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CELLULAR PATHWAY MODULATION BY CORONAVIRUSES: REGULATION OF AUTOPHAGY, APOPTOSIS, AND RELATED HOST PROCESSES

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Abstract

Coronaviruses have developed complex strategies to manipulate host cell pathways, in this way facilitating viral replication and enabling immune evasion. This review focuses on the interactions between coronaviruses and host cellular processes, especially on the modulation of autophagy, apoptosis, and additional regulatory pathways, including endoplasmic reticulum (ER) stress responses, interferon signaling, and lipid metabolism. Studies have shown that coronaviruses promote both the initiation of autophagy and inhibition of autophagic flux, resulting in the formation of non-degradative membrane compartments that support viral replication and limit immune detection of viral components. Furthermore, coronaviruses have a dual control over apoptotic signaling by both inducing and suppressing programmed cell death through mitochondrial pathways, caspase activation, and death receptor–mediated mechanisms. Clarification of these virus–host interactions provide important insights into coronavirus pathogenesis and identifies potential therapeutic targets, including autophagy modulators, kinase inhibitors, and agents targeting ER stress pathways and mitochondrial dysfunction.

Key words: cellular pathways, coronavirus, apoptosis, autophagy

INTRODUCTION

Coronaviruses constitute a large and diverse group of enveloped viruses with positive-sense RNA genomes that are responsible for respiratory infections that may evolve to severe and often fatal disease. The repeated emergence of highly pathogenic coronaviruses—SARS-CoV in 2003, MERS-CoV in 2012, and SARS-CoV-2 in 2019—has highlighted the importance of explaining virus–host interactions at the cellular and molecular levels (Fung and Liu, 2019). An important feature of these viruses is their capacity to remodel host cellular pathways in ways that favor viral replication and suppress the immune surveillance.

A central aspect of coronavirus pathogenesis is the manipulation of host pathways, particularly the tightly regulated processes of autophagy and apoptosis. Both pathways are critical for maintaining cellular homeostasis and coordinating host defense responses. Autophagy assures the cellular quality control and innate immunity by directing intracellular pathogens toward lysosomal degradation, whereas apoptosis eliminates infected cells to restrict viral dissemination (Miller et al., 2020; Cheng et al., 2024). Coronaviruses have gained the ability to escape from these protective mechanisms.

Recent studies regarding the molecular virology have revealed that coronaviruses can manipulate the host mechanisms beyond autophagy and apoptosis. Viral infection perturbs endoplasmic reticulum (ER) homeostasis, interferon signaling cascades, lipid metabolic pathways, and mitochondrial function (Singh et al., 2021). These alterations are produced by both structural and nonstructural viral proteins that interact with host factors, modulate intracellular signaling networks, and target important immune regulators for degradation (Zhang et al., 2025; Zhi et al., 2025).

Manipulation of the Autophagy Pathway

Autophagy represents one of the principal cellular pathways used by coronaviruses to support replication and evade the effectors of the immune system. This process involves the isolation of cytoplasmic material within double-membrane autophagosomes, which further fuses with lysosomes that will degrade the content under the action of digestive lysosomal enzymes. In normal conditions, autophagy contributes to antiviral defense through xenophagy, that eliminates the invading pathogens in a selective manner. Coronaviruses, however, have adapted to exploit autophagic machinery for their own benefit (Miller et al., 2020). The viral infection stimulates early

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autophagy signaling while blocking late stages of autophagy, leading to the accumulation of immature autophagic structures. This incomplete process is characterized by elevated levels of LC3-II and p62, reflecting impaired cargo degradation (He et al., 2022; Wang et al., 2025).

Such dysregulation creates a replication-permissive intracellular environment while preventing effective antiviral degradation. A hallmark of coronavirus infection is the generation of double-membrane vesicles that function as specialized replication organelles. These structures originate primarily from ER membranes and are closely associated with components of the autophagy machinery, although their formation does not require complete autophagic flux (Miller et al., 2020; Zhang et al., 2025). Viral nonstructural proteins such as nsp3, nsp4, and nsp6 cooperate to induce extensive membrane remodeling, giving rise to protected compartments that shield viral RNA from cytosolic detectors and provide a scaffold for replication complex assembly (Liang et al., 2022).

For example, the SARS-CoV-2 infection is characterized by a pronounced imbalance between autophagy initiation and completion. While the first steps of autophagy signaling is activated, the last steps including autophagosome-lysosome fusion are inhibited (He et al., 2022). This dysregulation involves suppression of key autophagy regulators such as AMPK (adenosine monophosphate-activated protein kinase), ULK1 (Unc-51 like autophagy activating kinase 1), and Beclin-1, thereby limiting efficient autophagic execution. Concurrently, activation of the AKT1/SKP2 pathway promotes degradation of essential autophagy components, further impairing flux completion. The resulting accumulation of intermediates supports viral replication without progressing to lysosomal degradation (He et al., 2022; Wang et al., 2025).

Multiple viral proteins contribute to autophagy modulation. Accessory proteins ORF3 and ORF3a play crucial roles in reorganizing intracellular membranes and inducing selective forms of autophagy. ORF3 promotes ER-specific autophagy through interactions with FAM134B and the HMGB1–Beclin-1 complex, while ORF3a cooperates with nsp3/4/6 to redirect lipid droplets via microlipophagy, supplying substrates for replication organelle formation (Zhang et al., 2025).

Viral proteases, including 3CLpro and PLpro, further enhance autophagy signaling by cleaving or modifying host regulatory proteins (He et al., 2022; Zhi et al., 2025). Beyond the autophagy disruption, coronaviruses employ selective autophagy to target specific immune components for degradation. Through the coordinated recruitment of ubiquitin ligases and autophagy receptors, viral infection directs antiviral signaling molecules toward lysosomal or proteasomal elimination. For instance, nsp14-mediated degradation of the adaptor protein TRAF3 (Tumor necrosis factor receptor-associated factor 3) suppresses type I interferon signaling in betacoronaviruses by disassembling a critical immune signaling node (Shin et al., 2020).

ORF3-induced ERphagy also triggers ER stress and inflammatory signaling, contributing to disease pathology while limiting antiviral protein synthesis. These mechanisms allow coronaviruses to improve the intracellular conditions for enhancing replication while limiting host defense systems.

Although the way in which coronaviruses disrupt autophagy is conserved across coronaviruses, some differences exist among species. SARS-CoV-2 exhibits pronounced inhibition of autophagic flux coupled with ORF3-dependent ERphagy, while MERS-CoV displays more autophagy variations dependent on viral strain and cell type (Miller et al., 2020; Zhang et al., 2025).

Regulation of Apoptosis by Coronaviruses

Studies showed that coronaviruses have the ability to promote or inhibit apoptosis, controlling in this way the host cell survival. During early infection stages, apoptosis is suppressed and that act permits viral replication, whereas later activation facilitates viral release and tissue dissemination (Yapasert et al., 2021; Li et al., 2025). The suppression and activation of apoptosis is influenced by viral protein expression levels, infection stage, cell type, and host immune status, with dysregulated apoptosis contributing to inflammation and tissue injury in severe disease (Cheng et al., 2024).

Coronavirus infection activates intrinsic apoptotic signaling through mitochondrial damage. Viral proteins compromise mitochondrial membrane integrity, that leads to cytochrome c release and caspase activation. Elevated mitochondrial reactive oxygen species further stimulates stress-activated kinases, including JNK (c-Jun N-terminal kinase) and p53, amplifying apoptotic signaling (Yapasert et al., 2021; Li et al., 2025). Excessive mitophagy is linked to metabolic failure leading to inflammatory and apoptotic processes (Wang et al., 2025).

Both initiator and effector caspases are activated during coronavirus infection. Studies showed that caspase-8 and caspase-9 initiate apoptotic signaling, while caspase-3 and caspase-7

execute cellular dismantling. Alterations in Bcl-2 family protein balance favor pro-apoptotic signaling, as studies show increased Bax/Bcl-2 ratios in infected cells (Zhi et al., 2025).

Some viral proteins can directly promote apoptosis. ORF3a induces cell death through ion channel formation, ER stress, and caspase activation. ORF7a and nsp1 also contribute to apoptotic signaling while suppressing host gene expression and intensifying cellular damage (Cheng et al., 2024).

To increase the replication period, coronaviruses activate survival pathways such as NF-κB signaling, which induces anti-apoptotic gene expression delaying cell death, allowing efficient viral progeny production before apoptosis finally occurs (Yapasert et al., 2021).

Coronavirus-induced apoptosis interconnects with additional regulated cell death pathways, including pyroptosis and necroptosis. In severe infections, combined activation of apoptosis, pyroptosis, and necroptosis—referred to as PANoptosis—leads to hyperinflammation and extensive tissue damage, particularly in COVID-19 (Li et al., 2022).

Endoplasmic Reticulum Stress

The endoplasmic reticulum (ER) is the primary site of coronavirus replication and assembly. As a result, the coronavirus infection induces ER stress and activates the unfolded protein response (Fung and Liu, 2014). SARS-CoV-2 ORF3a promotes ER-selective autophagy through FAM134B and HMGB1–Beclin1, linking ERphagy to ER stress and inflammatory signaling. While controlled unfolded protein response activation may enhance viral replication by supporting protein folding and membrane biogenesis, sustained signaling drives apoptosis and inflammation, contributing to severe disease (Fung and Liu, 2014).

Interferon Signaling and Innate Immune Suppression

Coronaviruses block early antiviral signaling and permit viral replication before adaptive immune activation. Viral proteins induce degradation of immune adaptors, such as nsp14-mediated TRAF3 depletion via autophagy and proteasomal pathways (Shin et al., 2020). In addition, viral proteases (such as 3CLpro, PLpro) cleave signaling regulators, disrupting MAVS/TBK1 and NF-κB activation (Zhi et al., 2025), while other viral factors sequester or mislocalize immune components (Fung and Liu, 2019).

Lipid Metabolism

Studies showed that coronaviruses disturb the lipid metabolism also. SARS-CoV-2 ORF3a collaborates with nsp3/4/6 to induce microlipophagy, supplying fatty acids necessary for membrane biosynthesis (Zhang et al., 2025). Recruitment of phosphatidylinositol 4-kinase IIIβ (PI4KB) generates PI4P-enriched membrane domains that enhance replication organelle formation and protein recruitment. Coronaviruses exploit multiple membrane sources, including the ER, Golgi apparatus, and lipid droplets (Zhang et al., 2025; Liang et al., 2022).

Mitochondrial Modulation

Coronavirus infection remodels mitochondrial function beyond its role in apoptosis. Viral replication alters mitochondrial fusion–fission mechanisms, the energy produced being used by the processes involved in virus replication instead of normal cellular metabolism (Singh et al., 2021). In parallel, interference with mitochondrial antiviral signaling protein (MAVS) through mitophagy, proteolytic cleavage, or direct interactions suppresses interferon signaling (Shin et al., 2020; Singh et al., 2021). Persistent mitochondrial dysfunction may contribute to long-term metabolic disturbances associated with post-COVID syndromes (Singh et al., 2021).

Inflammatory Responses

Organelle stress and impaired autophagic flux promote activation of the NLRP3 inflammasome during coronavirus infection. Viral pathogen-associated signals and damage-associated molecules from stressed mitochondria trigger caspase-1 activation and IL-1β/IL-18 maturation (Li et al., 2022). Excessive inflammasome activity contributes to hyperinflammation, cytokine storm, and acute respiratory distress syndrome in severe COVID-19. Accordingly, NLRP3 inhibition, including agents such as MCC950, has emerged as a potential therapeutic approach (Li et al., 2022).

CONCLUSIONS

Coronaviruses have developed a complicated network of strategies to control host cell pathways central to survival, immunity, and metabolism. Through coordinated manipulation of autophagy, apoptosis, ER and mitochondrial stress, innate immune signaling, and lipid metabolism, these viruses built for themselves replication-permissive niches while evading host defenses. Studying the

effects of coronavirus replication into the host cell and how these modulate the cellular pathways may provide useful information for developing protective strategies against both current and emerging coronaviruses.

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