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International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Coronavirus (SARS-CoV-2) Infection and Pathogenicity: The Roles of Cell Death and Autophagy

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DOI: https://doi.org/10.55248/gengpi.4.1223.0111

ABSTRACT

SARS-CoV-2, also known as COVID-19 (coronavirus disease 2019), is a serious threat to public health, the global economy, and society at large. In addition to inducing immunological and inflammatory reactions, viral infections also lead to programmed cell death in infected cells, which is essential for preserving regular cell function. Several cell death pathways have been better characterized over the last few decades. It is widely accepted that both cell autophagy and death are critical for preserving host homeostasis and playing a role in the etiology of illness. Viruses may employ a range of strategies to precisely regulate cell death. There is growing evidence that suggests the nature of these mechanisms during virus infection is dualistic. On the one hand, the virus is stopped from multiplying and spreading by killing off infected cells. On the other hand, dysregulated cell death leads to abnormal immune response and unmanageable cell damage. Meanwhile, viruses can employ cell autophagy to their advantage for immune evasion, extracellular release, and replication. Although the relationship between SARS-CoV-2, cell death, and cell autophagy is not fully understood, but previous research on SARS-CoV and MERS-CoV can provide some conclusions. Proper study of pathology and underlying mechanisms is crucial for developing effective preventative and treatment plans for this dangerous illness.

Key words: autophagy; cell death; homeostasis; SARS-CoV-2; pathology

Introduction

Cell autophagy and death are well recognized as essential cellular processes that are vital to both disease etiology and homeostasis maintenance. According to earlier research, viruses may be able to carefully control cell death in a variety of cell types by utilizing a variety of methods **[1].** There is increasing evidence to suggest that these processes during virus infection are like two-edged swords **[2, 3].** The removal of contaminated cells by cell death, on the one hand, prevents the virus from replicating and spreading. On the other side, aberrant immune response and uncontrollable cell damage result from dysregulated cell death. In the meantime, viruses have the ability to manipulate cell autophagy to their benefit for extracellular release, immune evasion, and reproduction niches **[4].** Although the connection between SARS-CoV-2, cell death, and cell autophagy is not fully understood at this time, it is possible to draw some conclusions from earlier research on SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). **[5].** Here, we address the roles that cell death and cell autophagy play in the pathophysiology and intervention therapy of COVID-19, offering a possible avenue for the repurposing of existing medications and the creation of brand-new ones.

The novel coronavirus that causes coronavirus disease 2019 (COVID-19) is called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) **[6, 7]**. The "cytokine storm" is the result of the production of many pro-inflammatory cytokines during viral infection. Among them, interleukin (IL)-6, tumor necrosis factor-α (TNF-α), and IL-1β appear to be crucial for the development and aggravation of the illness, causing immune cells to be drawn to infection sites **[8, 9].** Autophagy is a lysosomal degradation system that has been retained throughout evolution and is involved in various aspects of lymphocyte activity. It has recently been shown that IL-6, TNF-α, and IL-1β are involved in the control of autophagy **[10].** Additionally, early research revealed that SARS-CoV-2 may infect lymphocytes and influence autophagy **[8, 10].**

With genomic sizes varying from 26 to 32 kb, coronaviruses are categorized into four genera: alpha-, beta-, gamma-, and delta-coronavirus **[11].** With a length of 29.9 kb, SARS-CoV-2 is an enveloped, positive-sense single-stranded RNA (+ssRNA). This genomic RNA is composed of thirteen open reading frames (ORFs) that encode nonstructural proteins (NSP1–16) and accessory proteins, and four structural sections that encode the proteins spike (S), envelope (E), membrane (M), and nucleocapsid (N) **[12]** They are all involved in the entry of viruses, the translation of the machinery needed for virus replication, the translation of structural proteins, the assembly of virion, and the discharge of viruses**.[13]** Additionally, next-generation sequencing revealed that SARS-CoV-2 and SARS-CoV share 50% and 79.4% of the same homology **[14].**

Modulation of Apoptosis during SARS-CoV-2 infection

Apoptosis is a type of programmed cell death (PCD) that is commonly characterized by apoptotic bodies, chromatin breakage, and cell shrinkage **[15]**. It is essential for controlling physiological and pathological processes as well as preserving cellular homeostasis. Both intrinsic and extrinsic mechanisms can cause apoptosis. When extracellular death ligands, like FasL, TNF-α, TRAIL, and IFN-γ, come into contact with death receptors, procaspase-8 is cleaved and caspases-3/6/7 are activated **[16].** The BH3 interacting domain death agonist has the ability to translocate into mitochondria, whereupon it triggers the release of apoptotic factors and the B-cell lymphoma-2-associated X/Bcl-2 homologous killer-mediated mitochondrial outer membrane permeabilization (MOMP). Stress and damage to DNA can result in mitochondrial damage and the production of cyt c by MOMP **[15].**

During SARS-CoV-2 infection, apoptosis is an essential event because it can increase the expression of c-FLIP, a cellular FADD-like interleukin-1 (IL-1)-converting enzyme-inhibitory protein, which inhibits the activation of caspase-8/10 **[16].** The transcriptional expression of apoptosis inhibitors like as Bcl-2, X-linked inhibitor of apoptosis proteins (XIAPs), and c-FLIP can be upregulated by the nuclear factor kappa B (NF-κB) pathway **[17].** The NF-κB pathway is impacted by SARS-CoV-2 proteins, and in human and animal lung epithelial cells, the S protein triggers the TLR2-dependent NF-κB signaling pathway **[17, 18].** This implies that in order to evade elimination and buy time for early reproduction, SARS-CoV-2 inhibits apoptosis. Research has indicated that SARS-CoV-2 proteins are also important for inducing apoptosis. A viroporin called SARS-CoV-2 ORF3a has the ability to create an ion channel on the cell membrane, which can upset intracellular homeostasis and encourage virus release **[19, 20]**. By cleaving and activating caspase-8 for the extrinsic route and cross-talking with the intrinsic pathway via tBID, which results in the release of cyt c and the activation of caspase-9, ORF3a can cause apoptosis **[19].** In Vero E6 and HEK293T cells, ORF7b triggers TNF-α-dependent apoptosis and increases TNF-α expression **[21].** Apoptosis can be induced by structural proteins via many ways. SARS-CoV-2 E protein functions as an ion channel and is found in the endoplasmic reticulum-Golgi intermediate compartment. SARS-CoV-2 M protein suppresses the 3-phosphoinositide-dependent protein kinase 1 (PDK1)-protein kinase B (PBK)/AKT axis and inhibits Bcl-2 ovarian killer (BOK) ubiquitination to control cell apoptosis **[22].** The SARS-CoV-2 S protein has the ability to promote autophagy-triggered apoptosis and inflammation via activating the phosphoinositide 3-kinase (PI3K)/AKT/mTOR pathways, which are blocked by reactive oxygen species (ROS) **[23, 24]**. The higher number of asymptomatic patients with broad viral transmission may be explained by SARS-CoV-2's lower pro-apoptotic activity compared to SARS-CoV.

Apoptosis plays a pivotal role in the pathophysiology of COVID-19, impacting multiple organs including the liver, kidney, pancreas, immune system, lung, and pancreas. Research has demonstrated that in infected NHP lungs, apoptosis is activated in a variety of cell types, including T cells, macrophages, vascular endothelial cells, and alveolar type 1 and type 2 cells **[25, 26].** Signaling pathways linked to apoptosis are activated when SARS-CoV-2 is infected. Reduced levels of CD4+ and CD8+ T lymphocytes, or lymphopenia, are indicative of a more severe case of COVID-19 in individuals **[27, 28].** Compared to healthy controls, COVID-19 patients have much higher levels of FasL expression on their CD4+ and CD8+ T cells, which promotes cell death. T cells from patients with the infection also exhibit caspase activation linked to apoptosis. Genes linked to cell death are upregulated in CD3+ T cells from COVID-19 patients, according to single-cell RNA sequencing (scRNA-seq) studies **[29].** The degree of SARS-CoV-2 infection is correlated with the lower percentage of dendritic cells (DCs) in COVID-19 patients. Monocyte-derived macrophages and DCs exhibited damaged mitochondria and caspase-3 activation-dependent apoptosis, which could be avoided by administering anti-IFNγ medication **[30].** Apoptotic gene profiles associated with low-frequency pDCs and disease severity, such as BRCA2, CASP3, CASP8, BID, BAK1, and XBP1, were found to be considerably elevated in plasmacytoid DCs from COVID-19 **[31].**

Considering the various stages of the infection, two treatment modalities for SARS-CoV-2 infection should be taken into account. Preventing host cell apoptosis during the early stages of the virus can help it replicate. Patients with COVID-19 may be treated with histone deacetylase (such as LBH589) inhibitors to prevent c-FLIP **[32]**. Because they suppress the NF-κB pathway, anti-inflammatory and antioxidant medications such as macrolide antibiotics **[33],** phillyrin **[34],** and dexamethasone **[35],** have a negative impact on SARS-CoV-2 replication.

Later on, SARS-CoV-2 causes a robust apoptotic response in host cells, which speeds up the development and mortality of the disease by causing tissue damage and loss of function. Reducing viral propagation and slowing the progression of the disease is suggested to be possible through impeding apoptotic pathways by limiting the caspase cascade and DRs signaling **[36].** It has been revealed that human cortical neural progenitors are shielded against caspase-3-induced cell death during Zika virus infection by the irreversible pan-caspase inhibitor emirciasan **[36].**

TNF-α is essential for the development of malignant tumors, inflammatory processes, and infectious illnesses **[37].** One promising treatment for SARS-CoV-2 infection is to target TNF-α and its receptor. A mouse-human chimeric monoclonal antibody called infliximab ((NCT04425538) has been approved for the treatment of psoriatic arthritis, ankylosing spondylitis, rheumatoid arthritis, and plaque psoriasis **[38].** For severe COVID-19 patients, a randomized controlled trial has been conducted using a humanized anti-TNF-α monoclonal antibody called adalimumab **[39].**

Modulation of Autophagy during SARS-CoV-2 infection

Autophagy is a strictly regulated catabolic mechanism for self-preservation in which redundant or damaged components are broken down **[40].** This process, which allows cells to adapt to a range of circumstances such starvation, endoplasmic reticulum (ER) stress, pathogen infection, or hypoxia, is mostly regulated by autophagy-related (ATG) genes and is believed to be a survival mechanism **[41, 42].** Cytoplasmic vacuoles and autophagic bodies are visible morphological features of autophagy. Three categories exist for autophagy: selective autophagy, microautophagy, and macroautophagy (also

known as autophagy). Under canonical autophagy, the unwanted components are engulfed by subcellular membranes (such as those of the ER, Golgi complex, mitochondria, and endosomes) to form a double-membrane structure called a phagophore. The autophagosome is formed when the phagophore membrane lengthens and contracts, fusing with the lysosome to create the autophagolysosome, which is then degraded in an acidic environment. On the other hand, in cells devoid of apoptosis or under extreme or prolonged stress, autophagy may play a role in cell death. Although autophagy regulates both cell survival and death, the exact reason for these dual functions is unknown.

Research indicates that the relationship between autophagy and SARS-CoV-2 is intricate and still developing. Human epithelial cells that are infected have been found to have double-membrane vesicles (DMVs), which are thought to facilitate the rearrangement of ER membranes to produce DMVs **[43].** In order to create DMVs derived from ER membranes, SARS-CoV-2 can divert autophagy flux. This creates niches for immune evasion and viral RNA replication **[44].**

The SARS-CoV-2 visible proteins can stimulate autophagy to control the host's immunological response. Via the Tu translation elongation factor (TUFM), the SARS-CoV-2 M protein translocates to the mitochondria where it interacts with LC3-II via its LC3-interacting region (LIR) to trigger mitophagy, or mitochondrial autophagy. In order to facilitate mitophagy, SARS-CoV-2 ORF10 directly interacts with the mitochondrial receptor Bcl-2 interacting protein 3 like (BNIP3L)/NIX **[45, 46].**

Degradation of mitochondrial antiviral signaling protein (MAVS) results from activated mitophagy, and this degradation can activate transcription factors IRF3 and NF-κB to upregulate genes associated to inflammation and immunological response. SARS-CoV-2 M and ORF10 induce mitophagy-mediated degradation of MAVS, which attenuates type I IFN response and pro-inflammatory cytokines. Mitophagy inhibits NLRP3 inflammasome-mediated cell pyroptosis and cytokine secretion by reducing the release of mtDNA and ROS **[47].**

Autophagy is an antiviral mechanism that disrupts the life cycle of viruses by removing their particles and components and facilitating the presentation of antigens to trigger adaptive immunity. Through a number of methods, including interactions with the UVRAG gene, incomplete autophagy, the unfolded protein response (UPR), and sequestering VPS39 in endosomes and lysosomes **[48],** SARS-CoV-2 can impede autophagy. As a result, autophagosomes and lysosomes cannot fuse, leading to the defective HOPS complex. Viral egress can be facilitated by SARS-CoV-2 ORF3a through lysosomal exocytosis, which is regulated by the Ca2+ channel TRPML3, the lysosomal trafficker BORC-ARL8b complex, and the exocytosis-related STX4-SNAP23-VAMP7 SNARE complex **[49].** SARS-CoV-2 NSP15 influences autophagosome production through its interaction with the mTOR axis, which can be reversed by rapamycin. The mTOR axis inhibits autophagy by forbidding the ULK1 complex, whereas SARS-CoV-2 PLpro protein directly cleaves ULK1 to destroy the formation of the ULK1-ATG13 complex **[50, 51].** During SARS-CoV-2 infection, cell autophagy has two faces: one that induces virophage and regulates immune response, while SARS-CoV-2 manipulates autophagy to favor replication and transmission.

Autophagy mediators as a therapeutic targets in SARS-CoV-2 infection

Autophagy mediators could be a useful therapeutic approach because cell autophagy is essential for both the host response and SARS-CoV-2 infection. By controlling autophagy, chloroquine (CQ) and its less hazardous derivative, hydroxychloroquine (HCQ), demonstrate antiviral efficacy. Proposed medications target Zika, HIV, and SARS-CoV **[52-54]**. Unfortunately, the majority of these medications have produced unsatisfactory results, having little to no impact on COVID-19 patients' 28-day mortality or length of hospital stay.

Inhibiting autophagy-associated complexes, like the PIK3C3 and ULK1 complexes, is one way to suppress autophagy. Inhibitors of the ULK1 complex need more research in order to counteract SARS-CoV-2 infection, as studies have demonstrated that PIK3C3 complex inhibitors potently reduced SARS-CoV-2 replication **[55, 56].**

Autophagy activators for anti-viral and anti-inflammatory purposes may be useful when treating severe COVID-19 patients with uncontrolled inflammatory responses. Cell autophagy is mediated by mTOR signaling; AMPK and p53-suppressed mTOR induces autophagy, whilst AKT and MAPK-activated mTOR can prevent it **[57].** FDA-approved mTOR inhibitor rapamycin, also marketed as sirolis, has promising antiviral activity against MERS-CoV, H1N1, transmissible gastroenteritis virus, and pig epidemic diarrhea virus and others **[58, 59].**

The FDA-approved antidiabetic medication metformin increases autophagy by downregulating mTOR and upregulating AMPK. Its shown ability to directly prevent viral entry and infection, as well as to modulate immunological and inflammatory responses, provide a foundation for its sensible use in COVID-19 patients **[60-62].**

The capacity of a number of medications, including as resveratrol, trehalose, ivermectin, and nitazoxanide, to activate autophagy in response to anti-virus therapy has been studied; however, it is still unknown what their underlying processes are for treating COVID-19.

Conclusion and future perspective

SARS-CoV-2 controls autophagy and cell death, which contributes to the spread of COVID-19. Although these pathways can stop viruses from spreading, they can also cause tissue damage, viral dissemination, cytokine storms, and ineffective immune responses. Determining whether to stimulate or inhibit these pathways is therefore critical. ..Inhibitors and agonists that target these pathways can be used in future studies to better understand the variety of effects they have on COVID-19 development. High-throughput techniques including as proteomics, spatial omics, single-cell sequencing, and metabonomics can be used to identify new pathways in COVID-19 as well as the interactions between various pathways. To fully comprehend the

connection between SARS-CoV-2 mutations and modified cell death and autophagy pathways, more thorough investigations are required. Although therapeutic approaches have been investigated, the outcomes are debatable. Patients with COVID-19 should have their treatment window estimated based on the severity and course of their illness. Critical points for therapy can be identified with the aid of real-time information on laboratory parameters, imaging findings, and clinical symptoms.

Figure Ligands

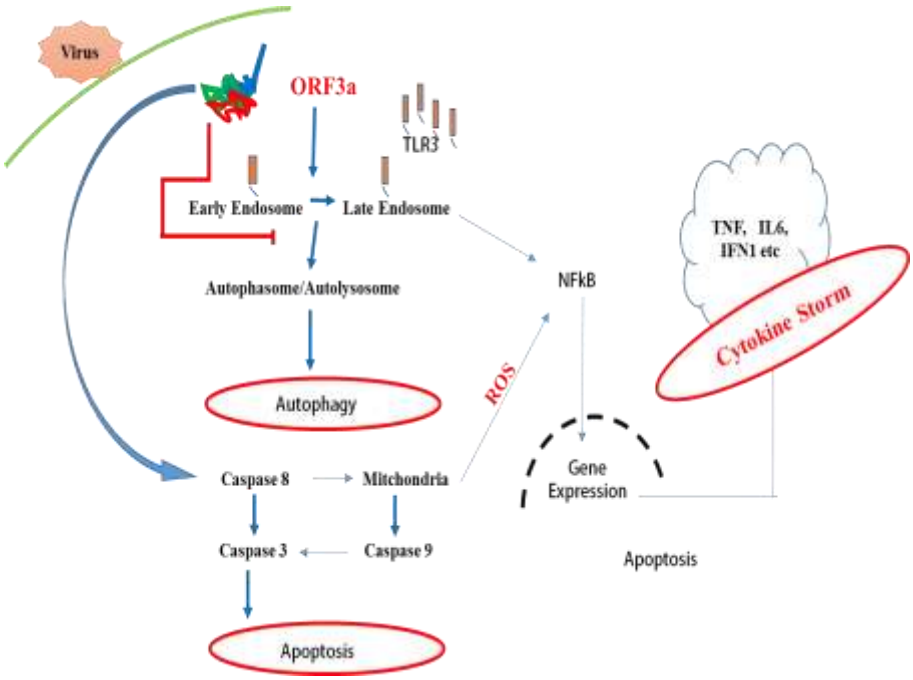

Figure 1: Schematic representation of how coronavirus disrupts signaling pathways (autophagy, MMP loss, ROS, cytokine storm and induces cell death.

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