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Immunometabolic crosstalk during bacterial infection

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Following detection of bacteria, macrophages switch their metabolism from oxidative respiration through the tricarboxylic acid cycle to high-rate aerobic glycolysis. This immunometabolic shift enables pro-inflammatory and antimicrobial responses and is facilitated by the accumulation of fatty acids, tricarboxylic acid-derived metabolites and catabolism of amino acids. Recent studies have shown that these immunometabolites are co-opted by pathogens as environmental cues for expression of virulence genes. We review mechanisms by which host immunometabolites regulate bacterial pathogenicity and discuss opportunities for the development of therapeutics targeting metabolic host–pathogen crosstalk.

Interactions between pathogens and their hosts result in metabolic changes that ultimately drive infection outcomes. Host immune cells are equipped with pattern-recognition receptors that detect pathogen-associated molecular patterns[1] and activate host defences. Over the past decade, it has been shown that immune-cell activation following detection of viruses or bacteria is accompanied by changes in energy metabolism that have been named 'immunometabolism'[2]. Metabolic reprogramming regulates the expression of cytokines, chemokines, interferons and antimicrobial processes of innate and adaptive immune cells[2–4]. Metabolic reprogramming of innate immune cells—for example, macrophages—and the consequent accumulation of immunometabolites is thought to promote the clearance of pathogens. Strikingly, recent evidence indicates that immunometabolites can be sensed and used by bacterial pathogens to optimize their survival and establish infection. We highlight the implications of immunometabolism on bacterial infection.

Macrophage metabolism and inflammation

Pathogen recognition and metabolic reprogramming. The activation of macrophages is a dynamic process, ranging from pro- to anti-inflammatory polarization states characterized either by induction of antimicrobial mechanisms or inflammation resolution. Detection of bacterial components by macrophages mainly involves Toll-like receptors (TLRs) located on the cell surface, on the phagosomal membrane or in the cytosol. The TLRs recognize unique or overlapping pathogen-conserved structures. For example, Gram-positive bacterial lipoproteins and lipoteichoic acid are recognized by TLR2, whereas Gram-negative lipopolysaccharide (LPS) is recognized by TLR4 (ref. [1]). Pathogen-derived molecules were recently shown to activate cytosolic sensors (for example, the cytosolic protein stimulator of interferon genes, STING[5]). Receptor recognition activates signal transduction cascades, resulting in metabolic reprogramming of macrophage energy metabolism, from mitochondrial oxidative phosphorylation to high-rate aerobic glycolysis. This reprogramming results in the synthesis and accumulation of immunometabolites that regulate the immune activation of macrophages, as detailed below and in Fig. 1.

Disruption of oxidative phosphorylation. Metabolic reprogramming is induced by the rewiring of a central metabolic hub, the tricarboxylic acid (TCA) cycle, caused by two break points that disrupt the cellular carbon flux through the cycle and promote the accumulation of TCA intermediates. The first TCA-cycle break, increasing intracellular citrate and *cis*-aconitate, is regulated by two molecular mechanisms. First, the TCA-cycle enzyme isocitrate dehydrogenase 1 (IDH1) is transcriptionally repressed by the type I interferon pathway, which results in citrate accumulation in LPS-activated macrophages[6,7]. Second, nuclear factor-κB (NF-κB) activation drives the expression of inducible nitric oxide synthase (iNOS; encoded by *Nos2*), which converts L-arginine to the highly reactive NO and L-citrulline[8]. Nitric-oxide targeting and inhibition of both IDH1 and the TCA enzyme aconitase (ACO2) contribute to citrate and *cis*-aconitate accumulation[8,9]. In parallel, NO-mediated inhibition of mitochondrial electron transport complexes reduces mitochondrial respiration and promotes the metabolic shift to glycolysis[9]. In the context of infection, NO radicals also support antibacterial processes, including damage to bacterial DNA and protein structure[10]. It was recently reported that iNOS-deficient macrophages upregulate glycolysis following LPS stimulation and activated human macrophages undergo metabolic reprogramming despite producing NO radicals at low levels[9,11]. TCA-independent induction, mediated by deacetylation of the glycolytic enzyme pyruvate kinase M2 (PKM2), was recently demonstrated[12].

Itaconate is an antimicrobial immunometabolite. Following immune activation, cells of the myeloid lineage induce the expression of the mitochondrial enzyme immune-responsive gene 1 (*Irg1*, also known as *Acod1*)[13]. *Cis*-aconitate that accumulates following the first break in the TCA cycle is catalysed to itaconate by IRG1. Itaconate then acts as a competitive inhibitor that blocks the active site of succinate dehydrogenase (SDH), leading to the second break in the TCA cycle and the accumulation of succinate[14]. Itaconate also acts as an antimicrobial agent that is directly delivered by the guanosine triphosphatase RAB32 to the macrophage phagosome, where the acidic environment increases the antimicrobial activity of itaconate[15,16]. Within the phagosome, itaconate is taken up by bacterial cells, where it inhibits the conversion of isocitrate to both succinate and glyoxylate by the isocitrate lyase (Icl)[13]. Itaconate also exerts its bactericidal effects via inhibition of propionyl-coA

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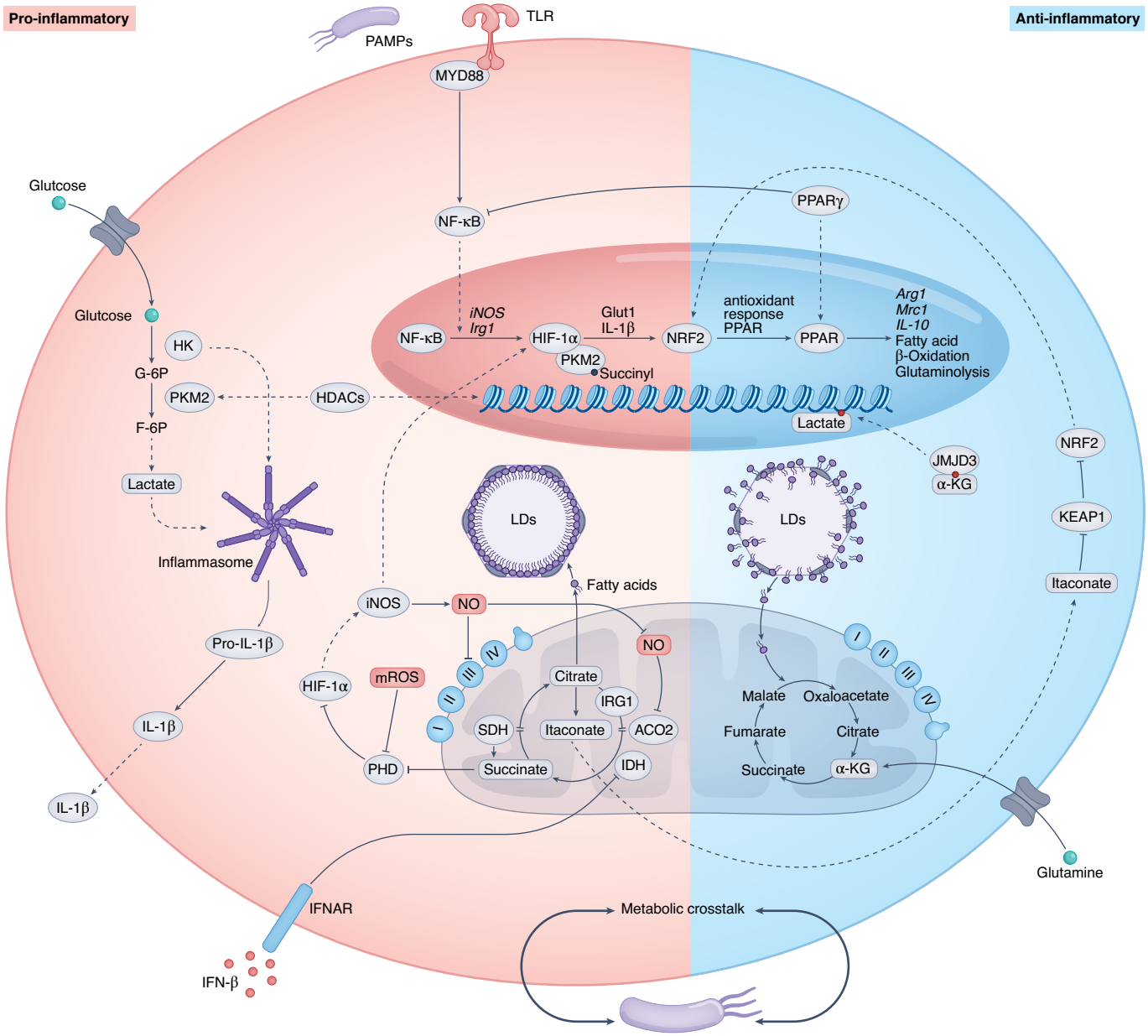

Fig. 1 | Immunometabolic changes fuel the antimicrobial response of macrophages. In response to bacterial ligands, macrophages change their metabolism to activate a pro-inflammatory programme (pink; left). Pathogen-associated-molecular-pattern (PAMP) detection by TLRs activates the NF-κB pathways leading to expression of *iNOS* and *Irg1*. Signalling by type I interferon (IFN) and NO generated by iNOS regulate the first break in the TCA cycle, leading to citrate accumulation and lipid synthesis. Conversion of citrate to itaconate by IRG1 regulates the second break in the TCA cycle, leading to succinate accumulation. Succinate and mROS release HIF-1α from its PHD-mediated inhibition. HIF-1α interacts with succinylated PKM2 and induces the expression of glycolytic genes and the pro-inflammatory cytokine IL-1β. Histone deacetylases (HDACs) activate PKM2 and induce glycolysis. Hexokinase (HK) and lactate from the glycolysis pathway regulate the activation of the NLRP3 inflammasome, leading to the processing and secretion of pro-IL-1β to IL-1β. Next, resolution of inflammation is driven by another metabolic change of macrophages to an anti-inflammatory programme (blue; right). Itaconate, accumulated by pro-inflammatory macrophages, promotes the post-transcriptional modification of KEAP1, which releases it from the NRF2 complex and promotes NRF2 activation. NRF2 induces the expression of the antioxidant response and PPARγ. PPARγ inhibits the NF-κB pathway and induces the expression of anti-inflammatory genes, fatty-acid β-oxidation and glutaminolysis. Glutamine and fatty acids fuel the TCA cycle to support oxidative-phosphorylation respiration. Lactate and α-KG promote cysteine modifications that induce the expression of anti-inflammatory genes. These metabolic changes are co-opted by several pathogenic bacteria, which underlie an immunometabolic host–pathogen crosstalk during infection. F-6P, fructose 6-phosphate.

carboxylase, thus blocking bacterial acetate and propionate metabolism[17]. As will be discussed later, several bacterial pathogens have acquired an itaconate-degradation machinery that converts itaconate to pyruvate and acetyl-CoA[18]. This defence mechanism has been suggested to be a bacterial adaptation strategy for macrophage metabolic reprogramming.

Succinate accumulation promotes HIF-1α activation. In unstimulated macrophages, hypoxia-inducible factor 1α (HIF-1α) is inhibited by prolyl hydroxylase (PHD), an enzyme that regulates its proteasome-mediated degradation. Following infection, several layers of succinate-mediated regulation support HIF-1α activation. Accumulated succinate inhibits PHD activity and stabilizes

HIF-1α[19]. Mitochondrial reactive oxygen species (mROS), generated by electron transport complexes due to succinate-mediated reverse electron transport, also inhibit PHD activity and promote HIF-1α stabilization[20]. These mitochondrial-derived radicals also act as antimicrobial effectors that support bacterial eradication[21]. Moreover, accumulated succinate regulates HIF-1α activation via post-translational modifications (PTM). Succinylation of PKM2 promotes its interaction with HIF-1α and leads to protein activation[22,23]. HIF-1α then induces the expression of *interleukin (IL)-1β* and other aerobic glycolysis-related genes that regulate the polarization of a pro-inflammatory immune response against invading pathogens[19].

Aerobic glycolysis drives a pro-inflammatory programme. The induction of aerobic glycolysis activates pro-inflammatory macrophages and several host defences. For example, hexokinase (the first enzyme in glycolysis) and lactate (the end-point metabolite of glycolysis) were found to regulate the activation of the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome[24,25]. This interaction promotes synchronization between *IL-1β* gene expression, mediated by HIF-1α activation, to processing and secretion of this pro-inflammatory cytokine by NLRP3 inflammasomes. Interestingly, hexokinase was found to act as a pattern-recognition receptor for the detection of Gram-positive bacterial peptidoglycan, which activates NLRP3 inflammasomes[25]. Gram-positive-dependent activation might have evolved as a compensatory mechanism for the moderate metabolic changes coupled to TLR2 activation[26]. NLRP3 inflammasome is also activated by mROS generated as part of the inflammatory responses[20,27].

Lipid metabolism and macrophage defence. Aerobic glycolysis promotes the formation of lipid droplets (LDs), single-membrane organelles that are considered as an immune hub against invading pathogens. LDs originate in the endoplasmic reticulum and acquire fatty acids (mainly triacylglycerol and cholesterol) by either exogenous uptake or enzymatic synthesis[28–30]. During aerobic glycolysis, accumulated citrate is directed to synthesize fatty-acyl chains on glycerol head groups for triacylglycerols[31]. Triacylglycerol synthesis was recently found to promote the secretion of pro-inflammatory effectors—including IL-1β, IL-6 and PGE_2—and support bacterial phagocytosis[32]. Following their formation, LDs act as signalling hubs, regulating the activation of the pro-inflammatory response[33]. Moreover, LDs directly regulate the antimicrobial responses and cellular metabolism of macrophages. LDs were shown to detach from the LD–mitochondria complex and interact with the intracellular bacteria following bacterial uptake. Assembly of host defence proteins such as the antimicrobial cathelicidin (CAMP) was found to cluster in LDs during the LD–bacteria interaction to promote bacterial killing[30]. In addition, uncoupling of LDs from mitochondria was suggested as a molecular switch that reduces mitochondrial β-oxidation of LDs and decreases oxidative-phosphorylation respiration, fuelling the pro-inflammatory state[30].

Immunometabolites and post-transcriptional modifications. As infection progresses, TCA and glycolysis-derived immunometabolites, accumulated in pro-inflammatory macrophages, serve as epigenetic modifications and PTMs that regulate macrophage transition towards anti-inflammatory polarization. This state is characterized by the recovery of mitochondrial respiration, shut off of antimicrobial defences and release of anti-inflammatory mediators that promote resolution of inflammation.

Itaconate accumulation has been recently identified as a cysteine modifier regulating protein activation via a modification termed 2,3-dicarboxypropylation. This PTM alters several key glycolytic enzymes, leading to impaired glycolytic flux[34]. Moreover, itaconate-mediated modification of cysteine residues on the protein Kelch-like ECH-associated protein 1 (KEAP1) releases KEAP1 from erythroid 2-related factor 2 (NRF2)[35,36]. Activated NRF2 can then bind to the promoters of pro-inflammatory cytokines, including IL-6 and IL-1β, and repress their transcription[37]. Furthermore, NRF2 induces the antioxidant response to reduce cellular ROS and decrease pro-inflammatory activation[38]. NRF2 also regulates the expression of the nuclear receptor peroxisome proliferator-activated receptor (PPAR) γ[39]. PPARγ and PPARδ restrain the pro-inflammatory response and control the expression of anti-inflammatory genes—such as arginase 1 (*Arg1*), *Mrc1* and the cytokine *IL-10*—in macrophages[40–42]. In addition, PPARs can regulate cellular pathways through protein–protein interactions[43]. Interactions between PPARs and proteins from the NF-κB pathway were shown to repress NF-κB signalling, cessation of the pro-inflammatory response and restoration of mitochondrial respiration[44]. Downregulation of iNOS expression, resulting from NF-κB inactivation, reduces the concentration of NO and releases mitochondrial electron transport complexes from NO inhibition[8,44]. Moreover, PPARs facilitate the expression of transcriptional programmes responsible for fatty-acid β-oxidation and glutamine metabolism (glutaminolysis). Importantly, induction of these metabolic pathways provides carbon sources refuelling the TCA cycle and play an integral role in anti-inflammatory activation[40,45].

Lactate, the end-point metabolite of the glycolysis pathway, was suggested to modify histone lysines (that is, lactylation). In contrast to histone acetylation, which facilitates the induction of pro-inflammatory genes, histone lactylation induces the expression of anti-inflammatory genes, including *Arg1* (ref. [46]). Thus, the temporal dynamics of histone PTMs can act as a molecular timer regulating the switch between pro- and anti-inflammatory states[46]. Another metabolite regulating anti-inflammatory activation via epigenetic modification is α-ketoglutarate (α-KG)[47]. JMJD3, a key enzyme involved in histone methylation, is activated by α-KG generated during glutaminolysis[48]. αKG-dependent JMJD3 activation regulates histone modifications and promotes the expression of anti-inflammatory polarization genes. Moreover, α-KG-mediated suppression of NF-κB and HIF-1α activation via PHD-mediated PTMs was shown to repress pro-inflammatory polarization and induce anti-inflammatory activation[19,47].

As the field of immunometabolism uncovers metabolic changes driving immunity, it has become clear that, in the context of bacterial infection, these changes are intertwined with pathogen virulence and metabolic crosstalk. Immunometabolites are co-opted by pathogens to promote their adaptation to the host environment. This metabolic crosstalk between bacterial pathogens and immunometabolism further underlies clinically relevant bacterial phenotypes, such as replication, biofilm or dormant non-replicative persisters that contribute to antibiotic tolerance, and states of chronic infection[49,50]. In the following sections, we review metabolic reprogramming and accumulation of immunometabolites from the point of view of the invading bacteria and how these organisms sense and adapt to these environmental cues.

Immunometabolism and bacterial tissue colonization

Mitochondrial immunometabolites in the airway. The airway is a site of bacterial infection, which can lead to host death. Opportunists that are able to establish long-term pulmonary infection, such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*, are often aspirated from the environment, from the same nasal cavity or acquired from surgical paraphernalia (for example, during ventilator-associated pneumonia)[51,52]. These organisms have diverse metabolic capabilities as well as multiple mechanisms of immune evasion. Despite relatively low glucose levels, the airway contains many TCA cycle-associated immunometabolites, especially in the presence of inflammation[53], providing substrates for bacterial proliferation. These pathogens must adapt to these immunometabolites,

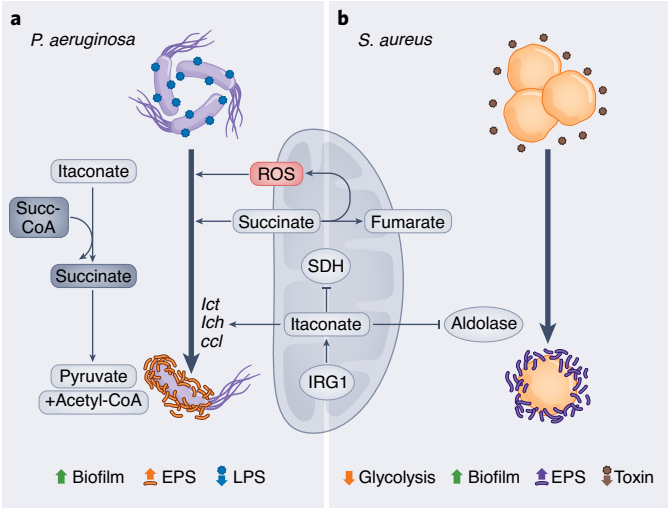

Fig. 2 | Immunometabolites drive adaptive changes in respiratory pathogens. a, Following macrophage infection, succinate is oxidized (ROS) and released. *P. aeruginosa* senses both ROS and succinate, and increases the synthesis of protective EPS and biofilm. Itaconate, produced by IRG1, stimulates the *ict–ich–ccl* locus in *P. aeruginosa*, driving the carbon flux towards succinate, pyruvate and acetyl-CoA, which favour bacterial biofilm formation. Itaconate-exposed *P. aeruginosa* reduce LPS synthesis but increase EPS generation. **b**, *S. aureus* induces and senses itaconate, which blocks the function of bacterial aldolase and glycolysis. These strains are metabolically less active. Reduced carbohydrate breakdown diminishes toxin production, selecting for strains that divert sugars into EPS and biofilm formation.

as evidenced in the lungs of patients with ventilator-associated pneumonia, chronic obstructive pulmonary disease and cystic fibrosis[54,55]. This ongoing metabolic adaptation also enables the selection of multidrug-resistant pathogens[56–58], representing an additional component of the bacterial pathogenic response.

***P. aeruginosa* adapts to host succinate.** The aspiration of environmental strains of *P. aeruginosa*—as represented by the classically studied PAO1 strain or other laboratory isolates that express flagellae, LPS and toxins—activates a robust pro-inflammatory response with the outpouring of succinate and other TCA-cycle components into the airway[59,60]. Succinate is a preferred substrate for *P. aeruginosa*, which is consumed through its catabolite repressor *crc* locus until depleted[61,62]. However, a succinate-dominated diet, as is available in the lungs of patients with cystic fibrosis, generates substantial endogenous oxidant stress for the organisms. Mutations that compromise the abundance of cystic fibrosis transmembrane conductance regulator (CFTR) in the plasma membrane, as seen in individuals with cystic fibrosis, reduce the antioxidant function of the phosphatase PTEN in the mitochondria of airway cells[60,63]. Deficient PTEN regulation induces the release of succinate and stimulation of oxidative metabolism in *P. aeruginosa*. Immune cells that are recruited into the airway but lack sufficient CFTR–PTEN generate more succinate and oxidants, adding to the metabolic pressure imposed on the pathogens trapped in the cystic fibrosis lung. Oxidative damage induced by the excessive mucus found in the cystic fibrosis airway further drives bacterial stress and metabolic adaptation. This environment selects for *P. aeruginosa* strains that are better prepared to cope with oxidant stress—that is, strains that synthesize protective extracellular polysaccharides (EPSs) at increased levels (Fig. 2a).

Itaconate and chronic *P. aeruginosa* infection. Abundant airway succinate signalling is accompanied by itaconate release. Itaconate imposes major metabolic pressure on inhaled opportunistic pathogens, enhancing clearance by macrophage metabolic reprogramming[64,65]. However, in contrast to most opportunists, the large *P. aeruginosa* genome harbours three genes devoted to itaconate metabolism: *ict*, *ich* and *ccl*[18]. *P. aeruginosa* isolates from chronically infected individuals exhibit adaptive changes at both the genotypic and the phenotypic level that reflect a shift in metabolism from succinate to itaconate as a preferred carbon source[66]. Itaconate breakdown provides *P. aeruginosa* with pyruvate and acetyl-coA, which feeds the TCA cycle and the antioxidant glyoxylate shunt, which supports the synthesis of EPS[67]. In addition, itaconate degradation generates succinate, as *ict* transfers a CoA group from succinyl-CoA to itaconate, fuelling succinate into the bacterial TCA cycle[18] (Fig. 2a). Thus, itaconate catabolism seems to fuel the preferred pathways used by these organisms to proliferate. Chronically adapted strains of *P. aeruginosa* further stimulate *Irg1* expression and itaconate release by airway myeloid cells through the expression of EPS[66], and these strains preferentially consume itaconate[66]. This metabolic adaptation is accompanied by a diminished surface display of LPS, which, in addition to the increased production of EPS, favours biofilm formation[60,66]. Biofilm provides further protection to the organisms from oxidant stress as well as a barrier to opsonization and phagocytosis, and antimicrobial penetration[56,68,69].

Irg1 stimulates *S. aureus* biofilm formation. *S. aureus* is also a frequent cause of airway infection, sharing the same environmental niche as *P. aeruginosa* in the human airway[70,71]. However, *S. aureus* does not contain LPS or promote inflammation via succinate[72]. *S. aureus* instead preferentially consumes glucose or its congeners to support its metabolic activity, chiefly glycolysis in the lung. *S. aureus* glycolysis generates sufficient oxidant stress in the mitochondria of airway cells to activate *Irg1* expression and the accumulation of airway itaconate[50,72]. Itaconate is not a substrate for *S. aureus* catabolism but it acts to suppress *S. aureus* glycolysis by inhibiting aldolase activity (Fig. 2b). This metabolic pressure selects for *S. aureus* strains that in turn divert their own carbohydrate flux into the production of protective EPS to form biofilm. Analysis of a longitudinal collection of *S. aureus* isolates derived from a patient with cystic fibrosis and long-term *S. aureus* infection revealed that these organisms cope with itaconate stress by upregulating both the components of EPS and the production of biofilm[50]. Thus, staphylococcal stimulation of mitochondrial reprogramming not only releases bactericidal metabolites but also imposes selection for variants better able to form communities that cope with shared oxidative stress.

Macrophage metabolites can provide substrates for proliferation of major human-airway pathogens, but they also contribute to the oxidant tone of the airway. Although genetically programmed to use glycolysis and the TCA cycle, both *S. aureus* and *P. aeruginosa*, respectively, divert their carbohydrate utilization into the pathways that serve to dissipate their own generation of oxidants in the airway. In response to succinate and itaconate, their utilization of carbohydrates is mainly diverted to generate EPS and biofilms, which provides protection from local oxidants and phagocytosis. The accumulation of succinate in infected mucosal niches is limited by host recycling mechanisms. Upregulation of the proteins SUCNR1; (refs. [73,74]) and SLC26A6 (ref. [75]) transport succinate back into macrophages. Inflammatory phagocytes deplete glucose from their local milieu by expressing carbohydrate transporters[76], like glucose transporter 1 (GLUT1), and limiting pathogen access to substrates for EPS biosynthesis. However, in certain metabolic diseases—such as diabetes, which increases glucose in many tissues—the expression of these carbohydrate transporters is compromised, facilitating extracellular glucose accumulation, *S. aureus* glycolysis and disease[77,78]. It remains unclear how higher glucose levels predispose individuals to *S. aureus* pulmonary infection[79–81]; we predict this might be due to increased bacterial EPS synthesis.

Immunometabolism and intracellular bacterial pathogens

The key to the success of intracellular pathogens is their ability to evade the immune defences of the host and establish an intracellular niche, especially in macrophages. Within this niche, intracellular pathogens have the long-term ability to persist and cause latent/chronic infection. Intracellular pathogens establish a heterotrophic lifestyle that dictates metabolic flexibility due to the differing available carbon sources as the cellular host environment changes following infection and the variety of macrophage subsets. The metabolic environment of the host also dictates phenotypic changes of the intracellular bacteria as they transition from replicative to non-replicative states, contingent on the availability of nutrients[82,83]. Beyond carbon availability, macrophages eliminate intravacuolar pathogens, such as *Salmonella enterica* serovar Typhimurium and *Mycobacterium tuberculosis*, by introducing harsh conditions of low pH; Mg^{2+}, Fe^{2+} and phosphate concentrations; and micronutrient availability (for example, amino acids and minerals[84,85])—a phenomenon known as 'nutritional immunity'[86]. However, intracellular pathogens have evolved to sense these stresses as a cue to the transition from extracellular to intravacuolar environments and drive virulence programmes that promote their survival and growth[87]. Fluctuations in immunometabolism, virulence and energy balance dictate bacterial and host adaptations to drive diverse cellular phenotypes. The interplay between macrophage metabolic changes that are co-opted by intracellular bacteria is becoming central to our understanding of infection outcome.

***M. tuberculosis* synchronizes with host metabolism.** *M. tuberculosis*, the causative agent of tuberculosis, is estimated to have infected a quarter of the human population[88]. Most people exposed to *M. tuberculosis* present with latent tuberculosis infection, where *M. tuberculosis* remains dormant in its host. Only 5–10% of people progress to active disease, in which yet-to-be-described signals drive dormant bacteria to resuscitate. Unlike other pathogens, *M. tuberculosis* has evolved in humans. This co-evolution has resulted in an infection that induces only partial immunity, with sustained coexistence of the host and pathogen. The distinctive inflammatory nature of *M. tuberculosis* is due to its unique mycobacterial cell wall that contains an inner leaflet of mycolic acids and an outer leaflet with various complex lipids, including phthiocerol dimycocerosates (PDIMs), which are important for *M. tuberculosis* virulence[89]. The fate of *M. tuberculosis* in macrophages is mediated by the ESX-1 type VII secretion system, which is involved in various mechanisms to enable colonization, replication and survival of *M. tuberculosis* in macrophages[90]. Although the factors underlying phenotypes of rapid replication or persistence—sometimes for years in a host cell—are yet to be determined, the host metabolic environment of different macrophage subsets is suggested to play an essential role in shaping bacterial survival[91].

In macrophages *M. tuberculosis* utilizes the glyoxylate shunt to exploit cholesterol and fatty acids for ATP synthesis[92] (Fig. 3a). *M. tuberculosis* mutants deficient in the fatty-acid and cholesterol transporters Mce1 and Mce4 or in the glyoxylate shunt enzymes Icl1 and Icl2 have impaired intramacrophage survival in culture and during in vivo infections[92,93]. However, the mechanism that facilitates the transport of host fatty acids to the *M. tuberculosis*-containing phagosome requires further study. In addition to cholesterol and fatty acids, glucose metabolism was found to also be essential for long-term intramacrophage survival[94].

During the early stages of infection, macrophage metabolic reprogramming promotes the accumulation of host LDs enriched with cholesterol and fatty acids. Once believed to be part of the bacterial pathogenic strategy to generate a safe and nutrient-enriched environment[95], LDs also provide a defence mechanism used by macrophages to limit the ability of bacteria to utilize host lipids. Moreover, LDs serve as antimicrobial hubs, enriched with multiple host defence proteins that interact with intracellular bacteria to promote their eradication[30,96,97]. To overcome LD restriction, *M. tuberculosis* relies on the accumulation of host metabolic intermediates derived from increased glycolytic flux. Unlike other intracellular pathogens in which carbon metabolism is regulated by catabolite repression, *M. tuberculosis* uniquely allows co-catabolism of different carbon sources[98]. During the first hours of infection, a total of 33 different host-derived compounds can be co-utilized by the intracellular bacteria as carbon sources[99]. For example, utilization of L-lactate by *M. tuberculosis* was found to be essential for its intracellular survival and can be used as a sole carbon source for growth in culture media[100] (Fig. 3a). This metabolic plasticity suggests a bacterial strategy that promotes adaptation to pro-inflammatory metabolic changes of the host.

During macrophage metabolic reprogramming, *M. tuberculosis* is exposed to host oxidative and nitrosative stress derived from the accumulation of mROS and iNOS induction. To survive, *M. tuberculosis* downregulates its metabolism to enter a non-replicating dormant state. This state also provides *M. tuberculosis* with better tolerance to antibiotics and hypoxic conditions[101,102]. Bacterial dormancy is regulated by two sensor histidine kinases, DosS and DosT, that detect NO and CO and activate the dormancy-survival regulator (DosR; Fig. 3a)[103]. Itaconate inhibits the *M. tuberculosis* enzymes Icl and propionyl-coA carboxylase that are part of the glyoxylate shunt and citramalate cycle[13,17]. During intracellular infection, *M. tuberculosis* requires these enzymes for cholesterol and fatty-acid metabolism. *M. tuberculosis* has acquired an itaconate-degradation operon that, unlike other bacterial species, contains a bifunctional enzyme (Rv2498c). In addition to its role in itaconate degradation, Rv2498c participates in the catabolism of L-leucine, an essential amino acid for *M. tuberculosis* virulence and intracellular survival[104–106]. Interestingly, leucine uptake by *M. tuberculosis*-infected macrophages regulates pro-inflammatory activation[107]. In LPS-activated macrophages, catabolism of branched-chain amino acids (for example, leucine) regulates itaconate induction and glycolysis[108] (Fig. 4a). This suggests a host–pathogen crosstalk that converges on itaconate and leucine metabolism[109], and proposes a model whereby *M. tuberculosis* adapts to changes in the metabolic environment of macrophages following infection.

In addition to their role in energy metabolism, host fatty acids and cholesterol are essential for *M. tuberculosis* virulence. Accumulation and metabolism of host fatty acids were suggested as a mechanism that promotes transcriptional adaptation of *M. tuberculosis* to the hypoxic environment of infected macrophages[95,101]. One example of an allosteric interaction of *M. tuberculosis* with its host macrophage is when propionyl-CoA, a toxic metabolite for *M. tuberculosis*, accumulates due to the metabolism of host cholesterol. To reduce propionyl-CoA toxicity, *M. tuberculosis* converts propionyl-CoA to methylmalonyl-CoA, a metabolite that can fuel bacterial energy metabolism or be transformed to lipids such as PDIM (Fig. 4a). These lipid-virulence factors are essential for intracellular infection[110,111].

Host immunometabolism during *M. tuberculosis* infection is also dependent on the infecting *M. tuberculosis* strain. Modification of the cell-wall lipid composition of multidrug-resistant *M. tuberculosis* strains was shown to modulate macrophage metabolic reprogramming[112]. The host metabolic response following infection depends on whether the bacteria are pathogenic or non-pathogenic species and live or dead, and is distinct from the metabolic profile of LPS-treated macrophages[113,114]. Although several molecular mechanisms by which *M. tuberculosis* subverts the pro-inflammatory response of the host via manipulation of its metabolic state and epigenetic modifications were recently described[115,116], a comprehensive understanding of both the host and the different *M. tuberculosis* species throughout the infection process is still lacking.

***Salmonella* is a metabolic generalist.** *S. enterica* serovar Typhimurium is a Gram-negative facultative intracellular pathogen. Unlike *M. tuberculosis*, *S.* Typhimurium has evolved to survive and grow in a wide range of environments and can infect a broad range of hosts. In humans, *S.* Typhimurium causes disease ranging from acute self-limiting gastroenteritis to systemic infection in susceptible patients[117]. The highly inflammatory nature of LPS derived from *S.* Typhimurium induces rapid activation of host macrophages (through TLR4) and rapid metabolic changes[26]. Adaptation of *S.* Typhimurium to different environmental conditions and rapidly fluctuating intracellular niches shaped its ability to utilize numerous carbon sources to fuel its energy metabolism. During intracellular infection of macrophages, *S.* Typhimurium resides within the *Salmonella*-containing vacuole (SCV), a specialized membrane-bound compartment characterized by a nutrient-poor environment[118]. From within the SCV, *S.* Typhimurium employs type-three secretion systems encoded on the *Salmonella* pathogenicity islands (SPI) 1 and 2 that penetrate the vacuole membrane and secrete a set of bacterial proteins, termed effectors, into its host cytosol. These effectors are aimed at subverting the macrophage defences and promote assembly of an intracellular protective niche necessary for bacterial survival and replication[118]. *S.* Typhimurium is considered to be a metabolic generalist that is able to exploit numerous host metabolites to meet the bacterial energetic demands for intracellular growth[119] (for a detailed in-depth analysis of *S.* Typhimurium intracellular metabolism, see a recent review[120]). The metabolic arms race between intracellular *S.* Typhimurium and its host leads to the emergence of host resistance factors that restrict nutrient availability to intracellular *S.* Typhimurium[82]. In parallel, *S.* Typhimurium evolved mechanisms for host-nutrient acquisition. One such bacterial mechanism is mediated by *Salmonella*-induced filaments, tubular membrane compartments generated by bacterial manipulation of the host endosomal system that promote cargo-hijacking of host nutrients[121]. However, it is still unclear what host nutrients are available to *S.* Typhimurium within the SCV and how they enter the vacuole.

The metabolic crosstalk between host macrophages and *S.* Typhimurium can be assessed in two main models of infection that differ in their metabolic profiles. Acute infection models are characterized by an aggressive inflammatory response. Mouse strains (for example, C57BL6/J mice) that lack a functional *Nramp1* gene (also known as *Slc11a1*), which is responsible for exporting divalent metal cations out of the SCV, afford an *S.* Typhimurium-sensitive acute infection phenotype[82]. In these mice, intracellular *S.* Typhimurium rapidly replicates in macrophages and induces a robust pro-inflammatory response that relies on glucose metabolism of the host[122]. In contrast, chronic infection models involve *S.* Typhimurium persistence for

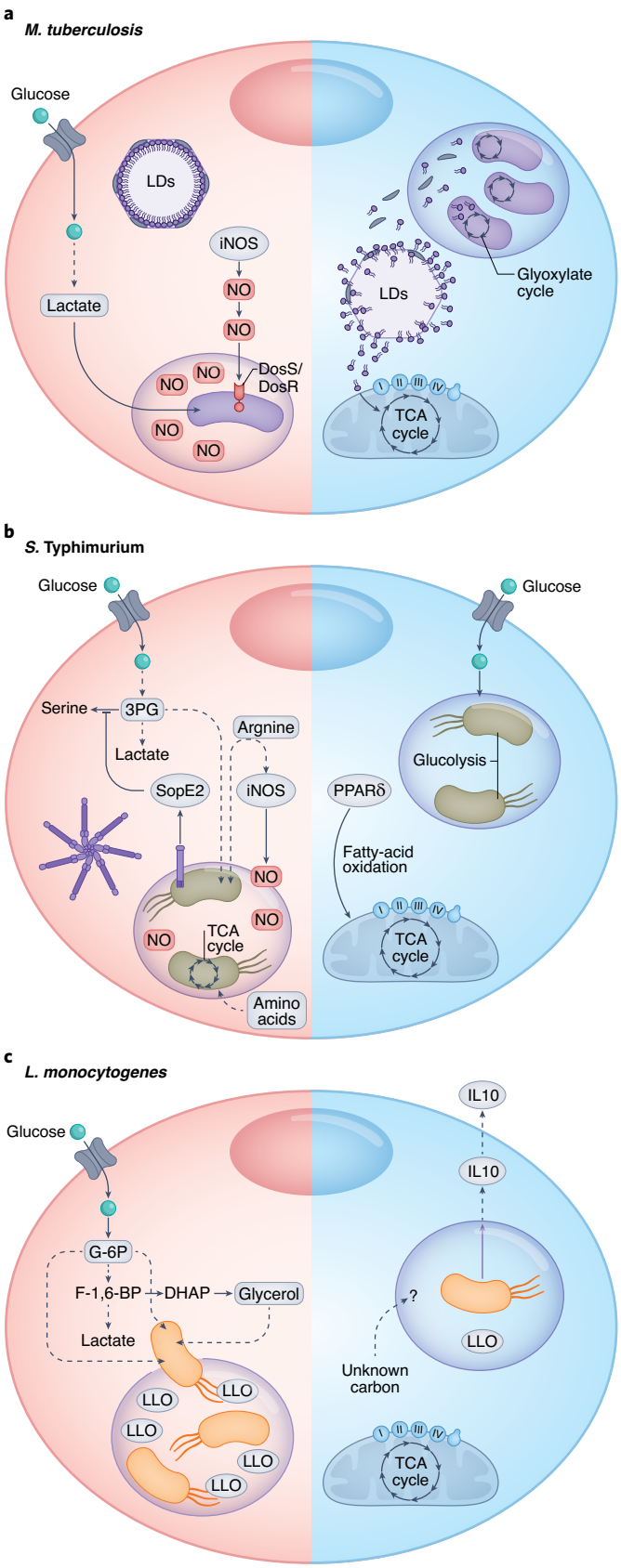

Fig. 3 | Immunometabolites as precursors for carbon metabolism of intracellular pathogens. a, *M. tuberculosis* residing in pro-inflammatory macrophages (pink; left) utilize host lactate as a carbon source. NO generated by iNOS is detected by the DosS–DosR two-component system to promote bacterial persisters. *M. tuberculosis* residing in anti-inflammatory macrophages (blue; right) utilize cholesterol and fatty acids as a carbon source fuelling the bacterial glyoxylate cycle. **b**, In pro-inflammatory macrophages (pink; left), the *S. enterica* serovar Typhimurium effector SopE2 inhibits host serine metabolism and promotes bacterial accessibility to 3PG as a carbon source. Arginine uptake by *S.* Typhimurium reduces the arginine accessibility to host iNOS, leading to a decrease in NO synthesis. Bacterial uptake of host amino acids fuels its TCA cycle and prevents inflammasome activation. In anti-inflammatory macrophages (blue; right), fatty-acid oxidation mediated by PPARδ activation promotes glucose uptake by *S.* Typhimurium, fuelling bacterial glycolysis. **c**, Cytosolic *L. monocytogenes* in pro-inflammatory macrophages (pink; left) utilize G-6P and glycerol accumulated in the macrophage cytosol during glucose metabolism. In anti-inflammatory macrophages (blue; right), *L. monocytogenes* resides in SLAPs and induces secretion of the antimicrobial cytokine IL-10. DHAP, dihydroxyacetone phosphate; F-1,6-BP, fructose 1,6-bisphosphate.

long durations with only minor immune responses. Mouse models of chronic infection mainly require complementation of a functional *Nramp1* gene (for example, 129sv mice[123]). During chronic infection, anti-inflammatory macrophages switch their energy metabolism to fatty-acid oxidation to fuel their anti-inflammatory activation state, which is regulated by PPARδ. In turn, bacterial availability to host glucose due to macrophage fatty-acid oxidation support the intracellular metabolism and survival of *S.* Typhimurium[124]. Besides glucose metabolism, the persistence of *S.* Typhimurium during chronic infection requires fatty-acid utilization through the glyoxylate shunt[125] (Fig. 3b). Further characterization of the immunometabolic crosstalk can provide insight to chronic infection and persistence of intracellular pathogens.

In addition to its role in supplying energy demands, bacterial carbon metabolism can induce processes that mitigate the antimicrobial defences of pro-inflammatory macrophages. To reduce host-induced nitrosative stress, *S.* Typhimurium takes up host arginine and depletes the cytosolic arginine that is required for NO synthesis by iNOS arginine metabolism[126]. Furthermore, ROS produced by pro-inflammatory macrophages were shown to collapse the proton motive force across *S.* Typhimurium membranes, leading to impaired folding of bacterial periplasmic proteins. To reduce the electron flow over the membrane, *S.* Typhimurium metabolism shifts to glycolysis as an antioxidant defence to preserve its ΔpH[127]. The *S.* Typhimurium shift to glucose metabolism may also be harmful for the bacterial infection cycle. Bacterial utilization of host glucose disrupts macrophage glycolytic flux and acts as a signal for rapid activation of the host NLRP3 inflammasome and host-cell death[128]. This paradox of *S.* Typhimurium glycolysis shift has recently been resolved. Instead of disrupting the glucose metabolism of its host, *S.* Typhimurium exploits the glycolysis intermediate 3-phosphoglycerate (3PG)[122]. Accumulation of 3PG is achieved through secretion of the SPI-1 effector SopE2, which subverts the host serine synthase pathway. Moreover, to evade inflammasome detection and prevent the induction of the inflammasome-mediated pro-inflammatory response, *S.* Typhimurium inhabiting pro-inflammatory macrophages were shown to also rely on amino-acid and fatty-acid metabolism to fuel their TCA cycle[129,130] (Fig. 3b). Additional bacterial effectors that help *S.* Typhimurium elude pro-inflammatory cytotoxicity of the host are SopD2 and GtgE, which target host RAB32 and prevent itaconate delivery to the SCV[15]. Finally, a bacterial strategy to evade the macrophage antibacterial defences is to actively reprogramme host polarization to an anti-inflammatory state[49]. Secreted steE, an SPI-2 effector, was shown to interact with the host enzyme GSK3 to

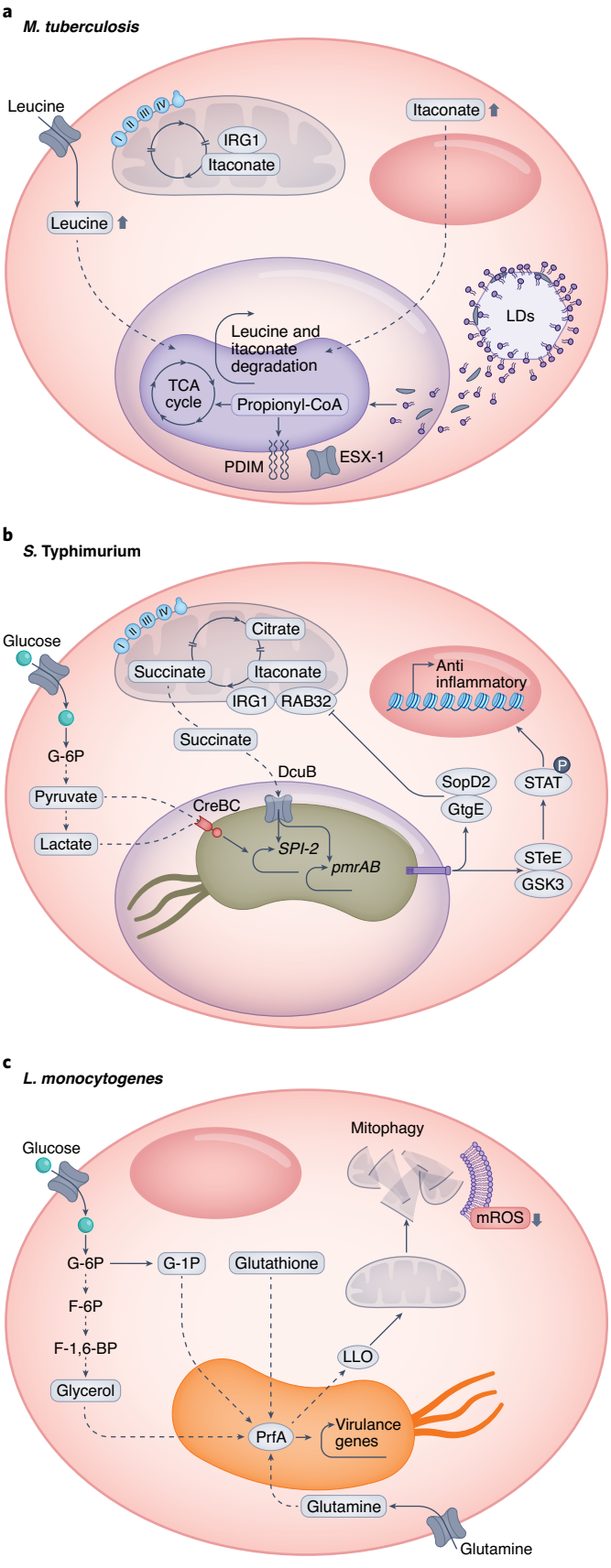

Fig. 4 | Immunometabolites as signalling cues that induce bacterial virulence. a, Intracellular *M. tuberculosis* utilize host cholesterol and fatty acids from LD degradation, resulting in the accumulation of propionyl-CoA. Propionyl-CoA is directed to fuel bacterial respiration or transformed to PDIMs, inducing bacterial virulence, including regulation of the ESX-1 secretion system. Leucine and itaconate accumulated in pro-inflammatory macrophages are detected by *M. tuberculosis* and induce the expression of the leucine and itaconate-degradation operon. **b**, Pyruvate and lactate accumulated in pro-inflammatory macrophages are detected by *S.* Typhimurium via the two-component system CreBC to induce the expression of the SPI-2 virulence regulon. Succinate accumulated in pro-inflammatory macrophages is taken up by the bacteria via the DcuB transporter to induce expression of the SPI-2 and PmrAB virulence regulons. The bacterial effectors SopD2 and GtgE target the host RAB32 and prevent itaconate delivery to the SCV. SteE interacts with the host GSK3 protein and promotes STAT3 phosphorylation, leading to the expression of anti-inflammatory genes. **c**, Host glucose-1-phosphate (G-1P), glycerol and glutathione (which accumulate in pro-inflammatory macrophages) as well as glutamine (which accumulates in anti-inflammatory macrophages) activate PrfA, the virulence master regulator of *L. monocytogenes*, to induce the expression of bacterial virulence genes. LLO secreted by *L. monocytogenes* promotes mitochondrial mitophagy and reduces the levels of mROS.

promote STAT3 phosphorylation. This phosphorylation leads to STAT3 nuclear translocation and expression of the host anti-inflammatory gene profile, and promotes long-term bacterial persisters[131] (Fig. 4b).

Host immunometabolites that accumulate in pro-inflammatory macrophages also act as signals for the induction of *S.* Typhimurium virulence, independently of their role in central metabolism. Bacterial sensing of host-derived pyruvate and lactate by the two-component system CreBC was shown to induce signal transduction that results in the induction of the SPI-2 regulon[122]. Moreover, host-derived succinate was shown to induce the expression of both SPI-2 and PmrAB regulons, essential for bacterial antimicrobial peptides resistance[132] (Fig. 4b). Interestingly, whereas pyruvate and lactate induce bacterial virulence through membrane signalling, succinate-induced virulence requires active bacterial uptake of succinate, mediated by the C4-dicarboxy transporter DcuB (Fig. 4b). The intracellular signalling pathway responsible for succinate-induced virulence of *S.* Typhimurium is yet to be determined. Importantly, disruption of host-derived metabolite signalling in bacteria deficient in lactate and pyruvate sensing or succinate transport leads to impaired intracellular survival and in vivo infection.

Intracellular lifestyle of *Listeria monocytogenes* and immunometabolism. *L. monocytogenes*, the causative agent of listeriosis, is a Gram-positive facultative intracytosolic pathogen. The energy metabolism and virulence of *L. monocytogenes* are tightly intertwined and regulated by signals coming from the metabolic environment of the host. Following macrophage uptake, the secretion of the pore-forming toxin listeriolysin O (LLO) and phospholipase C by *L. monocytogenes* promotes its rapid escape from the nutrient-deprived environment of the phagosome into the glycolytic intermediate-enriched environment of the host cytosol[133]. This escape is controlled by the master virulence regulator PrfA, a transcriptional regulator responsible for the expression of most of *L. monocytogenes* virulence genes[134]. Interestingly, PrfA also regulates the bacterial uptake of host glycerol and glucose-6-phosphate (G-6P), metabolites that accumulate in the cytosol of pro-inflammatory macrophages during metabolic reprogramming[135–137] (Fig. 3c). ^{13}C-isotopologue profiling of the carbon metabolism of *L. monocytogenes* during intracytosolic infection has shown that these metabolites are exploited to fuel bacterial energy metabolism and anabolic processes essential for intracytosolic replication and survival[138]. Conversely, multiple host-derived metabolites associated with both pro- and anti-inflammatory macrophages regulate PrfA activation. The host pro-inflammatory metabolites glucose-1-phosphate and glycerol were shown to act as signals that activate PrfA[136,139]. Uptake of these metabolites was suggested to release PrfA from interactions with the phospho-enolpyruvate phosphotransferase system complex. Moreover, host-derived glutathione, accumulated in pro-inflammatory macrophages, was shown to regulate PrfA activation through allosteric binding[140,141]. Glutamine, which fuels the activation of anti-inflammatory macrophages, was shown to be essential for *L. monocytogenes* virulence induction and regulate PrfA activation through protein–metabolite interactions[6,142]. Thus, host immunometabolic changes are sensed by *L. monocytogenes* to repress its virulence outside the host, in the presence of phospho-enolpyruvate phosphotransferase system-dependent sugars (such as glucose), and for timely activation within the cytosolic milieu[143] (Fig. 4c).

Although mostly considered for its cytosolic lifestyle, *L. monocytogenes* has an alternative intracellular fate and can reside in spacious *Listeria*-containing phagosomes (SLAPs), a phagosomal niche mediated by bacterial manipulation of the LC3-associated phagosome[144]. *L. monocytogenes* inhabiting the SLAP environment have been characterized as slow-growing bacteria expressing low concentrations of LLO and suggested to be the core of persistent infection[144,145]. Intraphagosomal *L. monocytogenes* were shown to induce IL-10 secretion mediated by constant endosomal TLR2 signalling[146]. IL-10 secretion suppresses host adaptive immunity and promotes bacterial survival. However, the metabolic environment of SLAPs and bacterial metabolism under this host activation state are still not well understood (Fig. 3c).

The strategy employed by *L. monocytogenes* to evade host defences and regulate its intracellular fates is mediated by targeting the host mitochondria. Secretion of LLO was shown to promote mitochondrial fragmentation and mitophagy, which leads to decreased mROS production and promotes *L. monocytogenes* survival[145,147] (Fig. 4c). Moreover, a recent study has shown that LLO-mediated modulation of mitochondrial Ca^{2+} signalling alters mitochondrial metabolism and increases acetyl-coA accumulation. This hijacking of the mitochondrial metabolic pathways promotes its escape from phagosomes[148].

Outlook for immunometabolic drugs

The ability of pathogens to exploit metabolites that accumulate in inflamed mucosae or in the intracellular environment provides druggable targets to inhibit or prevent infection. Drugs aimed at clearing bacterial disease need to take into consideration not only the capacity of pathogens to adapt to metabolic stress but also how alternative routes used to generate energy are linked to the local metabolic response to infection. A few highly effective antibiotics—such as those that target the folic-acid pathway, the sulfonamides and trimethoprim—selectively block bacterial, but not host, metabolism. However, the overlap in many bacterial and host metabolic enzymes limit the effectiveness of other cell-unspecific drugs that might damage host cells and the mucosa while inflicting damage to the opportunists. Future studies involving docking dynamics for new molecules on both host and pathogen proteins might facilitate the selective inhibition of metabolic routes that both potentiate host immunity and clear infection.

Immunometabolites in the intracellular niche. Passage of immunometabolites across plasma membranes requires active transport; the mechanisms that afford immunometabolites transport into the bacterial phagosome remain to be determined. Phagosomal-transporter candidates might be found within the solute carrier family. Solute carrier proteins facilitate the transport of diverse substrates across biological membranes, including C4-dicarboxylate metabolites such as the immunometabolite succinate and monocarboxylates like lactate and pyruvate[75]. Future studies may determine whether these transporters are located on the bacterial phagosome and, if so, whether the pathogen phagocytosis is directed to areas of the macrophage membrane enriched with these transporters.

Immunometabolites as bacterial signalling molecules. Host immunometabolites were shown to regulate bacterial virulence through activation of two-component systems[122]. It is tempting to speculate that immunometabolites can regulate bacterial virulence via a yet-to-be-described PTM, similar to what was shown for host cellular processes[35]. Alternatively, immunometabolites can modify gene expression via chromatin-associated modifications[46,47] that may also be relevant in bacteria. Access restriction of pathogens to immunometabolites can be used to restrain pathogen virulence. This restriction can be mediated by preventing the entry of immunometabolites to the phagosome or inhibiting bacterial transporters that facilitate immunometabolite uptake. As a viable option, the transporter responsible for bacterial itaconate uptake is yet to be determined.

Immunometabolites and biofilm formation. Bacteria often respond to stress induced by the host, such as itaconate, by altering

their metabolic activity to generate protective glycoconjugates, which have a major antioxidant function. This is the case for EPS that are synthetized by strains recovered from patients with chronic infection who have received antimicrobial therapies. Accepted dogma indicates that these surface polymers are less immunostimulatory than LPS and are produced to protect biofilm communities from membrane stress, oxidants, complement and antibodies generated by the host. However, these EPS are indeed associated with the activation of host metabolic signalling, including the generation of itaconate. The development of microbial communities encased in biofilm becomes a protected nidus of infection, harbouring organisms with diminished metabolic activity that are less susceptible to the cidal activity of antimicrobial agents and able to persist. Prevention of biofilm development could be achieved by blocking the signals that activate bacterial EPS biosynthesis, such as those derived from the host and the pathogen itself.

Conclusion

Although awareness of the pathways that sustain the metabolic entanglement between bacteria and their host may provide new opportunities for antimicrobials, most of this knowledge relies on studies of LPS-treated cultured macrophages[19]. What is needed now is an understanding of the different metabolic states of macrophage subsets within the tissue during in vivo infection[91]. For example, CFTR correctors, which rescue CFTR function in cystic-fibrosis cells, recently approved by the FDA might restore itaconate metabolic homeostasis in CFTR mutant phagocytes and thus limit *Pseudomonas* persistence. This rationale might be applied to other pathological states, such as chronic gut inflammation, and to other pathogens. Moreover, our knowledge of the metabolic profile of human macrophages is limited and further metabolic adaptations may yet be discovered[11,149,150].

Understanding the metabolic preferences of specific pathogens in specific tissues and organs in humans might enable metabolotherapy to prevent infection. Innovative complementary therapies that target host or bacterial metabolism could contribute to improved medicines for infectious diseases.

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Competing interests

The authors declare no competing interests.

Additional information

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