ISSN 0006-2979, Biochemistry (Moscow), 2024, Vol. 89, No. 5, pp. 817-838 © Pleiades Publishing, Ltd., 2024.

REVIEW

Metabolic Adaptations and Functional Activity of Macrophages in Homeostasis and Inflammation

Taisiya R. Yurakova[1], Ekaterina A. Gorshkova[1], Maxim A. Nosenko[2], and Marina S. Drutskaya[1,3,a]*

[1]*Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, 119991 Moscow, Russia*

[2]*Trinity Biomedical Sciences Institute, Trinity College Dublin, D02F306 Dublin, Ireland*

[3]*Division of Immunobiology and Biomedicine, Center of Genetics and Life Sciences, Sirius University of Science and Technology, 354340 Federal Territory Sirius, Russia*

[a]*e-mail: marinadru@gmail.com*

Received November 27, 2023
Revised February 6, 2024
Accepted February 8, 2024

Abstract—In recent years, the role of cellular metabolism in immunity has come into the focus of many studies. These processes form a basis for the maintenance of tissue integrity and homeostasis, as well as represent an integral part of the immune response, in particular, inflammation. Metabolic adaptations not only ensure energy supply for immune response, but also affect the functions of immune cells by controlling transcriptional and post-transcriptional programs. Studying the immune cell metabolism facilitates the search for new treatment approaches, especially for metabolic disorders. Macrophages, innate immune cells, are characterized by a high functional plasticity and play a key role in homeostasis and inflammation. Depending on the phenotype and origin, they can either perform various regulatory functions or promote inflammation state, thus exacerbating the pathological condition. Furthermore, their adaptations to the tissue-specific microenvironment influence the intensity and type of immune response. The review examines the effect of metabolic reprogramming in macrophages on the functional activity of these cells and their polarization. The role of immunometabolic adaptations of myeloid cells in tissue homeostasis and in various pathological processes in the context of inflammatory and metabolic diseases is specifically discussed. Finally, modulation of the macrophage metabolism-related mechanisms reviewed as a potential therapeutic approach.

DOI: 10.1134/S0006297924050043

Keywords: proinflammatory cytokines, macrophage polarization, immunometabolism

INTRODUCTION

The majority of immunological studies in cell and animal models have been focused on the functions of immune cells, in particular, antigen recognition, as well as elimination and production of active compounds and cytokines. Because of this, immune response has become increasingly viewed as a systemic body response leading to metabolic rewiring and functional changes in tissues and organs. The association between metabolism and immune system was first discovered in the last century by physiologist Otto Warburg, who noticed that upregulation of glycolysis was characteristic not only of tumor cells, but also of the activated leukocytes [1, 2]. Now, it is commonly recognized that metabolic adaptations are an integral part

Abbreviations: 2-DG, 2-deoxyglucose; 2-HG, 2-hydroxyglutarate; ARG1, arginase 1; ACLY, ATP citrate lyase; AMPK, AMP-activated protein kinase; CPT, carnitine palmitoyltransferase; DMF, dimethyl fumarate; ETC, electron transport chain; FA, fatty acid; HIF-1α, hypoxia-inducible factor 1-alpha; IDH, isocitrate dehydrogenase; iNOS, inducible nitric oxide synthase; LDHA, lactate dehydrogenase; LPS, lipopolysaccharide; mTOR, mammalian target of rapamycin; OXPHOS, oxidative phosphorylation; PGE_2, prostaglandin E2; PKM2, pyruvate kinase M2; PPP, pentose phosphate pathway; ROS, reactive oxygen species; SDH, succinate dehydrogenase.

* To whom correspondence should be addressed.

of the immune response [3-8]. The discovery of regulatory pathways involved in the metabolic control of immune processes during infection, cancer, and tissue regeneration at the cellular, tissue, and organ levels have led to the emergence of a new interdisciplinary field of research, immunometabolism [3, 8]. Immunometabolic disorders are responsible for many diseases typical for the modern human population, including obesity, diabetes, sepsis, autoimmune and autoinflammatory diseases [3]. Hence, understanding the mechanisms by which physiological microenvironment of immune cells in tissues and organs regulates their functions is very important. Among immune cells, macrophages are of a special interest because they can be found in almost all animal tissues and represent an integral component in the maintenance of tissue homeostasis [9]. The review describes the relationship between the functional and metabolic features of macrophages in homeostasis and immunometabolic disorders, as well as discusses possible therapeutic approaches based on the modulation of macrophage metabolism.

FUNCTIONAL AND PHENOTYPIC DIVERSITY OF MACROPHAGES

Macrophages had been initially considered as a part of the mononuclear phagocytic system responsible for the removal of pathogens and apoptotic cells, but the current understanding of the functions and

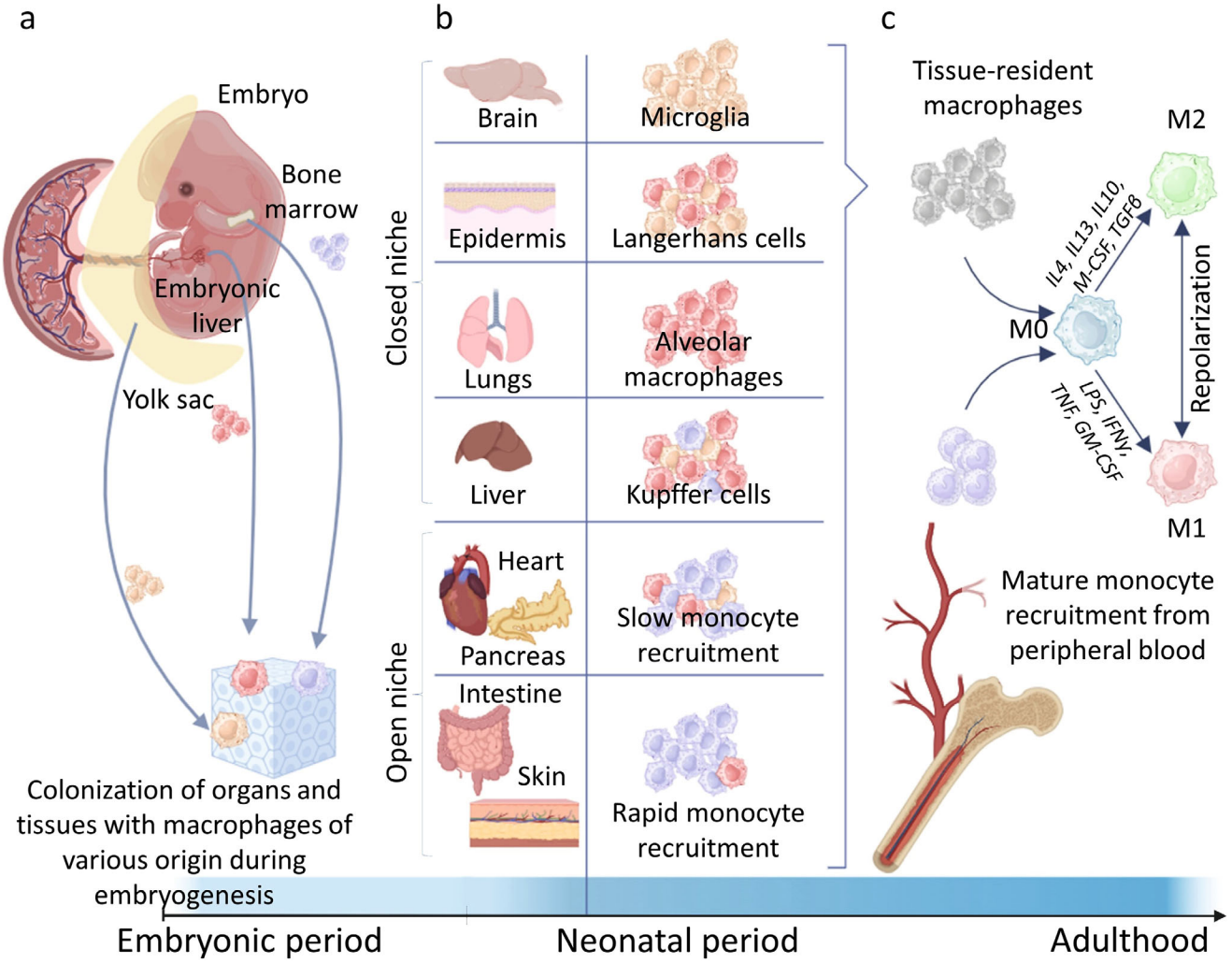

Fig. 1. Macrophage differentiation and polarization. a) Tissue-resident macrophages differentiate from three types of hematopoietic stem cell precursors found in the yolk sac, embryonic liver, and bone marrow. b) Origin of tissue-resident macrophages in different organs. Tissue-resident macrophages are formed in closed niches during embryogenesis; in adults, peripheral blood monocytes do not migrate into these niches. In open niches, monocytes are recruited at different rates (slow or fast) and replace tissue-resident macrophage pool formed during embryogenesis. c) Phenotype of tissue-resident macrophages is a result of their differentiation and polarization. Macrophages polarize into pro-inflammatory (M1) or anti-inflammatory (M2) phenotypes under the influence of external stimuli. Created with the BioRender.com based on previously published data [20, 24-26].

the origin of macrophages have been significantly expanded. Macrophages were shown to play an important role in homeostasis, tissue formation during embryogenesis, and wound healing, as well as in various tissue-specific functions [10]. Thus, tissue-specific macrophages determine normal development and functioning of the brain, bones, ovaries, and adipose tissue. Macrophages are involved in the control of systemic metabolism and temperature adaptation [11, 12]. Finally, macrophages play an important role in the development of metabolic diseases, such as atherosclerosis [13], osteoporosis, obesity, and type 2 diabetes [14, 15]. Pathogenic contribution of macrophages to fibrosis [16] and tumor development has been recognized as well [17].

Tissue-resident macrophages can vary dramatically in both phenotype and functions. A population of macrophages in an organ or tissue is characterized by the functional heterogeneity that depends on the cell location, tissue condition, cell origin, and many other factors. Tissue-resident macrophages can differentiate from the precursors of hematopoietic stem cells found in the yolk sac, embryonic liver, and bone marrow [18, 19]. The proportion of macrophages originating from different migration waves varies depending on the organ [20] (Fig. 1, a and b).

The phenotype of a macrophage largely depends on the surrounding signals [21]. The two main macrophage phenotypes are pro-inflammatory (M1) and anti-inflammatory (M2). M1 macrophages induce and maintain inflammation via release of pro-inflammatory cytokines, activation of endothelial cells, and attraction of other immune cells to the site of inflammation. M2 macrophages counteract inflammation by phagocytosis of apoptotic cells, triggering of collagen deposition, coordination of tissue repair processes, and release of anti-inflammatory cytokines [22]. It should be noted that the M1 and M2 phenotypes could be clearly distinguished mainly in *in vitro* experiments using certain combinations of stimuli. Under physiological conditions, the phenotype of macrophages is greatly influenced by various signaling molecules and tissue microenvironment, so pure M1 or M2 phenotypes are rarely observed *in vivo* [23]. Depending on the context, macrophages acquire an intermediate or unique phenotype and are typically represented by a mixed heterogeneous population of M1 and M2 cells [23]. Therefore, macrophage polarization *in vivo* should be viewed as a complex tissue-specific process developing in time (Fig. 1) [24-26].

There are two stages of "decision-making" at the molecular level in polarization [27]. The first one is alteration in the functional state of M1/M2 macrophages that involves activation of signaling pathways associated with either innate immunity, such as signaling via pattern recognition receptors (PRR), or stimuli from T cells [28, 29]. Signals leading to macrophage polarization *in vivo* are often difficult to identify [21]. Bacterial endotoxin, lipopolysaccharide (LPS), or a combination of LPS and interferon gamma (IFNγ, main Th1-associated cytokine) are generally used to polarize M1 macrophages *in vitro*. M2 macrophages are polarized using Th2-associated cytokine interleukin-4 (IL-4) or a combination of IL-4 and IL-13 [22]. IRF, STAT, and NF-κB transcription factors play a key role in the control of M1/M2 polarization, M1 regulators (NF-κB-p50-p65, STAT1, IRF5, SOCS3, and HIF-1α) being antagonists of M2 regulators (NF-κB-p50-p50, STAT6, IRF4, SOCS1, and HIF-2). The second stage of "decision-making" involves interaction of transcription factors [30] and is closely related to the activity of the two main regulators of cellular metabolism – AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR). The most important outcome of the second stage is altered expression of metabolism-associated genes, which affects a variety of metabolic processes, such as glycolysis, Krebs cycle, oxidative phosphorylation (OXPHOS), pentose phosphate pathway (PPP), formation of NADPH and reactive oxygen species (ROS), biosynthesis of nucleotides and amino acids, as well as nitrogen metabolism.

METABOLIC ADAPTATIONS OF MACROPHAGES DURING POLARIZATION

To meet the demands for ATP and NADPH, M1 macrophages use aerobic glycolysis and PPP, leading to the breaks in the Krebs cycle at two points and reduction in the cellular respiration, in particular, OXPHOS, as well changes in the metabolism of fatty acids (FAs) (upregulation of beta oxidation and suppression of synthesis of FAs). M2 macrophages do not depend on glycolysis and mainly use OXPHOS as a source of energy, so that there are no breaks in the Krebs cycle. During M2 polarization, glucose is utilized mainly by the PPP and used for the synthesis of uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) [31]. The changes in the metabolism of FAs in M2 macrophages are opposite to those observed in M1 cells, i.e., the synthesis of FAs is decreased and their beta oxidation is upregulated [22, 30]. Based on the changes in the characteristic properties of M1 or M2 phenotypes (Table 1) acquired as a result of pharmaceutical or genetic suppression of metabolic enzymes, it is possible to assess the contribution of particular metabolic pathways to the macrophage polarization. Below, we discuss in detail the metabolic changes that occur during macrophage polarization.

Glucose metabolism. Glucose is important in both M1 and M2 polarization [32, 33], but its distribution between metabolic pathways is different for these two

Table 1. Properties of M1 and M2 macrophages

Polarization property	M1 (LPS + IFNγ)	M2 (IL-4 + IL-13)
Stimuli	LPS + IFNγ; bacterial products; LPS and other ligands of Toll-like receptors (TLRs); cytokines of Th1 lymphocytes (IFN-γ, TNF)	IL-4 + IL-13; basophiles; mast cells; Th2 lymphocytes
Cell-derived mediators	TNF, IL-1β, IL-6, IL-12, IL-23; ROS, PGE_2	IL-10, TGFβ, IGF-1, VEGF-A, EGF, PDGF
Cell surface markers	CD80, CD86, CIITA, MHCII	mannose receptor (CD206), CD36, IL1Rα, CD163 CD36, RELMα (FIZZ1 in humans), MMP
Signaling pathways	NF-κB (p50-p65), STAT1, IRF5, HIF-1α, SOCS3, AP1; inflammasome activation	NF-κB (p50-p50), STAT6, IRF4, HIF2, SOCS1, GATA3, PPARγ, (in mice also YM1)
Functions	elimination of bacteria; tumor resistance; Th1 response; pathogen elimination and antigen presentation to T lymphocytes	anti-inflammatory response; tissue remodeling; wound healing; angiogenesis

types of macrophage activation. M1 macrophages significantly increase glucose entry via upregulation of the GLUT1 transporter [34], while glucose utilization by M2 macrophages remains unchanged [35]. Glycolysis has been considered as the main metabolic pathway conjugated with ATP production in immunometabolism. However, recent data indicate an important role of PPP and glycosylation in the metabolism of activated immune cells. The studies of glucose metabolism typically use glucose analogue 2-deoxyglucose (2-DG). However, the effect of this compound in immune cells is nonspecific, as it blocks all glucose catabolism pathways, not only glycolysis [36]. As a result, 2-DG disrupts polarization of both M1 and M2 macrophages, which has led to erroneous conclusion on a significant contribution of glycolysis to both types of macrophage polarization.

A more detailed study has demonstrated a critical importance of glycolysis for M1 macrophages [31]. Activation of M1 macrophages is associated with the increase in the expression of several variants of the key glycolysis enzyme – phosphofructokinase (PFK1-M and PFK2) [35, 37]. The reaction catalyzed by this enzyme is irreversible and represents a commitment step for glycolysis. Upregulation of the PFK-M expression is associated with the suppression of production of microRNA-21 upon macrophage stimulation by IFNγ [37]. PFK2 suppression leads to a decrease in the expression of inducible NO synthase (iNOS) and mitogen-inducible form of cyclooxygenase (COX2) by M1 macrophages [35]. Only M1 (but not M2) macrophages demonstrate increased expression of the phosphofructokinase regulator (PFKFB3); inhibition of this protein prevents upregulation of glycolysis and activation of M1 macrophages [38]. Inhibition of glyceraldehyde 3-phosphate dehydrogenase (GAPDH), one of the key glycolytic enzymes, suppresses IL-1β production similar to 2-DG [32, 39]. Finally, suppression of lactate dehydrogenase (LDHA) and pyruvate dehydrogenase 1 (PDK1) genes also caused a decrease in the IL-1β production by the macrophages [40]. The critical importance of glycolysis for M1 macrophages remains poorly understood. Presumably, it might be due to the OXPHOS suppression during M1 polarization, which requires a compensatory upregulation of glycolysis to ensure ATP production. OXPHOS remains active in M2 macrophages, making glycolysis nonessential for maintaining energy balance [36].

The most important transcription factor regulating glycolysis is hypoxia-inducible factor 1-alpha (HIF-1α) [41]. HIF-1α controls expression of genes coding for glycolytic enzymes, glucose transporter GLUT1, inflammatory mediators, LDHA, and PDK. LDHA catalyzes pyruvate conversion to lactate; PDK inactivates pyruvate dehydrogenase (PDH) and reduces pyruvate entry into the Krebs cycle. Pyruvate conversion to lactate is important for M1 macrophages as it provides restoration of the NAD^+ pool in order to maintain glycolytic reactions. HIF-1α expression is regulated by signals from the innate immune receptors and proinflammatory cytokines via NF-κB [42-44] and growth factors. For example, granulocyte-macrophage colony-stimulating factor (GM-CSF) activates HIF-1α through the PI3K/AKT/mTOR pathway [45-49]. Although HIF-1α is inactivated in the presence of oxygen, it can be stabilized by succinate produced

in the mitochondria due to breaks in the Krebs cycle [22, 32].

Expression of different isoforms of pyruvate kinase M2 (PKM2) accounts for different regulation of glycolysis in M1 and M2 macrophages [35, 50, 51]. PKM2 has two conformations: the tetramer is enzymatically active and participates in glycolysis, while the dimer, which lacks the enzymatic activity, localizes to the nucleus and functions as a transcription factor that regulates expression of HIF-1α-dependent genes, including *Il1b*. Stabilization of the PKM2 tetramer with the small TEPP-46 molecule reduces activation of M1 macrophages and makes them phenotypically similar to M2 cells [50].

Pentose phosphate pathway takes place in the cytoplasm. The oxidative phase of PPP plays an important role in the metabolism of M1 macrophages [32, 52]. During this phase, glucose-6-phosphate is converted to ribulose-5-phosphate, which is accompanied by the NADPH formation from H and $NADP^+$. NADPH is involved in the synthesis of glutathione, an antioxidant that protects cells from oxidative stress. On the other hand, NADPH is a substrate for many ROS-producing enzymes, for example, NADPH oxidases (NOXs) are essential for the pathogen destruction by M1 macrophages [22, 53]. NADPH is also required for the synthesis of FAs and prostaglandins.

PPP is less important in M2 macrophages and is involved in cell metabolism to a much lesser extent. On the one hand, UDP-GlcNAc synthesized from ribose-5-phosphate produced during the PPP oxidation stage, is used in N-glycosylation of the mannose receptor abundantly present on the surface of M2 macrophages [54]. UDP-GlcNAc can be synthesized from glucose-1-phosphate independently of PPP during M2 polarization [31]. The importance of N-glycosylation for the M2 phenotype development has been confirmed in the experiments using the inhibitor of N-glycosylation tunicamycin [31]. On the other hand, it was recently demonstrated that activation of PPP suppresses efferocytosis (phagocytosis of tolerogenic apoptotic cell) that is characteristic for M2 macrophages [55].

Oxidative phosphorylation. OXPHOS is the main source of ATP in the cells under normoxic conditions, including inactive macrophages (M0). Polarization increases energy requirements of the cells regardless of polarization type, but the activity of OXPHOS in M1 and M2 macrophages differs. M1 macrophages are characterized by OXPHOS suppression, while M2 polarization, on the contrary, increases the activity of the electron transport chain (ETC) [56]. Nitric oxide (NO) suppresses OXPHOS in M1 macrophages by blocking the ETC and prevents their repolarization into M2 macrophages [57]. Besides, recognition of live bacteria by the macrophages results in the reduction of active complexes I and III of the ETC due to the ROS production [58]. Activation of STAT6 during M2 polarization leads to the upregulated expression of genes involved in the FA oxidation and OXPHOS [59]. OXPHOS suppression, in turn, interferes with the expression of M2 markers, such as arginase 1 (ARG1) and mannose receptor.

The functioning of the ETC is inevitably accompanied by the generation of ROS. Thus, ROS generation in the mitochondria is a result of electron leakage through the complexes I, II, and III in the case of disruption of the ETC or mitochondrial membrane potential. ROS production in the mitochondria depends on the metabolic state of these organelles [60, 61]. It should be noted that the decrease in the respiration during M1 polarization is associated with the increase in the production of mitochondrial ROS, which stimulates secretion of proinflammatory cytokines [62]. Thus, activation of macrophages with LPS leads to the ROS production, apparently, via reverse electron flow from the succinate dehydrogenase (SDH) complex in the ETC. Moreover, activation of the toll-like receptors (TLRs) 1, 2, and 4 stimulates mitochondrial ROS generation due to the TRAF6 translocation into the mitochondria [63]. Macrophages produce ROS in response to a pathogen or activation by proinflammatory cytokines; ROS generation is associated with the activation of NOXs and is independent of cyanides that block the complex IV of the respiratory chain. ROS production by cells of the innate immune system, including macrophages, is necessary to fight pathogens, however, a prolonged inflammatory process increases ROS production, resulting in oxidative stress, which leads to the dysfunction of the vascular endothelium and other disorders [64].

The Krebs cycle, also known as the tricarboxylic acid cycle, is a central metabolic pathway that provides cells with ATP. During macrophage activation, many processes, such as proliferation, synthesis of cytokines and other proinflammatory mediators, migration, and phagocytosis, require ATP. Moreover, M2 macrophages need ATP to maintain high levels of glycosylation of lectin and mannose receptors. Intermediate metabolites of the Krebs cycle are also important for the macrophage activation and polarization. Their accumulation in the cell can result from the breaks in the Krebs cycle due to the inhibition of isocitrate dehydrogenase (IDH) or SDH. The impact of Krebs cycle intermediates (citrate, itaconate, succinate, fumarate, and alpha-ketoglutarate) on the macrophage polarization is described in detail in [65, 66].

Citrate is synthesized in the Krebs cycle via condensation of oxaloacetate and acetyl-CoA formed from pyruvate or as a product of FA catabolism. M1 macrophages accumulate citrate in the cytosol due to the IDH suppression at the transcriptional level and overexpression of the mitochondrial citrate carrier (CIC) [67].

Despite its ability to suppress glycolysis by affecting phosphofructokinases directly and pyruvate kinase indirectly, as well as to stimulate gluconeogenesis [68], citrate seems to be essential in the regulation of FA synthesis in M1 macrophages. Citrate is a substrate of ATP-citrate lyase (ACLY), an important source of acetyl-CoA utilized in the FA synthesis cycle. Inhibition of ACLY leads to a decrease in the production of prostaglandin E2 (PGE_2), NO, and ROS, that play an important role in the inflammation and oxidative stress [69].

Itaconate is one of the most abundant metabolites in M1 polarization [31]. It is produced from *cis*-aconitate by aconitate decarboxylase 1 (ACOD1), whose expression is upregulated in M1 macrophages. On one hand, itaconate is a competitive SDH inhibitor that interrupts the Krebs cycle and suppresses OXPHOS in proinflammatory macrophages [70, 71]. On the other hand, itaconate binds covalently to cysteine residues in proteins [72], thus suppressing their biological functions. For example, itaconate alkylates cysteines in fructose-1,6-bisphosphate aldolase (ALDOA), GAPDH, and LDHA, i.e., the key glycolytic enzymes, thus blocking their activity and leading to the reduction of glucose consumption and lactate production by the cells [72]. By alkylating KEAP1, itaconate activates NRF2 transcription factor which stimulates expression of genes involved in cell protection from the oxidative stress [73]. Finally, itaconate inhibits the production of NO and proinflammatory cytokines (TNF, IL-6, IL-1β, IL-12, and IL-18) by M1 macrophages [70, 74] partially due to the suppression of IκBζ, a regulator of transcriptional activity of NF-κB. Itaconate promotes Activating transcription factor 3 (ATF3) production in cultured macrophages, which, in turn, leads to IκBζ suppression at the post-transcriptional level [75]. In the case of IL-1β, itaconate not only suppresses expression of the *Il1b* gene, but also interferes with the cytokine production at the post-translational level by reducing caspase-1 activity [76]. Moreover, some itaconate derivatives alkylate NLRP3 directly, preventing the assembly of the inflammasome [77]. Itaconate presumably participates in the feedback loop involved in acquisition of the M1 phenotype by slowing down and limiting the activation of M1-associated genetic programs, which may play an important role in the control of immune response. M2 macrophages do not produce itaconate, but can uptake it from the medium [78]. It was recently shown that exogenous itaconate inhibits differentiation of M2 macrophages by suppressing the IL-4 signaling pathway mediated by JAK1/STAT6 [79]. There are also data that macrophage-derived itaconate affects tumor cells [80] and T cells [81]. Although itaconate is a specific metabolite of M1 polarization, it exerts a wide range of effects on surrounding cells, contributing to the formation of the M1-favorable microenvironment.

Succinate is generated in the Krebs cycle from succinyl-CoA by succinyl-CoA-ligase and is converted to fumarate by SDH. SDH is a part of the Krebs cycle and a component of the complex II of the ETC. Itaconate accumulating during M1 polarization reduces SDH activity, leading to the accumulation of succinate in the mitochondria [70]. Succinate can be transported by the dicarboxylate transporter (DIC, SLC25A10) from the mitochondria to the cell cytoplasm, where it has multiple functions. First, succinate inhibits prolyl hydroxylase (PHD) and thereby blocks HIF-1α degradation in the presence of oxygen. This results in the HIF-1α accumulation and activation of aerobic glycolysis, also known as the Warburg effect, as well as production of proinflammatory cytokines (e.g., IL-1β) [32]. Second, it causes post-translational changes in proteins via succinylation of lysine residues. For example, succinylation of pyruvate kinase in M1 macrophages leads to the HIF-1α-mediated increase in the IL-1β production [82]. Finally, succinate serves as a cell–cell mediator of inflammation; it is secreted by inflammatory macrophages and interacts with G protein-coupled SUCNR1/GPR91 receptors, thus promoting IL-1β production [83, 84]. It should be noted that expression of succinate receptors on the macrophage surface increases in response to inflammatory signals (LPS, TNF, and IFNγ) [67].

Fumarate is a product of SDH activity. However, fumarate levels are significantly elevated in M1 macrophages despite the inhibition of SDH, which is due to the increased expression of argininosuccinate synthase (ASS1), an enzyme of the urea cycle, in proinflammatory macrophages. ASS1 catalyzes the synthesis of argininosuccinate, which is then decomposed into arginine and fumarate. Fumarate, a by-product of the urea cycle, has a significant effect on the total fumarate level which increases with inflammation. Moreover, according to some data, fumarate and argininosuccinate are among the most produced metabolites in activated macrophages compared to inactive cells [85]. Fumarate inhibits IL-10 production, thereby increasing TNF biosynthesis. The effect of fumarate on IL-10 production may be associated with suppression of the ERK signaling pathway and PI3K signaling [85].

Alpha-ketoglutarate (α-KG) is formed by IDH via isocitrate conversion in the Krebs cycle. It is involved in many immune processes [86], e.g., epigenetic reprogramming. First of all, α-KG is the main cofactor in several families of histone demethylases, such as JMJD (Jumonji C-domain-containing histone demethylases) and TET (ten-eleven translation) enzymes [87, 88]. α-KG promotes transcription of IL-4-dependent genes due to its action on JMJD3. On the other hand, exosomal α-KG is also involved in M2 polarization by activating TET-mediated DNA demethylation, which leads to the suppression of the STAT3/NF-κB pathways [89].

Finally, α-KG stimulates FA oxidation, which is a common feature of M2 macrophages. Interestingly, a high α-KG/succinate ratio contributes to M2 polarization, while the low one, on the contrary, determines the proinflammatory M1 phenotype. Since α-KG is a cofactor of JMJD3, while succinate inhibits this enzyme, their combined action allows to regulate H3K27 demethylation [90].

2-Hydroxyglutarate (2-HG), which exists in both L- and D-isoforms, is also involved in the epigenetic regulation. 2-HG can be synthesized by the nonspecific activity of several enzymes, such as malate dehydrogenase (MDH), LDHA, and mutant IDH1/2mut isoform found in tumor cells [91, 92]. 2-HG, succinate, and fumarate inhibit α-KG at the epigenetic level [93, 94], therefore, the ratio between these compounds, especially between 2-HG and α-KG, is important in several immune processes. 2-HG accumulates in tissues under hypoxic conditions or at low pH [95], as well as in M1 macrophages in response to LPS activation [96]. *In vitro* experiments have shown that L-2-HG inactivates HIF prolyl hydroxylase, stabilizes HIF-1α, and thus promotes IL-1β production and activation of glycolysis [96]. In contrast, D-2-HG, also formed in M1 cells, contributes to the suppression of inflammatory processes at the late stage of LPS-induced response *in vitro* and is a regulator of local and systemic inflammatory reactions *in vivo* [97].

Amino acid metabolism is important not only in cell homeostasis and protein synthesis, but also in many immune processes, including macrophage polarization [98]. The deficit of amino acids in the medium impairs migration, proliferation, maturation, and effector functions of immune cells. The effects of arginine, glutamine, glycine, and serine on the macrophage functions have been studied in more detail.

Activated macrophages require arginine as a substrate for two competing enzymes – ARG1 and iNOS. Typically, ARG1 expression in M2 macrophages is increased. ARG1 converts arginine into urea and ornithine; ornithine initiates the synthesis of polyamines involved in tissue repair. Overall, ARG1 contributes to the anti-inflammatory phenotype of macrophages and thereby suppression of T cell proliferation and cytokine production [94]. Ornithine is also essential for the immune functions of macrophages in the context of *Mycobacterium tuberculosis* infection [99, 100]. The expression of iNOS in macrophages is upregulated by proinflammatory stimuli (LPS, TNF, IFNγ). iNOS converts arginine to nitric oxide and citrulline; NO spontaneously reacts with oxygen and ROS, resulting in the generation nitrogen and oxygen species with the antimicrobial and regulatory activities. ASS1 converts citrulline into argininosuccinate, which is further degraded to arginine and thus maintains NO production. In addition to the ROS generation, NO is involved in the remodeling of mitochondrial ETC during M1 polarization. Thus, the treatment of macrophages with LPS/IFNγ leads to the induction of NO synthesis along with the decrease in the activity of complexes I and II; the short-term action of NO on the macrophages results in the reversible inhibition of complex IV, due to the NO competition with oxygen for the enzyme catalytic site [101, 102]. Although disturbances in the functioning of complex I contribute to the increase in the ROS production in the mitochondria and expression of proinflammatory factors such as IL-1β and TNF [103], recent studies have shown that this process is not directly related to the NO action [104, 105]. Apparently, at later stages of activation, NO has the regulatory functions due to the ability to inhibit mitochondrial complexes and to reduce their number [106]. Moreover, the effect NO on the ETC leads to changes in the mitochondrial morphology and is one of the factors preventing repolarization of M1 macrophages to the respiration-dependent M2 phenotype [57].

Another important compound for the macrophages is glutamine which is required for the synthesis of amino acids and nucleotides, production of NADPH and energy, and many other biosynthetic processes [107, 108]. Depending on the metabolic pathway, glutamine stimulates either M1 or M2 macrophage polarization. On one hand, glutamine can enter the Krebs cycle through α-KG, thereby stimulating the synthesis of succinate in M1 macrophages [32], which is also significant for the HIF-1α stabilization and glycolysis maintenance [109]. At the same time, upregulation of succinate biosynthesis is accompanied by an increase in the expression of the SLC3A2 glutamine transporter gene and activation of glutamine uptake [110, 111]. Interestingly, some of succinate in LPS-activated macrophages is produced by the gamma-aminobutyric acid (GABA) shunt. In this pathway, which bypasses the Krebs cycle, glutamine is used for the sequential synthesis of glutamate, GABA, succinic semialdehyde, and eventually succinate. Inhibition of GABA transaminase, the key enzyme of this pathway, significantly reduces the amount of succinate produced from glutamine and, as a result, prevents HIF-1α stabilization and IL-1β secretion in response to LPS [32]. On the other hand, the deficiency of glutamine in the medium or inhibition of glutaminase by its selective blocker bis-2-(5-phenylacetamido-1,3,4-thiadiazole-2-diyl) ethyl sulfide (BPTES) during macrophage activation by LPS prevents the development of endotoxin tolerance [90], similar being demonstrated in a mouse model of toxic shock [112]. Endotoxin tolerance is an important mechanism of homeostasis maintenance, as acquisition of the tolerance toward repeated LPS stimulation by the macrophages helps to protect the body against possible excessive immune system activation [113]. Therefore, glutamine is involved in both

inflammatory response of M1 macrophages to LPS and their subsequent negative regulation through the tolerance formation.

Glutamine metabolism can also contribute to the M2 polarization, mainly by stimulating accumulation of α-KG [90]. Like glucose, glutamine is necessary for the synthesis of UDP-GlcNAc that is used by M2 macrophages for glycosylation of mannose receptor and RELMα [31]. M2 macrophages not only import glutamine from the environment, but also synthesize it from glutamate and ammonia using glutamine synthetase (GS). GS is fundamental for the M2 phenotype. It is almost absent in M1 macrophages and is highly expressed in M2 macrophages, especially in response to IL-10 [114]. Therefore, both the lack of glutamine in the medium and the inhibition of glutaminolysis by BPTES lead to disturbances in the alternative polarization of macrophages [31, 90].

Serine and glycine play an important role in the regulation of redox balance, as both of them are involved in the synthesis of glutathione. The maintenance of the redox balance is important for the M1 polarization of macrophages, since ROS produced by these cells cause oxidative stress [63, 115, 116]. This triggers the activity of the NRF2 transcription factor and results in the reduction of the LPS-induced NF-κB activity, in particular, due to the regulation of glutathione metabolism [117, 118]. Serine conversion to glycine may be necessary for glutathione production [119]. At the same time, endogenous synthesis of serine in LPS-activated macrophages is known to lead to the production of S-adenosylmethionine, which is involved in the epigenetic regulation of IL-1β expression [119].

Fatty acid synthesis and oxidation. FAs are essential for the synthesis of cell membranes and various bioactive compounds, e.g., eicosanoids. Moreover, FAs are another important “energy currency” of the body; their oxidation results in the synthesis of ATP. Macrophage polarization is highly dependent on FA metabolism. Thus, FA anabolism is typical for M1 macrophages: activation of TLRs, e.g., by IFNγ, causes accumulation of triacylglycerides (in a form of fat droplets), diacylglycerides, and cholesterol esters [120, 121], which correlates with the phenotype of foam cells, i.e., macrophages associated with atherosclerosis, granulomas, and other inflammatory pathologies [122]. Accumulation of fats is preceded by the activation of lipogenesis due to the activity of the transcription factor SREBP-1 [123] and ACLY, which produces acetyl-CoA from citrate for subsequent utilization by fatty acid synthase (FAS) [124]. Macrophages from mice deficient for these transcription factors, enzymes, and some carrier proteins involved in FA anabolism, such as uncoupling protein 2 (UCP2) [125] and acetyl-CoA carboxylase (ACC) [126]), demonstrated a decreased ability for proinflammatory response, mainly due to the inflammasome disruption. It was recently shown that fat droplets in M1 macrophages serve as a source of PGE_2 production. PGE_2 is responsible for the activation of phagocytosis and production of IL-1β and IL-6 in macrophages. The blockade of DGAT1 (carrier involved in FA deposition) causes suppression of the *in vitro* and *in vivo* inflammatory responses of macrophages [120].

As mentioned above, the Krebs cycle remains undisturbed in alternatively activated macrophages, which maintains higher OXPHOS levels; the main source of acetyl-CoA in M2 macrophages is FA. Beta oxidation occurs in the mitochondria, and the entry of FAs into these organelles is provided by carnitine palmitoyltransferases 1 (CPT1, located in the outer mitochondrial membrane) and 2 (CPT2, located in the inner mitochondria membrane). Recent experiments with pharmacological and genetic blockade of CPT1/2 have shown that the inhibition of beta oxidation does not block the acquisition of the M2 phenotype by mouse [127] and human [128] macrophages, contrary to the previous views [129]. Both synthesis and beta oxidation of FAs are important for the inflammasome functioning. Thus, NLRP3 activation can be inhibited by the activity of NOX4, which, in turn, regulates CPT1A [130]. The balance between the FA synthesis and oxidation is the most important regulator of inflammasome activation, and, therefore, of the inflammatory response of M1 macrophages [131]. Although, the role of FA metabolism in the M2 phenotype is currently undergoing revision, modulation of FA metabolism is still considered as a promising therapy for reprogramming tumor-associated M2-like macrophages [132, 133].

REGULATION OF METABOLIC REPROGRAMMING OF MACROPHAGES DURING POLARIZATION

Reprogramming of metabolic pathways during macrophage activation largely depends on the key metabolic master regulators mTOR and AMPK [134-136]. mTOR forms two types of complexes: mTORC1 and mTORC2 [137]. mTORC1 integrates information coming from the extracellular (growth factors, cellular stress) and intracellular stimuli (concentration of amino acids in the lysosomes, sugar levels, and lipid content) and transmits it further, activating HIF-1α, PPARγ, SREBP-1, and MYC, which promotes cell division, activates biosynthesis of nucleic acids, proteins, and lipids, and suppresses catabolic processes and autophagy [136, 137]. The balance of the mTORC1/mTORC2-mediated signaling is critically important for the macrophage differentiation and polarization and is controlled by signaling cascades mediated by innate immunity

Table 2. Correlation between metabolic changes and macrophage polarization

Metabolic pathway and factors	M1 (LPS + IFNγ)	M2 (IL-4 + IL-13)
Glycolysis	highly activated; involved in maintaining the pro-inflammatory properties of macrophages	activated; important for macrophage response to IL-4
GLUT1	↑	–
PFK	↑	–
6-Phosphofructo-2-kinase/ fructose-2,6-bisphosphatase 3 (PFKFB3)	↑	–
PKM2	dimer	tetramer
PPP	activated; essential for ROS generation by NOX, NO production, nucleotide and protein synthesis	participates in the synthesis of UDP-GlcNAC
Oxidizing phase of PPP: phosphogluconate dehydrogenase (PGD)	↑	–
Non-oxidizing phase of PPP: sedoheptulose kinase carbohydrate kinase-like protein (CARKL)	↓	↓
Krebs cycle and OXPHOS	weakened by NO and itaconate; reverse electron transport, ROS production, HIF-1α stabilization; IL-1β expression	OXPHOS activation; intact Krebs cycle
Mitochondrial morphology	predominance of fragmented mitochondria	predominance of mitochondrial networks
Citrate = first cycle break		
IDH	↓	–
CIC	↑	–
ACLY	↑	–
Itaconate ACOD1	↑	–
Succinate = second cycle break SDH	↓	–
Amino acid metabolism		
Arginine		
iNOS	↑	↓
ARG1	↓	↑
Tryptophan		
Indoleamine 2,3-dioxygenase (IDO)	↓	↑
Glutamine		
GS	↓	↑
PHD	↑	↓
Lipid metabolism	fatty acids synthesis ↑	fatty acids oxidation ↑
SREBP	↑	–
Liver X receptor (LXR)	–	↑

Note. “↑”, green, increased compared to inactivated macrophages (M0); “–”, grey, no changes compared to M0; “↓”, red, decreased compared to M0.

receptors, cytokines, and growth factors [138]. mTORC1 is essential for M1 polarization, while mTORC2 appears to be important for both types of macrophage activation [137]. The involvement of mTORC1 is largely associated with its ability to regulate anabolism via coordination of production of many factors mediating the functions of activated macrophages. Thus, SREBP-1 activation by mTORC1 is critically important for cytokine production, synthesis of lipids and lipid mediators, and phagocytosis. SREBP-1 also controls NADH production in the PPP necessary for the ROS generation [136]. The PI3K/AKT/mTOR signaling pathway is important for the stimulation of glycolysis and cell proliferation [136, 139]. Finally, mTOR is associated with glutamine metabolism. The mTORC2/IRF4 signaling pathway is involved in metabolic reprogramming occurring during alternative macrophage activation [140]. mTORC1 also promotes M2 polarization, in particular, by stimulating the synthesis of UDP-GlcNAc and N-glycosylation of lectins [31]. Moreover, the mTORC1-dependent synthesis of lipid mediators (which is associated with the expression of COX2 in M1 macrophages and of COX1 in M2 macrophages) is involved in the production of both proinflammatory and anti-inflammatory mediators [141].

AMPK, along with mTOR, participates in the integration of various signals and regulates cell metabolism through the enzyme-mediated post-translational modification of target proteins [142]. These master regulators complement each other. While mTOR senses the level of nutrients and triggers anabolic processes, AMPK detects the deficit in energy and activates catabolic processes aimed at ATP synthesis [143]. Thus, in the case of energy deficit (e.g., during starvation), AMPK responds to the intracellular AMP content and phosphorylation state of RAPTOR and TSC2 proteins and suppresses signaling pathways associated with mTORC1 [144]. Therefore, AMPK activation in macrophages typically results in the suppression of inflammatory response and M1 polarization [145-149]. The absence of AMPK leads to the hyperpolarization of macrophages towards the M1 phenotype in response to the LPS stimulation and to the upregulation of expression of the key enzymes involved in the metabolism of glucose, arginine, prostaglandins, and cholesterol and synthesis of itaconate. This results in the increased production of PGE_2, NO, IL-6, and IL-12 and reduction in the biosynthesis of IL-10 [150]. In addition, AMPK is necessary for the acquisition of the M2 phenotype by the macrophages, for example, during muscle regeneration [146].

Summarizing all the above, metabolic changes play an essential role in the polarization of macrophages and their immunological functions (Table 2). These processes are not only interconnected, but also dependent on each other. On one hand, regulation of immunometabolic enzymes is mediated by nutrients and metabolites (amino acids, citrate, succinate, itaconate, FAs, etc.). This method of control appeared at the early stages of evolution and has been functioning successfully so far. On the other hand, the regulation of cell functions, including immune response, in accordance with the body's needs and environmental conditions is impossible without more complex mechanisms that had evolved later. Such mechanisms mediated, for example, by mTOR and AMPK, include integration of intracellular signals with subsequent post-translational modification of proteins and epigenetic modification of genes [142]. Immunometabolic adaptation of macrophages to incoming signals underlies the maintenance of homeostasis not only in individual tissues, but in an entire organism as well. As a result, disruption of such regulation can lead to the development of various diseases and maladaptive states.

MODULATION OF MACROPHAGE METABOLISM AS A THERAPEUTIC STRATEGY

Disruption of macrophage immunometabolic functions as a pathology factor. Recently, the understanding of the role of macrophages in various pathological processes has significantly expanded [23, 151] (Fig. 2). On one hand, M2 macrophages are involved in the metabolic control, while M1 macrophages, on the contrary, are associated with metabolic pathologies, such as diabetes, obesity, metabolic syndrome, and insulin resistance. On the other hand, M1 macrophages mediate the antitumor effects, while M2 macrophages create an immunosuppressive environment and promote tumor development. M2 macrophages are responsible for maintaining tissue homeostasis and wound healing; however, excessive or prolonged activation of both M1 and M2 macrophages results in tissue damage and impaired function in such diseases as arthritis, atherosclerosis, glomerulonephritis, and atopic dermatitis. Macrophages, which provide body protection against bacteria, viruses, and macroparasites, are at the same time able to cause a cytokine storm and an unbalanced response to harmless environmental factors, thus participating in the pathogenesis of allergies and asthma. Since macrophages play a key role in many diseases, they have become an important subject in the exploration of new therapeutic strategies.

As described above, activated and polarized macrophages undergo metabolic adaptations. Therefore, modification of macrophage metabolism entails changes in the direction and strength of their polarization. At the same time, due to the unique features of metabolism in the activated macrophages, such effects will be specific and should not affect other body cells, which can open up the prospects for using this ap-

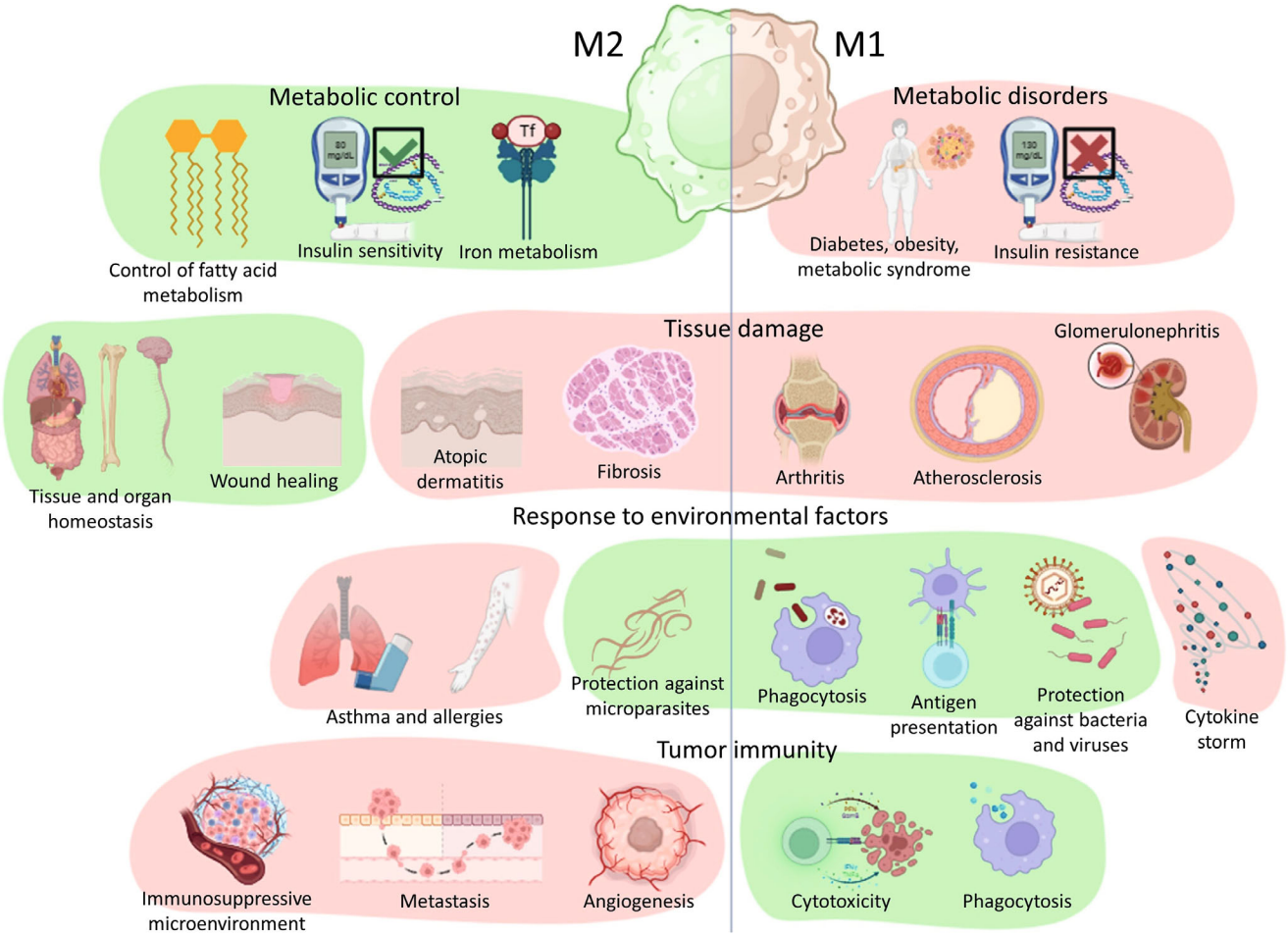

Fig. 2. Macrophage polarization in normal and pathological conditions. Pink, polarization associated with pathology development; green, physiological functions of macrophages. Created with BioRender software based on previously published data [23, 151].

proach in the therapy of inflammatory diseases with substantial role of macrophage. Below, we discuss how modulation of certain metabolic pathways in macrophages could be used as a therapeutic approach.

mTOR and AMPK modulation. As mentioned above, mTOR is involved in the polarization of both M1 and M2 macrophages [134]. Treatment of cultured macrophages with rapamycin, an inhibitor of mTORC1, contributed to the acquisition of the anti-inflammatory phenotype, while activation of mTORC1, on the contrary, promoted formation of the inflammatory phenotype [138]. In the model of the CLP (cecal ligation and puncture)-induced sepsis, rapamycin protected the mice from death by acting on M1 macrophages [152]. Apparently, the effect of rapamycin is due to its ability to cause autophagy, leading to a decrease in the IL-1β and IL-18 production by M1 macrophages. This regulation takes place at the post-transcriptional level and is associated with a decrease in the mitochondrial ROS and pro-IL-1β [153]. Modulation of mTOR can also be used in the therapy of ulcerative colitis. Thus, dioscin (steroid saponin) simultaneously inhibits signals through the mTORC1/HIF-1α pathway and activates mTORC2/PPAR-γ signaling, which results in the suppression of aerobic glycolysis, increase in the FA oxidation, and shift in macrophage polarization from M1 to M2, resulting in the mouse protection against the DSS (dextran sodium sulfate)-induced ulcerative colitis [154]. On the other hand, in many studies, the use of rapamycin has led to the shift toward the M1 phenotype. A combination of rapamycin and hydroxychloroquine caused the elimination of anti-inflammatory M2 macrophages in the glioblastoma model and increased the effectiveness of checkpoint inhibitors [155]. Moreover, the blockade of mTOR contributed to the M1 polarization of macrophages and ensured plaque stabilization in the arteries during progressive atherosclerosis [156]. The same effect was achieved by another mTOR blocker, arsenic trioxide [157].

Modulation of AMPK provides another approach to the regulation of macrophage metabolism. Metformin is used in the clinic for targeting AMPK. It inhibits the ETC complex I, which controls ATP and ROS

production. Blocking ATP production leads to the increase in the AMP content and ADP/ATP ratio, thereby activating AMPK [158]. Metformin is known to inhibit the LPS-induced IL-1β production and to promote IL-10 production [115]. Some studies have shown that metformin regulates the functions of macrophages in atherosclerosis by suppressing monocyte differentiation and reducing inflammation, oxidative stress, and apoptosis [159]. It is important to note that metformin can regulate macrophage functions through the AMPK-independent pathways (NF-κB, ABCG5/8, SIRT1, FOXO1/FABP4, and HMGB1). In the future, a combination of metformin with drugs affecting the macrophage functions (e.g., SGLT2 inhibitors, statins, IL-1β inhibitors) can enhance and expand its therapeutic potential [159].

Glycolysis blockade. Most conclusions on the role of glycolysis in the polarization of macrophages have been made based on the studies using 2-DG, an inhibitor of glycolysis that also induces various other effects [54]. New blockers based on 2-DG may have a higher specificity [160]. Currently, such compounds are investigated for the anti-cancer activity, while their effect on the macrophage metabolism remains unclear. Recent studies have shown that cancer and immune cells can accumulate a dimeric form of the PKM2 capable of regulating the expression of HIF-1α-dependent genes [50, 161]. The small-molecule inhibitor TEPP-46, which inhibits this process and restores the PKM2 enzymatic activity, has shown promising results in experimental models of cancer and infectious diseases [50, 162]. TEPP-46 suppresses activation of M1 macrophages and promotes mitochondrial biogenesis [163]. Another approach is the direct HIF-1α inhibition. PX-478 (selective HIF-1α blocker) suppressed tumor cell growth [164] and was found to be efficient in the mouse model of atherosclerosis [165]. However, the detailed mechanism of this inhibitor on macrophage polarization still has to be elucidated.

Application of Krebs cycle metabolites in therapy. Inflammatory processes and malignant transformation are accompanied with the reprogramming of the Krebs cycle, associated genes, and metabolites [70, 166, 167]. Dimethylmalonate and 4-octilitaconate (4-OI) are small molecules that target SDH and were found to reduce inflammation in several experimental models [73, 168]. As mentioned above, itaconate and its derivatives activate NRF2, leading to the stimulation of the antioxidant response and upregulation of expression of cytokine-limiting ATF3 [73, 75]. In particular, 4-OI targets the NRF2/KEAP1 pathway and prevents cytokine storm during acute infection in mice [73]. Moreover, itaconate has recently been shown to inhibit NLRP3 inflammasome [77]. Such significant immunomodulatory potential of itaconate and its derivatives can be used in therapy. It was shown recently that itaconate affects M2 polarization of macrophages by inhibiting the JAK1/STAT6 signaling pathway. A decrease in the severity of steroid-resistant asthma in mice administered with 4-OI indicates the therapeutic potential of this metabolite in Th2-dependent diseases [79].

As a compound affecting the NRF2 pathway and glycolysis, dimethyl fumarate (DMF, a derivative of fumarate) is currently used as an immunomodulatory drug in the treatment of multiple sclerosis and psoriasis [169-171]. DMF also inhibits NF-κB, ERK, and other signaling pathways. It activates NRF2, resulting in cell protection against oxidative stress, and promotes the anti-inflammatory phenotype in macrophages [172]. DMF also affects glycolysis by reducing the GAPDH activity, suggesting that DMF can also be used to modulate immunometabolism during infectious diseases [170].

Modulation of amino acid and FA metabolism. The difference between arginine consumption by M1 and M2 macrophages is a basis for a potential selective therapy. Thus, the inhibition of iNOS with aminoguanidine prevented NO production by the macrophages and reduced the symptoms of disease in the mouse model of multiple sclerosis [173]. Other iNOS inhibitors have shown efficacy in the mouse models of ischemic kidney disease and lung inflammation [174, 175]. At the same time, inhibition of ARG1 by CB-1158 shifted macrophage polarization towards the M1 phenotype in the mouse model of carcinogenesis. This resulted in the inhibition of the immunosuppressive microenvironment and increased the efficacy of antitumor therapy [176, 177]. Currently, the efficacy of ARG1 inhibition in cancer therapy is tested in a number of clinical trials (NCT02903914, NCT03910530, NCT03314935, NCT03837509, NCT03361228). Inhibition of enzymes involved in glutamine metabolism by BPTES or CB-839 has shown promising results in the models of multiple sclerosis [178] and rheumatoid arthritis [179]. Finally, amino acid deficiency can also be used for targeting the macrophages. For example, serine restriction attenuates excessive macrophage activation during endotoxemia [180], so it could be useful in the treatment of sepsis. Halofuginone, which mimics amino acid deficiency by activating GCN2 (general control nonderepressible 2 kinase), reduces intestinal inflammation [181] and induces autophagy [182].

The role of FA metabolism in the formation of pathogenetic macrophage phenotype is only partly understood. In recent years, special attention has been focused on the drugs that suppress expression or block the activity of carnitine palmitoyltransferases (e.g., etomoxir) [183]. The effect of these compounds on the development of colitis-associated cancer [184, 185], bronchial asthma [186] and obstructive pulmonary disease [187] is currently under study. Some of these studies have emphasized the correlation between the

FA synthesis/oxidation and activity of NLRP3 inflammasome, since the inflammasome is significantly involved in the chronic inflammation and carcinogenesis [184].

CONCLUSION

Taken together, the results of studies in recent decades clearly suggest a close relationship between the metabolism and functional characteristics of immune cells, including macrophages, upon their activation. The metabolic needs of activated cells are inextricably linked to their functional features, so that there is a significant difference between the cellular metabolism of pro- and anti-inflammatory immune cells. At the same time, many aspects of macrophage metabolism remain poorly understood. The use of drugs aimed at metabolism reprogramming is hindered by the limited selectivity of available inhibitors. Currently known inhibitors tend to affect central processes, e.g., glucose catabolism (in the case of 2-DG) or mTOR signaling. The development of more specific drugs targeting certain metabolic pathways will allow to explore their effect on the macrophage polarization in more detail. It also opens new prospects for immunometabolic therapy through modulation of macrophage involvement in disease pathogenesis.

Acknowledgments. The authors express their gratitude to D. Anisov for discussions and valuable remarks.

Contributions. M.S.D. supervised the study and developed the concept of the review; T.R.Y., E.A.G., and M.A.N. carried out the search of literature sources and discussed the data; T.R.Y. and M.A.N. prepared the manuscript; M.S.D. and E.A.G. edited the manuscript; T.R.Y. prepared the images.

Funding. This work was supported by the Russian Science Foundation (project no. 19-75-30032).

Ethics declaration. This work does not describe any studies involving humans or animals as objects performed by any of the authors. The authors of this work declare that they have no conflicts of interest in financial or any other sphere.

REFERENCES

1. Warburg, O. (1956) On the origin of cancer cells, *Science*, **123**, 309-314, doi: 10.1126/science.123.3191.309.
2. Warburg, O., Wind, F., and Negelein, E. (1927) The metabolism of tumors in the body, *J. Gen. Physiol.*, **8**, 519-530, doi: 10.1085/jgp.8.6.519.
3. Lercher, A., Baazim, H., and Bergthaler, A. (2020) Systemic immunometabolism: challenges and opportunities, *Immunity*, **53**, 496-509, doi: 10.1016/j.immuni.2020.08.012.
4. Febbraio, M. A., Hiscock, N., Sacchetti, M., Fischer, C. P., and Pedersen, B. K. (2004) Interleukin-6 is a novel factor mediating glucose homeostasis during skeletal muscle contraction, *Diabetes*, **53**, 1643-1648, doi: 10.2337/diabetes.53.7.1643.
5. Hotamisligil, G. S., Shargill, N. S., and Spiegelman, B. M. (1993) Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance, *Science*, **259**, 87-91, doi: 10.1126/science.7678183.
6. Wieman, H. L., Wofford, J. A., and Rathmell, J. C. (2007) Cytokine stimulation promotes glucose uptake via phosphatidylinositol-3 kinase/Akt regulation of Glut1 activity and trafficking, *Mol. Biol. Cell.*, **18**, 1437-1446, doi: 10.1091/mbc.e06-07-0593.
7. Pearce, E. L., Walsh, M. C., Cejas, P. J., Harms, G. M., Shen, H., Wang, L. S., Jones, R. G., and Choi, Y. (2009) Enhancing CD8 T-cell memory by modulating fatty acid metabolism, *Nature*, **460**, 103-107, doi: 10.1038/nature08097.
8. Wang, A., Luan, H. H., and Medzhitov, R. (2019) An evolutionary perspective on immunometabolism, *Science*, **363**, eaar3932, doi: 10.1126/science.aar3932.
9. Gordon, S., Crocker, P. R., Morris, L., Lee, S. H., Perry, V. H., and Hume, D. A. (1986) Localization and function of tissue macrophages, *Ciba Found Symp.*, **118**, 54-67, doi: 10.1002/9780470720998.ch5.
10. Okabe, Y., and Medzhitov, R. (2016) Tissue biology perspective on macrophages, *Nat. Immunol.*, **17**, 9-17, doi: 10.1038/ni.3320.
11. Wynn, T. A., Chawla, A., and Pollard, J. W. (2013) Macrophage biology in development, homeostasis and disease, *Nature*, **496**, 445-455, doi: 10.1038/nature12034.
12. Gordon, S., Pluddemann, A., and Martinez Estrada, F. (2014) Macrophage heterogeneity in tissues: phenotypic diversity and functions, *Immunol. Rev.*, **262**, 36-55, doi: 10.1111/imr.12223.
13. Moore, K. J., and Tabas, I. (2011) Macrophages in the pathogenesis of atherosclerosis, *Cell*, **145**, 341-355, doi: 10.1016/j.cell.2011.04.005.
14. Chawla, A., Nguyen, K. D., and Goh, Y. P. (2011) Macrophage-mediated inflammation in metabolic disease, *Nat. Rev. Immunol.*, **11**, 738-749, doi: 10.1038/nri3071.
15. Olefsky, J. M., and Glass, C. K. (2010) Macrophages, inflammation, and insulin resistance, *Annu. Rev. Physiol.*, **72**, 219-246, doi: 10.1146/annurev-physiol-021909-135846.
16. Wynn, T. A., and Barron, L. (2010) Macrophages: master regulators of inflammation and fibrosis, *Semin. Liver Dis.*, **30**, 245-257, doi: 10.1055/s-0030-1255354.
17. Noy, R., and Pollard, J. W. (2014) Tumor-associated macrophages: from mechanisms to therapy, *Immunity*, **41**, 49-61, doi: 10.1016/j.immuni.2014.06.010.
18. Ginhoux, F., and Jung, S. (2014) Monocytes and macrophages: developmental pathways and tissue homeo-

stasis, *Nat. Rev. Immunol.*, **14**, 392-404, doi: 10.1038/nri3671.
19. Epelman, S., Lavine, K. J., and Randolph, G. J. (2014) Origin and functions of tissue macrophages, *Immunity*, **41**, 21-35, doi: 10.1016/j.immuni.2014.06.013.
20. Varol, C., Mildner, A., and Jung, S. (2015) Macrophages: development and tissue specialization, *Annu. Rev. Immunol.*, **33**, 643-675, doi: 10.1146/annurev-immunol-032414-112220.
21. Hussell, T., and Bell, T. J. (2014) Alveolar macrophages: plasticity in a tissue-specific context, *Nat. Rev. Immunol.*, **14**, 81-93, doi: 10.1038/nri3600.
22. Viola, A., Munari, F., Sanchez-Rodriguez, R., Scolaro, T., and Castegna, A. (2019) The metabolic signature of macrophage responses, *Front. Immunol.*, **10**, 1462, doi: 10.3389/fimmu.2019.01462.
23. Sica, A., and Mantovani, A. (2012) Macrophage plasticity and polarization: *in vivo* veritas, *J. Clin. Invest.*, **122**, 787-795, doi: 10.1172/JCI59643.
24. Ginhoux, F., and Guilliams, M. (2016) Tissue-resident macrophage ontogeny and homeostasis, *Immunity*, **44**, 439-449, doi: 10.1016/j.immuni.2016.02.024.
25. Hoeffel, G., and Ginhoux, F. (2015) Ontogeny of tissue-resident macrophages, *Front. Immunol.*, **6**, 486, doi: 10.3389/fimmu.2015.00486.
26. Wculek, S. K., Dunphy, G., Heras-Murillo, I., Mastrangelo, A., and Sancho, D. (2022) Metabolism of tissue macrophages in homeostasis and pathology, *Cell. Mol. Immunol.*, **19**, 384-408, doi: 10.1038/s41423-021-00791-9.
27. Wang, N., Liang, H., and Zen, K. (2014) Molecular mechanisms that influence the macrophage m1-m2 polarization balance, *Front. Immunol.*, **5**, 614, doi: 10.3389/fimmu.2014.00614.
28. Mills, C. D., Kincaid, K., Alt, J. M., Heilman, M. J., and Hill, A. M. (2000) M-1/M-2 macrophages and the Th1/Th2 paradigm, *J. Immunol.*, **164**, 6166-6173, doi: 10.4049/jimmunol.164.12.6166.
29. Biswas, S. K., and Mantovani, A. (2010) Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm, *Nat. Immunol.*, **11**, 889-896, doi: 10.1038/ni.1937.
30. Geiss, C., Salas, E., Guevara-Coto, J., Regnier-Vigouroux, A., and Mora-Rodriguez, R. A. (2022) Multistability in macrophage activation pathways and metabolic implications, *Cells*, **11**, 404, doi: 10.3390/cells11030404.
31. Jha, A. K., Huang, S. C., Sergushichev, A., Lampropoulou, V., Ivanova, Y., Loginicheva, E., Chmielewski, K., Stewart, K. M., Ashall, J., Everts, B., Pearce, E. J., Driggers, E. M., and Artyomov, M. N. (2015) Network integration of parallel metabolic and transcriptional data reveals metabolic modules that regulate macrophage polarization, *Immunity*, **42**, 419-430, doi: 10.1016/j.immuni.2015.02.005.
32. Tannahill, G. M., Curtis, A. M., Adamik, J., Palsson-McDermott, E. M., McGettrick, A. F., Goel, G., Frezza, C., Bernard, N. J., Kelly, B., Foley, N. H., Zheng, L., Gardet, A., Tong, Z., Jany, S. S., Corr, S. C., Haneklaus, M., Caffrey, B. E., Pierce, K., Walmsley, S., Beasley, F. C., et al. (2013) Succinate is an inflammatory signal that induces IL-1beta through HIF-1alpha, *Nature*, **496**, 238-242, doi: 10.1038/nature11986.
33. Lin, J., Kong, Q., Hao, W., and Hu, W. (2020) High glucose contributes to the polarization of peritoneal macrophages to the M2 phenotype *in vivo* and *in vitro*, *Mol. Med. Rep.*, **22**, 127-134, doi: 10.3892/mmr.2020.11130.
34. Fukuzumi, M., Shinomiya, H., Shimizu, Y., Ohishi, K., and Utsumi, S. (1996) Endotoxin-induced enhancement of glucose influx into murine peritoneal macrophages via GLUT1, *Infect. Immun.*, **64**, 108-112, doi: 10.1128/iai.64.1.108-112.1996.
35. Rodriguez-Prados, J. C., Traves, P. G., Cuenca, J., Rico, D., Aragones, J., Martin-Sanz, P., Cascante, M., and Bosca, L. (2010) Substrate fate in activated macrophages: a comparison between innate, classic, and alternative activation, *J. Immunol.*, **185**, 605-614, doi: 10.4049/jimmunol.0901698.
36. Wang, F., Zhang, S., Vuckovic, I., Jeon, R., Lerman, A., Folmes, C. D., Dzeja, P. P., and Herrmann, J. (2018) Glycolytic stimulation is not a requirement for M2 macrophage differentiation, *Cell Metab.*, **28**, 463-475, doi: 10.1016/j.cmet.2018.08.012.
37. Hackett, E. E., Charles-Messance, H., O'Leary, S. M., Gleeson, L. E., Munoz-Wolf, N., Case, S., Wedderburn, A., Johnston, D. G. W., Williams, M. A., Smyth, A., Ouimet, M., Moore, K. J., Lavelle, E. C., Corr, S. C., Gordon, S. V., Keane, J., and Sheedy, F. J. (2020) *Mycobacterium tuberculosis* limits host glycolysis and IL-1beta by restriction of PFK-M via microRNA-21, *Cell Rep.*, **30**, 124-136, doi: 10.1016/j.celrep.2019.12.015.
38. Chen, R., Wang, J., Dai, X., Wu, S., Huang, Q., Jiang, L., and Kong, X. (2022) Augmented PFKFB3-mediated glycolysis by interferon-gamma promotes inflammatory M1 polarization through the JAK2/STAT1 pathway in local vascular inflammation in Takayasu arteritis, *Arthritis Res. Ther.*, **24**, 266, doi: 10.1186/s13075-022-02960-1.
39. Galvan-Pena, S., Carroll, R. G., Newman, C., Hinchy, E. C., Palsson-McDermott, E., Robinson, E. K., Covarrubias, S., Nadin, A., James, A. M., Haneklaus, M., Carpenter, S., Kelly, V. P., Murphy, M. P., Modis, L. K., and O'Neill, L. A. (2019) Malonylation of GAPDH is an inflammatory signal in macrophages, *Nat. Commun.*, **10**, 338, doi: 10.1038/s41467-018-08187-6.
40. Xie, M., Yu, Y., Kang, R., Zhu, S., Yang, L., Zeng, L., Sun, X., Yang, M., Billiar, T. R., Wang, H., Cao, L., Jiang, J., and Tang, D. (2016) PKM2-dependent glycolysis promotes NLRP3 and AIM2 inflammasome activation, *Nat. Commun.*, **7**, 13280, doi: 10.1038/ncomms13280.
41. Wang, T., Liu, H., Lian, G., Zhang, S. Y., Wang, X., and Jiang, C. (2017) HIF 1alpha-induced glycolysis metabolism is essential to the activation of inflammatory

macrophages, *Mediators Inflamm.*, **2017**, 9029327, doi: 10.1155/2017/9029327.

42. van Uden, P., Kenneth, N. S., and Rocha, S. (2008) Regulation of hypoxia-inducible factor-1α by NF-κB, *Biochem. J.*, **412**, 477-484, doi: 10.1042/BJ20080476.
43. Blouin, C. C., Page, E. L., Soucy, G. M., and Richard, D. E. (2004) Hypoxic gene activation by lipopolysaccharide in macrophages: implication of hypoxia-inducible factor 1alpha, *Blood*, **103**, 1124-1130, doi: 10.1182/blood-2003-07-2427.
44. Rius, J., Guma, M., Schachtrup, C., Akassoglou, K., Zinkernagel, A. S., Nizet, V., Johnson, R. S., Haddad, G. G., and Karin, M. (2008) NF-kappaB links innate immunity to the hypoxic response through transcriptional regulation of HIF-1alpha, *Nature*, **453**, 807-811, doi: 10.1038/nature06905.
45. Joshi, S., Singh, A. R., Zulcic, M., and Durden, D. L. (2014) A macrophage-dominant PI3K isoform controls hypoxia-induced HIF1alpha and HIF2alpha stability and tumor growth, angiogenesis, and metastasis, *Mol. Cancer Res.*, **12**, 1520-1531, doi: 10.1158/1541-7786.MCR-13-0682.
46. Arranz, A., Doxaki, C., Vergadi, E., Martinez de la Torre, Y., Vaporidi, K., Lagoudaki, E. D., Ieronymaki, E., Androulidaki, A., Venihaki, M., Margioris, A. N., Stathopoulos, E. N., Tsichlis, P. N., and Tsatsanis, C. (2012) Akt1 and Akt2 protein kinases differentially contribute to macrophage polarization, *Proc. Natl. Acad. Sci. USA*, **109**, 9517-9522, doi: 10.1073/pnas.1119038109.
47. Cheng, S. C., Quintin, J., Cramer, R. A., Shepardson, K. M., Saeed, S., Kumar, V., Giamarellos-Bourboulis, E. J., Martens, J. H., Rao, N. A., Aghajanirefah, A., Manjeri, G. R., Li, Y., Ifrim, D. C., Arts, R. J., van der Veer, B. M., Deen, P. M., Logie, C., O'Neill, L. A., Willems, P., van de Veerdonk, F. L., et al. (2014) mTOR- and HIF-1alpha-mediated aerobic glycolysis as metabolic basis for trained immunity, *Science*, **345**, 1250684, doi: 10.1126/science.1250684.
48. Kelley, T. W., Graham, M. M., Doseff, A. I., Pomerantz, R. W., Lau, S. M., Ostrowski, M. C., Franke, T. F., and Marsh, C. B. (1999) Macrophage colony-stimulating factor promotes cell survival through Akt/protein kinase B, *J. Biol. Chem.*, **274**, 26393-26398, doi: 10.1074/jbc.274.37.26393.
49. Vergadi, E., Ieronymaki, E., Lyroni, K., Vaporidi, K., and Tsatsanis, C. (2017) Akt signaling pathway in macrophage activation and M1/M2 polarization, *J. Immunol.*, **198**, 1006-1014, doi: 10.4049/jimmunol.1601515.
50. Palsson-McDermott, E. M., Curtis, A. M., Goel, G., Lauterbach, M. A., Sheedy, F. J., Gleeson, L. E., van den Bosch, M. W., Quinn, S. R., Domingo-Fernandez, R., Johnston, D. G., Jiang, J. K., Israelsen, W. J., Keane, J., Thomas, C., Clish, C., Vander Heiden, M., Xavier, R. J., and O'Neill, L. A. (2015) 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 Metab.*, **21**, 65-80, doi: 10.1016/j.cmet.2014.12.005.
51. Mills, E. L., and O'Neill, L. A. (2016) Reprogramming mitochondrial metabolism in macrophages as an anti-inflammatory signal, *Eur. J. Immunol.*, **46**, 13-21, doi: 10.1002/eji.201445427.
52. Baardman, J., Verberk, S. G. S., Prange, K. H. M., van Weeghel, M., van der Velden, S., Ryan, D. G., Wust, R. C. I., Neele, A. E., Speijer, D., Denis, S. W., Witte, M. E., Houtkooper, R. H., O'Neill, L. A., Knatko, E. V., Dinkova-Kostova, A. T., Lutgens, E., de Winther, M. P. J., and Van den Bossche, J. (2018) A defective pentose phosphate pathway reduces inflammatory macrophage responses during hypercholesterolemia, *Cell Rep.*, **25**, 2044-2052, doi: 10.1016/j.celrep.2018.10.092.
53. Yi, L., Liu, Q., Orandle, M. S., Sadiq-Ali, S., Koontz, S. M., Choi, U., Torres-Velez, F. J., and Jackson, S. H. (2012) p47(phox) directs murine macrophage cell fate decisions, *Am. J. Pathol.*, **180**, 1049-1058, doi: 10.1016/j.ajpath.2011.11.019.
54. Haschemi, A., Kosma, P., Gille, L., Evans, C. R., Burant, C. F., Starkl, P., Knapp, B., Haas, R., Schmid, J. A., Jandl, C., Amir, S., Lubec, G., Park, J., Esterbauer, H., Bilban, M., Brizuela, L., Pospisilik, J. A., Otterbein, L. E., and Wagner, O. (2012) The sedoheptulose kinase CARKL directs macrophage polarization through control of glucose metabolism, *Cell Metab.*, **15**, 813-826, doi: 10.1016/j.cmet.2012.04.023.
55. He, D., Mao, Q., Jia, J., Wang, Z., Liu, Y., Liu, T., Luo, B., and Zhang, Z. (2021) Pentose phosphate pathway regulates tolerogenic apoptotic cell clearance and immune tolerance, *Front. Immunol.*, **12**, 797091, doi: 10.3389/fimmu.2021.797091.
56. Huang, S. C., Everts, B., Ivanova, Y., O'Sullivan, D., Nascimento, M., Smith, A. M., Beatty, W., Love-Gregory, L., Lam, W. Y., O'Neill, C. M., Yan, C., Du, H., Abumrad, N. A., Urban, J. F., Jr., Artyomov, M. N., Pearce, E. L., and Pearce, E. J. (2014) Cell-intrinsic lysosomal lipolysis is essential for alternative activation of macrophages, *Nat. Immunol.*, **15**, 846-855, doi: 10.1038/ni.2956.
57. Van den Bossche, J., Baardman, J., Otto, N. A., van der Velden, S., Neele, A. E., van den Berg, S. M., Luque-Martin, R., Chen, H. J., Boshuizen, M. C., Ahmed, M., Hoeksema, M. A., de Vos, A. F., and de Winther, M. P. (2016) Mitochondrial dysfunction prevents repolarization of inflammatory macrophages, *Cell Rep.*, **17**, 684-696, doi: 10.1016/j.celrep.2016.09.008.
58. Garaude, J., Acin-Perez, R., Martinez-Cano, S., Enamorado, M., Ugolini, M., Nistal-Villan, E., Hervas-Stubbs, S., Pelegrin, P., Sander, L. E., Enriquez, J. A., and Sancho, D. (2016) Mitochondrial respiratory-chain adaptations in macrophages contribute to antibacterial host defense, *Nat. Immunol.*, **17**, 1037-1045, doi: 10.1038/ni.3509.
59. Vats, D., Mukundan, L., Odegaard, J. I., Zhang, L., Smith, K. L., Morel, C. R., Wagner, R. A., Greaves, D. R.,

Murray, P. J., and Chawla, A. (2006) Oxidative metabolism and PGC-1beta attenuate macrophage-mediated inflammation, *Cell Metab.*, **4**, 13-24, doi: 10.1016/j.cmet.2006.05.011.

60. Turrens, J. F. (2003) Mitochondrial formation of reactive oxygen species, *J. Physiol.*, **552**, 335-344, doi: 10.1113/jphysiol.2003.049478.
61. Suski, J. M., Lebiedzinska, M., Bonora, M., Pinton, P., Duszynski, J., and Wieckowski, M. R. (2012) Relation between mitochondrial membrane potential and ROS formation, *Methods Mol. Biol.*, **810**, 183-205, doi: 10.1007/978-1-61779-382-0_12.
62. Bulua, A. C., Simon, A., Maddipati, R., Pelletier, M., Park, H., Kim, K. Y., Sack, M. N., Kastner, D. L., and Siegel, R. M. (2011) Mitochondrial reactive oxygen species promote production of proinflammatory cytokines and are elevated in TNFR1-associated periodic syndrome (TRAPS), *J. Exp. Med.*, **208**, 519-533, doi: 10.1084/jem.20102049.
63. West, A. P., Brodsky, I. E., Rahner, C., Woo, D. K., Erdjument-Bromage, H., Tempst, P., Walsh, M. C., Choi, Y., Shadel, G. S., and Ghosh, S. (2011) TLR signalling augments macrophage bactericidal activity through mitochondrial ROS, *Nature*, **472**, 476-480, doi: 10.1038/nature09973.
64. Agita, A., and Alsagaff, M. T. (2017) Inflammation, immunity, and hypertension, *Acta Med. Indones.*, **49**, 158-165.
65. He, W., Miao, F. J., Lin, D. C., Schwandner, R. T., Wang, Z., Gao, J., Chen, J. L., Tian, H., and Ling, L. (2004) Citric acid cycle intermediates as ligands for orphan G-protein-coupled receptors, *Nature*, **429**, 188-193, doi: 10.1038/nature02488.
66. Hooftman, A., and O'Neill, L. A. J. (2019) The immunomodulatory potential of the metabolite itaconate, *Trends Immunol.*, **40**, 687-698, doi: 10.1016/j.it.2019.05.007.
67. Infantino, V., Iacobazzi, V., Menga, A., Avantaggiati, M. L., and Palmieri, F. (2014) A key role of the mitochondrial citrate carrier (*SLC25A1*) in TNFα- and IFNγ-triggered inflammation, *Biochim. Biophys. Acta*, **1839**, 1217-1225, doi: 10.1016/j.bbagrm.2014.07.013.
68. Icard, P., Coquerel, A., Wu, Z., Gligorov, J., Fuks, D., Fournel, L., Lincet, H., and Simula, L. (2021) Understanding the central role of citrate in the metabolism of cancer cells and tumors: An Update, *Int. J. Mol. Sci.*, **22**, 6587, doi: 10.3390/ijms22126587.
69. Infantino, V., Pierri, C. L., and Iacobazzi, V. (2019) Metabolic routes in inflammation: the citrate pathway and its potential as therapeutic target, *Curr. Med. Chem.*, **26**, 7104-7116, doi: 10.2174/0929867325666180510124558.
70. Lampropoulou, V., Sergushichev, A., Bambouskova, M., Nair, S., Vincent, E. E., Loginicheva, E., Cervantes-Barragan, L., Ma, X., Huang, S. C., Griss, T., Weinheimer, C. J., Khader, S., Randolph, G. J., Pearce, E. J., Jones, R. G., Diwan, A., Diamond, M. S., and Artyomov, M. N. (2016) Itaconate links inhibition of succinate dehydrogenase with macrophage metabolic remodeling and regulation of inflammation, *Cell Metab.*, **24**, 158-166, doi: 10.1016/j.cmet.2016.06.004.
71. Nemeth, B., Doczi, J., Csete, D., Kacso, G., Ravasz, D., Adams, D., Kiss, G., Nagy, A. M., Horvath, G., Tretter, L., Mocsai, A., Csepanyi-Komi, R., Iordanov, I., Adam-Vizi, V., and Chinopoulos, C. (2016) Abolition of mitochondrial substrate-level phosphorylation by itaconic acid produced by LPS-induced Irg1 expression in cells of murine macrophage lineage, *FASEB J.*, **30**, 286-300, doi: 10.1096/fj.15-279398.
72. Qin, W., Qin, K., Zhang, Y., Jia, W., Chen, Y., Cheng, B., Peng, L., Chen, N., Liu, Y., Zhou, W., Wang, Y. L., Chen, X., and Wang, C. (2019) S-glycosylation-based cysteine profiling reveals regulation of glycolysis by itaconate, *Nat. Chem. Biol.*, **15**, 983-991, doi: 10.1038/s41589-019-0323-5.
73. Mills, E. L., Ryan, D. G., Prag, H. A., Dikovskaya, D., Menon, D., Zaslona, Z., Jedrychowski, M. P., Costa, A. S. H., Higgins, M., Hams, E., Szpyt, J., Runtsch, M. C., King, M. S., McGouran, J. F., Fischer, R., Kessler, B. M., McGettrick, A. F., Hughes, M. M., Carroll, R. G., Booty, L. M., et al. (2018) Itaconate is an anti-inflammatory metabolite that activates Nrf2 via alkylation of KEAP1, *Nature*, **556**, 113-117, doi: 10.1038/nature25986.
74. Zhu, X., Guo, Y., Liu, Z., Yang, J., Tang, H., and Wang, Y. (2021) Itaconic acid exerts anti-inflammatory and antibacterial effects via promoting pentose phosphate pathway to produce ROS, *Sci. Rep.*, **11**, 18173, doi: 10.1038/s41598-021-97352-x.
75. Bambouskova, M., Gorvel, L., Lampropoulou, V., Sergushichev, A., Loginicheva, E., Johnson, K., Korenfeld, D., Mathyer, M. E., Kim, H., Huang, L. H., Duncan, D., Bregman, H., Keskin, A., Santeford, A., Apte, R. S., Sehgal, R., Johnson, B., Amarasinghe, G. K., Soares, M. P., Satoh, T., et al. (2018) Electrophilic properties of itaconate and derivatives regulate the IkappaBzeta-ATF3 inflammatory axis, *Nature*, **556**, 501-504, doi: 10.1038/s41586-018-0052-z.
76. Bambouskova, M., Potuckova, L., Paulenda, T., Kerndl, M., Mogilenko, D. A., Lizotte, K., Swain, A., Hayes, S., Sheldon, R. D., Kim, H., Kapadnis, U., Ellis, A. E., Isaguirre, C., Burdess, S., Laha, A., Amarasinghe, G. K., Chubukov, V., Roddy, T. P., Diamond, M. S., Jones, R. G., et al. (2021) Itaconate confers tolerance to late NLRP3 inflammasome activation, *Cell Rep.*, **34**, 108756, doi: 10.1016/j.celrep.2021.108756.
77. Hooftman, A., Angiari, S., Hester, S., Corcoran, S. E., Runtsch, M. C., Ling, C., Ruzek, M. C., Slivka, P. F., McGettrick, A. F., Banahan, K., Hughes, M. M., Irvine, A. D., Fischer, R., and O'Neill, L. A. J. (2020) The immunomodulatory metabolite itaconate modifies NLRP3 and inhibits inflammasome activation, *Cell Metab.*, **32**, 468-478, doi: 10.1016/j.cmet.2020.07.016.

78. Puchalska, P., Huang, X., Martin, S. E., Han, X., Patti, G. J., and Crawford, P. A. (2018) Isotope tracing untargeted metabolomics reveals macrophage polarization-state-specific metabolic coordination across intracellular compartments, *iScience*, **9**, 298-313, doi: 10.1016/j.isci.2018.10.029.
79. Runtsch, M. C., Angiari, S., Hooftman, A., Wadhwa, R., Zhang, Y., Zheng, Y., Spina, J. S., Ruzek, M. C., Argiriadi, M. A., McGettrick, A. F., Mendez, R. S., Zotta, A., Peace, C. G., Walsh, A., Chirillo, R., Hams, E., Fallon, P. G., Jayamaran, R., Dua, K., Brown, A. C., et al. (2022) Itaconate and itaconate derivatives target JAK1 to suppress alternative activation of macrophages, *Cell Metab.*, **34**, 487-501, doi: 10.1016/j.cmet.2022.02.002.
80. Weiss, J. M., Davies, L. C., Karwan, M., Ileva, L., Ozaki, M. K., Cheng, R. Y., Ridnour, L. A., Annunziata, C. M., Wink, D. A., and McVicar, D. W. (2018) Itaconic acid mediates crosstalk between macrophage metabolism and peritoneal tumors, *J. Clin. Invest.*, **128**, 3794-3805, doi: 10.1172/JCI99169.
81. (2023) Myeloid-derived itaconate suppresses antitumor immunity, *Cancer Discov.*, **13**, 255, doi: 10.1158/2159-8290.CD-RW2022-213.
82. Wang, F., Wang, K., Xu, W., Zhao, S., Ye, D., Wang, Y., Xu, Y., Zhou, L., Chu, Y., Zhang, C., Qin, X., Yang, P., and Yu, H. (2017) SIRT5 desuccinylates and activates pyruvate kinase M2 to block macrophage IL-1beta production and to prevent DSS-induced colitis in mice, *Cell Rep.*, **19**, 2331-2344, doi: 10.1016/j.celrep.2017.05.065.
83. Kelly, B., and O'Neill, L. A. (2015) Metabolic reprogramming in macrophages and dendritic cells in innate immunity, *Cell Res.*, **25**, 771-784, doi: 10.1038/cr.2015.68.
84. Littlewood-Evans, A., Sarret, S., Apfel, V., Loesle, P., Dawson, J., Zhang, J., Muller, A., Tigani, B., Kneuer, R., Patel, S., Valeaux, S., Gommermann, N., Rubic-Schneider, T., Junt, T., and Carballido, J. M. (2016) GPR91 senses extracellular succinate released from inflammatory macrophages and exacerbates rheumatoid arthritis, *J. Exp. Med.*, **213**, 1655-1662, doi: 10.1084/jem.20160061.
85. Hooftman, A., Peace, C. G., Ryan, D. G., Day, E. A., Yang, M., McGettrick, A. F., Yin, M., Montano, E. N., Huo, L., Toller-Kawahisa, J. E., Zecchini, V., Ryan, T. A. J., Bolado-Carrancio, A., Casey, A. M., Prag, H. A., Costa, A. S. H., De Los Santos, G., Ishimori, M., Wallace, D. J., Venuturupalli, S., et al. (2023) Macrophage fumarate hydratase restrains mtRNA-mediated interferon production, *Nature*, **615**, 490-498, doi: 10.1038/s41586-023-05720-6.
86. Zaslona, Z., and O'Neill, L. A. J. (2020) Cytokine-like roles for metabolites in immunity, *Mol. Cell*, **78**, 814-823, doi: 10.1016/j.molcel.2020.04.002.
87. Tsukada, Y., Fang, J., Erdjument-Bromage, H., Warren, M. E., Borchers, C. H., Tempst, P., and Zhang, Y. (2006) Histone demethylation by a family of JmjC domain-containing proteins, *Nature*, **439**, 811-816, doi: 10.1038/nature04433.
88. Tahiliani, M., Koh, K. P., Shen, Y., Pastor, W. A., Bandukwala, H., Brudno, Y., Agarwal, S., Iyer, L. M., Liu, D. R., Aravind, L., and Rao, A. (2009) Conversion of 5-methylcytosine to 5-hydroxymethylcytosine in mammalian DNA by MLL partner TET1, *Science*, **324**, 930-935, doi: 10.1126/science.1170116.
89. Liu, Z., Gan, L., Zhang, T., Ren, Q., and Sun, C. (2018) Melatonin alleviates adipose inflammation through elevating alpha-ketoglutarate and diverting adipose-derived exosomes to macrophages in mice, *J. Pineal Res.*, **64**, e12455, doi: 10.1111/jpi.12455.
90. Liu, P. S., Wang, H., Li, X., Chao, T., Teav, T., Christen, S., Di Conza, G., Cheng, W. C., Chou, C. H., Vavakova, M., Muret, C., Debackere, K., Mazzone, M., Huang, H. D., Fendt, S. M., Ivanisevic, J., and Ho, P. C. (2017) alpha-ketoglutarate orchestrates macrophage activation through metabolic and epigenetic reprogramming, *Nat. Immunol.*, **18**, 985-994, doi: 10.1038/ni.3796.
91. Dang, L., White, D. W., Gross, S., Bennett, B. D., Bittinger, M. A., Driggers, E. M., Fantin, V. R., Jang, H. G., Jin, S., Keenan, M. C., Marks, K. M., Prins, R. M., Ward, P. S., Yen, K. E., Liau, L. M., Rabinowitz, J. D., Cantley, L. C., Thompson, C. B., Vander Heiden, M. G., and Su, S. M. (2009) Cancer-associated IDH1 mutations produce 2-hydroxyglutarate, *Nature*, **462**, 739-744, doi: 10.1038/nature08617.
92. Dang, L., White, D. W., Gross, S., Bennett, B. D., Bittinger, M. A., Driggers, E. M., Fantin, V. R., Jang, H. G., Jin, S., Keenan, M. C., Marks, K. M., Prins, R. M., Ward, P. S., Yen, K. E., Liau, L. M., Rabinowitz, J. D., Cantley, L. C., Thompson, C. B., Vander Heiden, M. G., and Su, S. M. (2010) Cancer-associated IDH1 mutations produce 2-hydroxyglutarate, *Nature*, **465**, 966, doi: 10.1038/nature09132.
93. Carey, B. W., Finley, L. W., Cross, J. R., Allis, C. D., and Thompson, C. B. (2015) Intracellular alpha-ketoglutarate maintains the pluripotency of embryonic stem cells, *Nature*, **518**, 413-416, doi: 10.1038/nature13981.
94. Sciacovelli, M., Goncalves, E., Johnson, T. I., Zecchini, V. R., da Costa, A. S., Gaude, E., Drubbel, A. V., Theobald, S. J., Abbo, S. R., Tran, M. G., Rajeeve, V., Cardaci, S., Foster, S., Yun, H., Cutillas, P., Warren, A., Gnanapragasam, V., Gottlieb, E., Franze, K., Huntly, B., et al. (2016) Fumarate is an epigenetic modifier that elicits epithelial-to-mesenchymal transition, *Nature*, **537**, 544-547, doi: 10.1038/nature19353.
95. Du, X., and Hu, H. (2021) The roles of 2-hydroxyglutarate, *Front. Cell Dev. Biol.*, **9**, 651317, doi: 10.3389/fcell.2021.651317.
96. Williams, N. C., Ryan, D. G., Costa, A. S. H., Mills, E. L., Jedrychowski, M. P., Cloonan, S. M., Frezza, C., and O'Neill, L. A. (2022) Signaling metabolite L-2-hydroxyglutarate activates the transcription factor HIF-1alpha in lipopolysaccharide-activated macrophages, *J. Biol. Chem.*, **298**, 101501, doi: 10.1016/j.jbc.2021.101501.

97. de Goede, K. E., Harber, K. J., Gorki, F. S., Verberk, S. G. S., Groh, L. A., Keuning, E. D., Struys, E. A., van Weeghel, M., Haschemi, A., de Winther, M. P. J., van Dierendonck, X., and Van den Bossche, J. (2022) d-2-Hydroxyglutarate is an anti-inflammatory immunometabolite that accumulates in macrophages after TLR4 activation, *Biochim. Biophys. Acta Mol. Basis. Dis.*, **1868**, 166427, doi: 10.1016/j.bbadis.2022.166427.
98. Kieler, M., Hofmann, M., and Schabbauer, G. (2021) More than just protein building blocks: how amino acids and related metabolic pathways fuel macrophage polarization, *FEBS J.*, **288**, 3694-3714, doi: 10.1111/febs.15715.
99. Sivangala Thandi, R., Radhakrishnan, R. K., Tripathi, D., Paidipally, P., Azad, A. K., Schlesinger, L. S., Samten, B., Mulik, S., and Vankayalapati, R. (2020) Ornithine-A urea cycle metabolite enhances autophagy and controls *Mycobacterium tuberculosis* infection, *Nat. Commun.*, **11**, 3535, doi: 10.1038/s41467-020-17310-5.
100. Gutierrez, M. G., Master, S. S., Singh, S. B., Taylor, G. A., Colombo, M. I., and Deretic, V. (2004) Autophagy is a defense mechanism inhibiting BCG and *Mycobacterium tuberculosis* survival in infected macrophages, *Cell*, **119**, 753-766, doi: 10.1016/j.cell.2004.11.038.
101. Brown, G. C., and Cooper, C. E. (1994) Nanomolar concentrations of nitric oxide reversibly inhibit synaptosomal respiration by competing with oxygen at cytochrome oxidase, *FEBS Lett.*, **356**, 295-298, doi: 10.1016/0014-5793(94)01290-3.
102. Cleeter, M. W., Cooper, J. M., Darley-Usmar, V. M., Moncada, S., and Schapira, A. H. (1994) Reversible inhibition of cytochrome *c* oxidase, the terminal enzyme of the mitochondrial respiratory chain, by nitric oxide. Implications for neurodegenerative diseases, *FEBS Lett.*, **345**, 50-54, doi: 10.1016/0014-5793(94)00424-2.
103. Jin, Z., Wei, W., Yang, M., Du, Y., and Wan, Y. (2014) Mitochondrial complex I activity suppresses inflammation and enhances bone resorption by shifting macrophage-osteoclast polarization, *Cell Metab.*, **20**, 483-498, doi: 10.1016/j.cmet.2014.07.011.
104. McNeill, E., Crabtree, M. J., Sahgal, N., Patel, J., Chuaiphichai, S., Iqbal, A. J., Hale, A. B., Greaves, D. R., and Channon, K. M. (2015) Regulation of iNOS function and cellular redox state by macrophage Gch1 reveals specific requirements for tetrahydrobiopterin in NRF2 activation, *Free Radic. Biol. Med.*, **79**, 206-216, doi: 10.1016/j.freeradbiomed.2014.10.575.
105. Seim, G. L., Britt, E. C., John, S. V., Yeo, F. J., Johnson, A. R., Eisenstein, R. S., Pagliarini, D. J., and Fan, J. (2019) Two-stage metabolic remodelling in macrophages in response to lipopolysaccharide and interferon-gamma stimulation, *Nat. Metab.*, **1**, 731-742, doi: 10.1038/s42255-019-0083-2.
106. Palmieri, E. M., Gonzalez-Cotto, M., Baseler, W. A., Davies, L. C., Ghesquiere, B., Maio, N., Rice, C. M., Rouault, T. A., Cassel, T., Higashi, R. M., Lane, A. N., Fan, T. W., Wink, D. A., and McVicar, D. W. (2020) Nitric oxide orchestrates metabolic rewiring in M1 macrophages by targeting aconitase 2 and pyruvate dehydrogenase, *Nat. Commun.*, **11**, 698, doi: 10.1038/s41467-020-14433-7.
107. Byles, V., Covarrubias, A. J., Ben-Sahra, I., Lamming, D. W., Sabatini, D. M., Manning, B. D., and Horng, T. (2013) The TSC-mTOR pathway regulates macrophage polarization, *Nat. Commun.*, **4**, 2834, doi: 10.1038/ncomms3834.
108. Newsholme, P., Gordon, S., and Newsholme, E. A. (1987) Rates of utilization and fates of glucose, glutamine, pyruvate, fatty acids and ketone bodies by mouse macrophages, *Biochem. J.*, **242**, 631-636, doi: 10.1042/bj2420631.
109. Meiser, J., Kramer, L., Sapcariu, S. C., Battello, N., Ghelfi, J., D'Herouel, A. F., Skupin, A., and Hiller, K. (2016) Pro-inflammatory macrophages sustain pyruvate oxidation through pyruvate dehydrogenase for the synthesis of itaconate and to enable cytokine expression, *J. Biol. Chem.*, **291**, 3932-3946, doi: 10.1074/jbc.M115.676817.
110. Funk, J. L., Feingold, K. R., Moser, A. H., and Grunfeld, C. (1993) Lipopolysaccharide stimulation of RAW 264.7 macrophages induces lipid accumulation and foam cell formation, *Atherosclerosis*, **98**, 67-82, doi: 10.1016/0021-9150(93)90224-i.
111. Hu, L., Yu, Y., Huang, H., Fan, H., Hu, L., Yin, C., Li, K., Fulton, D. J., and Chen, F. (2016) Epigenetic rRegulation of interleukin 6 by histone acetylation in macrophages and its role in paraquat-induced pulmonary fibrosis, *Front. Immunol.*, **7**, 696, doi: 10.3389/fimmu.2016.00696.
112. Zhang, Q., Zhao, K., Shen, Q., Han, Y., Gu, Y., Li, X., Zhao, D., Liu, Y., Wang, C., Zhang, X., Su, X., Liu, J., Ge, W., Levine, R. L., Li, N., and Cao, X. (2015) Tet2 is required to resolve inflammation by recruiting Hdac2 to specifically repress IL-6, *Nature*, **525**, 389-393, doi: 10.1038/nature15252.
113. Biswas, S. K., and Lopez-Collazo, E. (2009) Endotoxin tolerance: new mechanisms, molecules and clinical significance, *Trends Immunol.*, **30**, 475-487, doi: 10.1016/j.it.2009.07.009.
114. Palmieri, E. M., Menga, A., Martin-Perez, R., Quinto, A., Riera-Domingo, C., De Tullio, G., Hooper, D. C., Lamers, W. H., Ghesquiere, B., McVicar, D. W., Guarini, A., Mazzone, M., and Castegna, A. (2017) Pharmacologic or genetic targeting of glutamine synthetase skews macrophages toward an M1-like phenotype and inhibits tumor metastasis, *Cell Rep.*, **20**, 1654-1666, doi: 10.1016/j.celrep.2017.07.054.
115. Kelly, B., Tannahill, G. M., Murphy, M. P., and O'Neill, L. A. (2015) Metformin inhibits the production of reactive oxygen species from NADH:Ubiquinone oxidoreductase to limit induction of interleukin-1beta (IL-1beta) and boosts interleukin-10 (IL-10) in lipopoly-

saccharide (LPS)-activated macrophages, *J. Biol. Chem.*, **290**, 20348-20359, doi: 10.1074/jbc.M115.662114.

116. Zhou, R., Yazdi, A. S., Menu, P., and Tschopp, J. (2011) A role for mitochondria in NLRP3 inflammasome activation, *Nature*, **469**, 221-225, doi: 10.1038/nature09663.
117. Thimmulappa, R. K., Lee, H., Rangasamy, T., Reddy, S. P., Yamamoto, M., Kensler, T. W., and Biswal, S. (2006) Nrf2 is a critical regulator of the innate immune response and survival during experimental sepsis, *J. Clin. Invest.*, **116**, 984-995, doi: 10.1172/JCI25790.
118. Kobayashi, E. H., Suzuki, T., Funayama, R., Nagashima, T., Hayashi, M., Sekine, H., Tanaka, N., Moriguchi, T., Motohashi, H., Nakayama, K., and Yamamoto, M. (2016) Nrf2 suppresses macrophage inflammatory response by blocking proinflammatory cytokine transcription, *Nat. Commun.*, **7**, 11624, doi: 10.1038/ncomms11624.
119. Yu, W., Wang, Z., Zhang, K., Chi, Z., Xu, T., Jiang, D., Chen, S., Li, W., Yang, X., Zhang, X., Wu, Y., and Wang, D. (2019) One-carbon metabolism supports S-adenosylmethionine and histone nethylation to drive inflammatory macrophages, *Mol. Cell*, **75**, 1147-1160, doi: 10.1016/j.molcel.2019.06.039.
120. Castoldi, A., Monteiro, L. B., van Teijlingen Bakker, N., Sanin, D. E., Rana, N., Corrado, M., Cameron, A. M., Hassler, F., Matsushita, M., Caputa, G., Klein Geltink, R. I., Buscher, J., Edwards-Hicks, J., Pearce, E. L., and Pearce, E. J. (2020) Triacylglycerol synthesis enhances macrophage inflammatory function, *Nat. Commun.*, **11**, 4107, doi: 10.1038/s41467-020-17881-3.
121. Morgan, P. K., Huynh, K., Pernes, G., Miotto, P. M., Mellett, N. A., Giles, C., Meikle, P. J., Murphy, A. J., and Lancaster, G. I. (2021) Macrophage polarization state affects lipid composition and the channeling of exogenous fatty acids into endogenous lipid pools, *J. Biol. Chem.*, **297**, 101341, doi: 10.1016/j.jbc.2021.101341.
122. Guerrini, V., and Gennaro, M. L. (2019) Foam cells: one size doesn't fit all, *Trends Immunol.*, **40**, 1163-1179, doi: 10.1016/j.it.2019.10.002.
123. Im, S. S., Yousef, L., Blaschitz, C., Liu, J. Z., Edwards, R. A., Young, S. G., Raffatellu, M., and Osborne, T. F. (2011) Linking lipid metabolism to the innate immune response in macrophages through sterol regulatory element binding protein-1a, *Cell Metab.*, **13**, 540-549, doi: 10.1016/j.cmet.2011.04.001.
124. Batista-Gonzalez, A., Vidal, R., Criollo, A., and Carreno, L. J. (2019) New insights on the role of lipid metabolism in the metabolic reprogramming of macrophages, *Front. Immunol.*, **10**, 2993, doi: 10.3389/fimmu.2019.02993.
125. van Dierendonck, X., Sancerni, T., Alves-Guerra, M. C., and Stienstra, R. (2020) The role of uncoupling protein 2 in macrophages and its impact on obesity-induced adipose tissue inflammation and insulin resistance, *J. Biol. Chem.*, **295**, 17535-17548, doi: 10.1074/jbc.RA120.014868.
126. Yeudall, S., Upchurch, C. M., Seegren, P. V., Pavelec, C. M., Greulich, J., Lemke, M. C., Harris, T. E., Desai, B. N., Hoehn, K. L., and Leitinger, N. (2022) Macrophage acetyl-CoA carboxylase regulates acute inflammation through control of glucose and lipid metabolism, *Sci. Adv.*, **8**, eabq1984, doi: 10.1126/sciadv.abq1984.
127. Nomura, M., Liu, J., Rovira, I., Gonzalez-Hurtado, E., Lee, J., Wolfgang, M. J., and Finkel, T. (2016) Fatty acid oxidation in macrophage polarization, *Nat. Immunol.*, **17**, 216-217, doi: 10.1038/ni.3366.
128. Divakaruni, A. S., Hsieh, W. Y., Minarrieta, L., Duong, T. N., Kim, K. K. O., Desousa, B. R., Andreyev, A. Y., Bowman, C. E., Caradonna, K., Dranka, B. P., Ferrick, D. A., Liesa, M., Stiles, L., Rogers, G. W., Braas, D., Ciaraldi, T. P., Wolfgang, M. J., Sparwasser, T., Berod, L., Bensinger, S. J., et al. (2018) Etomoxir inhibits macrophage polarization by disrupting CoA homeostasis, *Cell Metab.*, **28**, 490-503, doi: 10.1016/j.cmet.2018.06.001.
129. Van den Bossche, J., O'Neill, L. A., and Menon, D. (2017) Macrophage immunometabolism: where are we (going)? *Trends Immunol.*, **38**, 395-406, doi: 10.1016/j.it.2017.03.001.
130. Moon, J. S., Nakahira, K., Chung, K. P., DeNicola, G. M., Koo, M. J., Pabon, M. A., Rooney, K. T., Yoon, J. H., Ryter, S. W., Stout-Delgado, H., and Choi, A. M. (2016) NOX4-dependent fatty acid oxidation promotes NLRP3 inflammasome activation in macrophages, *Nat. Med.*, **22**, 1002-1012, doi: 10.1038/nm.4153.
131. Olona, A., Leishman, S., and Anand, P. K. (2022) The NLRP3 inflammasome: regulation by metabolic signals, *Trends Immunol.*, **43**, 978-989, doi: 10.1016/j.it.2022.10.003.
132. Kumar, S., Mittal, S., Gupta, P., Singh, M., Chaluvally-Raghavan, P., and Pradeep, S. (2022) Metabolic reprogramming in tumor-associated macrophages in the ovarian tumor microenvironment, *Cancers (Basel)*, **14**, 5224, doi: 10.3390/cancers14215224.
133. Wu, L., Zhang, X., Zheng, L., Zhao, H., Yan, G., Zhang, Q., Zhou, Y., Lei, J., Zhang, J., Wang, J., Xin, R., Jiang, L., Peng, J., Chen, Q., Lam, S. M., Shui, G., Miao, H., and Li, Y. (2020) RIPK3 orchestrates fatty acid metabolism in tumor-associated macrophages and hepatocarcinogenesis, *Cancer Immunol. Res.*, **8**, 710-721, doi: 10.1158/2326-6066.CIR-19-0261.
134. Covarrubias, A. J., Aksoylar, H. I., and Horng, T. (2015) Control of macrophage metabolism and activation by mTOR and Akt signaling, *Semin. Immunol.*, **27**, 286-296, doi: 10.1016/j.smim.2015.08.001.
135. Kang, S., and Kumanogoh, A. (2020) The spectrum of macrophage activation by immunometabolism, *Int. Immunol.*, **32**, 467-473, doi: 10.1093/intimm/dxaa017.
136. Dibble, C. C., and Manning, B. D. (2013) Signal integration by mTORC1 coordinates nutrient input with biosynthetic output, *Nat. Cell Biol.*, **15**, 555-564, doi: 10.1038/ncb2763.

137. Weichhart, T., Hengstschlager, M., and Linke, M. (2015) Regulation of innate immune cell function by mTOR, *Nat. Rev. Immunol.*, **15**, 599-614, doi: 10.1038/nri3901.
138. Weichhart, T., Costantino, G., Poglitsch, M., Rosner, M., Zeyda, M., Stuhlmeier, K. M., Kolbe, T., Stulnig, T. M., Horl, W. H., Hengstschlager, M., Muller, M., and Saemann, M. D. (2008) The TSC-mTOR signaling pathway regulates the innate inflammatory response, *Immunity*, **29**, 565-577, doi: 10.1016/j.immuni.2008.08.012.
139. Robey, R. B., and Hay, N. (2009) Is Akt the "Warburg kinase"?-Akt-energy metabolism interactions and oncogenesis, *Semin. Cancer Biol.*, **19**, 25-31, doi: 10.1016/j.semcancer.2008.11.010.
140. Huang, S. C., Smith, A. M., Everts, B., Colonna, M., Pearce, E. L., Schilling, J. D., and Pearce, E. J. (2016) Metabolic reprogramming mediated by the mTORC2-IRF4 signaling axis is essential for macrophage alternative activation, *Immunity*, **45**, 817-830, doi: 10.1016/j.immuni.2016.09.016.
141. Biswas, S. K., and Mantovani, A. (2012) Orchestration of metabolism by macrophages, *Cell Metab.*, **15**, 432-437, doi: 10.1016/j.cmet.2011.11.013.
142. Beltrao, P., Bork, P., Krogan, N. J., and van Noort, V. (2013) Evolution and functional cross-talk of protein post-translational modifications, *Mol. Syst. Biol.*, **9**, 714, doi: 10.1002/msb.201304521.
143. Stein, S. C., Woods, A., Jones, N. A., Davison, M. D., and Carling, D. (2000) The regulation of AMP-activated protein kinase by phosphorylation, *Biochem. J.*, **345**, 437-443, doi: 10.1042/bj3450437.
144. O'Neill, L. A., and Hardie, D. G. (2013) Metabolism of inflammation limited by AMPK and pseudo-starvation, *Nature*, **493**, 346-355, doi: 10.1038/nature11862.
145. Nath, N., Khan, M., Rattan, R., Mangalam, A., Makkar, R. S., de Meester, C., Bertrand, L., Singh, I., Chen, Y., Viollet, B., and Giri, S. (2009) Loss of AMPK exacerbates experimental autoimmune encephalomyelitis disease severity, *Biochem. Biophys. Res. Commun.*, **386**, 16-20, doi: 10.1016/j.bbrc.2009.05.106.
146. Mounier, R., Theret, M., Arnold, L., Cuvellier, S., Bultot, L., Goransson, O., Sanz, N., Ferry, A., Sakamoto, K., Foretz, M., Viollet, B., and Chazaud, B. (2013) AMPKalpha1 regulates macrophage skewing at the time of resolution of inflammation during skeletal muscle regeneration, *Cell Metab.*, **18**, 251-264, doi: 10.1016/j.cmet.2013.06.017.
147. Sag, D., Carling, D., Stout, R. D., and Suttles, J. (2008) Adenosine 5′-monophosphate-activated protein kinase promotes macrophage polarization to an anti-inflammatory functional phenotype, *J. Immunol.*, **181**, 8633-8641, doi: 10.4049/jimmunol.181.12.8633.
148. Vasamsetti, S. B., Karnewar, S., Kanugula, A. K., Thatipalli, A. R., Kumar, J. M., and Kotamraju, S. (2015) Metformin inhibits monocyte-to-macrophage differentiation via AMPK-mediated inhibition of STAT3 activation: potential role in atherosclerosis, *Diabetes*, **64**, 2028-2041, doi: 10.2337/db14-1225.
149. Seneviratne, A., Cave, L., Hyde, G., Moestrup, S. K., Carling, D., Mason, J. C., Haskard, D. O., and Boyle, J. J. (2021) Metformin directly suppresses atherosclerosis in normoglycaemic mice via haematopoietic adenosine monophosphate-activated protein kinase, *Cardiovasc. Res.*, **117**, 1295-1308, doi: 10.1093/cvr/cvaa171.
150. Phair, I. R., Nisr, R. B., Howden, A. J. M., Sovakova, M., Alqurashi, N., Foretz, M., Lamont, D., Viollet, B., and Rena, G. (2023) AMPK integrates metabolite and kinase-based immunometabolic control in macrophages, *Mol. Metab.*, **68**, 101661, doi: 10.1016/j.molmet.2022.101661.
151. Kadomoto, S., Izumi, K., and Mizokami, A. (2021) Macrophage polarity and disease dontrol, *Int. J. Mol. Sci.*, **23**, 144, doi: 10.3390/ijms23010144.
152. Wang, Z., Li, Y., Yang, X., Zhang, L., Shen, H., Xu, W., and Yuan, C. (2019) Protective effects of rapamycin induced autophagy on CLP septic mice, *Comp. Immunol. Microbiol. Infect. Dis.*, **64**, 47-52, doi: 10.1016/j.cimid.2019.01.009.
153. Ko, J. H., Yoon, S. O., Lee, H. J., and Oh, J. Y. (2017) Rapamycin regulates macrophage activation by inhibiting NLRP3 inflammasome-p38 MAPK-NFkappaB pathways in autophagy- and p62-dependent manners, *Oncotarget*, **8**, 40817-40831, doi: 10.18632/oncotarget.17256.
154. Wu, M. M., Wang, Q. M., Huang, B. Y., Mai, C. T., Wang, C. L., Wang, T. T., and Zhang, X. J. (2021) Dioscin ameliorates murine ulcerative colitis by regulating macrophage polarization, *Pharmacol. Res.*, **172**, 105796, doi: 10.1016/j.phrs.2021.105796.
155. Hsu, S. P. C., Chen, Y. C., Chiang, H. C., Huang, Y. C., Huang, C. C., Wang, H. E., Wang, Y. S., and Chi, K. H. (2020) Rapamycin and hydroxychloroquine combination alters macrophage polarization and sensitizes glioblastoma to immune checkpoint inhibitors, *J. Neurooncol.*, **146**, 417-426, doi: 10.1007/s11060-019-03360-3.
156. Sun, R. Z., Fan, Y., Liang, X., Gong, T. T., Wang, Q., Liu, H., Shan, Z. Y., and Lei, L. (2018) Rapamycin and FTY720 alleviate atherosclerosis by cross talk of macrophage polarization and autophagy, *Biomed. Res. Int.*, **2018**, 1010248, doi: 10.1155/2018/1010248.
157. Fang, S., Wan, X., Zou, X., Sun, S., Hao, X., Liang, C., Zhang, Z., Zhang, F., Sun, B., Li, H., and Yu, B. (2021) Arsenic trioxide induces macrophage autophagy and atheroprotection by regulating ROS-dependent TFEB nuclear translocation and AKT/mTOR pathway, *Cell Death Dis.*, **12**, 88, doi: 10.1038/s41419-020-03357-1.
158. Ursini, F., Russo, E., Pellino, G., D'Angelo, S., Chiaravalloti, A., De Sarro, G., Manfredini, R., and De Giorgio, R. (2018) Metformin and autoimmunity: a "new deal" of an old drug, *Front. Immunol.*, **9**, 1236, doi: 10.3389/fimmu.2018.01236.

159. Feng, X., Chen, W., Ni, X., Little, P. J., Xu, S., Tang, L., and Weng, J. (2021) Metformin, macrophage dysfunction and atherosclerosis, *Front. Immunol.*, **12**, 682853, doi: 10.3389/fimmu.2021.682853.
160. Pajak, B., Siwiak, E., Soltyka, M., Priebe, A., Zielinski, R., Fokt, I., Ziemniak, M., Jaskiewicz, A., Borowski, R., Domoradzki, T., and Priebe, W. (2019) 2-Deoxy-d-glucose and its analogs: from diagnostic to therapeutic agents, *Int. J. Mol. Sci.*, **21**, 234, doi: 10.3390/ijms21010234.
161. Luo, W., Hu, H., Chang, R., Zhong, J., Knabel, M., O'Meally, R., Cole, R. N., Pandey, A., and Semenza, G. L. (2011) Pyruvate kinase M2 is a PHD3-stimulated coactivator for hypoxia-inducible factor 1, *Cell*, **145**, 732-744, doi: 10.1016/j.cell.2011.03.054.
162. Anastasiou, D., Yu, Y., Israelsen, W. J., Jiang, J. K., Boxer, M. B., Hong, B. S., Tempel, W., Dimov, S., Shen, M., Jha, A., Yang, H., Mattaini, K. R., Metallo, C. M., Fiske, B. P., Courtney, K. D., Malstrom, S., Khan, T. M., Kung, C., Skoumbourdis, A. P., Veith, H., et al. (2012) Pyruvate kinase M2 activators promote tetramer formation and suppress tumorigenesis, *Nat. Chem. Biol.*, **8**, 839-847, doi: 10.1038/nchembio.1060.
163. Yi, Z., Wu, Y., Zhang, W., Wang, T., Gong, J., Cheng, Y., and Miao, C. (2020) Activator-mediated pyruvate kinase M2 activation contributes to endotoxin tolerance by promoting mitochondrial biogenesis, *Front. Immunol.*, **11**, 595316, doi: 10.3389/fimmu.2020.595316.
164. Welsh, S., Williams, R., Kirkpatrick, L., Paine-Murrieta, G., and Powis, G. (2004) Antitumor activity and pharmacodynamic properties of PX-478, an inhibitor of hypoxia-inducible factor-1alpha, *Mol. Cancer Ther.*, **3**, 233-244, doi: 10.1158/1535-7163.233.3.3.
165. Villa-Roel, N., Ryu, K., Gu, L., Fernandez Esmerats, J., Kang, D. W., Kumar, S., and Jo, H. (2022) Hypoxia inducible factor 1alpha inhibitor PX-478 reduces atherosclerosis in mice, *Atherosclerosis*, **344**, 20-30, doi: 10.1016/j.atherosclerosis.2022.01.002.
166. Mills, E. L., Kelly, B., Logan, A., Costa, A. S. H., Varma, M., Bryant, C. E., Tourlomousis, P., Dabritz, J. H. M., Gottlieb, E., Latorre, I., Corr, S. C., McManus, G., Ryan, D., Jacobs, H. T., Szibor, M., Xavier, R. J., Braun, T., Frezza, C., Murphy, M. P., and O'Neill, L. A. (2016) Succinate dehydrogenase supports metabolic repurposing of mitochondria to drive inflammatory macrophages, *Cell*, **167**, 457-470, doi: 10.1016/j.cell.2016.08.064.
167. Yen, K. E., Bittinger, M. A., Su, S. M., and Fantin, V. R. (2010) Cancer-associated IDH mutations: biomarker and therapeutic opportunities, *Oncogene*, **29**, 6409-6417, doi: 10.1038/onc.2010.444.
168. Chouchani, E. T., Pell, V. R., Gaude, E., Aksentijevic, D., Sundier, S. Y., Robb, E. L., Logan, A., Nadtochiy, S. M., Ord, E. N. J., Smith, A. C., Eyassu, F., Shirley, R., Hu, C. H., Dare, A. J., James, A. M., Rogatti, S., Hartley, R. C., Eaton, S., Costa, A. S. H., Brookes, P. S., et al. (2014) Ischaemic accumulation of succinate controls reperfusion injury through mitochondrial ROS, *Nature*, **515**, 431-435, doi: 10.1038/nature13909.
169. Gross, C. C., Schulte-Mecklenbeck, A., Klinsing, S., Posevitz-Fejfar, A., Wiendl, H., and Klotz, L. (2016) Dimethyl fumarate treatment alters circulating T helper cell subsets in multiple sclerosis, *Neurol. Neuroimmunol. Neuroinflamm.*, **3**, e183, doi: 10.1212/NXI.0000000000000183.
170. Kornberg, M. D., Bhargava, P., Kim, P. M., Putluri, V., Snowman, A. M., Putluri, N., Calabresi, P. A., and Snyder, S. H. (2018) Dimethyl fumarate targets GAPDH and aerobic glycolysis to modulate immunity, *Science*, **360**, 449-453, doi: 10.1126/science.aan4665.
171. Mrowietz, U., Szepietowski, J. C., Loewe, R., van de Kerkhof, P., Lamarca, R., Ocker, W. G., Tebbs, V. M., and Pau-Charles, I. (2017) Efficacy and safety of LAS41008 (dimethyl fumarate) in adults with moderate-to-severe chronic plaque psoriasis: a randomized, double-blind, Fumaderm((R)) - and placebo-controlled trial (BRIDGE), *Br. J. Dermatol.*, **176**, 615-623, doi: 10.1111/bjd.14947.
172. Han, R., Xiao, J., Zhai, H., and Hao, J. (2016) Dimethyl fumarate attenuates experimental autoimmune neuritis through the nuclear factor erythroid-derived 2-related factor 2/hemoxygenase-1 pathway by altering the balance of M1/M2 macrophages, *J. Neuroinflammation*, **13**, 97, doi: 10.1186/s12974-016-0559-x.
173. Cross, A. H., Misko, T. P., Lin, R. F., Hickey, W. F., Trotter, J. L., and Tilton, R. G. (1994) Aminoguanidine, an inhibitor of inducible nitric oxide synthase, ameliorates experimental autoimmune encephalomyelitis in SJL mice, *J. Clin. Invest.*, **93**, 2684-2690, doi: 10.1172/JCI117282.
174. Chatterjee, P. K., Patel, N. S., Sivarajah, A., Kvale, E. O., Dugo, L., Cuzzocrea, S., Brown, P. A., Stewart, K. N., Mota-Filipe, H., Britti, D., Yaqoob, M. M., and Thiemermann, C. (2003) GW274150, a potent and highly selective inhibitor of iNOS, reduces experimental renal ischemia/reperfusion injury, *Kidney Int.*, **63**, 853-865, doi: 10.1046/j.1523-1755.2003.00802.x.
175. Dugo, L., Marzocco, S., Mazzon, E., Di Paola, R., Genovese, T., Caputi, A. P., and Cuzzocrea, S. (2004) Effects of GW274150, a novel and selective inhibitor of iNOS activity, in acute lung inflammation, *Br. J. Pharmacol.*, **141**, 979-987, doi: 10.1038/sj.bjp.0705683.
176. Miret, J. J., Kirschmeier, P., Koyama, S., Zhu, M., Li, Y. Y., Naito, Y., Wu, M., Malladi, V. S., Huang, W., Walker, W., Palakurthi, S., Dranoff, G., Hammerman, P. S., Pecot, C. V., Wong, K. K., and Akbay, E. A. (2019) Suppression of myeloid cell arginase activity leads to therapeutic response in a NSCLC mouse model by activating anti-tumor Immunity, *J. Immunother. Cancer*, 7, 32, doi: 10.1186/s40425-019-0504-5.
177. Steggerda, S. M., Bennett, M. K., Chen, J., Emberley, E., Huang, T., Janes, J. R., Li, W., MacKinnon, A. L.,

Makkouk, A., Marguier, G., Murray, P. J., Neou, S., Pan, A., Parlati, F., Rodriguez, M. L. M., Van de Velde, L. A., Wang, T., Works, M., Zhang, J., Zhang, W., et al. (2017) Inhibition of arginase by CB-1158 blocks myeloid cell-mediated immune suppression in the tumor microenvironment, *J. Immunother. Cancer*, **5**, 101, doi: 10.1186/s40425-017-0308-4.

178. Kono, M., Yoshida, N., Maeda, K., and Tsokos, G. C. (2018) Transcriptional factor ICER promotes glutaminolysis and the generation of Th17 cells, *Proc. Natl. Acad. Sci. USA*, **115**, 2478-2483, doi: 10.1073/pnas.1714717115.
179. Takahashi, S., Saegusa, J., Sendo, S., Okano, T., Akashi, K., Irino, Y., and Morinobu, A. (2017) Glutaminase 1 plays a key role in the cell growth of fibroblast-like synoviocytes in rheumatoid arthritis, *Arthritis Res. Ther.*, **19**, 76, doi: 10.1186/s13075-017-1283-3.
180. Rodriguez, A. E., Ducker, G. S., Billingham, L. K., Martinez, C. A., Mainolfi, N., Suri, V., Friedman, A., Manfredi, M. G., Weinberg, S. E., Rabinowitz, J. D., and Chandel, N. S. (2019) Serine metabolism supports macrophage IL-1beta production, *Cell Metab.*, **29**, 1003-1011, doi: 10.1016/j.cmet.2019.01.014.
181. Ravindran, R., Loebbermann, J., Nakaya, H. I., Khan, N., Ma, H., Gama, L., Machiah, D. K., Lawson, B., Hakimpour, P., Wang, Y. C., Li, S., Sharma, P., Kaufman, R. J., Martinez, J., and Pulendran, B. (2016) The amino acid sensor GCN2 controls gut inflammation by inhibiting inflammasome activation, *Nature*, **531**, 523-527, doi: 10.1038/nature17186.
182. Chen, G. Q., Gong, R. H., Yang, D. J., Zhang, G., Lu, A. P., Yan, S. C., Lin, S. H., and Bian, Z. X. (2017) Halofuginone dually regulates autophagic flux through nutrient-sensing pathways in colorectal cancer, *Cell Death Dis.*, **8**, e2789, doi: 10.1038/cddis.2017.203.
183. Wang, M., Wang, K., Liao, X., Hu, H., Chen, L., Meng, L., Gao, W., and Li, Q. (2021) Carnitine palmitoyltransferase system: a new target for anti-inflammatory and anticancer therapy? *Front. Pharmacol.*, **12**, 760581, doi: 10.3389/fphar.2021.760581.
184. Qiao, S., Lv, C., Tao, Y., Miao, Y., Zhu, Y., Zhang, W., Sun, D., Yun, X., Xia, Y., Wei, Z., and Dai, Y. (2020) Arctigenin disrupts NLRP3 inflammasome assembly in colonic macrophages via downregulating fatty acid oxidation to prevent colitis-associated cancer, *Cancer Lett.*, **491**, 162-179, doi: 10.1016/j.canlet.2020.08.033.
185. Peng, S., Chen, D., Cai, J., Yuan, Z., Huang, B., Li, Y., Wang, H., Luo, Q., Kuang, Y., Liang, W., Liu, Z., Wang, Q., Cui, Y., Wang, H., and Liu, X. (2021) Enhancing cancer-associated fibroblast fatty acid catabolism within a metabolically challenging tumor microenvironment drives colon cancer peritoneal metastasis, *Mol. Oncol.*, **15**, 1391-1411, doi: 10.1002/1878-0261.12917.
186. Esteves, P., Blanc, L., Celle, A., Dupin, I., Maurat, E., Amoedo, N., Cardouat, G., Ousova, O., Gales, L., Bellvert, F., Begueret, H., Thumerel, M., Dupuy, J. W., Desbenoit, N., Marthan, R., Girodet, P. O., Rossignol, R., Berger, P., and Trian, T. (2021) Crucial role of fatty acid oxidation in asthmatic bronchial smooth muscle remodelling, *Eur. Respir. J.*, **58**, 2004252, doi: 10.1183/13993003.04252-2020.
187. Jiang, Z., Knudsen, N. H., Wang, G., Qiu, W., Naing, Z. Z. C., Bai, Y., Ai, X., Lee, C. H., and Zhou, X. (2017) Genetic control of fatty acid beta-oxidation in chronic obstructive pulmonary disease, *Am. J. Respir. Cell Mol. Biol.*, **56**, 738-748, doi: 10.1165/rcmb.2016-0282OC.