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Pattern-Recognition Receptors and Immunometabolic Reprogramming: What We Know and What to Explore

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Keywords

Immunometabolism · Infection · Inflammation · Toll-like receptors · NOD-like receptors · cGLRs · Retinoic acid-inducible gene-1-like receptors · Glycolysis · Oxidative phosphorylation

Abstract

Background: Evolutionarily, immune response is a complex mechanism that protects the host from internal and external threats. Pattern-recognition receptors (PRRs) recognize MAMPs, PAMPs, and DAMPs to initiate a protective pro-inflammatory immune response. PRRs are expressed on the cell membranes by TLR1, 2, 4, and 6 and in the cytosolic organelles by TLR3, 7, 8, and 9, NLRs, ALRs, and cGLRs. We know their downstream signaling pathways controlling immunoregulatory and pro-inflammatory immune response. However, the impact of PRRs on metabolic control of immune cells to control their pro- and anti-inflammatory activity has not been discussed extensively. ***Summary:*** Immune cell metabolism or immunometabolism critically determines immune cells' pro-inflammatory phenotype and function. The current article discusses immunometabolic reprogramming (IR) upon activation of different PRRs, such as TLRs, NLRs, cGLRs, and RLRs. The duration and type of PRR activated, species studied, and location of immune cells to specific organ are critical factors to determine the IR-induced immune response. ***Key Message:*** The work herein describes IR upon TLR, NLR, cGLR, and RLR activation. Understanding IR upon activating different PRRs is critical for designing better immune cell-specific immunotherapeutics and immunomodulators targeting inflammation and inflammatory diseases.

Introduction

Inflammation is a protective host immune response seen during acute trauma or microbes/pathogens and associated microbial/pathogen-associated molecular patterns (MAMPs/PAMPs) exposure to contain the damage or the pathogen responsible for the infection [1]. Furthermore, cellular injury also produces death or damage-associated molecular patterns (DAMPs). The recognition of different molecular patterns (MAMPs, PAMPs, and DAMPs) by pattern-recognition receptors (PRRs) initiates the NF-κB, inflammasome, and interferon (IFN)-releasing factors (IRFs)-dependent pro-inflammatory immune response. The inflammatory process involves a complex network of cellular and molecular signaling cascades to restore the tissue or organ homeostasis, repair, and regeneration. However, severe local or systemic acute inflammation may result in pathology, organ failure, and

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death, as seen during sepsis. Furthermore, persisting chronic inflammation may cause chronic inflammatory diseases, such as cancers, autoinflammation, and autoimmunity [2–5].

The cellular components of the immune system playing an active role in the inflammatory process involve endothelial cells, epithelial cells, monocytes/macrophages, mast cells, neutrophils, dendritic cells, innate lymphoid cells, mucosal-associated invariant T cells, natural killer cells, and different subsets of T cells [6–9]. These immune cells express different types of PRRs such as Toll-like receptors (TLRs), NOD-like receptors (NLRs), absent in melanoma-2 (AIM-2)-like receptors (ALRs), C-type lectin receptors (CLRs), Retinoic acid-inducible gene-1 (RIG-1)-like receptors (RLRs), and cGLRs, recognizing different PAMPs and DAMPs to initiate the protective pro-inflammatory cascade. However, the metabolic status of immune cells governs their pro- and anti-inflammatory function, which also depends on their location site.

Immunometabolism combines classical immunology with metabolism and can be classified into cellular and tissue immunometabolism [10]. Cellular immunometabolism deals with the impact of metabolic programming on the cellular fate and functions (pro- and anti-inflammatory) of immune cells. In contrast, tissue immunometabolism deals with the impact of immune cells on the tissue and systemic metabolism, governing the host's adaptation to environmental changes [10]. The concept of systemic immunometabolism has also emerged, which supports the notion that different organs are specialized for specific metabolic tasks with the potential to impact systemic immune response [11]. For example, liver, adipose tissue (AT), and immune response have well-established crosstalk [12, 13]. Similarly, the gut-brain-microbiota axis impacts systemic and local immune response [11, 14, 15].

Immune cells (macrophages, DCs, neutrophils, and T cells) with a reprogramed immunometabolism from oxidative phosphorylation (OXPHOS) coupled with Krebs or tricarboxylic acid (TCA) cycle to increased glycolysis develop a pro-inflammatory phenotype and secrete pro-inflammatory cytokines and molecules, such as IL-1β, IL-6, IL-18, type 1 IFNs, and IFN-γ secretion [16]. The shift from OXPHOS to aerobic glycolysis in immune cells is required to meet the increased energy (adenosine triphosphate or ATP molecules) demand to clear the invading pathogen or DAMP by increasing their pro-inflammatory function. The increase in glycolytic enzymes, such as hexokinase 1 and 2 (HK 1 and 2), glyceraldehyde 3 phosphate dehydrogenase (GAPDH), pyruvate kinase isoenzyme M2 (PKM2) expression, and glucose transporters (GLUTs) such as GLUT1 are critical for a glycolysis shift [16, 17]. The details of immunometabolic reprogramming (IR) among different immune cells during inflammatory conditions, such as sepsis and cancer, have been discussed elsewhere [18–24]. Therefore, the present article discusses the impact of PRR activation on IR, which governs the pathogenesis of inflammation and inflammatory diseases.

TLRs in Inflammation and Immunity and Associated IR

TLRs are the first discovered PRRs critical for inflammation pathogenesis and recognition of different PAMPs and DAMPs [25, 26]. Humans and mice have ten and thirteen different functional TLRs (expressed extra and intracellularly) recognizing PAMPs/MAMPs and DAMPs discussed in detail elsewhere [26–29]. TLR signaling depends on myeloid differentiation primary-response protein 88 (MyD88) and TIR-domain-containing adapter-inducing interferon-β (TRIF) or TIR-domain-containing adapter molecule 1 to generate NF-κB and IRF-dependent pro-inflammatory immune response [30–33]. We will not discuss the signaling cascade associated with extracellular (TLR1, TLR2, TLR4, TLR5, and TLR6) and intracellular (TLR3, TLR7, TLR8, and TLR9) TLRs to generate the NF-κB and IRF-dependent pro-inflammatory cytokines and chemokines release as they are discussed in detail elsewhere [26–28, 34, 35]. Therefore, the primary focus of this section is to discuss the impact of TLR signaling on IR in response to the immunorecognition of PAMPs and DAMPs via TLRs.

TLR Signaling-Induced Downstream Pro-Inflammatory IR at Early Time Course (0–4 h of Stimulation)

The duration of TLR stimulation is critical for IR as it is governed by several metabolic pathways and controlling factors. For example, a recent study has indicated the impact of lipopolysaccharide (LPS) treatment on macrophage immunometabolism during early time course (0–4 h) [36]. The LPS-mediated TLR4 activation induces tumor necrosis factor receptor-associated factor 6 (TRAF6) and TANK-binding kinase 1 (TBK1) recruitment, activation, and their interaction in macrophages within 10 min, which disappears after 2 h [37]. The activated TBK1 phosphorylates TRAF6 bound signal transducer and activator of transcription 3 (STAT3) on serine 727 (Ser727) within 20 min of stimulation of macrophages with LPS [37]. The STAT3 phosphorylation non-canonically activates glycolysis, succinate production, and inflammatory cytokine (IL-1β) production by translocating to the mitochondria, which alters their

metabolism and reactive oxygen species (ROS) production (Fig. 1) [37, 38]. The TLR2, TLR3, TLR7, and TLR9 activation also induces STAT3 Ser727 phosphorylation within 20 min of their activation. The STAT3 Ser727 phosphorylation occurs independently of STAT3 Y705 tyrosine (Tyr or Y) phosphorylation and mitochondrial electron transport chain (ETC) complex II integrity [39]. Notably, STAT3 Ser727 and Y705 phosphorylation are also critical for steady-state IL-10 production.

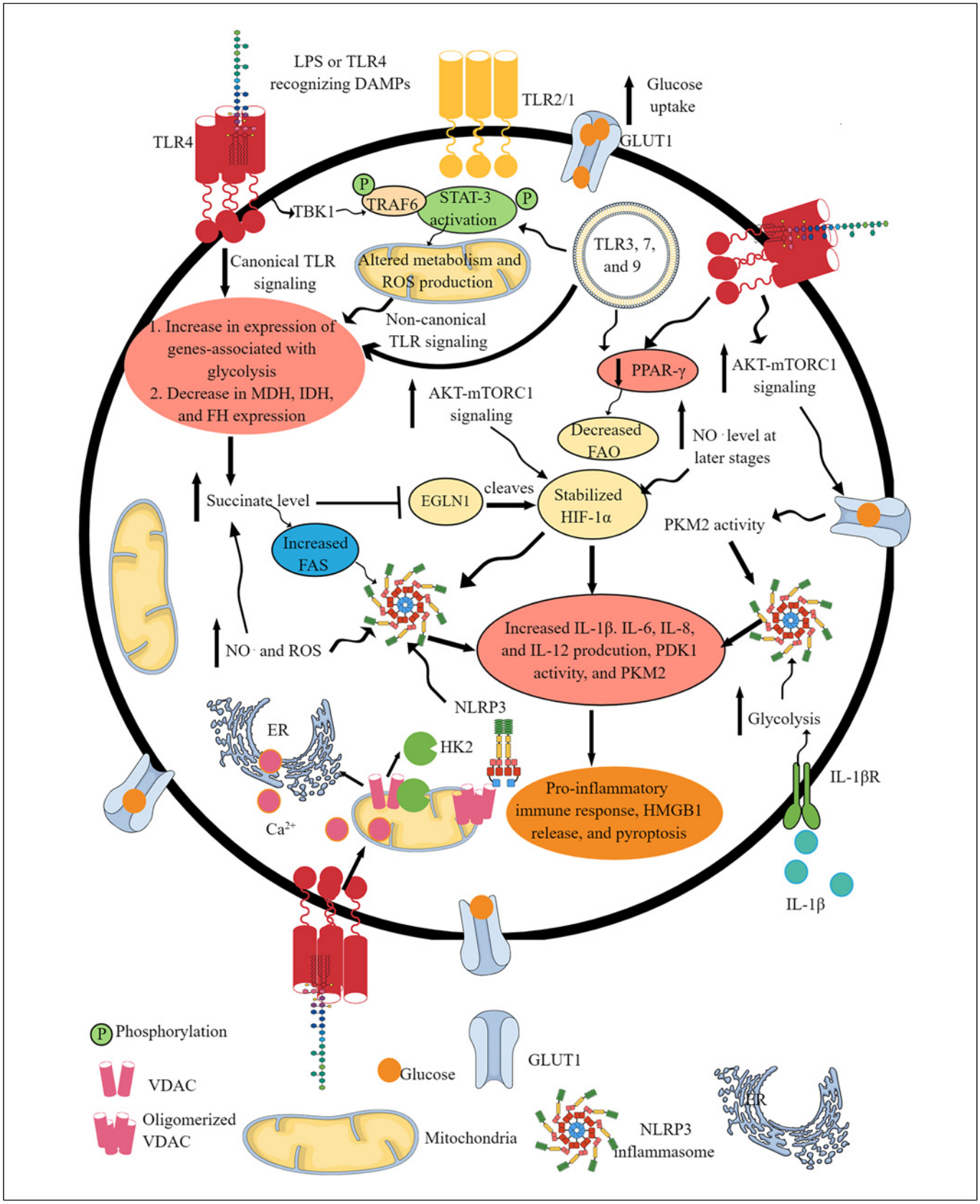
Both, catalytic subunits succinate dehydrogenase A and B (SDHA and SDHB) of the SDH or complex II of the ETC are critical for hypoxia-inducible factor-1α (HIF-1α) stabilization and IL-1β production in macrophages [39]. Furthermore, the phosphorylation of serine and tyrosine are critical for maximum transcription by STAT3 [40]. Hence, TLR signaling-mediated canonical and non-canonical (STAT3-dependent) pathways are involved in glycolysis and IR to initiate the inflammatory immune response (Fig. 1). Additionally, TLR7-mediated mitochondrial RNA recognition also increases cytosolic fumarate level by suppressing fumarate hydratase for enhanced type 1 IFN (IFN-β) production [41]. Furthermore, TLR signaling (TLR4, TLR1/TLR2, TLR2/TLR6, TLR7/8, TLR9, and TLR3)-mediated TBK1, inhibitory kinase β kinase ε (IKKε), and AKT (protein kinase B) activation are critical for glycolysis during DC activation by promoting the glycolytic enzyme HK2 association with mitochondria [42].

The early course (2 h) of LPS treatment to macrophages induces a rapid glucose uptake to promote glycolysis and TCA cycle volume to over-generate citric acid or citrate. The GLUTs (GLUT1) mediate a rapid glucose uptake, and their expression increases upon TLR activation, giving a pro-inflammatory phenotype to immune cells, such as macrophages, DCs, and T cells (Fig. 1) [18, 43, 44]. For example, TLR4 activation in macrophages activates phosphatidyl inositol 3-kinase (PI3K) via B-cell adapter for PI3K (BACP, an adapter molecule with a functional N-terminal TIR homology domain), activating AKT and mechanistic or mammalian target of rapamycin complex 1 [44–46]. The activated AKT increases the GLUT1 endosomal recycling and its surface expression on macrophages and other immune cells (Fig. 1) [47]. BCAP critically regulates IL-1R-induced phosphoinositide 3-kinase (PI3K)-Akt-mTOR activation-induced pro-inflammatory Th17 immune cell differentiation in response to IL-1β [48].

MyD88 and TRIF-dependent coordinated downstream signaling is critical for complete adenosine triphosphate (ATP) citrate lyase (ACLY) activation in response to the LPS stimulation [36]. For example, MyD88 and TRIF exert an additive effect on immediate IR, such as increased glucose uptake and cytosolic acetyl-Coenzyme (Ac-CoA) and oxaloacetic acid or oxaloacetate (OAA) synthesis via ACLY upregulation to prime macrophages in response to early after TLR4 stimulation. Furthermore, the upregulated ACLY activity during glycolysis promotes glucose-dependent Ac-CoA incorporation into histones [36]. The ACLY translocation to the nucleus under inflammatory conditions, including sepsis in macrophages, induces NF-κB acetylation that supports their full activation and pro-inflammatory function, including the overexpression of SLC25A1, encoding citrate career and ACLY [49]. Furthermore, LPS-induced ACLY activity is critical for histone acetylation at the IL-12b gene locus and associated enhancer, indicating its role in facilitating enhancer chromatin accessibility [36]. AKT inhibitor (MK-2206) blunts LPS-inducible ACLY phosphorylation, indicating that the AKT signaling is also critical for its phosphorylation [36, 50]. However, ACLY inhibition does not affect the expression of early genes, such as CXCL1, CXCL2, IL-1α, and IL-1β, but downregulates the expression of the late genes, including IL-6, IL-12b, IL-18, IL-27, CXCL9, and CXCL10 [36]. Of note, ACLY inhibition stimulates the overexpression of anti-inflammatory genes, such as IL-10 and IL-1 receptor antagonist (IL-1RA). Thus, ACLY inhibition does not affect inflammation in general but affects it at a specific level by modulating innate immune response and inflammation upon TLR4 activation.

The histone acetylation in macrophages during early LPS treatment due to increased glycolysis enhances the induction and translation of critical pro-inflammatory genes. For example, induction of IL-1β and chemokine (C-X-C motif) ligand 1 (CXCL1) genes in macrophages occurs within 30 min of LPS treatment and peaks at 2 h [36]. At the same time, the transcription of IL-6 and IL-12b genes (secondary response genes) in macrophages (bone-marrow-derived macrophages or BMDMs) occurs at 2 h post-LPS treatment, which stays 4 h. Therefore, early IR in BMDMs upon LPS stimulation may alter pro-inflammatory gene induction. For example, macrophages' mitochondrial potential and ROS production decrease early after LPS stimulation without mitochondrial mass alteration, which increases later. Furthermore, mitochondria are well-known inflammation regulators, as discussed elsewhere [51–53].

LPS induces a time-dependent transition of metabolism in macrophages (BMDMs) from basal to pro-inflammatory state, and lactate, succinate, and itaconate



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levels increase within 2 h, which are very high at 24 h (Table 1). Both oxidized and reduced glutathione levels decreased compared to early and late time courses after LPS stimulation. The initial mitochondrial ROS (mtROS) production is also low, indicating a tightly controlled redox balance. After 2 h of LPS stimulation in BMDMs, the adenosine diphosphate (ADP) ribose production is highest due to the poly (ADP ribose) polymerase (PARP, needs nicotinamide adenine dinucleotide (NAD^+) as a cofactor, which also serves as a coenzyme for redox reactions) overactivity that is crucial for the pro-inflammatory phenotype of macrophages [54, 55]. The LPS treatment to macrophages increases nicotinamide phosphoribosyl transferase (NAMT, a key enzyme in NAD^+ salvage), which maintains sufficient NAD^+ pool for PARP and GAPDH activity and Warburg effect (a shift from OXPHOS to aerobic glycolysis to meet frequent energy requirement) to induce pro-inflammatory macrophage phenotype and function [56]. The Warburg effect was first reported by Otto Warburg in cancer cells in 1924 to meet high energy demand for maintaining uncontrolled growth and proliferation [57]. The Warburg effect involves increased glucose uptake and its conversion to lactate to meet high energy demand by cancer cells and immune cells during infections and inflammatory conditions [58–60].

Furthermore, de novo synthesis of NAD^+ in macrophages is critical for macrophage-driven inflammatory conditions as a decreased NAD^+/NADH ratio inhibits glycolysis due to an increase in intracellular NADH or a decrease in the intracellular NAD^+ [61, 62]. The *Mycobacterium tuberculosis* (Mtb) infection depletes NAD^+ in MICs to inhibit glycolysis, which lowers protective immunity in patients with tuberculosis by decreasing the early recruitment of different immune cells and IFN-γ production [63]. Macrophage TLR stimulation under high glucose conditions critically downregulates HIF-1α levels and induces their pyroptosis due to methylglyoxal (MGO, a side product of glycolysis) overexpression [64]. Hence, extracellular glucose levels determine macrophages' fate and function, including pro-inflammatory cytokine release and pyroptosis upon TLR stimulation-dependent IR such as glycolysis.

TLR Signaling-Induced Downstream Pro-Inflammatory IR at Later Time Course (12–24 h or More)

The comprehensive metabolic map of macrophages stimulated with LPS or endotoxin for 24 h shows an increase in the genes associated with glycolysis and a decrease in the mitochondrial genes, such as TCA cycle genes, including malate dehydrogenase (MDH), isocitrate dehydrogenase (IDH), and FH (Fig. 1) [41, 65]. Furthermore, LPS also increases succinate (a Krebs cycle intermediate) levels through glutamine-dependent anaplerosis (mainly) and gamma-aminobutyric acid (GABA)-shunt pathway [41, 65]. However, increased citrate and FA levels indicate the diversion of the TCA cycle for biosynthetic or anabolic needs. The citrate upregulation upon treatment of macrophages with the combination of LPS and interferon (IFN)-γ indicates that TCA cycle fragmentation is critical for generating M1 macrophages [66]. However, aspartate-argininosuccinate shunt (AAS) induction due to aspartate-aminotransferase (AAT) activation compensates TCA cycle fragmentation to generate $NO^{\cdot}$ and IL-6 upon LPS+IFN-γ treatment inducing M1 macrophage polarization. The details of citrate in IR and inflammation are discussed elsewhere [67, 68].

Furthermore, AAS induction upon LPS stimulation (acute and prolonged) in macrophages is supported by the

Fig. 1. TLR and NLR signaling pathway activation-induced IR. Activation of different TLRs, such as TLR4, TLR2/1, TLR3, TLR7, and TLR9, shifts OXPHOS to glycolysis as indicated by the upregulation of glycolysis genes and downregulation of mitochondrial genes involved in OXPHOS and FAO. This IR occurs downstream of canonical and non-canonical (involves TBK1-TRAF6-STAT3 axis) TLR signaling pathways. The GLUT1 overexpression upon TLR activation further supports glycolysis by increasing glucose uptake. The TLR signaling decreases the PPAR-γ expression, which further decreases FAO to support the pro-inflammatory immune cell phenotype and function. TLR activation increases glucose uptake via increased mTOR-AKT signaling that also supports HIF-1α stabilization. The succinate accumulation upon pro-inflammatory TLR signaling activation further supports HIF-1α stabilization by inhibiting EGLN1. The $NO^{\cdot}$ generation at later stages activates NLRP3 inflammasome activity and succinate accumulation. The TLR signaling-induced glycolysis, increased succinate level, HIF-1α stabilization and accumulation, PKM2, mammalian target of rapamycin complex 1, and AKT overactivity support NLRP3 inflammasome activation and IL-1β release. The HK2 dissociation from VDAC at the outer mitochondrial membrane during TLR signaling-induced glycolysis activates IP3 receptors in the ER to release Ca^{2+} in the cytosol – mitochondria uptake cytosolic Ca^{2+} molecules for VDAC oligomerization. The oligomerized VDACs aggregate with NLRP3 during its initial assembly to form the NLRP3 inflammasome complex. Furthermore, IL-1β released due to the NLRP3 inflammasome activity supports glycolysis through binding to IL-1βR. Thus, TLRs and NLRs (NLRP3) support each other's pro-inflammatory function through IR.

Table 1. Outline of immunometabolic reprograming upon activation of different PRRs

PRRs	Immunometabolic shift/reprogramming	Metabolic pathway enzymes upregulated	Metabolites upregulated
TLR4, TLR2, TLR1, TLR3, TLR6, TLR7, TLR8, and TLR9	OXPHOS to glycolysis FAO to FAS Increased glutaminolysis Increased TCA or Krebs cycle	EGLN1, a prolyl hydroxylase, decreases that stabilizes HIF-1α HK2 activity increases to support glycolysis ACOD1 activity increases PDK1 activity increases ACC activity increases Inactive PKM2 expression increases GAPDH malonylation is critical for TNF-α production	1. Succinate levels increases till 48 h, subsides, and then increases at 72 h 2. Itaconate level increases similarly
cGLRs (cGAS/STING signaling)	OXPHOS to glycolysis	Glycolysis enzymes expression and activity increases	Succinate and itaconate production increases in a time-dependent manner
NLRP3	OXPHOS to glycolysis FAO to FAS	Glycolysis enzyme upregulate, such as PKM2 activity increases	Succinate and itaconate production increases in a time-dependent manner
CLRs	OXPHOS to glycolysis	Glycolytic enzymes	Succinate and itaconate accumulation
RLRs	Inhibit glycolysis and support glucose utilization to PPP and HBP for type I and III IFN production	Enzymes supporting PPP and HBP	Decrease PEP, pyruvate, and lactate levels Decrease succinate, fumarate, malate, and aconitate levels without affecting OAA levels

increased argininosuccinate synthase 1 (ASS1) expression and also increases cytosolic fumarate and associated protein succination [41]. The process of succination involves a reaction between fumarate and cysteine residues of protein to produce S-(2-succinyl)cysteine (2SC) [69]. During acute LPS treatment to macrophages, the ASS1 induction is critical for fumarate accumulation, whereas FH suppression upon prolonged LPS stimulation depends on FH inhibition. Notably, overexpressed ASS1, causing fumarate accumulation, mildly regulates IL-10 and TNF-α production in LPS-stimulated macrophages. Furthermore, fumarate or FH-regulated IL-10-TNF-axis is active in human macrophages. Therefore, sustained FH expression and enzymatic activity controlling cytosolic fumarate level is a critical regulator of IL-10 and TNF-α production in macrophages upon TLR activation [41]. The argininosuccinate lyase (ASSL) cleaving argininosuccinate to fumarate also plays a role in fumarate accumulation, indicating the role of AAS in fumarate accumulation.

The dicarboxylic acid transporter transports excess succinate from mitochondria to cytosol. The cytosolic citrate stabilizes HIF-1α by inhibiting its hydroxylation through egg-laying abnormal (EGL)-9 family hypoxia-inducible factor 1 (EGLN1), serving as a prolyl hydroxylase 2 or PHD 2, recognizing its two conserved prolyl residues (Pro564 and Pro402) by von Hippel-Lindau tumor suppressor protein (pVHL) (Fig. 1; Table 1) [70–73]. For example, hydroxylated conserved prolyl residues of HIF-1α are recognized by pVHL due to the generation of the high-affinity pVHL binding site, causing HIF-1α polyubiquitination and proteasomal degradation [74]. EGLN1 catalyzes the posttranslational formation of 4-hydroxyproline in HIF-1α. Thus, LPS-induced glycolysis, elevated succinate (regulates HIF-1α and IL-1β axis) levels, and succinylation of several proteins increase IL-1β production to induce inflammation (Fig. 1) [65]. Furthermore, SDH oxidizes succinate. This phenomenon increases the reduced ubiquinone or ubiquinol ($CoQH_2$) level, making it hard to efficiently consumed by complex III, causing reverse electron transport (RET, where electron transfer occurs in the reverse direction from $CoQH_2$ to ubiquinone or CoQ) at complex I

and increasing mtROS production, which further supports HIF-1α stabilization and IL-1β synthesis [75, 76]. The details of ETC-mediated immunometabolism or IR regulations have been discussed elsewhere [77].

Interestingly, extracellular succinate serves as metabokine and alarmin to modulate the immune response and alter the myeloid immune cell, such as macrophages and DCs function via binding to its cognate succinate receptor 1 [78, 79]. For example, extracellular succinate via succinate receptor 1 exerts pro-inflammatory action on macrophages in autoimmune diseases, such as rheumatoid arthritis [78]. However, it exerts anti-inflammatory action in the AT and tumor microenvironment, such as lung cancer, by promoting the generation of anti-inflammatory M2 macrophages [78, 80].

Similarly, citrate career transports excess citrate from mitochondria to the cytosol and supports lipogenesis via ACLY activity [67, 68]. LPS or TLR4 stimulation-induced ACLY breaks citrate into OAA and Ac-CoA, serving as a substrate for fatty acid synthesis (FAS) [81]. Furthermore, cytosolic citrate and ACLY support the generation of pro-inflammatory molecules, including ROS, $NO^{\cdot}$, and prostaglandin E2 (PGE_2) [81–83]. Thus, cytosolic citrate and succinate accumulation are critical for IR, supporting the pro-inflammatory phenotype of immune cells, including macrophages, upon TLR activation at early and late time courses.

The $NO^{\cdot}$ overproduction further increases HIF-1α level, NLRP3 activity, and IL-1β production to support pro-inflammatory macrophage phenotype and function at later stages (72 h onward) (Fig. 1). However, $NO^{\cdot}$ is not a critical/fundamental inducer of glycolysis as macrophages without $NO^{\cdot}$ undergo glycolysis and support inflammatory phenotype and function. It is important to note that in this study, macrophages were stimulated overnight (16 h) with LPS and IFN-γ, which confirms earlier findings that early or within the first 2 h ROS or $NO^{\cdot}$ is not a critical factor in pro-inflammatory IR but involve at a later stage [36, 84]. Even mitochondrial potential and ROS production in macrophages are reduced during early time points (30 min–2 h) of LPS stimulation [36]. However, $NO^{\cdot}$ at later stages (48 h) reroutes pyruvate in inflammatory macrophages away from pyruvate dehydrogenase (PDH), suppresses their metabolism to mitochondrial aconitase (ACO2), and promotes glutamine-based anaplerosis [85]. Thus, $NO^{\cdot}$ accumulation at later stages shuts mitochondrial ETC complexes and decreases the production of inflammatory mediators such as HIF-α and IL-1β.

The HIF-α stabilization (supporting glycolysis and lactate accumulation) causing its abundance induces the pyruvate dehydrogenase kinase 1 (PDK1) gene expression that phosphorylates PDH for its inhibition (Table 1) [86, 87]. The increased PDK1 inhibits the PDH flux via phosphorylation, increasing the pyruvate-derived Ac-CoA level for citrate overproduction [87]. The increased citrate production keeps in check the rate of reductive carboxylation of α-ketoglutarate (α-KG) and increases FAS and itaconate production. The PDK1 upregulation in $CD8^{+}$T cells upon IL-2 stimulation in an mTOR-HIF-1α-axis dependent way also sustains glucose uptake and glycolysis. Furthermore, TLR7 activation induces IR to glycolysis in $CD8^{+}$T cells to enhance their effector functions [88]. Thus, TLR signaling-mediated overexpressed PDK1 is critical for innate and adaptive immune cells' IR to glycolysis. The PDH inhibition decreases the pyruvate oxidation to citrate in the mitochondria.

Citrate is required to synthesize itaconate and lipogenesis. The increased demand for itaconate and lipid molecules decreases citrate oxidation via the Krebs cycle. Furthermore, the unchanged PDK1 abundance maintains PDH flux even in the presence of HIF-1α, a critical node for TLR4 activation-mediated macrophage activation [87]. Hence, PDH targeting is a metabolic intervention to treat chronic inflammatory diseases. For example, LPS treatment or TLR4 activation increases glycolysis, glutamine uptake, and glutaminolysis to support the TCA cycle and lipogenesis or FAS to transform naïve macrophages into pro-inflammatory or M1 macrophages (Table 1) [18, 87]. Along with supporting the TCA cycle, glutaminolysis supports AAS metabolites, including fumarate and glutathione production [41]. During this process, activated TLRs (TLR2, 3, 4, and 7) reduce the peroxisome-proliferator-activated receptor-γ (PPAR-γ) expression in MICs (macrophages and DCs) in an NF-κB-dependent manner to maintain their pro-inflammatory phenotype and function (Fig. 1) [89]. For example, pro-inflammatory cytokines (TNF-α and IFN-γ) inhibit PPAR-γ expression in macrophages [90].

PPAR-γ activation critically regulates lipid/fat metabolism (increases fatty acid oxidation or FAO and uptake of oxidized lipid through CD36 overexpression) in immune cells (macrophages and DCs), and its activation induces anti-inflammatory phenotype (M2 or alternatively activated macrophages or AAMs or foam cells) and function [91–97]. Furthermore, PPAR-γ also controls the AAM or M2 phenotype and function by regulating glutaminolysis [98]. Therefore, TLRs and PPAR-γ have inverse crosstalk where activation of one inhibits the other, as discussed elsewhere [99, 100].

The pulmonary alveolar macrophages (PAMs) highly express PPAR-γ and exhibit higher FAO or β-oxidation of lipids and OXPHOS with relatively lower glycolysis

levels than interstitial pulmonary macrophages (IPMs, exhibit high glycolysis) that affects their pro-inflammatory function upon PRR, such as TLR stimulation [101, 102]. Furthermore, glycolysis upregulation does not occur in tissue-resident PAMs as seen in BMDMs upon TLR4 activation, and glycolysis inhibition in PAMs does not affect their pro-inflammatory function [102]. However, HIF-1α stabilization upon TLR4 stimulation or hypoxia shifts OXPHOS of PAMs to glycolysis, which is not sufficient to produce glycolysis-dependent pro-inflammatory immune response but supports their survival under different pro-inflammatory conditions, including acute lung injury (ALI) [102, 103].

Human PAMs depend on OXPHOS but not glycolysis for pro-inflammatory immune response upon LPS exposure or TLR4 activation, as seen in MDMs [104]. A further study has shown that lung environment, including the relative absence of glucose in alveoli, is critical to determine the IR among PAMs upon different stimuli, such TLR activation and stimulation with IL-4 as pro-inflammatory stimuli, including LPS, TNF-α, and IFN-γ increase airway surface liquid (ASL) glucose levels [105–107]. Hence, tissue location and type of immune cells such as macrophages, DCs, and T cells may affect their IR upon TLR and other PRR activation, which needs further investigation. For example, TLR8 activation in human regulatory T cells (T_{regs}) inhibits glycolysis by inhibiting mTOR signaling, HIF-1α synthesis and stabilization, and glucose uptake, which reverses the immunosuppressive function of T_{regs} that can be used in different solid tumors such as melanoma as an immunotherapeutic approach [108].

Of note, the TCA cycle remodeling occurs in two stages upon LPS-induced TLR4 activation with the alteration of succinate and itaconate levels, which increase initially and then decrease at a later stage [109]. The pyruvate and oxoglutarate dehydrogenase complex (PDHC and OGDC are members of the mitochondrial α-ketoacid dehydrogenase family) inhibition decreases succinate and itaconate levels at a later stage (48 h). The dynamic changes in the lipoylation of PDHC and OGDC E2 subunits regulate acyl group transfer to CoA, and the PDHC E1 subunit phosphorylation controls PDHC and OGDC inhibition. The PDHC and OGDC inhibition at later stages (48 h) involves $NO^{\cdot}$ or reactive nitrogen species (RNS), which covalently alter thiol groups on their lipoic arms to generate a series of adducts that block catalytic activity, including nitroxyl (HNO) [110, 111]. For example, S-Nitroso-CoA, a product of RNS and the E2 subunit's natural substrate, can deliver these modifications to lipoic arms. This dynamic metabolic reprogramming-induced transient metabolic state favors HIF-1α stabilization during the early stages of TLR4 activation that subsides with time (after 48 h) and reactivates at 72 h (a second increase) with succinate and itaconate increase (Table 1) [109, 111]. Hence, the succinate and itaconate fluctuation upon TLR activation influences the dynamics of HIF-1α and pro-inflammatory phenotype upon continual and acute activation in MICs, such as macrophages and DCs. Thus, changing macrophage immunometabolism can regulate functional transitions during an immune response that may aggravate and subside depending on the external stimulus and HIF-1α availability.

Furthermore, LPS treatment increases the PKM2 (a critical metabolic regulator) expression in murine BMDMs (Fig. 1). However, this PKM2 primarily forms an enzymatically inactive dimer or monomer. Furthermore, inducing PKM2 tetramer (enzymatically active retains in the cytosol) formation by DASA-58 (a potential pyruvate kinase isozyme (PKM2) allosteric activator) and TEPP-46 (a PKM2 activator) treatment inhibits LPS-induced PKM2 nuclear translocation without affecting cytosolic PKM2 in BMDMs.

The LPS-induced Warburg effect in murine macrophages is critical for IL-1β release but not for TNF-α release, as indicated by the 2-deoxyglucose (2-DG, a glycolysis inhibitor) treatment [65]. However, macrophage TNF-α and IL-10 release upon LPS stimulation are under the control of FH expression/activity or fumarate levels [41]. The treatment of LPS-stimulated BMDMs and peritoneal macrophages with DASA-58 and TEPP-46 inhibits the production of pro-IL-1β without affecting TNF-α and IL-6 production as the Warburg effect is not critical for their production [17, 65]. Furthermore, the PKM2 activation in macrophages inhibits LPS-induced expression of proglycolytic and HIF-1α-dependent genes. M1 macrophages overexpress inactive PKM2 as activated PKM2 in LPS-stimulated macrophages boosts the anti-inflammatory M2 cytokine, IL-10 expression. Thus, LPS treatment to macrophages increases inactivated PKM2 in the cytosol and nucleus that support HIF-1α overexpression and increased IL-1β production. Furthermore, LPS increases the binding of PKM2 to the HIF-1α-specific binding site of IL-1β promoter, which gets inhibited in the presence of TEP-46 and DASA-58. Therefore, PKM2 activators inhibit LPS-induced glycolysis and succinate accumulation in macrophages to lower the inflammation and promote polarization of pro-inflammatory M1 to anti-inflammatory M2 macrophages.

In addition to TLR4, the activation of TLR2, 6, and 9 also increases PKM2 expression, HIF-1α, and pro-IL-1β

expression. Hence, TLR2, 4, 6, and 9 activations reprogram macrophage immunometabolism to glycolysis by increasing PKM2 that binds to HIF-1α-specific binding site of IL-1β promoter to generate pro-inflammatory IL-1β cytokine without affecting TNF-α and IL-6 production. However, LPS stimulation of macrophages induces TNF-α production via malonylation of GAPDH that dissociates it from TNFα mRNA to promote its translation (Table 1) [112]. Thus, glycolysis is not directly involved in TNF-α production. However, an altered TCA cycle via a citrate-derived molecule called malonyl-CoA and FH inhibition causing fumarate accumulation are critical for TNF-α production. For example, in resting macrophages, GAPDH suppresses the translation of several inflammatory mRNAs, including the TNF-α one. Furthermore, activated PKM2 counteracts the LPS-mediated inflammatory events, mostly by inhibiting the Warburg effect or glycolysis in vivo [17]. The PKM2 activation strategy to decrease the inflammation may work during sterile inflammatory conditions but needs caution during infections as a decreased inflammatory response at the initial stages of infection may prove detrimental to the host due to infection dissemination that may later lead to sepsis [17]. The immunometabolic changes supporting IL-1β release and ROS production among macrophages upon LPS stimulation are late-stage inflammatory responses (12–24 h).

Furthermore, pyruvate transport to mitochondria through mitochondrial pyruvate carrier (MPC), followed by its utilization in the Krebs cycle, is dispensable [113]. Therefore, MPC is not required for pro-inflammatory IR and activation of M1 macrophages, given that MPC deletion in MICs does not affect their inflammatory function and macrophage polarization to M1 phenotype in murine endotoxemia. Furthermore, although mice and human microglia exhibit pro-inflammatory phenotypes and function upon LPS-mediated TLR4 signaling, their IR differs. For example, murine microglia overexpress HK2, whereas human microglia overexpress phosphofructokinase (PFK) [114, 115]. Hence, a species-specific investigation in IR downstream of PRR, such as TLR signaling, is critical for translational research for target-specific therapy.

Notably, TEPP-46 treatment not only inhibits macrophages pro-inflammatory function via activating PKM2 (enzymatically active PKM2 tetramer) but it also inhibits T cell glycolysis that is critical for pro-inflammatory cytokines, such as IL-17 and IFN-γ release [116]. For example, TLR4 signaling in T cells promotes their inflammatory functions, including in autoinflammation, such as experimental autoimmune encephalomyelitis (EAE) or multiple sclerosis (MS) [117]. However, TLR4 activation through TRIF adapter on effector $CD4^{+}$T cells inhibits ERK1/2 activation that inhibits IFN-γ synthesis and release but increases IL-17A production upon subsequent T cell receptor (TCR) activation by inducing mitogen-activated protein kinase (MAPK) phosphatase 3 (MKP-3) and acts as a tonic inhibitor and inhibits inflammation in experimental colitis model [118]. Furthermore, co-stimulation of TLR4 and TCR does not exert the same inhibitory effect on ERK1/2 activation and IFN-γ production. Thus, TLR4-dependent pro- and anti-inflammatory action on T cells depends on T cell type and TCR stimulation. Hence, we need further studies on TLR-based IR among T cell types and other immune cells, including macrophages and DCs.

TLR-Dependent IR in Pro-Inflammatory M1 to Anti-Inflammatory M2 Macrophage Polarization

Acetyl-CoA carboxylase (ACC) is a lipid biosynthesis regulatory enzyme, which also regulates TLR4 stimulation-mediated early glycolysis and remodeling of macrophages' lipidome to control the secretion of pro-inflammatory cytokines (IL-1β and IL-6) and molecules [119]. There are two forms of ACCs: (1) ACC1, which localizes in the cytosol, and (2) ACC2 residing on the outer mitochondrial membrane, but both convert Ac-CoA to malonyl-CoA for de novo FAS to produce long chain FAs [120]. For example, ACC deficient or ACC inhibitor (firsocostat) treated macrophages exhibit significantly decreased IL-1β, IL-6, and inducible nitric oxide synthase (iNOS) expression without affecting CD80 and CD86 expression at 6 h post-stimulation with TLR4 or TLR2 agonists. Furthermore, ACC deficiency shifts macrophages to a hyperglycolytic bioenergetic state. It increases GLUT1 expression compared to wild-type macrophages, which sets an upper limit of glycolytic rate in LPS-stimulated $ACC^{-/-}$ macrophages [119]. ACC deficiency does not affect SDH activity. Notably, ACC is dispensable for IL-4-mediated M2 macrophage polarization at early time course (first 6 h post-stimulation) as indicated by the similar levels of STAT6 phosphorylation at tyrosine-641 and arginase in control and IL-4 treated macrophages.

In macrophages stimulated with IL-4 for a longer duration (18–24 h), ACC1 upregulation is critical for M2 polarization, and its inhibition at this time course abrogates M2 polarization without affecting M1 macrophages [121]. Thus, duration and stimulation type determine the ACC1-dependent macrophage polarization. For example, granulocyte macrophages colony-stimulating factor-treated human monocyte-derived macrophages (hMDMs) exhibit ACC1 overexpression than murine BMDMs at 18–24 stimulation along with other M1 macrophage immunometabolic markers

(GLUT1, PKM, G6PD, and SDHA). Furthermore, macrophage colony-stimulating factor treatment on hMDMs has an anti-inflammatory action, whereas granulocyte macrophage colony-stimulating factor (GM-CSF) exerts a pro-inflammatory effect through IR.

Interestingly, IL-4 treatment to macrophages via AKT-mammalian target of rapamycin complex 1 (mTORC1) signaling controls ACLY activity that induces M2 macrophage polarization through increased histone acetylation-dependent induction of a specific subset of M2 genes, regulating their proliferation and chemokine production [50]. Thus, ACLY activation in response to the anti-inflammatory (IL-4, a type II cytokine that supports M2 macrophages via IL-4 receptor alpha chain (IL-4Rα) that dimerizes to form type 1 signaling complex) and pro-inflammatory (LPS) stimuli is critical to determine macrophage phenotype and function [36, 50, 122]. Furthermore, IL-4 treatment to macrophages upregulates GLUT3 expression, critical for M2 macrophage polarization independently of glucose uptake, but induces IL-4/IL-4R complex endocytosis, which phosphorylates STAT6 for M2 polarization [123, 124]. Interestingly, IL-4 also induces overexpression of lipid (CD36, CPT1A) and amino acid (CD98) transporters on M2 macrophages [121].

It is important to note that the AAMs/M2 macrophage phenotype or their differentiation does not require glycolysis in intact OXPHOS [125]. For example, the activated arginase 2 (Arg2) regulates IL-10. IL-10 is an anti-inflammatory cytokine and downregulates inflammatory mediators, including succinate, HIF-1α, and IL-1β in M1 macrophages [126]. IL-10 in M1 macrophages regulates Arg2, is a mitochondrial microRNA-155 (miR-155). For example, Arg2 is critical for IL-10-induced mitochondrial dynamics and oxidative respiration modulation by increasing the SDH or complex II activity [126]. Thus, M1 to M2 macrophage polarization also involves IR from glycolysis to OXPHOS. Furthermore, GLUT3 upregulation is critical for macrophage polarization to M2 macrophages [123, 124]. GLUT3, without affecting glucose transport (uptake or efflux), thus the glucose metabolism induces Ras-mediated IL-4/IL-4 receptor (IL-4R) complex endocytosis that phosphorylates and dimerizes STAT6 for, inducing and maintaining M2 macrophage phenotype and function [123, 124]. Furthermore, exogenous metabolic cofactor coenzyme A (CoA) support IL-4-induced M2 macrophage polarization by providing a weak TLR4 signal through activating MyD88 downstream signaling [127]. The CoA-induced TLR4-mediated MyD88 signaling in macrophages primes them for increased receptivity for IL-4 signaling by reshaping chromatin accessibility for increased transcription of IL-4-associated genes [127]. Thus, host metabolic DAMPs, such as exogenous CoA, can prime macrophages to M2 phenotype by activating TLR4-MyD88 signaling to control inflammation. The detailed M2 macrophage IR has been discussed elsewhere [18, 128].

TLR Signaling-Induced Anti-Inflammatory Immunometabolites and Their Analogs to Control Pro-Inflammatory IR

Itaconate is an endogenous SDH inhibitor and increases succinate levels, and itaconate production decreases in immune-responsive gene 1 (Irg1)-deficient macrophages [129]. Irg1 is one of the most highly expressed enzymes in pro-inflammatory macrophages, and its enzymatic product, called cis-aconitate decarboxylase 1 (ACOD1), catalyzes the itaconate formation from cis-aconitate (a TCA cycle metabolite) in immune cells (Table 1) [129, 130]. Citroaconate inhibits ACOD1 or Irg1 activity, decreasing itaconate levels, and is a nuclear factor erythroid 2 (NFE2)-related factor 2 (NRF2) agonist [131]. Citroaconate (an endogenous ACOD1 inhibitor) exerts its antiviral and immunomodulatory action against influenza A virus (IAV) that is recognized by TLR7/8, RLRs, and nucleotide-binding domain and leucine-rich-repeat-containing protein 3 (NLRP3) by decreasing mtROS, IL-6, IL-1β, CXCL10, TNF-α, macrophage inflammatory protein-1β (MIP-1β) or chemokine (C-C motif) ligand 4 (CCL4), and IFN-induced protein with tetratricopeptide repeats 1 (IFIT1) and increasing CXCL8 or IL-8 and CCL5 levels [131, 132]. Notably, murine ACOD1 is more active than human ACOD1 in generating itaconate (5–10 times) in activated macrophages [133, 134]. Hence, ACOD1 is less prominent in controlling human inflammation than mice. ACOD1-depleted induced pluripotent stem cell-derived chimeric antigen receptor (CAR)-macrophages (CAR-iMACs) manifest increased ROS production, more potent phagocytosis, and enhanced cytotoxic functions against cancer cells due to reduced itaconate (an immunometabolite) production [135]. It would be interesting to observe similar findings in human CAR-MACs, although human ACOD1 is less potent in itaconate generation than murine macrophages.

Irg1 overexpression also promotes MHC-1 expression and genes involved in antigen processing, such as transporter-associated with antigen processing 1 (TAP1) and proteasome subunit beta type 9 (PSMB9) in macrophages by regulating STAT1/3 phosphorylation that depends on pentose phosphate pathway or shunt (PPP or PPS) and NADPH oxidase-mediated ROS production

[136]. Notably, activated iNOS, which requires tetrahydrobiopterin (BH4) as a cofactor)-mediated $NO^{\cdot}$ production upon LPS and IFN-γ stimulation in macrophages due to upregulated glycolysis, Krebs cycle remodeling, and mitochondrial respiration inhibition further support glycolysis by increasing citrate, succinate, and itaconate levels [84, 137]. Itaconate also inhibits ten-eleven translocation (TET) DNA dioxygenases in LPS-stimulated pro-inflammatory macrophages to limit inflammatory immune response in mice subjected to endotoxemia [138]. The details of itaconate in the host immunity and inflammation have been discussed elsewhere [139, 140].

The treatment of LPS-stimulated pro-inflammatory macrophages with dimethyl itaconate inhibits SDH, which is a part of complex II of the mitochondrial ETC. Thus altered mitochondrial respiration, as indicated by the decreased oxygen consumption rate, limits the IL-1β, IL-8, IL-6, IL-12, $NO^{\cdot}$, and HIF-1α levels without affecting TNF-α levels [130]. Another study has indicated that 4-octyl itaconate (4-OI, a cell-permeable itaconate derivative) also inhibits GAPDH by alkylating its cysteine 22 residue to downregulate aerobic glycolysis in M1 macrophages in vitro and in vivo in a lethal endotoxemia model [141]. Notably, both studies have used itaconate chemical derivatives (DIM and 4-OI) in murine macrophages.

Mesaconate is an itaconate metabolite that does not inhibit SDH activity as potently as itaconate but exerts immunomodulatory action by inhibiting IL-6 and IL-12 production by inhibiting glycolysis and promoting CXCL10 production independently of NRF2 and activating transcription factor 3 (ATF3) activation in mouse BMDMs and hMDMs and white blood cells (WBCs) [131, 142]. It is important to note that mesaconate and itaconate did not inhibit IL-1β production and inflammasome activation in normal murine BMDMs, hMDMs, and WBCs upon LPS treatment or TLR4 activation [142]. However, itaconate or mesaconate pre-treated RAW264.7 macrophages (which have a cancerous origin and have high glycolysis to maintain their proliferation) show a decreased LPS-induced IL-1β, IL-6 and IL-10 expression and IL-6 and IL-10 production. In their study, the authors have observed similar findings with DMI and 4-OI as anti-inflammatory agents, which decrease IL-1β, IL-6, and TNF-α production upon pretreatment to LPS-stimulated or TLR4-activated macrophages. However, they are more cytotoxic [142]. Furthermore, with 1 mM DMI and 4-OI pretreatment to RAW264.7 macrophages stimulated with LPS, no itaconate production occurs and exerts a more drastic impact on other metabolites due to their high toxicity. Therefore, mesaconate has an anti-inflammatory activity equal to non-derivatives of itaconate, and itaconate chemical derivatives (DMI and 4-OI) do not exert similar anti-inflammatory action as itaconate itself and are more cytotoxic.

The anti-inflammatory action of 4-OI also involves NRF2 activation, which is dispensable for the itaconate and mesaconate's anti-inflammatory action [142, 143]. 4-OI alkylates cysteine residues 151, 257, 288, 273, and 297 on Kelch-like ECH-associated protein 1 (KEAP1, a central player in antioxidant response) to enable NRF2 to promote the expression of downstream genes with antioxidant and anti-inflammatory functions [143, 144]. DMI and 4-OI pre- and posttreatment also inhibit NLRP3 inflammasome-mediated IL-1β production in macrophages, not shown by itaconate and mesaconate treatment [142]. Thus, itaconate and mesaconate inhibit IL-1β secretion but not pro-IL-1β formation [145]. DMI also inhibits NLRC4 inflammasome-dependent IL-1β production. Furthermore, LPS stimulation or TLR4 activation is dispensable for mesaconate production from the intracellular itaconate, indicating the independence of this metabolic pathway on a previous macrophage activation [142]. Along with inhibiting glycolysis, itaconate also inhibits the TCA cycle, but mesaconate only inhibits glycolysis.

The detailed analysis of the impacts of itaconate and mesaconate activity on TLR4-stimulated macrophages indicates their immunomodulatory action rather than a simple anti-inflammatory action [142, 145]. For example, itaconate and mesaconate treatment decreases the expression of most chemokines and various cytokines by decreasing the antigen (Ag) presentation potential and T-cell activation [142]. Mesaconate and itaconate increase CXCL10, IFN-β1, IL-23A, and IL-17RA expression, and both molecules exert immunomodulatory action in the murine endotoxemia model and increase their survival upon pretreatment. Thus, itaconate, including 4-OI and mesaconate, can target TLR-mediated inflammatory diseases, including autoimmune ones, such as systemic lupus erythematosus (SLE), where TLR7 and 9 are critical for inflammation and inflammatory organ damage such as SLE-associated nephritis by targeting altered TLR signaling-mediated pro-inflammatory IR in immune cells such as macrophages and B cells [146–149]. Furthermore, itaconate can target T-cell IR due to increased glycolysis, lipid biosynthesis, oxidative stress, and mTOR signaling in autoimmune and inflammatory diseases, including SLE [150]. For example, itaconate

targeted aberrant glycolysis and OXPHOS in Th17 and T_{regs} polarizing T cells and adoptive transfer of itaconate-treated Th17 polarizing T cells ameliorates EAE, an animal model for human MS [151].

NLRs in IR

The details of NLR family members in innate immunity, inflammation, and their role as cell death sensors have been discussed elsewhere [152–154]. Therefore, we are not discussing them here. NLRP3 is the most studied and prominent inflammasome generating IL-1β, IL-18, gasdermin-D, and inducing pyroptosis. TLR (TLR 2, 3, 4, and 7) signaling mediated by MyD88 adapter protein-dependent NF-κB activation primes NLRP3 inflammasome activation via generating pro-IL-1β and other non-transcriptional and posttranslational modification mechanisms (Fig. 1) [155–158]. TLR signaling-induced glycolysis stabilizes HIF-1α and induces IL-1β and IL-6 release; accordingly, IR to glycolysis further stimulates NLRP3 inflammasome-dependent release of mature IL-1β for inflammation (Fig. 1). For example, TLR signaling-induced glycolysis involves HK 1 and 2 overexpression and dissociation from the outer mitochondrial membrane (Fig. 1) [159, 160]. The dissociation of HK2 from the voltage-dependent anion channel (VDAC) of the outer mitochondrial membrane activates inositol triphosphate (IP_3) receptors to release calcium (Ca^{2+}) from the ER (Fig. 1) [160]. Mitochondria uptake this cytosolic Ca^{2+} for VDAC oligomerization, forming macromolecule-sized pores in the outer mitochondrial membrane to release proteins and mitochondrial DNA [160]. Furthermore, the VDAC oligomers aggregate with NLRP3 during its initial assembly to form the NLRP3 inflammasome complex (Fig. 1).

During Gram-positive bacterial infection, HK serves as an innate immune receptor and recognizes N-acetylglucosamine released from the phagocytosed cytosolic peptidoglycan (PGN) as a PAMP to activate NLRP3 inflammasome, independently of potassium (K^+) efflux [159, 161]. Thus, TLR signaling-induced IR (glycolysis induction and upregulation) is critical for NLRP3 inflammasome complex formation and activation (Fig. 1). Hence, NLRP3 inflammasome can sense altered glycolytic flux depending on the enzyme and glycolytic step [162]. Furthermore, the pro-inflammatory TLR signaling-induced ROS generation can also activate NLRP3 inflammasome (Fig. 1) [163]. Notably, the priming of immune cells such as macrophages with LPS induces c-Jun N- terminal protein kinase 1 (JNK1), which phosphorylates NLRP3 at S194, facilitating the self-association of NLRP3 to form NLRP3 oligomer [164]. However, another study indicates that LPS priming is dispensable in human monocytes but not in monocyte-derived macrophages for NLRP3 inflammasome activation in vitro [165].

The LPS-primed and ATP-stimulated macrophages activate PKM2 enzymatic activity that modulates eukaryotic translation initiation factor 2 alpha kinase 2 (EIF2AK2) phosphorylation to promote glycolysis for NLRP3 and AIM-2 inflammasomes dependent IL-1β, IL-18, and high mobility group box 1 protein (HMG-B1) release and pyroptosis [166, 167]. Furthermore, hyperglycemia might also increase PKM2 activity in macrophages to increase NLRP3 inflammasome activity to enhance plaque vulnerability in patients with diabetes mellitus and chronic heart disease [168]. NLRP3 inflammasome activation-induced IL-1β further increases glycolysis by increasing the glycolytic enzyme PFKFB3 as NLRP3- and IL-1R-deficient mice exhibit decreased glycolysis [169]. Thus, TLR-MyD88 signaling-dependent glycolysis is further increased by the NLRP3 inflammasome-dependent IL-1β through IL-1R signaling [170]. Hence, induction of glycolytic IR upon TLR, NLRP3, and cGAS/STING signaling activation supports each other to aggravate inflammation through the mechanisms discussed (Fig. 1; Table 1).

Furthermore, glycolysis inhibitors itaconate and 4-OI inhibit NLRP3-dependent IL-1β secretion in monocytes isolated from cryopyrin-associated periodic syndrome patients and decrease the inflammation in urate-induced murine peritonitis by inhibiting the NLRP3- and NIMA-related kinase 7 (NEK7, a shortest NEK protein among NEK family members) [171]. NEK7 is a serine-threonine kinase, a critical ROS, and K^+-sensing (stimulus for NLRP3 inflammasome formation). It interacts directly with the curved leucine-rich repeat (LRR) domains of the NLRP3 for activating the canonical NLRP3 inflammasome signaling [172–176]. Furthermore, ROS and K^+ efflux trigger chloride intracellular channel (CLIC) proteins CLIC1 and CLIC4. For example, mtROS induces CLIC translocation to the plasma membrane to induce chloride (Cl^-) efflux, which drives NEK7 and NLRP3 inflammasome activation for IL-1β production [177, 178]. However, human monocytes use an alternative NLRP3 inflammasome activation pathway upon LPS stimulation without involving K^+ efflux to release IL-1β [179]. Therefore, NEK7 activity is dispensable in LPS-primed human macrophages, where IKKβ activation recruits NLRP3 to phosphatidylinositol-4-

phosphate (PIP_4, a phospholipid enriched on the trans-Golgi network) [180].

The itaconate and 4-OI do not inhibit AIM-2 and NLRC4 inflammasome activation. However, prolonged priming of macrophages with LPS establishes tolerance to late NLRP3 inflammasome activation as itaconate acts synergistically with iNOS and prevents full caspase 1 (CASP1) activation and GSDMD processing through posttranslational modification [181]. This uncontrolled IR in inflammatory macrophages induces tolerance to the NLRP3 inflammasome activation, which may cause pyroptosis and aggravate inflammatory tissue damage. Dimethyl itaconate (DMI), 4-OI, dimethyl fumarate (DMF, an approved treatment for multiple sclerosis or MS), and Monomethyl fumarate (MMF) inhibit NLRP3 inflammasome activation in response to lysophosphatidylcholine (LPC), which activates TLR4 and TLR2/TLR1 signaling that via pro-inflammatory IR controls NLRP3 inflammasome priming and activation [182, 183]. However, it is noteworthy that in the presence of classic TLR activators, such as LPS, LPC suppresses some TLR-mediated intracellular pro-inflammatory events, including NF-κB translocation, iNOS expression, and $NO^{\cdot}$ synthesis. In murine macrophages, it activates p38MAP kinase and JNK but blocks ERK activation, which is not seen in TLR-transfected human embryonic kidney (HEK)-293A cells. Thus, LPC alone serves as an inflammogen by activating TLR signaling and dependent NLRP3 inflammasome activation. However, in the presence of other TLR stimulatory agents, it counteracts some pro-inflammatory events downstream of TLR signaling. Hence, it will be interesting to investigate the altered IR in the presence of LPC and other TLR agonists with the potential to activate NLRP3 inflammasome.

DMF breaks into MMF, a ligand for a niacin receptor 1 (Niacr1) gene-encoded G protein-coupled receptor called GPR109a or hydroxycarboxylic acid receptor 2 (HCAR2). The MMF recognition by GPR109a in the lysosomes of immune cells inhibits NLRP3 inflammasome-dependent IL-1β production along with L-6, IL-12, and TNF-α [184]. Furthermore, GPR109a activation in macrophages and DCs induces anti-inflammatory molecules, such as IL-10 and aldehyde dehydrogenase 1 family member 1A (ALDH1A) expression [185]. Meanwhile, macrophages and DCs lacking GPR109a or Niacr1 overexpress pro-inflammatory IL-6. Butyrate, a short-chain fatty acid (SCFA) produced by gut microbiota, activates GPR109a in macrophages and DCs to exert anti-inflammatory action [185]. DMF and endogenous fumarate also inhibit NLRC4 and AIM-2 inflammasome activation along with NLRP3 inflammasome-induced cell death (pyroptosis) and lactate dehydrogenase (LDH) release by interacting with the cysteine residues of gasdermin-D (GSDMD), forming S-(2-succinyl)-cysteine, which prevents its interaction with caspases, limiting its processing, oligomerization, and capability to induce pyroptotic cell death [186]. Disulfiram (a USFDA-approved drug for alcoholism) also inhibits pyroptosis by covalently modifying human/mouse Cys191/Cys192 in GSDMD, which prevents pore formation to prevent the IL-1β release and death in mice with endotoxemia [187].

Butyrate inhibits NF-κB and NLRP3 inflammasome expression, activation, and function in innate immune cells, such as endothelial cells, macrophages, and adipocytes, during sterile inflammatory conditions, such as colitis-induced colon cancer [188–191]. However, butyrate potentiates the NLRP3 inflammasome activation and the production of antimicrobial proteins (AMPs, calprotectin) during bacterial infection with *Escherichia coli*, *Enterococcus fecalis*, *Streptococcus gordonii*, *Staphylococcus aureus*, and *Bacillus subtilis* to restrict their growth [192–194]. It is important to note that butyrate is not critical for increased antimicrobial action of macrophages at the time of infection. The butyrate treatment increases the antimicrobial action of macrophages by increasing the AMP production without affecting phagocytosis, inflammatory cytokine (IL-1β and TNF-α) production, and apoptosis [193].

Butyrate increases the antimicrobial function of macrophages by inhibiting histone deacetylase (HDAC) activity, specifically HDAC3 activity that occurs upstream of metabolic changes and antimicrobial response. Notably, butyrate-induced elevated antimicrobial action of macrophages is independent of GPR109a activation [193]. Butyrate treatment decreases the IL-10 production from macrophages in the presence of bacterial pathogens. The butyrate-treated lamina propria macrophages showed a decreased glycolysis, glycolytic capacity, and glycolytic reserve, as indicated by the decreased extracellular acidification rate due to reduced glucose concentration [193]. However, butyrate treatment did not alter mitochondrial OXPHOS in macrophages compared to controlled macrophages, but it increased their adenosine monophosphate (AMP) level. The elevated AMP induces AMPK (affected by AMP/ATP ratio) overexpression, which phosphorylates tuberous sclerosis complex 2 (TSC2, a tumor suppressor protein) [195, 196]. The phosphorylated TSC2 inhibits S6K and 4EBP1 phosphorylation, which inhibits the mechanistic target of rapamycin (mTOR, a master regulator of autophagy and glycolysis) activity [195–198]. mTOR is an energy-sensing pathway downstream of TSC2 [195]. Hence,

NLRP3 inflammasome-dependent pro- and anti-inflammatory actions of butyrate vary with the nature (sterile and infectious) of inflammatory disease and need further investigation.

The increase in FAS upon TLR activation also increases NLRP3 inflammasome activation (Fig. 1; Table 1). For example, mice with reduced FAS exhibit a decreased NLRP3-mediated CASP1 activation. FA synthase (FASN), a key enzyme involved in FAS that catalyzes the palmitic acid and FASN or palmitic acid synthesis inhibition, blocks NLRP3 activation and the IL-1β and IL-18 production [199]. Thus, FASN-mediated FAS and NLRP3 palmitoylation are critical for NLRP3 inflammasome activation. Furthermore, IL-1β via IL-1Ra increases FAS to support the pro-inflammatory environment [200]. Thus, NLRP3 activation supports glycolysis and FAS to support pro-inflammatory IR in immune cells such as macrophages (Fig. 1; Table 1). Therefore, strategies to inhibit IL-6 and NLRP3 (both support glycolysis) in several acute inflammatory conditions, such as coronavirus disease 2019 (COVID-19), are emerging [201].

GB111-NH2 inhibits GAPDH and α enolase (glycolytic enzymes) and impairs NADH (decreased production) and mtROS production to induce NLRP3 activation-mediated IL-1β secretion and pyroptosis [202]. The succinate and pyruvate treatment inhibit GB111-NH2-induced NLRP3 activation. However, pyruvate supplementation did not affect ATP and nigericin-induced NLRP3 inflammasome activation [202]. Koningic acid (KA inhibits GAPDH in glycolysis) and ENOblock (EB inhibits α enolase in glycolysis) also inhibit NLRP3 inflammasome activation. Thus, immunometabolites, including succinate, pyruvate, and KA may have immunomodulatory action depending on the local tissue environment, PRR, and immune cells primarily involved in the inflammatory process. We need further studies in this direction.

cGAS-STING Signaling or cGLRs in Immune Cells and IR

cGAS is a cytosolic PRR for double-stranded DNA (dsDNA) in the cytosol, which can be host and pathogen-derived. We and others have discussed the cGAS-STING signaling in detail elsewhere [203–207]. Briefly, cGAS catalyzes cytosolic dsDNA into cGAMP, which activates STING (an adapter molecule) (Fig. 2). The activated STING phosphorylates TBK1, which initiates NF-κB and interferon regulatory factor 3 (IRF3)-dependent downstream signaling to produce pro-inflammatory cytokines and type 1 IFNs (Fig. 2). Therefore, it is critical to discuss the impact of IR on cGAS-STING or cGLR signaling and vice versa. STING regulates glycolysis through HIF-1α stabilization by increasing the mtROS and succinate production that shifts macrophage OXPHOS towards increased aerobic glycolysis for their pro-inflammatory phenotype and function (enhanced $NO^{\cdot}$ production by upregulating iNOS or NOS2 expression, inflammasome activation, and IL-1β release) (Table 1; Fig. 2) [208]. On the other hand, in tumor immune microenvironment, aerobic glycolysis in activated DCs drives STING signaling to facilitate their antitumor action [209]. Mechanistically, glycolysis-mediated ATP overproduction increases STING signaling that stabilizes HIF-1α, supporting glycolysis to exert protective pro-inflammatory action to clear cancer cells (Fig. 2). Thus, STING activation promotes glycolysis in macrophages and DCs as an anti-infection and anti-cancer defense (Table 1). The liver X receptor (LXR, a member of the nuclear hormone receptor family) activation in macrophages inhibits pro-inflammatory immune response through different mechanisms, such as inhibition of osteopontin, iNOS, cyclo-oxygenase-II, and IL-6 activity and production upon LPS-mediated TLR4, TNF-α, IL-1β, and IFN-γ activation [210–215]. The synthesis and activation of ADP-ribosylation factor-like 7 (ARL7) upon LXR activation have also been recognized as a metabolic and anti-inflammatory target [216]. However, LXR activation-mediated lipid metabolism in macrophages suppresses cGAS-STING activation by inducing the sphingomyelin phosphodiesterase acid-like 3A (SMPDL3A) expression, which degrades cGAMP and restricts STING activation and suppresses cGAS/STING signaling-dependent pro-inflammatory immune response [217]. Hence, we critically need further studies in this direction.

The cytosolic dsDNA activates cGLRs (cGAS/STING signaling pathway), and exploring the impact of pro-inflammatory TLR signaling-induced IR on cGAS/STING signaling activation needs an investigation. For example, during polymicrobial sepsis, activated TLR1/TLR2 signaling increases intracellular hydrogen peroxide (H_2O_2) and mtROS production in leukocytes (Fig. 3) [218]. TLR4 activation induces ROS-mediated mitochondrial oxidative stress (Fig. 3) [219]. It is important to note that TLR3 and TLR9 activation do not result in ROS production. The mtROS-induced damaged mitochondrial DNA can progressively be released into the cytosol for activating the pro-inflammatory cGAS/STING signaling pathway (Fig. 3). TLR activation induces glycolysis that supports HIF-1α stabilization for releasing pro-inflammatory cytokines (IL-1β, IL-6, and IL-12).

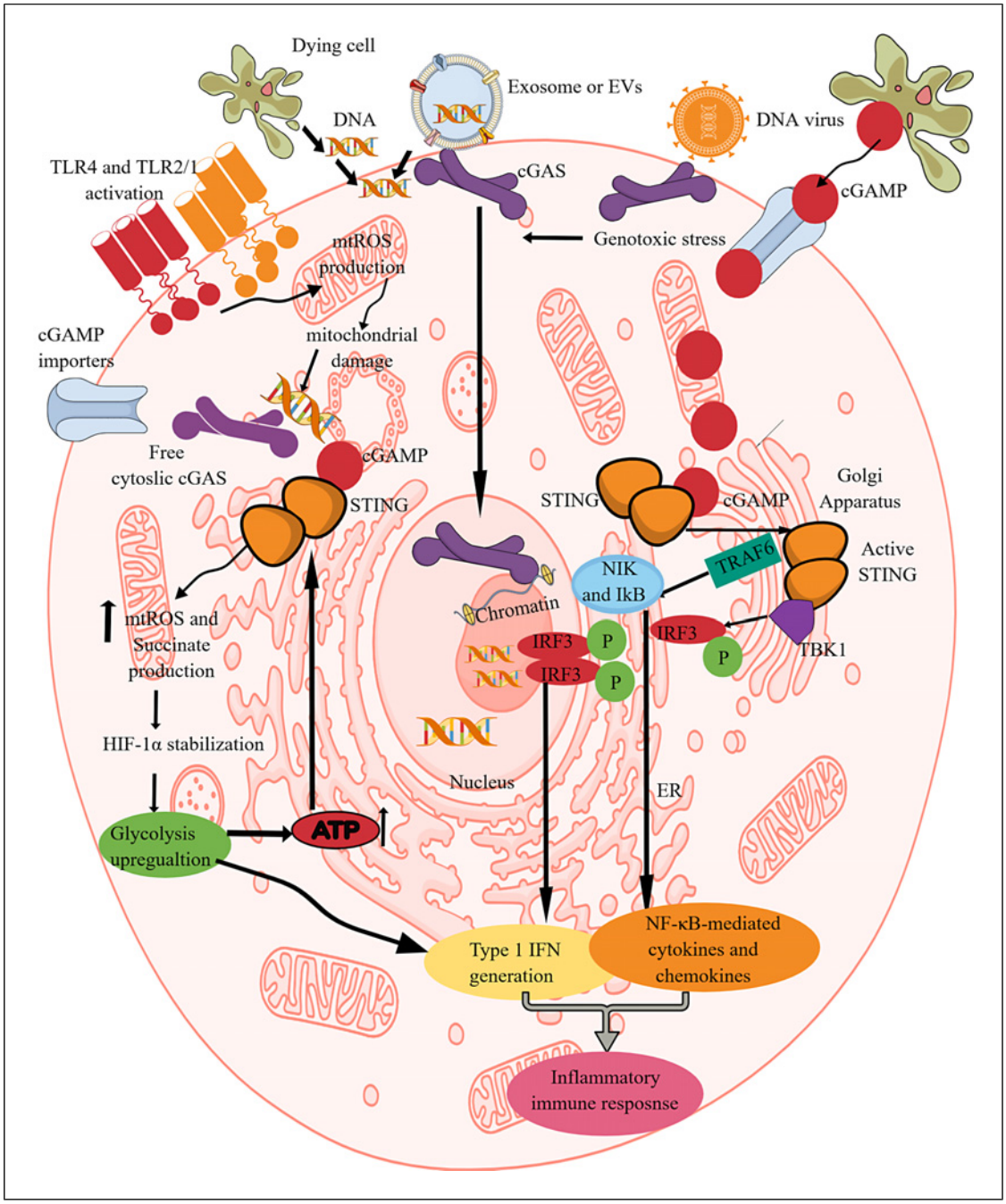

Fig. 2. cGAS/STING (cGLR) signaling-dependent IR. cGLRs or cGAS/STING signaling is critical for recognizing the cytosolic dsDNA and generating type 1 IFNs and NF-κB-dependent cytokines. cGAS-mediated cytosolic dsDNA recognition by cGAS generates cGAMP. STING recognizes cGAMP and undergoes dimerization to become active. The activated STING activates TBK1 and TRAF6, which activate IRF3 and NF-κB-dependent type 1 IFNs and cytokines. This process also activates glycolysis by increasing mtROS production, succinate accumulation, and HIF-α stabilization. The increased glycolysis overproduces ATP molecules, which further increases STING activation. Furthermore, TLR activation induced mtROS production and mitochondrial damage, releasing the mitochondrial DNA into the cytosol that the cGAS recognizes to initiate the cGAS/STING signaling. Hence, TLR and cGAS/STING signaling support each other through IR or glycolysis.

The cytosolic dsDNA-induced STING activation further stabilizes HIF-1α for pro-inflammatory phenotype and function of immune cells. STING activation induces macrophage itaconate production (Table 1) [220]. Furthermore, IL-6 supports aerobic glycolysis by supporting HK2 and 6-phoshofructo-2-kinase/fructose-2,6-bisphosphatase-3 (PFKFB3) overexpression by activating STAT3 in different inflammatory conditions varying from infections to cancers [221–223]. Hence, IL-6 inhibition exerts its anti-inflammatory effect by targeting pro-inflammatory IR. We need further investigations to explore cGLRs-dependent IR and the impact of other PRR-signaling-induced IR of cGLR activity.

RLR Signaling Pathway in IR

RLRs are cytosolic PRRs for viral infections and recognize viral RNAs as PAMPs (Fig. 3). However, they can also sense host-derived RNAs as DAMPs and viral (herpes simplex virus 1, Epstein-Barr virus, vaccinia, and adenovirus) dsDNA as PAMPs to initiate type 1 IFN-dependent pro-inflammatory immune response [224]. The nuclear-resident RIG-1 also senses viral replication and induces antiviral immunity, which involves canonical or cytosolic RLR signaling as a signal to sense IAV replication in the nucleus for generating a cooperative induction of type 1 IFNs [225]. However, nuclear RIG-1 signaling remains inactive upon infection with cytoplasmic-replicating Sendai virus but signals upon nucleus-derived viral agonists, including pregenomic RNA of hepatitis B virus. RLR protein family has three known members: (1) RIG-1, also known as DDX58, (2) melanoma differentiation-associated protein 5 or MDA5 or IFIH1, and (3) laboratory for genetics and physiology 2 or LGP2. LGP2 is a positive regulator of RIG-1 and MDA5-dependent antiviral immune response and synergizes MDA5 in RLR-dependent antiviral immunity [226–228]. For example, LGP2 interacts with mitochondrial antiviral protein signaling (MAVS, which is anchored into mitochondria, mitochondria-associated endoplasmic reticulum membranes (MAMs), and peroxisomes via its transmembrane (TM) domain) in microsomes and blocks RIG-1/MAVS interaction in the resting stage, indicating that microsomes harbor RLR family members but not mitochondria (Fig. 3) [229]. The virus infection or cytosolic RNA induces LGP2 localization to mitochondria from the microsome and leaves MAVS free, which correlates well with IRF3 activation (Fig. 3). The viral or host-derived RNA recognition by RIG-1 and MDA5 (RLRs) activates the adapter protein MAVS via caspase activation and recruitment domains that oligomerize upon recognition of viral and host RNA [224, 230].

MAVS is also known by other names, such as caspase activation recruitment domain adapter-inducing IFN-β (CARDIF), interferon-beta promoter stimulator 1, and virus-induced signal adapter [231–234]. Virus-induced signal adapter or MAVS is involved in TLR3 and RLR-dependent antiviral immune response via interacting with TRIF and TRAF6 (Fig. 3) [233]. Subsequently, MAVS interacts and activates TBK1 and IKK-ε, which are critical components of the IRF3 and IRF7 signaling pathway to generate type 1 IFNs and NF-κB-dependent pro-inflammatory immune response (Fig. 3) [235, 236]. IRF3 activation occurs on the endoplasmic reticulum (ER)-derived membranes but not on the mitochondria (Fig. 3) [229]. Hence, ER-derived membranes are key RLR signaling platforms.

The LGP2-MAVS complex in the microsome negatively regulates RIG-1 activation during immune homeostasis that translocates to the mitochondria to release MAVS for facilitating antiviral RLR signaling-dependent immune response (Fig. 3). Upon dsRNA, poly(I: C) challenge, mitochondrial protein phosphoglycerate mutase family member 5 (PGAM5) overexpression, and oligomerization take place along with their direct interaction with MAVS, which is critical for downstream TBK1 and IRF3 phosphorylation-mediated type 1IFN production (Fig. 3) [237]. Furthermore, PGAM5-deficient cells are defective in clearing vesicular stomatitis virus (VSV) infection and type 1 IFN production. On the other hand, upon LPS stimulation, mitochondrial PGAM5 in macrophages dephosphorylate dynamin-related protein 1 (Drp1) to generate mtROS and promote pro-inflammatory M1 macrophage phenotype exhibiting glycolysis, generating pro-inflammatory cytokines and molecules downstream to NF-κB and MAPK pathways [238]. Thus, stimulus or PRR type determines the downstream immunoregulatory functioning of the PGAM5, including glycolysis support or MAVS-dependent type 1 IFN release. Details of RLR signaling in the infection and immunity have been discussed elsewhere [224, 239–242]. The following sections discuss RLR signaling-induced IR and the impact of IR induced by other PRRs on RLR signaling.

RIG-1 activation induces MAVS activation, which hijacks HK binding to MAVS to impair HK mitochondrial localization and activation [243]. The RLR activation decreases most metabolic intermediates downstream of glucose metabolism, such as phosphoenolpyruvate

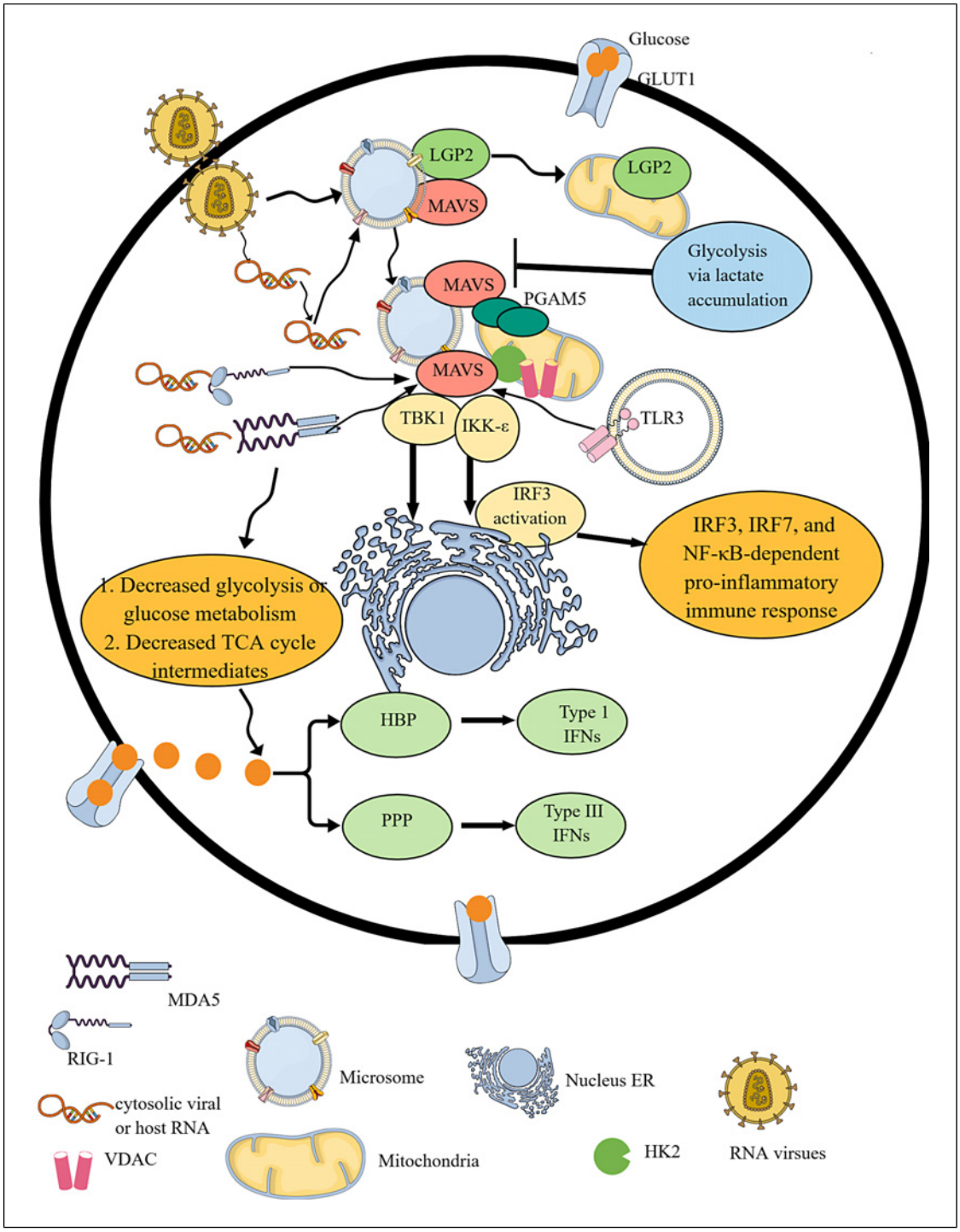

Fig. 3. RLR signaling activation-mediated IR. RLR signaling activation involves the recognition of cytosolic RNA via RIG-1 and MDA5. During homeostasis, LGP2 is bound to the MAVS in the microsome. LGP2 moves to mitochondria upon viral infection, leaving MAVS free in the microsome. Thus, upon recognizing cytosolic RNA, RIG-1 and MDA5 interact with MAVS, which directly interacts with the oligomerized mitochondrial PGAM5. The RIG-1 and MDA5 interaction with MAVS interacting with oligomerized PGAM5 is critical for the downstream TBK1 and IRF3 phosphorylation-mediated type 1 IFN release. IRF3 activation occurs at the ER. The RIG-1 and MDA5 activation suppress glycolysis and the TCA cycle. Instead of glycolysis, cellular glucose undergoes PPP and HBP to generate type III and IFNs. Furthermore, glycolysis via increased lactate accumulation suppresses MAVS activity through binding to its TM domains. TLR3 activation also activates MAVS.

(PEP), pyruvate, and lactate levels, at the initial stages of type 1 IFN production (Fig. 3; Table 1). At this initial step, TCA intermediates, including succinate, fumarate, aconitate, and malic acid (malate), decrease due to reduced pyruvate levels without affecting OAA levels [243]. Thus, RLR signaling impairs glucose metabolism (Fig. 3; Table 1). Furthermore, 2-DG (inhibits HK to block glycolysis) increases RLR signaling-dependent type 1 IFN and IL-6 release. Hence, decreased glycolysis promotes RLR signaling-dependent antiviral or pro-inflammatory immune response due to decreased HK activity at the early stages of RLR signaling [243].

The HK2 (which stays bound to MAVS on the mitochondria) activity gets hijacked upon RLR signaling activation-mediated MAVS-RIG-1 recognition, causing an impaired HK2 localization in the mitochondria and its activation. The HK2 interacts with MAVS through VDAC1 (which is involved in glycolysis regulation) in the mitochondria [159, 243, 244]. MAVS in the mitochondria recruits NLRP3 (resting NLRP3 co-localizes ER membranes) there and facilitates its oligomerization for CASP1-dependent IL-1β production and NLRP3 inflammasome-dependent pro-inflammatory activities during glycolysis that further supports glycolysis [245, 246]. Furthermore, VDAC dysregulation or inhibition suppresses mitochondrial activity that inhibits ROS generation and NLRP3 inflammasome activation [247]. Thus, glycolysis may also inhibit RLR signaling due to the involvement of MAVS in the NLRP3 recruitment to mitochondria for NLRP3 inflammasome activation and dependent pro-inflammatory immune response. For example, cytosolic dsRNA activates NLRP3 inflammasome-dependent IL-1β production through mitochondrial MAVS that triggers membrane permeabilization and potassium (K^+) efflux, which occurs independently of TLR3 and RLR (RIG-1 and MDA5) signaling [248]. Furthermore, hypoxia induces MAVS, NLRP3, and CASP1 overexpression, and increased production of IL-1β, IL-6, and IL-18 further supports that MAVS is critical for NLRP3 inflammasome during hypoxia and glycolysis [249]. NLRX1 overexpression inhibits MAVS-dependent NLRP3 inflammasome activation during hypoxia to prevent pro-inflammatory damage.

Anaerobic glycolysis via lactate production is a negative signal to repress RLR signaling-mediated MAVS activation and type 1 IFN and other NF-κB-dependent pro-inflammatory cytokines production (Fig. 3) [243]. Cells lacking PDH upon RLR activation show a robust decrease in TBK1 and IRF3 phosphorylation and MAVS aggregation due to lactate overproduction and accumulation. On the other hand, LDH decreasing lactate production and accumulation enhances TBK1 and IRF3 phosphorylation along with increased type 1 IFN production upon RLR stimulation. Hence, cellular lactate accumulation inhibits anaerobic glycolysis during RLR signaling in vitro and in vivo [243]. The accumulated lactate directly binds MAVS TM domains and inhibits its mitochondrial localization, association with RIG-1, and aggregation required for downstream TBK1 and IRF3 phosphorylation and activation to produce type I IFNs (Fig. 3).

The activated MAVS shifts glycolysis to the PPP or PPS and hexosamine biosynthesis pathway during RLR signaling (Fig. 3; Table 1) [250]. The activated MAVS associates with glucose-6-phosphate dehydrogenase (G6PD) and TRAF6 on peroxisomes during viral infections, activating RLR signaling to initiate PPP and type III IFN (IFN-λ) production. The MAVS association with glutamine-fructose-6-phosphate transaminase 2 (GFPT2, a rate-limiting enzyme of the HBP and generates fructose-6-phosphate (F6P) to the HBP end-product uridine diphosphate N-acetylglucosamine [UDP-GlcNAc]), TRAF2, and TRAF6 on MAMs activates HBP metabolism and type 1 IFN production during viral infections [250, 251]. Thus, VSV infection or poly (I:C) treatment increases glucose flux to PPP and HBP instead of glycolysis to generate RLR signaling-dependent type 1 and III IFNs (Fig. 3). Interestingly, peroxisome-located MAVS guides glucose flux to PPP for generating type III IFNs, and MAMs-associated MAVS supports glucose flux to HBP for type 1 IFN production [250]. The HBP-mediated O-linked β-N-acetylglucosamine (O-GlcNAc) signaling promotes antiviral RLR signaling by O-GlcNAcylation of MAVS on serine 366 for K63-linked ubiquitination of MAVS and subsequent activation of downstream TBK1 and IRF3 axis to generate type 1 IFNs [252, 253]. The HBP-mediated O-GlcNAc transferase (OGT), a key enzyme for protein O-GlcNAcylation also induces O-GlcNAcylation of the receptor-interacting protein kinase 3 (RIPK3, a serine-threonine kinase) on threonine 467 (T467) to prevent RIPK3-RIPK1 hetero- and RIPK3-RIPK3 homo-interaction to inhibit downstream innate immune response and necroptosis [254]. RIPK3 via CASP8 activation induces NLRP3-CASP1 inflammasome-dependent inflammatory signaling and pyroptosis [255, 256]. Thus, RLR signaling-induced HBP may suppress NLRP3 inflammasome activation and necroptosis to mount an effective type 1 IFN-dependent immune response. D-glucosamine, a dietary supplement, protects against lethal viral infections induced by the human influenza virus, coxsackievirus, VSV, and SARS-CoV-2 in mice through increasing MAVS O-GlcNAcylation [253, 257]. The MAVS O-GlcNAcylation downstream of the RLR signaling pathway may inhibit NLRP3 inflammasome activation to

prevent cell death for effective antiviral immunity, which needs further investigation.

Furthermore, GLUT4 translocation to the plasma membrane from its intracellular compartment also inhibits RLR signaling by sequestering RLRs into the plasma membrane in muscle cells [258]. Insulin treatment and viral infections alter RLR activation by promoting the GLUT4 and RLR translocation to the plasma membrane [258]. UBXN9 (a ubiquitin-domain-containing protein) regulates GLUT4 translocation to the plasma membrane, and its disruption supports GLUT4 translocation to the plasma membrane from its intracellular compartment. However, in muscle cells, RLR signaling inhibition upon insulin treatment occurs independently of glycolysis but is dictated by GLUT4 translocation to the plasma membrane. UBXN proteins (UBXN1, UBXN9, and UBXN11) inhibit retrovirus and lentivirus production by regulating RLR signaling and canonical NF-κB signaling by stabilizing inhibitory κBα (IκBα) [259].

Furthermore, phorbol 12-myristate 13-acetate (PMA) and LPS stimulation of white blood cells or immune cells, such as monocytes/macrophages, B cells, and T cells, upregulate GLUT1, GLUT3, and GLUT4 expression that enhances glucose uptake to support IR for glycolysis from OXPHOS, which further increases in the presence of insulin [260]. However, in neutrophils, only GLUT1 and GLUT3 overexpression on the plasma membrane occurs upon LPS stimulation. Thus, activation of other PRRs (TLRs, NLRs, and cGLRs) supporting glycolysis may inhibit RLR signaling, and we need further studies in this direction. For example, succinate accumulation during TLR and NLR activation also inhibits RLR signaling by suppressing the MAVS aggregation required to activate the downstream MAVS-TBK1-IRF3 to generate type 1 IFNs CXCL10, and INF stimulated gene 15 (ISG15) during VSV infection [261]. This finding further supports the idea that immune metabolites (lactate and succinate) supporting glycolytic IR suppress RLR signaling-dependent immunity.

Adipocytes also regulate inflammation and immunity through different PRRs and release several adipokines and cytokines [262]. They also express RLRs, and GLUT4 overexpression in hyperplastic adipocytes can impair their RLR signaling-mediated antiviral immune response [263, 264]. Thus, obese people may exert a lower RLR-mediated antiviral and inflammatory immune response. For example, dysregulated RLR signaling during obesity abolishes ER stress-induced Type 1 IFN generation to promote obesity and insulin resistance [265]. Thus, we need further explorations in IR downstream to RLR signaling for understanding immune response under diverse conditions.

Future Perspective and Conclusion

PRRs are critical for the maintenance of immune homeostasis. Their activation plays a significant role in the recognition and clearance of potential MAMPs, PAMPs, and DAMPs through generating pro-inflammatory immune responses. However, IR governs pro- and anti-inflammatory stages or functions of immune cells. For example, transition from OXPHOS to glycolysis and FAO to FAS critically determines the pro-inflammatory functions of innate immune cells such as macrophages, neutrophils, DCs, and NK cells upon the activation of TLRs, NLRP3 inflammasomes, CLRs (recognizing fungal (*Candida albicans*) infection) and cGAS/STING (cGLR) signaling pathway to initiate the pro-inflammatory immune response (Table 1) [266]. Furthermore, molecules or cytokines (IL-1β) released through their corresponding receptors further support glycolysis in these immune cells for the continued pro-inflammatory response. For example, TNF-α also supports glycolysis through upregulating HK2 [267].

Furthermore, TNF-α treatment may support antiviral immune response by supporting PPP and HBP that work upon activation of RLRs to synthesize type 1 and III IFNs. The pro-inflammatory cytokine IL-6 also supports glycolysis [223]. Thus, targeting glycolysis through immunometabolic approaches, for example, 2-DG, can be effective downstream of TLR, NLRP3, ALRs, and cGLRs, which support inflammation through glycolysis. However, this strategy fails during RLR signaling pathway activation, which does not support glycolysis.

The lactate accumulation due to glycolysis during hypoxia seen in various inflammatory conditions, including cancers and infections, induces histone lactylation at lysine, which has different temporal dynamics from lactylation [268]. For example, histone lactylation in M1 macrophages induces M2-like genes (arginase 1 or ARG1) in M1 macrophages that are critical for inflammation resolution and wound healing but also support immunosuppressive TIME. P300 is a potential histone lactylation writer protein under hypoxic conditions supporting glycolysis [268]. Thus, lactate accumulation is critical to protect the tissue from aggravated injury during acute inflammation and supports chronic inflammatory conditions such as cancers. Thus, the PRR activation intensity and chronicity further reshape the IR to suppress or aggravate the inflammation to maintain immune homeostasis.

Furthermore, some inhibitory PRRs, which are anti-inflammatory in action and critical to maintaining immune homeostasis, exist [269]. Even TLR4 activation in

the endosomes or phagosomes exerts anti-inflammatory action through TRAM and TRIF-dependent type 1 IFN generation and antagonizes the pro-inflammatory action of the cell membrane-bound TLR4 [270, 271]. Therefore, it will be interesting to investigate the impact of inhibitory PRRs on IR of PRR-regulated immunometabolism and to design novel strategies to target immunometabolism to maintain immune homeostasis.

HIF-1α stability is critical for glycolysis downstream to TLR and TCR signaling in $CD8^+$T cells for their effector function. However, mitochondrial dysregulation under stressful conditions such as chronic infections and cancers prevents the HIF-α degradation through the ubiquitin-proteasome system (UPS), causing enhanced glycolysis precursor T-cell population (T_{pex}) to generate exhausted T cells [272–274]. Therefore, metabolic engineering of CAR T cells is a novel approach for enhanced stemness and functionality of T_{pex} cells for cancer immunotherapy. Furthermore, these metabolically engineered CAR T cells with lower glycolysis may have enhanced RLR signaling through LGP2 controls survival and fitness of antigen-specific $CD8^+$T cells during peripheral T-cell expansion [275]. RLR signaling also determines the quality of polyfunctional T-cell response [276]. Hence, metabolically engineered CAR T cells or CAR macrophages with intact RLR signaling may prove better immunotherapeutic approaches for cancer with lower side effects. For example, patients undergoing CAR T-cell therapy are highly immunosuppressive and develop severe bacterial and viral (IAV) infections [277, 278]. RLR activation in mice attenuates TLR-mediated Th1 cell and Th17 immune response, inducing death at sublethal bacterial infection by suppressing the transcription of the gene encoding the p40 subunit of interleukin 12 (IL-12b) [279]. It is well known that RLR signaling (PPP and HBP) and TLR signaling (glycolysis) induce different IR to generate corresponding immune responses. Therefore, it is critical to understand detailed IR downstream to different PRRs for designing better immunotherapeutic approaches for infectious and inflammatory diseases, including autoimmunity and cancers. For example, along with mitochondria, lysosomes and peroxisomes coordinate cellular metabolic processes and expression of PRRs such as TLRs (TLR2, TLR4, and TLR6 upregulate along with cytosolic endosomal TLRs) and NLRP3 alters in these organelles upon microbial (bacteria and viruses, such as herpes simplex virus 1) stimuli in immune cells such as macrophages, indicating altered immunometabolism also dysregulates PRR expression [280–282].

Furthermore, different tissue macrophages differ in their characteristics; for example, large intestinal macrophages overexpress metabolic proteins than small intestinal macrophages, liver macrophages (Kupffer cells) highly express ACC1 and CPT1A than splenic macrophages, PAMs highly express CD36, but it is lower than that of colonic, splenic, liver, and peritoneal macrophages [121]. On the other hand, brain macrophages or microglia highly express GLUT1, indicating their higher reliance on glucose utilization due to their location in high glucose-consumption organs. Peritoneal macrophages highly express different pro-inflammatory metabolic markers (GLUT1, PKM, SDHA, G6PD, CPT1A, and ACC1) but have lower CD38 and CD98 expression than splenic and liver macrophages [121]. Therefore, timing, and PRR type activation critically depend on the immune cell type (macrophages, DCs, T cells, and B cells) and their tissue location. For example, macrophage-mediated efferocytosis depends on FAS; therefore, macrophages (peritoneal macrophages) overexpressing ACC1 at homeostasis will need lower doses of PRR-based immunometabolism modulator than macrophages (PAMs) with its lower expression. Due to higher metabolic instability or poor mitochondrial fitness in mature small intestinal macrophages (overexpressing PD-L1 marker, which is inversely associated with ACC1 expression), their PRR-based IR targeting needs caution [121]. The negative association between PD-L1 and ACC1 expression in intestinal macrophages indicates an association between PD-L1 and FAS in these macrophages. Therefore, these parameters are critical for future immunotherapeutics targeting immune cell-specific IR through PRRs for their success.

Conflict of Interest Statement

Authors declare no competing interest.

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Author Contributions

Vijay Kumar conceived the idea, wrote the manuscript, and developed the figures. John H. Stewart IV has done the final editing.

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