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REVIEW

SPECIAL ISSUE: CELL BIOLOGY OF HOST–PATHOGEN INTERACTIONS

Cellular metabolism in the defense against microbes

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ABSTRACT

The study of metabolic changes associated with host–pathogen interactions have largely focused on the strategies that microbes use to subvert host metabolism to support their own proliferation. However, recent reports demonstrate that changes in host cell metabolism can also be detrimental to pathogens and restrict their growth. In this Review, I present a framework to consider how the host cell exploits the multifaceted roles of metabolites to defend against microbes. I also highlight how the rewiring of metabolic processes can strengthen cellular barriers to microbial invasion, regulate microbial virulence programs and factors, limit microbial access to nutrient sources and generate toxic environments for microbes. Collectively, the studies described here support a critical role for the rewiring of cellular metabolism in the defense against microbes. Further study of host–pathogen interactions from this framework has the potential to reveal novel aspects of host defense and metabolic control, and may inform how human metabolism impacts the progression of infectious disease.

KEY WORDS: Microbes, Metabolism, Mitochondria, Nutrients, Metabolites, Cellular defense, Immunity, Host–pathogen interaction

Introduction

A property common to most, if not all, pathogens is the need and capacity to scavenge metabolites from the host cell (Brown et al., 2008). Accordingly, the perception of the metabolic host–pathogen interaction is that microbes shape host metabolism to accommodate their nutrient needs (Eisenreich et al., 2019; Thaker et al., 2019). However, a logical evolutionary consequence of the microbial dependence on host nutrients is the emergence of metabolic mechanisms that enable host cells to counter microbial infection. Although we have reached a significant level of comprehension of the ways in which microbes manipulate the host cell to acquire the nutrients they need (Abu Kwaik and Bumann, 2015; Best and Abu Kwaik, 2019; Brown et al., 2008; Thaker et al., 2019), we are surprisingly limited in our understanding of the mechanisms and the extent to which the host cell rewires metabolic processes to defend itself against microbes.

In this Review, I describe metabolic mechanisms that cells use to protect against infection with diverse intracellular pathogens, including viruses, bacteria and parasites. I begin by outlining how the modulation of the plasma membrane composition hinders microbial invasion. Next, I discuss how the host cell exploits metabolite-based regulation of protein activity and gene expression to attenuate the virulence and slow the proliferation of microbes that have successfully invaded. Finally, I provide an overview of strategies by which the host cell starves microbes of nutrients, and conversely, delivers metabolites that are harmful to microbes. Altogether, the examples and framework presented here indicate that the metabolism of a host cell should not simply be perceived as a 'growth medium' for intracellular microbes, but as a key executor of host defense during microbial infection.

Cellular strategies of metabolic defense against microbes

Keeping strangers out – metabolic modulation of the plasma membrane

Residence within a host cell is required for intracellular pathogens that have lost their capacity to live outside of their hosts, and can also protect pathogens against immune defenses, such as neutrophil killing and complement activation (Casadevall, 2008). Consequently, pathogens have evolved diverse mechanisms for achieving cell entry, many of which rely on the structural lipids of the host plasma membrane (PM) (Pizarro-Cerda and Cossart, 2006). Cholesterol, which constitutes 20–25% of host PM lipids (Ikonen, 2008), is a key molecule in this regard because it is used by a variety of viruses and bacteria for cell adhesion and internalization (Bukrinsky et al., 2020; Goluszko and Nowicki, 2005; Ikonen and Jansen, 2008). Not surprisingly, the host cell exploits the dependence of pathogens on PM cholesterol to thwart bacterial entry. For example, a recent study found that epithelial cells treated with medium from interferon-γ (IFNγ)-treated murine bone marrow-derived macrophages (mBMDMs) become highly resistant to infection with the bacterium *Listeria monocytogenes* (Abrams et al., 2020). This resistance was conferred by an increase in the levels of the oxysterol 25-hydroxycholesterol (25-HC), which triggers the internalization of PM cholesterol in a manner dependent on the enzyme acyl-CoA:cholesterol acyltransferase (ACAT), rendering it inaccessible to *L. monocytogenes* (Fig. 1). An analogous mechanism also protects against specific pore-forming toxins that are secreted by bacteria and require membrane cholesterol for their effector function (Zhou et al., 2020) (Fig. 1). Given the ubiquitous importance of cholesterol for processes essential for microbial invasion, such as cellular adhesion by diverse bacteria, fusion-based entry of diverse viruses, such as influenza, and the release of effector proteins by *Toxoplasma*, the relocalization of PM cholesterol to intracellular storage likely protects cells against invasion by other pathogens that coopt host cholesterol for entry (Coppens and Joiner, 2003; Goluszko and Nowicki, 2005; Takeda et al., 2003).

Plasma membrane sphingolipids are also used by certain microbes to promote entry, and their intracellular distribution can be remodeled to restrict microbial invasion (Kunz and Kozjak-Pavlovic, 2019). Under conditions of cellular stress, acid sphingomyelinase (ASM) translocates from the lysosome to hydrolyze PM sphingomyelin, giving rise to ceramide-rich platforms and decreasing access of the bacterium *Shigella flexneri* to the sphingolipids required for its attachment and entry into intestinal epithelial cells (Lafont et al., 2002; Tawk et al., 2018) (Fig. 1). Furthermore, the free replication of *S. flexneri* in the cytosol

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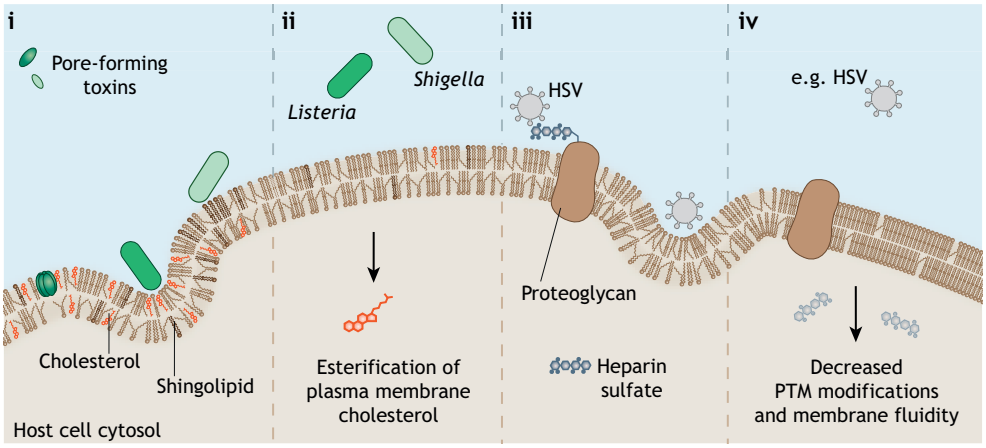

Fig. 1. Metabolic modulation of cellular barriers to limit pathogen entry. Host plasma membrane factors important for microbial entry, and established and hypothetical strategies to limit microbial invasion through modulation of the PM are depicted. (i) Cell surface cholesterol mediates *Listeria* invasion and the insertion of bacterial pore-forming toxins into the PM, whereas *Shigella* utilizes host sphingolipids for invasion. (ii) Mobilizing cell surface cholesterol for esterification inhibits *Listeria* invasion and the insertion of pore-forming toxins. Acid-spingomyelase decreases *Shigella* access to the host sphingolipids. (iii) Heparan sulfation of proteoglycans is required for binding of herpes simplex 1 virus (HSV). (iv) The modulation of plasma membrane fluidity and membrane protein modifications are hypothetical scenarios that could restrict invasion by pathogens.

activates ASM-mediated membrane remodeling and suppresses re-infection, suggesting that, following an initial infection, cells employ strategies to defend against secondary microbial invasion events (Tawk et al., 2018).

Metabolite-based post-translational modifications (PTMs) of the PM, such as the heparan sulfation of proteoglycans, are also essential for microbial invasion. Experimental manipulations that decrease the availability of sulfated proteoglycans prevent infection by several microbes, including the eukaryotic pathogen *Toxoplasma gondii*, hepatitis C virus (HCV) and herpes simplex 1 virus (HSV) (Barth et al., 2003; Carruthers et al., 2000; Shukla et al., 1999) (Fig. 1). Thus, the modulation of PTMs coopted by microbes for invasion may be an additional host mechanism that restricts microbial entry. Of note, the bacterium *Pseudomonas aeruginosa* glycosylates surface pili to protect against phage attachment and infection, demonstrating that the metabolic modulation of surface molecules is a viable strategy to restrict infection, although to date this has only been demonstrated in prokaryotes (Harvey et al., 2018).

Pulling the strings – host modulation of microbial gene expression and protein function

A pathogen that has successfully invaded a host cell must adapt to an intracellular lifestyle and assemble the machinery required for its replication, virulence and exit from the host cell (Casadevall, 2008). Such adaptations, whether they occur at the protein, transcriptional or epigenetic level, can be regulated by metabolites (Rinschen et al., 2019). Because most microbes reside in the cytosol or in membrane-bound compartments accessible by host metabolites, the host has an opportunity to interfere with these processes and thus undermine microbial success.

Previous work has focused on host modifications of microbial effector proteins that benefit the invading microbe (Popa et al., 2016). For example, the host-mediated farnesylation of the *Legionella pneumophila* effector protein AnkB is required for its anchorage to the bacterial vacuole and promotes the virulence of *L. pneumophila* in mice (Ivanov et al., 2010; Price et al., 2010). However, recent work has shown that host metabolites can also modify the activity of a pathogen protein to its detriment. Herpesvirus human cytomegalovirus (HCMV) proteins, such as the viral tegument protein pUL26, which is essential for HCMV replication, are acetylated throughout different stages of infection (Mathers et al., 2014; Murray et al., 2018; Stamminger et al., 2002). Importantly, the introduction of an acetyl-mimic of pUL26 reduces HCMV production, whereas a non-acetylatable charge-mimic of pUL26 (K203R) produces a higher virus titer than the wild-type protein, supporting the idea that host acetylation of viral proteins serves to restrict viral proliferation (Murray et al., 2018) (Fig. 2).

Host metabolites can also attenuate microbial virulence by targeting the transcriptional regulation of the type III secretion system (TTSS), a syringe-like structure that enables bacteria to inject effector proteins into host cells. Plants infected with *Pseudomonas syringae* accumulate the metabolite sulforaphane, which modifies a bacterial transcription factor required for the expression of TTSS genes and thus effectively neutralizes the pathogen in the extracellular space (Deng et al., 2017; Wang et al., 2020). Emerging evidence suggests that mammalian metabolites may also subvert transcriptional regulation of the TTSS in microbes. The levels of 5′methylthioadenosine (MTA), a methionine salvage pathway metabolite that represses the *Salmonella* pathogenicity island-1 (SPI-1)-encoded TTSS gene expression (Fig. 2), transiently increase in the serum of mice infected with *Salmonella enterica* (Bourgeois et al., 2018; Wang et al., 2017). However, the mechanism by which host MTA affects *Salmonella* gene expression, and whether MTA is produced at high enough levels during infection to dysregulate *Salmonella* SPI-1 gene expression, remain open questions. Metabolites are key players in epigenetic, transcriptomic and proteomic regulation (Rinschen et al., 2019); therefore, addressing how host metabolites influence microbial ‘omics’ to benefit the host represents an exciting new chapter in studying host–pathogen interactions.

Hunger games – minimizing microbial access to host nutrients

Perhaps the biggest challenge a microbe faces is the acquisition of the nutrients needed to satisfy the substrate and energetic demands for proliferation, such as the estimated ∼8–20 billion ATP molecules required for the generation of an *E. coli* daughter cell (Feist et al., 2007; Orth et al., 2011). For certain microbes, this

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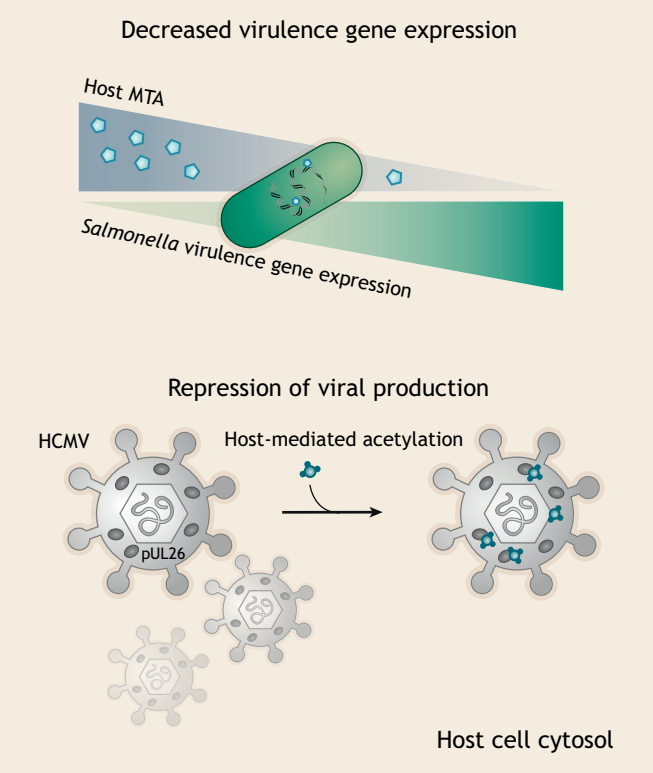

Fig. 2. Modulation of microbial processes by host metabolites. Host metabolites impact protein function, transcription and epigenetic regulation in microbes. Top, methylthioadenosine (MTA), a methionine salvage pathway metabolite, decreases *Salmonella typhimurium* virulence by repressing pathogenicity island-1 (SPI-1) genes. Bottom, the acetylation of the human cytomegalovirus (HCMV) pUL26 proteins inhibits viral production.

challenge is additionally coupled with a dependence on the host for essential nutrients that they have lost the capacity to synthesize. For example, the apicomplexan parasite *Toxoplasma*, which resides in a non-fusogenic vacuole within its host cell, is both auxotrophic for cholesterol and purines, which are needed for membrane and nucleic acid synthesis, respectively (Tymoshenko et al., 2015). Viruses, of course, are wholly dependent on their host for every building block required for their replication (Eisenreich et al., 2019; Thaker et al., 2019). Thus, host strategies that limit the access of pathogens to key nutrients would inhibit their proliferation and promote the chances of the host of clearing the infection.

Starving microbes of trace metals, which are cofactors in many essential biological processes (Andreini et al., 2008), restricts microbial virulence and proliferation and underlies the well-appreciated host defense known as nutritional immunity (Palmer and Skaar, 2016; Weinberg, 1975). Cells can starve phagosome-dwelling microbes, including *Salmonella, Mycobacteria* and *Leishmania*, of essential metals, such as iron and manganese (Fe^{2+}/Fe^{3+} and Mn^{2+}), by redirecting their transport from the phagosome into the cytosol through the natural resistance-associated macrophage protein 1 (NRAMP1; also known as SLC11A1) transporter (Cunrath and Bumann, 2019; Wessling-Resnick, 2015). Alternatively, iron can be relocated to the extracellular medium by the PM transporter ferroportin to prevent access by cytosolic pathogens (Chlosta et al., 2006; Nairz et al., 2007) (Fig. 3). Additionally, metal chelators like ferritin enable the host cell to maintain intracellular stores of metals while simultaneously rendering them inaccessible to certain intracellular pathogens. For a comprehensive discussion of nutritional immunity, I direct readers to a recent review (Palmer and Skaar, 2016).

Independent lines of evidence illustrate a key role for mitochondria in a nutritional immunity-like defense, particularly against microbes that reside within a membrane-bound niche within the host cell, and thus have reduced access to cytosolic nutrients. During infection with *Toxoplasma,* mitochondria elongate by fusion to enhance fatty acid (FA) uptake; in cells deficient for mitochondrial fusion and FA oxidation (FAO), parasites acquire more host FAs and grow faster (Pernas et al., 2018) (Fig. 3). Importantly, the pharmacological activation of FAO restricts parasite proliferation (Pernas et al., 2018). Together, these findings support a model in which mitochondria restrict *Toxoplasma* access to a key nutrient to limit its growth (Fig. 3). In addition to oxidizing substrates such as FAs to produce ATP, mitochondria generate anabolic precursors for biosynthetic processes, for example citrate (Pernas and Scorrano, 2016; Spinelli and Haigis, 2018). In low-oxygen environments, such as in many inflamed and infected tissues, hypoxia-inducible factor 1 α (HIF1α) impedes *Coxiella burnetti* replication by promoting a metabolic switch from oxidative phosphorylation to anaerobic glycolysis that consequently reduces intracellular citrate levels (Hayek et al., 2019). The exogenous addition of citrate rescues *Coxiella* replication during hypoxia, whereas the growth of bacteria upon inhibition of the mitochondrial citrate transporter in normoxic conditions phenocopies the low bacterial replication seen in hypoxic cells (Hayek et al., 2019). As major metabolic hubs, mitochondria profoundly impact the nutrient state of the cell – the sequestration of nucleotides by defective mitochondria can even limit the deoxynucleoside triphosphate (dNTPs) available for nuclear genome replication (Hamalainen et al., 2019). Therefore, investigating the competition for nutrients between mitochondria and microbes will undoubtedly be an interesting topic for future studies.

Metabolic enzymes can also function in host defense by catabolizing nutrients important for pathogen proliferation, such as dNTPs, which are essential for retroviruses that reverse transcribe viral RNA to a DNA intermediate in the host cytosol. Following its induction due to IFNγ stimulation or viral infection, the dNTP triphosphohydrolase (dNTPase) SAMHD1 restricts the replication of retroviruses, such as human immunodeficiency virus type 1 (HIV-1), by lowering the concentration of dNTPs below that required for efficient synthesis of viral DNA. Remarkably, the exogenous expression of SAMHD1 can reduce cellular dNTP pools by up to 95% (Baldauf et al., 2012; Laguette et al., 2011; Lahouassa et al., 2012; Li et al., 2000). The addition of exogenous nucleotides partially reverses SAMHD1-mediated restriction of HIV-1, supporting that nucleotide pool depletion by SAMHD1 inhibits viral replication (Baldauf et al., 2012; Lahouassa et al., 2012). Moreover, cells can also decrease intracellular levels of tryptophan, which is mediated by the IFNγ-dependent or -independent induction of indoleamine 2,3-dioxygenase (IDO-1) and limits the growth of several vacuole-dwelling microbes, including *Toxoplasma* and *Chlamydia* (Byrne et al., 1986; Pfefferkorn, 1984; Ziklo et al., 2019) (Fig. 3). Finally, the enzymatic processing of the polyunsaturated fatty acid (PUFA) arachidonic acid into pro-inflammatory prostaglandins, or of the amino acid arginine into nitric oxide (NO), which is converted into highly reactive oxygen species with antimicrobial properties, is a common consequence of microbial infection (Chakravortty and Hensel, 2003; Dupont, 1987; Hanna and Hafez, 2018; Jones et al., 2010). Interestingly, certain eukaryotic and prokaryotic pathogens are predicted to be auxotrophic for arachidonic acid and/or arginine, raising the question of whether the synthesis of prostaglandins and NO

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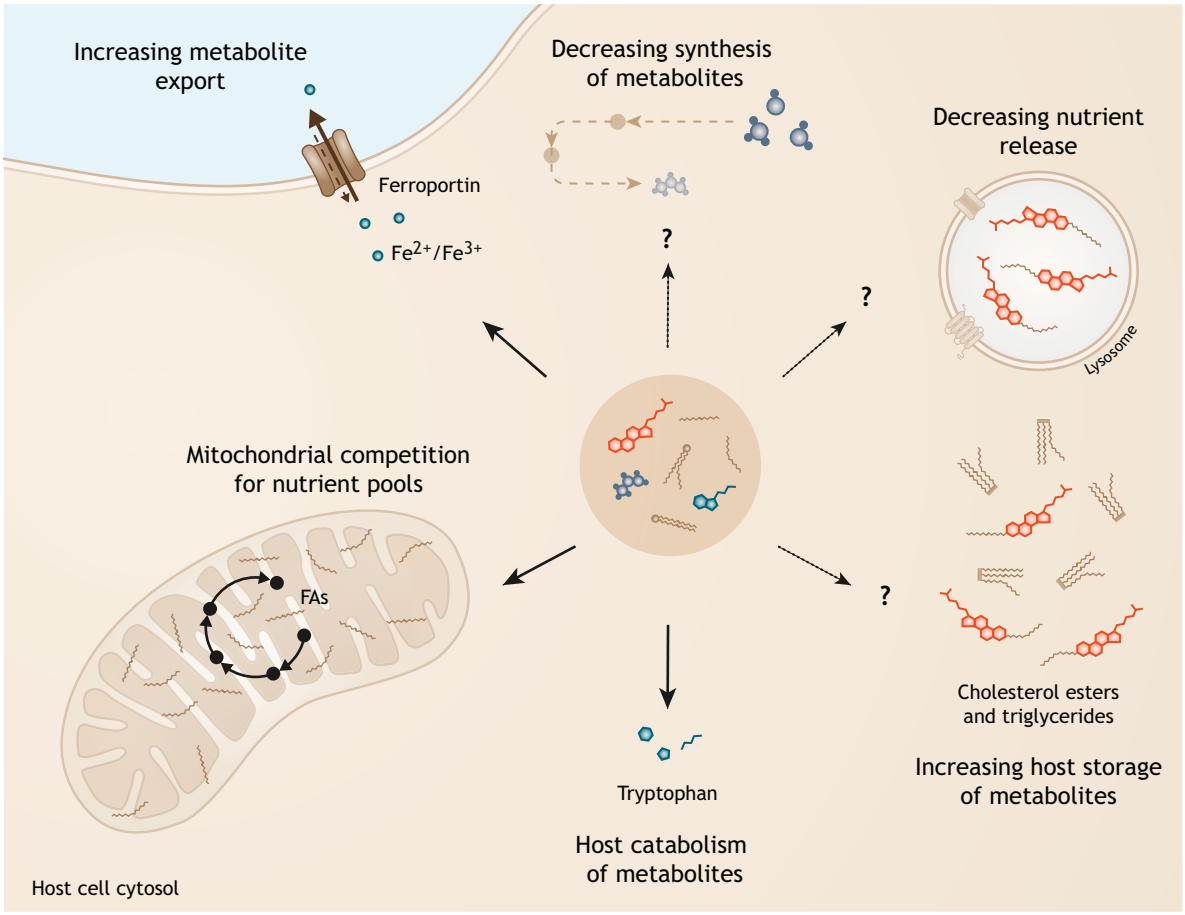

Fig. 3. Minimizing microbial access to host nutrients. A schematic of established and hypothetical strategies by which cells can limit microbial access to host nutrients is shown. Established strategies include the efflux of iron (Fe^{2+}/Fe^{3+}) into the extracellular medium by ferroportin to keep it from cytosolic pathogens, the degradation of tryptophan and enhanced mitochondrial uptake of fatty acids (FAs). Hypothetical strategies (indicated with dotted line-arrows and question mark) include the decreased synthesis of metabolites, decreasing the efflux of nutrients, such as cholesterol from the lysosome, and enhanced storage of energy-rich molecules, such as FAs, into triglycerides.

additionally serves to restrict pathogen access to these essential nutrients (Seif et al., 2020; Tymoshenko et al., 2015). As exemplified by the mechanisms described here, the diverse repertoire of metabolic processes of a mammalian cell can be weaponized to limit microbial fitness by restricting the levels of nutrients that pathogens rely on as growth signals, building blocks and energy sources.

Trojan horses – host metabolites that are deleterious to microbes

The mechanisms that enable microbes to import the metabolites needed to sustain vital processes leave them susceptible to host metabolites that have antimicrobial activity. Perhaps an example that best highlights the antimicrobial potential of such a molecule is the antibiotic penicillin, a fungal metabolite that is derived from cysteine, valine and the non-proteogenic amino acid α-aminoadipate and inhibits cell wall formation in bacteria (Clardy et al., 2009; Fleming et al., 1947). Although the synthesis of metabolites that inhibit the growth or reduce the viability of microbial invaders has been predominantly characterized as a defense strategy in non-mammalian organisms (Kronheim et al., 2018; Schwachtje et al., 2018), growing evidence supports their importance in the mammalian defense against microbial infection.

The metabolite itaconate has recently gained much attention for its role as an immunomodulatory factor and antimicrobial molecule (O'Neill and Artyomov, 2019) (Fig. 4). The immune-responsive gene 1 protein (IRG1) decarboxylates cis-aconitate, a metabolite made by the tricarboxylic acid (TCA) cycle in mitochondria, to generate itaconate following immune stimulation (e.g. by bacterial lipopolysaccharide) (Michelucci et al., 2013). The antimicrobial property of itaconate derives from its ability to inhibit isocitrate lyase, a bacterial enzyme of the glyoxylate cycle that is not present in mammals, but that enables the replenishment of TCA intermediates required for bacterial survival on fatty acid or acetate substrates (Cordes et al., 2015; Michelucci et al., 2013). Indeed, itaconate was shown to inhibit the growth of *Salmonella enterica* and *Mycobacterium tuberculosis* in medium supplemented with acetate (Michelucci et al., 2013). The development of a biosensor for itaconate has revealed that it accumulates in *Salmonella* upon epithelial cell infection and has identified Rab32 as a host factor required to deliver itaconate to the *Salmonella*-containing vacuole (Chen et al., 2020). The existence of dedicated machinery to deliver host itaconate into a microbial compartment suggests that the synthesis and delivery of antimicrobials may be a more widespread mechanism of the mammalian defense against microbes than currently appreciated (Chen et al., 2020). Unlike itaconate, which is newly synthesized following an immune stimulus, PUFAs, an important class of metabolites with broad anti-microbial activity, are generally present in membrane

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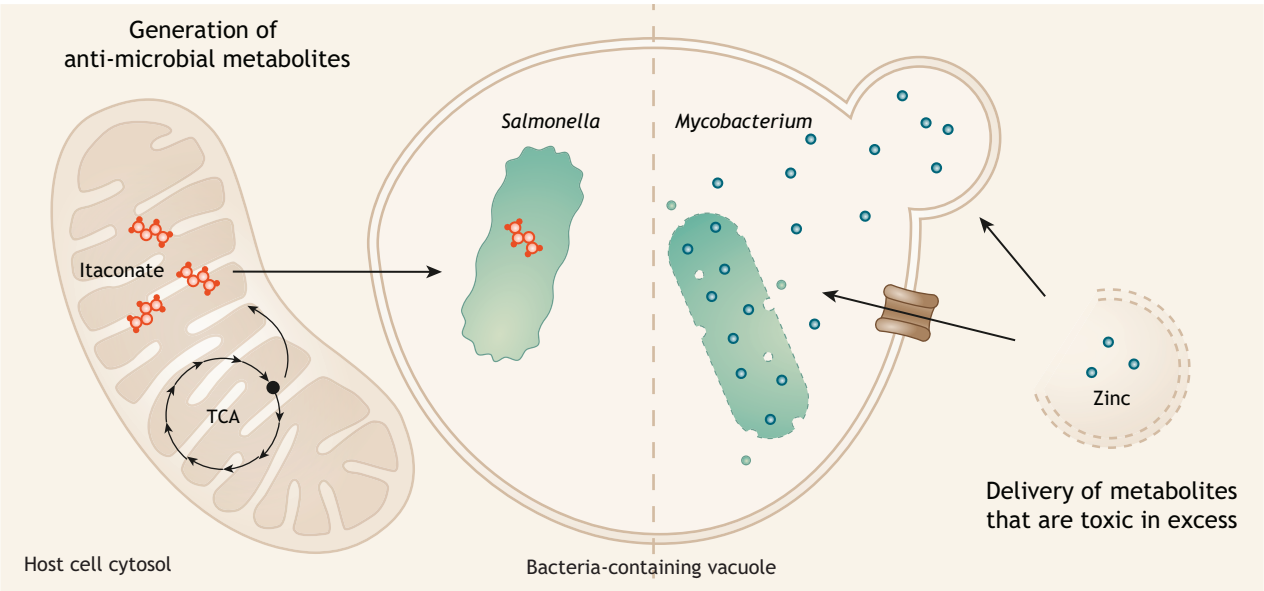

Fig. 4. Host supply of metabolites that are deleterious to microbes. Left, itaconate is generated by IRG1-mediated decarboxylation of the TCA cycle intermediate cis-aconitate, and is delivered to, and accumulates in, host vacuoles containing *Salmonella*, where it inhibits the essential glyoxylate shunt component isocitrate lyase (ICL) to restrict bacterial growth. Right, delivery of the micronutrient zinc promotes the death of *Mycobacteria* in the soil amoeba *Dictyostelium discoideum*.

phospholipids (Das, 2018). Levels of free PUFAs, like the omega-6 arachidonic acid, are increased during infection with diverse pathogens, including human coronavirus 229E (H-CoV-229E) and Middle East respiratory syndrome coronavirus (MERS-CoV) (Yan et al., 2019). However, whether arachidonic acid is released at high enough levels to act as an antimicrobial agent intracellularly, and the mechanism by which it inhibits viral proliferation, are not well understood.

When present in excess, certain essential metabolites, such as transition metals, are also deleterious to microbes (Sheldon and Skaar, 2019). Increasing the delivery of such nutrients to the intracellular niche in which microbes reside creates a toxic microenvironment inside the microbial vacuole, but spares the host cell. The soil amoeba *Dictyostelium discoideum* uses such a strategy to pump the micronutrient zinc (Zn^{2+}) into *Mycobacterium marinarum* vacuoles to enhance bacterial killing (Barisch et al., 2018) (Fig. 4). Similarly, following the internalization of group A *Streptococcus pyogenes* (GAS) through phagocytosis, neutrophils increase intracellular levels of free zinc, which reduces bacterial viability and renders GAS susceptible to host clearance by impairing both glucose metabolism and the synthesis of the protective polysaccharide capsule (Ong et al., 2014, 2015, 2018). Copper (Cu^{2+}) is similarly weaponized and shunted into the phagosomal niche of *Mycobacterium tuberculosis* and *E. coli*, where it intoxicates the bacteria through oxidative damage by disrupting iron-sulfur (Fe-S) clusters, which are required for the function of key metabolic enzymes (Samanovic et al., 2012; Wagner et al., 2005; White et al., 2009). Although the study of microbicidal host factors have largely centered on the production of anti-microbial peptides or proteins, reports such as those highlighted here support that the synthesis of anti-microbial metabolites and the use nutrients to intoxicate microbes is a parallel and conserved innate host defense strategy in mammalian systems.

Conclusions – food for thought

The metabolic defenses described here play into a so-called ‘arms race’. Hosts are under pressure to develop mechanisms to impede the exploitation of nutrients by microbes, and that would be expected to lead to the emergence of microbial resistance mechanisms (Best and Abu Kwaik, 2019; Eisenreich et al., 2019; Thaker et al., 2019). For example, although lentiviral reverse transcriptases can function in relatively low dNTPs environments, host factors like SAMHD1 further deplete dNTPs to inhibit viral replication (Baldauf et al., 2012; Diamond et al., 2004; Lahouassa et al., 2012). In turn, SAMHD1-mediated restriction can be counteracted by certain viral proteins that promote the proteasomal degradation of SAMHD1 (Hrecka et al., 2011; Laguette et al., 2011). Additionally, host mitochondria increase fatty acid (FA) uptake to counter the siphoning of host fatty acids by *Toxoplasma* (Nolan et al., 2017; Pernas et al., 2018). Interestingly, mitochondrial metabolic dysfunction and fragmentation occurs at late stages of infection with *Toxoplasma* and several other microbes including *Legionella*, hinting at microbial counter defense strategies that target host mitochondria (Escoll et al., 2017; Pernas et al., 2018; Syn et al., 2017). Finally, the extracellular pathogen and fungus *Candida albicans* depletes the levels of glucose required for macrophage survival and triggers cell death (Tucey et al., 2018). The ability to outcompete macrophages for glucose is likely attributable to an expanded family of at least 20 high-affinity glucose transporters (HGTs) in *Candida*, and raises the question of whether nutrient transporter abundance and substrate affinity is a dynamic front in the ‘arms race’ between host and microbe (Fan et al., 2002). Further study of the metabolic perspective of the host–pathogen interaction has the potential to reveal interactions that shape the metabolic diversity of the host and microbe, and provide new insights into the regulation of metabolism during infection.

We have a significant understanding of how microbes rewire the metabolism of the host cell to their benefit (Eisenreich et al., 2019; Escoll and Buchrieser, 2018; Thaker et al., 2019). We are, however, only beginning to explore the mechanisms through which the host cell rewires its metabolism to harm pathogens. A possible strategy not discussed here includes modulation of the fluidity of the PM (Fig. 1), through the reacylation of membrane phospholipids or the

regulation of PM cholesterol levels, to control endocytosis or membrane ruffling, processes commonly subverted by pathogens for invasion (Bonazzi and Cossart, 2006; Cossart and Helenius, 2014; Pizarro-Cerda and Cossart, 2006). The diversion of glucose, fatty acids and cholesterol into storage polymers could also limit their availability to microbes, thus slowing their proliferation. The recent discovery that deamidated nicotinamide adenine dinucleotide (NAD) precursors from *Mycoplasma* bacteria can be used by mammalian cells raises the question of whether host cells may siphon nutrients made by invading microbes to reduce their viability (Shats et al., 2020). The strategies listed in this Review are by no means exhaustive, but are aimed to provide a framework to consider how changes in host cell metabolism may restrict the growth or pathogenicity of a microbe. They also raise several questions.

First, it is well established that microbial infection results in dramatic changes in the metabolism of a host cell – but which of these changes are a reaction to, rather than an adaptation to or an indirect consequence of infection (Eisenreich et al., 2019; Escoll and Buchrieser, 2018; Thaker et al., 2019)? Signals that might induce defensive metabolic changes include those that alert the cell to the presence of a pathogen including pathogen-associated molecular pattern molecules (PAMPs), cytokines, pathogen-induced mechanostress or metabolites from nearby infected cells, such as damage-associated molecular pattern molecules (DAMPs) (Colaco and Moita, 2016; Drame et al., 2020). It would be advantageous for the cell to link the sensing of such signals with the regulation of host nutrient storage and release (Colaco and Moita, 2016). Proteins that are poised to effect such changes include mitochondrial antiviral signaling protein (MAVS) and stimulator of interferon genes protein (STING), key coordinators of the immune response to viral RNA and bacteria-derived cyclic dinucleotides (CDNs), which are located on the mitochondria and the endoplasmic reticulum, respectively (Barber, 2015; Wu and Hur, 2015). An interesting topic for future research will be to determine whether these proteins contribute to microbial defense through the rewiring of the metabolism of these organelles.

Second, how does a cell detect the coordinates of a pathogen within the cytosol and direct a metabolic ‘attack’? An inherent challenge to metabolite-based defenses that the host cell must overcome is to compartmentalize metabolites and modulate their levels without disrupting cellular homeostasis. One possibility might be for the host to shift from synthesis to acquisition, when possible; for example, cholesterol synthesized in the cytosol might be more readily accessible to non-vacuolar microbes than low density lipoprotein (LDL)-derived cholesterol that is subsequently sequestered in the endocytic pathway. Alternatively, host cells can exploit the vacuolar lifestyle of pathogens and target enzymes to pathogen niches to locally affect metabolite levels. Finally, an increase in whole-cell levels of certain metabolites, or exploiting differential affinities of host and microbial enzymes for metabolites, might increase the chance of inducing modifications to the microbe at the protein, transcriptional or epigenetic level.

Third, how does the metabolic reprogramming known to occur in activated immune cells synergize with metabolic defenses such as those described here? Metabolism is now well-appreciated to regulate the effector function of immune cells, a rapidly growing field of study known as immunometabolism (Buck et al., 2017; O’Neill et al., 2016; Wang et al., 2019; Weinberg et al., 2015). For example, glycolysis and fatty acid synthesis-related processes are enhanced in lipopolysaccharide (LPS)-activated macrophages and effector T-cells. LPS-induction of glycolysis in macrophages is required for the release of proinflammatory cytokines such as IL-1β, and might additionally serve to limit bacterial growth by restricting glucose (Tannahill et al., 2013). Consistent with this idea, *Salmonella typhimurium* acquires more glucose and replicates faster in interleukin-4 (IL-4) stimulated macrophages, which, in contrast to LPS-activated macrophages, mainly use oxidative phosphorylation and fatty acids to generate energy (Eisele et al., 2013; O’Neill et al., 2016).

Following a discussion of the metabolic programming of immune cells, a fourth question arises – how effective are metabolic defense strategies relative to innate and adaptive immune mechanisms, such as cytotoxic T cells and antibodies? Limiting microbial growth rate or virulence through the strategies described here could translate into profound decreases in the number of microbes that can potentially damage the host. Beyond serving as sources for anti-microbial defenses or reprogramming immune cell metabolism, nutrients play a key role in promoting survival through increasing host tolerance to the damage of infection (Ayres and Schneider, 2012; Soares et al., 2017). For example, glucose is required to prevent ER stress-mediated neuronal damage during influenza infection, whereas its restriction limits reactive oxygen species-induced damage that results from anti-bacterial inflammation (Wang et al., 2016). Recent work has shown that the administration of specific nutrients can also mitigate microbe-induced damage independently of pathogen load and host-induced damage. Remarkably, iron-supplementation of mice infected with *Citrobacter* increases the levels of intestinal glucose, which protects against pathogen-induced intestinal damage by selecting for attenuated *Citrobacter* strains (Sanchez et al., 2018).

Finally, what is the relevance of human metabolism during infection? Several reports suggest that dietary intake strongly influences human susceptibility to infectious diseases. Children infected with malaria and fed with carbohydrates had increased fever cycles (Murray et al., 1978), raising the question of whether these carbohydrates translate into an added energy source or growth signal for parasites (Mancio-Silva et al., 2017). Additionally, certain antimalarial treatments are less likely to succeed in patients receiving folate supplements (van Eijk et al., 2008) and the implementation of trehalose as a food additive helped fuel a bacterial epidemic due to the emergence of bacterial mechanisms to metabolize it even when at low concentrations (Collins et al., 2018). More than half of the world’s population takes vitamin and nutrient supplements – which of these might promote microbial infections? Further supporting a role for metabolism in infection, metabolic disorders have emerged as major risk factors for microbial infection in humans. Defects in insulin signaling cause hyperglycemia and an array of subsequent metabolic changes that are highly associated with bacterial infection (Casqueiro et al., 2012; Joshi et al., 1999). Inborn errors of mitochondrial metabolism are also known to predispose children to more recurrent microbial infections (Gessner et al., 2013; Walker et al., 2014a,b). A routine examination of infection history in addition to metabolic profiling (i.e. blood glucose and lipid levels) in patients with inborn errors of metabolism or metabolic disorders will likely reveal novel risk factors for infectious disease, as will studies addressing the impact of diet and metabolic status on the progression of microbial infection.

The metabolism of a host cell should not simply be perceived as being subverted by intracellular microbes for their nutritional benefit, but as a key executor of host defense during microbial infection. Approaching the host–pathogen interaction from a framework in which host metabolic processes can be rewired to actively suppress pathogen proliferation will increase our knowledge of the mechanisms employed by cells to defend

against microbes, and broaden our understanding of how metabolism influences susceptibility to infectious disease.

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Competing interests
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