

Metabolic regulation of type I interferon production

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Summary

Over the past decade, there has been a surge in discoveries of how metabolic pathways regulate immune cell function in health and disease, establishing the field of immunometabolism. Specifically, pathways such as glycolysis, the tricarboxylic acid (TCA) cycle, and those involving lipid metabolism have been implicated in regulating immune cell function. Viral infections cause immunometabolic changes which lead to antiviral immunity, but little is known about how metabolic changes regulate interferon responses. Interferons are critical cytokines in host defense, rapidly induced upon pathogen recognition, but are also involved in autoimmune diseases. This review summarizes how metabolic change impacts interferon production. We describe how glycolysis, lipid metabolism (specifically involving eicosanoids and cholesterol), and the TCA cycle-linked intermediates itaconate and fumarate impact type I interferons. Targeting these metabolic changes presents new therapeutic possibilities to modulate type I interferons during host defense or autoimmune disorders.

KEYWORDS

Immunometabolism, interferons, macrophage, metabolism

1 | INTRODUCTION

1.1 | Innate immune defense mechanisms

Innate immune cells constitute, along with the epithelial barriers, one of the first lines of defense against viral or bacterial infections. Recognition of pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) by pattern recognition receptors (PRRs) leads to the induction of an inflammatory response. Interferons (IFNs) form part of the innate defense mechanism against infections. IFNs are separated into families based on receptor binding, structure, and biological activity. The type I family comprises IFN- α , IFN- β , and multiple other less well-characterized IFNs. All type I IFNs bind to the heterodimeric IFNAR1/IFNAR2 receptor complex,¹ leading to the recruitment of the Janus kinases

(JAK) JAK1 and tyrosine kinase 2 (TYK2) to receptor intracellular domains resulting in their phosphorylation. Canonical signaling directs phosphorylation of signal transducer and activator of transcription (STAT) 1 and STAT2 inducing expression of a large number of genes which are termed interferon stimulated genes (ISGs).^{2–5}

A surge in discoveries in recent years regarding how PRR activation causes metabolic changes which regulate the effector function of immune cells such as myeloid and lymphoid cells has established the field of immunometabolism. In particular, when macrophages are challenged with lipopolysaccharide (LPS), a component of gram-negative bacteria which is sensed by TLR4, aerobic glycolysis is increased to meet the energetic demands of M1 macrophage effector function leading to cytokine production, phagocytosis, and antigen presentation. This response is similar to the increased demand for glucose and glycolysis observed by Otto

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Warburg in tumors.⁶ LPS challenge in macrophages also causes breakpoints in the TCA cycle, leading to changes in levels of metabolites such as succinate, citrate, itaconate, and fumarate which regulate macrophage function. For example, succinate directly blocks prolyl hydroxylases (PHDs), leading to HIF-1 α stabilization and subsequent IL-1 β production.

Metabolic reprogramming has mostly been studied in the context of immune cells challenged with bacteria or bacterial components. But it is now known that viral infection also causes immunometabolic changes. Viruses such as influenza A virus (IAV) manipulate host cellular metabolism by upregulating glucose uptake, glycolysis, as well as lactate efflux. Increased glycolysis promotes the production of nucleotide biosynthesis via the pentose phosphate pathway (PPP) for viral replication.^{7–10} In this review, we discuss recent findings on how metabolic pathways regulate type I interferon responses. New therapeutic possibilities are emerging from these findings which could prove useful for antiviral immunity or in the context of autoimmunity.

1.2 | Glycolysis and interferon responses

Inflammatory activation of dendritic cells (DCs) or macrophages with purified bacterial components results in increased glycolysis and activation of the PPP, albeit metabolic changes during live pathogen infection are more complex.^{11,12} Activation of glycolysis is important for the induction of an antiviral response.¹³ While infection with live *Mycobacterium tuberculosis* (Mtb) decreases oxygen consumption rate (a measure of oxidative phosphorylation), and glycolysis, heat inactivated Mtb infection increases glycolysis without impacting oxygen consumption rate.¹⁴ Further the authors showed that exogenous type I IFNs induced a similar profile in bone marrow-derived macrophages (BMDM) compared to live Mtb infection, stating that induction of type I IFNs might explain the decreased glycolytic flux and reduced mitochondrial respiration.¹⁴ Indeed, infection of IFNAR^{-/-} BMDMs did not result in reduced glycolysis during live Mtb infection and resulted in elevated glycolytic capacity in alveolar macrophages and monocyte-derived macrophages during in vivo infection of IFNAR^{-/-} mice compared to wild type mice. Additionally, IFN- β can restrain the LPS-induced shift towards aerobic glycolysis in BMDMs.

The hexosamine biosynthesis pathway (HBP) branches off glycolysis synthesizing uridine-5'-di-phospho-N-acetylglucosamine (UDP-GlcNAc) used for protein glycosylation which has been shown to regulate the key interferon regulator IRF5. The enzyme O-GlcNAc transferase (OGT) then catalyzes transfer to target proteins, resulting in protein O-GlcNAcylation. Viral RNA is recognized by retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) which further recruit mitochondrial antiviral-signaling protein (MAVS) and induce downstream type I IFN production.¹⁵ Viral infection promotes aerobic glycolysis.¹⁶ Activation of glucose metabolic pathways upon viral infection induces OGT-mediated O-GlcNAcylation of IRF5 and further inflammatory cytokine production, including IFN- β as shown

in Figure 1.^{13,17} Also, IAV infected individuals had increased blood glucose levels and O-GlcNAcylation of IRF5 in PBMCs.¹⁷ Activation of RLRs by RNA viruses shifts glucose flux from glycolysis to the PPP and the HBP. Activation of those two pathways is necessary for an antiviral immune response and IFN production upon vesicular stomatitis virus (VSV) infection in mice. O-GlcNAcylation of MAVS itself has been shown to induce antiviral immunity, including induction of ISGs and IFN- β production.¹⁸ Another study identified MAVS subcellular localisation as important for the induction of a specific IFN response. Translocation of MAVS to peroxisomes induces type III IFN production via the PPP and IRF1 activation, while MAVS translocation to mitochondria-associated ER membranes induces the HPB and production of type I IFNs as shown in Figure 1. Infection with VSV induces production of type I and III IFNs, while inhibition of either the PPP or the HPB reduced survival upon VSV infection. This shows that the regulation of glucose metabolism and MAVS are coregulated and important for antiviral immune responses.^{18,19}

Glucose levels impact on RLR activation by poly(I:C), with low glucose levels leading to stronger induction of IFN- β .²⁰ This effect was transferrable to mice as fasted mice supplemented with low glucose also showed higher IFN- β production after VSV infection compared to animals that were supplemented with high glucose. Low glucose supplemented animals also had lower viral replication, suggesting that downregulated glucose metabolism promoted the type I IFN response and antiviral response. Recognition of viral particles by RLRs, leads to dissociation of MAVS from hexokinase resulting in hexokinase inactivation and association of MAVS with RIG-I to induce type I IFNs. Therefore, downstream products of hexokinase are reduced during RLR activation, while TBK1 and IRF3 are activated. Downregulation of glucose metabolism has also been shown to lead to an antiviral response, as lactate derived from anaerobic glycolysis binds to MAVS, inhibits its mitochondrial localization and further interaction with RIG-I that are essential for induction of downstream IFN- β production as shown in Figure 1. In line with this, increased type I IFN production during VSV infection of fasted mice supplemented with low glucose was reversed by additional supplementation of lactate, as was the effect in lactate dehydrogenase A-deficient mice.²⁰

This shows that modulation of glucose metabolism during viral infections is an important aspect of antiviral responses including induction of type I IFNs. Metabolic flux to lactate inhibits antiviral responses by targeting MAVS, while induction of the PPP or the HBP promotes MAVS-dependent antiviral responses.

1.3 | Cholesterol metabolism and IFNs

Early work demonstrated the importance of the cholesterol pathway in the regulation of host defense and induction of IFNs.^{21–23} Infection with cytomegalovirus (CMV) or administration of type I IFNs blocks sterol regulatory element binding protein 2 (SREBP2) and thereby sterol biosynthesis.²¹ SREBP2 inhibition, as well as statins, which are inhibitors of HMG-CoA reductase, can constrain viral replication.^{24,25}

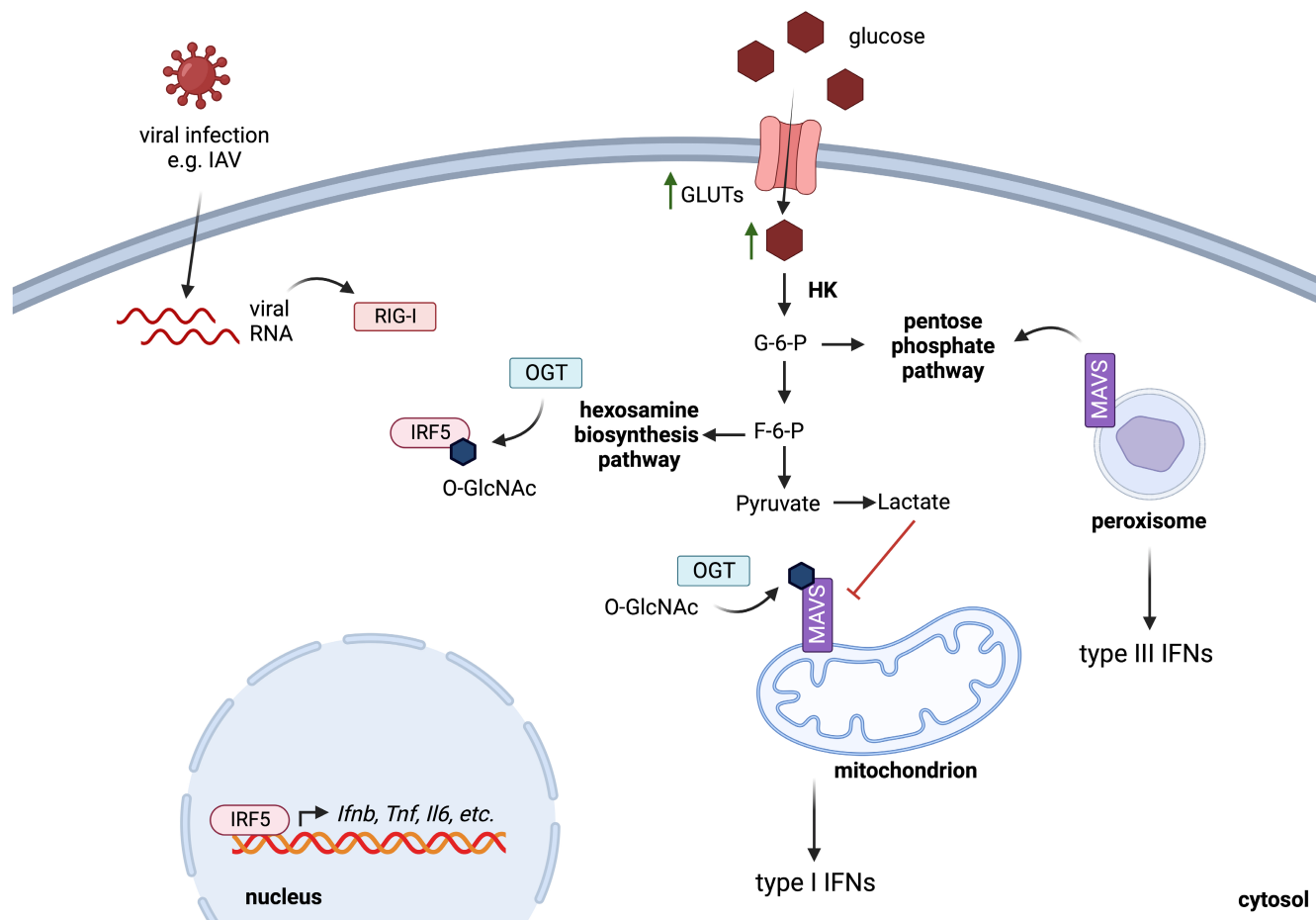


FIGURE 1 Viral infections induce increased glucose metabolism after recognition of viral RNA by RIG-I and MAVS activation. Activation of the hexosamine biosynthesis pathway and OGT (O-GlcNAc transferase) lead to O-GlcNAcylation of IRF5 and increased expression of IFNs, as well as inflammatory cytokines. MAVS is also subjected to O-GlcNAcylation and induction of an antiviral response. Additionally, MAVS subcellular localization impacts on induction of a different IFN response. Peroxisomal MAVS induces the PPP and leads to type III IFN production, while translocation to mitochondria-associated ER membranes induces the HPB and production of type I IFNs. Lactate inhibits MAVS activation and therefore induction of an antiviral response. F-6-P, fructose-6-phosphate; G-6-P, glucose-6-phosphate; GLUT, glucose transporter; HK, hexokinase.

Reduced cholesterol biosynthesis therefore was antiviral. More recently there has been a focus on 25-hydroxycholesterol (25-HC) as shown in Figure 2.

The endoplasmic-reticulum-associated enzyme cholesterol-25-hydroxylase (*CH25H*) catalyzes the oxidation of cholesterol to 25-HC. 25-HC serves as a corepressor of cholesterol biosynthesis through inhibition of SREBP processing.²⁶ In macrophages and DCs *CH25H* expression is increased by various TLR agonists, as well as IFN- α and IFN- β , making it an ISG²⁷ (Figure 2A). 25-HC induction by type I IFNs was completely dependent on IFNAR1 signaling in murine macrophages, with exogenous IFN- γ also boosting 25-HC levels.²⁸ Treatment of BMDM with 25-HC blocked replication of different enveloped DNA and RNA viruses, while this was not the case for non-enveloped viruses.^{28,29} IFN- β and IFN- γ treated macrophages exhibited antiviral effects via 25-HC secretion. Transfer of supernatant from those stimulated macrophage could inhibit viral replication in target cells, indicating antiviral activity can also work in a paracrine manner. In vitro treatment with 25-HC also inhibited

human immunodeficiency virus (HIV) entry via cell membrane remodeling.²⁹ Furthermore, in vivo administration of 25-HC reduced HIV infection in humanized mice. In Zika virus (ZIKV) infection 25-HC was protective by inhibiting viral entry independent of IFNAR1 signaling. 25-HC administration reduced mortality in mice in vivo, in wild type and in IFNAR1 deficient mice, while also reducing viremia in rhesus monkeys. Thus, the type I IFN inducible gene *CH25H* through its product 25-HC acts as an antiviral agent^{28–31} (Figure 2A). Overall, 25-HC blocks viral entry by altering membrane composition and thereby impairs viral fusion,²⁹ while also blocking postentry viral growth.²⁸ Also, 25-HC and 27-HC lead to the accumulation of cholesterol in late endosomes, encapsulating viral particles and thus inhibiting their replication.³² Furthermore, 25-HC induces the accumulation of oxysterol binding protein 1 at the Golgi-ER interface, thus leading to endosomal accumulation of cholesterol and blocking replication of human rhinoviruses.³³ Therefore, 25-HC changes the accessibility of cholesterol in the cell membrane via different mechanisms which reduce viral entry and replication.

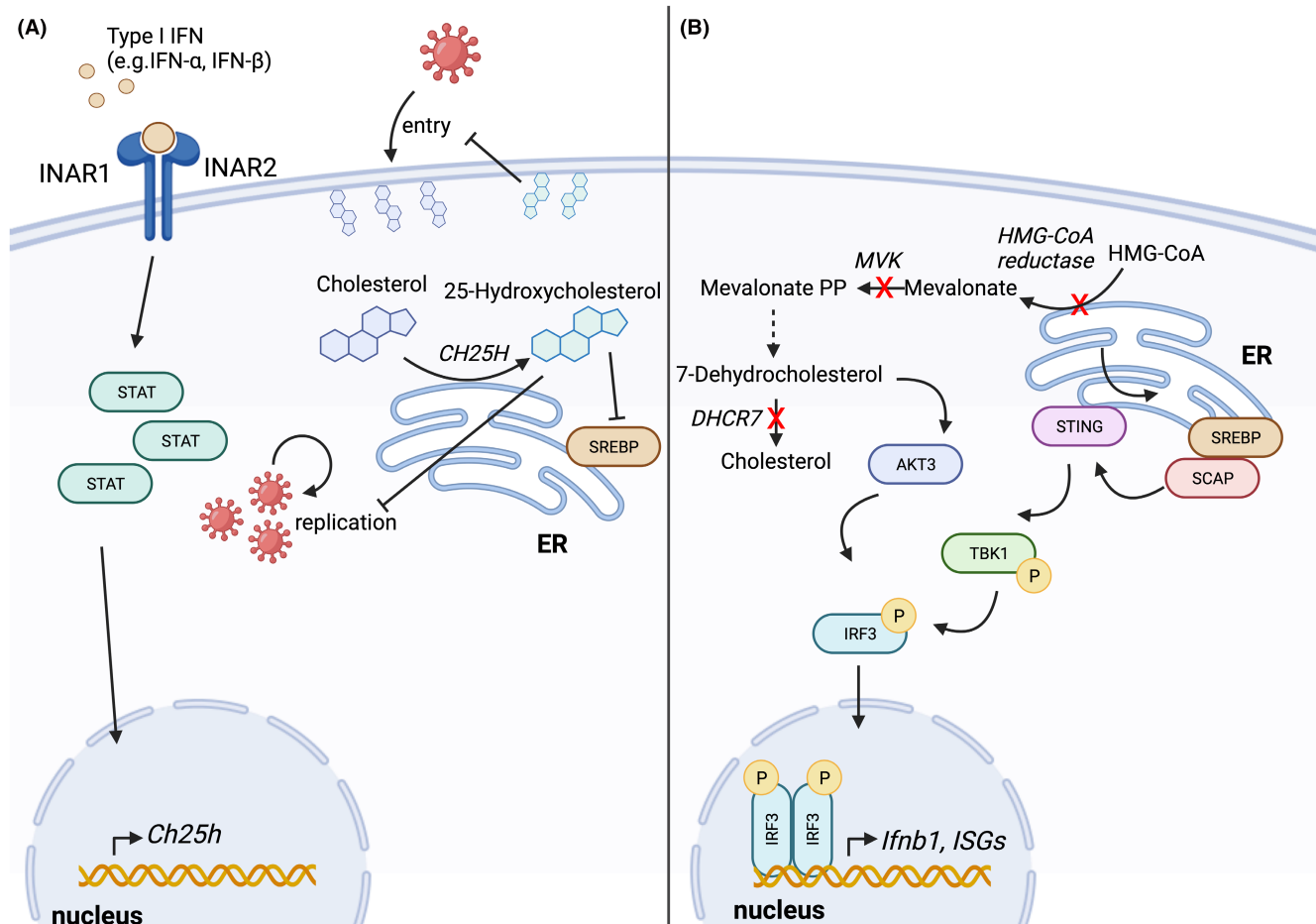


FIGURE 2 Influence of cholesterol on IFN response. (A) Membrane cholesterol facilitates viral entry. Type I IFNs modulate cholesterol metabolism from de novo synthesis to increased import. This is conferred through the induction of CH25H and its product 25-hydroxycholesterol (25-HC), suppressing SREBP processing and thereby cholesterol biosynthesis. 25-HC has been shown to limit viral entry and replication. (B) Alterations in cholesterol metabolism induce type I IFN response and expression of ISGs. Genetic perturbations in the mevalonate pathway leading to reduced ER cholesterol levels activate STING, which further phosphorylates TBK1 and IRF3, and induce the expression of *Ifnb1* and ISGs. Accumulation of 7-Dehydrocholesterol (e.g., through inhibition of 7-dehydrocholesterol reductase (DHCR7)) induces AKT3 and IRF3 phosphorylation and further ISG expression.

Apart from viral infections, LPS induces CH25H in an IFNAR-dependent manner.³⁰ In vivo lethal LPS administration led to increased IL-1 β production in *Ch25h*^{-/-} mice and earlier death. Infecting mice with the bacterium *Listeria monocytogenes* induced *Ch25h* via type I IFNs, while in this case *Ch25h*^{-/-} mice displayed reduced susceptibility to infection. 25-HC therefore participates in a negative feedback loop, downregulating IL-1 β expression, inhibiting caspase-1 activity, and further IL-1 β processing, thereby reducing inflammasome activation.³⁰ This was shown for different NLRP3 inflammasome activators, including ATP, nigericin and alum, as well as the NLRC4-inflammasome flagellin and AIM2-inflammasomes. Increased IL-1 β production in *Ch25h* deficient mice relied on ASC-dependent inflammasome activation and involved the DNA sensor AIM2. Treatment of BMDMs with methyl-beta cyclodextrin cholesterol, used to deliver cholesterol to membranes, increased mitochondrial ROS production, suggesting that increased cholesterol levels induced mitochondrial dysfunction. Additionally, the authors describe how *Ch25h*^{-/-} BMDMs

showed impaired mitochondrial respiration and accumulated mitochondrial DNA (mtDNA) in the cytosol after LPS stimulation. This links increased mitochondrial, or total, cholesterol levels to mtDNA release and AIM2 activation.

Pathogens can also target membrane cholesterol via cholesterol-dependent cytolysins (CDCs), toxins produced by gram-positive bacteria, inducing pore formation and loss of membrane integrity further leading to cell death. Several repair mechanisms exist, including membrane internalization and releasing or shedding damaged membranes as microvesicles.^{34–36} Type I and II IFNs can alter availability of the membrane cholesterol pool and thereby provide resistance to CDCs in macrophages and neutrophils.³⁷ The effect was conferred by increased production of 25-HC that further reduced de novo cholesterol synthesis. In vivo administration of 25-HC also reduced CDC-mediated tissue damage.³⁷

Type I IFNs can shift lipid metabolism from fatty acid and cholesterol de novo synthesis to their import, through changes in gene expression and altered metabolic flux.^{28,29,37–39} However, alterations

in cholesterol and fatty acid metabolism impact IFN production. BMDMs deficient for SREBP cleavage-activating protein (SCAP), an important regulator of SREBP processing, show reduced lipid biosynthesis without affecting the total lipid pool. Additionally, genetic deletion of *Scap* or *Srebp2* in BMDMs resulted in induction of a type I IFN response characterized by increased transcription of *Irfn1* and several ISGs (e.g., *Mx2*, *Irf7*, *Ccl2*, and *Cxcl10*) and subsequent protection from viral infections.³⁸ Further characterizing the mechanism, the authors showed that deletion of mevalonate kinase (MVK) or HMG-CoA reductase are sufficient to induce type I IFNs, while cholesterol replenishment reduced the expression of ISGs (Figure 2B). Also, Blanc et al., showed, that the mevalonate pathway was important for 25-HC antiviral functions, suggesting that a decreased flux through the mevalonate pathway prompts type I IFN-mediated inflammation.^{28,38} Stimulator of interferon genes (STING) has been shown to facilitate IRF3 phosphorylation and nuclear translocation, as well as *Irfn1* transcription in response to cytosolic double-stranded DNA or RNA,⁴⁰ as well as through binding of ligands generated by cyclic GMP-AMP synthase (cGAS).^{41,42} *Srebp2* deficient cells showed high basal cGAS expression, and STING activity, leading to increased TANK-binding kinase 1 (TBK1) and IRF3 phosphorylation.³⁸ Addition of cholesterol to *Scap*-deficient BMDM reduced their increased phospho-TBK1 levels and *Irfn1* expression, showing that low cholesterol directly influences STING activation. As cGAMP levels (a STING ligand) were similar between *Srebp2*-deficient and control cells, low levels of ER membrane cholesterol might facilitate interactions between STING and TBK1. Inhibiting the mevalonate pathway reduced type I IFN production after poly(I:C) or LPS stimulation of BMDM through diminished PI(3)K activation.⁴³ All these data indicate that perturbations in cholesterol and mevalonate metabolism directly affect STING function, thereby regulating type I IFN production as shown in Figure 2.

In line with the impact of MVK or HMG-CoA reductase on IFN response, alterations of 7-dehydrocholesterol reductase (DHCR7) all affect the type I IFN response.⁴⁴ DHCR7 is the enzyme converting 7-dehydrocholesterol (7-DHC) to cholesterol. IFN- β reduced the expression of DHCR7, while siRNA knockdown of DHCR7 enhanced *Irfn1* expression upon poly(I:C) or viral treatment. Accumulation or administration of 7-DHC augmented *Irfn1* production, and ISGs, in an IRF3 dependent manner, also promoting viral clearance.⁴⁴ In this setting AKT3 was involved in IRF3 Ser-385 phosphorylation, facilitating IRF3 Ser-386 phosphorylation by TBK1 and thus promoting IRF3 dimerization. IRF3 nuclear translocation resulted in an enhanced antiviral response through IFN- β production and ISG induction (Figure 2B).

Reduced de novo cholesterol biosynthesis and limiting the availability of cholesterol induces antiviral activity. This is either conferred by decreasing flux through the mevalonate pathway or by reducing DHCR7, as well as increasing expression of CH25H. The product 25-HC then reduces SREBP processing as well as proteasomal degradation of HMG-CoA and therefore feeds back to reducing cholesterol synthesis.^{26,45} Apart from the effect on cholesterol metabolism, 25-HC mediated antiviral functions via inhibition of

pathogen entry or viral replication, while also limiting inflammasome activation. It might seem counterintuitive that limiting cholesterol biosynthesis as well as increasing 25-HC production both show antiviral effects and indeed some studies describe antiviral effects of exogenously supplemented 25-HC (which is not affected by reduced cholesterol synthesis). However, limiting cholesterol synthesis did not affect the total cholesterol pool, while shifting reduced synthesis to increased import. Also, utilising CH25H knockout mice clearly established the antiviral role of 25-HC during virus infections.³⁸

1.4 | Impact of eicosanoids on type I interferons

Eicosanoids are another class of lipid mediators implicated in the regulation of type I IFNs as shown in Figure 3. They are bioactive molecules derived from the polyunsaturated fatty acids arachidonic acid through different pathways including the cyclooxygenase (COX) pathway for the formation of prostanoids or the lipoxygenase (LOX) pathway. 5-LOX synthesizes leukotrienes (LTs), while 12/15-LOX forms 12-/15-HETE, as well as a range of specialized pro-resolving mediators such as lipoxin A4.

1.5 | Leukotrienes

Previously, leukotriene (LT) production has been mostly attributed to myeloid cells, while recent studies established specialized epithelial cells, tuft cells, as LT producers.^{46,47}

LTB₄ is a proinflammatory chemotactic metabolite signaling through the high-affinity B leukotriene receptor 1 (BLT1) and the lower-affinity receptor BLT2.⁴⁸ IAV infection leads to increased production of LTB₄ in the broncho-alveolar lavage (BAL) fluid, lungs, and serum of infected mice as shown in Figure 3A.⁴⁹ LTB₄ administration during IAV infection resulted in a reduction in viral load and increased survival,^{50,51} suggesting LTB₄ as part of the antiviral immune response. Pernet et al. showed that LTB₄ via BLT1 could induce IFN- α production by pulmonary interstitial macrophages, which reduced inflammatory monocyte-derived macrophage proliferation and thereby limited IAV immunopathology and mortality, see Figure 3B.⁴⁹ Another study showed that additional LTB₄ administration during IAV infection could increase survival and viral clearance via IFN- β production, as depicted in Figure 3B. The authors propose that this effect was conferred through potentiating NOD2 signaling through TAK1, IRF3 and NF- κ B/MAPK.⁵¹ Several viruses increase host LT production (including LTB₄)^{49,52,53} and might thereby contribute to a protective innate immune response through regulation of the IFN response.

IFNs also regulate LT production. Peritoneal macrophages pre-stimulated with IFN- α increased the production of LTB₄ after zymosan stimulation.⁵⁴ In a sepsis model, macrophage IFN- β production resulted in reduced production of LTB₄ by recruited neutrophils. Furthermore, IFNAR1 deficiency limited LTB₄ production, as well as inflammation and survival during sepsis.⁵⁵

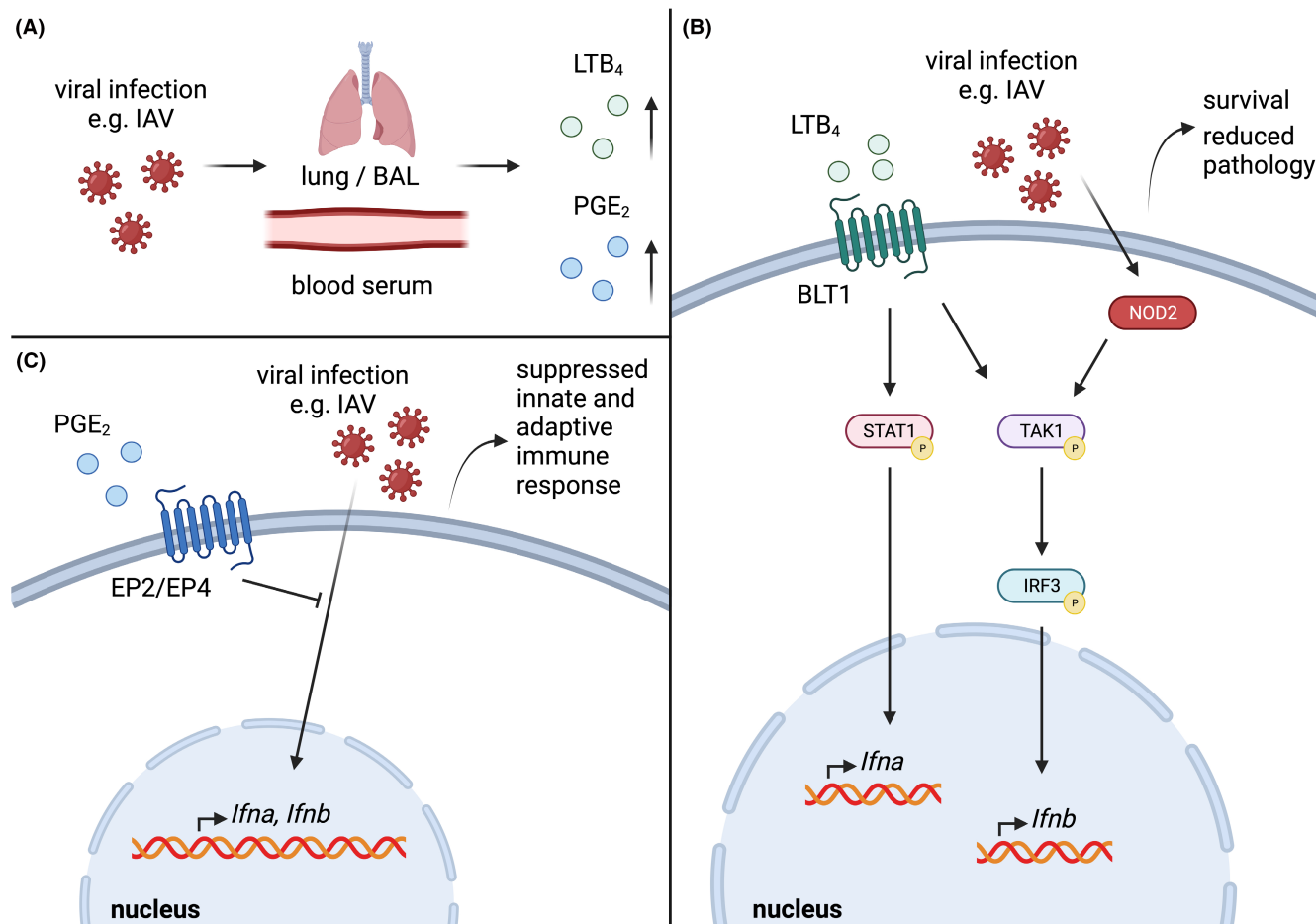


FIGURE 3 Eicosanoids effect on viral defense mechanisms. (A) During viral infections like IAV (influenza A virus) LTB₄ and PGE₂ are increased in the lungs, BAL fluid, as well as serum. (B) During viral infections LTB₄ signaling via BLT1 induces STAT1 phosphorylation and can lead to increased transcription of *Ifna*. Additionally, LTB₄–BLT1 signaling can lead to TAK1 phosphorylation, which further promotes IRF3 activation and *Ifnb* transcription. NOD2 signaling can potentiate this effect. LTB₄ thus increases survival and reduces pathology during viral infections. (C) PGE₂ ligation to the EP2/EP4 receptor can reduce viral induced *Ifna* and *Ifnb* transcription and production in macrophages and thereby suppress antiviral macrophage activity and delay the adaptive immune response.

Additionally, LTB₄ can upregulate TLR2 and TLR9 expression in human polymorphonuclear neutrophils (PMNs)^{50,56} and activate STAT1 phosphorylation in murine macrophages.⁵⁷ Most studies did not investigate the impact of LTs on IFNs or ISGs, leaving the interplay between LTs and IFNs open for further investigations.

1.6 | Prostaglandins

PGE₂, a COX derived metabolite, exerts its effect through G protein-coupled E prostanoïd (EP) receptors 1–4. Depending on the cell type and activated receptor, it can be pro- or anti-inflammatory.⁵⁸ PGE₂ impairs the host response to IAV infection by inhibiting type I IFN production, while prostaglandin E synthase deficient (Ptges^{−/−}) mice exhibited enhanced protection⁵⁹ (Figure 3C). Another study investigated IAV infection in aged mice, since the elderly human population is more at risk of developing complications and succumbing to viral infections.^{60,61} The authors found that in aged mice senescent type II alveolar epithelial cells contribute to increased

PGE₂ production in the lungs before and during IAV infection that limit alveolar macrophage proliferation. Blocking of the EP2 receptor increased IFN-β production and could improve survival in aged (but not young) mice.⁶² This suggested an age-dependent difference, which might be targeted therapeutically. Also other pathways may contribute to the disparity in developing complications to viral infections between different age groups. Deficiency of 15-lipoxygenase (Alox15, 15-LOX), catalyzing the formation of 15-HETE and several anti-inflammatory metabolites termed specialized pro-resolving lipid mediators, promoted senescence in alveolar macrophages via enhanced PGE₂ production.⁶³ In line with Coulombe et al.⁵⁹ the enhanced production of PGE₂ in Alox15^{−/−} mice resulted in delayed IFN-β production after IAV infection and increased viral load.⁶³

More work is therefore needed on the interplay between eicosanoids and IFNs. Especially as the most used drugs for milder viral infections (e.g., common cold, flu) are non-steroidal anti-inflammatory drugs, like aspirin or ibuprofen which inhibit COX enzymes. This provides pain and fever relief but might have additional beneficial

effects by preventing PGE₂ production in infected tissues and boosting type I IFN production.

2 | TCA CYCLE-DERIVED METABOLITES MODULATE INTERFERONS

2.1 | Itaconate

Recently a role for TCA cycle derived metabolites in the regulation of IFNs has emerged, specifically in regard to itaconate and fumarate.

Itaconate is the most abundantly produced metabolite in LPS challenged macrophages, produced from the TCA cycle intermediate aconitate via aconitate decarboxylase 1 (ACOD1), encoded by the gene *immunoresponsive gene 1* (*Irg1*) as shown in Figure 4. Due to its α , β -unsaturated dicarboxylic acid structure containing two double bonds and two carboxyl groups, it can covalently modify cysteines on target proteins in a Michael addition reaction. This covalent modification of proteins alters protein function.⁶⁴ Itaconate has demonstrated antibacterial, antiviral, and anti-inflammatory properties.^{65,66} Itaconate boosts IFNs as *Irg1*^{-/-} BMDMs have significantly reduced IFN- β and reduced type I interferon signature which is restored upon itaconate treatment.⁶⁷ A mechanism whereby itaconate might regulate type I interferon could include succinate dehydrogenase (SDH) inhibition. As itaconate is structurally similar to succinate, itaconate competitively inhibits the active site of SDH. It has been demonstrated that SDHA and SDHB (two subunits of SDH) knockout in RAW 264.7 macrophage cell lines increases IFN- β production.⁶⁸ Furthermore, pharmacological irreversible inhibition of SDH by 3-nitropropionic acid (3-NPA) and dimethyl malonate (DMM) also boost the IFN signature in YUMM1.7 male mouse melanoma cell line and BMDMs, respectively.^{69,70} SDH, therefore, impacts on IFN production, but the mechanism by which this occurs is still unknown.

2.2 | Itaconate derivatives

Itaconate can be further metabolized into isomers citraconate and mesaconate as reported in the mouse RAW264.7 macrophage cell line as shown in Figure 4. Mesaconate differs only in the location of a double bond and is synthesized via both itaconate and glutamine metabolism. Between itaconate, citraconate, and mesaconate, citraconate is the most electrophilic of the three, fails to block SDH, and is the most potent nuclear factor erythroid 2-related factor 2 (NRF2) activator. Citraconate treatment blocks IFN responses in THP1 human monocyte cell line and A549 human airway epithelial in the context of IAV infection.⁷¹

Mesaconate is endogenously synthesized from itaconate in macrophages including the RAW264.7 cell line. Mesaconate is a weaker SDH inhibitor than itaconate. It is the least electrophilic of the three itaconate related metabolites. Pretreatment of RAW264.7 murine macrophage cell line with mesaconate for 4h followed by 3-h LPS challenge significantly boosted IFNB1 levels compared to LPS alone.⁷¹

Itaconate derivatives have been created to increase cell permeability. These include derivatives such as 4-octyl itaconate (4-OI) and dimethyl itaconate (DI). Although itaconate derivatives and the endogenous metabolite overlap in many contexts, there are also unique properties to each of these derivatives in their immunomodulatory effects. A comparative study has illustrated the differences between itaconate and its derivatives in the content of multiple immune pathways in murine macrophages. In the context of IFNs, they show that itaconate boosts IFNs whereas 4-OI is a potent suppressor of IFNs as shown in Figure 4.⁶⁷ Mechanistically, 4-OI inhibits STING phosphorylation by alkylating STING on cysteine 91 and 147 and prevents palmitoylation of STING and its activation.^{72,73} 4-OI also alkylates JAK1 on Cys-816 located on the pseudokinase domain, necessary for JAK1 phosphorylation and signaling.⁷⁴

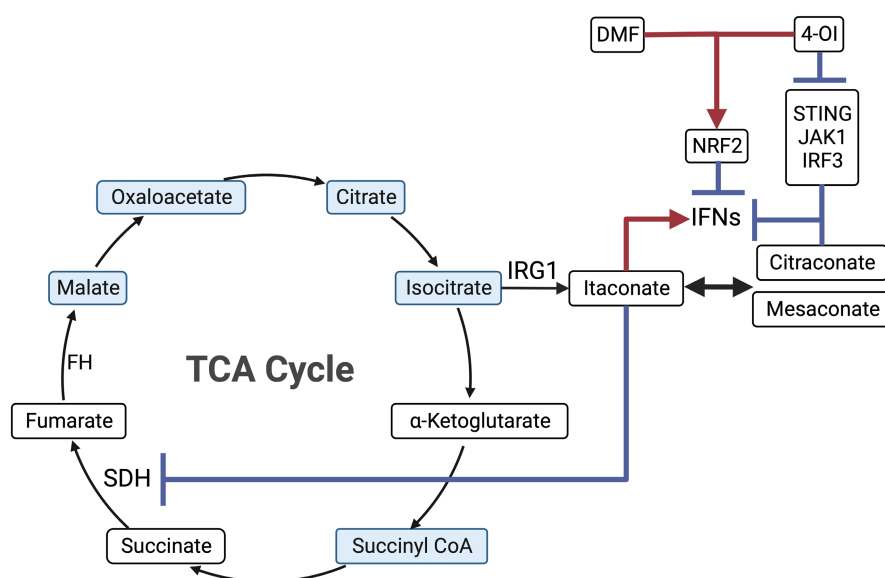


FIGURE 4 The effect of TCA cycle metabolites and derivatives on interferons. Itaconate is the most upregulated metabolite in LPS challenged macrophages. Itaconate blocks SDH essential for macrophage effector function. Both itaconate accumulation and SDH inhibition boost IFN. Itaconate isomers citraconate and mesaconate are more electrophilic and fail to block SDH and induce IFN production. Itaconate derivative 4-OI blocks IFN via alkylation of STING, JAK1, and IRF3.

4-OI can also regulate IFNs via NRF2. Under homeostatic conditions, NRF2 undergoes constant polyubiquitination and proteasomal degradation regulated by Kelch-like ECH-associated protein 1 (KEAP1). 4-OI alkylates KEAP1 at Cys-151, leading to the liberation of NRF2 where it translocates to the nucleus and, along with musculoaponeurotic fibrosarcoma proteins (MAF), acts as both a transcription factor, binding to the antioxidant response element (ARE) and induction of anti-inflammatory and cytoprotective genes, and the direct inhibition of inflammatory gene transcription including IL-6 and IL-1 β by blocking RNA-pol II recruitment.^{75,76} NRF2 negatively regulates *Irfn1*.⁷⁷ Furthermore, 4-OI blocks IRF3 dimerization in an NRF2-dependent manner in HaCaT cells and A549 cells.⁷⁸ 4-OI has been shown to be beneficial in a mouse model of COVID-19. COVID-19 is a coagulopathy mediated by tissue factor (TF) production and thrombin generation which leads to elevated fibrinogen, collagen deposition, lung inflammation and subsequent thrombo-inflammation. A severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection mouse model had elevated TF levels. TF is an ISG which can be blocked by the itaconate derivative 4-OI. In vivo 4-OI reduced the clinical score, lung inflammation, inflammatory cell infiltration to the lungs, viral loads, and ACE2 expression in SARS-CoV-2 infected mice.⁷⁹

2.3 | Fumarate

Dimethyl fumarate (DMF) is a derivative of fumarate which is clinically approved under the name Tecfidera for the treatment of relapsing remitting multiple sclerosis and psoriasis. DMF, like 4-OI, is electrophilic and cysteine reactive. Like 4-OI, DMF has been shown to inhibit SARS-CoV-2 replication and suppress the inflammatory response, including *IFNB1* and subsequent TF expression.⁷⁸

Fumarate hydratase (FH, encoded by *Fh1* in mice) catalyzes the reversible hydration of fumarate to malate, either in the mitochondria as part of the TCA cycle or in the cytosol. Prolonged LPS challenge in macrophages causes a downregulation of FH.⁸⁰ RNAseq analysis revealed that FH inhibition in combination with LPS stimulation resulted in increased expression of *Irfn1* and ISGs including *Irf1*, *Irfh1*, *Rsad2*, and *Ifit2* compared to LPS alone. Both mitochondrial RNA (mtRNA) and mtDNA were released into the cytosol, increasing IFN- β production. The effect of mtRNA was mediated via MDA5 and TLR7. MtRNA release likely depended on changes in mitochondrial membrane potential, as the ATP synthase inhibitor oligomycin, K⁺ ionophore valinomycin A and the uncoupler CCCP could all induce mtRNA release into the cytosol. In mice, in vivo administration of the FH inhibitor before LPS injection increased serum IFN- β levels. Finally, PBMCs from systemic lupus erythematosus (SLE) patients which have elevated type I interferons showed reduced FH expression compared to healthy controls and IFN- β could suppress FH expression.⁸⁰ Overall, FH suppression leads to mtRNA release and in turn IFN- β production as displayed in Figure 5. This may be

important in the pathogenesis of diseases such as SLE or other interferonopathies.

FH and fumarate have also been shown to drive type I and type II IFN responses in cancer.⁸¹ In rare forms of cancer such as hereditary leiomyomatosis and renal cell cancer (HLRCC), FH deficiency occurs, leading to fumarate accumulation which acts as an oncometabolite.⁸² Transcriptomic analysis of mouse kidneys from tamoxifen-inducible *Fh1*^{-/-} mice revealed induction of an innate inflammatory response, including an increase in cytokines, chemokines, and ISGs. Cytosolic accumulation of mtDNA activated a STING-TBK1-IRF3 cascade and further upregulated ISG expression as shown in Figure 5. cGAS and the RNA sensor RIG-I were necessary to induce TBK1 and IRF3 phosphorylation. The mtDNA was released in a selective way through mitochondrial-derived vesicles (MDVs),⁸³ dependent on the protein Sorting nexin-9 (SNX9), that had been shown to coordinate intracellular trafficking.⁸⁴ Human FH-deficient tumors also displayed different cell composition, as well as cytokine responses, that might link mitochondrial perturbations to cancer immunopathology.⁸¹

These studies expand the role of FH, from a metabolic enzyme to its role in oncological and inflammatory diseases via effects on type I IFNs as shown in Figure 5.

It has been shown previously that mtDNA can induce an inflammatory response via TLR7 or the cGAS-STING pathway.^{85,86} Also, release of mtRNA has been linked to mitochondrial stress and senescence, potentially connected to the disease pathogenesis of primary osteoarthritis.⁸⁷ So far, many different sensors have been shown to recognize mitochondrial nucleic acids in the cytosol leading to ISG induction. Mitochondrial nucleic acids are additionally released into the extracellular space,⁸⁷ that might drive an IFN response in target cells and thereby promote inflammation in the surrounding cells and tissues.⁸⁸

3 | THERAPEUTIC POSSIBILITIES

Might the targeting of metabolic pathways be useful clinically to promote antiviral immunity or limit autoimmunity via modulation of type I IFNs? Statins, which are targeting cholesterol metabolism significantly reduced risk of viral infection, including SARS-CoV-2^{89,90} while data on mortality are unclear.⁹¹ However, studies comparing the efficacy in humans are mostly retrospective, therefore comparing patients already using statins with cohorts without statin treatment.^{89,92-94} So, the effect of statins on an active viral infection are unclear. While murine models showed benefits of inhibiting cholesterol metabolism or supplementation of 25-HC during viral infection,^{21,28,29} the effect in humans still needs to be investigated. Therefore, targeting CH25H, and its product 25-HC, or otherwise reducing cholesterol in cell membranes in humans might provide further drug targets. Targeting prostaglandins or leukotrienes might also prove effective in regulating the production of type I IFNs in viral infection.

DMF has also been shown to inhibit viral replication, as well as suppressing the anti-inflammatory response and could be a

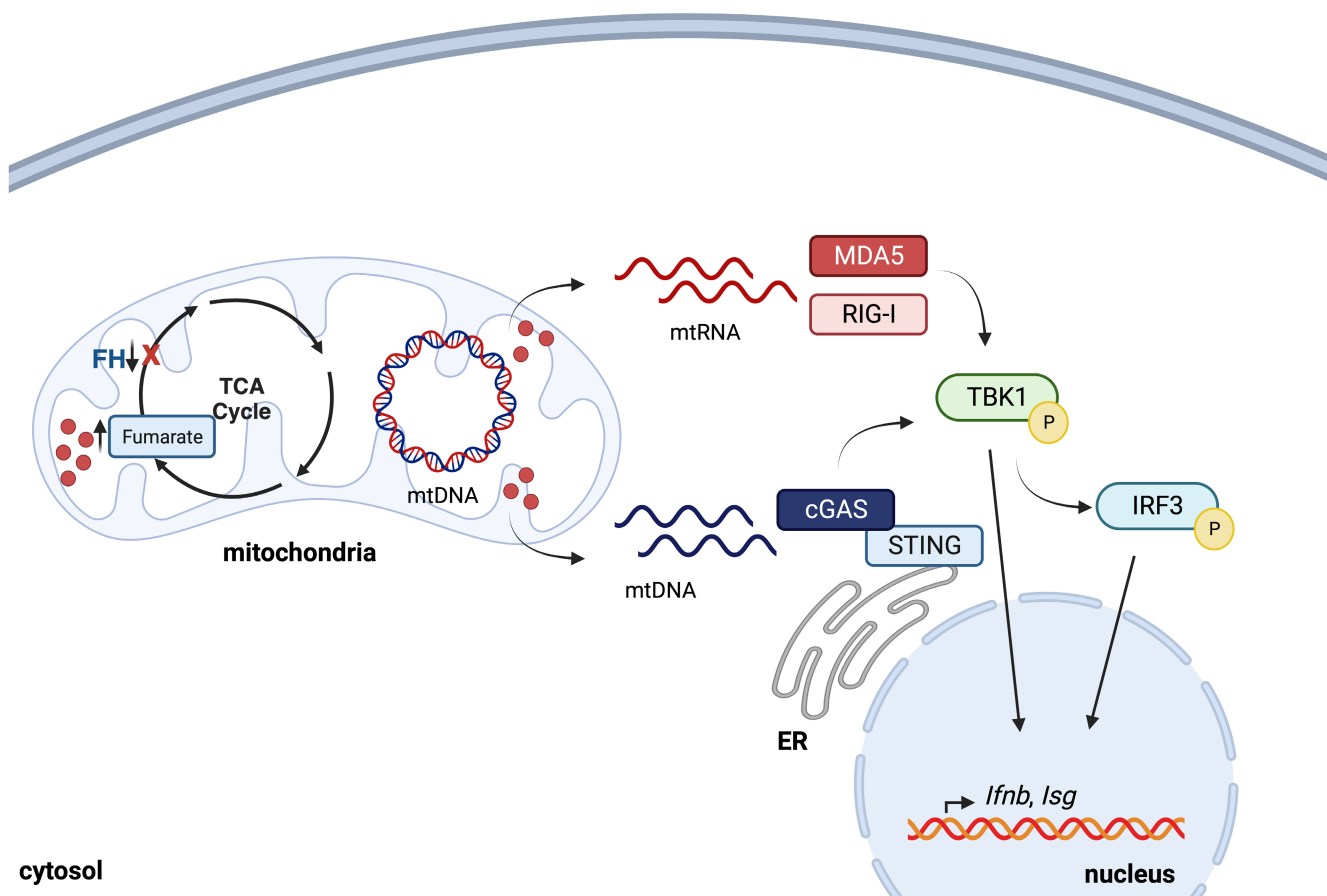


FIGURE 5 Effect of fumarate on IFN response. Inhibition or genetic ablation of fumarate hydratase (FH) leads to accumulation of fumarate, followed by release of mtDNA or mtRNA (depending on the setting and cell type). Those are either recognized by MDA5 and RIG-I or by cGAS-STING and induce TBK1 and IRF3 phosphorylation, as well as expression of type I IFNs and ISGs.

useful adjuvant to antiviral therapies. Itaconate and itaconate-derivatives have been shown to be effective in promoting host defense against bacterial and viral infections (recently reviewed here^{64,65,95}). Among others itaconate reduced viral replication and disease pathology in ZIKV infection and rescued increased viral burden in ACOD1 deficient mice,⁹⁶ and controlled inflammation.⁹⁷ Endogenous itaconate levels could be modulated by specific ACOD1 targeting compounds, or generation of new itaconate derivatives that mimic certain mechanisms of itaconate biology. 4-OI functions as a three in one, an anticoagulant, antiviral, and anti-inflammatory compound. 4-OI blocks IFNs and downstream interferon-mediated coagulopathy. Furthermore, 4-OI can block IAV replication cycle by alkylating chromosomal maintenance 1 protein (CRM1), also known as exportin 1 (XPO1) on Cys-528, thus retaining IAV nucleoprotein in the nucleus which might also apply to other CRM1-dependent viruses.⁹⁸ 4-OI and further derivatives based on it should be investigated further for their therapeutic potential in interferon-related diseases such as coagulopathies and viral infection.

Macrophage fumarate hydratase restrains mtRNA-mediated interferon production. In diseases like multiple sclerosis and SLE, a reduced expression of FH might be linked to disease onset or severity so therefore targeting FH could have therapeutic potential.

4 | CONCLUSION

A complex and dynamic relationship between metabolism and IFNs has therefore recently emerged. Further understanding the metabolic regulation of IFNs by cholesterol, eicosanoids, and TCA cycle-linked metabolites will hopefully deepen our appreciation of host-pathogen interactions and provide therapeutic opportunities for the treatment of diseases where the modulation of IFNs might be beneficial.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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There are no data related to this publication.

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