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Investigating how dengue virus-induced metabolic changes affect the host immune response and how to develop Immunomodulatory strategies

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Abstract

Dengue virus (DENV) infection imposes a significant global health burden, driven by its ability to manipulate host cellular processes to facilitate replication and evade immune defenses. This review explores the complex interplay between DENV, host immunometabolism, and signaling pathways. DENV induces metabolic reprogramming, including glycolytic upregulation, lipid droplet utilization through lipophagy, and alterations in amino acid metabolism, to fulfill its energy and biosynthetic needs. The virus also disrupts mitochondrial dynamics, leading to increased reactive oxygen species (ROS) production, which modulates immune responses but may also contribute to oxidative stress and severe pathology. Concurrently, DENV hijacks host signaling pathways, including PI3K/Akt, NF-κB, and JAK/STAT, to suppress apoptosis, evade type I interferon responses, and drive pro-inflammatory cytokine production. The interplay between these signaling and metabolic pathways highlights a dual role of host processes: enabling viral replication while activating antiviral immune responses. The review also examines potential therapeutic strategies targeting metabolic and signaling pathways to combat DENV infection, including glycolysis inhibitors, lipid metabolism modulators, and host-directed therapies. While significant progress has been made in understanding DENV-induced immunometabolism, further research is needed to elucidate the precise molecular mechanisms and translate these findings into clinical applications. This study underscores the importance of integrating metabolic and signaling insights to identify novel therapeutic targets against DENV and related flaviviruses, addressing the critical need for effective antiviral interventions.

Keywords DENV, Metabolic pathway, Immune response, Viral infection

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Introduction

Immunometabolism is an interdisciplinary field that investigates the interplay between immune system functions and metabolic processes within immune cells [1]. It focuses on how cellular metabolism impacts the development, activation, and response of immune cells during various physiological and pathological states such as infections, cancer, and autoimmune diseases [2]. Immune cells, upon activation, undergo metabolic reprogramming to meet their increased bioenergetic and biosynthetic demands, which is critical for their effector functions [3]. Understanding these metabolic shifts provides insights into immune cell fate decisions and reveals opportunities for therapeutic interventions aimed at modulating immune responses, offering potential solutions for infections, chronic diseases, and cancer [1, 3, 4].

Investigating immunometabolism in the context of viral infections is crucial as viruses often hijack host metabolic pathways to support their replication and survival [5]. Viral infections trigger significant metabolic reprogramming in host cells, which affects the immune system's ability to respond effectively. By studying these metabolic changes, researchers can gain a deeper understanding of how viruses manipulate host metabolism to evade immune detection, which can pave the way for novel therapeutic strategies.

Dengue virus (DENV), a member of the Flaviviridae family, is a mosquito-borne pathogen that causes dengue fever, which is endemic in over 100 countries. It is primarily transmitted by Aedes mosquitoes and presents a significant global health threat, especially in tropical and subtropical regions [6]. DENV infections range from asymptomatic to severe forms such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), which can be life-threatening [7, 8]. With over 390 million cases annually [8], DENV imposes a substantial burden on healthcare systems, especially in Southeast Asia and the Americas [9]. The World Health Organization (WHO) estimates that approximately 3.9 billion people are at risk of dengue infection globally [10] and approximately 500,000 people, mostly children, are hospitalized with severe dengue annually, with a case fatality rate of around 2.5% [10]. Urbanization, climate change, and inadequate vector control measures have contributed to the rising incidence of dengue worldwide [11–14], highlighting the urgent need for effective prevention, management, and control strategies.

DENV alters host cell metabolism to support its replication, impacting immune responses in the process. However, it is important to note that the four DENV serotypes (DENV-1 to DENV-4) and their numerous strains exhibit distinct metabolic profiles, influencing their interactions with the host immune system and replication efficiency. Researchers identified key metabolic nodes and pathways exploited by the virus. Targeting of such metabolic alterations may present therapeutic opportunities by disrupting viral replication and improve clinical outcomes in DENV-infected patients.

In this review, we have comprehensively researched the DENV life cycle and its associated metabolic requirements, focusing on the intricate relationship between viral replication and host metabolic pathways. We explored the immune response to DENV infection and detailed the metabolic reprogramming and immune modulation induced by the virus, emphasizing how these changes facilitate viral persistence and impact host immunity. In addition to outlining these fundamental processes, we discussed the therapeutic implications of targeting DENV-induced metabolic shifts, highlighting potential treatment strategies aimed at modulating immune metabolism to enhance antiviral responses. Finally, we addressed the challenges in developing such therapies and proposed future directions for research in the field of DENV and immunometabolism.

DENV life cycle and metabolic requirements

DENV life cycle includes several stages, each with specific metabolic needs essential for the virus's entry into the host cell, replication, and release.

DENV initiates infection by attaching to specific receptors on the host cell surface, a process mediated by the viral envelope (E) protein, which facilitates viral entry through receptor-mediated endocytosis. Identified receptors involved in DENV entry include heparan sulfate, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), mannose receptor, and the low-density lipoprotein receptor-related protein [15]. Following binding to the receptor, DENV enters the host cell through receptor-mediated endocytosis typically involving clathrin-coated pits, though other endocytic pathways may also be involved. Once inside the cell, the acidic environment of the endosome induces a structural change in the E protein, facilitating fusion between the viral envelope and the endosomal membrane. This fusion releases the viral RNA genome into the cytoplasm, initiating replication [16].

Once the DENV's positive-sense single-stranded RNA (+ssRNA) genome is released into the cytoplasm, it is quickly translated by the host's ribosomes. The viral genome encodes a single polyprotein, which is then cleaved by both host and viral proteases (NS2B-NS3pro) into three structural proteins (C, prM, and E) and seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) [17–19]. The NS proteins, particularly NS3 and NS5, are vital for assembling the replication complex. This complex assembles on the cytoplasmic side of the endoplasmic reticulum (ER) membrane, providing a specialized environment for RNA synthesis. The

replication complex includes viral RNA-dependent RNA polymerase (NS5) and helicase (NS3), along with host factors that aid in the replication [17, 18]. DENV replication involves the synthesis of a negative-sense RNA (-ssRNA) intermediate, which is used as a template for the produce new + ssRNA genomes.

The newly synthesized viral genomes are assembled into immature virions at the ER. This assembly process is crucially dependent on the structural proteins C, prM, and E. The C protein encapsulates the viral RNA to form the nucleocapsid, which then associates with the ER membrane, where the prM and E proteins are located. The prM protein serves as a chaperone, preventing the E protein from premature fusion and ensuring the correct assembly of the virion [20, 21]. Immature virions are transported from the ER through the Golgi apparatus, where they undergo maturation. This process involves the cleavage of prM by the host protease furin, resulting in the formation of mature, infectious virions. The cleavage of prM to M is essential for the virus to acquire its fusogenic properties, which are necessary for infecting new host cells [22]. Mature virions are transported to the cell surface in vesicles and released into the extracellular space through exocytosis. This final step in the viral life cycle requires the host cell's secretory machinery, including components of the cytoskeleton and vesicular trafficking pathways. The release of infectious virions into the bloodstream allows DENV to spread to new target cells and, ultimately, to new hosts via mosquito vectors [23, 24].

Immune response to DENV

The immune response to DENV involves both innate and adaptive components, with each playing a vital role in controlling viral replication and determining disease outcomes. The innate immune response is the body's first defense against DENV infection, featuring key cells like macrophages, dendritic cells (DCs), and natural killer (NK) cells. Macrophages serve as antiviral effectors and antigen-presenting cells (APCs), recognizing DENV through pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs). These receptors trigger antiviral responses by activating signaling pathways that enhance the phagocytosis of viral particles and promote the production of cytokines, including interferons (IFNs), TNF-α, and interleukins [25, 26]. Although macrophages are crucial for virus control, excessive activation can cause systemic inflammation, contributing to severe manifestations like hemorrhagic fever and shock. DCs also play a significant role by bridging innate and adaptive immunity. Upon infection, DCs recognize DENV through PRRs and secrete IFNs and pro-inflammatory cytokines, driving the adaptive immune response by presenting antigens to CD8 + cytotoxic T lymphocytes (CTLs) and CD4 + helper T cells [27, 28]. NK cells, recognizing stress-induced ligands on infected cells, release cytotoxic granules and produce cytokines, such as IFN-γ, which enhance macrophage activity, modulating the immune response to balance viral clearance with immune-mediated damage [29, 30].

Cytokines produced during DENV infection shape the immune response and can influence disease progression. Type I and III IFNs are essential for controlling viral replication by inducing interferon-stimulated genes (ISGs) that inhibit viral replication [31]. However, excessive pro-inflammatory cytokine production, including TNF-α and IL-6, is associated with severe dengue disease, characterized by vascular leakage and shock [32, 33]. Anti-inflammatory cytokines like IL-10 also play a regulatory role in mitigating excessive immune responses, but a dysregulated balance between pro- and anti-inflammatory cytokines can lead to severe immunopathology, such as the "cytokine storm" seen in advanced dengue cases [34, 35].

Specialized B cells produce dengue-specific antibodies, initially Immunoglobulin M (IgM) and later IgG, which neutralize the virus and prevent it from infecting new cells. These antibodies also facilitate the destruction of the virus by marking it for uptake by phagocytes. Meanwhile, T cells play a crucial role; helper T cells (CD4+) release cytokines that enhance the overall immune response, including the activation of B cells and cytotoxic T cells. The cytotoxic T cells (CD8+) identify and destroy infected cells, preventing further viral replication. Memory B and T cells are generated, providing long-term immunity and a quicker response to future infections by the same serotype [36].

However, the immune response to Dengue is complex, and prior infection with one serotype can lead to antibody-dependent enhancement (ADE). In individuals who have been previously infected with one serotype of DENV, non-neutralizing cross-reactive antibodies can bind to a different serotype during a subsequent infection. Instead of neutralizing the virus, these antibodies facilitate viral entry into Fc gamma receptor (FcγR)-bearing cells, such as monocytes and macrophages, via the Fc portion of the antibody [37, 38]. This process leads to increased viral replication and a higher viral load, which is associated with severe disease manifestations like DHF and DSS [39]. ADE not only facilitates viral entry and replication but also induces significant metabolic reprogramming in host cells, including alterations in glucose, lipid, and amino acid metabolism. These changes exacerbate inflammation and contribute to severe disease outcomes. Additionally, the viral infection induces excessive cytokine production, resulting in a hyperinflammatory state known as a cytokine storm,

which contributes to severe tissue damage, vascular permeability, and shock [40–43].

Immunometabolism changes in DENV infection

DENV has also evolved sophisticated mechanisms to hijack host cell metabolic pathways to facilitate its replication and propagation. These changes not only support the metabolic needs of the virus but also modulate immune responses. Known as metabolic reprogramming, this viral manipulation of cellular metabolism is critical for meeting the substantial biosynthetic and energetic demands necessary for viral persistence, immune evasion, and immunopathology [4]. This section provides an in-depth analysis of the pivotal metabolic pathways targeted by DENV, exploring the resulting reprogramming events within infected cells and their connections to immune responses throughout infection.

Glucose metabolism

DENV significantly reprograms host metabolism to meet the energy and biosynthetic demands essential for its replication. However, metabolic reprogramming is not uniform across all DENV serotypes. For instance, DENV-2 has been shown to upregulate glycolysis more strongly than DENV-1, altering glucose metabolism in a serotype-dependent manner [44]. Additionally, distinct DENV strains exhibit differential regulation of glycolytic enzymes and glucose uptake, which may influence viral replication efficiency and immune evasion strategies [45]. One of the most prominent changes occurs in glycolysis, a central metabolic pathway that converts glucose into pyruvate, producing adenosine triphosphate (ATP) and critical intermediates. DENV infection induces a marked upregulation of glycolysis, enhancing glucose uptake and boosting the expression of glycolytic enzymes by inducing the expression of glucose transporter 1 (GLUT1) and hexokinase 2 (HK2) [46, 47], leading to increased lactate production (Fig. 1). This metabolic adaptation, known as the Warburg effect, not only meets the virus's immediate energy requirements but also supports the biosynthesis of viral components like RNA and proteins [48, 49].

The glycolytic shift observed in DENV-infected cells has far-reaching effects on immune cell function. Glycolytic intermediates and enzymes, such as glyceraldehyde-3-phosphate dehydrogenase (GAPDH), play pivotal roles in immune modulation. The direct interaction between the DENV NS1 and the GAPDH, increases its activity [46]. It has been shown that GAPDH can bind to and suppresses translation of several inflammatory mRNAs, including TNFα in resting macrophages. This links the upregulation of glycolysis immediately after infection directly to the inflammatory response characteristic of the innate immune cells [50]. This metabolic reprogramming extends to immune cells such as macrophages and DCs, where glycolysis supports the production of reactive oxygen species (ROS) and cytokines essential for the antiviral response [4]. However, unchecked glycolysis and excessive cytokine production can exacerbate inflammation, contributing to the pathogenesis of severe dengue.

DENV further exploits the host's metabolic machinery by activating the phosphoinositide 3 kinase (PI3K)/Akt/ mammalian (or mechanistic) target of rapamycin (mTOR) pathway, a crucial signaling network that enhances glycolytic flux and promotes cell survival during infection by blocking the caspase-dependent apoptotic cell death at the early stage of virus infection [51, 52]. DENV hijacks the PI3K/Akt/mTOR pathway to skew immune responses, impairing antiviral defenses and enhancing viral survival. This manipulation extends to immune modulation via Akt-mediated phosphorylation of FOXO transcription factors. Normally residing in the nucleus, FOXO proteins activate genes involved in cell cycle arrest, apoptosis, and DNA repair. Phosphorylation by Akt excludes FOXO proteins from the nucleus, preventing them from initiating antiviral gene expression. Additionally, DENV can induce the ubiquitination and proteasomal degradation of FOXO proteins, further diminishing their activity. By downregulating FOXO activity, DENV effectively dampens the host's immune defenses, creating an environment conducive to viral persistence and spread [53–55]. Beyond these effects, the PI3K/Akt/mTOR pathway intersects with other signaling networks, such as GSK-3β and NF-κB, which are critical for regulating pro-inflammatory cytokine production. Interaction of GSK-3β with the PI3K/Akt pathway influences viral replication and apoptosis, enhancing viral release from infected cells. This pathway also modulates microRNA biogenesis, potentially suppressing DENV infection through mechanisms involving miR-34 family members, which impact type I IFN signaling. GSK-3β is known to modulate the NF-κB signaling pathway, influencing nitric oxide (NO) production and apoptosis when triggered by anti-NS1 antibodies. DENV-2 inhibits GSK-3 activity via Akt activation to promote immune evasion via MHC class-I chain A and B and IL-12 production in dendritic cells [56].

The NF-κB pathway plays a crucial role in both metabolic reprogramming and immune responses during DENV infection. As a key mediator of immune and inflammatory responses, this pathway connects cellular metabolic processes with immune function. One of the key metabolic changes driven by NF-κB activation is the shift towards glycolysis [57]. Activated by viral components like NS1 protein and viral RNA through PRRs such as TLRs and RLRs, the NF-κB pathway drives the transcription of genes encoding pro-inflammatory cytokines, chemokines, and adhesion molecules. The upregulation of glycolytic enzymes and enhancement of glycolysis by

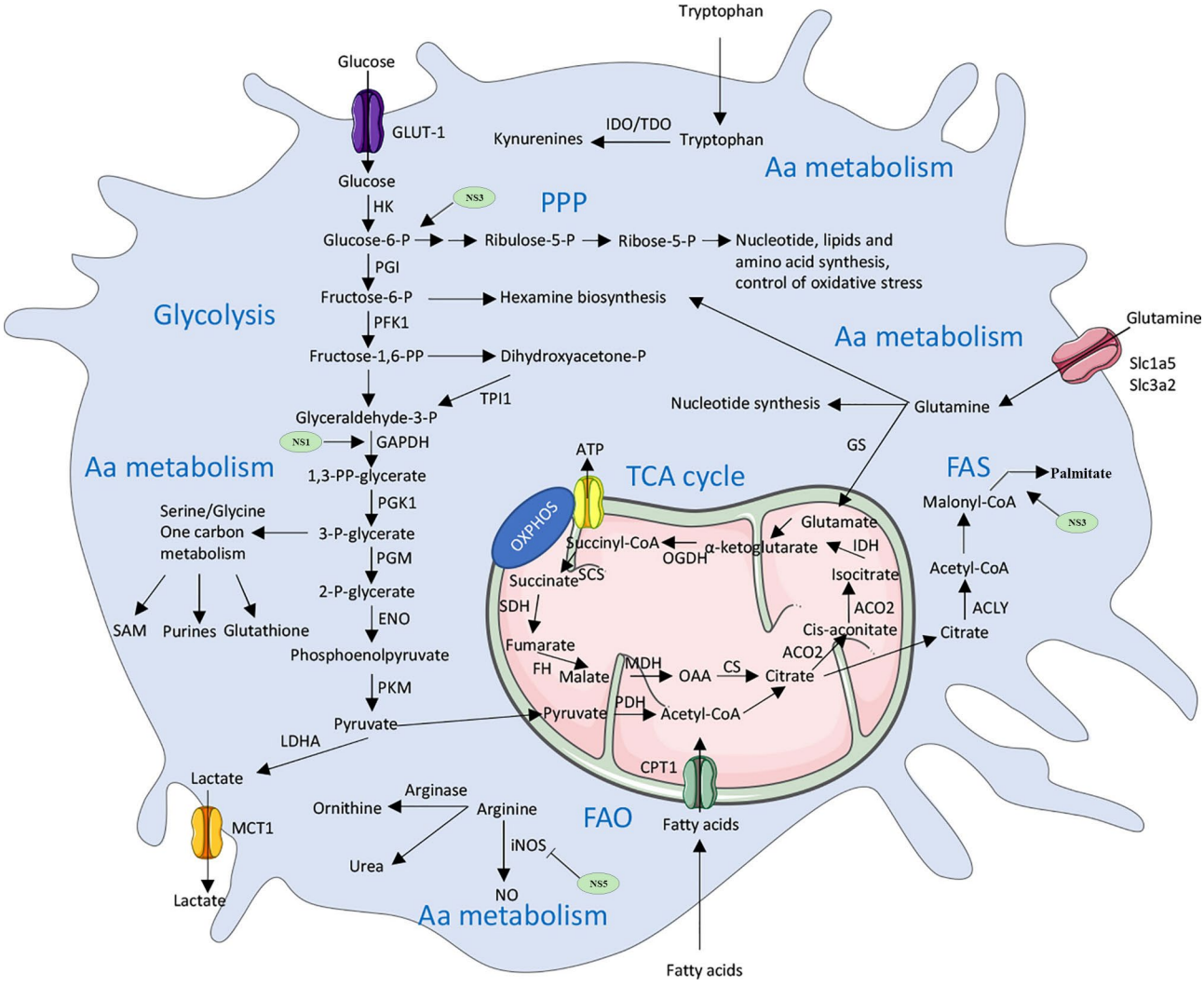

Fig. 1 The summary of the main metabolism pathways in DENV infected cells. glycolysis, TCA (Tricarboxylic acid) cycle, PPP (Pentose phosphate pathway), FAS (Fatty acid synthesis) and FAO (Fatty acid oxidation) and amino acid (Aa) metabolism. ACLY: ATP citrate lyase; ACO2: Aconitase 2; ATP: Adenosine triphosphate; CPT1: Carnitine palmitoyltransferase 1; CS: Citrate synthase; ENO: Enolase; FH: Fumarase; GAPDH: Glyceraldehyde 3-phosphate dehydrogenase; GLUT1: Glucose transporter 1; HK: Hexokinase; GS: Glutamine synthetase; IDH: Isocitrate dehydrogenase; IDO: Indoleamine 2,3-dioxygenase; LDHA: Lactate dehydrogenase; MCT1: Monocarboxylate transporter 1; MDH: Malate dehydrogenase; NO: Nitric oxide; iNOS: inducible NO synthase; OAA: Oxaloacetate; OGDH: α-ketoglutarate dehydrogenase; OXPHOS: Oxidative phosphorylation; P: Phosphate; PDH: Pyruvate dehydrogenase; PFK1: Phosphofructokinase 1; PGK1: Phosphoglycerate kinase 1; PGI: Phosphoglucoisomerase; PGM: Phosphoglycerate mutase; PKM: Pyruvate kinase muscle isotype; PP: bisphosphate; SAM: S-Adenosyl methionine; SCS: Succinyl coenzyme A synthetase; SDH: Succinate dehydrogenase; SLC: Solute carrier; TDO: Tryptophan 2,3-dioxygenase; TPI1: Triosephosphate isomerase 1. Reprinted with permission from ref [47]

NF-κB ensures a continuous supply of ATP and metabolic intermediates, which are vital for both viral replication and immune function [57, 58]. However, excessive NF-κB activation can lead to an overproduction of cytokines like TNF-α, IL-6, and IL-1β, contributing to immunopathology and tissue damage observed in severe dengue cases [59].

In parallel, the activity of NF-κB upon viral infection and inducing the production of type I IFNs can activate the JAK/STAT pathway (JAK1) and tyrosine kinase 2 (TYK2) and further transcription factor STAT1 and STAT2 activation, leading to the expression of ISGs (Fig. 2), enhancing inflammatory response and limiting viral replication [60–64]. However, DENV has evolved mechanisms to interfere with this pathway, notably through its NS5 protein, which degrades STAT2, impairing the activation of ISGs and weakening the host's antiviral defenses (Fig. 2). This suppression of IFN signaling allows DENV to replicate more efficiently [61, 65]. This relationship exemplifies the complex regulatory mechanisms that maintain immune balance. This complex interaction between the JAK/STAT and NF-κB pathways [66] underlines the intricate immune evasion strategies employed by DENV to maintain a balance between

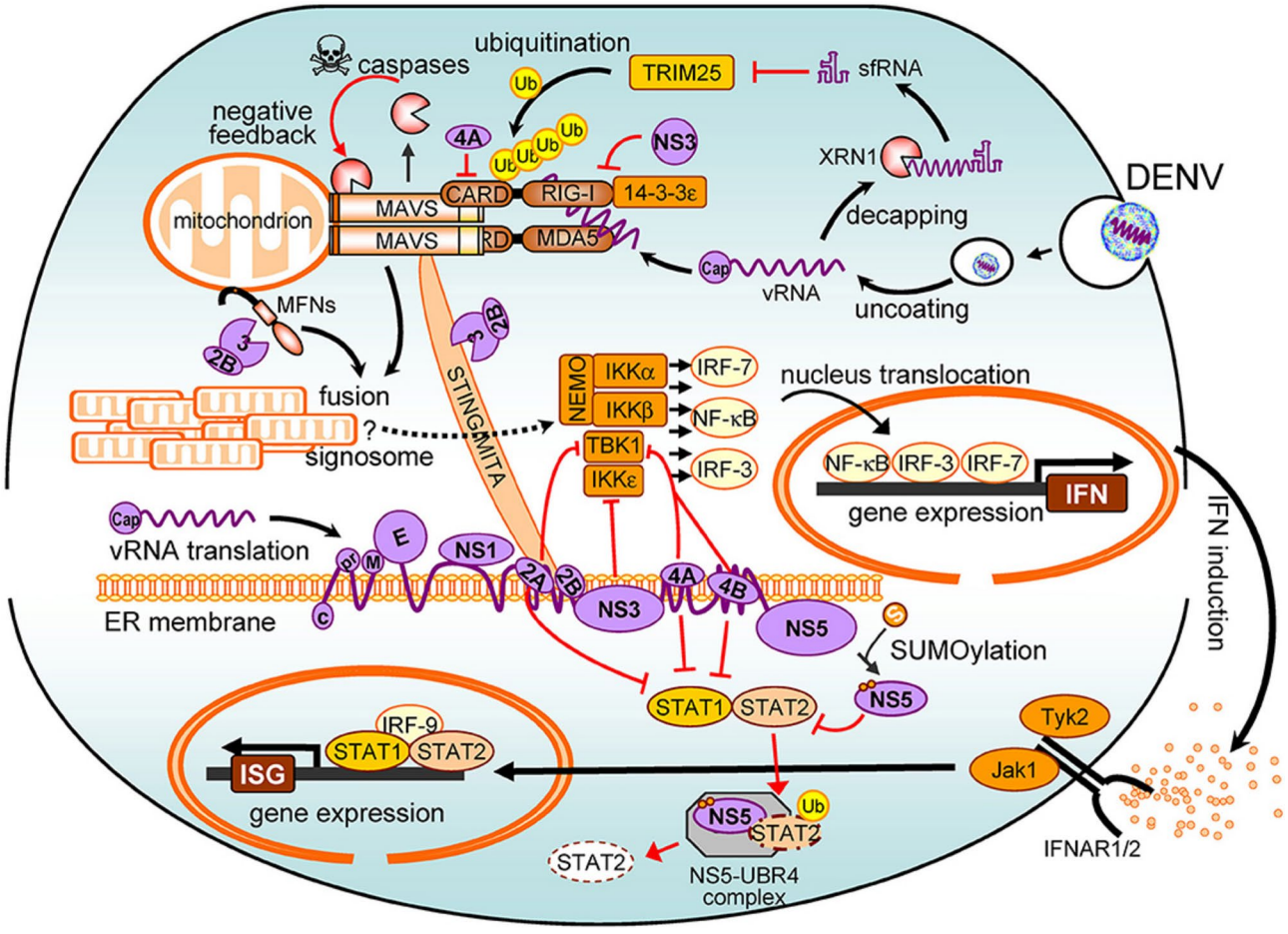

Fig. 2 Mechanisms of immune evasion in DENV-infected cells. vRNA, viral RNA; RIG-I, retinoic acid-inducible gene I; MDA5, melanoma differentiation-associated protein 5; CARD, caspase activation and recruitment domain; Ub, ubiquitin; MAVS, mitochondrial antiviral signaling protein; sfRNA, subgenomic flavivirus RNA; TRIM25, tripartite motif protein 25; MFN, mitofusin; STING, stimulator of interferon genes; MITA, mediator of IRF3 activation; NF-κB, nuclear factor kappa B; NEMO, NF-κB essential modulator; TBK1, TANK binding kinase-1; IKKα/β/ε, IκB kinase alpha/beta/epsilon; IRF, interferon regulatory factor; IFN, interferon; IFNAR, IFN-α/β receptor; STAT, signal transducer and activator of transcription; ISG, IFN-stimulated gene; Jak1, Janus kinase 1; Tyk2, tyrosine kinase 2; UBR4, ubiquitin protein ligase E3 component n-recognin 4; XRN1, 5′-3′ exoribonuclease 1. Reprinted with permission from ref [62]

effective viral replication and avoidance of host immune clearance [26, 28, 67]. Additionally, DENV manipulates upstream cytokine signaling to inhibit JAK activation, further dampening the immune response and contributing to viral persistence (Fig. 2). DENV's manipulation of the JAK/STAT pathway extends to its control over cytokine production, a hallmark of Dengue pathogenesis [42, 43].

Moreover, several studies have demonstrated that while glucose is essential for DENV replication, the virus actively enhances glycolytic activity to meet its biosynthetic demands. DENV promotes glycolysis while simultaneously redirecting glucose-derived intermediates into the pentose phosphate pathway (PPP), ensuring a steady supply of nucleotides and NADPH for viral replication (Fig. 1). This metabolic adaptation maintains ATP production through glycolysis while supporting biosynthetic pathways critical for viral genome synthesis and immune evasion [48, 68]. This metabolic shift helps the virus to efficiently replicate and assemble new virions within the host cell. Studies have shown that DENV interacts with GAPDH, a key enzyme in glycolysis, leading to its reduced activity. For example, 48 h after infection, DENV's NS3 interacts with GAPDH, potentially redirecting glucose towards the PPP [68, 69]. This interaction diverts glucose metabolism towards the PPP, supporting viral replication. The PPP is another metabolic process hijacked by DENV to meet its biosynthetic needs. Enhanced glycolytic flux, driven by DENV, diverts intermediates like glucose-6-phosphate and fructose-6-phosphate into the PPP, providing NADPH and ribose-5-phosphate. NADPH is crucial for maintaining redox balance and supporting anabolic reactions, while ribose-5-phosphate is essential for nucleotide biosynthesis, which is critical for viral RNA replication (Fig. 1). By upregulating the PPP, DENV ensures a steady supply

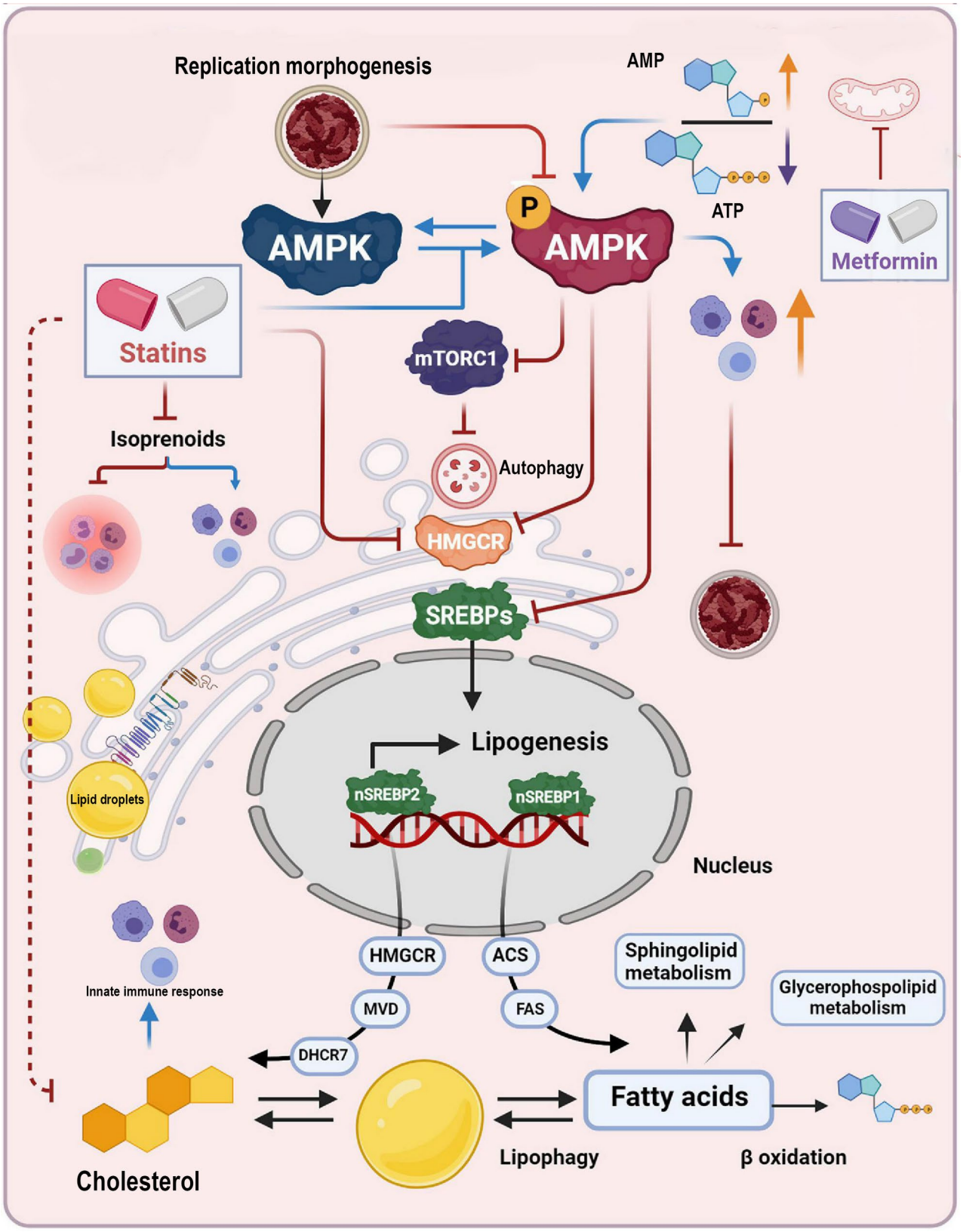

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Fig. 3 DENV-induced AMPK inactivation enhances HMGCR activity by activating SREBPs, leading to increased cholesterol accumulation in the ER. In contrast, transient AMPK activation coupled with mTORC1 inhibition is crucial for DENV-induced lipophagy, facilitating lipid droplet depletion and autophagy to support viral replication. Statins inhibit HMGCR, disrupting cholesterol biosynthesis and DENV replication while enhancing the innate immune response by suppressing isoprenoid synthesis. Similarly, metformin activates AMPK, reducing cholesterol and fatty acid synthesis via direct enzyme inactivation and SREBP regulation, while also inducing IFN-mediated responses to strengthen antiviral immunity. AMPK: AMP-Activated Protein Kinase; HMCGR: 3-Hydroxy-3-Methylglutaryl-CoA Reductase; mTORC1: Mechanistic Target of Rapamycin Complex 1; SREBP: Sterol Regulatory Element-Binding Protein; ACS: Acyl-CoA Synthetase; FAS: Fatty Acid Synthase; MVD: Mevalonate Diphosphate Decarboxylase; DHCR7: 7-Dehydrocholesterol Reductase. Reprinted with modifications by permission from ref [99]

of the resources required for genome replication and protein synthesis, while also generating antioxidants to counteract the oxidative stress induced by viral replication [70]. Oxidative stress triggers the activation of various signaling molecules in DENV infection, including interferon regulatory factors 3 (IRF-3) and 7 (IRF-7), STAT-1, and NF-κB, which are involved in antiviral defense mechanisms. Studies have shown that a reduction in ROS levels, caused by inhibiting the NADPH-oxidase (NOX) complex, impairs innate immune responses, thereby facilitating DENV replication [71, 72].

Lipid immunometabolism

DENV heavily modulates lipid metabolism in host cells as a strategy to facilitate viral replication and evade the host immune system. However, lipid metabolism alterations have been shown to differ among DENV serotypes and strains. For example, DENV-2 infection leads to a more pronounced increase in lipid droplet biogenesis compared to DENV-3, suggesting serotype-specific strategies for lipid exploitation. Similarly, DENV-1 and DENV-4 exhibit differences in cholesterol metabolism regulation, affecting viral replication efficiency and immune responses [73]. Recent findings highlight how viral-induced metabolic alterations impact immune regulation, particularly through lipid metabolism and autophagy. The interplay between these pathways provides a survival advantage to DENV by enabling immune evasion and sustaining viral replication [73]. This modulation of lipid metabolism involves the reorganization of fatty acid synthesis, lipid droplets (LDs), and cholesterol metabolism, all of which contribute to immune evasion.

Fatty acid synthesis is primarily driven by the fatty acid synthase enzyme (FASN), which catalyzes the reaction starting from acetyl CoA and malonyl CoA (Fig. 1) [74]. The product, palmitate, can be elongated into long-chain fatty acids for membrane production or stored in LDs as triacylglycerols or esterified cholesterol [75, 76]. In the context of DENV infection, the virus exploits host lipid metabolism by recruiting FASN to viral replication complexes through interactions mediated by Rab18 and DENV's NS3 protein [75]. This recruitment enhances fatty acid biosynthesis. Inhibiting FASN has been shown to reduce DENV replication in both human and mosquito cells, demonstrating its crucial role in the viral life cycle. Research has also shown that the increases in the number and size of LDs after DENV infection, provide a platform for viral assembly and genome encapsidation. DENV infection promotes the interaction of viral proteins with LD-associated proteins, such as perilipin 3 (PLIN3), which facilitates viral encapsidation. The capsid protein of DENV binds to PLIN3 at the surface of LDs, helping to assemble viral particles. The accumulation of the viral capsid on LDs not only aids in viral production but also shields the virus from immune detection, as the viral proteins are hidden from cytosolic immune sensors that would typically recognize and degrade viral components [77].

Mitochondria, lipophagy, and lipid metabolism in DENV infection

Mitochondria are central hubs of metabolic reprogramming during DENV infection, providing the ATP and biosynthetic precursors necessary for viral replication. However, DENV significantly disrupts mitochondrial dynamics and bioenergetics, leading to mitochondrial fragmentation and dysfunction. This process is associated with increased reactive oxygen species (ROS) production, which plays a dual role in infection. While ROS modulate immune responses and activate signaling pathways, including type I IFN production, excessive ROS levels cause oxidative stress, damaging cellular components and contributing to the severe pathology observed in dengue [78–80]. Additionally, mitochondrial ROS activate key immune pathways, such as NF-κB and the NLRP3 inflammasome, driving pro-inflammatory cytokine production and immune cell activation [81, 82]. Mitochondrial fission and fusion dynamics, which are regulated by proteins such as Drp1 and Mfn2, are significantly altered during DENV infection. This impairment affects mitochondrial ATP production and intermediate generation, both of which are essential for immune cell activation and antiviral responses [83, 84]. Importantly, mitochondria and lipid metabolism are intricately connected, and DENV exploits this link to ensure an adequate supply of energy and membrane components for viral replication.

Lipophagy, a specialized form of autophagy that degrades LDs, plays a crucial role in fueling DENV replication. During infection, DENV triggers lipophagy, releasing fatty acids that undergo β-oxidation in mitochondria, providing energy for viral proliferation. The

autophagy-dependent degradation of LDs supplies lipids that are essential for progeny virion formation (Fig. 3) [85, 86]. Studies have demonstrated that DENV infection depletes LDs in hepatocytes and kidney fibroblast cells, suggesting that while LDs initially accumulate as part of the host's antiviral response, DENV later exploits them to meet its metabolic needs [85, 87]. Interestingly, LD accumulation is modulated by immune signaling pathways, including TLRs and immune deficiency pathways. DENV infection activates these pathways, inducing LD formation, yet inhibition of these pathways reduces LD accumulation [88, 89]. This indicates that DENV regulates LD dynamics not only for lipid supply but also to manipulate host immune defenses.

DENV exploits host lipid metabolism through key signaling pathways, including the Akt/mTOR axis and PTEN, which coordinate lipid homeostasis and immune responses during infection. PTEN, a lipid phosphatase, is hijacked by DENV to enhance autophagy and lipophagy, ensuring a continuous supply of fatty acids for β-oxidation in mitochondria. By acting as a negative regulator of the PI3K/Akt pathway, PTEN suppresses Akt activation, thereby enhancing the transcriptional activity of FoxO1 and Maf1, both of which regulate lipid biosynthesis and metabolic adaptation [90]. Additionally, DENV modulates the Akt/AMPK/mTOR signaling pathway to promote lipophagy and delay autophagosome-lysosome fusion, which helps the virus evade immune degradation while securing metabolic substrates for replication [91, 92]. AMPK activation and mTOR inhibition are crucial for this process, emphasizing the virus's ability to rewire host metabolism for its survival (Fig. 3) [49, 93].

DENV infection also significantly alters mitochondrial lipid composition, particularly cholesterol homeostasis, to facilitate viral replication. Sterol regulatory element-binding proteins (SREBPs), which regulate lipid biosynthesis, are activated during infection to increase the production of cholesterol and fatty acids needed for viral replication complexes (Fig. 3) [86, 94, 95]. Cholesterol, synthesized in the ER and trafficked to mitochondria, is essential for maintaining mitochondrial membrane integrity and function. The SREBP-SCAP complex plays a key role in this process by activating genes involved in cholesterol biosynthesis, such as HMGCR and FASN, thereby creating a lipid-rich environment that benefits DENV replication [96, 97]. Furthermore, DENV modulates cholesterol metabolism by inactivating AMPK and upregulating HMGCR activity, leading to cholesterol accumulation in both the ER and mitochondria. This alteration enhances viral replication by optimizing membrane structures for viral assembly and immune evasion [91, 97–99].

Alterations in lipid metabolism during DENV infection impact immune signaling and inflammatory responses. A recent clinical and in vitro study found that LD accumulation in leukocytes and macrophages is linked to severe dengue cases (DHF). Moreover, migration inhibitory factor (MIF), a key inflammatory mediator, colocalizes with LDs in DENV-infected cells, suggesting a role in driving excessive inflammation [100, 101]. Similarly, sphingosine-1-phosphate (S1P) signaling is implicated in disease progression. Patients with severe dengue exhibit lower S1P levels, which correlate with increased vascular leakage, pleural effusions, and multi-organ failure [100, 101]. Interestingly, sphingosine kinase 1 (SK1), which converts sphingosine to S1P, is essential for type I IFN responses. Inhibiting SK1 alters IFNAR1 and IRF1 expression, potentially compromising antiviral immunity [87, 102]. Additionally, DENV-infected platelets aggregate with monocytes, triggering LD biogenesis and secretion of inflammatory mediators such as CXCL8/IL-8, IL-10, CCL2, and PGE2. This platelet-monocyte interaction plays a crucial role in reprogramming lipid metabolism in monocytes, contributing to pro-inflammatory responses and immune modulation [103]. DENV strategically manipulates the RIG-I/MDA5 pathway to evade immune detection. The viral NS2B3 protease cleaves key components of the RIG-I/MAVS pathway, suppressing IRF3 and NF-κB activation, thereby reducing type I IFN production [104–106]. Additionally, NS4B disrupts TBK1 signaling, further weakening the host's antiviral defenses [107–109]. Interestingly, DENV also exploits autophagy to degrade immune signaling proteins, such as STING, thereby dampening IFN responses and enhancing viral persistence [110]. Autophagy further modulates cytokine production, allowing DENV to fine-tune inflammatory responses for its benefit [111, 112]. Moreover, a DENV-encoded long non-coding RNA (sfRNA) inhibits RIG-I and TRIM25, preventing IFN-β transcription and weakening antiviral defenses [113]. Notably, serotype-specific differences in autophagy modulation exist—DENV-2 induces autophagic flux more strongly than DENV-4, affecting immune evasion strategies and disease severity [49].

Through a coordinated strategy involving mitochondrial reprogramming, lipid metabolism modulation, and autophagy regulation, DENV creates a metabolic environment conducive to viral replication while evading immune responses. The interplay between mitochondrial dynamics, lipid metabolism, and immune modulation underscores mitochondria as key targets for antiviral strategies. Targeting mitochondrial metabolism and lipid pathways could provide novel therapeutic interventions, offering potential strategies to counteract DENV replication and severe disease outcomes.

Amino acid and protein metabolism

The interplay between amino acid metabolism and immune modulation in DENV-infected cells is a crucial aspect of viral pathogenesis. In a recent study, the metabolomic profile of THP-1-derived macrophages revealed significant metabolic alterations. DENV infection caused changes in 23.7% of amino acids, being the most affected. The infection led to global amino acid depletion, particularly affecting essential amino acids. A total of 48 amino acids and their derivatives showed altered levels, with 20 of them exhibiting significant changes. Notably, DENV infection alone and ADE both reduced the levels of most amino acids, although some, like 4-hydroxyproline, lysine, and methylcysteine, were elevated in ADE infection [114].

Glutamine, for example, is crucial for the synthesis of nucleotides and the production of other amino acids through the glutaminolysis pathway. DENV infection increases the uptake and metabolism of glutamine, which is converted to glutamate and subsequently enters the tricarboxylic acid (TCA) cycle to produce ATP and biosynthetic precursors [48]. Glutamine-derived α-ketoglutarate is an essential intermediate in the TCA cycle, linking amino acid metabolism to energy production and redox balance [115, 116]. This metabolic pathway not only supports the synthesis of viral proteins and nucleic acids but also impacts immune cell function (Fig. 1). Glutamine is essential for the activation and proliferation of immune cells, including T lymphocytes and macrophages, which are pivotal in mounting an effective immune response against DENV [48, 117].

The role of arginine metabolism in DENV infection is particularly intriguing. Arginine is metabolized by nitric oxide synthase (NOS) to produce nitric oxide (NO), a molecule with antiviral properties. However, DENV can modulate this pathway to favor viral survival. The virus can induce the expression of arginase, an enzyme that competes with NOS for arginine, leading to the production of ornithine and urea instead of NO (Fig. 1). This shift reduces the availability of NO, thereby dampening its antiviral effects and contributing to immune evasion. Furthermore, the reduction in NO production can impair the function of macrophages and other immune cells, weakening the host's ability to control the infection [118].

Another critical aspect is the role of tryptophan and its metabolites. Tryptophan is metabolized through the kynurenine pathway, which produces several immunomodulatory metabolites. DENV infection can upregulate the expression of indoleamine 2,3-dioxygenase (IDO), an enzyme that catalyzes the first step in the kynurenine pathway. The increased activity of IDO leads to a depletion of tryptophan and an accumulation of kynurenine and other metabolites (Fig. 1), which can suppress T cell proliferation and induce Treg responses. This immunosuppressive environment helps the virus evade the immune system and persist in the host [114, 119].

Metabolic consequences of ADE

A major risk factor for severe dengue is secondary infection with a heterologous DENV serotype, where pre-existing antibodies enhance viral infection through ADE. This mechanism increases viral loads and exacerbates metabolic reprogramming, shifting host cell metabolism in ways that favor viral replication while exacerbating immune dysfunction.

It has shown that ADE significantly affects host metabolism by impeding the downregulation of ribosomal genes typically observed in canonical receptor-mediated Dengue DENV entry. This lack of ribosomal gene downregulation under ADE conditions enhances viral protein translation, as DENV relies on host ribosomes located in the ER for RNA translation. Furthermore, ADE upregulates DENV host dependency factors, including genes related to mRNA processing (HNRNPU, SNRPF, SF3B1, SUPT6H) and vesicle-mediated transport (SCFD1, PREB), creating an intracellular environment favorable for viral replication and trafficking. By maintaining ribosomal protein expression and elevating host dependency factors, ADE-mediated entry facilitates increased viral RNA synthesis, protein production, and immune evasion compared to canonical DENV infection pathways [120].

Another study showed that DENV-ADE alters host metabolism by suppressing the expression and activity of inducible NOS2, an important effector of the innate immune system. NOS2-derived NO plays a pivotal role in antiviral defense, as it can inhibit DENV RNA synthesis by targeting the RNA-dependent RNA polymerase (RdRp) activity of the DENV NS5 protein. However, in DENV-ADE, NOS2 transcription is persistently reduced, and early suppression of NOS2 translation (within 4–8 h post-infection) appears to help the virus evade detection by the innate immune system. The decreased NO levels, observed in vitro and correlated with severe dengue symptoms, weaken the host's antiviral defenses, enabling enhanced viral replication. This suppression of NOS2 may result from the inhibition of RIG-I/MDA5-mediated signaling pathways, which normally activate NF-κB and promote NOS2 expression. Consequently, DENV-ADE drives metabolic conditions favorable for viral persistence while impairing innate immune responses critical for controlling infection [121].

Their results also showed that in DENV-ADE infection, key autophagy-related proteins, such as ATG5 and ATG12, are upregulated at both transcriptional and protein levels during early infection (within 0.5-to-1-hour post-infection). This upregulation supports the formation of autophagosomes. Experimental treatments with autophagy modulators—rapamycin (an

autophagy accelerator) and 3-MA (an autophagy inhibitor)—revealed that rapamycin increased intracellular viral RNA synthesis in a dose-dependent manner, while 3-MA decreased viral RNA levels, further implicating autophagy in viral replication. Additionally, ATG5 knockout in infected cells significantly reduced intracellular viral RNA synthesis during both DENV and DENV-ADE infections. Interestingly, overexpression of ATG5 was found to impair NF-κB activation and NOS2 expression, potentially aiding viral replication by weakening innate immune defenses. Moreover, elevated ATG5 and ATG12 expression during DENV-ADE infection may antagonize RLR signaling through MAVS interaction, thereby suppressing antiviral signaling pathways [121].

Host metabolic factors influencing DENV infection outcomes

Baseline metabolic factors, including gender, nutrition, age, and pre-existing immunity, play critical roles in determining the outcomes of DENV infections. Gender differences are evident, with males often experiencing more severe symptoms, such as dengue hemorrhagic fever and shock syndrome, compared to females. This disparity may be attributed to hormonal influences and variations in immune responses and metabolic activity. Nutrition also significantly impacts DENV outcomes; malnutrition weakens immune defenses, increasing susceptibility to severe disease, while balanced nutrition supports better recovery. However, both undernutrition and obesity have been linked to worsened disease severity, emphasizing the importance of maintaining optimal metabolic health (Ng et al., 2016). Age is another critical factor, as younger individuals, particularly children, often experience severe manifestations due to immature immune systems and metabolic limitations, while older adults may face complications related to slower metabolism and comorbidities (Lima et al., 2022). Pre-existing immunity from prior DENV infections can either protect against or exacerbate disease severity. Cross-reactive antibodies may provide temporary protection but can also lead to ADE, increasing risks during secondary infections. The interplay between immune metabolism, viral serotypes, and metabolic status further complicates disease outcome. These factors collectively highlight the complex interactions between host metabolic characteristics and DENV pathogenesis, underscoring the importance of considering metabolic variability when developing host-targeted therapeutic interventions.

Therapeutic implications

Despite numerous therapeutic strategies aimed at combating DENV infection—including targeting metabolic pathways, enhancing immune responses, host-directed therapies, and vaccine and immune priming—no vaccines or antiviral drugs have been officially approved for the prevention or treatment of dengue. Numerous studies have explored key immunometabolic pathways and their molecular components, identifying potential targets for novel treatments or repurposing existing drugs with anti-DENV effects [18, 122–126]. Here, we review the most important and recent investigations that highlight the potential for metabolic interventions to disrupt viral replication and improve host immune responses against DENV infection.

Repurposing of currently available drugs

As DENV infection induces significant metabolic changes in host cells, inhibiting metabolic pathways presents a promising therapeutic approach. Glycolysis inhibitors, such as 2-deoxy-D-glucose (2-DG), have shown efficacy in reducing viral replication by limiting the energy supply required for viral processes [48]. Many studies on the effectiveness of metformin, a known inhibitor of hepatic gluconeogenesis, yielded discordant and confusing results. Recent research suggests that metformin has shown promise in reducing cellular DENV infection and viral production by decreasing glycolysis in liver cells and diverting glucose toward nucleoside production [68]. Other studies have shown that metformin can enhance mitochondrial respiration or stabilize mitochondrial membranes to maintain cellular energy levels and support the antiviral state [127]. Furthermore, DENV's NS3 interacts with glucokinase regulator protein (GCKR) in the liver, enhancing glycolysis and viral replication. Inhibition of glycolysis through NAD(H) biosynthesis reduction using antimetabolite 6-Amino-Nicotinamide (6-AN) successfully decreased DENV replication in both in vitro and primary organotypic liver cultures [128]. Moreover, celgosivir is an α-glucosidase inhibitor that targets host glycoprotein processing pathways, which are essential for viral replication. By inhibiting α-glucosidase, Celgosivir disrupts the proper folding and maturation of viral glycoproteins, thereby reducing the production of infectious virions. Despite its promising mechanism, clinical trials like the CELADEN trial showed that while Celgosivir was safe and well-tolerated, it did not significantly reduce viral load or fever burden in dengue patients [129, 130]. This suggests that while Celgosivir has potential, it may need optimization or combination with other therapies to enhance its efficacy.

Similarly, inhibitors of lipid synthesis, such as FAS inhibitors, can disrupt the formation of viral replication complexes that rely on lipid droplets [75, 85]. Recently, in silico-driven drug repurposing has also identified compounds that modulate immune-metabolic pathways in DENV infection. Drugs such as oxprenolol, digoxin, auranofin, and statins like atorvastatin have shown potential by inhibiting the NF-κB pathway, ATPase activity, and

cholesterol metabolism, which are key in DENV pathogenesis [131]. Natural compounds like cordycepin also have demonstrated both antiviral and anti-inflammatory effects in DENV-infected cells by targeting the viral NS5 protein, inhibiting replication and NF-κB signaling, and reducing cytokine production, presenting a dual-action strategy for dengue treatment [132]. Compounds such as zileuton, trimethadione, and linalool, along with their proposed combinations, showed moderate inhibition of DENV NS3 protease activity, offering new leads for drug development through molecular docking and in vitro testing [133]. Other promising candidates include sofosbuvir, traditionally used against HCV, which showed suppression of DENV1 replication in human hepatic cells, making it a potential anti-DENV therapeutic [134].

Anti-viral and new experimental approaches

Host-directed therapies aim to enhance the host's intrinsic defenses against viral infection. By targeting host factors essential for viral replication, these therapies can reduce viral load and improve clinical outcomes. For instance, modulating the activity of host proteins involved in viral entry, replication, or assembly can provide therapeutic benefits. Small molecules that inhibit host factors, such as kinase inhibitors, are being investigated for their antiviral potential [135]. Enhancing host metabolic resilience involves bolstering the host's metabolic capacity to withstand the stress of viral infection. This can include the use of metabolic modulators that improve cellular energy production, such as antioxidants or compounds that enhance mitochondrial function. Such strategies can help maintain cellular homeostasis and support effective immune responses during infection [136].

Immunemodulatory agents

Furthermore, a balanced immune response is essential for effectively managing DENV infection and reducing disease severity. Therapeutic strategies that modulate immune responses are vital to preventing excessive inflammation while preserving antiviral activity are essential. These strategies involve the use of immunomodulatory agents that regulate cytokine production, boost the activity of regulatory T cells (Tregs), or inhibit pro-inflammatory pathways. By fine-tuning the immune response, these approaches aim to reduce the risk of severe outcomes and improve patient recovery [137, 138]. The manipulation of immune checkpoints offers an avenue for therapeutic intervention. Immune checkpoint inhibitors, such as those targeting PD-1 or CTLA-4, can enhance T-cell responses against viral infections. By blocking these inhibitory pathways, the immune system's ability to target and eliminate infected cells can be restored, potentially reducing viral load and improving outcomes [139]. Moreover, enhancing antiviral T-cell responses is critical in controlling DENV infection. Strategies that promote T-cell activation and proliferation can improve the host's ability to combat the virus. For instance, cytokines such as IL-2 and IL-7 can be used to boost T-cell responses, while therapeutic vaccines designed to elicit strong T-cell immunity are also being explored [140]. However, DENV infection can lead to severe immunopathology, including cytokine storm and vascular leakage. Therapeutic approaches aimed at reducing immunopathology focus on dampening excessive inflammatory responses while preserving antiviral immunity. Anti-inflammatory drugs, such as corticosteroids, and cytokine inhibitors, such as IL-6 or TNF-α blockers, can help manage severe inflammatory responses [141, 142].

A recent study investigated the multifaceted role of antibodies in DENV immunity and pathogenesis, focusing on targeting infected cells for immunologic clearance without triggering ADE. The results revealed that DENV structural proteins, including the E protein, are expressed on the surface of infected cells and can be opsonized by immune sera and monoclonal antibodies. Importantly, DENV E-specific antibodies facilitate the phagocytic uptake of infected cell material, with the target-cell membrane localizing to the phagocyte's endosomes, demonstrating their role beyond neutralization. Notably, there was no selective enrichment of DENV genomic material in phagocytic monocytes compared to nonphagocytic counterparts, highlighting a distinct pathway for clearance [143]. Similarly, another recent research explored the role of NS1-specific antibodies in DENV infection, highlighting their multifunctionality and immunogenic nature. Through an analysis of plasma samples collected prior to symptomatic or subclinical secondary infections, researchers evaluated NS1-specific antibody binding, NK cell activation, and. The results revealed that NS1 antibodies are serotype cross-reactive, with higher preinfection levels correlating to subclinical rather than symptomatic infections. Additionally, strong positive associations between antibody binding and NK cell activation were observed [144]. These findings underscore the protective role of antibodies against both structural and nonstructural proteins in DENV infections, demonstrating their capacity to mediate antibody-dependent cellular cytotoxicity while bypassing the risks associated with ADE and suggesting therapeutic potential.

Vaccination remains a key strategy in preventing DENV infection. However, vaccine development must consider metabolic aspects to enhance efficacy. Metabolic modulation during vaccination, such as using activators or inhibitors of specific metabolic pathways as adjuvants, is an innovative approach to enhance vaccine efficacy by modulating the host's immune response. This

strategy involves targeting specific metabolic pathways to improve the immunogenicity of vaccines. For example, adjuvants can activate pathways such as glycolysis or the PPP, which can lead to a more robust immune response. By stimulating these pathways, adjuvants can enhance the production of cytokines and other immune mediators, promoting a stronger and more effective immune response [145–147]. Additionally, metabolic adjuvants can help prime the immune system, ensuring that immune cells are in an optimal state to respond to the vaccine. This approach can also reduce vaccine reactogenicity and improve the overall safety profile of vaccines [145–147]. For example, studies have shown that the mammalian target of mTOR complex plays a significant role in immune cell regulation. Inhibiting the mTOR complex significantly reduces the production of IFN-α in pDCs. Additionally, the mTOR complex is crucial for the expansion of effector T cells and the production of the germinal center B cell response [147]. By integrating metabolic considerations into vaccine design, researchers aim to develop more effective vaccines that provide long-lasting protection against infectious diseases.

The development of effective DENV vaccines requires consideration of the metabolic state of immune cells. Vaccines that can induce a metabolic shift towards glycolysis or oxidative phosphorylation in immune cells may enhance the magnitude and quality of the immune response. Understanding the metabolic requirements of effective immune activation can guide the design of next-generation vaccines [148]. For instance, targeting metabolic pathways such as glycolysis or fatty acid oxidation in DCs can improve their ability to present antigens and activate T-cells. Additionally, metabolic modulators can be used as adjuvants to enhance vaccine-induced immunity, providing a more robust and long-lasting protective response [149]. Two notable clinical trials for DENV fever treatment are currently undergoing Phase II clinical trials, showcasing the advancements in antiviral therapies. These two drugs target the RNA replication process of DENV. One such emerging drug is JNJ-1802, also known as Mosnodenvir, developed by Johnson & Johnson (NCT04906980). This potent inhibitor targets the DENV and various other flaviviruses, such as West Nile Virus, Japanese Encephalitis Virus, and Zika Virus. JNJ-1802 blocks the interaction between NS3 and NS4B within the viral replication complex. The drug has demonstrated broad-spectrum antiviral activity and is currently for its efficacy in treating Dengue Fever. Another promising candidate is EYU-688, a small molecule drug being developed by Novartis Pharmaceuticals (NCT06006559). It specifically targets NS4B and somatostatin receptor (SSTR). EYU-688, administered orally, is designed to disrupt viral replication and alleviate the symptoms of Dengue Fever. These ongoing trials are part of a broader effort by pharmaceutical companies to introduce novel therapeutic approaches to combat Dengue Fever, targeting specific viral proteins to inhibit replication and reduce disease severity.

Emerging novel approaches

Emerging approaches, such as drug delivery systems, hold great promise, particularly for the delivery of nucleic acid-based vaccines and the repurposing of drugs with poor solubility, offering new avenues for effective dengue therapies [150–153]. A most recent study suggests that nanoengineered niclosamide holds promise as an antiviral agent against the DENV. Researchers confirmed that niclosamide efficiently suppressed viral protein expression, delayed viral release, and neutralized the acidic pH within endosomes, inhibiting dsRNA replication. This led to the release of immature and noninfectious virus particles. Beyond its action on DENV, niclosamide's antiviral effects may extend to other viral families by inducing autophagy, a key process in the innate immune response. However, niclosamide's poor water solubility and rapid metabolism in the liver and intestines have limited its bioavailability. To overcome these challenges, researchers are exploring nanoengineering techniques to enhance niclosamide delivery, preventing rapid metabolism and improving its therapeutic potential without the safety concerns associated with enzyme inhibitors. This innovative approach could make niclosamide more viable as an antiviral treatment [154].

Complexities and challenges of targeting host metabolism

Targeting host metabolism for therapeutic interventions against DENV infection presents both opportunities and significant challenges. While metabolic pathways are integral to the viral life cycle, offering potential points of intervention, these pathways also play critical roles in maintaining normal cellular and immune functions. This duality introduces complexities in designing effective and safe therapeutic strategies.

One of the main challenges lies in the non-specificity of metabolic interventions. Many metabolic pathways targeted by DENV, such as glycolysis, lipid metabolism, and amino acid synthesis, are also critical for the normal functioning of various host tissues, especially those with high energy demands like the brain, liver, and immune cells. Inhibiting these pathways to impair viral replication may inadvertently harm the host, leading to undesirable side effects, including immune suppression or tissue damage. For instance, while glycolysis inhibitors are effective at reducing DENV replication, could also impair the function of immune cells that rely on glycolysis for activation and cytokine production. Additionally, the context-specific nature of metabolic shifts poses further challenges. The metabolic requirements of DENV

Table 1 Therapeutic interventions for DENV infection

Therapeutic Strategy	Key Insights	Examples/Drugs	References
Metabolic Pathway Inhibitors	Target glycolysis, lipid metabolism, amino acid metabolism and host glycoprotein processing to disrupt viral replication.	2-Deoxy-D-Glucose (2-DG), Metformin, 6-Amino-Nicotinamide (6-AN), FAS inhibitors, Celgosivir.	[48, 68, 127–130]
Drug Repurposing	Identify existing drugs that modulate immune-metabolic pathways.	Oxprenolol, Digoxin, Auranofin, Atorvastatin.	[131]
Natural Compounds	Use natural molecules with dual antiviral and anti-inflammatory effects.	Cordycepin (targets NS5 and NF-κB), Zileuton, Trimethadione, Linalool.	[132, 133]
RNA Replication Inhibitors	Target viral RNA replication mechanisms.	Sofosbuvir, JNJ-1802 (Mosnodenvir), EYU-688.	([134], NCT04906980, NCT06006559)
Host-Directed Therapies	Enhance host defenses and metabolic resilience against DENV.	Kinase inhibitors, Antioxidants, Niclosamide (nanoengineered for improved delivery).	[135, 136]
Immune Modulation	Fine-tune immune responses to reduce inflammation and enhance antiviral immunity.	Immune checkpoint inhibitors (PD-1, CTLA-4), IL-2 and IL-7 cytokines, Anti-inflammatory drugs (corticosteroids, IL-6 inhibitors).	[137–141]
Vaccination and Immune Priming	Develop vaccines and adjuvants targeting metabolic pathways to improve immune responses.	Next-generation vaccines (glycolysis/oxidative phosphorylation modulators), Metabolic adjuvants for DCs.	[148, 149, 157, 158]
Advanced Drug Delivery Systems	Improve delivery and bioavailability of therapeutic agents with poor solubility or stability.	Nanoengineered delivery of nucleic acid-based vaccines or repurposed drugs (e.g., Niclosamide).	[150–154]

vary across different cell types and stages of infection. For example, while the virus may rely on glycolysis early in infection, it may exploit lipid metabolism during later stages for the assembly of progeny virions. This dynamic reliance makes it difficult to identify a single therapeutic target that is consistently effective throughout the infection cycle. Another complexity arises from individual variability in baseline metabolism. Factors such as age, gender, nutritional status, and pre-existing metabolic disorders can influence the host's metabolic state and, consequently, the efficacy and safety of metabolic interventions. For instance, older adults with slower metabolic rates may respond differently to metabolic therapies compared to younger adults [155]. Similarly, patients with conditions like diabetes or obesity, which alter glucose and lipid metabolism, may experience exaggerated effects or complications from interventions targeting these pathways [156]. Lastly, the potential for viral adaptation and resistance must be considered. As metabolic therapies exert pressure on the virus by disrupting its replication cycle, DENV may evolve alternative mechanisms to exploit host metabolism, reducing the long-term efficacy of these treatments.

To address these challenges, researchers are exploring strategies such as combination therapies; using metabolic inhibitors alongside antiviral drugs or immunomodulators to target the virus through multiple mechanisms while minimizing host damage; developing interventions that target specific metabolic pathways at distinct stages of infection to align with the virus's metabolic demands as temporal targeting; incorporating personalized medicine approaches, informed by metabolomic profiling, to tailor therapies based on individual metabolic states and susceptibilities as host-specific profiling; and identifying and targeting viral-host protein interactions that are critical for metabolic reprogramming while sparing broader host metabolic processes. These approaches aim to balance the need for effective viral inhibition with the preservation of host health, underscoring the importance of continued research into the complex interplay between viral replication, metabolism, and host physiology (Table 1).

Conclusion

The intricate metabolic reprogramming induced by DENV infection represents a finely tuned interplay between viral manipulation and host immune responses. By hijacking key metabolic pathways—such as glycolysis, lipid metabolism, and mitochondrial function—DENV ensures its replication while modulating immune defenses. These virus-host interactions not only provide insight into pathogenesis but also highlight metabolic vulnerabilities that could be exploited for therapeutic intervention. However, targeting these pathways without disrupting essential cellular functions remains a key challenge, as metabolic responses are highly context-dependent, varying by immune cell type, infection stage, and baseline metabolic state. Therapeutic strategies aimed at modulating host metabolism must strike a delicate balance: enhancing antiviral immunity while avoiding exacerbation of disease severity. Despite advances, translating in vitro and computational discoveries into clinical applications remains a significant hurdle. Large-scale clinical trials are essential to validate the efficacy, safety, and optimal dosing of metabolic interventions across diverse populations. Metabolomic profiling offers a promising

tool for patient-specific therapies, allowing researchers to tailor treatments based on gender, age, nutrition, and pre-existing conditions. Systems biology and high-throughput screening technologies can further refine host-targeted drug discovery, accelerating the identification of novel metabolic targets for dengue treatment. Given the complexity of host metabolism, combination therapies that synergistically target multiple metabolic and signaling pathways may hold the greatest therapeutic potential. Strategies that integrate metabolic inhibitors with immunomodulatory agents could enhance antiviral defenses while mitigating the risks of metabolic compensation and viral adaptation. Emerging gene-editing tools like CRISPR-Cas9 provide unprecedented precision in studying metabolic gene functions, offering insights that can refine drug development and resistance mechanisms. Beyond antiviral therapy, metabolic insights are poised to transform vaccine development. By leveraging metabolic adjuvants—compounds that fine-tune metabolic pathways like glycolysis or lipid metabolism—researchers could enhance vaccine efficacy and optimize long-term immune protection. The integration of metabolic regulation into vaccine strategies represents a frontier in dengue prevention, offering potential solutions to enhance immune memory and durability of protective responses. Ultimately, the convergence of systems biology, immunometabolism, and therapeutic innovation marks a promising shift in dengue treatment. By bridging fundamental research with clinical application, metabolic-targeted strategies could reshape antiviral therapy, providing precision medicine approaches that improve patient outcomes while mitigating the burden of severe dengue disease.

Abbreviations

DENV	Dengue virus
DHF	Dengue hemorrhagic fever
DSS	Dengue shock syndrome
WHO	World Health Organization
+ssRNA	Positive-sense single-stranded RNA
DCs	Dendritic cells
NK	Natural killer
APCs	Antigen-presenting cells
PRRs	Pattern recognition receptors
TLRs	Toll-like receptors
RIG-I	Retinoic acid-inducible gene I
CTLs	Cytotoxic T lymphocytes
ISGs	Interferon-stimulated genes
ADE	Antibody-dependent enhancement
FcγR	Fc gamma receptor
HK2	Hexokinase 2
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
TYK2	Tyrosine kinase 2
PPP	Pentose phosphate pathway
IRF	Interferon regulatory factors
NOX	NADPH-oxidase
LDs	Lipid droplets
FASN	Fatty acid synthase enzyme
PLIN3	Perilipin 3
SREBPs	Sterol regulatory element-binding proteins
SCAP	SREBP cleavage-activating protein
ER	Endoplasmic reticulum
MIF	Migration inhibitory factor
S1P	Sphingosine-1-phosphate
SK1	Sphingosine kinase 1
TCA	Tricarboxylic acid
NOS	Nitric oxide synthase
NO	Nitric oxide
lncRNA	Long non-coding RNA
ATP	Adenosine triphosphate
GLUT1	Glucose transporter 1
PI3K	phosphoinositide 3 kinase
mTOR	mammalian (or mechanistic) target of rapamycin
ROS	Reactive oxygen species

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Competing interests
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