2024

Metabolism Shapes Immune Responses to Staphylococcus aureus.

Prabhakar Arumugam

Tammy Kielian

Journal of Innate Immunity

Review Article

J Innate Immun 2024;16:12–30
DOI: 10.1159/000535482

Received: October 4, 2023
Accepted: November 21, 2023
Published online: November 28, 2023

Metabolism Shapes Immune Responses to *Staphylococcus aureus*

Prabhakar Arumugam Tammy Kielian

Department of Pathology, Microbiology, and Immunology, University of Nebraska Medical Center, Omaha, NE, USA

Keywords
Staphylococcus aureus · Biofilm · Immunometabolism · Macrophage · Myeloid-derived suppressor cell · Neutrophil

Abstract

Background: *Staphylococcus aureus* (*S. aureus*) is a common cause of hospital- and community-acquired infections that can result in various clinical manifestations ranging from mild to severe disease. The bacterium utilizes different combinations of virulence factors and biofilm formation to establish a successful infection, and the emergence of methicillin- and vancomycin-resistant strains introduces additional challenges for infection management and treatment. ***Summary:*** Metabolic programming of immune cells regulates the balance of energy requirements for activation and dictates pro- versus anti-inflammatory function. Recent investigations into metabolic adaptations of leukocytes and *S. aureus* during infection indicate that metabolic crosstalk plays a crucial role in pathogenesis. Furthermore, *S. aureus* can modify its metabolic profile to fit an array of niches for commensal or invasive growth. ***Key Messages:*** Here we focus on the current understanding of immunometabolism during *S. aureus* infection and explore how metabolic crosstalk between the host and *S. aureus* influences disease outcome. We also discuss how key metabolic pathways influence leukocyte responses to other bacterial pathogens when information for *S. aureus* is not available. A better understanding of how *S. aureus* and leukocytes adapt their metabolic profiles in distinct tissue niches may reveal novel therapeutic targets to prevent or control invasive infections.

Introduction

Staphylococcus aureus (*S. aureus*) is a common human commensal and significant opportunistic pathogen. Approximately 30% of humans are carriers of *S. aureus*, primarily in the nose and frequently at other body sites such as the skin and throat [1, 2], and *S. aureus* colonization is a known risk factor for developing invasive infections [3]. *S. aureus* is a leading cause of skin and soft tissue infections, endocarditis, bacteremia, pneumonia, osteomyelitis, and medical device infections typified by biofilm formation. Disease typically originates from the invasion of colonizing strains into the bloodstream or following a breach of protective epithelial or mucosal barriers during injury or medical device placement; however, in rare cases, isolates can be transferred between individuals. *S. aureus* encodes an array of virulence factors and immune evasion strategies that facilitate both commensal and opportunistic lifestyles [4–6].

S. aureus can cause either acute or chronic infections, which is dictated by various host and bacterial factors [7–10]. In terms of leukocyte responses, neutrophils (PMNs) play a significant role in controlling infection as

karger@karger.com
www.karger.com/jin

Correspondence to:
Tammy Kielian, tkielian@unmc.edu

patients with chronic granulomatous disease, typified by mutations in nicotinamide dinucleotide phosphate (NADPH) oxidase, are more susceptible to recurrent *S. aureus* infections due to impaired reactive oxygen species (ROS) production [11]. Macrophages (MΦs), T cells, and B cells also play important roles in regulating bacterial growth. However, *S. aureus* has the potential to circumvent these protective responses by a number of mechanisms [12], including inhibiting PMN and MΦ extravasation, activation, and phagocytosis [13–15]. *S. aureus* also encodes various toxins such as leukocidins, phenol-soluble modulins, and hemolysins that kill leukocytes and promote bacterial survival [16–18]. Furthermore, *S. aureus* can form biofilm, which programs the immune response to an anti-inflammatory state that facilitates chronic infection [19–23].

Current attempts to develop a *S. aureus* vaccine have proven unsuccessful, highlighting the immune evasive properties of the pathogen [24, 25]. The poor translation of protection from animal models to humans is likely influenced by *S. aureus* virulence factors that selectively target human but not mouse leukocytes, human-adapted *S. aureus* strains, and differences in immune reactivity between species [26–28]. Individuals with *S. aureus*-reactive antibodies can become infected with the pathogen and *S. aureus* causes recurrent infections [29–31], additional evidence that the organism possesses a heightened ability to evade immune mechanisms, unlike other bacteria where effective vaccines have been developed. Newer vaccine platforms being explored in mouse models are targeting different *S. aureus* antigens (i.e., α-toxin, leukocidins) than those used in prior clinical trials [32, 33], but it remains to be determined whether this will translate into clinical efficacy. *S. aureus* also has a high propensity to acquire antibiotic resistance through horizontal gene transfer as reflected by the increased prevalence of methicillin-resistant and vancomycin-resistant *S. aureus* strains, representing another major challenge for treatment [34, 35]. In addition, *S. aureus* exhibits antibiotic tolerance during biofilm infections such as endocarditis, medical device-associated infections, and conjunctivitis, representing an additional barrier to treatment [36].

Therefore, effective infection management will benefit from developing alternate strategies that critically depend on a better understanding of host-pathogen interactions. Both the host and pathogen undergo substantial metabolic adaptations that can either augment or hinder the immune system, affecting disease pathogenesis. Immune cell activation is regulated by metabolic rewiring after encountering pathogens [37]. These metabolic changes influence cytokine/chemokine expression, ROS production, and the functional properties of innate and adaptive immune cells. The study of how metabolism programs immune cell activity is termed immunometabolism [38] and a significant amount of foundational knowledge in this field comes from studies with MΦs. For example, proinflammatory MΦs exhibit a bias toward glycolysis, which generates intermediates required for proinflammatory cytokine and prostaglandin production, in addition to NADPH to fuel ROS. Conversely, anti-inflammatory MΦs depend on the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OxPhos) along with fatty acid oxidation (FAO) [39]. Metabolism also influences T cell, B cell, and epithelial cell responses during infection, highlighting the intricate association between cellular metabolism and functional activity [40].

On the other side of the coin, recent studies have demonstrated that bacterial metabolites also act on host cells to regulate homeostasis, differentiation, and proliferation [41, 42]. Bacterial metabolites can either stimulate host defense mechanisms or inhibit antimicrobial activity to mitigate or promote infection, respectively [43]. This review will summarize recent findings on metabolic alterations that occur during *S. aureus* infection, both from the bacterial and host perspectives, with a focus on innate immunity and possible implications on pathogenesis. We also discuss the impact of these metabolic pathways in other bacterial infections when information on *S. aureus* is lacking. The reader is directed to a recent comprehensive review on *S. aureus* metabolism [44], which is outside the scope of this work.

Brief Introduction to Cellular Bioenergetic Pathways

Immune cells alter their metabolic pathways following a pathogen encounter to tailor their effector functions [43, 45, 46]. Key pathways that generate intermediates and end products required for leukocyte proliferation, activity, and survival include glycolysis, pentose phosphate pathway (PPP), TCA, FAO, fatty acid synthesis (FAS), and amino acid metabolism (Fig. 1). Although these metabolic pathways generate different end products, they are interdependent for overall energy production.

Glucose uptake from the extracellular environment initiates glycolysis in the cytosol where glucose is converted through ten enzymatic reactions to pyruvate. Glycolysis is an inefficient means of energy production, yielding only two ATP per unit of glucose, which raises

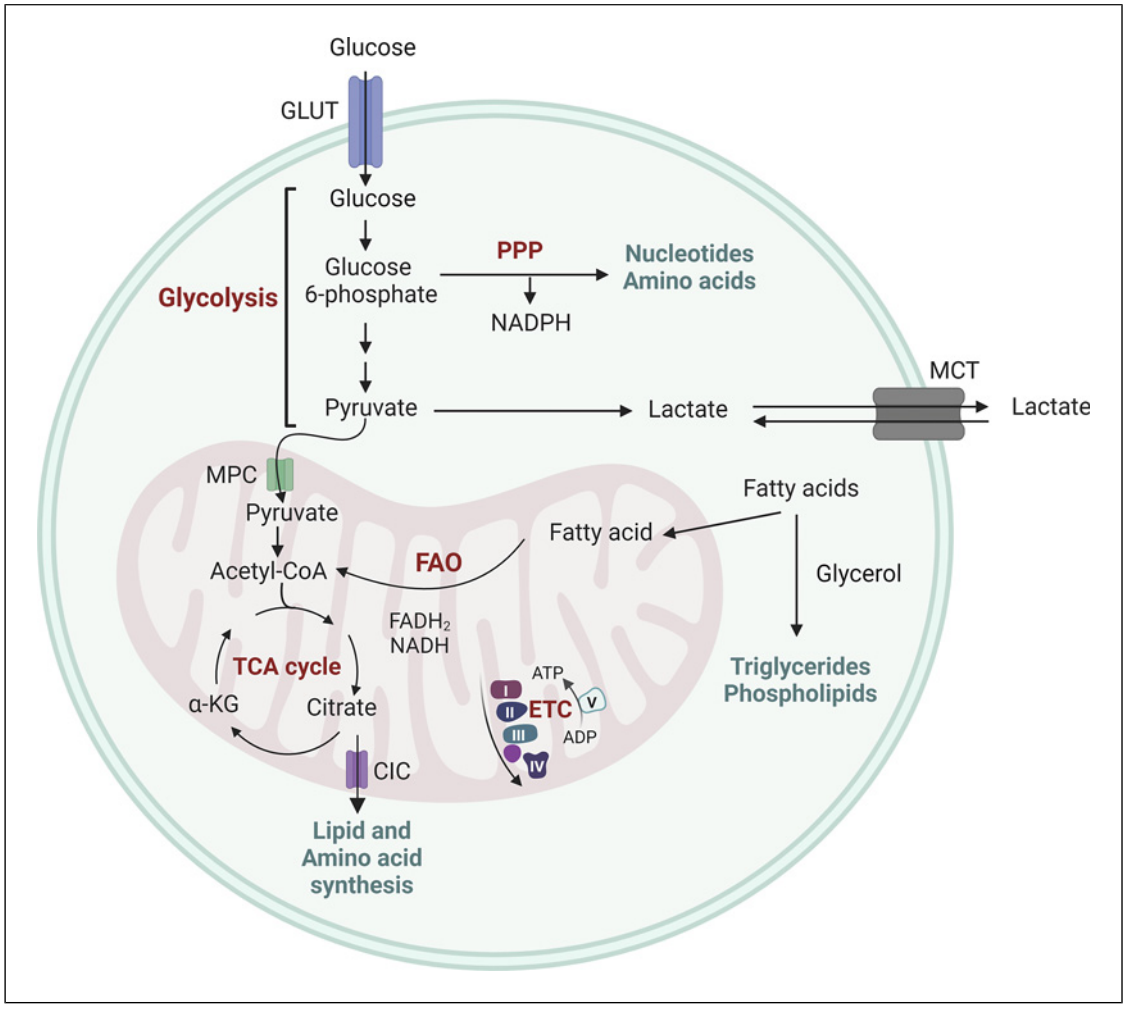

Fig. 1. Overview of major metabolic pathways. Glucose is transported into cells and converted to pyruvate during glycolysis, which can be metabolized to lactate or enter the tricarboxylic acid (TCA) cycle to generate NADH and $FADH_2$. Fatty acid oxidation (FAO) produces NADH, $FADH_2$, and acetyl-CoA of which acetyl-CoA enters the TCA cycle. NADH and $FADH_2$ are utilized in the electron transport chain (ETC) for ATP production. Intermediates from glycolysis feed into the pentose phosphate pathway (PPP), which generates NADPH and precursors for nucleotides and amino acids. Citrate from the TCA cycle is used in lipid and amino acid synthesis. Fatty acids combine with glycerol to synthesize triglycerides and phospholipids in the cytosol (figure created using BioRender). GLUT, glucose transporter; MCT, monocarboxylate transporter; MPC, mitochondrial pyruvate carrier; CIC, citrate/isocitrate carrier; α-KG, alpha-ketoglutarate.

the question of why cells would prefer this metabolic pathway, even in the presence of oxygen (aerobic glycolysis). This is because glycolytic intermediates are also used to synthesize nucleotides and amino acids as well as regulate ROS production, making this a preferred pathway for proinflammatory cells that require robust biomolecule synthesis for antibacterial activity [47]. Pyruvate is the final product of glycolysis and is either actively transported into mitochondria to initiate the TCA cycle or converted to lactate in the cytosol and excreted to maintain glycolytic flux and NAD^+/NADH levels. Under hypoxic conditions, lactate production is increased due to diminished electron transport chain (ETC) activity that requires oxygen. The PPP diverts glycolytic intermediates to produce nucleotides and amino acids and also generates NADPH, which is critical for maintaining cellular redox balance and fueling NADPH oxidase activity as well as cholesterol and fatty acid synthesis [48]. The TCA cycle occurs in mitochondria and utilizes pyruvate-generated acetyl-CoA to initiate the cycle, generating NADH and $FADH_2$ that drive the ETC to produce ATP. Like glycolysis, TCA

intermediates are used for amino acid and lipid synthesis [49]. FAO is the process of catabolizing fatty acids into acetyl-CoA, which can feed into the TCA cycle and ETC to generate ATP.

Other biosynthetic pathways include FAS that requires citrate, whereas branched chain fatty acid production uses amino acids for elongation. Furthermore, glycerol is used as a substrate for triglycerides and phospholipids that are crucial components of cellular membranes and organelles. Apart from being precursors for protein synthesis, amino acids can be shuttled into other metabolic pathways. For example, glutamine and aspartate are used for de novo nucleotide biosynthesis and glutamine is converted to α-ketoglutarate, which feeds into the TCA cycle [50]. Also, L-arginine is used by inducible nitric oxide synthase (iNOS) to generate the free radical nitric oxide that exerts antimicrobial activity through protein nitrosylation, lipid peroxidation, and DNA damage [51]. Given the interconnection between these metabolic pathways (Fig. 1), several studies have identified their importance in regulating the immune response against *S. aureus* infection and disease pathogenesis, which are discussed below.

Glycolysis Shapes Host Immune Responses to *S. aureus*

Increased glycolytic activity is an essential pathway for MΦ, dendritic cell, and PMN activation in response to proinflammatory stimuli such as Toll-like receptor and other pattern recognition receptor ligands [52–56]. For example, lipopolysaccharide (LPS) treatment of MΦs leads to hypoxia-inducible factor 1a (HIF-1a) stabilization, which promotes the transcription of several genes encoding glycolytic enzymes including hexokinase 2 (HK2) and phosphofructokinase as well as glucose transporters (i.e., GLUT3) to increase IL-1β production [57–60]. Recently, MΦ glycolytic activity was shown to induce antibiotic tolerance in *S. aureus* by limiting glucose and ATP availability for the bacterium [61]. This was attributed to the ability of *S. aureus* α-toxin to activate the NLR family pyrin domain containing 3 (NLRP3) inflammasome since antibiotic efficacy was increased in a mouse bacteremia model when NLRP3 was inhibited. This highlights a "tug of war," where glycolysis is typically required for MΦ proinflammatory activity, yet it places pressure on *S. aureus* to become more metabolically dormant to evade antibiotics that require active cell wall and protein biosynthesis for efficacy. However, since most *S. aureus* infections are eventually cleared, it remains to be determined whether this phenotype is selective for specific antibiotic classes, how the timing between infection and antibiotic dosing influences antibiotic sensitivity versus tolerance, and how other immune effector mechanisms compensate for the acquisition of *S. aureus* antibiotic tolerance within the MΦ niche.

Importance of Glycolysis in Keratinocytes and Mammary Epithelial Cells during *S. aureus* Infection

Keratinocytes defend against cutaneous infections by providing physiological and immunological barriers in the skin. *S. aureus* infection enforces metabolic stress on keratinocytes and induces glycolysis through HIF-1a activation to promote IL-1β and IL-18 expression [62] (Fig. 2a). Interestingly, this response was dependent on bacterial glycolysis since neither a *S. aureus* glycolytic mutant (Δ*pyk*) nor PAMPs alone were able to promote keratinocyte glycolysis. Hexokinase (HK) represents the first irreversible step in glycolysis, which is inhibited by 2-deoxyglucose (2-DG), and 2-DG typically suppresses proinflammatory responses in many leukocyte populations [63, 64]. However, 2-DG treatment of mice infected with wild-type (WT) *S. aureus* resulted in larger skin lesions and delayed wound healing with no change in bacterial abundance. Interestingly, animals infected with Δ*pyk* had significantly lower bacterial burden and minimal dermonecrosis compared to WT bacteria, highlighting the importance of *S. aureus* glycolysis in promoting cutaneous infection. While bacterial glycolysis was critical for establishing infection, the larger skin lesions observed with 2-DG treatment suggest that host glycolysis is also required to control excessive inflammation but not *S. aureus* growth. It would be interesting to dissect whether glycolytic activity in keratinocytes versus invading leukocytes is responsible for this phenotype and whether inhibiting glycolysis after bacterial infection has any effect on pathology.

S. aureus has also been shown to increase glycolysis in mammary epithelial cells through a 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3)-dependent mechanism to augment HIF-1a and ROS levels [65]. This response was negated by blocking host glycolysis with either 2-DG or a PFKFB3 antagonist (PFK15). In a mouse model of *S. aureus* mastitis, PFK15 treatment attenuated inflammation resulting in reduced tissue damage and bacterial burden, suggesting a deleterious effect of glycolytic activity [65]. These findings reiterate the complexities of host cell

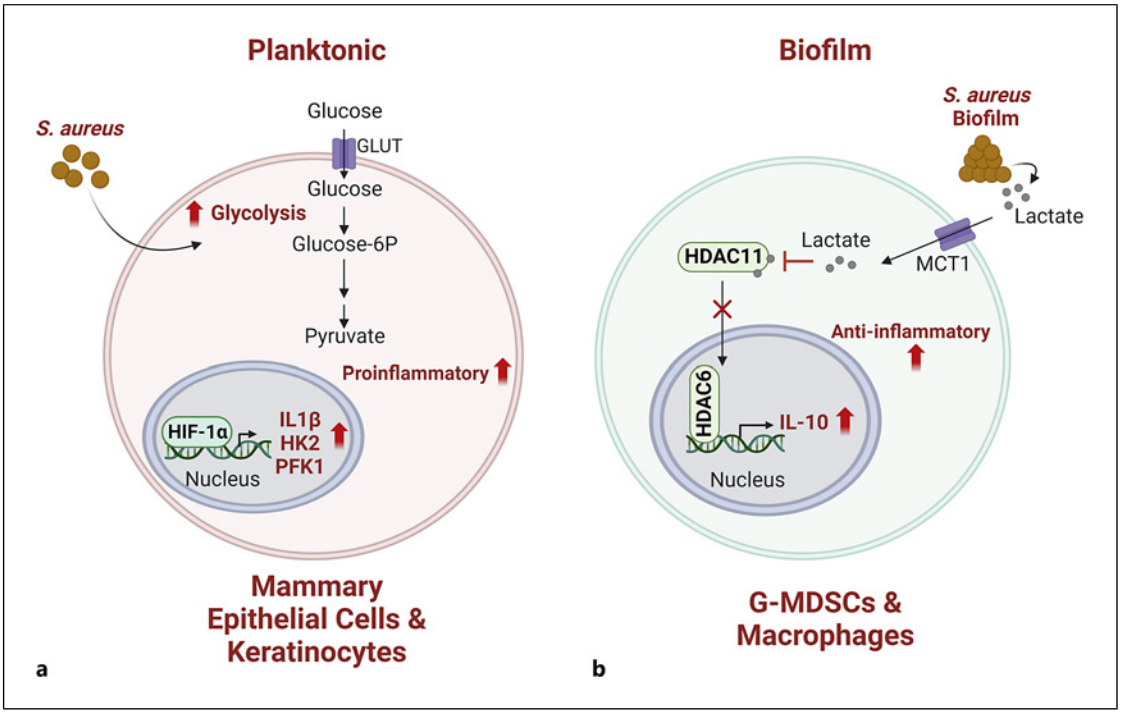

Fig. 2. Modulation of glycolysis during *S. aureus* infection. **a** Planktonic *S. aureus* promotes the expression of glycolytic enzyme (HK2 and PFK1) and proinflammatory (IL-1β) genes by increasing HIF-1a in mammary epithelial cells and keratinocytes. **b** Biofilms elicit a distinct metabolic response, whereby lactate released by *S. aureus* biofilm is transported into G-MDSCs and MΦs, where it inhibits HDAC11, a negative regulator of HDAC6. This results in unchecked HDAC6 activity, which is a transcriptional inducer of IL-10, leading to elevated IL10 production to promote biofilm persistence. During *S. aureus* biofilm infection, host lactate biosynthesis does not affect IL-10 levels (figure created using BioRender). GLUT, glucose transporter; MCT1, monocarboxylate transporter 1; HIF-1α, hypoxia-inducible factor 1α; HDAC, histone deacetylase.

glycolysis in dictating *S. aureus* infection outcome (Fig. 2a).

S. aureus small colony variants (SCVs) are often associated with persistent infections [66]. SCVs are slow growing, have a pinpoint colony size, and possess mutations in various genes, especially those associated with electron transport. Because of these mutations, SCVs have altered metabolism, with increased glycolysis and decreased TCA cycle activity and respiration [67]. Both a prototypic SCV (Δ*hemB*) and WT *S. aureus* induced glycolysis in keratinocytes, resulting in ROS production and necroptosis, unlike their heat-killed counterparts [68]. Interestingly, necroptosis had no effect on Δ*hemB* growth and instead induced a metabolic adaptation to augment *fumC* expression, an enzyme that degrades fumarate. Since fumarate is a negative regulator of glycolysis, increased *fumC* expression promoted glycolysis, providing permissive conditions for bacterial survival [68]. This study indicates that *S. aureus* can actively induce metabolic pathways that are beneficial for bacterial persistence in host cells.

Role of Glycolysis in PMN Antimicrobial Activity

Neutrophils rely on glycolysis for energy production since they have fewer mitochondria, and as such, inhibiting mitochondrial respiration does not impact ATP production [69–72]. In contrast, blocking glycolysis with 2-DG impairs PMN phagocytosis and ROS production, and thereby bacterial killing, highlighting the importance of glycolysis for their antimicrobial properties [73, 74]. The glycolytic intermediate glucose-6-phosphate fuels the PPP to generate NADPH, which is used by NADPH oxidase for ROS production in activated PMNs [75]. Pyruvate kinase M2 (PKM2), one of the rate-limiting glycolytic enzymes that converts phosphoenolpyruvate to pyruvate, was shown to regulate PMN ROS production without affecting phagocytosis during *S. aureus* infection [76]. Upon activation by the endogenous regulator fructose-1,6-bisphosphate, PKM2 forms a tetramer that promotes high glycolytic activity that is essential for ROS production. However, in the absence of an activator, PKM2 assumes a monomeric or dimeric form that

localizes to the nucleus and regulates transcription factor activation, including HIF-1a- and signal transduction and activator of transcription proteins [77]. NADPH oxidase activation requires protein kinase C-dependent phosphorylation, which is induced by diacylglycerol (DAG) [78]. DAG is synthesized from two independent pathways, namely, (1) phosphatidylinositol 4,5-bisphosphate hydrolysis by phospholipase C and (2) de novo synthesis from the glycolytic intermediate dihydroxyacetone phosphate [79]. While DAG produced from both pathways contributes to ROS production by PMNs, PKM2 regulates ROS release in activated PMNs by controlling de novo DAG synthesis. PKM2 was important for bacterial containment in *S. aureus* peritonitis and cutaneous infection models, where PKM2-deficient mice displayed higher bacterial burden and delayed wound healing compared to WT animals. An earlier study reported defective PMN pyruvate kinase activity in a patient experiencing recurrent *S. aureus* infections [80] and together, these studies demonstrate that glycolytic intermediates and the PPP are critical for PMN ROS production and subsequent antimicrobial activity.

Metabolism Shapes Myeloid-Derived Suppressor Cells during *S. aureus* Infection

Myeloid-derived suppressor cells (MDSCs) are immature myeloid cells that possess anti-inflammatory activity and are associated with various pathological conditions such as infection, cancer, and autoimmune diseases [81–84]. MDSCs are characterized into two major subsets, namely, granulocytic (G-MDSCs) or monocytic (M-MDSCs), based on their similarities with PMNs and monocytes, respectively [85]. In general, G-MDSCs exert their suppressive activity through ROS and arginase 1 (Arg-1), whereas M-MDSCs use iNOS and anti-inflammatory cytokines such as IL-10 and TGF-β to inhibit T cell responses [86–88]. G-MDSCs play a pathological role in mouse models of *S. aureus* infection by inhibiting proinflammatory responses, leading to increased bacterial survival [21, 89–93] and G-MDSCs have also been shown to accumulate at the site of prosthetic joint infection (PJI) in humans [94]. A recent study reported that glycolysis was important for driving G-MDSC maturation into PMNs in a mouse model of systemic *S. aureus* infection, although this had no effect on bacterial burden [95]. However, these observations were made in MDSCs distant from the infection site, which may affect their properties since MDSCs were not in direct contact with bacteria. T cells are important for generating protective immune responses to *S. aureus* [96, 97], which can be inhibited by MDSCs [91]. T cell proliferation during *S. aureus* infection was reported to be inhibited by lactate released from MDSCs, which prevented NAD^+ regeneration and glycolysis that is a hallmark of activated T cells [98]. However, the effects of lactate during *S. aureus* infection are likely influenced by the tissue niche and growth state of bacteria since our laboratory has shown that lactate production by host cells had no effect on *S. aureus* biofilm infection, but rather *S. aureus*-derived lactate was a potent driver of G-MDSC anti-inflammatory activity by eliciting IL-10 production [99]. Therefore, additional studies are needed to better understand the G-MDSC-pathogen metabolic dynamic in distinct niches of *S. aureus* infection.

Lactate Released from *S. aureus* Biofilm Programs G-MDSC and MΦ Anti-Inflammatory Activity

S. aureus can modulate the host immune response by secreting metabolites in the infection milieu. As mentioned earlier, our laboratory recently showed that lactate produced by *S. aureus* biofilm promoted IL-10 production by MΦs and G-MDSCs [99]. We leveraged *S. aureus* lactate dehydrogenase mutants and a monocarboxylate transporter 1 (MCT1) inhibitor to demonstrate that biofilm-derived lactate was transported into G-MDSCs and MΦs to inhibit histone deacetylase 11 (HDAC11). Under normal conditions, HDAC11 interacts with HDAC6 to inhibit IL-10 transcription [100]; however, during *S. aureus* biofilm infection, bacterial-derived lactate blocks this interaction to promote IL-10 transcription in G-MDSCs and MΦs (Fig. 2b). *S. aureus* lactate dehydrogenase mutants displayed less survival than WT bacteria with a concomitant decrease in anti-inflammatory G-MDSCs and increased PMN and monocyte infiltrates. This phenotype was shown to be IL-10-dependent, confirming the action of lactate on promoting IL-10 production, which is important for polarizing the anti-inflammatory biofilm milieu [21]. However, ChIP-seq demonstrated that *S. aureus* lactate also affected the expression of additional genes, revealing a larger footprint of biofilm-derived lactate on host responses. D-lactate levels were elevated in the synovial fluid of PJI patients compared to individuals with aseptic joint revision [99] and lactate has been shown to be a sensitive marker for diagnosing PJI in humans [101–103], supporting the importance of

bacterial lactate metabolism in the setting of biofilm infection.

Host lactate also plays a role in shaping leukocyte responses during various pathological conditions such as infection and cancer [104–106]. In LPS-activated MΦs, lactate was shown to suppress proinflammatory cytokine production via G protein-coupled receptor 81 (GPR81)-mediated signaling [107]. Lactate also impaired TLR4-mediated inflammasome activation through GPR81 signaling in MΦs and monocytes, and lactate administration attenuated inflammation and disease severity in models of acute pancreatitis and liver injury [108]. Lactate has been shown to modify mitochondrial antiviral-signaling protein to prevent its mitochondrial localization and interaction with RIG-1, thereby attenuating type I interferon production [109]. These data suggest that host lactate can target multiple mechanisms to regulate leukocyte proinflammatory activity.

Collectively, these studies highlight the importance of glycolysis, lactate, and glycolytic intermediates produced by both the host and *S. aureus* in shaping immune responses. However, it is clear that the effects of host versus pathogen metabolism are context-dependent. On the one hand, glycolysis in keratinocytes and PMNs drives proinflammatory responses to kill planktonic *S. aureus*, whereas in biofilm, bacterial-derived lactate is a major signal that leads to epigenetic remodeling in G-MDSCs and MΦs to promote IL-10 production that ensures bacterial persistence. Although the importance of glycolysis has been studied in keratinocytes, epithelial cells, and PMNs during *S. aureus* infection, less information is available in other key cell types involved in *S. aureus* infection, such as MΦs, G-MDSCs, and T cells. In addition, how host glycolysis is altered during biofilm infection requires further investigation as most of our current knowledge is derived from planktonic infections. Another enigma that remains to be understood relates to the dichotomy in infectious outcomes between *S. aureus* planktonic versus biofilm infection when proinflammatory cytokine expression is a hallmark of both. In the case of planktonic *S. aureus* infection, this response is typically linked to bacterial clearance [110, 111]. However, proinflammatory mediators are also produced during biofilm infection and although they have been shown to play a role in preventing *S. aureus* outgrowth [112–115], infection persists. Although seemingly counterintuitive, this may be explained, in part, by the fact that proinflammatory mediators are important for G-MDSC expansion and suppressive activity [85, 116], and *S. aureus* biofilm infections are typified by a large G-MDSC infiltrate [90, 92, 94, 117–119]. In addition, the large bacterial biomass associated with biofilm elicits continued proinflammatory mediator release, which would perpetuate the G-MDSC inhibitory loop. Another contributing factor is the induction of a robust IL-10 response during *S. aureus* biofilm infection that promotes infection persistence [93, 99]. Therefore, a better understanding of how leukocytes are seemingly refractory to the antimicrobial actions of proinflammatory cytokine stimulation during *S. aureus* biofilm infection may help to "flip the switch" to reprogram cells for enhanced bactericidal activity [120].

TCA Cycle Activity Influences Leukocyte Inflammatory Properties

Toll-like receptor ligands such as LPS induce glycolytic metabolism in proinflammatory MΦs, leading to break points in the TCA cycle [121]. This is typified by accumulation of the TCA cycle intermediates α-ketoglutarate, fumarate, itaconate, succinate, and citrate, which can modulate the immune response [122]. For example, succinate and α-ketoglutarate inhibit prolyl hydroxylases, proteins that bind the transcription factor HIF-1a, and promote its degradation under normoxia [123, 124]. However, during aerobic glycolysis, HIF-1a stabilization promotes the transcription of glycolytic genes, which acts in a positive feedback loop to augment glycolysis and IL-1β production in MΦs [63]. Succinate dehydrogenase (SDH), also known as mitochondrial complex II, is a TCA cycle enzyme that catalyzes the conversion of succinate to fumarate and is a key player in regulating MΦ proinflammatory gene expression following LPS stimulation by boosting succinate oxidation and mitochondrial ROS [125]. Inhibition of SDH reduced IL-1β concomitant with increased IL-10 and IL-1RA expression, thereby blocking the proinflammatory phenotype of LPS-induced MΦs. Citrate, another TCA cycle intermediate, is exported from mitochondria to the cytoplasm via citrate carrier where it promotes NO and prostaglandin production by MΦs in response to IFN-γ and TNF [126].

The TCA cycle break that ensues during glycolysis effectively reduces OxPhos substrates, highlighting how metabolic diversion can augment glycolysis to provide intermediates for the numerous biosynthetic reactions that are a hallmark of proinflammatory MΦs and PMNs. However, it is important to note that the TCA cycle is not completely inactive when cells are highly glycolytic; anaplerotic reactions can occur from amino acids feeding into various points in the TCA cycle, most notably glutamine conversion to α-ketoglutarate. This

highlights metabolic plasticity and that pathways are in a constant state of flux, adapting to the energetic requirements of the leukocyte and integrating exogenous signals from the infectious milieu to tailor immune cell polarization.

Itaconate Supports *S. aureus* Persistence

Itaconate, a metabolite derived from the TCA cycle intermediate cis-aconitate by the enzyme IRG1, is a competitive inhibitor of SDH due to its structural similarity with succinate. IRG1 deletion in MΦs resulted in unchecked SDH activity and heightened proinflammatory responses concomitant with increased HIF-1a activation [127]. The IRG1-SDH axis also plays a central role in regulating immune tolerance and trained immunity during LPS-induced sepsis [128]. 4-Octyl itaconate, an itaconate derivative, inhibited glycolysis in LPS-activated MΦs by targeting glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and thereby suppressed LPS-induced metabolic changes required for IL-1β and iNOS expression [129]. Further, Qin et al. [130] revealed that the glycolytic enzymes fructose-bisphosphate aldolase A (ALDOA), GAPDH, and lactate dehydrogenase A (LDHA) are modified by itaconate to inhibit glycolysis and promote MΦ anti-inflammatory activity [130]. Together, these studies suggest that itaconate utilizes multiple mechanisms to modulate MΦ activation.

In terms of *S. aureus*, itaconate was elevated in the bronchoalveolar lavage fluid during acute lung infection, concomitant with IRG1 induction [131]. Itaconate inhibited *S. aureus* aldolase activity, effectively blocking glycolysis, a preferred metabolic pathway for the bacterium during infection. This induced *S. aureus* metabolic adaptation, typified by increased extracellular polysaccharide production, reduced ribosomal activity, and decreased virulence factor expression, consistent with a transition to biofilm growth. This is supported by the finding that *S. aureus* acquired antibiotic tolerance in the presence of host-derived itaconate, which is a hallmark of biofilm formation. Like *S. aureus*, *P. aeruginosa* also exploits host itaconate during lung infection where it degrades and metabolizes itaconate to produce energy [132]. Although these studies reflect the ability of diverse bacterial species to utilize host-derived itaconate to their advantage, itaconate also influences leukocyte activity to prevent *S. aureus* clearance. For example, bacterial burden was significantly lower in *Irg1*$^{-/-}$ compared to WT mice in a *S. aureus* pneumonia model. This was attributed to itaconate production by PMNs, which inhibited their glycolytic activity and ROS production to impair bacterial killing [133] (Fig. 3a). In contrast to these anti-inflammatory effects, itaconate benefits the host during *Mycobacterium tuberculosis* (Mtb) and *Klebsiella pneumonia* infection by controlling excessive inflammation and limiting tissue damage [134, 135]. Likewise, itaconate can exert direct antibacterial activity by inhibiting the glyoxylate cycle in *Pseudomonas indigofera, Salmonella enterica*, and Mtb [136–139]. Therefore, the effector functions of itaconate during infection are context-dependent given its antibacterial properties and ability to induce adaptations in bacteria and/or modulate leukocyte activity.

Fumarate Mediates Trained Immunity to *S. aureus* Infection

Fumarate, another TCA cycle intermediate, participates in the induction of trained immunity in monocytes [140]. Specifically, fumarate inhibits the KDM5 family of histone demethylases, leading to enhanced histone H3 lysine 4 methylation to regulate proinflammatory cytokine gene expression [140]. Dimethyl fumarate (DMF), a fumarate derivative, succinylates the catalytic cysteine residue of GAPDH to suppress glycolysis, effectively mediating anti-inflammatory effects in myeloid and lymphoid cells [141]. Moreover, both DMF and fumarate modify gasdermin D to block its interaction with caspase-1, which is required for gasdermin D cleavage and oligomerization to induce cell death [142]. DMF treatment revealed beneficial effects in mouse models of LPS shock and experimental autoimmune encephalitis by its ability to inhibit gasdermin D [142].

While these studies suggest that fumarate can control both pro- and anti-inflammatory activity, fumarate was found to induce trained immunity and protect against secondary infection in a model of *S. aureus* cutaneous infection [68] (Fig. 3b). However, *S. aureus* SCVs that accumulate during infection upregulate fumarate hydratase (*fumC*) that converts fumarate to malate, effectively reducing fumarate levels in the infected skin. This decrease in fumarate allows SCVs to circumvent trained immunity, which prevents protection against subsequent bacterial challenge. Increased *fumC* expression has also been observed in *S. aureus* clinical isolates from cystic fibrosis and atopic dermatitis subjects, suggesting that fumarate is an important target for *S. aureus* pathogenesis [143, 144] (Fig. 3b).

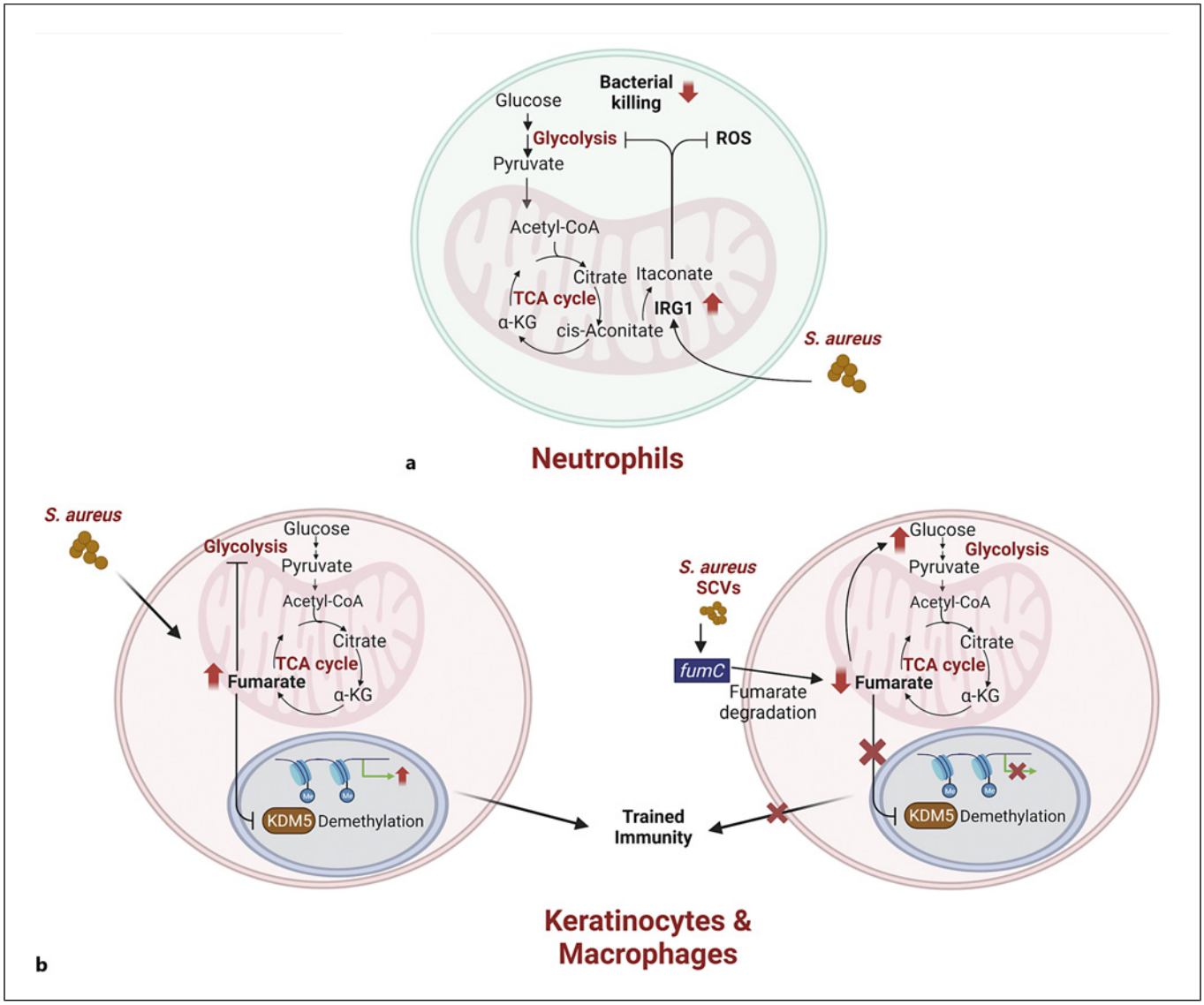

Fig. 3. Effect of TCA cycle intermediates during *S. aureus* infection. **a** *S. aureus* infection induces immune responsive gene 1 (IRG1)-mediated itaconate production in neutrophils. Itaconate inhibits ROS and glycolysis to attenuate neutrophil anti-bacterial activity. **b** During *S. aureus* infection, fumarate accumulation inhibits histone demethylase KDM5 to augment proinflammatory gene expression. *S. aureus* fumarate hydratase (*fumC*) is increased in SCVs that arise during infection, which degrades fumarate to promote glycolysis and impair proinflammatory gene expression through epigenetic modifications (figure created using BioRender). ROS, reactive oxygen species; α-KG, alpha-ketoglutarate; KDM5, lysine demethylase 5.

Recently, fumarate, along with itaconate and argino-succinate, was found to accumulate in LPS-activated MΦs to mediate protein succincylation [145]. Fumarate hydratase (FH) inhibition or genetic deletion increased intracellular fumarate levels resulting in TCA cycle re-wiring, suppression of mitochondrial respiration, and increased membrane potential. Mitochondrial dysfunction following FH inhibition led to mitochondrial RNA release, activating the intracellular RNA sensors Toll-like receptor 7 (TLR7), melanoma differentiation-associated protein 5 (MDA5), and retinoic acid-inducible gene I (RIG-I) to induce interferon-β production. Similar findings were reported in another study, where FH loss resulted in altered mitochondrial morphology and mitochondrial DNA release into the cytosol that was sensed by cyclic GMP-AMP synthase stimulator of interferon genes to induce type I interferon production [146]. Together, these results suggest that fumarate metabolism

plays an important role in regulating MΦ activation. However, additional studies are needed to explore how this pathway influences *S. aureus* infection.

OxPhos Activity Exerts Differential Effects on Leukocyte Responses to *S. aureus*

NADH from the TCA cycle enters OxPhos to transfer electrons in the ETC, where ATP is generated by ATP synthase using electron flow. In MΦs, LPS stimulation arrests ETC-dependent ATP production and succinate oxidation increases mitochondrial transmembrane potential, leading to reverse electron transport-mediated ROS synthesis [125]. This ROS can further activate the inflammasome or exert anti-microbial activity. In PMNs, mitochondrial ROS and NET production were shown to be dependent on ETC complexes during *S. aureus* infection [147]. Specifically, PMN bactericidal activity was attenuated when mitochondrial ROS was inhibited using either the complex III inhibitor antimycin A or the antioxidant mitoTEMPO. On the other hand, anti-inflammatory MΦs exhibit an OxPhos bias [148]. For example, we have shown that *S. aureus* biofilm skews monocytes/MΦs toward OxPhos over glycolysis in a mouse model of *S. aureus* PJI [118] (Fig. 4). Inhibiting oxidative metabolism in monocytes/MΦs using targeted nanoparticles containing the ATP synthase inhibitor oligomycin reprogrammed cellular metabolism in vivo, leading to heightened proinflammatory cytokine production and significant reductions in *S. aureus* burden. Further, monocyte/MΦ metabolic reprogramming in combination with systemic antibiotics effectively cleared an established biofilm infection that represents the most challenging treatment scenario [118]. This study also showed that monocyte/MΦ metabolic reprogramming influences G-MDSC metabolism, emphasizing the importance of metabolic crosstalk, not only between different leukocyte populations but also *S. aureus*. Based on these findings, it is evident that the effects of OxPhos during *S. aureus* infection are cell- and context-dependent. In addition, the growth phase of bacteria also likely plays a role, whether organisms are in a planktonic or biofilm state.

Significance of Lipid Metabolism in Host Immunity to *S. aureus* and Other Bacterial Pathogens

Both FAO and FAS are important for regulating leukocyte function (Fig. 5). For example, fatty acid uptake and triglyceride synthesis were increased in LPS-activated proinflammatory MΦs, whereas lipolysis was repressed [149]. In addition, inhibition of MΦ FAS decreased inflammation and MΦ recruitment in vivo [150]. This study showed that FAS was necessary for Rho GTPase trafficking and membrane remodeling to facilitate MΦ inflammatory signaling. In contrast, initial reports with etomoxir, an inhibitor of mitochondrial carnitine palmitoyl-transferase 1 (Cpt1), suggested that FAO was important for anti-inflammatory MΦ polarization in response to IL-4 [151]. However, subsequent studies using Cpt1a-deficient MΦs have shown that the anti-inflammatory effects of etomoxir are mediated through altered CoA levels and not FAO [152]. Again, this highlights the complexity of metabolism and the need for cleaner systems such as genetic deletion rather than relying on inhibitors alone to understand the importance of metabolism in shaping immune responses.

The role of FAO and FAS has been studied in various infections, such as Mtb and *S. enterica* [153–156]; however, whether these metabolic pathways influence *S. aureus* infection remains relatively unknown. While some omega-3 fatty acids have been shown to be antimicrobial and inhibit biofilm formation [157, 158], their effects on immune responses to *S. aureus* remain to be defined. In a mouse model of *S. aureus* sepsis, animals fed a polyunsaturated fatty acid diet displayed increased survival and PMN abundance compared to mice receiving a saturated fatty acid diet, although the exact role of polyunsaturated fatty acids in this setting is unknown [159]. Omega-3 fatty acids, either alone or in combination with vancomycin, reduced bacterial burden in the bone and implant concomitant with less TNF and IL-6 production in a rat model of *S. aureus* implant-associated osteomyelitis [160] (Fig. 5). Recently, a Cpt1a variant with reduced enzymatic activity has been identified in humans and linked to susceptibility to various infections, including *S. aureus* [161]. Cpt1a inhibition with etomoxir increased bacterial burden in a mouse model of *S. aureus* pneumonia (Fig. 5) and impaired PMN recruitment and fatty acid-mediated mitochondrial bioenergetics during *Acinetobacter baumannii* infection. In addition, FAO was found to be critical for amplifying chemotactic signals and PMN migration using both Cpt1a inhibitors and fatty acid supplementation [161]. Collectively, these findings raise the possibility that dietary fatty acids may influence PMN trafficking and potentially provide some benefit during *S. aureus* infection. However, as with any metabolic node, the net flux through other pathways, not to mention the metabolic status of bacteria, will likely dictate efficacy.

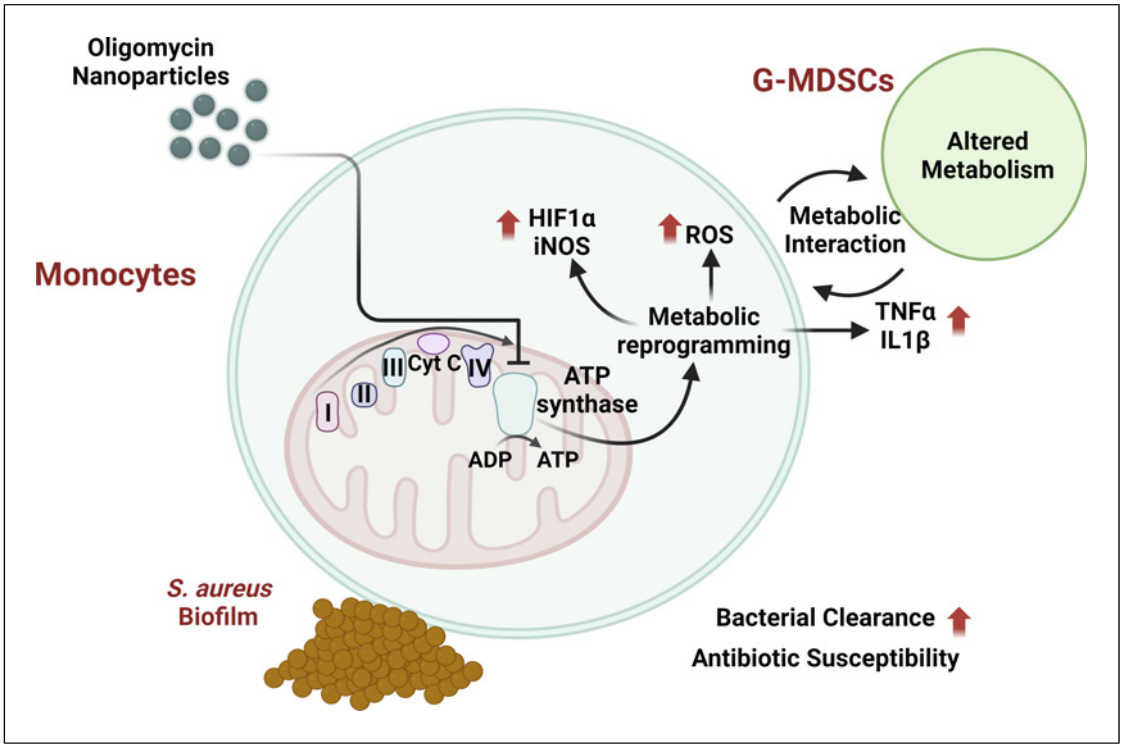

Fig. 4. OxPhos-mediated metabolic reprogramming during *S. aureus* biofilm infection. During *S. aureus* biofilm infection, monocyte and MΦ metabolism is reprogrammed to utilize oxidative phosphorylation (OxPhos) to promote anti-inflammatory activity and biofilm persistence. Inhibition of ATP synthase with oligomycin-loaded nanoparticles reprograms monocyte metabolism to promote ROS production and proinflammatory gene expression. This change in monocyte metabolism also alters G-MDSC metabolism. These metabolic alterations decreased bacterial burden and increased *S. aureus* susceptibility to systemic antibiotics to mitigate established biofilm infection (figure created using BioRender). G-MDSCs, granulocytic-myeloid-derived suppressor cells; ROS, reactive oxygen species; iNOS, inducible nitric oxide synthase; HIF-1a, hypoxia-inducible factor 1a.

Amino Acid Metabolism Shapes Leukocyte Effector Functions

Amino acid metabolism is important for both innate and adaptive immune cells [162, 163]. Glutamine flux into the TCA cycle is associated with anti-inflammatory MΦ polarization following IL-4 exposure, while the aspartate-arginosuccinate shunt is involved in proinflammatory MΦ programming by LPS [164]. Both Arg-1 and iNOS utilize arginine as a substrate to produce ornithine and nitric oxide, respectively. While iNOS is induced in proinflammatory MΦs to control bacterial growth, Arg-1 is associated with MΦ anti-inflammatory activity to promote fibrosis and wound healing via the action of polyamines that are synthesized from ornithine [51]. Polyamines are abundant in *S. aureus* abscesses and interfering with polyamine synthesis using difluoromethylornithine (DFMO), a potent inhibitor of ornithine decarboxylase, resulted in increased bacterial burden and decreased survival in mouse models of *S. aureus* sepsis and skin abscesses [165]. Additionally, skin lesions in DFMO-treated mice exhibited limited fibrosis, revealing an essential role for polyamines in wound healing. In a mouse model of sepsis, competitive inhibition of arginase with S-(2-boronoethyl)-L-cysteine protected against *S. aureus* infection, resulting in increased survival [166]. However, no phenotypes were observed when Arg-1 was deleted in myeloid cells using Arg-$1^{fl/fl}$ Tie-2^{Cre} mice in either biofilm models of *S. aureus* PJI or catheter-associated infection, whereas effects were detected in abscesses that have characteristics of planktonic growth [167]. Together, these results demonstrate that the role of Arg-1 and subsequent polyamine production in myeloid cells in response to *S. aureus* is context-dependent.

Differential preferences for iNOS and Arg-1 activity also typify MDSC subtypes, which are utilized by M-MDSCs and G-MDSCs, respectively, to mediate immunosuppression [168, 169]. Another amino acid that

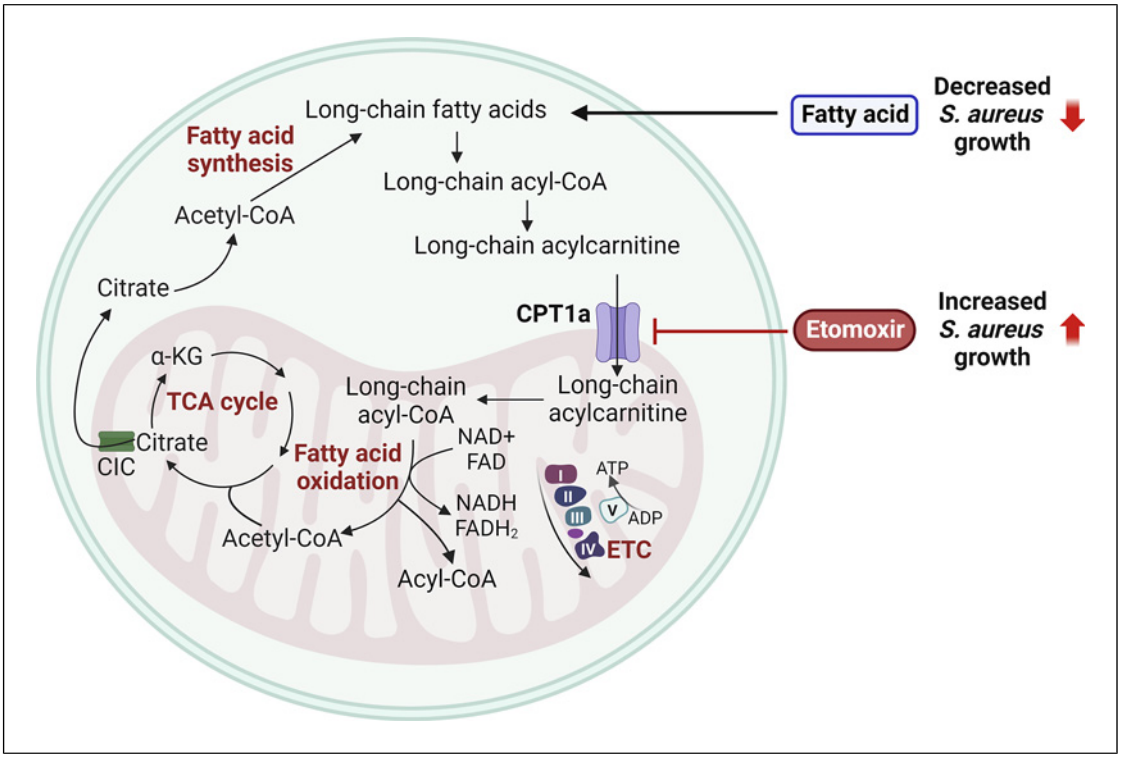

Fig. 5. Role of fatty acids in *S. aureus* infection. Long-chain fatty acids are imported into mitochondria through CPT1a and are oxidized to form acetyl-CoA, acyl-CoA, NADH, and $FADH_2$. NADH and $FADH_2$ provide electrons for the electron transport chain (ETC), while acetyl-CoA enters the TCA cycle. Citrate from the TCA cycle is transported to the cytosol, where it is converted to acetyl-CoA to drive fatty acid synthesis. Exogenous fatty acids can augment neutrophil antibacterial activity. Etomoxir inhibition of Cpt1a-dependent FAO impairs *S. aureus* killing resulting in increased infectious burden (figure created using BioRender). α-KG, alpha-ketoglutarate; CIC, citrate/isocitrate carrier; CPT1a, carnitine palmitoyltransferase 1a.

MDSCs utilize to inhibit T cell activation is tryptophan. Tryptophan is an essential amino acid and substrate of indoleamine 2,3-dioxygenase 1 (IDO1), which catalyzes tryptophan catabolism [170]. IDO1 expression by MDSCs reduces local tryptophan concentrations, thereby suppressing T cells that require tryptophan for proliferation [171]. Tryptophan catabolism also produces the immunoregulatory molecules kynurenine and serotonin, which have been reported to affect leukocyte function during infection. For example, human MΦs and dendritic cells produce kynurenine in an IDO1-dependent manner in response to *Listeria monocytogenes*, where kynurenine and other tryptophan catabolites promoted antimicrobial activity [172]. In addition, accumulation of tryptophan metabolites, such as 3-hydroxy-DL-kynurenine and alpha-picolinic acid, protected vascular allografts against methicillin-resistant *S. aureus*, *S. epidermidis*, *E. coli*, and *P. aeruginosa* [173, 174]. Collectively, these studies indicate that various products of amino acid metabolism can influence the pro- versus anti-inflammatory attributes of leukocyte populations that shape the infection milieu. This is likely important in tissues where glucose becomes limiting, such as chronic infections that are poorly perfused, where both the host and bacteria must metabolically adapt to utilize different carbon sources, such as amino acids resulting from protein degradation for de novo energy production via the pathways described above.

Potential Metabolic Targets to Modulate *S. aureus* Infection

Given the link between bacterial infections and metabolic diseases such as diabetes [175, 176], the potential efficacy of metabolic drugs to control infection and associated pathology has received increasing attention. Diabetic individuals are at increased risk for severe *S.*

aureus infections, primarily in the skin [177–179] that can progress to bacteremia [180]. This is also observed in mouse models, where *S. aureus* skin infection was more severe in diabetic mice and correlated with diminished ROS production, PMN activation, and impaired humoral responses compared to nondiabetic mice [181, 182]. *S. aureus* burden and infection severity were also significantly increased in abscesses and osteomyelitis following streptozotocin-induced hyperglycemia [183, 184]. Collectively, these findings support the fact that *S. aureus* thrives in a glucose-rich environment, which is known to induce a wide array of virulence factors that can augment host tissue damage and leukocyte dysfunction [183, 185, 186].

Targeting glycolytic enzymes such as HK, PFKFB3, and pyruvate kinase have shown benefit in attenuating inflammation during immune-mediated inflammatory diseases, such as experimental autoimmune encephalomyelitis and rheumatoid arthritis [187–191]. Similarly, GLUT1, HK, and phosphofructokinase are promising targets for cancer treatment [192]. These findings support the importance of glycolytic flux during chronic diseases, and it would be interesting to explore these drugs in the context of *S. aureus* infections. Metformin, a compound widely used in diabetes to reduce glucose levels, was shown to inhibit Mtb growth in MΦs and synergize with conventional antituberculosis chemotherapy to control Mtb infection in mice [193]. This was further evaluated in human cohorts, where metformin improved clinical outcome and decreased disease severity. A recent study reported that diabetic patients taking metformin experienced significantly less mortality following *S. aureus* bacteremia compared to control groups [194], suggesting a beneficial role for metabolic intervention and disease outcome, although additional studies are needed. Other notable drugs that control metabolism include methotrexate, rapamycin, and DMF that target dihydrofolate reductase, mammalian target of rapamycin (mTOR), and Kelch-like ECH-associated protein 1 (KEAP1), respectively [195–197]. However, there are currently no metabolic compounds approved or in clinical trials for *S. aureus* infection. Given the importance of various metabolic pathways in altering immune responses to *S. aureus*, drugs that selectively target key pathways, from either the host or bacterial perspectives, would be interesting to explore. As discussed previously, using oligomycin or fatty acids as adjunct therapy with antibiotics may improve treatment outcomes compared to antibiotics alone [118, 195]. An added advantage of utilizing drugs that target metabolic pathways is a lower chance of bacteria-developing resistance [198] and their well-documented safety record. This remains an area for future exploration in the context of *S. aureus*, particularly considering the myriad of tissues that the organism can exploit in humans and associated metabolic diversity in each niche.

Conclusions

Unlike many other bacterial infections that exhibit tropism for a particular tissue, *S. aureus* can adapt and survive within multiple cell types and locations in the body [199]. Our understanding of how *S. aureus* and leukocyte metabolism shapes infectious outcomes and the consequences of host-pathogen metabolic crosstalk has been expanding in recent years [27, 120, 200, 201]. Nevertheless, specific influences of diverse clinical isolates, infection sites, and planktonic versus biofilm modes of growth on leukocyte metabolism remain relatively unexplored. The ability of *S. aureus* to adapt to different metabolic intermediates during infection (i.e., itaconate) or actively secrete metabolites to thwart productive antibacterial immune responses (i.e., lactate) highlights the extensive metabolic flexibility of the organism. Advancements in the field using techniques that measure metabolism at the single-cell level, such as single-cell energetic metabolism by profiling translation inhibition (SCENITH) and MetFlow [202, 203], will improve our understanding of metabolic interactions between multiple leukocyte populations and at the tissue level. However, these methods measure metabolism at the protein, not the metabolite level, which requires conventional mass spectrometry approaches. The development of sensors that can monitor metabolites is expanding [204, 205] and real-time monitoring and spatiotemporal organization of metabolites during disease conditions will extend our understanding of metabolite shuttling and subsequent cellular responses. Recently, a correlative imaging approach, metaFISH [206], was developed by combining matrix-assisted laser desorption ionization-mass spectrometry imaging with fluorescence in situ hybridization, allowing the spatial distribution of metabolites to be identified in a tissue section. This is a significant advance to reveal the complex relationship of metabolites to host defense, cell-cell communication, and nutritional exchange during host-pathogen interactions. Integrating data from various animal models with findings from human samples from both the *S.*

aureus and leukocyte perspectives will be essential to gain a better understanding of the metabolic complexity of infectious niches and developing novel therapeutic approaches to combat this important human pathogen.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This work was supported by 3P01AI083211 Project 4 and R21 AI174381-01A1 to Tammy Kielian.

Author Contributions

Prabhakar Arumugam wrote the initial draft of the manuscript that was edited by Tammy Kielian. Prabhakar Arumugam created the figures using BioRender.

References

1 Ryu S, Song PI, Seo CH, Cheong H, Park Y. Colonization and infection of the skin by S. aureus: immune system evasion and the response to cationic antimicrobial peptides. Int J Mol Sci. 2014;15(5):8753–72.
2 Sakr A, Brégeon F, Mège JL, Rolain JM, Blin O. Staphylococcus aureus nasal colonization: an update on mechanisms, epidemiology, risk factors, and subsequent infections. Front Microbiol. 2018;9:2419.
3 Lowy FD. Staphylococcus aureus infections. N Engl J Med. 1998;339(8):520–32.
4 Brown AF, Leech JM, Rogers TR, McLoughlin RM. Staphylococcus aureus colonization: modulation of host immune response and impact on human vaccine design. Front Immunol. 2014;4:507.
5 Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler VG Jr. Staphylococcus aureus infections: epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev. 2015;28(3):603–61.
6 Troeman DPR, Hazard D, Timbermont L, Malhotra-Kumar S, van Werkhoven CH, Wolkewitz M, et al. Postoperative Staphylococcus aureus infections in patients with and without preoperative colonization. JAMA Netw Open. 2023;6(10):e2339793.
7 Stryjewski ME, Chambers HF. Skin and soft-tissue infections caused by community-acquired methicillin-resistant Staphylococcus aureus. Clin Infect Dis. 2008;46(Suppl 5):S368–77.
8 Popov LM, Marceau CD, Starkl PM, Lumb JH, Shah J, Guerrera D, et al. The adherens junctions control susceptibility to Staphylococcus aureus α-toxin. Proc Natl Acad Sci USA. 2015;112(46):14337–42.
9 Spaan AN, van Strijp JAG, Torres VJ. Leukocidins: staphylococcal bi-component pore-forming toxins find their receptors. Nat Rev Microbiol. 2017;15(7):435–47.
10 Cheung GYC, Bae JS, Otto M. Pathogenicity and virulence of Staphylococcus aureus. Virulence. 2021;12(1):547–69.
11 Marciano BE, Spalding C, Fitzgerald A, Mann D, Brown T, Osgood S, et al. Common severe infections in chronic granulomatous disease. Clin Infect Dis. 2015;60(8):1176–83.
12 Thammavongsa V, Kim HK, Missiakas D, Schneewind O. Staphylococcal manipulation of host immune responses. Nat Rev Microbiol. 2015;13(9):529–43.
13 Ko YP, Kuipers A, Freitag CM, Jongerius I, Medina E, van Rooijen WJ, et al. Phagocytosis escape by a Staphylococcus aureus protein that connects complement and coagulation proteins at the bacterial surface. PLoS Pathog. 2013;9(12):e1003816.
14 McGuinness WA, Kobayashi SD, DeLeo FR. Evasion of neutrophil killing by Staphylococcus aureus. Pathogens. 2016;5(1):32.
15 Pidwill GR, Gibson JF, Cole J, Renshaw SA, Foster SJ. The role of macrophages in Staphylococcus aureus infection. Front Immunol. 2020;11:620339.
16 Spaan AN, Vrieling M, Wallet P, Badiou C, Reyes-Robles T, Ohneck EA, et al. The staphylococcal toxins gamma-haemolysin AB and CB differentially target phagocytes by employing specific chemokine receptors. Nat Commun. 2014;5:5438.
17 Bhattacharya M, Berends ETM, Chan R, Schwab E, Roy S, Sen CK, et al. Staphylococcus aureus biofilms release leukocidins to elicit extracellular trap formation and evade neutrophil-mediated killing. Proc Natl Acad Sci USA. 2018;115(28):7416–21.
18 Schwan WR. Staphylococcus aureus toxins: armaments for a significant pathogen. Toxins. 2019;11(8):457.
19 Thurlow LR, Hanke ML, Fritz T, Angle A, Aldrich A, Williams SH, et al. Staphylococcus aureus biofilms prevent macrophage phagocytosis and attenuate inflammation in vivo. J Immunol. 2011;186(11):6585–96.
20 Hanke ML, Heim CE, Angle A, Sanderson SD, Kielian T. Targeting macrophage activation for the prevention and treatment of Staphylococcus aureus biofilm infections. J Immunol. 2013;190(5):2159–68.
21 Heim CE, Vidlak D, Kielian T. Interleukin-10 production by myeloid-derived suppressor cells contributes to bacterial persistence during Staphylococcus aureus orthopedic biofilm infection. J Leukoc Biol. 2015;98(6):1003–13.
22 Gries CM, Kielian T. Staphylococcal biofilms and immune polarization during prosthetic joint infection. J Am Acad Orthop Surg. 2017;25(Suppl 1):S20–4.
23 Alboslemy T, Yu B, Rogers T, Kim MH. Staphylococcus aureus biofilm-conditioned medium impairs macrophage-mediated antibiofilm immune response by upregulating KLF2 expression. Infect Immun. 2019;87(4):e00643-18.
24 Jansen KU, Girgenti DQ, Scully IL, Anderson AS. Vaccine review: "Staphyloccocus aureus vaccines: problems and prospects". Vaccine. 2013;31(25):2723–30.
25 Clegg J, Soldaini E, McLoughlin RM, Rittenhouse S, Bagnoli F, Phogat S. Staphylococcus aureus vaccine research and development: the past, present and future, including novel therapeutic strategies. Front Immunol. 2021;12:705360.
26 Miller LS, Fowler VG, Shukla SK, Rose WE, Proctor RA. Development of a vaccine against Staphylococcus aureus invasive infections: evidence based on human immunity, genetics and bacterial evasion mechanisms. FEMS Microbiol Rev. 2020;44(1):123–53.
27 Wong Fok Lung T, Chan LC, Prince A, Yeaman MR, Archer NK, Aman MJ, et al. Staphylococcus aureus adaptive evolution: recent insights on how immune evasion, immunometabolic subversion and host genetics impact vaccine development. Front Cell Infect Microbiol. 2022;12:1060810.
28 Teymournejad O, Li Z, Beesetty P, Yang C, Montgomery CP. Toxin expression during Staphylococcus aureus infection imprints host immunity to inhibit vaccine efficacy. NPJ Vaccin. 2023;8(1):3.
29 Miller LG, Eells SJ, David MZ, Ortiz N, Taylor AR, Kumar N, et al. Staphylococcus aureus skin infection recurrences among household members: an examination of host, behavioral, and pathogen-level predictors. Clin Infect Dis. 2015;60(5):753–63.

30 Vella V, Galgani I, Polito L, Arora AK, Creech CB, David MZ, et al. Staphylococcus aureus skin and soft tissue infection recurrence rates in outpatients: a retrospective database study at 3 us medical centers. Clin Infect Dis. 2021;73(5):e1045–53.
31 Tsai CM, Caldera JR, Hajam IA, Chiang AWT, Tsai CH, Li H, et al. Non-protective immune imprint underlies failure of Staphylococcus aureus IsdB vaccine. Cell Host Microbe. 2022;30(8):1163–72.e6.
32 Tam K, Lacey KA, Devlin JC, Coffre M, Sommerfield A, Chan R, et al. Targeting leukocidin-mediated immune evasion protects mice from Staphylococcus aureus bacteremia. J Exp Med. 2020;217(9):217.
33 Buckley PT, Chan R, Fernandez J, Luo J, Lacey KA, DuMont AL, et al. Multivalent human antibody-centyrin fusion protein to prevent and treat Staphylococcus aureus infections. Cell Host Microbe. 2023;31(5):751–65.e11.
34 Loomba PS, Taneja J, Mishra B. Methicillin and vancomycin resistant S. aureus in hospitalized patients. J Glob Infect Dis. 2010;2(3):275–83.
35 Turner NA, Sharma-Kuinkel BK, Maskarinec SA, Eichenberger EM, Shah PP, Carugati M, et al. Methicillin-resistant Staphylococcus aureus: an overview of basic and clinical research. Nat Rev Microbiol. 2019;17(4):203–18.
36 Tuon FF, Suss PH, Telles JP, Dantas LR, Borges NH, Ribeiro VST. Antimicrobial treatment of Staphylococcus aureus biofilms. Antibiotics. 2023;12(1):87.
37 Olive AJ, Sassetti CM. Metabolic crosstalk between host and pathogen: sensing, adapting and competing. Nat Rev Microbiol. 2016;14(4):221–34.
38 Mathis D, Shoelson SE. Immunometabolism: an emerging frontier. Nat Rev Immunol. 2011;11(2):81.
39 Russell DG, Huang L, VanderVen BC. Immunometabolism at the interface between macrophages and pathogens. Nat Rev Immunol. 2019;19(5):291–304.
40 Makowski L, Chaib M, Rathmell JC. Immunometabolism: from basic mechanisms to translation. Immunol Rev. 2020;295(1):5–14.
41 Passalacqua KD, Charbonneau ME, O'Riordan MXD. Bacterial metabolism shapes the host-pathogen interface. Microbiol Spectr. 2016;4(3).
42 Zhang Y, Chen R, Zhang D, Qi S, Liu Y. Metabolite interactions between host and microbiota during health and disease: which feeds the other? Biomed Pharmacother. 2023;160:114295.
43 Rosenberg G, Riquelme S, Prince A, Avraham R. Immunometabolic crosstalk during bacterial infection. Nat Microbiol. 2022;7(4):497–507.
44 Richardson AR. Virulence and metabolism. Microbiol Spectr. 2019;7(2).
45 Rao M, Dodoo E, Zumla A, Maeurer M. Immunometabolism and pulmonary infections: implications for protective immune responses and host-directed therapies. Front Microbiol. 2019;10:962.
46 Traven A, Naderer T. Central metabolic interactions of immune cells and microbes: prospects for defeating infections. EMBO Rep. 2019;20(7):e47995.
47 Chandel NS. Lipid metabolism. Cold Spring Harb Perspect Biol. 2021;13(9):a040576.
48 Patra KC, Hay N. The pentose phosphate pathway and cancer. Trends Biochem Sci. 2014;39(8):347–54.
49 Arnold PK, Finley LWS. Regulation and function of the mammalian tricarboxylic acid cycle. J Biol Chem. 2023;299(2):102838.
50 DeBerardinis RJ, Mancuso A, Daikhin E, Nissim I, Yudkoff M, Wehrli S, et al. Beyond aerobic glycolysis: transformed cells can engage in glutamine metabolism that exceeds the requirement for protein and nucleotide synthesis. Proc Natl Acad Sci USA. 2007;104(49):19345–50.
51 Rath M, Müller I, Kropf P, Closs EI, Munder M. Metabolism via arginase or nitric oxide synthase: two competing arginine pathways in macrophages. Front Immunol. 2014;5:532.
52 Everts B, Amiel E, Huang SC, Smith AM, Chang CH, Lam WY, et al. TLR-driven early glycolytic reprogramming via the kinases TBK1-IKKε supports the anabolic demands of dendritic cell activation. Nat Immunol. 2014;15(4):323–32.
53 Sadiku P, Willson JA, Ryan EM, Sammut D, Coelho P, Watts ER, et al. Neutrophils fuel effective immune responses through gluconeogenesis and glycogenesis. Cell Metab. 2021;33(5):1062–4.
54 Chou WC, Rampanelli E, Li X, Ting JP. Impact of intracellular innate immune receptors on immunometabolism. Cell Mol Immunol. 2022;19(3):337–51.
55 Namgaladze D, Brüne B. Rapid glycolytic activation accompanying innate immune responses: mechanisms and function. Front Immunol. 2023;14:1180488.
56 Schuurman AR, Butler JM, Michels EHA, Otto NA, Brands X, Haak BW, et al. Inflammatory and glycolytic programs underpin a primed blood neutrophil state in patients with pneumonia. iScience. 2023;26(7):107181.
57 Jantsch J, Chakravortty D, Turza N, Prechtel AT, Buchholz B, Gerlach RG, et al. Hypoxia and hypoxia-inducible factor-1 alpha modulate lipopolysaccharide-induced dendritic cell activation and function. J Immunol. 2008;180(7):4697–705.
58 Liu L, Lu Y, Martinez J, Bi Y, Lian G, Wang T, et al. Proinflammatory signal suppresses proliferation and shifts macrophage metabolism from Myc-dependent to HIF1α-dependent. Proc Natl Acad Sci USA. 2016;113(6):1564–9.
59 Wang T, Liu H, Lian G, Zhang SY, Wang X, Jiang C. HIF1α-Induced glycolysis metabolism is essential to the activation of inflammatory macrophages. Mediators Inflamm. 2017;2017:9029327.
60 Yu Q, Wang Y, Dong L, He Y, Liu R, Yang Q, et al. Regulations of glycolytic activities on macrophages functions in tumor and infectious inflammation. Front Cell Infect Microbiol. 2020;10:287.
61 Beam JE, Wagner NJ, Lu KY, Parsons JB, Fowler VG Jr, Rowe SE, et al. Inflammasome-mediated glucose limitation induces antibiotic tolerance in *Staphylococcus aureus*. iScience. 2023;26(10):107942.
62 Wickersham M, Wachtel S, Wong Fok Lung T, Soong G, Jacquet R, Richardson A, et al. Metabolic stress drives keratinocyte defenses against Staphylococcus aureus infection. Cell Rep. 2017;18(11):2742–51.
63 Tannahill GM, Curtis AM, Adamik J, Palsson-McDermott EM, McGettrick AF, Goel G, et al. Succinate is an inflammatory signal that induces IL-1β through HIF-1α. Nature. 2013;496(7444):238–42.
64 Pålsson-McDermott EM, O'Neill LAJ. Targeting immunometabolism as an anti-inflammatory strategy. Cell Res. 2020;30(4):300–14.
65 Gao X, Wang Z, Xu Y, Feng S, Fu S, Luo Z, et al. PFKFB3-Meditated glycolysis via the reactive oxygen species–hypoxic inducible factor 1α Axis contributes to inflammation and proliferation of *Staphylococcus aureus* in epithelial cells. J Infect Dis. 2023:jiad339.
66 Tuchscherr L, Heitmann V, Hussain M, Viemann D, Roth J, von Eiff C, et al. Staphylococcus aureus small-colony variants are adapted phenotypes for intracellular persistence. J Infect Dis. 2010;202(7):1031–40.
67 Kriegeskorte A, Grubmüller S, Huber C, Kahl BC, von Eiff C, Proctor RA, et al. Staphylococcus aureus small colony variants show common metabolic features in central metabolism irrespective of the underlying auxotrophism. Front Cell Infect Microbiol. 2014;4:141.
68 Wong Fok Lung T, Monk IR, Acker KP, Mu A, Wang N, Riquelme SA, et al. Staphylococcus aureus small colony variants impair host immunity by activating host cell glycolysis and inducing necroptosis. Nat Microbiol. 2020;5(1):141–53.
69 Bainton DF, Ullyot JL, Farquhar MG. The development of neutrophilic polymorphonuclear leukocytes in human bone marrow. J Exp Med. 1971;134(4):907–34.
70 Borregaard N, Herlin T. Energy metabolism of human neutrophils during phagocytosis. J Clin Invest. 1982;70(3):550–7.

71 Maianski NA, Geissler J, Srinivasula SM, Alnemri ES, Roos D, Kuijpers TW. Functional characterization of mitochondria in neutrophils: a role restricted to apoptosis. Cell Death Differ. 2004;11(2):143–53.
72 Injarabian L, Devin A, Ransac S, Marteyn BS. Neutrophil metabolic shift during their lifecycle: impact on their survival and activation. Int J Mol Sci. 2019;21(1):287.
73 Sbarra AJ, Karnovsky ML. The biochemical basis of phagocytosis. J Biol Chem. 1959;234(6):1355–62.
74 Boxer LA, Baehner RL, Davis J. The effect of 2-deoxyglucose on Guinea pig polymorphonuclear leukocyte phagocytosis. J Cell Physiol. 1977;91(1):89–102.
75 Britt EC, Lika J, Giese MA, Schoen TJ, Seim GL, Huang Z, et al. Switching to the cyclic pentose phosphate pathway powers the oxidative burst in activated neutrophils. Nat Metab. 2022;4(3):389–403.
76 Toller-Kawahisa JE, Hiroki CH, Silva CMd S, Nascimento DC, Públio GA, Martins TV, et al. The metabolic function of pyruvate kinase M2 regulates reactive oxygen species production and microbial killing by neutrophils. Nat Commun. 2023;14(1):4280.
77 Alves-Filho JC, Pålsson-McDermott EM. Pyruvate kinase M2: a potential target for regulating inflammation. Front Immunol. 2016;7:145.
78 Belambri SA, Rolas L, Raad H, Hurtado-Nedelec M, Dang PM, El-Benna J. NADPH oxidase activation in neutrophils: role of the phosphorylation of its subunits. Eur J Clin Invest. 2018;48(Suppl 2):e12951.
79 Rossi F, Grzeskowiak M, Della Bianca V, Sbarbati A. De novo synthesis of diacylglycerol from glucose. A new pathway of signal transduction in human neutrophils stimulated during phagocytosis of beta-glucan particles. J Biol Chem. 1991;266(13):8034–8.
80 Burge PS, Johnson WS, Hayward AR. Neutrophil pyruvate kinase deficiency with recurrent staphylococcal infections: first reported case. Br Med J. 1976;1(6012):742–5.
81 Dai J, El Gazzar M, Li GY, Moorman JP, Yao ZQ. Myeloid-derived suppressor cells: paradoxical roles in infection and immunity. J Innate Immun. 2015;7(2):116–26.
82 Medina E, Hartl D. Myeloid-derived suppressor cells in infection: a general overview. J Innate Immun. 2018;10(5–6):407–13.
83 Groth C, Hu X, Weber R, Fleming V, Altevogt P, Utikal J, et al. Immunosuppression mediated by myeloid-derived suppressor cells (MDSCs) during tumour progression. Br J Cancer. 2019;120(1):16–25.
84 Xu D, Li C, Xu Y, Huang M, Cui D, Xie J. Myeloid-derived suppressor cell: a crucial player in autoimmune diseases. Front Immunol. 2022;13:1021612.
85 Veglia F, Sanseviero E, Gabrilovich DI. Myeloid-derived suppressor cells in the era of increasing myeloid cell diversity. Nat Rev Immunol. 2021;21(8):485–98.
86 Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol. 2009;9(3):162–74.
87 Ohl K, Tenbrock K. Reactive oxygen species as regulators of MDSC-mediated immune suppression. Front Immunol. 2018;9:2499.
88 Shi H, Li K, Ni Y, Liang X, Zhao X. Myeloid-derived suppressor cells: implications in the resistance of malignant tumors to T cell-based immunotherapy. Front Cell Dev Biol. 2021;9:707198.
89 Heim CE, Vidlak D, Scherr TD, Kozel JA, Holzapfel M, Muirhead DE, et al. Myeloid-derived suppressor cells contribute to Staphylococcus aureus orthopedic biofilm infection. J Immunol. 2014;192(8):3778–92.
90 Heim CE, Vidlak D, Scherr TD, Hartman CW, Garvin KL, Kielian T. IL-12 promotes myeloid-derived suppressor cell recruitment and bacterial persistence during Staphylococcus aureus orthopedic implant infection. J Immunol. 2015;194(8):3861–72.
91 Tebartz C, Horst SA, Sparwasser T, Huehn J, Beineke A, Peters G, et al. A major role for myeloid-derived suppressor cells and a minor role for regulatory T cells in immunosuppression during Staphylococcus aureus infection. J Immunol. 2015;194(3):1100–11.
92 Heim CE, West SC, Ali H, Kielian T. Heterogeneity of Ly6G(+) Ly6C(+) myeloid-derived suppressor cell infiltrates during Staphylococcus aureus biofilm infection. Infect Immun. 2018;86(12):e00684-18.
93 Kak G, Van Roy Z, Heim CE, Fallet RW, Shi W, Roers A, et al. IL-10 production by granulocytes promotes Staphylococcus aureus craniotomy infection. J Neuroinflammation. 2023;20(1):114.
94 Heim CE, Vidlak D, Odvody J, Hartman CW, Garvin KL, Kielian T. Human prosthetic joint infections are associated with myeloid-derived suppressor cells (MDSCs): implications for infection persistence. J Orthop Res. 2018;36(6):1605–13.
95 Dietrich O, Heinz A, Goldmann O, Geffers R, Beineke A, Hiller K, et al. Dysregulated immunometabolism is associated with the generation of myeloid-derived suppressor cells in Staphylococcus aureus chronic infection. J Innate Immun. 2022;14(3):257–74.
96 Lin L, Ibrahim AS, Xu X, Farber JM, Avanesian V, Baquir B, et al. Th1-Th17 cells mediate protective adaptive immunity against Staphylococcus aureus and Candida albicans infection in mice. PLoS Pathog. 2009;5(12):e1000703.
97 Brown AF, Murphy AG, Lalor SJ, Leech JM, O'Keeffe KM, Mac Aogáin M, et al. Memory Th1 cells are protective in invasive Staphylococcus aureus infection. PLoS Pathog. 2015;11(11):e1005226.
98 Goldmann O, Medina E. Myeloid-derived suppressor cells impair CD4+ T cell responses during chronic Staphylococcus aureus infection via lactate metabolism. Cell Mol Life Sci. 2023;80(8):221.
99 Heim CE, Bosch ME, Yamada KJ, Aldrich AL, Chaudhari SS, Klinkebiel D, et al. Lactate production by Staphylococcus aureus biofilm inhibits HDAC11 to reprogramme the host immune response during persistent infection. Nat Microbiol. 2020;5(10):1271–84.
100 Cheng F, Lienlaf M, Perez-Villarroel P, Wang HW, Lee C, Woan K, et al. Divergent roles of histone deacetylase 6 (HDAC6) and histone deacetylase 11 (HDAC11) on the transcriptional regulation of IL10 in antigen presenting cells. Mol Immunol. 2014;60(1):44–53.
101 Yermak K, Karbysheva S, Perka C, Trampuz A, Renz N. Performance of synovial fluid D-lactate for the diagnosis of periprosthetic joint infection: a prospective observational study. J Infect. 2019;79(2):123–9.
102 Li Z, Li C, Wang G, Shi L, Li T, Fan X, et al. Diagnostic accuracy of synovial fluid D-lactate for periprosthetic joint infection: a systematic review and meta-analysis. J Orthop Surg Res. 2021;16(1):606.
103 Chen Y, Wang H, Chen X, Ma H, Zheng J, Cao L. Serum D-lactate, a novel serological biomarker, is promising for the diagnosis of periprosthetic joint infection. BMC Musculoskelet Disord. 2022;23(1):292.
104 Ivashkiv LB. The hypoxia-lactate axis tempers inflammation. Nat Rev Immunol. 2020;20(2):85–6.
105 Caslin HL, Abebayehu D, Pinette JA, Ryan JJ. Lactate is a metabolic mediator that shapes immune cell fate and function. Front Physiol. 2021;12:688485.
106 Certo M, Tsai CH, Pucino V, Ho PC, Mauro C. Lactate modulation of immune responses in inflammatory versus tumour microenvironments. Nat Rev Immunol. 2021;21(3):151–61.
107 Yang K, Xu J, Fan M, Tu F, Wang X, Ha T, et al. Lactate suppresses macrophage pro-inflammatory response to LPS stimulation by inhibition of YAP and NF-κB activation *via* GPR81-mediated signaling. Front Immunol. 2020;11:587913.
108 Hoque R, Farooq A, Ghani A, Gorelick F, Mehal WZ. Lactate reduces liver and pancreatic injury in Toll-like receptor- and inflammasome-mediated inflammation via GPR81-mediated suppression of innate immunity. Gastroenterology. 2014;146(7):1763–74.
109 Zhang W, Wang G, Xu ZG, Tu H, Hu F, Dai J, et al. Lactate is a natural suppressor of RLR signaling by targeting MAVS. Cell. 2019;178(1):176–89.e15.
110 Liu Q, Mazhar M, Miller LS. Immune and inflammatory reponses to Staphylococcus aureus skin infections. Curr Dermatol Rep. 2018;7(4):338–49.

111 Li M, Yu J, Guo G, Shen H. Interactions between macrophages and biofilm during Staphylococcus aureus-associated implant infection: difficulties and solutions. J Innate Immun. 2023;15(1):499–515.
112 Bernthal NM, Pribaz JR, Stavrakis AI, Billi F, Cho JS, Ramos RI, et al. Protective role of IL-1β against post-arthroplasty Staphylococcus aureus infection. J Orthop Res. 2011;29(10):1621–6.
113 Wang Y, Ashbaugh AG, Dikeman DA, Zhang J, Ackerman NE, Kim SE, et al. Interleukin-1β and tumor necrosis factor are essential in controlling an experimental orthopedic implant-associated infection. J Orthop Res. 2020;38(8):1800–9.
114 Menousek J, Horn CM, Heim CE, Van Roy Z, Korshoj LE, Kielian T. Transcriptional profiling of phagocytic leukocytes and microglia reveals a critical role for reactive oxygen species in biofilm containment during Staphylococcus aureus craniotomy infection. J Immunol. 2022;209(10):1973–86.
115 Van Roy Z, Shi W, Kak G, Duan B, Kielian T. Epigenetic regulation of leukocyte inflammatory mediator production dictates Staphylococcus aureus craniotomy infection outcome. J Immunol. 2023;211(3):414–28.
116 Sanchez-Pino MD, Dean MJ, Ochoa AC. Myeloid-derived suppressor cells (MDSC): when good intentions go awry. Cell Immunol. 2021;362:104302.
117 Heim CE, Vidlak D, Scherr TD, Kozel JA, Holzapfel M, Muirhead DE, et al. Myeloid-derived suppressor cells contribute to Staphylococcus aureus orthopedic biofilm infection. J Immunol. 2014;192(8):3778–92.
118 Yamada KJ, Heim CE, Xi X, Attri KS, Wang D, Zhang W, et al. Monocyte metabolic reprogramming promotes pro-inflammatory activity and Staphylococcus aureus biofilm clearance. PLoS Pathog. 2020;16(3):e1008354.
119 Aldrich AL, Horn CM, Heim CE, Korshoj LE, Kielian T. Transcriptional diversity and niche-specific distribution of leukocyte populations during Staphylococcus aureus craniotomy-associated biofilm infection. J Immunol. 2021;206(4):751–65.
120 Horn CM, Kielian T. Crosstalk between Staphylococcus aureus and innate immunity: focus on immunometabolism. Front Immunol. 2020;11:621750.
121 Viola A, Munari F, Sánchez-Rodríguez R, Scolaro T, Castegna A. The metabolic signature of macrophage responses. Front Immunol. 2019;10:1462.
122 Choi I, Son H, Baek JH. Tricarboxylic acid (TCA) cycle intermediates: regulators of immune responses. Life. 2021;11(1):69.
123 Selak MA, Armour SM, MacKenzie ED, Boulahbel H, Watson DG, Mansfield KD, et al. Succinate links TCA cycle dysfunction to oncogenesis by inhibiting HIF-alpha prolyl hydroxylase. Cancer Cell. 2005;7(1):77–85.
124 Zhao S, Lin Y, Xu W, Jiang W, Zha Z, Wang P, et al. Glioma-derived mutations in IDH1 dominantly inhibit IDH1 catalytic activity and induce HIF-1alpha. Science. 2009;324(5924):261–5.
125 Mills EL, Kelly B, Logan A, Costa ASH, Varma M, Bryant CE, et al. Succinate dehydrogenase supports metabolic repurposing of mitochondria to drive inflammatory macrophages. Cell. 2016;167(2):457–70.e13.
126 Infantino V, Iacobazzi V, Menga A, Avantaggiati ML, Palmieri F. A key role of the mitochondrial citrate carrier (SLC25A1) in TNFα- and IFNγ-triggered inflammation. Biochim Biophys Acta. 2014;1839(11):1217–25.
127 Lampropoulou V, Sergushichev A, Bambouskova M, Nair S, Vincent EE, Loginicheva E, et al. Itaconate links inhibition of succinate dehydrogenase with macrophage metabolic remodeling and regulation of inflammation. Cell Metab. 2016;24(1):158–66.
128 Domínguez-Andrés J, Novakovic B, Li Y, Scicluna BP, Gresnigt MS, Arts RJW, et al. The itaconate pathway is a central regulatory node linking innate immune tolerance and trained immunity. Cell Metab. 2019;29(1):211–20.e5.
129 Liao ST, Han C, Xu DQ, Fu XW, Wang JS, Kong LY. 4-Octyl itaconate inhibits aerobic glycolysis by targeting GAPDH to exert anti-inflammatory effects. Nat Commun. 2019;10(1):5091.
130 Qin W, Qin K, Zhang Y, Jia W, Chen Y, Cheng B, et al. S-glycosylation-based cysteine profiling reveals regulation of glycolysis by itaconate. Nat Chem Biol. 2019;15(10):983–91.
131 Tomlinson KL, Lung TWF, Dach F, Annavajhala MK, Gabryszewski SJ, Groves RA, et al. Staphylococcus aureus induces an itaconate-dominated immunometabolic response that drives biofilm formation. Nat Commun. 2021;12(1):1399.
132 Riquelme SA, Liimatta K, Wong Fok Lung T, Fields B, Ahn D, Chen D, et al. Pseudomonas aeruginosa utilizes host-derived itaconate to redirect its metabolism to promote biofilm formation. Cell Metab. 2020;31(6):1091–106.e6.
133 Tomlinson KL, Riquelme SA, Baskota SU, Drikic M, Monk IR, Stinear TP, et al. Staphylococcus aureus stimulates neutrophil itaconate production that suppresses the oxidative burst. Cell Rep. 2023;42(2):112064.
134 Nair S, Huynh JP, Lampropoulou V, Loginicheva E, Esaulova E, Gounder AP, et al. Irg1 expression in myeloid cells prevents immunopathology during M. tuberculosis infection. J Exp Med. 2018;215(4):1035–45.
135 Wong Fok Lung T, Charytonowicz D, Beaumont KG, Shah SS, Sridhar SH, Gorrie CL, et al. Klebsiella pneumoniae induces host metabolic stress that promotes tolerance to pulmonary infection. Cell Metab. 2022;34(5):761–74.e9.
136 McFadden BA, Purohit S. Itaconate, an isocitrate lyase-directed inhibitor in Pseudomonas indigofera. J Bacteriol. 1977;131(1):136–44.
137 Michelucci A, Cordes T, Ghelfi J, Pailot A, Reiling N, Goldmann O, et al. Immune-responsive gene 1 protein links metabolism to immunity by catalyzing itaconic acid production. Proc Natl Acad Sci USA. 2013;110(19):7820–5.
138 Ruetz M, Campanello GC, Purchal M, Shen H, McDevitt L, Gouda H, et al. Itaconyl-CoA forms a stable biradical in methylmalonyl-CoA mutase and derails its activity and repair. Science. 2019;366(6465):589–93.
139 Chen M, Sun H, Boot M, Shao L, Chang SJ, Wang W, et al. Itaconate is an effector of a Rab GTPase cell-autonomous host defense pathway against Salmonella. Science. 2020;369(6502):450–5.
140 Arts RJ, Novakovic B, Ter Horst R, Carvalho A, Bekkering S, Lachmandas E, et al. Glutaminolysis and fumarate accumulation integrate immunometabolic and epigenetic programs in trained immunity. Cell Metab. 2016;24(6):807–19.
141 Kornberg MD, Bhargava P, Kim PM, Putluri V, Snowman AM, Putluri N, et al. Dimethyl fumarate targets GAPDH and aerobic glycolysis to modulate immunity. Science. 2018;360(6387):449–53.
142 Humphries F, Shmuel-Galia L, Ketelut-Carneiro N, Li S, Wang B, Nemmara VV, et al. Succination inactivates gasdermin D and blocks pyroptosis. Science. 2020;369(6511):1633–7.
143 Acker KP, Wong Fok Lung T, West E, Craft J, Narechania A, Smith H, et al. Strains of Staphylococcus aureus that colonize and infect skin harbor mutations in metabolic genes. iScience. 2019;19:281–90.
144 Gabryszewski SJ, Wong Fok Lung T, Annavajhala MK, Tomlinson KL, Riquelme SA, Khan IN, et al. Metabolic adaptation in methicillin-resistant Staphylococcus aureus pneumonia. Am J Respir Cell Mol Biol. 2019;61(2):185–97.
145 Hooftman A, Peace CG, Ryan DG, Day EA, Yang M, McGettrick AF, et al. Macrophage fumarate hydratase restrains mtRNA-mediated interferon production. Nature. 2023;615(7952):490–8.
146 Zecchini V, Paupe V, Herranz-Montoya I, Janssen J, Wortel IMN, Morris JL, et al. Fumarate induces vesicular release of mtDNA to drive innate immunity. Nature. 2023;615(7952):499–506.
147 Dunham-Snary KJ, Surewaard BG, Mewburn JD, Bentley RE, Martin AY, Jones O, et al. Mitochondria in human neutrophils mediate killing of Staphylococcus aureus. Redox Biol. 2022;49:102225.
148 Mills EL, O'Neill LA. Reprogramming mitochondrial metabolism in macrophages as an anti-inflammatory signal. Eur J Immunol. 2016;46(1):13–21.

149 Castoldi A, Monteiro LB, van Teijlingen Bakker N, Sanin DE, Rana N, Corrado M, et al. Triacylglycerol synthesis enhances macrophage inflammatory function. Nat Commun. 2020;11(1):4107.
150 Wei X, Song H, Yin L, Rizzo MG, Sidhu R, Covey DF, et al. Fatty acid synthesis configures the plasma membrane for inflammation in diabetes. Nature. 2016;539(7628):294–8.
151 Huang SC, Everts B, Ivanova Y, O'Sullivan D, Nascimento M, Smith AM, et al. Cell-intrinsic lysosomal lipolysis is essential for alternative activation of macrophages. Nat Immunol. 2014;15(9):846–55.
152 Divakaruni AS, Hsieh WY, Minarrieta L, Duong TN, Kim KKO, Desousa BR, et al. Etomoxir inhibits macrophage polarization by disrupting CoA homeostasis. Cell Metab. 2018;28(3):490–503 e7.
153 Reens AL, Nagy TA, Detweiler CS. Salmonella enterica requires lipid metabolism genes to replicate in proinflammatory macrophages and mice. Infect Immun. 2019;88(1):e00776-19.
154 Chandra P, He L, Zimmerman M, Yang G, Köster S, Ouimet M, et al. Inhibition of fatty acid oxidation promotes macrophage control of Mycobacterium tuberculosis. mBio. 2020;11(4):e01139-20.
155 Wang Y, Wu C, Gao J, Du X, Chen X, Zhang M. Host metabolic shift during systemic Salmonella infection revealed by comparative proteomics. Emerg Microbes Infect. 2021;10(1):1849–61.
156 Yang H, Wang F, Guo X, Liu F, Liu Z, Wu X, et al. Interception of host fatty acid metabolism by mycobacteria under hypoxia to suppress anti-TB immunity. Cell Discov. 2021;7(1):90.
157 Desbois AP, Lawlor KC. Antibacterial activity of long-chain polyunsaturated fatty acids against Propionibacterium acnes and Staphylococcus aureus. Mar Drugs. 2013;11(11):4544–57.
158 Kim YG, Lee JH, Raorane CJ, Oh ST, Park JG, Lee J. Herring oil and omega fatty acids inhibit Staphylococcus aureus biofilm formation and virulence. Front Microbiol. 2018;9:1241.
159 Svahn SL, Grahnemo L, Pálsdóttir V, Nookaew I, Wendt K, Gabrielsson B, et al. Dietary polyunsaturated fatty acids increase survival and decrease bacterial load during septic Staphylococcus aureus infection and improve neutrophil function in mice. Infect Immun. 2015;83(2):514–21.
160 Zhou P, Wu J, Wang Y, Zhang H, Xia Y, Zhang Y, et al. The synergistic therapeutic efficacy of vancomycin and omega-3 fatty acids alleviates Staphylococcus aureus-induced osteomyelitis in rats. Biomed Pharmacother. 2019;111:1228–33.
161 Pham L, Komalavilas P, Eddie AM, Thayer TE, Greenwood DL, Liu KH, et al. Neutrophil trafficking to the site of infection requires Cpt1a-dependent fatty acid beta-oxidation. Commun Biol. 2022;5(1):1366.
162 Popovic PJ, Zeh HJ 3rd, Ochoa JB. Arginine and immunity. J Nutr. 2007;137(6 Suppl 2):1681S–86S.
163 Tomé D. Amino acid metabolism and signalling pathways: potential targets in the control of infection and immunity. Nutr Diabetes. 2021;11(1):20.
164 Jha AK, Huang SC, Sergushichev A, Lampropoulou V, Ivanova Y, Loginicheva E, et al. Network integration of parallel metabolic and transcriptional data reveals metabolic modules that regulate macrophage polarization. Immunity. 2015;42(3):419–30.
165 Thurlow LR, Joshi GS, Clark JR, Spontak JS, Neely CJ, Maile R, et al. Functional modularity of the arginine catabolic mobile element contributes to the success of USA300 methicillin-resistant Staphylococcus aureus. Cell Host Microbe. 2013;13(1):100–7.
166 Pang R, Zhou H, Huang Y, Su Y, Chen X. Inhibition of host arginase activity against staphylococcal bloodstream infection by different metabolites. Front Immunol. 2020;11:1639.
167 Yamada KJ, Heim CE, Aldrich AL, Gries CM, Staudacher AG, Kielian T. Arginase-1 expression in myeloid cells regulates Staphylococcus aureus planktonic but not biofilm infection. Infect Immun. 2018;86(7):e00206-18.
168 Movahedi K, Guilliams M, Van den Bossche J, Van den Bergh R, Gysemans C, Beschin A, et al. Identification of discrete tumor-induced myeloid-derived suppressor cell subpopulations with distinct T cell-suppressive activity. Blood. 2008;111(8):4233–44.
169 Wu Y, Yi M, Niu M, Mei Q, Wu K. Myeloid-derived suppressor cells: an emerging target for anticancer immunotherapy. Mol Cancer. 2022;21(1):184.
170 Smith C, Chang MY, Parker KH, Beury DW, DuHadaway JB, Flick HE, et al. IDO is a nodal pathogenic driver of lung cancer and metastasis development. Cancer Discov. 2012;2(8):722–35.
171 Schafer CC, Wang Y, Hough KP, Sawant A, Grant SC, Thannickal VJ, et al. Indoleamine 2,3-dioxygenase regulates anti-tumor immunity in lung cancer by metabolic reprogramming of immune cells in the tumor microenvironment. Oncotarget. 2016;7(46):75407–24.
172 Niño-Castro A, Abdullah Z, Popov A, Thabet Y, Beyer M, Knolle P, et al. The IDO1-induced kynurenines play a major role in the antimicrobial effect of human myeloid cells against Listeria monocytogenes. Innate Immun. 2014;20(4):401–11.
173 Saito A, Motomura N, Kakimi K, Narui K, Noguchi N, Sasatsu M, et al. Vascular allografts are resistant to methicillin-resistant Staphylococcus aureus through indoleamine 2,3-dioxygenase in a murine model. J Thorac Cardiovasc Surg. 2008;136(1):159–67.
174 Narui K, Noguchi N, Saito A, Kakimi K, Motomura N, Kubo K, et al. Anti-infectious activity of tryptophan metabolites in the L-tryptophan-L-kynurenine pathway. Biol Pharm Bull. 2009;32(1):41–4.
175 Peleg AY, Weerarathna T, McCarthy JS, Davis TM. Common infections in diabetes: pathogenesis, management and relationship to glycaemic control. Diabetes Metab Res Rev. 2007;23(1):3–13.
176 Chávez-Reyes J, Escárcega-González CE, Chavira-Suárez E, León-Buitimea A, Vázquez-León P, Morones-Ramírez JR, et al. Susceptibility for some infectious diseases in patients with diabetes: the key role of glycemia. Front Public Health. 2021;9:559595.
177 Lipsky BA, Tabak YP, Johannes RS, Vo L, Hyde L, Weigelt JA. Skin and soft tissue infections in hospitalised patients with diabetes: culture isolates and risk factors associated with mortality, length of stay and cost. Diabetologia. 2010;53(5):914–23.
178 Abu-Ashour W, Twells L, Valcour J, Randell A, Donnan J, Howse P, et al. The association between diabetes mellitus and incident infections: a systematic review and meta-analysis of observational studies. BMJ Open Diabetes Res Care. 2017;5(1):e000336.
179 Jneid J, Cassir N, Schuldiner S, Jourdan N, Sotto A, Lavigne JP, et al. Exploring the microbiota of diabetic foot infections with culturomics. Front Cell Infect Microbiol. 2018;8:282.
180 Smit J, Søgaard M, Schønheyder HC, Nielsen H, Frøslev T, Thomsen RW. Diabetes and risk of community-acquired Staphylococcus aureus bacteremia: a population-based case-control study. Eur J Endocrinol. 2016;174(5):631–9.
181 Rich J, Lee JC. The pathogenesis of Staphylococcus aureus infection in the diabetic NOD mouse. Diabetes. 2005;54(10):2904–10.
182 Farnsworth CW, Schott EM, Benvie A, Kates SL, Schwarz EM, Gill SR, et al. Exacerbated Staphylococcus aureus foot infections in obese/diabetic mice are associated with impaired germinal center reactions, ig class switching, and humoral immunity. J Immunol. 2018;201(2):560–72.
183 Thurlow LR, Stephens AC, Hurley KE, Richardson AR. Lack of nutritional immunity in diabetic skin infections promotes Staphylococcus aureus virulence. Sci Adv. 2020;6(46):eabc5569.

184 Butrico CE, Klopfenstein N, Green ER, Johnson JR, Peck SH, Ibberson CB, et al. Hyperglycemia increases severity of Staphylococcus aureus osteomyelitis and influences bacterial genes required for survival in bone. Infect Immun. 2023;91(4):e0052922.
185 Vitko NP, Spahich NA, Richardson AR. Glycolytic dependency of high-level nitric oxide resistance and virulence in Staphylococcus aureus. mBio. 2015;6(2):e00045-15.
186 Wei R, Wang X, Wang Q, Qiang G, Zhang L, Hu HY. Hyperglycemia in diabetic skin infections promotes Staphylococcus aureus virulence factor aureolysin: visualization by molecular imaging. ACS Sens. 2022;7(11):3416–21.
187 Yang Z, Fujii H, Mohan SV, Goronzy JJ, Weyand CM. Phosphofructokinase deficiency impairs ATP generation, autophagy, and redox balance in rheumatoid arthritis T cells. J Exp Med. 2013;210(10):2119–34.
188 Yin Y, Choi SC, Xu Z, Perry DJ, Seay H, Croker BP, et al. Normalization of CD4+ T cell metabolism reverses lupus. Sci Transl Med. 2015;7(274):274ra18.
189 Yin Y, Choi SC, Xu Z, Zeumer L, Kanda N, Croker BP, et al. Glucose oxidation is critical for CD4+ T cell activation in a mouse model of systemic lupus erythematosus. J Immunol. 2016;196(1):80–90.
190 Bustamante MF, Oliveira PG, Garcia-Carbonell R, Croft AP, Smith JM, Serrano RL, et al. Hexokinase 2 as a novel selective metabolic target for rheumatoid arthritis. Ann Rheum Dis. 2018;77(11):1636–43.
191 Angiari S, Runtsch MC, Sutton CE, Palsson-McDermott EM, Kelly B, Rana N, et al. Pharmacological activation of pyruvate kinase M2 inhibits CD4(+) T cell pathogenicity and suppresses autoimmunity. Cell Metab. 2020;31(2):391–405 e8.
192 Mortazavi Farsani SS, Verma V. Lactate mediated metabolic crosstalk between cancer and immune cells and its therapeutic implications. Front Oncol. 2023;13:1175532.
193 Singhal A, Jie L, Kumar P, Hong GS, Leow MK, Paleja B, et al. Metformin as adjunct antituberculosis therapy. Sci Transl Med. 2014;6(263):263ra159.
194 Lee JY, Kim ES, Chang E, Bae S, Jung J, Kim MJ, et al. Clinical impact of metformin exposure during Staphylococcus aureus bacteremia in patients with diabetes mellitus. Eur J Clin Microbiol Infect Dis. 2023;42(12):1439–47.
195 Gill AJ, Kolson DL. Dimethyl fumarate modulation of immune and antioxidant responses: application to HIV therapy. Crit Rev Immunol. 2013;33(4):307–59.
196 Cronstein BN, Aune TM. Methotrexate and its mechanisms of action in inflammatory arthritis. Nat Rev Rheumatol. 2020;16(3):145–54.
197 Patocka J, Kuca K, Oleksak P, Nepovimova E, Valis M, Novotny M, et al. Rapamycin: drug repurposing in SARS-CoV-2 infection. Pharmaceuticals. 2021;14(3):217.
198 Kaufmann SHE, Dorhoi A, Hotchkiss RS, Bartenschlager R. Host-directed therapies for bacterial and viral infections. Nat Rev Drug Discov. 2018;17(1):35–56.
199 Howden BP, Giulieri SG, Wong Fok Lung T, Baines SL, Sharkey LK, Lee JYH, et al. Staphylococcus aureus host interactions and adaptation. Nat Rev Microbiol. 2023;21(6):380–95.
200 Prince A, Wong Fok Lung T. Consequences of metabolic interactions during Staphylococcus aureus infection. Toxins. 2020;12(9):581.
201 Tomlinson KL, Prince AS, Wong Fok Lung T. Immunometabolites drive bacterial adaptation to the airway. Front Immunol. 2021;12:790574.
202 Ahl PJ, Hopkins RA, Xiang WW, Au B, Kaliaperumal N, Fairhurst AM, et al. Met-Flow, a strategy for single-cell metabolic analysis highlights dynamic changes in immune subpopulations. Commun Biol. 2020;3(1):305.
203 Argüello RJ, Combes AJ, Char R, Gigan JP, Baaziz AI, Bousiquot E, et al. SCENITH: a flow cytometry-based method to functionally profile energy metabolism with single-cell resolution. Cell Metab. 2020;32(6):1063–75.e7.
204 Jaffrey SR. RNA-based fluorescent biosensors for detecting metabolites in vitro and in living cells. Adv Pharmacol. 2018;82:187–203.
205 Chandris P, Giannouli CC, Panayotou G. Imaging approaches for the study of metabolism in real time using genetically encoded reporters. Front Cell Dev Biol. 2021;9:725114.
206 Bourceau P, Geier B, Suerdieck V, Bien T, Soltwisch J, Dreisewerd K, et al. Visualization of metabolites and microbes at high spatial resolution using MALDI mass spectrometry imaging and in situ fluorescence labeling. Nat Protoc. 2023;18(10):3050–79.