Biochemical Orchestration of Viral Infections: From Cellular Entry to Host Metabolic Reprogramming

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Abstract

Viral infections are driven by tightly coordinated biochemical interactions between invading virions and host cells that determine tissue tropism, replication efficiency, and clinical outcome. This article synthesizes current knowledge on major biochemical processes underlying viral infection, from attachment and entry through genome replication, assembly, and egress, with an emphasis on host–virus interplay at the levels of signaling, cell death regulation, and metabolic reprogramming. We discuss receptor engagement, endocytosis and fusion mechanisms, innate immune sensing via pattern-recognition receptors, and downstream interferon signaling and cytokine responses. We then examine how viruses manipulate apoptotic and pyroptotic pathways and remodel host metabolism, including glycolysis, nucleotide biosynthesis, and lipid synthesis, to support replication while evading innate immunity. Finally, we highlight emerging therapeutic strategies that target host metabolic and signaling nodes rather than viral proteins alone, offering broad-spectrum antiviral potential.

Keywords: viral infection, host–virus interactions, innate immunity, apoptosis, pyroptosis, cellular metabolism, glycolysis, nucleotide biosynthesis

Introduction

Viral infections represent paradigmatic examples of how compact genomes can hijack complex host biochemical networks to ensure replication and transmission. Viruses are obligate intracellular parasites that must attach to specific cell surface receptors, enter cells, exploit macromolecular synthesis machinery, and exit in ways that preserve their structural integrity while avoiding immediate immune elimination. The constellation of receptors, co-receptors, proteases, and intracellular factors expressed in a given tissue defines viral tropism, which in turn shapes pathogenesis and clinical phenotypes.[1][2][3][4][5]

At the biochemical level, every stage of the viral life cycle depends on orchestrated interactions with host proteins and metabolites. Attachment requires high-affinity receptor binding; entry often uses endocytic pathways or direct fusion; and replication depends on host nucleotide pools, membrane lipids, and ATP, which are frequently rewired by viral proteins. In parallel, host cells detect viral nucleic acids through

pattern-recognition receptors and mount interferon-driven antiviral responses that reprogram transcription, translation, and metabolism, sometimes culminating in programmed cell death to limit viral spread.[6][7][8][9][10][11][12][13]

Recent work highlights metabolic enzymes and pathways as central arbiters of the infection outcome, acting both as facilitators of viral replication and as effectors of innate immunity. Understanding these biochemical processes in an integrated manner is essential for rational antiviral drug design, especially for host-directed therapies that might circumvent rapid viral mutation. This article therefore reviews key biochemical events during viral infection, focusing on entry, innate sensing, cell death control, and metabolic reprogramming, and discusses how these processes can be therapeutically exploited.[7][8][3][10][12][6]

Methods

This narrative review integrates primary research articles, reviews, and authoritative textbooks retrieved from biomedical databases and curated open-access resources. Sources were identified using combinations of terms such as “viral entry biochemistry”, “host cell signaling in viral infection”, “interferon response”, “virus induced apoptosis pyroptosis”, and “metabolic reprogramming in virus infected cells”. Inclusion favored recent mechanistic and translational studies in peer-reviewed journals addressing: (1) receptor-mediated viral entry and intracellular trafficking, (2) innate immune sensing and interferon signaling, (3) regulated cell death pathways in viral infection, and (4) alterations in glucose, nucleotide, and lipid metabolism in infected cells. Conceptual synthesis emphasized common biochemical themes across different virus families rather than exhaustive coverage of individual pathogens.[1][6][7][8][3][9][10][12][13]

Results

Biochemical Basis of Viral Entry and Early Infection

Viral infection begins with specific binding of virions to host cell receptors, often accompanied by engagement of co-receptors and host proteases that together define cellular susceptibility. Expression and co-expression patterns of these molecules at the tissue level largely determine viral tissue tropism and disease manifestations. For example, co-expression of the receptor ACE2 and the serine protease TMPRSS2 in respiratory epithelial cells underlies efficient SARS-CoV-2 entry into the lung, while ACE2 expression in enterocytes, endothelial cells, and renal tubular cells explains gastrointestinal, vascular, and renal involvement. Many viruses similarly exploit nutrient transporters and other metabolic receptors for attachment and internalization, blurring the line between signaling and metabolic entry points.[1][7][3][10]

After attachment, viruses enter cells via endocytic or non-endocytic mechanisms that are tightly regulated by pH, membrane curvature, and host trafficking machinery. Enveloped viruses frequently undergo receptor-mediated endocytosis followed by low-pH–triggered fusion in endosomes or direct fusion at the plasma membrane when activated by cell surface proteases. Non-enveloped viruses often rely on receptor-

induced conformational changes that destabilize host membranes and facilitate genome translocation into the cytosol. Internalized virions exploit cytoskeletal motors, Rab GTPases, and vesicular trafficking pathways to reach replication-competent compartments such as the nucleus or the perinuclear cytoplasm, with precise routing modulating replication efficiency and immune detection.[2][14][3][4][5]

Biochemical interactions between viral proteins and host factors extend to the very first steps of uncoating and genome release. Host chaperones, proteases, and even metabolic enzymes can assist disassembly of the capsid or fusion pore formation, whereas antiviral factors such as cholesterol-25-hydroxylase convert cholesterol to 25-hydroxycholesterol, which inhibits membrane fusion and thereby restricts viral entry. These entry-proximal processes offer attractive targets for antiviral interventions, particularly host-targeted agents that block receptor function, protease activation, or fusion-supporting lipid remodeling.[7][3][10]

Innate Sensing and Interferon-Mediated Biochemical Responses

Once viral genomes and replication intermediates accumulate, host cells detect them through pattern-recognition receptors (PRRs) that recognize non-self nucleic acid features. Endosomal Toll-like receptors such as TLR3 and TLR7 detect double-stranded and single-stranded viral RNA, while cytosolic sensors including RIG-I and MDA5 recognize specific RNA motifs and longer double-stranded RNA; additional DNA sensors survey viral DNA in the cytoplasm. Activation of these PRRs initiates signaling cascades that converge on kinases such as TBK1 and transcription factors including interferon regulatory factors (IRF3, IRF7) and NF-κB, leading to robust type I interferon (IFN-α/β) and pro-inflammatory cytokine production.[6][9][11][13]

Secreted type I interferons bind to IFN receptors on infected and neighboring cells, triggering the JAK-STAT signaling pathway. This culminates in the transcription of dozens to hundreds of interferon-stimulated genes (ISGs) that collectively establish an antiviral state by inhibiting various stages of the viral life cycle, altering cell survival, and modulating protein translation. ISGs can directly degrade viral RNA, block entry or budding, or modify lipid and nucleotide metabolism to create a hostile environment for replication. Interferon signaling also interfaces with tissue repair and adaptive immunity by enhancing antigen presentation and shaping T and B cell responses, thereby connecting early biochemical sensing to systemic immune control.[7][9][10][12][13][6]

Interestingly, interferon-driven pathways can themselves reprogram cellular metabolism in ways that both support and constrain viral replication. For instance, interferon-mediated induction of enzymes such as nicotinamide phosphoribosyltransferase (NAMPT) replenishes cellular NAD to fuel ADP-ribosylation–dependent antiviral mechanisms, while inducible nitric oxide synthase (iNOS) generates nitric oxide that S-nitrosylates viral proteins, impairing their function. These metabolic effectors exemplify how innate immunity and biochemical

fluxes are intertwined, with viruses often evolving countermeasures to subvert or hijack these same pathways.[8][10][12][7]

Regulated Cell Death Pathways in Viral Infection

Programmed cell death represents a crucial biochemical strategy by which the host can limit viral spread, yet many viruses both trigger and evade death pathways depending on the phase of infection. Mitochondria-mediated (intrinsic) apoptosis is heavily implicated in viral pathogenesis, with type I interferon responses promoting either elimination of infected cells or controlled apoptosis to curtail replication. For example, the IRF-3/Bax pathway can induce mitochondrial outer membrane permeabilization and caspase-9 activation in response to viral RNA, thereby restricting viral propagation in vitro and in vivo. Conversely, numerous viruses encode proteins that block caspase activation, inhibit pro-apoptotic Bcl-2 family members, or sequester p53, thereby preventing premature cell death and allowing time for virion production.[9][11][13]

In addition to apoptosis, inflammatory forms of cell death such as pyroptosis have emerged as key determinants of the host response to respiratory and systemic viral infections. Influenza A virus, for instance, can induce apoptosis early in infection but shift toward pyroptosis at later stages, with this switch regulated by type I interferon signaling in respiratory epithelial cells. Pyroptosis, often mediated by caspase-1 and gasdermin D activation downstream of inflammasomes, results in membrane pore formation, cell lysis, and release of pro-inflammatory cytokines such as IL-1β, amplifying local inflammation while potentially limiting viral spread. Interferon signaling also upregulates cell death-inducing ISGs and members of the TNF-related apoptosis-inducing ligand (TRAIL) pathway, linking antiviral cytokine responses directly to death receptor signaling.[15][13]

The balance between apoptosis, pyroptosis, and survival is further modulated by viral interference with mitochondrial dynamics, reactive oxygen species production, and anti-apoptotic factors like Bcl-xL. Some viruses deliberately engage apoptosis late in infection to facilitate virion release and immune evasion, whereas others suppress death pathways to establish persistence. These findings underscore regulated cell death as a dynamic biochemical battlefield where host and virus continuously remodel signaling networks to favor their respective survival or clearance.[11][13][15][9]

Metabolic Reprogramming in Virus-Infected Cells

One of the most striking biochemical consequences of viral infection is extensive remodeling of host cell metabolism to satisfy the bioenergetic and biosynthetic needs of viral replication. Viral proteins interact with key glycolytic enzymes and signaling nodes to enhance glycolytic flux, often mimicking or co-opting oncogenic pathways such as PI3K–AKT–mTOR and HIF-1α signaling. Many viruses increase glucose uptake by upregulating or relocalizing glucose transporters such as GLUT1 and GLUT4 through RAS–PI3K–AKT or related pathways, thereby boosting substrate availability for ATP production and biosynthesis. Increased glycolysis supports nucleotide, amino acid, and lipid synthesis required for viral genome replication and

assembly, while lactate production may also modulate local immune responses.[8][10][12]

Detailed studies demonstrate that diverse viruses elevate expression and activity of glycolytic enzymes, including hexokinase and 6-phosphofructo-1-kinase (PFK-1), correlating with increased glucose consumption, lactate production, and ATP generation. For instance, Mayaro virus infection of Vero cells leads to approximately two-fold increases in glucose consumption, lactate secretion, and PFK activity, whereas adenovirus and rhinovirus infections enhance GLUT1 expression and glycolytic enzyme transcription through PI3K-regulated mechanisms. These metabolic changes may be driven by viral proteins that directly activate transcription factors such as Myc or stabilize HIF-1α, promoting expression of glycolytic genes and facilitating a Warburg-like metabolic phenotype in infected cells.[10][8]

Metabolic Reprogramming Modalities and Representative Examples

Process	Representative viruses	Mechanism and consequence (selected examples)
Glycolysis upregulation	Adenovirus, rhinovirus, Mayaro virus, HHV-6A	PI3K–AKT–mTOR and Myc activation, increased GLUT1/GLUT4 and glycolytic enzymes, higher glycolytic flux supporting replication[8][10]
Nucleotide synthesis activation	SARS-CoV-2, other RNA viruses	Activation of CAD and CTP synthetase, boosting de novo pyrimidine and CTP synthesis to expand nucleotide pools for viral genomes[7]
Lipid and fatty acid synthesis	HCV, SARS-CoV-2, HIV	Induction of fatty acid synthesis and lipid droplets, providing membranes and scaffolds for replication complexes and assembly[7][10]
Antiviral metabolic responses	Multiple	IFN-driven induction of NAMPT, iNOS, and cholesterol-25-hydroxylase to support NAD –dependent defenses, NO production, and fusion inhibition[7][10][12]

Nucleotide and lipid metabolism are also heavily rewired during infection. SARS-CoV-2, for example, activates the multifunctional enzyme CAD to enhance de novo pyrimidine synthesis and uses accessory proteins such as ORF7b and ORF8 to stimulate CTP synthetase 1, thereby expanding CTP pools while concurrently suppressing interferon production. Pharmacologic inhibition or genetic depletion of CAD depletes nucleotide pools, boosts antiviral inflammatory responses, and reduces viral replication in ex vivo and in vivo models, highlighting nucleotide metabolism as an actionable host target. Parallel upregulation of fatty acid synthesis and lipid droplet formation, exemplified in infections with HCV and SARS-CoV-2, supplies membranes

for replication organelles and supports trafficking of viral components to the plasma membrane.[7][10]

Importantly, metabolic enzymes can act as antiviral effectors rather than merely serving as resources for the virus. Cholesterol-25-hydroxylase converts cholesterol to 25-hydroxycholesterol, which blocks membrane fusion and inhibits viral entry, while interferon-induced NAMPT and iNOS, as noted above, enhance NAD availability and nitric oxide production to constrain replication. Thus, metabolic reprogramming during viral infection reflects a complex interplay between viral demands and host defense programs, with the net outcome determined by the balance of pro-viral and antiviral metabolic nodes engaged.[12][7][8][10]

Discussion

The biochemical processes that underlie viral infections reveal a multilayered host–pathogen interaction in which entry receptors, signaling cascades, cell death pathways, and metabolic circuits form an integrated network rather than independent modules. Tissue tropism and early infection dynamics are governed not only by the presence of specific receptors but by the co-expression of proteases, co-receptors, and metabolic entry factors, as exemplified by ACE2 and TMPRSS2 co-expression in SARS-CoV-2–targeted tissues. This combinatorial control implies that therapeutic strategies focusing on a single entry factor may be insufficient and that multi-target approaches, including protease inhibitors and lipid-modulating agents, may better disrupt early steps of infection.[1][7][3][10]

Innate immune sensing and interferon signaling emerge as central biochemical defenses that are deeply intertwined with cell metabolism and survival decisions. PRR activation rapidly induces type I interferon, which reprograms gene expression to restrict viral replication, modulate translation, and induce antiviral metabolic enzymes. Yet many viruses encode antagonists of PRR signaling or interferon pathways, enabling them to exploit the host transcriptional machinery while dampening antiviral effector programs. Understanding the structural and kinetic features of these antagonistic interactions may enable the design of small molecules or biologics that restore interferon responsiveness without causing excessive immunopathology.[6][7][9][11][13]

Regulated cell death is another critical biochemical arena where host and virus exert opposing pressures. While apoptosis and pyroptosis can limit viral dissemination, excessive or misdirected cell death contributes to tissue damage in diseases such as severe influenza and COVID-19. The demonstration that type I interferon signaling can bias respiratory epithelial cells toward pyroptosis at later stages of influenza infection raises the possibility that modulating specific death pathways, rather than globally suppressing inflammation, could mitigate pathology while preserving antiviral effects. Conversely, strategies that selectively enhance IRF-3/Bax-mediated apoptosis in infected cells may help eliminate viral reservoirs, provided off-target toxicity can be minimized.[15][9][11][13]

Perhaps the most rapidly evolving insight concerns metabolic reprogramming as both a vulnerability and a defense mechanism. The repeated observation that viruses drive glycolytic flux, nucleotide synthesis, and lipid generation via canonical growth pathways such as PI3K–AKT–mTOR, HIF-1α, and Myc suggests that metabolic checkpoint inhibitors and anti-cancer metabolic drugs might be repurposed as antivirals with broad-spectrum activity. At the same time, the dual roles of metabolic enzymes—supporting viral replication while mediating interferon-induced antiviral effects—underscore the need for precise targeting based on cell type, infection stage, and virus species. For instance, inhibiting CAD or CTP synthetase might effectively limit SARS-CoV-2 replication but could also alter immune cell function if applied systemically.[7][8][10][12]

Future research should prioritize systems-level approaches that integrate metabolomics, phosphoproteomics, and single-cell transcriptomics to map the dynamic biochemical states of infected cells across tissues and time points. Such integrative profiling will help identify nodal points where small perturbations can shift the balance decisively toward viral clearance with minimal host damage. Additionally, comparative analyses across virus families may distinguish conserved host dependencies from virus-specific adaptations, guiding the development of host-targeted antivirals with both breadth and acceptable safety profiles.[8][3][10][12][7]

Conclusion

Viral infections unfold as a complex, highly regulated choreography of biochemical events in which small, genetically economical pathogens commandeer sophisticated host machinery to replicate and spread. From the moment of receptor engagement and membrane fusion, through innate sensing and interferon-driven reprogramming, to the decision between cell survival, apoptosis, or pyroptosis, every step reflects a dynamic tug-of-war between host defense and viral exploitation. Central to this contest is the reconfiguration of cellular metabolism, where glycolysis, nucleotide biosynthesis, and lipid production are retuned to meet viral demands even as immune-driven metabolic enzymes attempt to push the system back toward an antiviral state.

Viewing viral infection through this integrated biochemical lens highlights several promising therapeutic avenues. Targeting host entry factors, modulating interferon and death signaling to favor controlled clearance, and selectively inhibiting virus-dependent metabolic pathways all hold potential to complement or, in some settings, outperform direct-acting antivirals. As high-resolution, multi-omic data increasingly illuminate these interconnected networks, biochemistry will remain at the heart of understanding and ultimately controlling viral diseases in both acute and chronic settings.

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