells [11], which might be involved in the building up of tumors. PPARα/β account for the activation of TAMs by enhancing IL-10 expression, which induces the macrophages to a pro-tumor phenotype [53]. PPARβ also plays an important role in regulating macrophage biology [54].

Although metabolism and macrophage polarization are regulated by many factors, these signals in metabolic regulation are not separate (Fig. 1). For example, HIF-1α is downstream of the PI3K-AKT pathway in macrophages [55]. Additionally, HIF-1α can be regulated by mTOR signals. c-Myc in M2 macrophages is correlated with *Hif-1α*, as the inhibition of c-Myc can block the expression of HIF-1α [56]. In addition, AMPK is reported to be downstream of PPAR [57].

## 3. Metabolic reprogramming of polarized macrophages in immune responses

Regulated by some factors, the metabolic profiles of macrophages are orchestrated in immune responses. It is important to determine how metabolic alterations in macrophages lead to pro- or anti-inflammatory effects (Fig. 2 and Table 1).

### 3.1. Glucose metabolism

Polarized macrophages display distinct patterns of glucose

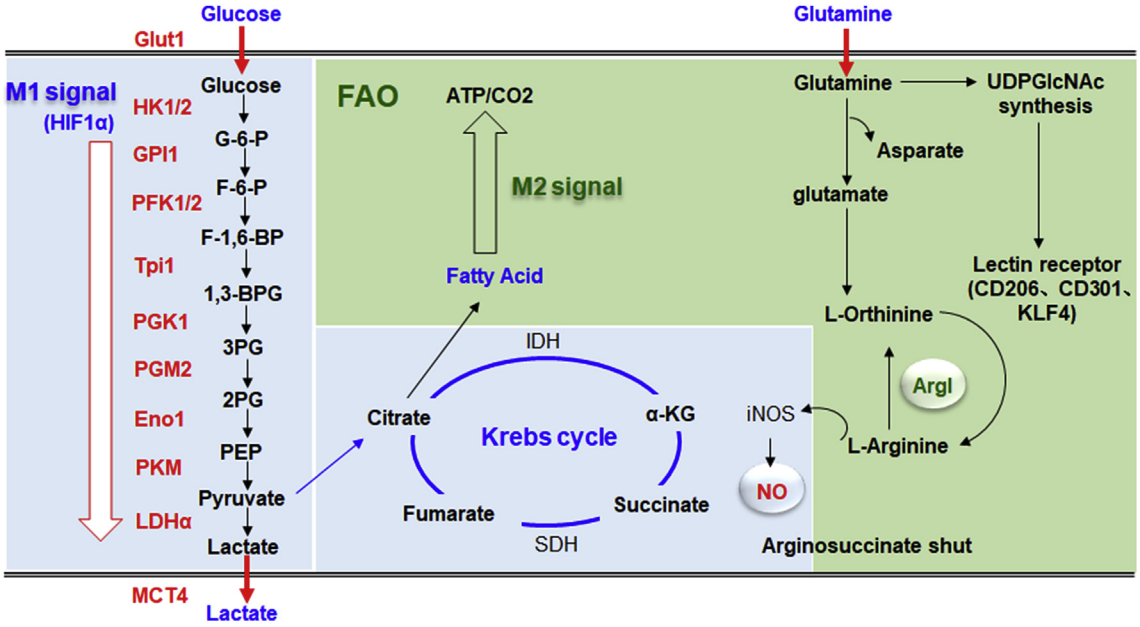


**Fig. 2.** Metabolic reprogramming of polarized macrophages. The glycolytic pattern of glucose metabolism is preferred by M1 macrophages. Fatty acid oxidation occurs in response to M2 stimuli. Arginosuccinate shunts under conditions of classical activation and glutamine metabolism in conditions of alternative activation. Glutamine metabolism gives rise to N-glycosylation of M2 markers as well.

metabolism. M1 macrophages, induced by LPSs and IFNγ, are characterized by boosted glycolysis alone. IL-4 exposure-induced M2 macrophages preferentially increase the rate of OXPHOS in *Mus musculus* [37,58]. Human monocytes, similarly, skew to the glycolytic mode with concomitant decreased OXPHOS under β-glucan treatment. This alteration is mediated *via* the AKT-mTOR-HIF-1α pathway [22].

More details on glucose metabolism are studied in mice. As mentioned above, HIF-1α can upregulate the expression of glycolysis-related enzymes and factors in M1 macrophages, such as Glut1, HK2, PFKFB3, pyruvate kinase 2 (PKM2) and phosphoglycerate kinase 1 (PGK1) [59,60]. In addition, over the course of the classical activation of macrophages, PFK2 is activated via an isoform switch from the liver form (L-PFK2) to the ubiquitous form (u-PFK2) [58]. LPS-induced preference of glycolysis in macrophages therefore leads to higher rates of glucose consumption through glycolysis. The pentose phosphate pathway (PPP), a bypass of glycolysis, is also found to play a role in promoting the metabolic shift and the classical activation of macrophages. Carbohydrate kinase-like protein (CARKL) is a factor responsible for the production of sedoheptulose-7-phosphate (S7P), a PPP intermediate and PPP flux restraint. In response to LPSs, CARKL is downregulated. Therefore, S7P is a restraint on the PPP. Thus, an enhanced PPP is found in response to M1 macrophage activation. In addition, over the course of the PPP, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase results in increased levels of reactive oxygen species (ROS), a typical product of classically activated macrophages. In contrast, overexpression of CARKL leads to repressed production of pro-inflammatory cytokines such as TNFα, providing additional support for the positive correlation between PPP and classical activation of macrophages [61].

In the tricarboxylic acid cycle (Krebs cycle, TCA) of M1 macrophages, there are two key points (Fig. 2). Expression of the isocitrate dehydrogenase (IDH) that converts citrate to α-ketoglutarate (α-KG) is downregulated, leading to citrate accumulation [37]. Citrate accumulation results in its conversion to itaconic acid, a metabolic intermediate involved in host defense against microbes [62]. Spared citrate also contributes to lipid biosynthesis. Another important point is at the succinate oxidation step. Because of the deficiency in succinate dehydrogenase (SDH) in activated M1 macrophages, succinate accumulates in cells. Succinate-derived fumarate is downregulated, in contrast to its upstream reactant. Fumarate and malate, supporting the Krebs cycle, are no longer converted from succinate here, but from an arginosuccinate shunt, providing aspartate aminotransferase-catalyzed fumarate and enhancing the production of NO and IL-6 [63]. On the other hand, accumulated succinate enhances the expression of pro-inflammatory IL-1β *via* HIF-1α, which can be rescued by the glycolysis blocker, 2-deoxyglucose (2-DG), in accordance with pro-inflammatory and glycolytic characteristics in M1 macrophages [37].

In M2 macrophages alternatively activated by IL-4, PFKFB1 is expressed followed by the main isoform of L-PFK2 and downregulated levels of fructose-2,6-bisphosphate. Glucose metabolism in cells switches to mitochondrial respiration and oxidative phosphorylation instead of glycolysis. This switch is known to be regulated by transcription factor STAT6, which responds to activation of IL-4 and then induces transcription factor PPARγ-coactivator-1β (PGC1β) [64]. Nuclear respiratory factor 1 (NRF1), estrogen-related receptor α and PGC1β signals together regulate the expression of functional components in the mitochondria, such as ATP synthase and cytochrome *c* [65] (Figs. 1 and 2). However, glycolysis is not just important to pro-inflammatory responses; it is also critical for the M2 macrophage activation induced by IL-4. The inhibition of mitochondrial ATP synthase with oligomycin and of glycolysis with 2-DG both can suppress IL-4-regulated genes, surface markers, and functions [66], which demonstrate that glucose fuels the TCA cycle for mitochondrial respiration in M2 macrophages [67]. In general, these current studies highlight the essential need for glycolysis in both inflammatory and anti-inflammatory macrophage responses.

### 3.2. Lipid metabolism

Under different microenvironmental stimuli, the lipid metabolism pattern of macrophages can also be altered (Fig. 2).

Fatty acid uptake and fatty acid oxidation (FAO) are downregulated in M1 macrophages [11]. In contrast, FAO and mitochondrial activity in IL-4-induced M2 macrophages are enhanced concurrently. Uptake of triacylglycerol (TAG) is found to be essential for FAO in M2 macrophages [26]. This regulation is orchestrated by PPAR and liver X receptor (LXR) [68]. Additionally, FAO is enhanced in macrophages promoted by IL4-STAT6 axis-triggered PGC1β. PGC1β can also promote

cells to an oxidative mode of glucose metabolism, which relies more on mitochondrial activity (Fig. 2) [11,64,69]. Similarly, etomoxir, an FAO inhibitor, can block IL-4-induced M2 macrophage polarization [26]. However, blocking FAO in human macrophages failed to block the IL-4 response [70], FAO can also contribute to inflammatory macrophage phenotypes through NLRP3 activation [71]. After all, these findings suggest that the requirement for FAO in M2 macrophage polarization is very complex and many questions remain to be answered.

In M1 macrophages classically activated by LPSs in combination with IFNγ, arachidonic acid metabolism displays distinct characteristics, such as higher levels of cyclooxygenase 2 (COX2), lower levels of COX1 and microsomal isoforms of Prostaglandin E synthase (mPGEs). In IL-4-induced M2 macrophages, contrasting changes are observed [14]. Lipidomic profiling of activated macrophages demonstrates the correlation between inflammation and lipid metabolism in macrophages, and these lipidomics can provide potential biomarkers for inflammation [72].

### 3.3. Amino acid metabolism

The metabolism mode of amino acids is also a distinct indicator of polarized macrophages (Fig. 2).

Altered L-arginine metabolism was one of the first characteristics used to classify macrophage polarization subsets, which varies under conditions of different stimuli [73]. In LPS- and IFNγ-induced M1 macrophages, inducible nitric oxide synthase (iNOS) is upregulated, supporting the urea cycle by converting L-arginine to NO and L-citrulline. In IL-4-induced M2 macrophages, the upregulated enzyme is liver type Arg1, which converts L-arginine to L-orthinine and drives polyamine synthesis [74]. Initially, the differences in arginine metabolism by either iNOS or arginase-1 were used to define classically and alternatively activated macrophage subsets, respectively.

Glutamine-related pathways are also highly involved in the polarization and function of macrophages. Glutamine is essential for three major functions of macrophages: antigen presentation, phagocytosis and cytokine secretion [75]. Glutaminolysis driven by glutaminase is the main event in glutamine metabolism. Related intermediates, including glutamate and glutamic-pyruvic transaminase 2 (GPT2), are upregulated in IL-4-induced M2 macrophages. In the absence of them, M2 polarization is decreased [76]. Glutamate also functions to support TCA; almost one-third of the carbons in the TCA cycle were derived from glutamine [77], which converted to α-ketoglutaric acid (α-KG) after deamination [77]. In addition, the N-glycosylation-essential uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) synthesis is also coupled with glutaminolysis, giving rise to N-glycosylation, thus promoting the expression of M2 macrophage markers, such as cluster of differentiation 301 (CD301), CD206 (Mannose receptor 1, Mrc1), interferon regulatory factor 4(IRF4), Krupple such as factor 4 (KLF4) and C-C motif ligand 22 (CCL22) [78].

### 3.4. Heme-iron metabolism

Macrophages can scavenge senescent RBCs, playing a crucial role in iron recycling and homeostasis. Changes in iron homeostasis are also involved in the polarization of macrophages (Table 1).

In LPSs in combination with IFNγ-induced M1 macrophages, iron is stored rather than exported. Therefore, less ferroportin (iron transporter) and low CD163 (heme uptake), coupled with higher levels of H-ferritin (iron storage), are expressed. In M2 macrophages, on the contrary, there is a higher level of ferroportin coupled with high levels of CD163 and CD94 (heme uptake) to work against ferritin, giving rise to iron secretion and release [79]. The hemeoxygenase-1 (HO-1), a rate-limiting enzyme in the heme degradation pathway which upregulates the expression of IL-10, is regarded as an indicator of M2 polarized macrophages [80]. An immunosuppressive phenotype of M2 macrophages that enhances tissue repair and regeneration is also regulated *via* increased iron excretion by ferroportin, enhanced heme catabolism by HO-1 and restricted iron retention by ferritin [81]. Lipocalin (LCN), another iron-releasing protein, is also upregulated in TAMs of human breast cancer cells [82]. However, the anti-inflammatory regulatory effect of iron-releasing HO-1 does not always occur. HO-1 is found to be pro-inflammatory in chronic metabolic inflammation that is related to obesity [83]. Taken together, recent studies have demonstrated a crucial role of iron metabolism in determining the polarized phenotype and functions of macrophages.

## 4. Metabolic profiles of macrophages in infection and cancer

An abundance of evidence indicates that metabolism is highly involved in macrophage polarization and function in both homeostasis maintenance and pathology. As there are shifts in macrophage metabolism patterns in response to microenvironmental changes, macrophages have distinct metabolic profiles during both infections and cancer occurrence. Infectious diseases and tumors related to macrophage development and function are listed. Metabolic changes during infectious diseases and cancer progression are specifically discussed (Table 1).

### 4.1. Metabolic profiles of macrophages during infection

In inflammation and host defense responses against infection, macrophages produce more pro-inflammatory cytokines and bactericidal molecules, such as TNF and ROS, respectively. (Fig. 3 and Table 1). Additionally, macrophage metabolism patterns, including glucose metabolism and amino acid metabolism, change concurrently.

The glucose metabolic mode is tightly associated with host defense. Bactericidal molecules, ROS, mainly come from two different pathways, NADPH oxidase and the mitochondria stress-dependent pathway [84]. When macrophages are activated by LPSs *via* TLR4 and glycolysis and PPP are enhanced, while OXPHOS and mitochondrial activity are suppressed. Additionally, the PPP flux restraint CARKL is repressed. Enhanced NADPH oxidase in the PPP leads to an increase in ROS levels [61,85]. HIF-1α and c-Myc are key factors in glycolysis and macrophage polarization. They also play pivotal roles in macrophage-mediated infections. Studies have shown that macrophage responses to *M. tuberculosis* infection can be modulated by nitric oxide through activation of HIF-1α and repression of NF-kB [86]. c-Myc is reported to function in human macrophages and as a novel *Leishmania* virulence factor that is essential for survival by targeting the host miRNA system [87]. On the other hand, regulated by TNF receptor-associated factor 6

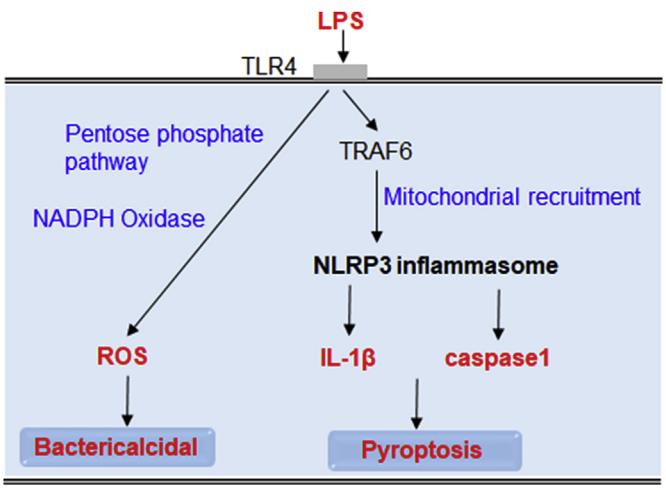


**Fig. 3.** Infections related to the metabolism of macrophages. Reactive oxidative species and pyroptosis occurs, performing pro-inflammatory functions during infection.

(TRAF6) [84], mitochondria are recruited towards phagolysosomes, enhancing the production of ROS as well [37]. Mitochondrial stress is also essential for the activation of the leucine-rich repeat pyrin-3 (NLRP3) inflammasome [88]. Under some conditions, such as bacterial and viral infection or under danger signals such as monosodium urate and extracellular ATP, this mitochondrial ROS production process is accompanied by an upregulated level of pyroptosis-essential Caspase-1 and pro-inflammatory IL-1β [89].

In accordance with the glycolytic or mitochondrial pattern of glucose metabolism, distinct modes of amino acid metabolism are also displayed. In M1 macrophages, arginine is utilized to contribute to iNOS production, which promotes the production of NO, one of the bactericidal molecules. Additionally, arginosuccinate shunts under pro-inflammatory stimuli, such as infections in M1 macrophages, to compensate for the TCA break [37]. Arginine is converted to polyamines by Arg1 when macrophages are alternatively activated [90].

### 4.2. Metabolic profiles of macrophages in cancer progression

The glucose, amino acid, lipid and iron metabolic profiles of macrophages have all been shown to be altered throughout tumor progression [91]. The metabolic signatures of macrophages have been studied in various types of tumors (Fig. 4 and Table 1).

Tumor-associated macrophages are typical lymphoreticular infiltrates that play an essential role in pro- or anti-tumor regulation [92,93]. Usually, TAMs are considered an anti-inflammatory phenotype. TAMs are able to produce pro-inflammatory cytokines such as TNFα, IL-1 and IL-6, as well as reactive oxygen intermediates (ROI) and reactive nitrogen intermediates (RNI) to enhance chronic inflammation that is related to tumors [94]. Macrophages can also regulate T cell functions in tumor progression. Recent studies have shown that M1 macrophage polarization contributes to preventing the disease progression of glioblastoma, along with increased T effector to T regulatory cell ratios [95]. In addition, $Ly6C^{low}F4/80^{+}$ macrophages that reside outside of the tumor microenvironment can promote infiltration of T cells into pancreatic ductal adenocarcinomas [96]. While it is not always the case, TAMs also play a role as negative regulators of tumorigenesis, as anti-inflammatory factors are upregulated in TAMs, such as IL-10, TGFβ and metalloprotease (MMP), rendering the tumor microenvironment a relatively immunosuppressive state, which gives rise to metastasis and extravasation of tumor cells [92,97]. Macrophages also provide tumor angiogenesis-related factors, such as VEGFA [98]. Some metabolism regulators also play important roles in macrophage-associated responses against tumors, including HIF and c-Myc. It has been reported that HIF-2α, induced by vascular niche IL-6, can induce alternative macrophage activation in glioblastoma [99]. While c-Myc is reported to be expressed in tumor-associated macrophages and can be a potential therapeutic target in pathologies [56], a dynamic plasticity in TAM function is observed, which might depend on different metabolic needs in different stages of tumor progression (Table 1).

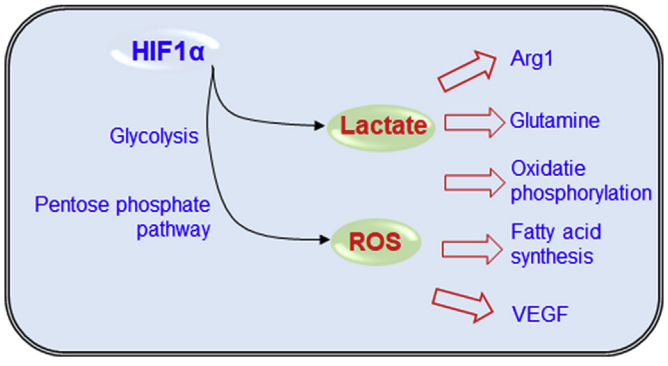


**Fig. 4.** Cancer progression in relation to metabolism of macrophages. Both M1 and M2 characteristics are present over the course of tumor progression.

During the onset stage of tumors, glucose metabolism appears more glycolytic, as HIF-1α upregulates the production of RNI and ROS. Apart from inflammatory effects, this pattern seems more adaptive to the hypoxic environment caused by fast growing tumors. Lactic acid, one of the accumulated glycolysis products, is crucial for a switch to the M2 mode of glucose metabolism that emphasizes OXPHOS of the TAMs. Lactic acid skews the TAMs to display a more immunosuppressive, tumor promoting state with upregulated Arg1, angiogenesis factors and other anti-inflammatory factors [78]. This process occurs gradually in tumors from early establishment to a late stably progressing stage. However, lactic acid does not always play an M2 inhibitory role but is also found to be supportive of pro-inflammatory IL-23 in murine B16 melanoma TAMs [100].

Arginine-derived polyamines contribute to tissue repair and cell proliferation, which occur in stable stages of tumor progression [101]. Upregulated Arg1 in immunosuppressive TAMs also leads to immunosuppression in T cells [102]. Data have shown that expression of Arg1 is upregulated in Lewis lung carcinoma and B16 melanoma [13,103]. Key enzymes in glutaminolysis, such as glutamine transaminase and synthetase (GLUL), are also upregulated in the M2 state [78]. In MDSCs, tryptophan is also involved in tumor progression, which provides another interesting point about TAM amino acid metabolism to study in the future [104].

In TAMs, fatty acid synthesis (FAS) is considered pro-tumor while being anti-inflammatory, with a supported expression of IL-10. This is controversial in specific cancer cells, such as Lewis lung carcinoma cells, in which increased FAS appears anti-tumor [53,105]. The expression of IFNβ is upregulated in these TAMs, along with an increased size of lipid droplets. IFNβ, on the other hand, plays a role in recruiting natural killer cells, which are responsible for the anti-tumor inflammation [106]. In lipid metabolism, there is also an obvious plasticity depending on tumor stage and specific metabolic needs.

HO-1, an iron metabolic marker for M2 macrophages, is reported to be a pro-tumor in the 4T1 mammary carcinoma model [107], indicating an involvement of iron metabolism in tumor progression as well. In addition, the intracellular iron level also casts an inhibitory effect on the stability of HIF-1α, which is associated with TAM development, survival and pro-tumor function [108].

### 4.3. Concluding remarks

Metabolic reprogramming is highly involved in the activation of macrophages. Either classically activated M1 or alternatively activated M2 macrophages display distinct metabolic features, which are closely associated with their function in innate immunity in response to microenvironmental stimuli. For M1 macrophages, glycolysis is the preferential pathway of glucose metabolism, even in aerobic conditions, which is described as the Warburg effect. The enhanced pentose phosphate pathway is employed accordingly in M1 macrophages. Upregulated lipid oxidation, glutaminolysis and L-arginine conversion are metabolic signatures for M2 macrophages activated by IL-4. N-glycosylation of other M2 markers executed by UDP-GlcNAc is also reported as a typical event in alternative activation conditions.

The profiles of glucose, lipid, amino acid and heme-iron metabolism of macrophages are regulated by broad intercellular and intracellular signaling, in which key regulatory agents are studied. The PI3K-AKT pathway is reported to be crucial in the regulation of glycolysis. The pro- or anti-inflammatory effects of macrophages mediated by mTORC1 and mTORC2 are still far from being known. HIF isoforms as transcription factors contribute to the expression of key glycolysis enzymes. AMPK, a downstream signal of the IL-4-STAT3 axis, is involved in oxidative phosphorylation, a known M2 metabolic event. PPAR regulated by STAT6 has been shown to account for the M2 characteristic lipid metabolism.

The metabolic profile of macrophages is closely associated with

immune-associated diseases, infectious diseases, cancer progression and anti-cancer immunotherapy. The redox status and arginine metabolism of M1 macrophages induce host defenses against infection. A switch from the M1-like to the M2-like state of TAMs over the course of tumor progression takes place in accordance with the build-up of an aerobic, proliferation-supporting microenvironment. Metabolic changes in line with immune-associated disease occurrence provide a meaningful etiologic view for us. However, determining how this knowledge can be converted to anti-cancer immunotherapeutic approaches requires further studies.

## Competing financial interests

The authors declare no competing financial interests.

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## References

[1] R.B. Vaughan, The romantic rationalist: a study of Elie Metchinkoff, Med. Hist. 9 (1965) 201–215.
[2] P.J. Murray, et al., Macrophage activation and polarization: nomenclature and experimental guidelines, Immunity 41 (2014) 14–20, https://doi.org/10.1016/j.immuni.2014.06.008.
[3] D. Tugal, X. Liao, M.K. Jain, Transcriptional control of macrophage polarization, Arterioscler. Thromb. Vasc. Biol. 33 (2013) 1135–1144, https://doi.org/10.1161/ATVBAHA.113.301453.
[4] C.F. Nathan, H.W. Murray, M.E. Wiebe, B.Y. Rubin, Identification of interderon-gamma as the lymphokine that activates human macrophage oxidative metabolism and antimocrobial activity, J. Exp. Med. 158 (1983) 670–689.
[5] G.C. Hard, Some biochemical aspects of the immune macrophage, Br. J. Exp. Pathol. 51 (1970) 97–105.
[6] P. Newsholme, R. Curi, S. Gordon, E.A. Newsholme, Metabolism of glucose, glutamine, long-chain fatty acids and keton bodies by murine macrophages, Biochem. J. 239 (1986) 121–125.
[7] J.C. Chow, D.W. Young, D.T. Golenbock, W.J. Christ, F. Gusovsky, Toll-like receptor-4 mediated lippopolysaccharide-induced signal transduction, J. Biol. Chem. 274 (1999) 10689–10692.
[8] M. Stein, S. Keshav, N. Harris, S. Gordon, Interleukin 4 potently enhances murine macrophage mannose receptor activity a marker of alternative immunologic macrophage activation, J. Exp. Med. 176 (1992) 287–292.
[9] I.M. Corraliza, G. Soler, K. Eichmann, M. Modolell, Arginase induction by suppressors of nitric oxide synthesis(IL-4, IL-10 and PGE2) in murine bone-marrow-derived macrophages, Biochem. Biophys. Res. Commun. 206 (1995) 667–673.
[10] M. Munder, K. Eichmann, M. Modolell, Alternative metabolic states in murine macrophages reflected by the nitric oxide synthase/arginase balance: competitive regulation by CD4+ T cells correlates with Th1/Th2 phenotype, J. Immunol. 160 (1998) 5348–5354.
[11] J.I. Odegaard, A. Chawla, Alternative macrophage activation and metabolism, Annu. Rev. Pathol. 6 (2011) 275–297, https://doi.org/10.1146/annurev-pathol-011110-130138.
[12] S.K. Biswas, A. Mantovani, Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm, Nat. Immunol. 11 (2010) 889–896, https://doi.org/10.1038/ni.1937.
[13] S.K. Biswas, A. Sica, C.E. Lewis, Plasticity of macrophage function during tumor progression: regulation by distinct molecular mechanisms, J. Immunol. 180 (2008) 2011–2017, https://doi.org/10.4049/jimmunol.180.4.2011.
[14] S.K. Biswas, A. Mantovani, Orchestration of metabolism by macrophages, Cell Metabol. 15 (2012) 432–437, https://doi.org/10.1016/j.cmet.2011.11.013.
[15] G. Liu, H. Yang, Modulation of macrophage activation and programming in immunity, J. Cell. Physiol. 228 (2013) 502–512, https://doi.org/10.1002/jcp.24157.
[16] X. Chen, et al., Intercellular interplay between Sirt1 signalling and cell metabolism in immune cell biology, Immunology 145 (2015) 455–467, https://doi.org/10.1111/imm.12473.
[17] H. Yang, et al., Multifaceted modulation of SIRT1 in cancer and inflammation, Crit. Rev. Oncog. 20 (2015) 49–64.
[18] M. Chang, J.A. Hamilton, G.M. Scholz, C.L. Elsegood, Glycolytic control of adjuvant-induced macrophage survival: role of PI3K, MEK1/2, and Bcl-2, J. Leukoc. Biol. 85 (2009) 947–956, https://doi.org/10.1189/jlb.0908522.
[19] M.C. Schmid, et al., Receptor tyrosine kinases and TLR/IL1Rs unexpectedly activate myeloid cell PI3kgamma, a single convergent point promoting tumor inflammation and progression, Canc. Cell 19 (2011) 715–727, https://doi.org/10.1016/j.ccr.2011.04.016.
[20] M. Laplante, D.M. Sabatini, mTOR signaling in growth control and disease, Cell 149 (2012) 274–293, https://doi.org/10.1016/j.cell.2012.03.017.
[21] H. Pan, T.F. O'Brien, P. Zhang, X.P. Zhong, The role of tuberous sclerosis complex 1 in regulating innate immunity, J. Immunol. 188 (2012) 3658–3666, https://doi.org/10.4049/jimmunol.1102187.
[22] S.C. Cheng, et al., mTOR- and HIF-1alpha-mediated aerobic glycolysis as metabolic basis for trained immunity, Science 345 (2014), https://doi.org/10.1126/science.1250684 1250684.
[23] J.J. Howell, B.D. Manning, mTOR couples cellular nutrient sensing to organismal metabolic homeostasis, Trends Endocrinol. Metabol.: TEM (Trends Endocrinol. Metab.) 22 (2011) 94–102, https://doi.org/10.1016/j.tem.2010.12.003.
[24] C.S. Yang, et al., Intracellular network of phosphatidylinositol 3-kinase, mammalian target of the rapamycin/70 kDa ribosomal S6 kinase 1, and mitogen-activated protein kinases pathways for regulating mycobacteria-induced IL-23 expression in human macrophages, Cell Microbiol. 8 (2006) 1158–1171, https://doi.org/10.1111/j.1462-5822.2006.00699.x.
[25] S.L. Weinstein, et al., Phosphatidylinositol 3-kinase and mTOR mediate lipopolysaccharide-stimulated nitric oxide production in macrophages via interferon-b, J. Leukoc. Biol. 67 (2000) 405–414.
[26] S.C. Huang, et al., Cell-intrinsic lysosomal lipolysis is essential for alternative activation of macrophages, Nat. Immunol. 15 (2014) 846–855, https://doi.org/10.1038/ni.2956.
[27] W.T. Festuccia, P. Pouliot, I. Bakan, D.M. Sabatini, M. Laplante, Myeloid-specific Rictor deletion induces M1 macrophage polarization and potentiates in vivo pro-inflammatory response to lipopolysaccharide, PLoS One 9 (2014) e95432, , https://doi.org/10.1371/journal.pone.0095432.
[28] M.D. Buck, et al., Mitochondrial dynamics controls T cell fate through metabolic programming, Cell 166 (2016) 63–76, https://doi.org/10.1016/j.cell.2016.05.035.
[29] V. Byles, et al., The TSC-mTOR pathway regulates macrophage polarization, Nat. Commun. 4 (2013) 2834, https://doi.org/10.1038/ncomms3834.
[30] H.Z. Imtiyaz, M.C. Simon, Hypoxia-inducible factors as essential regulators of inflammation, Curr. Top. Microbiol. Immunol. 345 (2010) 105–120.
[31] J.W. Kim, I. Tchernyshyov, G.L. Semenza, C.V. Dang, HIF-1-mediated expression of pyruvate dehydrogenase kinase: a metabolic switch required for cellular adaptation to hypoxia, Cell Metabol. 3 (2006) 177–185, https://doi.org/10.1016/j.cmet.2006.02.002.
[32] I. Papandreou, R.A. Cairns, L. Fontana, A.L. Lim, N.C. Denko, HIF-1 mediates adaptation to hypoxia by actively downregulating mitochondrial oxygen consumption, Cell Metabol. 3 (2006) 187–197, https://doi.org/10.1016/j.cmet.2006.01.012.
[33] J.W. Locasale, L.C. Cantley, Metabolic flux and the regulation of mammalian cell growth, Cell Metabol. 14 (2011) 443–451, https://doi.org/10.1016/j.cmet.2011.07.014.
[34] J. Jantsch, et al., Hypoxia and hypoxia-inducible factor-1 modulate lipopolysaccharide-induced dendritic cell activation and function, J. Immunol. 180 (2008) 4697–4705, https://doi.org/10.4049/jimmunol.180.7.4697.
[35] H.Z. Imtiyaz, et al., Hypoxia-inducible factor 2 alpha regulates macrophage function in mouse models of acute and tumor inflammation, J. Clin. Investig. 120 (2010) 2699–2714, https://doi.org/10.1172/JCI39506.
[36] G.L. Semenza, P.H. Roth, H.M. Fang, G.L. Wang, Transcriptional regulation of genes encoding glycolytic enzymes by hypoxia-inducible factor 1, J. Biol. Chem. 269 (1994) 23757–23763.
[37] G.M. Tannahill, et al., Succinate is an inflammatory signal that induces IL-1beta through HIF-1alpha, Nature 496 (2013) 238–242, https://doi.org/10.1038/nature11986.
[38] C. Li, et al., HIF1alpha-dependent glycolysis promotes macrophage functional activities in protecting against bacterial and fungal infection, Sci. Rep. 8 (2018) 3603, https://doi.org/10.1038/s41598-018-22039-9.
[39] G. Liu, et al., SIRT1 limits the function and fate of myeloid-derived suppressor cells in tumors by orchestrating HIF-1alpha-dependent glycolysis, Canc. Res. 74 (2014) 727–737, https://doi.org/10.1158/0008-5472.CAN-13-2584.
[40] Y. Wang, et al., Histone deacetylase SIRT1 negatively regulates the differentiation of interleukin-9-producing CD4(+) T cells, Immunity 44 (2016) 1337–1349, https://doi.org/10.1016/j.immuni.2016.05.009.
[41] I.N. Shalova, et al., Human monocytes undergo functional re-programming during sepsis mediated by hypoxia-inducible factor-1alpha, Immunity 42 (2015) 484–498, https://doi.org/10.1016/j.immuni.2015.02.001.
[42] H.Y. Fang, et al., Hypoxia inducible factors 1 and 2 are important transcriptional effectors in primary macrophages experiencing hypoxia, Blood 114 (2009) 844–859.
[43] M.Z. Noman, et al., PD-L1 is a novel direct target of HIF-1alpha, and its blockade under hypoxia enhanced MDSC-mediated T cell activation, J. Exp. Med. 211 (2014) 781–790, https://doi.org/10.1084/jem.20131916.
[44] P. Gao, et al., c-Myc suppression of miR-23a/b enhances mitochondrial glutaminase expression and glutamine metabolism, Nature 458 (2009) 762–765, https://doi.org/10.1038/nature07823.
[45] D.R. Wise, et al., Myc regulates a transcriptional program that stimulates mitochondrial glutaminolysis and leads to glutamine addiction, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 18782–18787, https://doi.org/10.1073/pnas.0810199105.
[46] O.M. Pello, et al., In vivo inhibition of c-MYC in myeloid cells impairs tumor-associated macrophage maturation and pro-tumoral activities, PLoS One 7 (2012) e45399, , https://doi.org/10.1371/journal.pone.0045399.
[47] O.M. Pello, et al., Role of c-MYC in alternative activation of human macrophages and tumor-associated macrophage biology, Blood 119 (2012) 411–421, https://doi.org/10.1182/blood-2011-02339911.
[48] Y.P. Zhu, J.R. Brown, D. Sag, L. Zhang, J. Suttles, Adenosine 5'-monophosphate-activated protein kinase regulates IL-10-mediated anti-inflammatory signaling pathways in macrophages, J. Immunol. 194 (2015) 584–594, https://doi.org/10.4049/jimmunol.1401024.
[49] D. Sag, D. Carling, R.D. Stout, J. Suttles, AMP-activated protein kinase promotes macrophage polarization to an anti-inflammatory functional phenotype, J. Immunol. 181 (2008) 8633–8641.

[50] F. Blaschke, et al., A nuclear receptor corepressor-dependent pathway mediates suppression of cytokine-induced C-reactive protein gene expression by liver X receptor, Circ. Res. 99 (2006) e88–99, https://doi.org/10.1161/01.RES.0000252878.34269.06.

[51] A. Szanto, et al., STAT6 transcription factor is a facilitator of the nuclear receptor PPARgamma-regulated gene expression in macrophages and dendritic cells, Immunity 33 (2010) 699–712, https://doi.org/10.1016/j.immuni.2010.11.009.

[52] J.I. Odegaard, et al., Macrophage-specific PPARgamma controls alternative activation and improves insulin resistance, Nature 447 (2007) 1116–1120, https://doi.org/10.1038/nature05894.

[53] J. Park, et al., M-CSF from cancer cells induces fatty acid synthase and PPARbeta/delta activation in tumor myeloid cells, leading to tumor progression, Cell Rep. (2015), https://doi.org/10.1016/j.celrep.2015.02.024.

[54] S. B, PPARβ in macrophages and atherosclerosis.%A Chinetti-Gbaguidi G, Biochimie 136 (2017) 59–64.

[55] S. AR, Z. M, D. DL, A macrophage-dominant PI3K isoform controls hypoxia-induced Hif-1α and HIF2α stability and tumor growth, angiogenesis, and metastasis. %A Joshi S, Mol. Canc. Res.: MCR 12 (2014) 1520–1531.

[56] D.P. M, et al., Role of c-MYC in alternative activation of human macrophages and tumor-associated macrophage biology.%A Pello OM, Blood 119 (2012) 411–421.

[57] S. G, B. SN, C. L, R. J, Z. P, Peroxisome proliferator-activated receptors gamma and alpha agonists stimulate cardiac glucose uptake via activation of AMP-activated protein kinase.%A Xiao X, J. Nutr. Biochem. 21 (2010) 621–626.

[58] J.C. Rodriguez-Prados, et al., Substrate fate in activated macrophages: a comparison between innate, classic, and alternative activation, J. Immunol. 185 (2010) 605–614, https://doi.org/10.4049/jimmunol.0901698.

[59] G.L. Semenza, Targeting HIF-1 for cancer therapy, Nat. Rev. Canc. 3 (2003) 721–732, https://doi.org/10.1038/nrc1187.

[60] E.M. Palsson-McDermott, et al., Pyruvate kinase M2 regulates Hif-1alpha activity and IL-1beta induction and is a critical determinant of the warburg effect in LPS-activated macrophages, Cell Metabol. 21 (2015) 65–80, https://doi.org/10.1016/j.cmet.2014.12.005.

[61] A. Haschemi, et al., The sedoheptulose kinase CARKL directs macrophage polarization through control of glucose metabolism, Cell Metabol. 15 (2012) 813–826, https://doi.org/10.1016/j.cmet.2012.04.023.

[62] T. Cordes, A. Michelucci, K. Hiller, Itaconic acid: the surprising role of an industrial compound as a mammalian antimicrobial metabolite, Annu. Rev. Nutr. 35 (2015) 451–473, https://doi.org/10.1146/annurev-nutr-071714-034243.

[63] A. Michelucci, et al., Immune-responsive gene 1 protein links metabolism to immunity by catalyzing itaconic acid production, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 7820–7825.

[64] J. St-Pierre, et al., Bioenergetic analysis of peroxisome proliferator-activated receptor gamma coactivators 1alpha and 1beta (PGC-1alpha and PGC-1beta) in muscle cells, J. Biol. Chem. 278 (2003) 26597–26603, https://doi.org/10.1074/jbc.M301850200.

[65] D. Shao, et al., PGC-1 beta-regulated mitochondrial biogenesis and function in myotubes is mediated by NRF-1 and ERR alpha, Mitochondrion 10 (2010) 516–527, https://doi.org/10.1016/j.mito.2010.05.012.

[66] J. Van den Bossche, et al., Mitochondrial dysfunction prevents repolarization of inflammatory macrophages, Cell Rep. 17 (2016) 684–696, https://doi.org/10.1016/j.celrep.2016.09.008.

[67] L.A. O'Neill, A metabolic roadblock in inflammatory macrophages, Cell Rep. 17 (2016) 625–626, https://doi.org/10.1016/j.celrep.2016.09.085.

[68] C. Traversari, S. Sozzani, K.R. Steffensen, V. Russo, LXR-dependent and -independent effects of oxysterols on immunity and tumor growth, Eur. J. Immunol. 44 (2014) 1896–1903, https://doi.org/10.1002/eji.201344292.

[69] Z. Czimmerer, et al., The transcription factor STAT6 mediates direct repression of inflammatory enhancers and limits activation of alternatively polarized macrophages, Immunity 48 (2018) 75–90, https://doi.org/10.1016/j.immuni.2017.12.010 e76.

[70] D. Namgaladze, B. Brune, Fatty acid oxidation is dispensable for human macrophage IL-4-induced polarization, Biochim. Biophys. Acta 1841 (2014) 1329–1335, https://doi.org/10.1016/j.bbalip.2014.06.007.

[71] J.S. Moon, et al., NOX4-dependent fatty acid oxidation promotes NLRP3 inflammasome activation in macrophages, Nat. Med. 22 (2016) 1002–1012, https://doi.org/10.1038/nm.4153.

[72] J.W. Lee, et al., UPLC-QqQ/MS-Based lipidomics approach to characterize lipid alterations in inflammatory macrophages, J. Proteome Res. 16 (2017) 1460–1469, https://doi.org/10.1021/acs.jproteome.6b00848.

[73] M. Rath, I. Muller, P. Kropf, E.I. Closs, M. Munder, Metabolism via arginase or nitric oxide synthase: two competing arginine pathways in macrophages, Front. Immunol. 5 (2014) 532, https://doi.org/10.3389/fimmu.2014.00532.

[74] M. Modolell, I.M. Corraliza, F. Link, G. Soler, K. Eichmann, Reciprocal regulation of the nitric oxide synthase/arginase balance in mouse bone marrow-derived macrophages by Th1 and Th2 cytokines, Eur. J. Immunol. 25 (1995) 1101–1104.

[75] P. Newsholme, Why is L-glutamine metabolism important to cells of the immune system in health, postinjury, surgery or infection? J. Nutr. 131 (2001) 2515–2522.

[76] H. SC, et al., Network integration of parallel metabolic and transcriptional data reveals metabolic modules that regulate macrophage polarization.%A Jha AK, Immunity 42 (2015) 419–430.

[77] A.K. Jha, et al., Network integration of parallel metabolic and transcriptional data reveals metabolic modules that regulate macrophage polarization, Immunity 42 (2015) 419–430, https://doi.org/10.1016/j.immuni.2015.02.005.

[78] O.R. Colegio, et al., Functional polarization of tumour-associated macrophages by tumour-derived lactic acid, Nature 513 (2014) 559–563, https://doi.org/10.1038/nature13490.

[79] G. Cairo, S. Recalcati, A. Mantovani, M. Locati, Iron trafficking and metabolism in macrophages: contribution to the polarized phenotype, Trends Immunol. 32 (2011) 241–247, https://doi.org/10.1016/j.it.2011.03.007.

[80] L.E. Otterbein, et al., Carbon monoxide has anti-inflammatory effects involving the mitogen-activated protein kinase pathway, Nat. Med. 6 (2000) 422–428, https://doi.org/10.1038/74680.

[81] Y. Okabe, R. Medzhitov, Tissue biology perspective on macrophages, Nat. Immunol. 17 (2016) 9–17, https://doi.org/10.1038/ni.3320.

[82] M. Jung, C. Mertens, B. Brune, Macrophage iron homeostasis and polarization in the context of cancer, Immunobiology 220 (2015) 295–304.

[83] A. Jais, et al., Heme oxygenase-1 drives metaflammation and insulin resistance in mouse and man, Cell 158 (2014) 25–40, https://doi.org/10.1016/j.cell.2014.04.043.

[84] A.P. West, et al., TLR signalling augments macrophage bactericidal activity through mitochondrial ROS, Nature 472 (2011) 476–480, https://doi.org/10.1038/nature09973.

[85] F. Aktan, iNOS-mediated nitric oxide production and its regulation, Life Sci. 75 (2004) 639–653, https://doi.org/10.1016/j.lfs.2003.10.042.

[86] S. SA, Nitric oxide modulates macrophage responses to infection through activation of HIF-1α and repression of NF-κB.%A braverman J, J. Immunol. 199 (2017) 1805–1816 Baltimore, Md.: 1950.

[87] L. U, F. O, W. WW, R. NE, c-Myc is a novel virulence factor by proxy that targets the host miRNA system and is essential for survival in human macrophages.%A Colineau L, J. Biol. Chem. 293 (2018) 12805–12819.

[88] M.T. Sorbara, S.E. Girardin, Mitochondrial ROS fuel the inflammasome, Cell Res. 21 (2011) 558–560, https://doi.org/10.1038/cr.2011.20.

[89] J. Tschopp, K. Schroder, NLRP3 inflammasome activation: the convergence of multiple signalling pathways on ROS production? Nat. Rev. Immunol. 10 (2010) 210–215, https://doi.org/10.1038/nri2725.

[90] P.J. Murray, T.A. Wynn, Protective and pathogenic functions of macrophage subsets, Nat. Rev. Immunol. 11 (2011) 723–737, https://doi.org/10.1038/nri3073.

[91] S.K. Biswas, Metabolic reprogramming of immune cells in cancer progression, Immunity 43 (2015) 435–449, https://doi.org/10.1016/j.immuni.2015.09.001.

[92] S.K. Biswas, P. Allavena, A. Mantovani, Tumor-associated macrophages: functional diversity, clinical significance, and open questions, Semin. Immunopathol. 35 (2013) 585–600, https://doi.org/10.1007/s00281-013-0367-7.

[93] B.Z. Qian, J.W. Pollard, Macrophage diversity enhances tumor progression and metastasis, Cell 141 (2010) 39–51, https://doi.org/10.1016/j.cell. 2010.03.014.

[94] S.I. Grivennikov, F.R. Greten, M. Karin, Immunity, inflammation, and cancer, Cell 140 (2010) 883–899, https://doi.org/10.1016/j.cell.2010.01.025.

[95] M. RL, R. SD, Macrophage polarization contributes to glioblastoma eradication by combination immunovirotherapy and immune checkpoint blockade.%A Saha D, Canc. Cell 32 (2017) 253–267 e255.

[96] W. R, et al., Exclusion of T Cells from pancreatic carcinomas in mice is regulated by Ly6C(low) F4/80(+) extratumoral macrophages.%A beatty GL, Gastroenterology 149 (2015) 201–210.

[97] A. Mantovani, P. Allavena, A. Sica, F. Balkwill, Cancer-related inflammation, Nature 454 (2008) 436–444, https://doi.org/10.1038/nature07205.

[98] C. Murdoch, M. Muthana, S.B. Coffelt, C.E. Lewis, The role of myeloid cells in the promotion of tumour angiogenesis, Nat. Rev. Canc. 8 (2008) 618–631, https://doi.org/10.1038/nrc2444.

[99] H. Z, et al., Vascular niche IL-6 induces alternative macrophage activation in glioblastoma through HIF-2α.%A Wang Q, Nat. Commun. 9 (2018) 559.

[100] H. Shime, et al., Tumor-secreted lactic acid promotes IL-23/IL-17 proinflammatory pathway, J. Immunol. 180 (2008) 7175–7183, https://doi.org/10.4049/jimmunol.180.11.7175.

[101] C.I. Chang, J.C. Liao, L. Kuo, Macrophage arginase promotes tumor cell growth and suppresses nitric oxide-mediated tumor cytotoxicity, Canc. Res. 61 (2011) 1101–1106.

[102] S. Kusmartsev, D.I. Gabrilovich, STAT1 signaling regulates tumor-associated macrophage-mediated T cell deletion, J. Immunol. 174 (2005) 4880–4891, https://doi.org/10.4049/jimmunol.174.8.4880.

[103] D.R. Sharda, et al., Regulation of macrophage arginase expression and tumor growth by the Ron receptor tyrosine kinase, J. Immunol. 187 (2011) 2181–2192, https://doi.org/10.4049/jimmunol.1003460.

[104] F.O. Martinez, S. Gordon, M. Locati, A. Mantovani, Transcriptional profiling of the human monocyte-to-macrophage differentiation and polarization: new molecules and patterns of gene expression, J. Immunol. 177 (2006) 7303–7311, https://doi.org/10.4049/jimmunol.177.10.7303.

[105] J.M. Poczobutt, et al., Eicosanoid profiling in an orthotopic model of lung cancer progression by mass spectrometry demonstrates selective production of leukotrienes by inflammatory cells of the microenvironment, PLoS One 8 (2013) e79633, , https://doi.org/10.1371/journal. pone.0079633.t00110.1371/journal.pone.0079633.g001.

[106] Y. Zhang, et al., Fatty acid-binding protein E-FABP restricts tumor growth by promoting IFN-beta responses in tumor-associated macrophages, Cancer Res. 74 (2014) 2986–2998, https://doi.org/10.1158/0008-5472.CAN-13-2689.

[107] R.T. Deng, Inhibition of tumor growth and alteration of associated macrophage cell type by an HO-1 inhibitor in breast carcinoma-bearing mice, J. Oncol. Res. 20 (10) (2013) 473–482.

[108] P.H. Maxwell, et al., The tumor suppressor protein VHL targets hypoxia-inducible factors for ox-ygen-dependent proteolysis, Nature 399 (1999) 271–275.