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Innate metabolic responses against viral infections

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Metabolic adaptation to viral infections critically determines the course and manifestations of disease. At the systemic level, a significant feature of viral infection and inflammation that ensues is the metabolic shift from anabolic towards catabolic metabolism. Systemic metabolic sequelae such as insulin resistance and dyslipidaemia represent long-term health consequences of many infections such as human immunodeficiency virus, hepatitis C virus and severe acute respiratory syndrome coronavirus 2. The long-held presumption that peripheral and tissue-specific 'immune responses' are the chief line of defence and thus regulate viral control is incomplete. This Review focuses on the emerging paradigm shift proposing that metabolic engagements and metabolic reconfiguration of immune and non-immune cells following virus recognition modulate the natural course of viral infections. Early metabolic footprints are likely to influence longer-term disease manifestations of infection. A greater appreciation and understanding of how local biochemical adjustments in the periphery and tissues influence immunity will ultimately lead to interventions that curtail disease progression and identify new and improved prognostic biomarkers.

Viruses have developed various mechanisms to evade the immune system and replicate. One of these mechanisms relies on manipulation of the host metabolism by targeting key metabolic nodes and disrupting critical metabolic pathways[1].

A long-standing view purports that, in response to viral infections, the innate immune system swiftly triggers the expression of several interferon-stimulated genes (ISGs), whose products directly restrict viral replication and spread. It has also been well established that metabolic-related diseases like insulin resistance and hepatic steatosis are clinical manifestations of viral infections, such as hepatitis C virus (HCV), a consequence and/or product of dysregulated lipid and glucose metabolism observed locally in the liver and in the periphery[2].

At the cellular level, different classes of viruses apply various mechanisms to metabolically reprogram cells in ways that are advantageous for viral replication, often regulating the evolutionarily conserved glycolytic/phosphoinositide 3-kinase (PI3K)–hypoxia-inducible factor HIF-1 alpha (HIF-1α) pathways[3–5]. For example, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in humans disrupts mitochondrial homeostasis, which is compensated for by increased glycolysis[6–8]. Likewise, human immunodeficiency virus (HIV) elevates both glycolysis and mitochondrial metabolism in $CD4^+$ T cells and monocytes/macrophages to generate metabolites that may support synthesis of lipids, nucleotides and structural viral proteins necessary to complete the HIV life cycle as well as facilitating latency[9–14]. Metabolic reprogramming of immune cells also controls their inflammatory states, which contribute to disease development[9,12,13,15].

A metabolic shift towards glycolysis in response to viral infection does not inevitably parallel a reduction in oxidative phosphorylation (OXPHOS), because increased pyruvate produced by glycolysis may be shunted to maintain the tricarboxylic acid (TCA) cycle through the pyruvate carboxylase (PC)-dependent carboxylation of pyruvate to oxaloacetate[16]. Furthermore, increased uptake of glutamate, a PC-independent anaplerotic substrate, has been documented during some viral infections[17]. These anaplerotic events may partially clarify the paradoxical increased OXPHOS in some in vitro HIV infection systems[18], likely a compensation mechanism to maintain sufficient intracellular ATP, NADH and NADPH levels. Increased glutamine metabolism may also accumulate TCA cycle intermediates for precursors in reactions beyond ATP production without depleting the TCA cycle. Disturbances in the TCA cycle during macrophage activation,

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and the degree to which the TCA cycle is skewed towards the oxidative or reductive arm, controls the levels of antiviral and proinflammatory and anti-inflammatory TCA metabolites[19].

Hosts have evolved complex processes that regulate metabolism differently in response to specific tissue-tropic viruses. For example, hepatotropic viruses have unique substrate reliance from SARS-CoV-2 and HIV. Despite these intrinsic differences, several metabolic processes and disease manifestations are shared between seemingly distinct viruses. SARS-CoV-2 and HIV have been shown to engage reactive oxygen species (ROS)-mediated stabilization of the transcription factor HIF-1α as a mechanism, driving reprogramming of $CD4^+$ T cells and macrophages towards glycolysis necessary for replication and inducing production of inflammatory cytokines and metabolites[4,20].

Besides providing substrates to support metabolic hijacking by viruses, recent evidence has revealed a significant metabolic defence mechanism in response to infection. Metabolites produced by activation of central carbon metabolism have been shown to directly interfere with the initial steps of the life cycle of viruses[19]. Such an 'innate metabolic response' intricately coordinates with the immune system to mount a robust and broad-spectrum antiviral response by engaging ISGs. A compelling body of work has supported this conjecture, provoking new concepts and theories on host metabolic response to infections.

In this Review, I briefly highlight how metabolism impacts immune cell function and outline how cell surface proteins that have been historically studied for their metabolic roles can serve as viral receptors and entry factors. I examine the emerging evidence that shows the intricate relationship between metabolism, inflammasome activation and type I interferon signalling, and how these processes are at the centre of the battle between virus replication and host metabolic defences. Throughout this Review, I provide general examples from different classes of viruses and eventually focus on two consequential viruses, HIV and SARS-CoV-2, to illuminate detailed concepts around viral-induced metabolic reprogramming and metabolic control of viral tropism. In this regard, I discuss the molecular and biochemical imprint of non-immune cells such as liver parenchymal cells, pancreatic beta cells and adipocytes, whose principal task has historically been viewed to turn over metabolites and regulate metabolism. The Review also covers how conserved metabolic processes are being exploited for antiviral therapies, and to mitigate host cell damage.

The endocrine effects of metabolites produced in tissues in response to infections have only recently been examined[21]. I discuss how dysfunctional tissue-specific metabolism during viral infections is likely to impact systemic metabolic homeostasis and long-term diseases, and how metabolic markers are being explored for prognostic purposes.

Although the outcome of viral infections may be influenced by external environment and physiological and neuroendocrine responses, this Review focusses on evidence to support a central role for a 'metabolic response' in regulating viral control and disease outcomes.

Metabolic receptors, viral entry factors and sensors

General remarks on metabolic activation

It is well established that rapid activation of the metabolic machinery occurs in $CD8^+$ T cells in response to T cell receptor (TCR) triggering during antigen presentation. Because the TCR has no intrinsic enzymatic activity, downstream TCR signalling is initiated by the association between pyruvate dehydrogenase kinase 1 (PDHK1, a mitochondrial enzyme at the interface between glycolysis and OXPHOS) and the tyrosine kinases Lck and Zap70 (ref. [22]). This interaction results in the diversion of pyruvate away from mitochondrial oxidation into lactate production[22]. Shifting towards a bioenergetically less efficient aerobic glycolysis ensures substrate availability for cellular growth and division, and for imprinting epigenetic programmes critical for mounting an antiviral and inflammatory response. Metabolic reconfiguration following TCR engagement has been elegantly reviewed elsewhere[23], but the concept of innate metabolic responses during viral infections has only recently been appreciated.

Metabolic receptors mediate viral entry and immunometabolic responses

Entry receptors play an essential role in viral attachment and internalization. They are also involved in triggering intracellular signalling and metabolic reprogramming that may support viral replication and regulate antiviral responses. For example, although HIV does not use classic nutrient transporters as its primary receptors, elevated cell surface glucose transporter-1 (Glut1) is necessary for the post-entry steps of HIV replication in $CD4^+$ T cells[13]. Glut1 is also known to be a key binding receptor for the deltaretroviruses human T lymphotropic virus type I and II envelopes on T cells while also increasing glucose uptake[24,25].

HCV envelope glycoprotein E1 is known to utilize the fatty acid transporter CD36 as a potential co-receptor[26]. Further, HCV nucleocapsid interacts with the triglyceride-synthesizing enzyme diacylglycerol acyltransferase 1, an interaction necessary for virus trafficking and lipid droplet formation[27] (Fig. 1). Viruses, such as HIV, Epstein–Barr virus, human cytomegalovirus (HCMV) and adenoviruses (AdVs) may cause increase nutrient uptake by host cells by interacting with cell surface receptors and activating signalling pathways and metabolic-regulating transcription factors that coordinate expression of nutrient transporters[12,28,29].

Here I highlight a model where interaction of HIV with its receptors activates signalling and metabolic pathways, leading to transcriptional activation of metabolic genes and trafficking of Glut1 to the cell surface (Fig. 1). Moreover, viruses can hijack metabolic pathways for precursors required for replication[12]. HCMV-infected cells have been shown to switch nutrient preference such as the anaplerotic use of glutamine to sustain the TCA cycle necessary for replication[30], and Zika virus (ZIKV) can divert glycolytic carbons into the pentose phosphate pathway (PPP)[31] (Fig. 1).

Disruption of bile acid metabolism is observed when hepatitis B virus interacts with its receptor[32], and the sodium-dependent neutral amino acid transporters ASCT1 and ASCT2 are functional receptors for the feline RD-114 endogenous retrovirus[33,34], human endogenous retrovirus type W[35], baboon endogenous retroviruses and simian type-D retroviruses[34]. Intriguingly, the complement receptor CD46, shown to bind and facilitate entry of HCMV[36], adenovirus type 11 (ref. [37]) and measles virus[38] has been shown to regulate Glut1 and the amino acid transporter LAT1 on $CD4^+$ T cells[39]. Moreover, CD46 activation increases glycolysis and OXPHOS, required for $CD4^+$ T cell effector functions[39]. CD46-Cyt-1, a C-terminal splice variant of CD46, is linked to measles virus-induced autophagy[38], a highly regulated self-degradative mechanism regulating recycling of cytoplasmic content important for cell survival and maintenance. Taken together, this supports the notion that some virus–receptor engagements can relay early host metabolic signals that reprogram metabolism in favour of virus replication.

Innate metabolic sensors in viral infections

Effective host responses against viruses may be defined by optimal activation of nucleic acid molecular sensors, and these can also act as rheostats to fine-tune metabolism. These responses are not educated by exposure to specific viral antigens but by a myriad of molecular patterns encoded by unrelated pathogens. Cyclic guanosine monophosphate–adenosine monophosphate synthase (GMP–AMP synthase; cGAS) consisting of an N-terminal, and inactive catalytic domain is activated by binding to cytosolic viral DNA and mitochondrial DNA from damaged mitochondria[40]. Activated cGAS produces cyclic dinucleotide 2′,3′-cyclic GMP–AMP (2′,3′-cGAMP), which activates stimulator of interferon genes (STING), an adaptor protein associated with the endoplasmic reticulum[40]. Activation of STING consequently leads to phosphorylation and nuclear translocation of interferon

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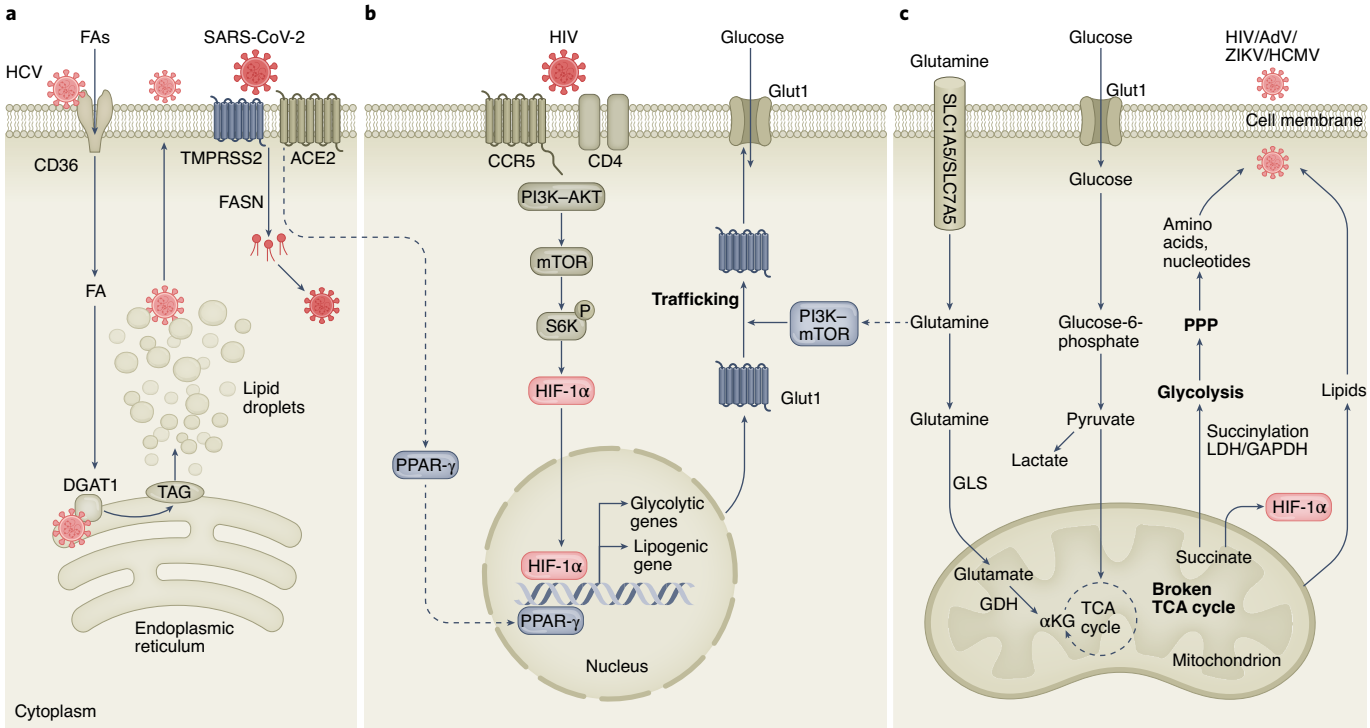

Fig. 1 | Host nutrient metabolism is altered in response to viruses. a, Viruses such as HCV and SARS-CoV-2 interact with entry/metabolic factors to increase fatty acid synthesis, triglycerides and lipid droplets essential for replication and trafficking of viruses to the cell membrane. **b**, Interactions between HIV and its entry/metabolic factors trigger PI3K–mTOR–HIF-1α activation, transcription of glycolytic genes, Glut1 trafficking to the cell membrane and increases in glucose uptake and glycolysis. Viruses such as SARS-CoV-2 may also activate PPAR-γ, driving its translocation to the nucleus and inducing lipogenic genes. **c**, Infection by viruses such as HIV, AdV, ZIKV and HCMV increase glutamine uptake and glutaminolysis. Glutaminolysis is the process by which glutamine is used to generate TCA cycle intermediates when pyruvate becomes limited. Glutamine is converted into glutamate by GLS, which is converted to α-ketoglutarate by GDH, restoring the TCA bioenergetic capacity. Increased TCA anaplerotic flux may also induce a 'broken TCA cycle' causing accumulation of inflammatory metabolites such as succinate, which can stabilize HIF-1α, succinylate glycolytic enzymes, increasing glycolysis and PPP, providing substrates for viral replication. AdV, adenovirus; CCR5, C-C chemokine receptor type 5; DGAT1, diacylglycerol *O*-acyltransferase 1; GDH, glutamate dehydrogenase; GLS, glutaminase; FA, fatty acid; αKG, alpha-ketoglutarate; PPAR-γ, peroxisome proliferator-activated receptor gamma; S6K, p70 ribosomal S6 kinase; TAG, triacylglycerol.

regulatory factor 3 (IRF3) and nuclear factor-κB (NF-κB) inducing type I interferon signalling and transcription of proinflammatory genes, comprehensively reviewed elsewhere[41]. Mitochondrial DNA released from SARS-CoV-2-infected endothelial cells has been shown to activate cGAS–STING signalling leading to cell death and type I interferon production[42].

Activation of the mechanistic target of rapamycin (mTOR), an evolutionarily conserved nutrient and redox sensor has been linked to STING-induced type I interferon production[43,44]. However, despite producing significant amounts of cytoplasmic DNA, poxviruses, which cause smallpox and monkey pox in humans, can evade the host antiviral response, and replicate efficiently. This evasion may be due to the deployment of the poxvirus protein F17, which sequesters mTOR complexes Raptor and Rictor in the Golgi and prevents cytosolic sensing by STING[45]. Reverse-transcribed DNA and mitochondrial reactive oxygen species (mtROS) generated during HIV replication can stabilize and activate HIF-1α, a heterodimeric and hypoxia-responsive transcription factor that controls genes regulating many glycolytic and inflammatory processes. However, increased metabolic activity of $CD4^+$ T cells in response to HIV infection in vitro is independent of cGAS–STING signalling[4], suggesting that blunt STING may constitute an immune evasion mechanism by only some viruses.

Inflammasomes such as nucleotide-binding oligomerization domain (NOD)-leucine-rich repeat pyrin domain-containing protein 3 (NLRP3) may take on an intracellular metabolic sensing role during virus invasion. The metabolic consequences of bacterial lipopolysaccharide (LPS)-induced NLRP3 inflammasome activation in inflammatory macrophages is well characterized. Hexokinase-1(HK1)/mTOR-dependent glycolysis is important for NLRP3 inflammasome activation and pro-interleukin (IL)-1β maturation in LPS-treated macrophages[46]. Moreover, double-stranded RNA-dependent protein kinase (PKR) phosphorylation and activation, which may be regulated by lactate, as well as the physical interaction between PKR and NLRP3 have been implicated in NLRP3 inflammasome activation in response to agonists including ATP, live *Escherichia coli*, anthrax lethal toxin and *Salmonella typhimurium* infection[47,48]. Viral RNA sensing (signal 1) by nucleotide-binding oligomerization domain-containing 2 and retinoic acid-inducible gene I can induce transcription of genes that encode components of the NLRP3 inflammasome. However, disruptions in the TCA cycle and OXPHOS generating abnormal levels of ROS and ATP constitutes important signals (signal 2) for NLRP3 inflammasome activation (Fig. 2).

Recent work using *Saccharomyces cerevisiae* and LPS-primed bone marrow-derived macrophages show mitochondrial electron transport chain-derived ATP induces NLRP3 inflammasome activation through phosphocreatine–ATP-dependent mechanisms independent of mitochondrial ROS[49]. However, other stimuli such as asbestos, silica and hydrogen peroxide have been shown to induce ROS-mediated NLRP3 inflammasome activation in human monocyte-derived macrophages and THP-1 monocytic cell lines[50,51].

The impact of viral infections on the interactions between inflammasomes and the metabolic machinery is under-researched, but metformin, an inhibitor of mitochondria complex 1 (ref. [52]) and an AMPK–mTOR–HIF-1α-dependent NLRP3 inhibitor[53–55], restrains

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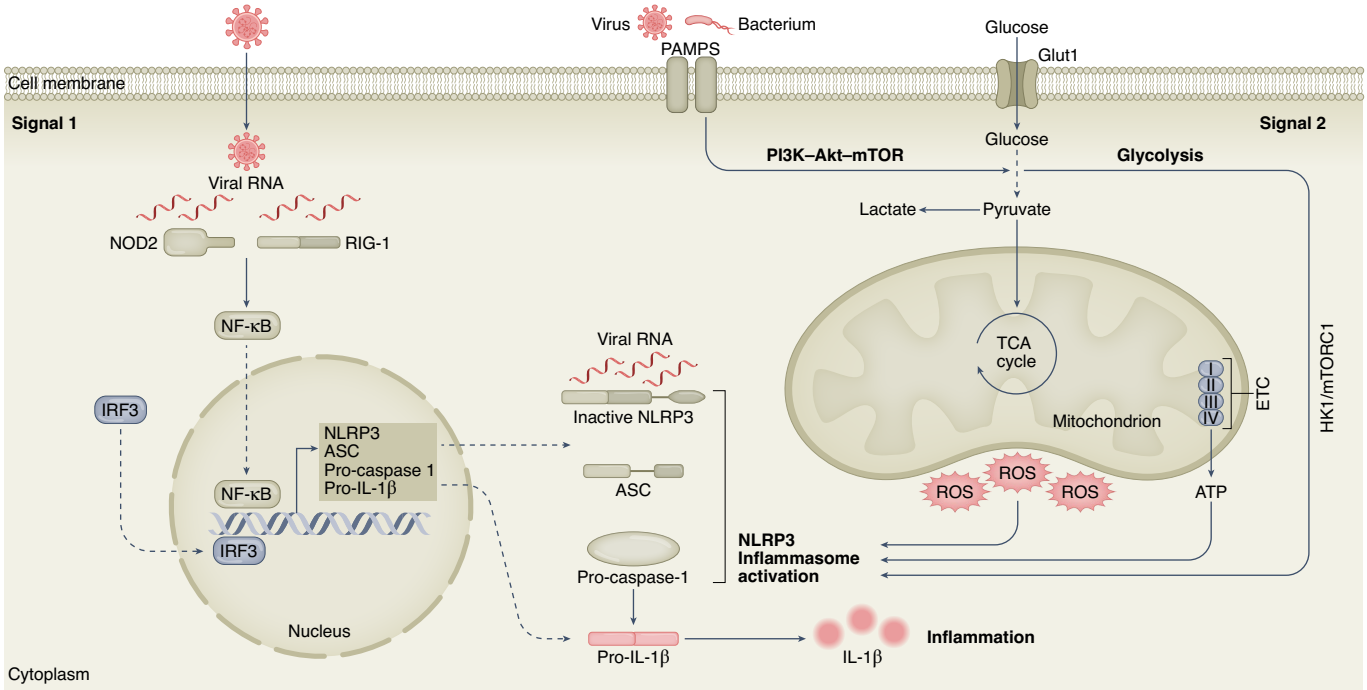

Fig. 2 | NLRP3 inflammasome activation occurs during viral infections. Activation of the NLRP3 inflammasome requires two signals. Signal 1 (priming signal): recognition of a pathogen-associated molecular pattern (PAMP) activates the NF-κB and interferon signalling, triggers the transcription of NLRP3, ASC pro-caspase-1 and pro-IL-1β. Signal 2 (activation signal): multiple DAMPs including mitochondrial ROS produced by dysfunctional mitochondrial OXPHOS and PAMPs induce NLRP3 inflammasome assembly and activation, which leads to the auto-cleavage of pro-caspase-1. Caspase-1 then mediates the proteolytic processing of pro-IL-1β. HK1/mTORC1-dependent glycolysis may also induce NLRP3 inflammasome activation and pro-IL-1β maturation. ASC, apoptosis-associated speck-like protein containing a CARD; DAMPS, damage-associated molecular patterns; ETC, electron transport chain; mTORC1, mechanistic target of rapamycin complex 1; NOD2, nucleotide-binding oligomerization domain-containing 2; PAMPS, pattern-associated molecular patterns; RIG-I, retinoic acid-inducible gene I.

NLRP3 inflammasome activation and IL-1β production in LPS-treated alveolar macrophages while also attenuating pulmonary inflammation and acute respiratory distress syndrome in SARS-CoV-2-infected transgenic mice expressing the human angiotensin converting enzyme 2 (hACE2)[52]. NLRP3 inflammasome activation is also reported in peripheral blood mononuclear cells and postmortem pulmonary tissues of patients with coronavirus disease 2019 (COVID-19)[56]. Because increased bacterial translocation is featured in moderate and severe COVID-19 disease[57], NLRP3 inflammasome is therefore a potential immunometabolic target for treating inflammatory complications of COVID-19.

Interestingly, 4-octyl-itaconate, a derivative of itaconate which is an anti-inflammatory TCA metabolite shown to inhibit NLRP3 inflammasome activation[58] and reduce ROS[59], attenuates airway inflammatory responses in SARS-CoV-2 infection[60] and suppresses pulmonary inflammation and mortality in influenza virus infection[19,59].

Metabolic responses regulate viral control and replication

Metabolic reprogramming during viral infections

Receptor systems that mediate antiviral responses are interwoven with metabolic pathways that are not simply a result of immune activation but an integral process. Immune cellular metabolic reprogramming during viral infections may occur to meet newly required bioenergetic and biosynthetic demands of the host to fight infection, but it can be exploited by the virus itself to replicate. This metabolic reprogramming during infection represents a coevolutionary mechanism that allows survival of both the virus and the host. Although increased anabolic metabolism, such as aerobic glycolysis is generally considered a hallmark of viral infection, more nuanced metabolic configurations depend on the activating stimuli, cell type, timing and local and systemic metabolic environments. Central to the innate antiviral responses is the interdependency between ISGs, metabolic factors such as ATP and nicotinamide adenine dinucleotide (NAD^+), as well as TCA cycle metabolites. How these factors influence the outcome of the virus–host cell interaction are discussed.

Interdependency between interferon-stimulated genes and metabolic factors during infection

The intricate association between cellular metabolism and the interferon response is a manifestation of the dichotomy between antiviral and viral-enhancing ISGs. The autocrine and paracrine engagement of these gene products with the interferon receptors activates the Janus tyrosine kinase (JAK)-signal transducer and activator of transcription 1 (STAT-1; JAK–STAT-1) pathways and ISGs[61,62] (Fig. 3). Among these ISGs are five members of the poly(ADP-ribose) polymerase (PARP) family of proteins, PARP7, PARP9, PARP10, PARP12 and PARP14, which are transcriptionally activated in response to inflammatory signals[62–64]. PARP11 has recently been identified as an anti-ZIKV ISG that interacts with PARP12 to enhance ZIKV NS1 and NS3 protein degradation[65]. PARPs can use NAD^+ produced by the NAD salvage pathway as their substrate to modify acceptor proteins with ADP-ribose modifications as an antiviral response. NAD^+ can also be consumed by receiving hydride produced from the conversion of glyceraldehyde 3-phosphate to 1,3-bisphosphoglycerate by glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and forming NADH, which serves as a central hydride donor for ATP synthesis via OXPHOS. However, the NAD salvage pathway may also be supported by the conversion of pyruvate to lactate by lactate dehydrogenase (LDH; Fig. 3).

NAD^+ is utilized during glycolysis to generate NADH, which can be transported to the mitochondrial matrix via the malate/aspartate shuttle and oxidized by complex I in the electron transport chain. Cellular decline in NAD^+ is associated with impairment of mitochondrial

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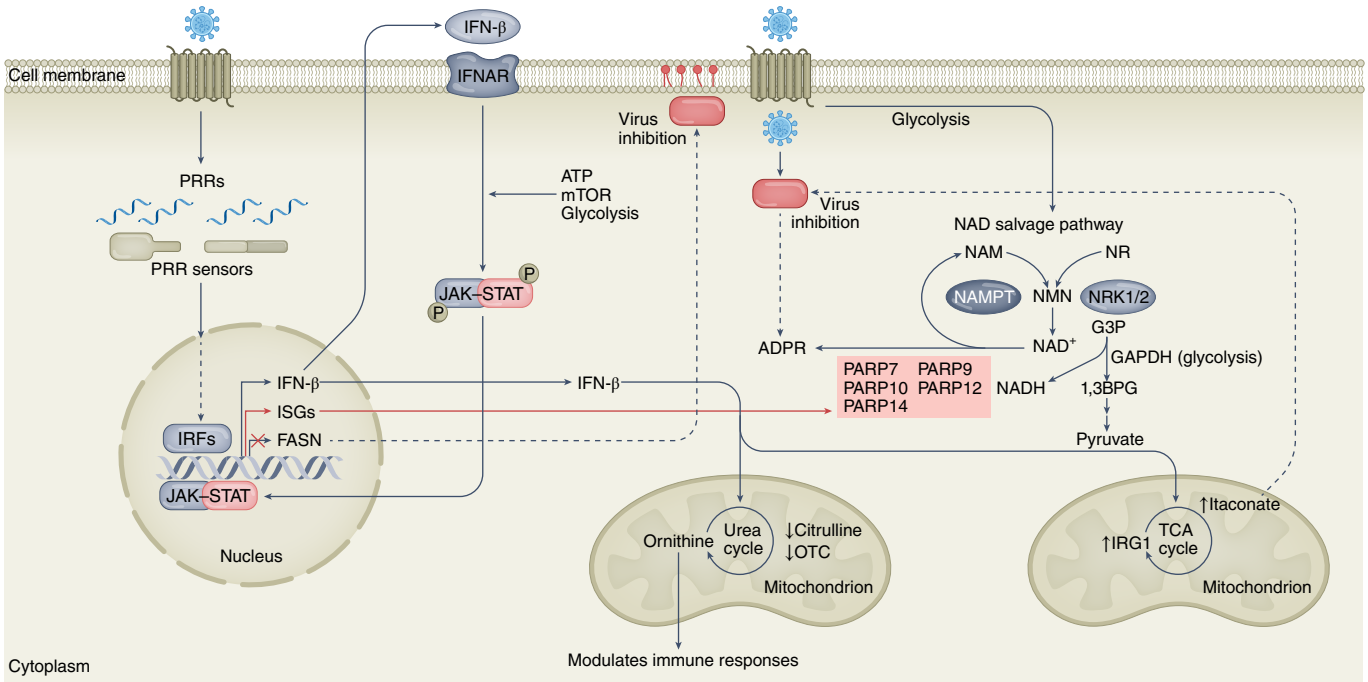

Fig. 3 | Interdependency between interferon-stimulated genes and metabolic factors during viral infections. Virus recognition of PRRs is known to stimulate glycolysis–mTOR–JAK–STAT-dependent regulation of ISGs including the PARP family of proteins. PARPs may compete with GAPDH for NAD^+, which they use as substrate to modify acceptor proteins with ADP-ribose modifications as an antiviral response. Type I interferons can regulate expression of enzymes such as OTC and IRG1 associated with the urea cycle and TCA cycle, respectively, to regulate viral control. FASN is a type I interferon-suppressed gene, involved in de novo fatty acid synthesis, and may limit fatty acid availability for viral replication. 1,3BPG, 1,3-bisphosphoglycerate; G3P, glyceraldehyde 3-phosphate; IRF, interferon regulatory factor; Irg1, immunoresponsive gene 1; NAM, nicotinamide; NAMPT, nicotinamide phosphoribosyltransferase; NMN, nicotinamide mononucleotide; NR, nicotinamide riboside; NRK1/2, nicotinamide riboside kinase 1/2; OTC, ornithine transcarbamylase; PRRs, pattern recognition receptors.

function associated with ageing, and pharmacologically increasing NAD^+ levels in old mice restores mitochondrial function comparable to that in young mice in a SIRT1-dependent manner[66,67]. Beyond the central role of the NAD^+/NADH system in cellular mitochondrial biogenesis, a significant decline in the plasma levels of oxidized NAD^+, and $NADP^+$, and increase in the reduced forms NADH and NADPH have been reported during normal ageing[68]. Systemic levels of mononucleotide, a key metabolite in NAD^+ metabolism is decreased with increasing COVID-19 severity[69]. Whether reduced NAD^+ in ageing, or pre-existing diseases that affect NAD^+ depletion contribute to poorer outcomes of the elderly or individuals with comorbidities during infections is unclear[62,68].

Discussed in detail below, the JAK–STAT-regulated type I interferon system can control expression of genes that encode enzymes in central metabolic pathways such as fatty acid synthase (FASN), ornithine transcarbamylase (OTC) of the urea cycle, and aconitate decarboxylase 1 (ACOD1), also named IRG1, which catalyses the production of itaconate from aconitate. Suppression of FASN and induction of IRG1 can limit viral replication, while dysregulation of OTC by hepatotropic viruses may influence blood levels of urea cycle metabolites and cause suppression of peripheral immune cell functions (Fig. 3).

In inflammatory macrophages, elevated glycolytic flux increases ATP, a necessary stimulus that sustains their inflammatory status. As such, aerobic glycolysis and ATP are critical for amplification and sustenance of interferon (IFN)-γ-triggered activation and translocation of JAK–STAT-1 from the cytoplasm to the nucleus[70], which may also be dependent on mTOR-associated increased glycolysis[71] (Fig. 3). Beyond classical immune cells, IFN-β-sensing by adipocytes can promote adipocyte glycolysis, and thus obesity-driven induction of interferon-α/β receptor (IFNAR) signalling may amplify virus-associated pathologies in obesity settings[72]. A recent report identified FASN as a type I interferon-suppressed gene involved in de novo fatty acid synthesis. Overexpression of FASN, or supplementation with its downstream product, palmitate, enhances SARS-CoV-2 replication[73]. In addition, irreversibly inhibiting FASN with epigallocatechin gallate, a catechin found in tea leaves, and cerulenin, an antifungal agent, exhibited a broad range of antiviral activities against enveloped viruses[73]. Thus, downregulation of metabolic genes by the type I interferon system may contribute to an early antiviral host defence mechanism, because many viruses rely on fatty acids to complete their life cycle.

The lymphocytic choriomeningitis virus mouse hepatitis model induces IFNAR1-dependent disruption of the hepatocyte urea cycle and repression of OTC and arginosuccinate synthetase 1. OTC catalyses the reaction between carbamoyl phosphate and ornithine to form citrulline, and arginosuccinate synthetase 1 combines citrulline and aspartate, to produce arginosuccinate. Hence, repression of these genes resulted in altered systemic metabolism, including decreased arginine, and accumulation of systemic ornithine and hyperammonaemia, and blunted T cell antiviral response[74] (Fig. 3). From a mechanistic standpoint, more work is needed to decipher whether and how changes in these metabolites modulate hepatic injury and determine the impact of differentially regulated metabolites on injury to other organs during some viral infections.

Interdependency between metabolites and antiviral responses

TCA metabolites, such as succinate, have been implicated in LPS-mediated inflammatory responses in macrophages through HIF-1α–IL-1β signalling[75]. In addition, mitochondrial oxidation of succinate via succinate dehydrogenase raises mitochondrial membrane potential and increases mtROS production, essentially repurposing mitochondria from ATP synthesis towards ROS production to maintain a proinflammatory state[76]. However, this may be counteracted in activated

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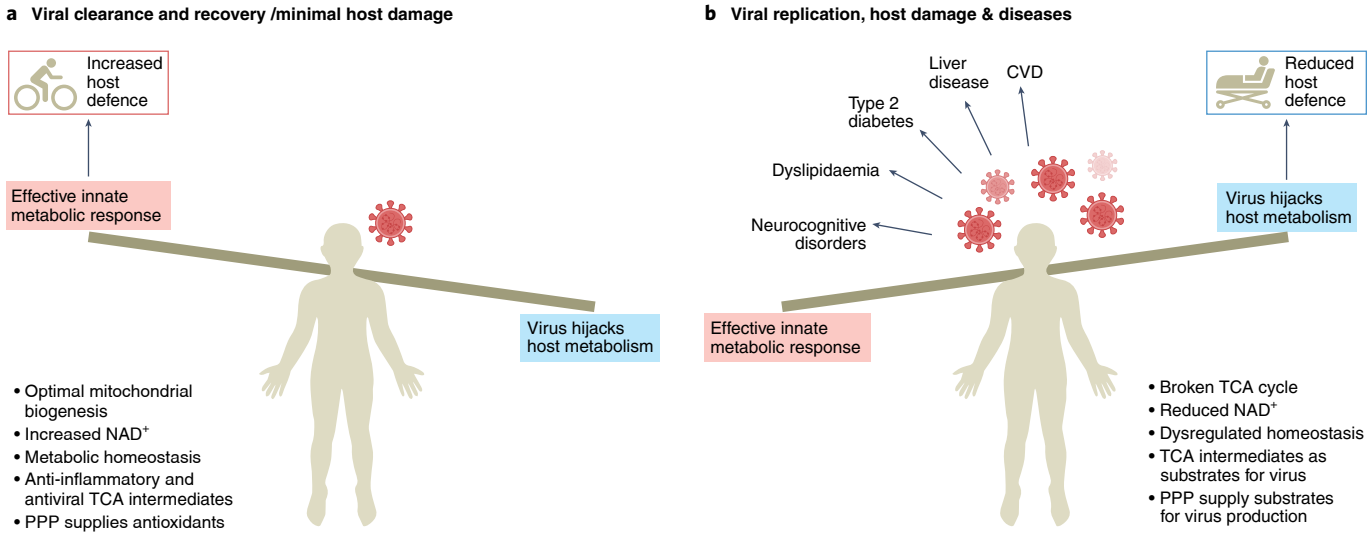

Fig. 4 | Striking the right balance during antiviral metabolic responses influences disease outcome. a, Efficient innate antiviral metabolic response improves host defences against viral infections. **b**, When a virus hijacks host metabolism and evades antiviral metabolic responses, host defence is compromised. CVD, cardiovascular disease.

macrophages by accumulated itaconate, a metabolic adaptation that suppresses succinate dehydrogenase-mediated oxidation of succinate[77]. In agreement with this, endogenous itaconate has been shown to be a major inducer of inflammatory tolerance after long LPS priming, by preventing full caspase-1 activation, and delaying NLRP3 activation[78].

Remarkably, succinate has been shown to participate in wider metabolic processes through succinylation of key glycolytic enzymes including GAPDH, LDH, malate dehydrogenase and the glutamate carrier 1 (refs. [75,76]). Of note, the succinate receptor SUCNR1 is highly abundant in white adipose tissue and adipocytes. This allows extracellular succinate to suppress lipolysis and accumulate triglycerides, suggesting that TCA cycle intermediates may regulate whole-body energy homeostasis[79].

It is unclear precisely how viruses regulate TCA metabolite hubs, but high-throughput metabolomic analysis reveals elevated plasma succinic acid in moderate and severe COVID-19 disease[57,69], and administration of dimethyl itaconate (a derivative of itaconate) during influenza A virus infection in mice reduced pulmonary inflammation and improved survival[59]. Another derivative, 4-octyl-itaconate, and the clinically approved dimethyl fumarate (DMF) potently suppress SARS-CoV-2 replication and inflammatory responses, independently of type I interferon signalling[60]. This inhibition is not restricted to SARS-CoV-2, because ZIKV and herpes simplex virus 1 and 2 are sensitive to these metabolite derivatives[60]. These observations illustrate that remodelling of the TCA cycle is an integral process in the metabolic response to viral infection.

Balancing virus metabolic hijacking and host metabolic responses

The increased carbon metabolism exhibited by virus-infected cells to produce energy and antiviral metabolic byproducts may be interpreted as a host metabolic response to infection. These metabolic intermediates may be used for virus replication or directed towards processes that limit substrates for viral reproduction. As such, metabolites produced by some ISG proteins can remodel cellular metabolism to mount broad-spectrum antiviral responses. For example, Viperin, also known as RSAD2, is an ISG which is essentially a radical *S*-adenosylmethionine-dependent enzyme that converts cytidine triphosphate (CTP), a pyrimidine nucleotide triphosphate (substrate for RNA synthesis) to its analogue 3′-deoxy-3′,4′-didehydro-CTP (ddhCTP), which functions as a chain terminator for virally encoded RNA-dependent RNA polymerase (RdRp)[80]. It has been shown that ddhCTP can be utilized by the RdRp of dengue and West Nile viruses, causing inhibition of full-length viral RNA[81]. Consistently, ZIKV RdRp and HCV RdRp are also susceptible to inhibition by ddhCTP, resulting in premature viral RNA chain termination[81].

Besides its direct antiviral role, ddhCTP can inhibit the NAD^+-dependent activity of GAPDH[82], increasing flux through the PPP to generate precursors for synthesis of amino acids, fatty acids and nucleotides, which can support viral replication. Likewise, NADPH also produced by the PPP may be used by NADPH oxidase to produce antimicrobial ROS[83]. NADPH can also reduce glutathione disulfide to the antioxidant glutathione as a protective host mechanism to counteract excess ROS and limit host damage[82]. Inhibition of NAD^+-dependent GAPDH activity may also drive imbalance between redox metabolism and energy production, leading to cell death and restriction of viral spread. RSAD2 is the only known ISG that produces a metabolite capable of directly inhibiting viral transcriptional machinery, making it a key metabolic sensor in host antiviral responses.

Optimal immune cellular responses, redox balance and mitochondrial biogenesis (Fig. 4) create an environment that bolsters host defences against viral infections. However, when these processes are compromised, immune evasion and viral persistence ensue leading to host cell damage and diseases.

Metabolic enzymes and metabolites: their roles beyond metabolic pathways

The traditional way of imagining metabolism has been as a series of enzymatic reactions in which metabolites are passed as enzyme substrates through linear steps to create a product. However, during viral infections, the non-canonical metabolic roles of glycolytic enzymes may have significant consequences on the battle between the virus and the host[84]. Another example pertains to the 'moonlighting' control of cytokine expression by some glycolytic enzymes. When aerobic glycolysis is increased during immune activation, GAPDH can disengage binding to the 3′ untranslated region of mRNAs encoding IFN-γ, causing its translation[85]. In addition to controlling enzyme activities in various metabolic pathways, metabolites also possess anti-inflammatory[86,87] and inflammatory[75] properties and regulate viral replication[60,88,89]. Metabolites such as acetyl-CoA can also reconfigure the cellular

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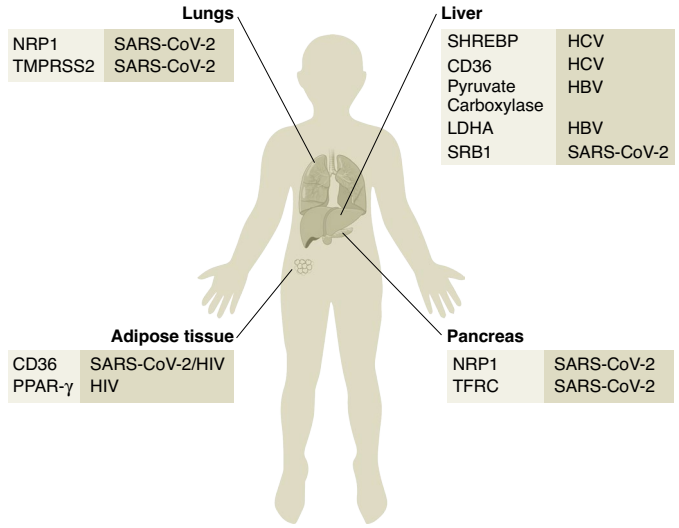

Fig. 5 | Metabolic factors influence tissue tropism of viruses. Metabolic factors can influence metabolic flexibility of cells allowing them to adapt to different microenvironments, which causes viruses to strive in specific niche. Metabolic organs such as the liver, pancreas and adipose tissue are targets for some viruses, which may lead to dysregulated systemic metabolic homeostasis and metabolic-related disease. SRB1, scavenger receptor class B type 1; SREBPs, sterol regulatory element-binding proteins; TFRC, transferrin receptor.

epigenome through the acetylation of histones, which increases the synthesis of effector molecules such as IL-1α, tumour necrosis factor and IFN-γ[90,91]. The translocation of the mitochondrial pyruvate dehydrogenase complex to the nucleus also facilitates the nuclear production of acetyl-CoA necessary for histone acetylation[88].

Cellular and systemic metabolism govern tissue-specific viral tropism and disease progression

Cell specific metabolism regulates viral tropism

Tissue-specific metabolic factors may contribute to the tropism of hepatotropic viruses due to their unique metabolic environment (Fig. 5). The liver is a central metabolic organ, but it also represents an immunoregulatory hub between hepatotropic pathogens and the peripheral immune and metabolic systems. Thus, the primary task of hepatocytes is to turn over metabolites during homeostasis. Yet hepatocytes are also critical immune and metabolic sensors and responders; for example, hepatic PC can catalyse the carboxylation of pyruvate to oxaloacetate, which represents a key anaplerotic pathway by which the TCA cycle intermediates are replenished to sustain lipid biosynthesis[92], which can support viral replication. Interestingly, increased anapleurotic influx to the TCA cycle through PC has been observed in fibroblasts infected with herpes simplex virus 1, which exemplifies the versatile responsibilities of the TCA cycle to support oxidative and biosynthetic metabolism[93].

Tissue-specific distribution of isoforms of enzymes represents unique opportunities for a more targeted approach to antiviral therapy. One such possibility is based on the observation that the two dominant isoforms of LDH are expressed in a tissue-specific manner, where lactate dehydrogenase A (LDHA) is highly abundant in the liver and lactate dehydrogenase B is highly expressed in the heart. Hepatitis B virus is known to activate glycolysis via LDHA-dependent lactate production to impede retinoic acid-inducible gene I-induced interferon production as an immune escape mechanism[94]. Strikingly, in the H9c2 myoblastic cell line, long-chain fatty acids inhibit LDHA, which may at least partly explain why fatty acids released from adipose tissue during fasting inhibit lactate production and increase hepatic glucose output[95].

Other key metabolic organs, such as adipose tissue and the pancreas, are central to both local and systemic metabolic homeostasis that not only shape the natural course of viral diseases but also can control the environmental milieu that influences host predisposition to infection and longer-term diseases (Fig. 5). However, it should be noted that some metabolic defects originating from impairments in the TCA cycle, gluconeogenesis and urea cycle functions (for example, due to rare human PC deficiency) are sometimes manifested as nonobvious metabolic diseases such as seizures and neurological conditions[96].

Cellular and systemic metabolism govern HIV disease pathogenesis

Reprogramming of cellular metabolism influences HIV replication machineries. The preferential bias for HIV towards glycolytic $CD4^+$ T cells also appears to be reliant on elevation in OXPHOS independent of their differentiation and activation status[11]. The accumulation of biomass that accompanies increases in these metabolic processes provides HIV with abundant and essential macromolecules for replication[12,15,18,97,98].

Although both glycolysis and OXPHOS are elevated in HIV-infected $CD4^+$ T cells, a balance towards aerobic glycolysis reinforces the PPP to make deoxynucleoside triphosphate readily available for HIV reverse transcription[12,98]. The PPP is also important for maintaining redox balance of cells, including the control of the antioxidant thioredoxin and glutathione systems shown to regulate HIV replication and latency in $CD4^+$ T cells and macrophages[99,100]. Intriguingly, glycolytic enzymes such as GAPDH, alpha-enolase and pyruvate kinase muscle type 2 have also been shown to directly regulate HIV reverse transcriptase activity and influence the infectivity profile of progeny virus[101].

Recent evidence shows that HIV directs the association of the mitochondrial innate immune receptor NLRX1 with the mitochondrial protein FASTKD5. This interaction is essential for the assembly of the respiratory chain complexes that drive glycolysis, OXPHOS and viral replication[102]. Inhibition of mitochondrial respiratory chain complex I with metformin, an US Food and Drug Administration (FDA)-approved antidiabetic drug, suppresses HIV replication in human $CD4^+$ T cells and humanized mice[102]. Thus, the NLRX1–FASTKD5-dependent induction of OXPHOS offers a new mechanistic understanding of HIV infection in $CD4^+$ T cells. Reducing pyruvate allocation to the mitochondria by the mitochondrial pyruvate carrier inhibitor UK5099 halts HIV infection, suggesting that not only does it prefer cells with high glycolytic and respiratory activity, but that this metabolic environment also supports its replication[102,103].

Glutamine-derived carbons have been shown to support the TCA cycle to promote early steps of HIV infection in $CD4^+$ T cells[18]. The impact of amino acid transporters in HIV replication and persistence is unclear, but they may help to synchronize nutrient supplies, routing them for anabolic reactions and essentially turning $CD4^+$ T cells into biosynthetic factories, which facilitates HIV infection[18,104]. Likewise, the effects of fatty acid metabolism on HIV replication are poorly understood; nevertheless, the enzymatic system that catalyses fatty acid synthesis may participate in later stages of HIV replication[105]. Besides exploiting metabolic machinery for transcription and assembly, the concept of a metabolically driven proliferation of $CD4^+$ cells in the HIV reservoir has been proposed but has not been mechanistically investigated[106].

Of note, the vast majority of residual HIV replication and HIV reservoirs (including macrophages) reside in sanctuary sites such as the gut, adipose tissue and brain. These organs represent unique metabolic environments in which $CD4^+$ T cells are exposed to and must therefore adapt to their changing nutrient composition. How this influences the capacity of $CD4^+$ T cells to reprogram metabolism that favours HIV replication and persistence is unknown. However, the lipid transporter CD36 is upregulated in resting $CD4^+$ T cells in adipose tissues in humans, monkeys and mice, while very little to no expression in $CD4^+$ T cells

in blood, spleen and lymph nodes[107]. Similarly, CD36 upregulation is observed in liver-resident CD4$^+$ T cells, indicating that these metabolic organs may enforce distinctive metabolic reprogramming, such as a greater reliance on lipids for resident CD4$^+$ T cells[107]. Interestingly, the adipocyte-derived soluble factor adiponectin reduces IFN-γ and IL-17 in CD4$^+$ T cells from high-fat-diet-induced obese mice by restraining glycolysis in an AMPK-dependent manner, suggesting that host nutritional status may be an important factor for HIV control[108]. It is noteworthy that metabolic changes of cytotoxic T cells in HIV-infected individuals can influence HIV control. HIV-specific CD8$^+$ T cells from non-controllers have increased glycolysis and rely heavily on glucose metabolism, while natural HIV controllers display enhanced metabolic plasticity[109]. Additionally, exhausted HIV-specific CD8$^+$ T cells, have elevated expression of Glut1, and impaired mitochondrial functions, reflecting significant metabolic defects[110].

Disruptions in systemic metabolic homeostasis in HIV infection. Although monocytes and macrophages harbour HIV[111], their overall contribution and significance to the total reservoir in individuals infected with HIV is unclear. Early reports suggest that glycolytic metabolism and the TCA cycle are activated in HIV-exposed macrophages, which may support long-term survival and persistence of HIV macrophage and microglia reservoirs, and cause neurocognitive dysfunction[14,112].

Chronically metabolically activated monocytes and macrophages are drivers of persistent inflammation that underpins long-term metabolic comorbidities in HIV-positive individuals regardless of their antiretroviral treatment status, as elegantly reviewed elsewhere[113–115]. Elevated Glut1 expression and glycolysis in circulating monocytes from HIV-infected persons associates with traditional markers of cardiovascular disease risks, diabetes and systemic inflammation[116,117]. Indeed, Glut1 expression is increased on intermediate monocytes from HIV-infected women with subclinical cardiovascular disease[117]. Moreover, elevated CD4$^+$ glucose metabolism is reported in HIV-infected women with diabetes mellitus[118].

Lipid metabolism is also linked to monocyte atherogenic properties. Transmigrated monocytes from HIV-positive individuals extracted from collagen gels demonstrate increased foam cell formation, and this proatherogenic phenotype is associated with impaired cholesterol efflux[119]. One prevailing theory purports that microbial products such as LPS and fungal β-D-glucan enter the blood by way of a breached gut barrier and represent key metabolic activating signals for monocytes and macrophages[120]. However, pro-glycolytic extracellular vesicles secreted by HIV-infected CD4$^+$ T cells have also been shown to induce glycolysis and promote M1-like macrophage inflammatory responses[4].

Lactate is widely known as a metabolic by-product of glycolysis. However, LPS-induced lactate stimulates histone lactylation in M1-like macrophages, an epigenetic mechanism that induces M2-like characteristics in late-phase activation[121]. Interestingly, lactate-dependent histone lactylation at H4K12la enriched at the promoters of glycolytic genes have been found in microglia adjacent to Aβ plaques in brain samples from mouse models of Alzheimer's disease and individuals with Alzheimer's disease [122]. Thus, the glycolysis–H4K12la–pyruvate kinase M2 axis has been linked to exacerbated microglial activation and dysfunction in Alzheimer's disease [122]. It will be interesting to decipher whether such mechanisms may be involved in neurocognitive diseases in chronic HIV infection.

While it has been traditionally thought that a shift towards aerobic glycolysis defines M1-like macrophages, it now appears that activating stimuli also induce a 'broken' and dysfunctional TCA cycle. Succinate, a TCA cycle metabolite, is elevated in LPS-treated macrophages and has been shown to stabilize HIF-1α. However, the mechanisms that underpin macrophage inflammation in long-term metabolic comorbidities that occur with HIV, such as insulin resistance, obesity and cardiovascular diseases, are multifactorial. High consumption of the Western diet increases proinflammatory lipids such as palmitate, which fuel macrophage oxidative catabolic metabolism through activation of the NLRP3 inflammasome and ROS production[123]. Further, even newer antiretroviral drugs used alone interfere with metabolic homeostasis such as lipogenesis, oxidative stress and insulin resistance[113,124,125], adding yet another layer of complexity underlying long-term HIV-associated comorbidities.

Cellular and systemic metabolism govern SARS-CoV-2 disease pathogenesis

Reprogramming of cellular metabolism influences SARS-CoV-2 replication. Coronavirus genomes do not encode enzymes that synthesize ATP and macromolecules for viral assembly and must therefore exploit host biosynthetic programmes to replicate. These programmes depend on the coenzymes NAD, NADH, NADP and NADPH, which accept and donate electrons during lipid, amino acid and nucleotide biosynthesis. They are also critical for generating and detoxifying ROS; however, the roles of these coenzymes in viral replication and antiviral responses have only recently become clear.

PARP is a superfamily of NAD-consuming isozymes, many of which are ISGs implicated in viral control. These enzymes utilize NAD to catalyse the linkage of a single or chain of ADP-ribose to proteins. Although poly(ADP-ribosylating) (PARylating) PARPs are best known for their DNA damage response, many non-canonical mono(ADP-ribosylating) (MARylating) PARPs are linked to antiviral responses. Induction of non-canonical PARP isozymes with MARylating activities, and enzymes of the NAD salvage pathways are observed in the tracheas and lungs of SARS-CoV-2-infected ferrets and humans, respectively[126]. As such, rather than polymerizing ADP-ribose, MARylating PARPs transfer single ADP-ribose units from NAD to proteins and modify their functions. Interestingly, coronaviruses possess an enzymatic activity that removes ADP-ribose modifications[127], thereby counteracting these ADP-ribosylating antiviral activities. Further, coronavirus infection can deplete cellular NAD$^+$ levels, and boosting NAD$^+$ with NAD precursors has been shown to enhance the antiviral activities of PARP isozymes[126].

It is conceivable that PARP-mediated scavenging of NAD may embody an antiviral response that deprives the virus of cellular substrates for its replication[126] (Fig. 3). However, early induction of PARP-dependent (MARylating) interferon signalling may benefit the host, because NAD$^+$ is also essential for critical host antioxidant and anti-inflammatory responses[62]. Thus, therapeutic reinforcement of the NAD$^+$ system has been proposed as a potential prophylaxis approach against viruses such as SARS-CoV-2 infection[62].

Gene expression analysis of lungs from deceased individuals with COVID-19 showed upregulation of glycolysis and OXPHOS in alveolar type 2 progenitor cells[126]. This is consistent with single-cell RNA-sequencing data from bronchoalveolar lavage of mild and severe COVID-19 patients showing elevated glycolysis in monocytes[3]. Ultimately, the outcome of this 'tug-of-war' is likely to be influenced by the nutritional status of the host.

Metabolic factors contribute to SARS-CoV-2 tissue tropism and metabolic diseases. The COVID-19 pandemic has illuminated how reciprocal regulation of intrinsic tissue metabolic response and whole-body metabolic homeostasis impact the outcome of viral infections. Although initial studies have focused on lung injury as the major manifestation of COVID-19, evidence also show a substantial increase in metabolic complications such as diabetes, diabetic ketoacidosis, cardiovascular diseases and metabolic-related neurocognitive disorders in people with COVID-19 (ref. [128]).

Tissue tropism is determined by the availability of virus receptors and entry cofactors on the surface of host cells. SARS-CoV-2 has widely been thought to primarily bind to the host cell membrane through the interaction between the viral spike glycoprotein (S) and the ACE2 receptor[129]. However, it is now clear that the repertoire of SARS-CoV-2 receptors is more diverse than originally thought. In fact, SARS-CoV-2

entry may also be dependent on the transmembrane serine protease 2 (TMPRSS2)[129,130], the PI3K/Akt activator neuropilin 1 (refs. [131–134]) and the transferrin receptor[135], which delivers circulating iron to cells. Therefore, while low abundance of ACE2 protein is expressed in pancreatic beta and alpha cells, there is a robust enrichment of the SARS-CoV-2 entry proteins neuropilin 1 and transferrin receptor in beta cells, a mechanism that is potentially fundamental to its tropism for the pancreas[135,136]. Thus, beta cells may represent one of many opportunities for secondary expansion of SARS-CoV-2 after the initial infection of the upper and lower airways and lungs.

Whether pre-existing levels of these entry factors in high-risk persons (such as those with obesity and diabetes) could partly explain the susceptibility of the pancreas to SARS-CoV-2 or the severity of COVID-19 is unclear, but type 2 diabetes has been identified as a significant post-acute sequela of SARS-CoV-2 (PASC)-anticipating risk factor[137]. These entry proteins are likely active players within a broader network of metabolic factors essential for infection. Another report that examined the endocrine effects of SARS-CoV-2 infection reveals higher ACE2 and TMPRSS2 expression in beta cells than alpha pancreatic cells[138]. This discrepancy may be due to differences in viral strains, experimental techniques and/or nutritional status and demography of patients with COVID-19 in these studies. Regardless of these potential confounders, other studies have confirmed infection of the pancreas by SARS-CoV-2. This causes profound morphological changes and impairs glucose-stimulated insulin secretion by pancreatic beta cells, resulting in aberrant glycometabolic control, contributing to acute and long-term health complications[136,139,140].

Elevated levels of liver enzymes aspartate aminotransferase and alanine aminotransferase are regularly observed in SARS-CoV-2-infected individuals who had no previous history of liver diseases, raising the possibility that SARS-CoV-2 may directly infect the liver. Using in situ hybridization, SARS-CoV-2 mRNA is robustly detected in hepatic parenchymal cells in liver from patients who died from COVID-19. Replication-competent SARS-CoV-2, as well as spike protein and ACE2 protein expression, is also readily detected in these liver samples[141]. Moreover, mRNA of the putative SARS-CoV-2 entry factors, TMPRSS2, procathepsin L and Ras-related protein Rab-7a are detected in hepatocytes from deceased COVID-19 patients[141]. However, other entry factors such as high-density lipoprotein scavenger receptor class B member 1 have been implicated in SARS-CoV-2 liver, and gut tropism[142].

SARS-CoV-2-infected liver is dominated by pronounced type I and II interferon responses, enhanced interferon-related JAK–STAT-1/2 signalling, higher lipid and phospholipid metabolism, and lower levels of amino acid metabolism and OXPHOS compared with uninfected samples[141]. The mounting evidence of multi-organ tropism by SARS-CoV-2, may at least in part account for the extrapulmonary manifestations and multi-organ injury reported in severe COVID-19 disease[143,144].

Analysis shows reduced levels of the insulin-sensitizing hormone adiponectin in plasma from patients with COVID-19 (ref. [145]). Moreover, SARS-CoV-2-infected hamsters have reduced expression of adiponectin protein in subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT) and serum compared with uninfected controls[145]. Elevated levels of SARS-CoV-2 viral RNA is also found in fat of infected hamsters, and primary murine and human adipocytes were found to be receptive to SARS-CoV-2 infection in vitro[145]. SARS-CoV-2 is also detected in SAT but not VAT in infected cynomolgus macaques on day 7 after infection, which may be due to higher expression of ACE2 in SAT compared to VAT[146]. Although it is unclear whether adipocytes can support productive infection, these data suggest that SARS-CoV-2 may trigger adipose tissue dysfunction contributing to glycometabolic disturbances during acute SARS-CoV-2 infection and long-COVID (PASC).

In a cohort study of 551 Italian patients hospitalized for COVID-19 abnormalities, glycometabolic control (46% hyperglycaemic), insulin resistance and altered beta cell function were observed in those who had no pre-existing history or diagnosis of diabetes. Remarkably, these abnormalities persist in recovered patients 2 months after onset of COVID-19 disease[139]. Furthermore, SARS-CoV-2 infection has been linked to increased morbidity and mortality in individuals with diabetes[147]. A retrospective analysis of data consisting of 27,292,879 patients from the Cerner Real-World Data shows significantly increased risk of new-onset type 1 diabetes disproportionally affecting American Indian/Alaskan Native, Asian/Pacific Islander, and Black populations with COVID-19 diagnosis[148]. Notwithstanding the general acknowledgement of a bidirectional relationship between COVID-19 and diabetes, some controversy exists, possibly due to variability in demographics/race and method/timing of glucometabolic analysis. In fact, one study found no evidence of long-term disruption of glycometabolic control after SARS-CoV-2 infection, but insulin levels were not assessed in that study[149].

Importantly, elevation of blood glucose by SARS-CoV-2 infection, which is associated with poor disease outcomes[150,151], may also involve mechanisms not directly implicating the pancreas or insulin sensitivity. Abnormal elevation of systemic glucose in COVID-19 patients is associated with increased circulating GP73, a type II transmembrane Golgi protein that stimulates hepatic gluconeogenesis via cAMP/PKA-dependent mechanisms[152]. GP73 remains elevated even in 'recovered' patients, and positively associates with blood plasma glucose levels. Thus, GP73 might contribute to SARS-CoV-2-induced hyperglycaemia by promoting hepatic glucose release into the circulation[152].

Inhibitors of FASN (which converts malonyl-CoA to palmitate) such as orlistat, an FDA-approved antiobesity drug, potently inhibits SARS-CoV-2 replication, perhaps by reducing cellular levels of free fatty acids and palmitoylated proteins[153]. Moreover, palmitoylation modification of the SARS-CoV-2 spike protein is essential for controlling membrane fusion and virion infectivity. Palmitoylation modifications may enhance S1 hydrophobicity and stability to facilitate interactions with other proteins[154]. In effect, addition of BSA-conjugated palmitic acid partly reversed the antiviral effect of orlistat. These biochemical disruptions in lipid metabolism will likely contribute to susceptibility to metabolic disease, and PASC[155].

It is controversial whether SARS-CoV-2 can directly infect and replicate in immune cells such as monocytes[156]. A recent report shows about 6% of blood monocytes of patients with COVID-19 are infected with SARS-CoV-2 and that infection is dependent on antibody-opsonized virus by Fcγ receptors[157]. It appears that SARS-CoV-2 replication in monocytes is abortive, and triggers NLRP3 and AIM2 inflammasome-mediated pyroptosis[157]. Other work shows that elevated subpopulations of metabolically hyperactive monocytes and $CD4^+$ and $CD8^+$ T cells correlate positively with disease severity[158].

Metabolic diseases predispose individuals to SARS-CoV-2 infection. Metabolic disorders may increase the vulnerability of individuals to SARS-CoV-2 and worsen disease prognosis. In a retrospective, multi-centre study of 7,337 cases of COVID-19 in Hubei Province, China, individuals with uncontrolled type 2 diabetes have poorer COVID-19 prognosis and higher mortality[159]. Shedding mechanistic insights, 1,5-anhydro-D-glucitol (1,5-AG), a glucose-like pyranoid polyol, is identified as an effective anti-SARS-CoV-2 metabolite, which is reduced in individuals with diabetes; 1,5-AG binds to the S2 subunit of the SARS-CoV-2 spike protein, disrupting membrane fusion and cell entry. Thus, low levels of 1,5-AG in people with diabetes might, in part, increase the risk of SARS-CoV-2 infection and disease severity. Indeed, supplementation of 1,5-AG to normal physiological level in SARS-CoV-2-infected diabetic mice significantly reduced COVID-19-associated pathology, suggesting amelioration of hyperglycaemia with 1,5-AG in patients with diabetes might reduce the incidence and/or severity of COVID-19 (ref. [160]).

Evolutionarily conserved metabolic response in viral infections

Despite the metabolic heterogeneity in immune cell phenotypes and diseases, conserved metabolic processes are observed in many viral

infections, illustrating potential generalized therapeutic interventions for diseases driven by dysfunctional metabolism. Viruses such as DENV, ZIKV, HIV and SARS-CoV-2 not only induce glycolysis in host cells but also take advantage of a glycolytic environment for replication[161]. Human adenovirus, an aetiological agent of some respiratory diseases, gastroenteritis and cystitis, increases glucose uptake and glycolysis as well as glutaminolysis to replenish TCA cycle metabolites required for viral nucleic and fatty acid biosynthesis[162]. Conserved metabolic processes in viral infections are elegantly discussed elsewhere[161,163]. However, species-specific metabolism has been documented between human and rat models[164], and thus requires cautious interpretation when studying virus-induced immunometabolic changes in different in vivo systems. In addition to nutrient metabolism, other factors including microbiome and housing temperatures outside the animals' thermoneutral zone will likely impact metabolic responses to infection. Hence, while animal models serve as powerful research platforms for interrogating virus–host relationships, these important factors will influence generalization, and require caution when making clinical predictions[165].

Complexities in metabolic responses in individuals as a function of demographics

Careful consideration should also be given to demographic factors such as age, sex, ethnicity, obesity and diet which can influence immunometabolic responses to infections. Inflammaging constitutes a common predisposing factor for comorbidities linked to HIV and severe COVID-19, especially in older people[166]. Furthermore, ageing has been linked to dysregulated metabolic homoeostasis and remodelling of metabolism in immune cells[167]. There is also significant sexual dimorphism in immunometabolism and metabolic homeostasis between males and females due to fundamental differences in the biological effects of sex hormones[168,169]. These differences are likely to contribute to sex bias in the prevalence of some metabolic and autoimmune diseases, as well as therapeutic responses[170]. Ethnic differences in metabolite signatures associated with metabolic diseases such as type 2 diabetes have been observed[171].

Obesity has been shown to increase the risks, severity, immune response and treatment response to viral infections. High body mass index and low adiponectin levels are associated with reduced HCV-specific T cell responses[172], increased liver injury[173] and poor virologic response to immune-based therapies[174]. More recently obesity has been shown to be associated with susceptibility and severity to influenza A H1N1pdm infection[175]. The microbiome influenced by diet[176,177] will also impact susceptibility and the natural course of viral infections. In fact, age-related microbiome composition of the upper respiratory microbiome influences SARS-CoV-2 susceptibility and disease severity[178]. Interestingly, pathogenic changes in the gut microbiome composition in men before HIV infection are associated with increased risk of HIV acquisition and development of AIDS[179].

Clinical translation and future research directions

Modulating metabolism in viral infections

While significant gains in knowledge have shed light on the sophisticated interactions between metabolism and viruses, the pleiotropic effects of virus–host molecular interactions have made it difficult to fully harness this knowledge towards better disease diagnosis, prognosis and therapeutics. Nonetheless, significant in vitro, preclinical and clinical studies are beginning to reveal the translational benefits of the immunometabolism era.

Suboptimal inhibition of glycolysis in $CD4^+$ T cells from HIV-infected individuals on antiretroviral therapy (ART) potently blocks viral reactivation and spread in vitro and induces the selective death of cells that had been pre-infected in vitro[11]. Drugs that target PI3K, mTOR, HIF-1-α, mtROS and glutamine metabolism have been shown to suppress HIV replication in primary $CD4^+$ T cells[4,12,18,98,106,180,181]. Metformin, which suppresses OXPHOS by targeting mitochondrial complex I, reduced HIV replication in primary $CD4^+$ T cells in vitro, and in mice reconstituted with human $CD4^+$ T cells in vivo[102]. Rapamycin, an mTOR inhibitor, administered to simian immunodeficiency virus (SIV)-infected rhesus macaques on ART for up to 44 weeks caused significant reductions in memory $CD4^+$ T cells in blood and tissues. However, there were no significant changes in the levels of cell-associated SIV DNA and SIV RNA between rapamycin-treated rhesus macaques relative to controls during ART, and no significant difference in the time of SIV rebound off ART[182]. Although rapamycin did modulate the expression of genes associated with metabolism in this study, its effects on mTOR post-transcriptional activities were not evaluated. Nonetheless, administration of metabolic drugs as part of a regimen to reactivate the HIV reservoir may limit deleterious inflammatory consequences[182]. Together, these studies suggest a need for future efforts to explore the administration of combination metabolic drugs during early-stage ART to help suppress residual HIV replication, and 'starving the HIV reservoir' in patients to potentially delay HIV rebound for more extended periods off ART[15,106]. Going forward, it will also be intriguing to investigate whether drugs that modulate important immunometabolic circuits in monocytes and macrophages can also be used to mitigate HIV-associated long-term metabolic complications[15,114,115,183].

Rapamycin was shown to reduce SARS-CoV-2 replication in vero kidney epithelial cells[16], corroborating the observation that SARS-CoV-2-infected cells exhibit an increase in mTORC1 activity[16]. Interestingly, kidney transplant recipients who were treated with the mTOR inhibitor everolimus show increased humoral and T cell-mediated immune response following 4–5 weeks of mRNA BNT162b2 (Pfizer-BioNTech) vaccination[184].

Metabolic processes may be modulated using metabolites such as fumarate and its derivatives monomethyl fumarate and DMF, which pose potent antioxidant and anti-inflammatory properties by improving mitochondrial function. In a study using rhesus macaques infected with SIV, treatment with DMF was shown to counteract oxidative stress in the brain[185]. DMF also induces a metabolic antiviral programme that potently inhibits replication of SARS-CoV-2 in cell lines and limits deleterious host inflammatory responses to SARS-CoV-2 infection associated with COVID-19 airway pathology[60].

As lipids represent the structural foundations of viral membranes, targeting lipid metabolism pathways presents a viable approach for early antiviral interventions. Orlistat suppresses in vitro replication of SARS-CoV-2 variants[153]. Likewise, in K18-hACE2 transgenic mice, injections of orlistat lowered SARS-CoV-2 levels in the lung and increased survival[153]. Orlistat also exhibits significant activity against dengue virus, Japanese encephalitis virus, ZIKV and chikungunya virus[186].

Opportunities for new metabolic biomarkers

Consistent with the understanding that viral infection can invoke a systemic bioenergetic crisis, metabolomic analysis of body fluids such as plasma and serum offers new opportunities to identify novel prognostic biomarkers capable of predicting rates of disease progression and severity[187]. Low levels of circulating NAD^+ are reported in severe COVID-19, and patients with moderate and severe COVID-19 have high plasma succinic acid and kynurenine/tryptophan ratios and low citrulline levels[57,69]. Interestingly, higher plasma succinate is related to poor cross-sectional and longitudinal measures of neurocognitive impairment in ART-treated HIV-positive persons[188], and plasma lipid profiles distinguished frail from non-frail HIV-positive men[189].

Plasma metabolomic and lipidomic analysis of HIV-positive individuals who underwent analytical HIV treatment interruption (ATI) showed that significantly higher pre-ATI levels of glycerophospholipids, and the glycolytic intermediates glyceraldheyde-3-phosphate, pyruvic acid and lactic acid are associated with shorter time to HIV rebound, while significantly elevated pre-ATI plasma glutamic acid and α-ketoglutaric acid are observed in those who had delayed viral

rebound[181,190]. Additionally, higher plasma levels of lactic acid and lower levels of glutamic acid are detected in transient compared to persistent HIV controllers[191].

These studies highlight the potential opportunities to harness metabolite composition in body fluid as biomarkers to improve the robustness of diagnosing and forecasting disease outcomes. Discovery of biomarkers that rely on host metabolic responses will also provide novel mechanistic insights into disease pathogenesis.

Future research directions

Future research directions should recognize the spatiotemporal metabolic changes during viral infections. Single-cell immunometabolic analysis should clarify the heterogeneity of the metabolic programmes within tissue compartments. Integrative technologies such as metabolic-based flow cytometry[9,192], flow cytometric-based mitochondrial dynamics analysis[193], mass-spectrometry coupled with liquid or gas chromatography[194,195], single-cell RNA sequencing[196,197], mass cytometry[198] and single-cell energetic metabolism by profiling translation inhibition[199,200] can be adapted to investigate these questions. Comparative studies of metabolic responses across animal models will also improve predictive clinical significance in humans.

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