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Decoding phosphoinositide signaling in viral pathogenesis and autoimmune disorders

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Abstract

Phosphoinositide (PIP) lipids are master regulators of cellular signaling, membrane dynamics, and trafficking. Dysregulation of PIP signaling contributes critically to autoimmune disorders, where it disrupts immune tolerance and promotes inflammatory tissue damage. Similarly, viruses extensively exploit host PIP signaling pathways for entry, replication, and immune evasion. However, a comprehensive analysis linking PIP dysregulation across specific viral infections to autoimmune mechanisms is lacking. This review bridges this gap by decoding the intricate roles of PIP signaling in both viral pathogenesis and autoimmunity. We detail how eight distinct viral pathogens manipulate PIP networks and explore the resulting implications for autoimmune initiation or exacerbation. We synthesize findings on key PIP species, their effector proteins, and the modulated immune pathways central to both disease contexts. By elucidating these shared and unique mechanisms, this review identifies promising PIP-centric targets for therapeutic intervention in viral diseases and autoimmune disorders.

Keywords: Phosphoinositides; Viral pathogenesis; Autoimmune diseases; Stress signaling

1. Introduction

Phosphoinositides, or phosphatidylinositol phosphates (PIPs), transcend their role as minor membrane phospholipids to function as master regulators of cellular signaling.[1] Derived from phosphatidylinositol (PI) through combinatorial phosphorylation of its inositol ring, the seven PIP species create spatiotemporally defined lipid codes that orchestrate vesicular trafficking, cytoskeletal dynamics, cell survival, and immune

responses.[2] These lipids recruit effector proteins through specialized domains to precisely control fundamental processes.[3] Critically, the PIP landscape is dynamically sculpted by kinases, phosphatases, and phospholipases, an enzymatic equilibrium essential for cellular homeostasis.[1,2,4]

The centrality of PIPs in immune regulation, governing antigen recognition, phagocytosis, lymphocyte activation, and cytokine signaling, renders this system vulnerable to pathogenic exploitation.[5-7] Viruses, as obligate intracellular parasites, strategically hijack PIP networks to facilitate entry, construct replication organelles, suppress host defenses, and evade immune surveillance.[8] Simultaneously, dysregulation of specific PIP pathways underpins autoimmune disorders.[7] Aberrant PIP metabolism, whether through genetic mutations, altered enzyme activity, or chronic inflammatory cues, drives loss of self-tolerance by hyperactivating B-cell receptor (BCR) and T-cell receptor (TCR), impairing regulatory T-cell function, and sustaining inflammatory tissue damage.[6,9,10]

This review synthesizes emerging insights into the dual role of PIP signaling at the intersection of viral infection and autoimmune pathogenesis. We explore how viral commandeering of PIP nodes (e.g., PI 3-kinase [PI3K]-protein kinase B [AKT] activation, PI 4-phosphate [PtdIns4P] manipulation) not only enables infection but may inadvertently prime autoimmune pathways. In addition, we examine how autoimmune-associated PIP dysregulation (e.g., phosphatase and tensin homolog [PTEN]/Src Homology 2 domain-containing inositol phosphatase [SHIP] deficiency, PI3K hyperactivity) mirrors viral subversion strategies. By decoding these shared mechanisms, where pathogens exploit and autoimmune disorders dysregulate convergent PIP hubs, we highlight novel therapeutic targets for modulating immune hyperactivity across disease spectra.

1.1. Phosphoinositide signaling

Phosphoinositides, also known as PIPs, are a specialized class of signaling lipids derived from PI (Figure 1).[11] Chemically, PI consists of a diacylglycerol lipid backbone linked to the cyclic polyalcohol myo-inositol through a phosphodiester bond.[1] Although PI represents a small fraction of cellular phospholipids, it serves as the precursor for the PIP family and plays a pivotal role in diverse biological functions.[1,12]

The phosphorylation of hydroxyl groups at the D-3, D-4, and/or D-5 positions of the inositol ring by specific lipid kinases generates seven key PIP species: PI 3-phosphate (PtdIns3P), PtdIns4P, PI 5-phosphate (PtdIns5P), PI 4,5-bisphosphate (PtdIns[4,5]P_2), PI 3,4-bisphosphate (PtdIns[3,4]P_2), PI 3,5-bisphosphate (PtdIns[3,5]P_2), and PI 3,4,5-trisphosphate (PtdIns[3,4,5]P_3).[1,12] This combinatorial phosphorylation pattern generates a unique "molecular barcode" for each PIP species.

Far beyond their roles as membrane components, PIPs form a dynamic and sophisticated signaling network. They define membrane identity and recruit effector proteins through specific lipid-binding domains, such as Pleckstrin Homology (PH),[13,14] Phox Homology,[15] Fab1, YOTB, Vac1, and EEA1 (FYVE),[16] and Epsin N-terminal Homology domains.[17]

Conventionally, PIP signaling has been considered membrane-associated and concentrated at the plasma membrane in response to agonist stimulation.[12] However, accumulating evidence reveals that PIP signaling extends to endomembrane systems, including endosomes, mitochondria, the Golgi apparatus, and the endoplasmic reticulum.[12,18,19] Moreover, PIPs have recently been recognized to function in non-membranous structures, such as the cytoskeleton, nucleoplasm, nuclear speckles, nuclear lipid islets, nucleoli, and chromatin, where they complex with proteins.[4,11,18,20-24]

In these diverse cellular contexts, PIPs act as second messengers, regulating critical processes, such as vesicular trafficking (endocytosis, exocytosis, and autophagy), cytoskeleton dynamics, cell survival, proliferation, migration, and immune cell activation.[2,4,7,10,12,25] One representative pathway is the PI3K-AKT signaling cascade: Upon agonist-stimulation and receptor activation (e.g., growth factor/cytokine receptors), class I PI3Ks phosphorylate PtdIns(4,5)P_2 to generate PtdIns(3,4,5)P_3.[26,27] This lipid second messenger recruits AKT and phosphoinositide-dependent kinase 1 (PDK1) to the membrane through their PH domains.[26,28] PDK1 then phosphorylates AKT at Thr308, while full activation requires Ser473 phosphorylation of AKT by mammalian target of rapamycin (mTOR) complex 2.[26,29] Activated AKT governs a wide array of cellular processes, including cell motility, survival, proliferation, and metabolism. Key pathways regulated by AKT include Arf-GTPase activating protein with coiled-coil, ankyrin repeat, and PH domain-containing protein 1 (ACAP1)-mediated endosomal trafficking, Forkhead box O (FOXO)-dependent transcriptional programs, mechanistic target of rapamycin complex 1 (mTORC1)-driven metabolic adaptation, and cytoskeletal remodeling through Vimentin and Rac1.[2,26,30] Together, these pathways modulate cellular responses to environmental cues and contribute to immune regulation.

Dysregulation of this PI3K-AKT axis and PIP signaling broadly has been implicated in numerous diseases, including cancer (via hyperactivation), neurodegeneration

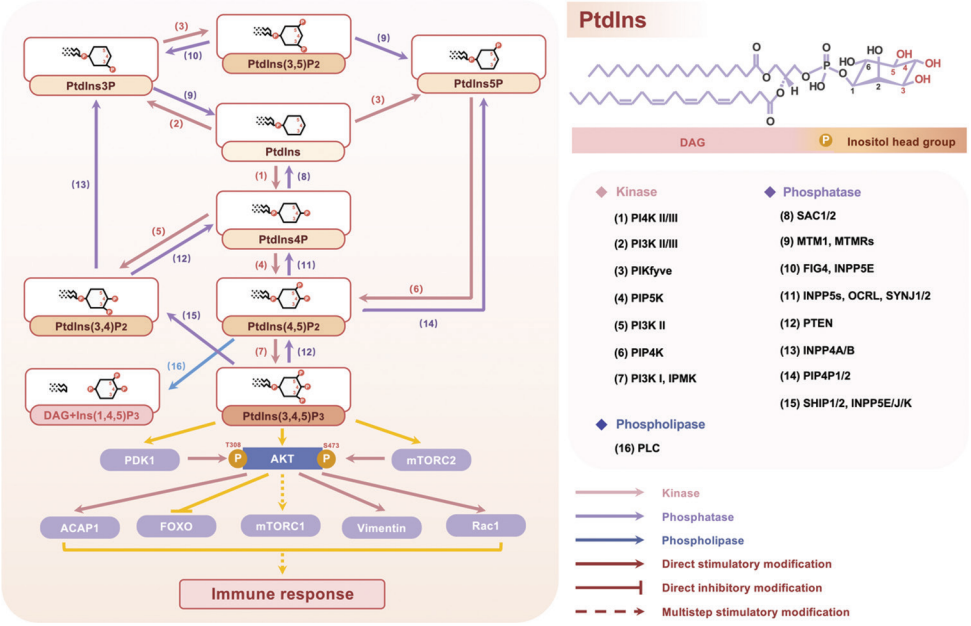

Figure 1. Phosphoinositide modification and regulation of the PI3K-AKT signaling axis. Reversible phosphorylation at the three hydroxyl positions of the inositol ring generates seven spatially distinct PIP species, defined by their phosphate group number and distribution. A set of tightly regulated enzymes, including lipid kinases, such as PI3K, phosphatases, and phospholipases, maintains the dynamic balance of this system. Among these, PtdIns(3,4,5)P_3 acts as a pivotal signaling lipid, triggering downstream cascades by recruiting proteins, including AKT. AKT activation requires sequential phosphorylation by PDK1 and mTORC2 in a PtdIns(3,4,5)P_3-dependent manner. Once fully activated, AKT regulates a broad spectrum of cellular processes, including ACAP1-mediated endosomal trafficking, FOXO-dependent transcriptional programs, mTORC1-driven metabolic adaptation, and cytoskeletal reorganization via Vimentin and Rac1. Together, these pathways modulate cellular responses to environmental cues and contribute to immune regulation. Image created by authors using Microsoft PowerPoint Software Version 16.66.

Abbreviations: ACAP1: Arf-GAP with coiled-coil, ankyrin repeat, and PH domain-containing protein 1; AKT: Protein kinase B; DAG: Diacylglycerol; FIG4: Factor-induced gene 4; FOXO: Forkhead box O; INPP: Inositol polyphosphate; mTOR: Mammalian target of rapamycin; MTM1: Myotubularin 1; MTMRs: Myotubularin-related proteins; OCRL: Oculocerebrorenal syndrome protein of Lowe; PDK1: 3-phosphoinositide-dependent protein kinase-1; PI3K: Phosphatidylinositol 3-kinase; PI4K: Phosphatidylinositol 4-kinase; PIKFYVE: Phosphoinositide kinase, Fab1, YOTB, Vac1, and EEA1; PIPK: Phosphatidylinositol phosphate kinase; PtdIns(3,4,5)P_3: phosphatidylinositol 3,4,5-trisphosphate (PtdIns[3,4,5]P_3); PtdIns(4,5)P_2: Phosphatidylinositol 4,5-bisphosphate; PtdIns3P: Phosphatidylinositol 3-phosphate; PtdIns4P: Phosphatidylinositol 4-phosphate; PtdIns5P: Phosphatidylinositol 5-phosphate; PTEN: Phosphatase and tensin homolog; SHIP: Src Homology 2 domain-containing inositol phosphatase; SYNJ: Synaptojanin.

(altered synaptic PIP dynamics), chronic inflammation, and autoimmune disorders, highlighting its potential as a therapeutic target.[6,7,31-34]

1.2. Autoimmune diseases

Autoimmune diseases encompass a diverse group of disorders caused by dysregulated immune responses against self-tissues (Figure 2).[35] This response stems from a failure of immune tolerance, leading to recognition of self-antigens as pathogenic and subsequent immune activation, resulting in sustained inflammation, autoantibody production, and progressive tissue damage.[36] More than 80 distinct autoimmune diseases are currently recognized,[36] affecting approximately 8.5% of the global population based on epidemiological studies and contributing significantly to disability and disease burden, including both systemic disorders (e.g., systemic lupus erythematosus [SLE], Sjögren's syndrome [SS]) and organ-specific diseases (e.g., type 1 diabetes [T1D], multiple sclerosis [MS]).[37]

The pathogenesis of autoimmunity involves a complex interplay of genetic predisposition, environmental triggers, and immune dysregulation.[38] Genetic factors include polymorphisms in *HLA* genes and immune regulators, such as protein tyrosine phosphatase non-receptor type 22 (affecting lymphocyte signaling), cytotoxic T-lymphocyte-associated protein 4 (a checkpoint inhibitor), and signal transducer and activator of transcription 4 (promoting pro-inflammatory responses).[39-41] Environmental triggers include infections (e.g., Epstein–Barr virus [EBV]), hormonal changes (e.g., estrogen fluctuations), smoking, vitamin D deficiency, and psychological stress, which may dysregulate immune responses and exacerbate disease susceptibility.[42] These factors converge to disrupt immune tolerance mechanisms, including central tolerance in the thymus and bone marrow and peripheral tolerance mediated by regulatory T cells (Tregs).[43] Aberrant activation of immune cells, driven by dysregulated signaling pathways, culminates in

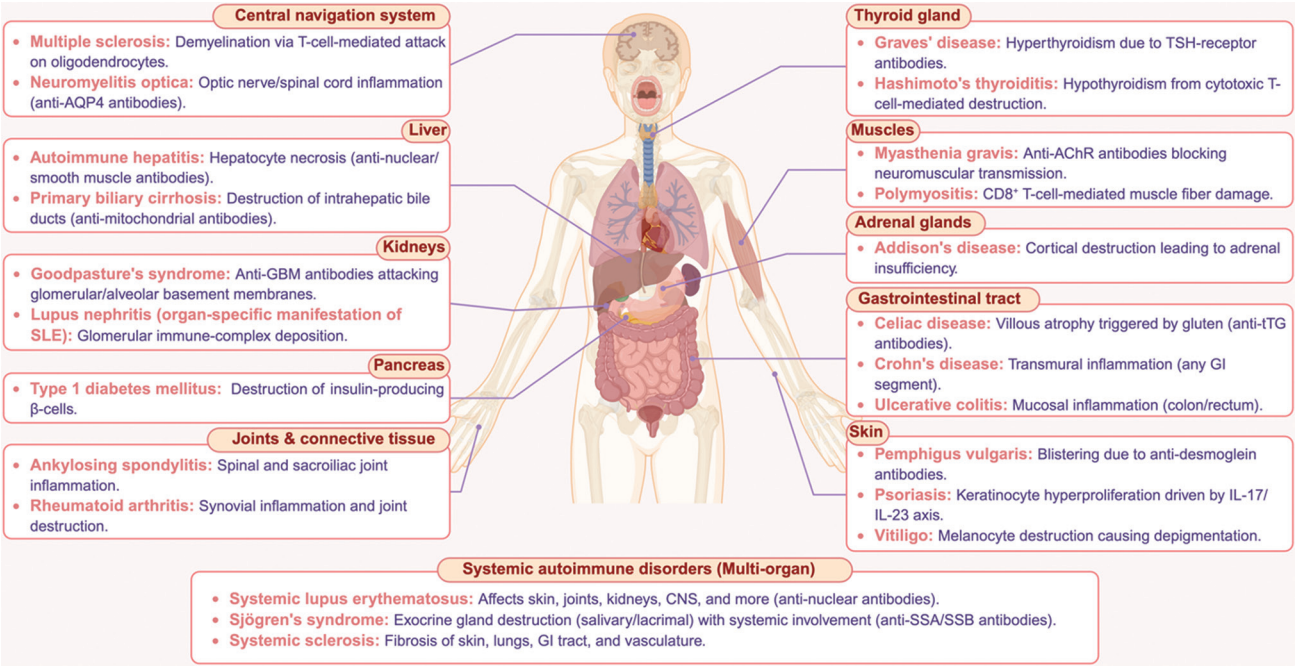

Figure 2. Major organs and associated autoimmune diseases. The schematic diagram outlines the human body's main organs and their related autoimmune diseases. Autoimmune diseases are diseases in which the immune system mistakenly attacks its own tissues. It can be divided into two categories based on the organs and scope involved: organ-specific and systemic. Created with BioRender. Chen, M. (2025) https://BioRender.com/0ssapnq.

autoantibody production, immune complex deposition, and tissue destruction.[44]

Phosphoinositide signaling plays a pivotal role in immune cell activation and tolerance.[7] Dysregulation of PIP metabolism, through altered activity of PI3Ks, PTEN, SHIP, and phospholipases, impairs key processes, such as BCR and TCR signaling, cytokine production, Treg function, and phagocytosis.[45] The hyperactivation of pathways, such as PI3K-AKT-mTOR, is frequently observed in autoimmune diseases,[46-48] promoting lymphocyte hyperresponsiveness, impaired Treg function, and inflammatory tissue damage.[49] Understanding these PIP-mediated dysfunctions is critical for unraveling autoimmune pathology and identifying therapeutic targets.

1.3. Viral infections and autoimmunity

The intricate relationship between viral infections and the development or exacerbation of autoimmune disorders represents a significant area of immunological research. While a robust and swift immune response during viral infection is essential for antigen clearance, immune regulatory mechanisms can sometimes fail, leading to the breakdown of self-tolerance and the development of autoimmune diseases. Present research indicates that viral infections can induce autoimmune diseases through various mechanisms, among which molecular mimicry, bystander activation, and epitope spreading are the most well-documented.[50]

Molecular mimicry serves as a classic paradigm, where structural or sequential homology between viral antigens and host self-antigens deceives the immune system, leading to cross-reactive T-cell activation or autoantibody production.[51] Large-scale virome analyses reveal that this phenomenon is particularly prevalent in the Herpesviridae and Poxviridae families, where short linear mimics frequently target host proteins involved in cellular replication and inflammatory pathways.[52] A well-documented example is the homology between the EBV nuclear antigen-1 and several lupus-associated autoantigens, such as SS-related antigen A and Smith antigen, contributing to SLE pathogenesis.[53] Similarly, cross-reactivity between Coxsackievirus B4 (an enterovirus) peptides and the glutamate decarboxylase 65 antigen in pancreatic islet cells is implicated in the initiation of T1D.[54]

Bystander activation provides another critical pathway. During an acute viral infection, intense local inflammation releases sequestered self-antigens and a milieu of pro-inflammatory cytokines (e.g., interleukin [IL]-1, IL-6, IL-8, and tumor necrosis factor [TNF]-α).[55-57] This "inflammatory storm" can non-specifically activate nearby autoreactive T lymphocytes that were previously ignorant or anergic, even in the absence of direct antigenic recognition of the virus itself.[55,58] The sheer magnitude of inflammation lowers the threshold for activation of these

autoreactive cells.[59] This mechanism is particularly relevant in tissues targeted by viruses, as demonstrated in the rat insulin promoter-glycoprotein transgenic mouse model of T1D, where lymphocytic choriomeningitis virus infection triggers both virus-specific and bystander activation of autoreactive $CD8^+$ T cells through inflammatory cytokines, such as IL-21 and IL-15, leading to destruction of pancreatic β-cells.[60]

Epitope spreading further amplifies the autoimmune response over time, especially during persistent infections. As an initial autoimmune response (potentially triggered by mimicry or bystander effects) causes tissue damage, new self-antigens are released and presented to the immune system. This leads to the activation of lymphocytes specific for these newly exposed epitopes, broadening the autoimmune attack beyond the initial target.[50,55,61] A prime example of this phenomenon is observed in Theiler's murine encephalomyelitis virus (TMEV) infection, where the virus persistently infects glial cells, including astrocytes, microglia, and oligodendrocytes.[62] In this model, the chronic infection drives an initial $CD4^+$ T cell response against the dominant myelin proteolipid protein (PLP) epitope 139–151, which then progressively expands to target the less immunogenic PLP 178–191 epitope through epitope spreading.[63-65] This intramolecular epitope spreading exemplifies how persistent viral infections can drive the diversification of autoimmune responses, ultimately leading to more widespread tissue damage and disease progression. Epidemiological and clinical evidence robustly links specific viruses to distinct autoimmune conditions.

Beyond the well-established link of EBV with MS[66-69] and its debated association with SLE,[70-74] and the connection between enteroviruses (e.g., Coxsackievirus B [CVB] and T1D,[75,76] potentially via molecular mimicry), other notable viral-autoimmune associations include: Human cytomegalovirus (HCMV), implicated in systemic sclerosis (SSc)[68,70] and proposed as a T1D risk factor;[69] hepatitis C virus (HCV), the primary cause of mixed cryoglobulinemia (MC);[77,78] human herpesvirus 6 (HHV-6), detected in MS plaques[79] but less consistently associated than EBV; congenital rubella virus (RuV) infection is a recognized T1D risk factor;[80,81] and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), temporally linked to autoimmune sequelae in long coronavirus disease 2019 (COVID-2019) (e.g., Guillain-Barré syndrome [GBS],[82] antiphospholipid syndrome [APS],[83] and immune thrombocytopenia [ITP][83]) through mimicry or immune dysregulation. TMEV, though not a human pathogen, is a key model for MS-like demyelination.[84,85] Investigating how these viruses manipulate host PIP signaling (e.g., PI3K-AKT-mTOR) to disrupt immune tolerance forms a core focus of this review.

2. Viral infection triggered phosphoinositide signaling in autoimmunity

This intricate relationship between viral infections, PIP signaling, and autoimmunity underscores the critical role of PIP pathways in bridging infection-induced immune dysregulation and autoimmune disease progression (Table 1). To elucidate the intricate relationship between viral infections and PIP signaling dysregulation in autoimmunity, we focus on eight representative viruses—CVB, EBV, HCMV, HCV, HHV-6, RuV, SARS-CoV-2, and TMEV. These pathogens were highlighted based on three key criteria. First, they span five distinct viral families (*Picornaviridae*, *Herpesviridae*, *Flaviviridae*, *Togaviridae*, and *Coronaviridae*), enabling broad mechanistic comparisons across evolutionary lineages. Second, each virus exhibits well-documented associations with autoimmune disorders and demonstrates specific strategies to hijack host PIP signaling pathways, providing a robust framework to explore shared and unique mechanisms. Third, while most are highly prevalent in humans (e.g., EBV infects >90% of adults), TMEV—though non-human-infecting—is included due to its established murine model for studying MS, offering critical insights into PIP-mediated demyelination. By analyzing how these viruses distinctly perturb PIP networks and downstream immune responses, we aim to decode their contributions to autoimmune pathogenesis.

2.1. Coxsackievirus B

Coxsackieviruses, members of the *Enterovirus* genus within the *Picornaviridae* family, are small RNA viruses characterized by a positive-sense, single-stranded genome.[134] They are categorized into two groups—Coxsackievirus A and CVB—each linked to a variety of diseases[135], including hand, foot, and mouth disease, T1D, acute myocarditis, and autoimmune myocarditis.[75,76,86,87,136-138] Among the six known serotypes of CVB (CVB1–CVB6), CVB1, CVB3, and CVB5 have been particularly associated with viral myocarditis.[139] Myocarditis, which involves inflammation of the heart muscle, can be triggered by a range of causes, both infectious and non-infectious, with viruses being the most frequently identified agents.[140,141] Clinical studies have reported that nearly half of patients with dilated cardiomyopathy (DCM) test positive for CVB-specific antibodies, implying a potential autoimmune component involving CVB and host cardiac antigens in the onset of myocarditis and DCM.[142-145]

Table 1. Viral pathogens' relative autoimmune diseases and impact on phosphoinositide signaling.

Viral pathogen	Relative autoimmune diseases	Effects on phosphoinositide signaling
CVB	AM,[86,87] T1D[75,76]	CVB's replication relies on the host PI4K/PtdIns4P,[88] and its infection activates the PI3K-AKT-mTOR signaling. [89]
EBV	APS,[90,91] MS,[66-69] RA,[92-94] SLE,[70-74] SS,[95,96] SSc[97]	EBV infection triggers the activation of PI4K, with the latent protein EBNA1 further enhancing PI4K and PIPK activities, resulting in elevated levels of PtdIns4P and PtdIns(4,5)P_2.[98] The EBV latent proteins LMP1 and LMP2A stimulate the PI3K-AKT signaling pathway and promote IRF4 activity. [99,100] LMP1 also suppresses PTEN expression by upregulating miR-21, thereby intensifying PI3K-AKT signaling. [101] Similarly, EBV-miRNA-BART7-3P supports PI3K-AKT activation by inhibiting PTEN.[99] Moreover, the EBV envelope protein gp350 binds to the CR2/CD21 receptor, further activating PI3K.[102,103]
HCMV	RA,[104-106] SLE,[107-109] SSc, [104,110,111] T1D[104,112]	HCMV infection upregulates the PI3K-AKT pathway, and inhibiting PI3K activity effectively suppresses its viral replication and downstream signaling. [113]
HCV	AITD,[114] MC[77,78]	The activation of PI3K-AKT signaling helps the virus enter cells, [115] possibly by altering cell polarity. [116] HCV's NS5A protein activates PI4KIIIα, creating PtdIns4P-rich membranes that attract OSBP lipid transporters, forming ideal replication platforms. [117] This process is enhanced when NS5A's BAAPP domain binds to PtdIns(4,5) P_2, strengthening interaction with the host factor TBC1D20.[118]
HHV-6	AITD,[119] IBD,[120] MS,[79] SSc, [121] T1D[122]	Inflammatory factors, such as TNF-α and IL-1 β in HHV-6-positive MS patients activate the downstream NF-κB signaling pathway, [123,124] which may further regulate the cellular inflammatory response through the PI3K-AKT pathway.
RuV	T1D[80,81]	RuV infection activates PI3K-AKT signaling, which is required for cell survival and virus production. [125]
SARS-CoV-2	APS,[83] AT,[126] GBS,[82] ITP[83]	The activation of the PI3K-AKT-mTOR signaling pathway promotes the replication of SARS-CoV-2, inhibits cell apoptosis, and increases cytokine release. [127,128] The viral ORF3a protein upregulates miR-155 to suppress SHIP1, and enhances the production of PtdIns(3,4,5)P_3, which activates AKT and NF-κB, leading to the amplification of pro-inflammatory cytokines. [129-131] Inhibiting PIKFYVE effectively blocks the fusion of the virus with endosomal membranes, preventing the release of the virus into the cytoplasm and thus inhibiting virus infection. [132]
TMEV	MS[84,85]	PI3K-AKT signaling participates in the progression of clinical symptoms in the TEMV model of MS.[133]

Abbreviations: AITD: Autoimmune thyroid diseases; AKT: Protein kinase B; AM: Autoimmune myocarditis; APS: Antiphospholipid syndrome; AT: Autoimmune thyroiditis; BAAPP: Basic amino acid PtdIns(4,5)P_2 pincer; CR2: Complement receptor type 2; CVB: Coxsackievirus B; EBNA1: Epstein–Barr virus nuclear antigen 1; EBV: Epstein–Barr virus; GBS: Guillain-Barré syndrome; HCMV: Human cytomegalovirus; HCV: Hepatitis C virus; HHV-6: Human herpesvirus 6; IBD: Inflammatory bowel disease; IL: Interleukin; IRF4: Interferon regulatory factor 4; ITP: Immune thrombocytopenia; LMP: Latent membrane protein; MC: Mixed cryoglobulinemia; MS: Multiple sclerosis; mTOR: Mammalian target of rapamycin; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; NS5A: Non-structural protein 5A; ORF3a: Open reading frame 3a; OSBP: Oxysterol-binding protein; PI3K: Phosphatidylinositol 3-kinase; PI4K: Phosphatidylinositol 4-kinase; PIKFYVE: Phosphoinositide kinase, Fab1, YOTB, Vac1, and EEA1; PIPK: Phosphatidylinositol phosphate kinase; PtdIns(3,4,5)P_3: phosphatidylinositol 3,4,5-trisphosphate; PtdIns(4,5)P_2: Phosphatidylinositol 4,5-bisphosphate; PtdIns4P: Phosphatidylinositol 4-phosphate; PTEN: Phosphatase and tensin homolog; RA: Rheumatoid arthritis; RuV: Rubella virus; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SHIP: Src Homology 2 domain-containing inositol phosphatase; SLE: Systemic lupus erythematosus; SS: Sjögren's syndrome; SSc: Systemic sclerosis; T1D: Type 1 diabetes; TBC1D20: TBC1 domain family member 20; TMEV: Theiler's murine encephalomyelitis virus; TNF: Tumor necrosis factor.

Coxsackievirus B replication is known to depend on host phosphatidylinositol 4-kinase (PI4K) activity and its product PtdIns4P.[88] Besides, CVB3 infection exhibits a sophisticated temporal regulation of the PI3K-AKT-mTOR signaling axis, demonstrating upstream PI3K-AKT activation coupled with downstream mTOR suppression. This strategic division facilitates viral replication through stage-specific modulation of host cell processes. Following cellular entry and initial replication steps, CVB3 activates AKT in a PI3K-dependent manner,[146] creating a biphasic apoptotic response that initially promotes cell death to facilitate viral release before transitioning to anti-apoptotic effects that preserve the cellular environment for sustained viral production.[146,147] Pharmacological inhibition of PI3K significantly reduces viral protein 1 (a major capsid protein that plays a crucial role in the virus's structure, antigenicity, and pathogenesis) expression while enhancing autophagy and suppressing viral replication, highlighting the critical role of this pathway in CVB3 life cycle completion.[89] Paradoxically, despite PI3K-AKT activation, CVB3 infection simultaneously suppresses mTOR activity, resulting in markedly elevated autophagy levels that paradoxically enhance viral replication, suggesting the virus has evolved mechanisms to uncouple these normally coordinated pathways.[89] Complementary studies with curcumin demonstrate additional complexity, as its

antiviral effects against CVB3 appear mediated through PI3K-AKT-dependent nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation, which amplifies pro-inflammatory cytokine production (TNF-α, IL-6, IL-1β) and potentiates host immune responses against the infection.[148]

This multilayered manipulation of PI3K-AKT-mTOR signaling underscores CVB3's remarkable capacity to differentially exploit various nodes within a single signaling cascade to optimize its replication strategy while modulating host defense mechanisms. Nevertheless, targeting the PIP signaling network presents a promising avenue for therapeutic intervention in CVB-related autoimmune diseases. Continued investigation is warranted to unravel this complex relationship and identify actionable targets within the pathway.

2.2. Epstein–Barr virus

Epstein–Barr virus, the first recognized human tumor virus,[149] is widespread globally, persisting as a lifelong infection in over 90% of adults.[68,150] While typically latent, EBV can act as a conditional pathogen when host-virus balance is disrupted,[151] and it is strongly associated with various human cancers.[152] These include epithelial-derived carcinomas, such as gastric[153] and nasopharyngeal carcinoma,[154] as well as B and T cell-derived lymphomas,[99,155-158] including Hodgkin lymphoma,[159] Burkitt lymphoma,[160] diffuse large B cell lymphoma,[161] plasmablastic lymphoma,[156,162] primary effusion lymphoma,[163] natural killer/T-cell lymphoma,[164] and post-transplant lymphoproliferative disorder.[165] This association underscores the virus's profound interaction with the immune system. Evidence suggests that EBV plays a role in autoimmune diseases,[155,166-168] as patients with conditions, such as APS,[90,91] MS,[66-69,169-171] rheumatoid arthritis (RA),[92-94,167] SLE,[70-74,171] SS,[95,96,171,172] and SSc[97,173] exhibit EBV antibodies in their plasma.

Reactivation of latent EBV, often linked to compromised immune surveillance, leads to abnormal disease pathogenesis and cellular proliferation.[174] EBV relies on host PIP metabolism for efficient replication, with PI4K and PtdIns4P being key components in this process.[88] Notably, EBV miRNAs and latent proteins significantly influence these pathways. For instance, EBV nuclear antigen 1 stimulates PI4K and PIP kinase activity, increasing PtdIns4P and PtdIns(4,5)P_2 levels in B cells.[98] Latent membrane protein 1 (LMP1) and latent membrane protein 2A (LMP2A), other latent EBV proteins, activate the PI3K-AKT pathway[175] and enhance interferon regulatory factor 4 activity,[31,52] which is essential for immune cell differentiation.[176,177]

In addition, LMP1 suppresses PTEN expression through miR-21 upregulation, amplifying PI3K-AKT signaling.[101,178] Similarly, EBV-miRNA-BART7-3P contributes to this pathway by inhibiting PTEN.[99,179] EBV employs gp350, its envelope-associated protein, to attach to the complement receptor type 2/CD21 receptor,[180-182] influencing pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-2, and IL-6.[102,183] The NF-κB pathway in gp350-treated cells is activated through protein kinase C and PI3K, impacting IL-1β and IL-6 expression.[102,103,184,185]

Although research on EBV-induced inflammation and its link to PIP signaling remains limited,[68,183] emerging evidence highlights a potential connection that warrants further exploration, particularly regarding autoimmune diseases and PIP metabolism (Figure 3).

2.3. HCMV

HCMV, a prototypical member of the *Betaherpesvirinae* subfamily,[186,187] is a widespread pathogen capable of infecting individuals across all age groups. A defining feature of HCMV is its ability to establish lifelong latency following primary infection, during which it exerts broad modulatory effects on both innate and adaptive immunity. These immunomodulatory properties make HCMV a compelling candidate in the etiology of various autoimmune diseases.[188,189]

Accumulating evidence suggests that HCMV is involved in the pathogenesis of several autoimmune conditions, including RA,[104-106] SLE,[107-109] SSc,[104,110,111] and T1D.[104,112] Proposed mechanisms for HCMV-associated autoimmunity include molecular mimicry, chronic inflammatory responses, and non-specific activation of B cells.[190-192] One frequently observed phenomenon is the elevation of autoantibody levels in HCMV-infected individuals, particularly in SLE and SSc, suggesting a potential role for the virus in driving or exacerbating autoimmune processes.[193] In some SLE and SSc patients, HCMV infection has been linked to increased serum concentrations of pro-inflammatory cytokines, such as interferon-γ, IL-4, and IL-2, along with expanded memory T-cell populations.[194] These immune alterations may contribute to fibrotic responses and vascular injury, hallmark features of these diseases.

Emerging evidence indicates that type II interferon signaling pathways orchestrate immune responses by modulating the PI3K-AKT-mTOR signaling axis.[195,196] Moreover, the PI3K-AKT pathway may play distinct regulatory roles during different phases of HCMV infection. During latency, viral proteins UL7 and UL138 activate the PI3K-AKT signaling cascade through epidermal growth factor receptor engagement.[197-199] This activation maintains

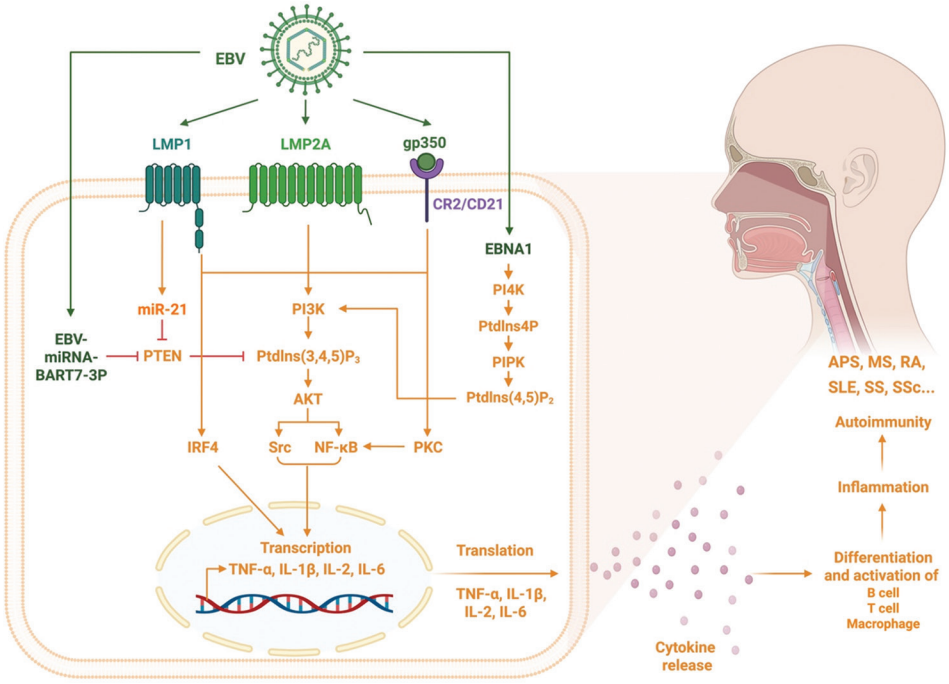

Figure 3. Proposed mechanism of EBV-induced PIP signaling in autoimmune diseases. EBV infection triggers PIP signaling through multiple interconnected pathways. EBV-miRNA-BART7-3P promotes PI3K-AKT signaling by suppressing PTEN. The latent viral proteins LMP1 and LMP2A further enhance PI3K-AKT and IRF activity, with LMP1 downregulating PTEN expression via miR-21 upregulation, thereby intensifying the PI3K-AKT cascade. The EBV envelope protein gp350 interacts with the complement receptor type 2/CD21 receptor, activating PI3K and PKC. Concurrently, the EBV protein EBNA1 stimulates PI4K and PIPK, increasing the synthesis of PtdIns4P and PtdIns(4,5)P_2. The cumulative activation of the PI3K-AKT pathway drives Src and NF-κB signaling, in combination with the effects of active IRF4, leading to the release of pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-2, and IL-6. These cytokines facilitate the differentiation and activation of B cells, T cells, and macrophages, resulting in an amplified inflammatory response that may contribute to the onset of autoimmune diseases. Created with BioRender.com. Chen, M. (2025) https://BioRender.com/fq68o3e.
Abbreviations: AKT: Protein kinase B; APS: Antiphospholipid syndrome; CR2: Complement receptor type 2; EBNA1: Epstein-Barr virus nuclear antigen 1; EBV: Epstein-Barr virus; IL: Interleukin; IRF4: Interferon regulatory factor 4; LMP: Latent membrane protein; MS: Multiple sclerosis; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K: Phosphatidylinositol 3-kinase; PI4K: Phosphatidylinositol 4-kinase; PIPK: Phosphatidylinositol phosphate kinase; PtdIns(4,5)P_2: Phosphatidylinositol 4,5-bisphosphate; PtdIns4P: Phosphatidylinositol 4-phosphate; PTEN: Phosphatase and tensin homolog; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; SS: Sjögren's syndrome; SSc: Systemic sclerosis; TNF: Tumor necrosis factor.

viral genome silencing through multiple mechanisms: (i) Suppression of FOXO transcription factors to prevent their nuclear translocation and subsequent activation of lytic genes; (ii) induction of anti-apoptotic pathways that enable viral persistence in short-lived myeloid cells, such as monocytes; and (iii) promotion of $CD34^+$ progenitor cell differentiation toward myeloid lineages, thereby creating a stable cellular niche for latent maintenance.[199-201] In stark contrast, during lytic replication, the viral UL38 protein activates mTORC1 through both tuberous sclerosis complex 2-dependent and -independent mechanisms.[202,203] This leads to the degradation of insulin receptor substrate 1, consequent inhibition of PI3K-AKT signaling, and subsequent nuclear translocation of FOXO3a. This triggers viral lytic gene expression and drives the viral replication cycle.[204] This biphasic regulation of PI3K-AKT signaling exemplifies HCMV's sophisticated strategy to temporally control host cell pathways for optimal viral persistence and replication.

Although direct links between PIP signaling and HCMV-induced autoimmunity remain to be clarified, the involvement of PI3K-AKT-mTOR in HCMV latency and Lytic replication, T cell activation, and cytokine secretion suggests that PIP signaling could play a role in mediating HCMV-driven immune dysregulation. This potential connection represents a promising direction for future investigation.

2.4. HCV

HCV, first identified in 1989,[205] is an enveloped positive-sense single-stranded RNA virus belonging to the genus *Hepacivirus* of the family *Flaviviridae*.[206] Upon infection, HCV's positive-sense single-stranded RNA genome directly functions as mRNA, enabling immediate viral

protein translation and subsequent hijacking of host cells for replication and virion assembly.[206] Despite the World Health Organization's 2030 elimination target, HCV still caused approximately 221,000 global deaths in 2022.[207]

HCV infection is associated with a range of liver diseases, including chronic hepatitis, cirrhosis, and hepatocellular carcinoma, as well as numerous extrahepatic diseases, such as kidney diseases, metabolic disorders, and autoimmune diseases.[208] These autoimmune manifestations include MC[77,78] and autoimmune thyroid diseases (AITD).[114] Under the persistent antigenic stimulation of HCV, B lymphocytes significantly increase the secretion of IgM antibodies with rheumatoid factor (RF) activity.[209] These RF-IgM antibodies bind to polyclonal IgG to form immune complexes that precipitate at low temperatures, resulting in MC, particularly type II MC, which is characterized by immune complexes composed of monoclonal IgM and polyclonal IgG.[210] In more severe pathological processes, the HCV E2 protein binds to the CD81 receptor on B-cell surfaces, inducing *BCL-2* gene rearrangement and t(14;18) chromosomal translocation, promoting malignant transformation, ultimately leading to B-cell lymphomagenesis.[211,212] Concurrently, HCV infection leads to T cell dysfunction, manifested as an increase in helper T cells (Th) and a decrease in Tregs.[213,214] Combined with antigenic similarity between HCV proteins and thyroid tissue components, immune dysfunction leads to thyroid tissue damage and subsequent development of AITD.[215,216]

The PIP signaling network plays stage-specific roles throughout HCV pathogenesis.[217] During early infection, the HCV envelope glycoprotein E2 interacts with its coreceptors CD81 and claudin-1 to rapidly activate AKT signaling, thereby enhancing viral entry efficiency,[115] possibly through deregulation of cell polarity.[116] In the viral replication process, HCV enhances neuroblastoma rat sarcoma viral oncogene homolog (NRAS) protein accumulation within detergent-resistant membranes (the site of viral replication complex assembly), consequently activating the NRAS-PI3K-AKT-mTOR signaling cascade. This pathway sustains basal viral replication while concurrently inhibiting host cell apoptosis. This dual mechanism facilitates persistent infection,[218] though the exact molecular details of this regulatory network require further characterization. Furthermore, HCV may alternatively activate the PI3K-AKT signaling pathway by perturbing host cellular miRNA networks (e.g., upregulation of miR-483-3p and miR-320c). This represents an additional layer of viral manipulation of host signaling cascades to facilitate persistent infection.[219] Simultaneously, HCV non-structural protein 5A (NS5A) protein activates PI4KIIIα to generate PtdIns4P-enriched membranes that recruit oxysterol-binding protein lipid transporters, creating optimal replication platforms.[117] This process is further enhanced when NS5A's basic amino acid PtdIns(4,5)P_2 pincer (BAAPP) domain binds PtdIns(4,5)P_2, inducing conformational changes that strengthen interaction with the host factor TBC1 domain family member 20.[118]

Many PIP signal inhibitors have shown promising anti-HCV effects;[220,221] thus, they may also inhibit HCV-induced autoimmunity. Besides, the broad cellular expression of PIP pathways and HCV's capacity to infect and replicate in immune cells suggest these signaling molecules may directly regulate immune functions in HCV-induced autoimmunity, though direct proof is currently absent.[222]

2.5. HHV-6

HHV-6 belongs to the β-herpesvirus subfamily of the *Herpesviridae*, which is the same subfamily as HCMV.[223] Since its first isolation in 1986 from patients with lymphoproliferative disorders, two main variants, HHV-6A and HHV-6B, have been recognized.[224,225] Available data indicate that HHV-6B accounts for the majority of infections in children, whereas HHV-6A appears to be associated with lower pathogenicity.[226] HHV-6 exhibits a broad cellular tropism and has been reported to infect T and B lymphocytes, among other cell types. It can establish long-term latency and may reactivate under conditions of immunosuppression or other stimuli, events that have been linked to chronic inflammation and sustained immune stimulation.[227,228]

The PIP signaling pathway is thought to be important for maintaining immune homeostasis and immune responses. The activation of the PI3K-AKT signaling pathway has been implicated in promoting cell proliferation, differentiation, and memory T cell formation, as well as regulating the differentiation of Th cell subsets and Treg functions.[229] In B lymphocytes, PIP signaling can be engaged through BCR-associated co-receptors to modulate survival and plasma-cell differentiation.[230] Collectively, these observations raise the possibility that HHV-6 might contribute to autoimmunity through the interaction with PIP-dependent pathways.

Previous studies have explored potential links between HHV-6 and autoimmune diseases, including MS,[79] SSc,[121] AITD,[119] T1D,[122] and inflammatory bowel disease (IBD).[120] Among these, the association with MS has received the most attention. HHV-6 nucleic acids and proteins have frequently been detected in peripheral blood mononuclear cells, cerebrospinal fluid, and brain tissue from MS patients, and some studies report that their abundance correlates with disease activity or relapse.[79,231-233] Seropositive MS

patients have been found to display elevated levels of TNF-α, IL-1β, and IL-6, cytokines that can activate NF-κB signaling and, in turn, may influence the PI3K-AKT cascade.[123,124,234,235] Due to the association of other viruses with MS, research investigated the interactions between neurotropic viruses. Emerging evidence suggests that HHV-6 could trans-activate EBV, potentially modulating MS progression through PIP-related pathways.[236]

A meta-analysis on the cumulative incidence (incidence ratio) of HHV reactivation in COVID-19 patients also found the presence of HHV-6 virus reactivation,[237] highlighting the need to investigate post-viral autoimmune sequelae further. Moreover, in AITD, elevated HHV-6 levels have been reported in thyroid tissue, leading to the hypothesis that the virus might initiate disease through infection of thyroid or immune cells.[238] Similarly, HHV-6B has been detected in pancreatic islets of T1D patients, and it has been postulated that transient reactivation could trigger β-cell-directed autoimmunity.[122]

Although the precise inter-relationship among HHV-6 infection, PIP signaling, and autoimmune pathogenesis remains to be fully elucidated, their intertwined interactions warrant continued investigation, which may offer new insights into disease mechanisms.

2.6. Rubella virus

Rubella virus, the only member of the *Rubivirus* genus within the *Togaviridae* family,[239] is widely regarded as the causative agent of rubella, commonly referred to as German measles. Although widespread immunization efforts have contributed to a global decline in RuV incidence, the virus continues to circulate in regions with insufficient vaccine coverage.[240] Persistent, chronic RuV infections involving multiple organ systems—as well as the accompanying generation of autoantibodies—have been suggested to contribute to the development of autoimmune diseases.[241,242]

Growing evidence has associated RuV, along with other viruses, such as HCMV and CVB, with an increased risk of T1D.[75,76,80,81,104,112] Two principal mechanisms have been hypothesized by which viruses may contribute to T1D pathogenesis: Direct cytolytic damage to pancreatic β cells and virus-induced immune responses that trigger autoimmunity and subsequent β cell destruction.[242] Persistent RuV infection has been correlated with the presence of islet cell autoantibodies, suggesting a potential role in initiating autoimmune T1D.[243-245] Preserving β-cell viability and metabolic activity appears critical for preventing and treating T1D.[246] The PI3K-AKT signaling pathway, known for its regulatory functions in cell survival, proliferation, and metabolism, has been proposed as a promising target in this context. RuV has been reported to activate the PI3K-AKT pathway during infection, a process thought to support both host cell survival and efficient viral replication.[125] This pathway may also modulate β-cell function, possibly delaying the onset of autoimmune destruction.

Therapeutic strategies to enhance PI3K-AKT signaling in β cells have shown preliminary promise. For example, FhHDM-1—a 68-amino-acid peptide secreted by the parasitic helminth *Fasciola hepatica*—has been observed to directly stimulate PI3K-AKT signaling in β cells, promoting survival and protecting against cytokine-induced apoptosis without triggering uncontrolled proliferation.[247,248] In addition, gamma-aminobutyric acid has been reported to exert both anti-apoptotic and proliferative effects on β cells, suggesting its potential utility as an adjunct in islet transplantation therapies.[249]

While conclusive evidence linking RuV to PI3K-pathway dysregulation in autoimmune disease is still lacking, available data indicate that both factors may contribute to disease progression. Investigating the interplay among RuV infection, PI3K signaling, and autoimmunity may provide insights into disease mechanisms and inform novel therapeutic approaches. Continued research will be necessary to clarify these complex relationships and to determine their clinical relevance.

2.7. SARS-CoV-2

SARS-CoV-2, a member of the *Coronaviridae* family, has caused the global COVID-19 pandemic, affecting millions of individuals worldwide since its emergence in late 2019. This virus is composed of four structural proteins—spike, envelope, membrane, and nucleocapsid—and a single-stranded positive-sense RNA genome.[250] While the primary manifestation of SARS-CoV-2 infection is respiratory illness, emerging evidence suggests that the virus can also induce a range of autoimmune disorders through complex mechanisms involving molecular mimicry (where viral proteins resemble human antigens), epitope spreading (exposure of hidden self-antigens), and bystander activation (non-specific T-cell stimulation).[251] These mechanisms have been implicated in the emergence of conditions, such as GBS,[82] multisystem inflammatory syndrome in children,[252] autoimmune thyroiditis (AT),[126] APS,[83] and ITP.[83]

Central to the pathogenesis of SARS-CoV-2 infection is the viral S protein, which mediates host cell infection by binding to the angiotensin-converting enzyme 2 receptors on the cell surface.[253] This binding event triggers a cascade of intracellular signaling pathways, including the PI3K-AKT-mTOR pathway, which has been shown to promote viral replication and enhance the severity of COVID-19.[127] Targeting mTORC1, a key component of

the PI3K-AKT-mTOR pathway, has been proposed as a potential therapeutic strategy to suppress the metabolic reprogramming induced by the virus, thereby inhibiting disease progression.[254] The PI3K-AKT-mTOR pathway also plays a crucial role in modulating the immune response during SARS-CoV-2 infection. Activation of this pathway promotes protein synthesis, inhibits apoptosis, and enhances cytokine release, all contributing to the development of an autoimmune storm.[128] This inflammatory cascade is further exacerbated by the viral open reading frame 3a (ORF3a) protein, which upregulates miR-155 to suppress SHIP1, a suppressor of the PI3K pathway by dephosphorylating PtdIns(3,4,5)P_3.[129,130] This suppression enhances the production of PtdIns(3,4,5)P_3, which activates AKT and NF-κB, leading to the amplification of pro-inflammatory cytokines, such as IL-6 and TNF-α. These cytokines are key drivers of the hyperinflammatory state observed in severe COVID-19 cases and may contribute to the development of autoimmune disorders.[131]

Recent studies have also identified phosphoinositide kinase (PIK)FYVE, a PtdIns3P 5-kinase,[2] as a potential therapeutic target.[132] PIKFYVE inhibitors have been shown to effectively block viral fusion with endosomal membranes, preventing the release of the virus into the cytoplasm and thus inhibiting SARS-CoV-2 infection. This suggests that targeting specific components of the PIP signaling pathway may provide a novel approach to combating COVID-19.[132]

Notably, in addition to the PIP signaling pathway, the sphingolipid signaling pathway also plays a significant role in SARS-CoV-2 infection. Ceramide can facilitate viral entry and release by modulating membrane fluidity, making it easier for the virus to infect host cells. Conversely, sphingosine-1-phosphate has been shown to suppress viral infection and replication by regulating inflammatory responses and promoting cell survival.[255] This highlights the complex interplay between lipid signaling pathways and viral pathogenesis.

In conclusion, the PIP signaling pathway, particularly the PI3K-AKT-mTOR axis, plays a pivotal role in SARS-CoV-2 infection by promoting viral replication and driving autoimmune and inflammatory responses (Figure 4). Targeting this pathway offers significant therapeutic potential for mitigating COVID-19 severity and preventing associated autoimmune complications. Further research on the interplay between viral proteins and host signaling pathways is essential for developing effective treatments.

2.8. Theiler's murine encephalomyelitis virus

Theiler's murine encephalomyelitis virus is a naturally occurring picornavirus that infects rodents and is widely used as an experimental model for studying virus-triggered autoimmune demyelinating diseases, particularly MS.[84,85,256] In the development of TMEV-induced demyelinating disease (TMEV-IDD)—a well-established model that mimics aspects of MS—initial viral infection of brain endothelial cells plays a pivotal role in disease initiation.[133]

Research has indicated that autoantibodies may intensify the inflammatory cascade during TMEV-IDD, highlighting the contribution of immune-mediated mechanisms to demyelination.[257] The brain endothelium is central to this pathological process. Cyclooxygenase-2 (COX-2), an enzyme known to mediate inflammation in central nervous system (CNS) disorders, including MS, is expressed by brain endothelial cells and has been implicated in TMEV pathology.[258] Inflammatory cells, such as macrophages and microglia, in active demyelinating lesions—as well as degenerating oligodendrocytes—also express COX-2, contributing to elevated levels of COX-derived prostaglandins observed in the CNS of MS patients.[259,260]

Emerging data suggest that cannabinoids may help mitigate the progression of TMEV-IDD, potentially through signaling pathways involving PIPs.[258] One such example is the synthetic cannabinoid agonist WIN 55212-2, which has been shown to activate the PI3K-AKT signaling axis, subsequently increasing the expression of COX-2 and prostaglandin E2. This upregulation alleviates disease symptoms in TMEV models by modulating cerebral blood flow and dampening intracerebral immune responses.[133]

Autoimmune disorders driven by TMEV have profound effects on neurological and psychological health. Targeting the PI3K signaling pathway may offer promising strategies for preventing or treating these conditions. Ongoing research into this pathway could unlock novel therapeutic options and deepen our understanding of virus-induced autoimmune diseases.

3. Discussion and future perspectives

The intricate relationship between viral infections and autoimmune diseases has long been a focal point in immunological research. This review delves into the pivotal role of PIP signaling in this complex interplay, uncovering how viruses exploit PIP pathways to facilitate their lifecycle while simultaneously triggering autoimmune responses.

The functional specialization of individual PIP species and their regulatory enzymes underpins their consequential roles in immune regulation beyond generic signaling cascades. PtdIns4P, concentrated at the Golgi and endosomal membranes, governs vesicular trafficking and organelle identity. Its exploitation by viruses, such as CVB and HCV (via PI4KIIIα activation by HCV NS5A),

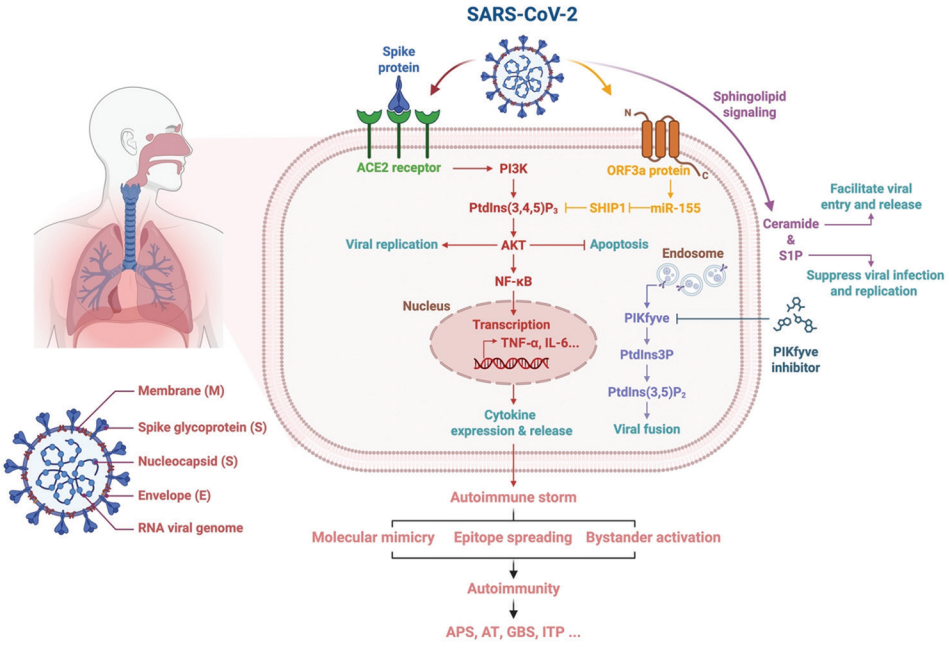

Figure 4. Key lipid signaling pathways in SARS-CoV-2 pathogenesis and autoimmunity. This schematic depicts key host signaling pathways exploited by SARS-CoV-2 to drive pathogenesis and autoimmune complications. SARS-CoV-2 infection hijacks host lipid signaling pathways, primarily the PI3K-AKT-mTOR cascade, to promote viral replication, inhibit apoptosis, and drive pro-inflammatory cytokine release (TNF-α, IL-6), contributing to a hyperinflammatory "autoimmune storm." Viral proteins like ORF3a further enhance PI3K signaling by suppressing PtdIns(3,4,5)P_3 phosphatase SHIP1 via miR-155. Concurrently, sphingolipid signaling influences infection: ceramide facilitates viral entry/release, while S1P suppresses it. Molecular mimicry, epitope spreading, and bystander activation link infection to autoimmune disorders (such as APS, AT, GBS, and ITP). Targeting key nodes in these pathways, such as mTORC1 or PIKFYVE (blocking endosomal viral fusion), represents a promising therapeutic strategy to mitigate the inflammatory state. Created with BioRender.com. Chen, M. (2025) https://BioRender.com/eyln0kh.

Abbreviations: ACE: Angiotensin-converting enzyme 2; AKT: Protein kinase B; APS: Antiphospholipid syndrome; AT: Autoimmune thyroiditis; GBS: Guillain-Barré syndrome; IL: Interleukin; ITP: Immune thrombocytopenia; mTOR: Mammalian target of rapamycin; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; ORF3a: Open reading frame 3a; PI3K: Phosphatidylinositol 3-kinase; PIKFYVE: Phosphoinositide kinase, Fab1, YOTB, Vac1, and EEA1; PtdIns(3,4,5)P_3: phosphatidylinositol 3,4,5-trisphosphate (PtdIns[3,4,5]P_3); PtdIns(4,5)P_2: Phosphatidylinositol 4,5-bisphosphate; PtdIns3P: Phosphatidylinositol 3-phosphate; PTEN: Phosphatase and tensin homolog; S1P: Sphingosine-1-phosphate; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SHIP: Src Homology 2 domain-containing inositol phosphatase; TNF: Tumor necrosis factor.

facilitates the assembly of viral replication organelles, directly linking PtdIns4P abundance to viral persistence. Conversely, PtdIns(3,4,5)P_3—a key cell membrane and nuclear resident lipid messenger—acts as a master regulator of immune cell activation by recruiting PH domain-containing effectors, such as AKT and PDK1. In autoimmunity, excessive PtdIns(3,4,5)P_3 production due to PTEN/SHIP deficiency or PI3K hyperactivation (e.g., in SLE T cells) lowers activation thresholds for BCR/TCR signaling, promoting loss of self-tolerance. Viruses, such as EBV, exacerbate this through latent proteins (LMP1/LMP2A) and miRNAs (BART7-3p) that suppress PTEN, thereby amplifying PI3K-AKT-driven inflammatory responses and bystander activation.

The spatial restriction of PIPs (e.g., nuclear PIPs modulating transcription vs. plasma membrane-endomembrane pools controlling receptor signaling) and the substrate specificity of kinases (PI3K vs. PI4K) and phosphatases (PTEN dephosphorylating PtdIns[3,4,5]P_3) explain why dysregulation of distinct PIP nodes has non-redundant consequences: PtdIns4P manipulation primarily subverts intracellular membrane dynamics for viral replication, while PtdIns(3,4,5)P_3 dysregulation directly skews immune cell fate decisions, bridging viral pathogenesis to autoimmune initiation.

Different PIP signaling pathways play distinct roles in immune regulation. Viral infections can induce markedly divergent activation patterns and immunomodulatory effects even within the same pathway. Despite their distinct tissue tropisms, diverse viruses have evolved sophisticated strategies to hijack the host PI3K-AKT signaling pathway, a pivotal regulatory hub. Our systematic analysis reveals that these pathogens employ unique molecular mechanisms to activate PI3K-AKT signaling, thereby inducing cellular changes conducive to viral replication, including apoptosis inhibition, metabolic reprogramming, and membrane

restructuring. Strikingly, different virus families have developed highly specific regulatory tactics: EBV achieves sustained pathway activation through miRNA-mediated PTEN silencing; SARS-CoV-2 induces SHIP1 degradation through ORF3a-driven miR-155 production; while HCMV demonstrates exquisite spatiotemporal control, employing distinct effector proteins during latent and lytic phases to modulate pathway activity precisely.

These differential activation patterns directly shape viral replication strategies: HCV maintains basal pathway activity to sustain persistent infection; CVB3 employs phase-specific regulation to induce autophagy, favoring viral release; and rubella virus ingeniously utilizes transient activation to protect host cells. These differential regulatory patterns lead to distinct immunopathological outcomes: Ranging from EBV-associated systemic autoimmunity to SARS-CoV-2-triggered acute neuroimmune disorders, and even to neuroprotective effects in the TMEV model. These findings collectively establish the PI3K-AKT pathway as a conserved metabolic hub essential for viral replication, and more importantly, as a decisive regulator of post-infection immune equilibrium, with outcomes critically dependent on virus-specific modulation patterns.

The shared exploitation of PIP signaling nodes by diverse viruses and their disruption of immune homeostasis present compelling therapeutic opportunities. Among these nodes, the PI3K-AKT, PI4K, and PIKFYVE pathways are particularly critical, as emerging evidence highlights their dual roles in viral pathogenesis and immune dysregulation. The PI3K-AKT pathway, a well-established target in oncology, has already yielded multiple FDA-approved inhibitors (e.g., Idelalisib, Copanlisib, Duvelisib, Alpelisib, and Umbralisib) for cancer therapy.[261] Although initially focused on oncology, PI3K inhibitors are now being explored for their potential in autoimmune diseases.[262] While no PIKFYVE inhibitors have yet reached the market, the first small-molecule inhibitor targeting PIKFYVE has advanced to a Phase 2a clinical trial (NCT05163886) for ALS. In addition, pre-clinical studies have highlighted the role of PIKFYVE inhibitors in suppressing viral infections.[263,264] In contrast, although PI4K plays a critical role in HCV infection, the development of PI4P-targeting inhibitors remains in the pre-clinical stage. These challenges underscore the need for further research to optimize the safety and efficacy of PIP-targeted therapies—particularly through isoform-selective drug design and combinatorial strategies that address both viral persistence and immune dysregulation.

While this review highlights the central role of PIP signaling at the virus-autoimmunity interface, several critical knowledge gaps and technical challenges remain. First, present research predominantly focuses on proteomic analyses of PIP regulatory proteins (particularly kinases and phosphatases) in virus-induced autoimmunity, while the spatiotemporal dynamics of individual PIP species during acute versus persistent infection remain poorly resolved. Advanced PIP biosensors enabling real-time tracking of lipid dynamics at organelle resolution are urgently needed to map viral-induced PIP rewiring in living systems.[265] Second, the field lacks isoform-selective chemical tools targeting key PIP regulators (kinases, phosphatases, transporters, and phospholipases) with optimal specificity and safety profiles, as individual PIP-metabolizing enzymes play distinct roles under specific physiological and pathological conditions.[266] Structure-guided development of inhibitors against virus-hijacked PIP nodes (e.g., HCV-NS5A-activated PI4KIIIα or EBV-suppressed PTEN) could achieve pathogen-selective disruption while preserving physiological signaling.

Moreover, existing pre-clinical studies rely heavily on cell models (particularly cancer cell lines), which poorly recapitulate systemic aspects of viral infection and autoimmunity. Tissue-specific conditional knockout models targeting PIP-modifying enzymes in virally infected hosts are crucial for establishing causal mechanisms. Finally, integrating phosphoinositide omics with proteomics and single-cell omics in human cohorts—correlating viral load, PIP flux, and autoimmune signatures—will enable patient stratification, while clustered regularly interspaced short palindromic repeats screening in human organoids can identify virus-specific PIP dependencies. Addressing these challenges will advance mechanistic insights and facilitate precision therapies that disentangle viral pathogenesis from autoimmune cascades.

4. Concluding remarks

This review bridges the understanding of PIP signaling in viral pathogenesis and autoimmune disorders, offering a comprehensive framework for future research and therapeutic development. By targeting the shared PIP-centric mechanisms, we may unlock new strategies to combat both viral infections and their autoimmune sequelae, ultimately improving patient care and outcomes.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

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Writing – review & editing: All authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Availability of data

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