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Review article

# Cellular pathways exploited by SARS-CoV-2 for replication and immune evasion: a comprehensive analysis of viral hijacking mechanisms

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## ABSTRACT

The SARS-CoV-2 virus has shown incredible finesse in using the cellular machinery of its hosts to replicate itself while in addition escaping the host's immune system. This pivotal review covers the detailed and complex cellular mechanisms that SARS-CoV-2 employs to subvert various cellular processes within the host and focuses on some aspects of the virus cellular entry and replication processes and immune system evasion. After carefully collating the data that has been recently published, we have identified and described the virus mediated cellular subversion of the endoplasmic reticulum stress response, autophagy, innate immune system and its signalling, and cellular metabolism. Our thorough understanding of these processes cellular subverted by SARS-CoV-2 will guide future therapeutic interventions, and will illuminate some of the complex and devious host–pathogen interactions that drive the pathology of COVID-19.

**Keywords:** SARS-CoV-2, cellular pathways, viral replication, immune evasion, host-pathogen interactions, COVID-19.

## INTRODUCTION

The arrival of SARS-CoV-2 at the end of 2019 started a global health crisis which shifted the paradigm of how we understood and studied the pathogenecity of coronaviruses and how these viruses interact with the host. SARS-CoV-2 was the first of its kind with a large variety of clinical outcomes ranging from no symptoms at all to life threatening illnesses, such as severe acute respiratory distress syndrome. One of the main reasons for the versatility of the virus was the ability of the virus to control the host cell systems and to use the most basic and vital processes of the cell for the virus increasingly growing needs [1,2].

As positive sense RNA viruses, coronaviruses like SARS-CoV-2 use host cell systems to replicate and the viruses do not contain any of the systems required for autonomous replication. The virus had included in its arsenal a number of the ability to stealthy use some of the cell systems and turn the infected cell into a cell which becomes a factory producing only the virus. The infected cell becomes a factory for the production of the virus. The virus also suppresses any immune responses effectively turning the immune system off. This two pronged (resource use and immune evasion) tactic of the virus is a hallmark of successful pathogens and is a primary cause of the cellular changes seen during COVID-19 along with the immune response.

The viral lifecycle starts with receptor binding and membrane fusion. These phenomena elicit responses from the cell. Rather than succumbing to the cell's response mechanisms, however, SARS-CoV-2 has developed mechanisms to nullify the response and even recruit the cellular defenses to the virus' advantage. The virus achieves this through the precise control of the cell's protein synthesis machinery, membrane trafficking systems, organelles, and signal transduction systems [3,4].

In the fields of molecular virology and systems biology, the extent of metabolic reprogramming, stress response and immune signal reprogramming by SARS-CoV-2 has become appreciated. It reprograms the cell's defenses to help the virus manage its response and reprogram the defenses of the host cell. These results are important for forecasting the progression of the disease and for the targeting of therapeutic strategies, as well as anticipating evolution patterns of the virus. The numerous interdependencies and tight coupling of the control systems of the host cell suggest that sufficient antiviral strategies will have to address several mechanisms at the same time.

The virus has evolved a large set of control mechanisms to make sure that its objectives get achieved with sufficient ease [5,6].

**Viral entry and initial cellular responses**

**ACE2-mediated entry and membrane fusion**

When the SARS-CoV-2 virus interacts with host cells for the first time, the virus spike protein attaches to the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell. This reaction activates a series of events within the cell triggered by the host cell and facilitate the entry of the virus. Subsequently, the host cell responses start. Subsequently, the host cell responses start. The spike protein features additional folded structures attached to the protein to protect it from the immune system. After ACE2 binding, a portion of the spike protein (the fusion protein) that enables the merging of the viral membrane with the host cell membrane is exposed [7].

After ACE2 receptor binding, the viral encoded cell membrane fusion protein (the spike protein) is targeted and also cleaved by the host cell's TMPRSS2 protein. This TMPRSS2-mediated cleavage activates the receptor for cell membrane fusion with the viral membrane. This cleavage not only activates the protein necessary for the viral entry to the host cell, but it also is a determinant for the SARS-CoV-2 virus ability to infect that tissue. Cells that express high levels of ACE2 and TMPRSS2 are pneumocytes and enterocytes. These cells are primarily targeted by the virus [8].

The activation of innate immune cell receptors also induces membrane repair and injury response receptors. However, to control viral pathogenesis and the overall outcome of the infection, the early host cell responses must be overridden. This adaptation of early cellular responses to viral infection is a hallmark of SARS-CoV-2 [9].

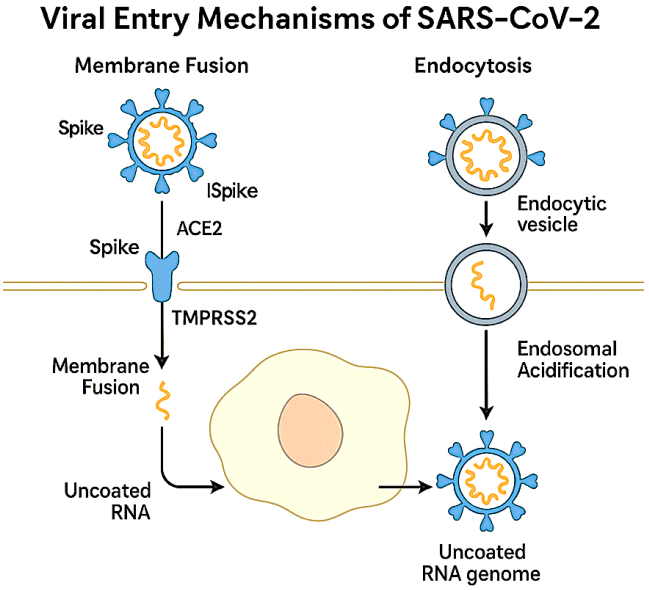
**Endosomal trafficking and viral uncoating**

An alternative mechanism for the entry of the virus into the cell is through endocytic uptake of the virus. This process captures virions and traffics them through the endosomal system. The later endosomal structures undergo a conformational change of the spike protein due to the acidic pH of the environment; this is required for fusion of the endosomal membrane and the release of the viral genome. This mechanism of viral entry is of special relevance to cells with low expression of TMPRSS2 as it broadens the number of cell types that can be infected [10].

The endosomal entry of the viruses is coordinated with a number of other cellular trafficking processes such as clathrin mediated endocytosis and also macropinocytosis. With SARS-CoV-2, there is evidence that multiple endocytic pathways are being utilized for improved viral uptake, Across cell types, viruses such as SARS-CoV-2, are known to interfere with endosomal maturation and fusion, possibly as a mechanism to avoid lysosomal degradation [11].

The entry of the viral genome into the cytoplasm is uncoating, and it occurs when the virus is still membrane bound, either to the plasma membrane or to the membranes of the endosomes. As the viral RNA is released into the cytoplasm, it is immediately translated by host cell ribosomes, and the viral protein translation begins the formation of replicase/director complexes. Viral entry and replicative transition to this phase notably occur with remarkable rapidity, exemplifying the rapid commandeering of the cellular machinery that is typical of highly evolved viruses [12].

**Figure 1:** Schematic of Viral Entry Mechanisms




The above figure displays an illustration showing the dual entry pathways detailing ACE2 binding with TMPRSS2-mediated membrane fusion and the alternative endocytic uptake with subsequent uncoating [13].

**Manipulation of protein synthesis and processing**

**Ribosomal hijacking and translation control**

SARS-CoV-2 demonstrates advanced manipulation of the host Protein Synthesis Machinery (PSM), commandeering the usually allocated translation capacity of the host to synthesise viral proteins. Redirection of the host's resources in the viral protein synthesis is achieved through host macro translation suppression and viral translation priority. This mechanism of macro suppression aids in even more of the required synthesis of viral proteins and balances host defence proteins [14].

Viral RNAs possess certain structural features that recognize host PSM, such as IRES and uORF, which promote the synthesis of viral proteins. These structural features increase the chances of viral RNAs in competing for ribosomes as PSM is generally stressed and resources are low. The virus also improves it's chances of translation of proteins that are required in higher quantity through commandeering scanning of ribosomes and translation re-initiations [15].

The viral proteins also vacuum ribosome PSM through direct binding with PSM ribosome components. The nucleocapsid protein is known to bind to the RNA of ribosomes which impacts the assembly of ribosomes, while numerous non-structural protains adjust the factors that regulate translation initiation. These elements form a feedback mechanism that greatly diverts the PSM of the host to the viral protein synthesis [16].

**Endoplasmic reticulum stress and protein folding**

Viral protein production tremendously increases stress on the endoplasmic reticulum (ER). ER as a cellular compartment, is

responsible for protein folding and processing. Interactions of SARS-CoV-2 with ER trigger the unfolded protein response (UPR), which is a cellular stress response aimed at re-establishing ER homeostasis. However, the virus is evolutionary equipped to shift to a control strategy of UPR signalling at the same time preventing pro-apoptotic signalling, which would end the infection.

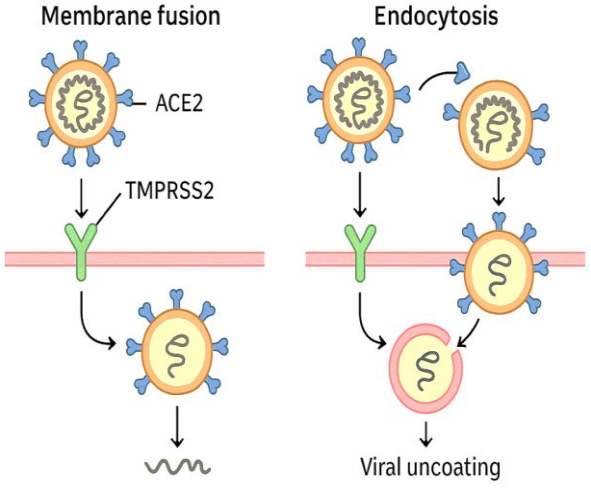
UPR is constituted of three major signalling pathways: PERK, IRE1α, and ATF6. With respect to the UPR, SARS-CoV-2 is observed to activate some pathways and inhibit others, hence creating a cellular environment that is a replica of a viral replicative phenotype. The virus promotes the formation of extra ER membranes and increased concentration of ER chaperones to enable production and processing of a large viral protein.

Proper folding and maturation of viral proteins that interact with intracellular ER protein chaperones and folding enzymes. The spike protein is especially notable for requiring considerable glycosylation and formation of disulfide bonds and is therefore reliant on ER machinery. The virus is able to capture control of cellular resources and ER stress responses to evade cellular shut-down processes [17-220].

**Table 1:** ER stress responses

| ER Stress Response Component | Normal Function | Viral Manipulation | Outcome for Virus |
|---|---|---|---|
| PERK pathway | Attenuates translation | Selectively activated | Reduces host protein synthesis |
| IRE1α pathway | Activates XBP1 transcription factor | Partially suppressed | Prevents apoptosis |
| ATF6 pathway | Upregulates ER chaperones | Selectively activated | Enhances viral protein folding |
| ER-associated degradation (ERAD) | Removes misfolded proteins | Inhibited | Prevents viral protein degradation |
| ER membrane expansion | Increases ER capacity | Enhanced | Provides replication platforms |

**Figure 2:** Diagram of host protein synthesis hijacking and er stress responses




The above diagram illustrates how SARS-CoV-2 suppresses host mRNA translation, co-opts ribosomal machinery, and manipulates the UPR (highlighting the PERK, IRE1α, and ATF6 pathways) to favour viral protein production.

**Replication complex formation and organelle remodeling**
**Double-membrane vesicle formation**

A defining feature of viral infections, including ones caused by the coronavirus, is the construction of double-membrane vesicles (DMVs), which function as scaffolds for the viral replication of RNA. For viral RNA replication to occur safely, these vesicles, which are formed from the membranes of the Endoplasmic Reticulum (ER) cellular membranes, house the RNA safely. While the SARS-CoV-2 Virus extensively remodels membranes to spawn replication organelles, the drastic modification of the cellular architecture with the DMVs is of equal importance.

A coordinated assembly of viral non-structural proteins (nsps) leads to the crafting of DMVs, with each of these proteins coordinating action with cellular membrane-trafficking machineries. These proteins divert the cellular activity of autophagy, membrane fusion, and organelle biogenesis, to establish the membrane structures necessary for the viral replication process. The observed extensive membrane networks in the infected cells result from the effective commandeering of the cellular membrane synthesis by the virus.

In the DMVs, the viral replication machinery is concentrated which accelerates the rate and volume of viral replication. Protective double membranes may also shield the viral RNA from the innate immune cellular sensors and detection efforts that otherwise activate the immune responses. Furthermore, these membranes also promote efficient interaction with other replication proteins and cellular cofactors as well as the viral RNA to promote replication.

**Mitochondrial dysfunction and metabolic reprogramming**

Infected with SARS-CoV-2, cells show aberrancies in their mitochondrial structures and functions, while altering their metabolic profiles in a way that facilitates viral proliferation. As a result, cells lose their energetic capabilities. The virus optimizes, driving out mitochondria, functions of the respiratory chain, and metabolic flux to cultivate environments in which the virus can replicate itself. These phenomena result in a losing battle for the cells, a case of continuing with the hijacked functions of the cell, and continuing the infection in COVID-19.

Mitochondrial respiratory chain functions, and hence, ATP synthesis, are further compromised because of viral proteins. Affected cells suffer from this energy crisis and are forced to pivot towards an inefficient glycolytic pathway for their ATP needs. This change, referred to as the 'glycolytic shift,' supplies the virus with more than enough metabolic building blocks, particularly for the synthesis of the viral RNA and the proteins that the virus needs. The virus also increases the recruitment of glucose, along with the enzymes controlling the glycolytic pathway, while putting a stop to mitochondrial proliferation.

Viral manipulation of mitochondrial functions also extends to the control of cell death and innate immune system. Mitochondria are central to the control of antiviral immune response and, as a result, have the control of type I interferon response in infected cells. The virus selectively targets the mitochondrial functions that control viral functions while retaining the mitochondrial functions that enable the production of more viral agents.

**Manipulation of the autophagy pathway**

Autophagy is a principal mechanism of quality control functioning in all cells to eliminate defective cell components and to remove misfolded proteins. However, SARS-CoV-2 has developed complex strategies to exploit autophagy. In the case of COVID -19 Autophagy is not a protective mechanism but rather a viral succour. The virus inhibits and activates select entrap of cellular autophagy phenomenology and aspects to yield a favourable cell state for the virus to reproduce even more [21-25].

Autophagy begins when a de novo synthesized autophagosome, a double-membrane structure, engulfs cytosolic components destined for lysis and degradation. SARS-CoV-2 seems to commandeer the cellular machinery of autophagosome construction for the incorporation of replication-competent virus for the construction of viral membrane structure. In this case, several viral proteins are reported to interact with known key regulators of autophagy such as, but not limited to, ULK1, Beclin-1, and LC3 to coordinate modulating such activities toward the beneficial for the virus replication.

The virus is known to block the fusion of the autophagic vacuole with the lysosome preventing degradation of viral nucleic acids but allows autophagic membrane polyphosphoinositide synthesis. In such a case the cell is left with truncated autophagy which statically works to bolster the biogenic viral replicative compartments while also statically completing the anti-viral defences of the host cell degradation. Also not the manipulation of autophagy results with no immune suppression, the autophagy cell defence mechanism requires to present the antigens and garners the multifaceted cell cytokines to sustain the immune cell activity enhancing suppression of the immune system.

An integrated illustration showing the formation of double-membrane vesicles (DMVs), mitochondrial dysfunction with metabolic reprogramming, and the diversion of autophagy pathways for replication complex support.

**Immune evasion mechanisms**

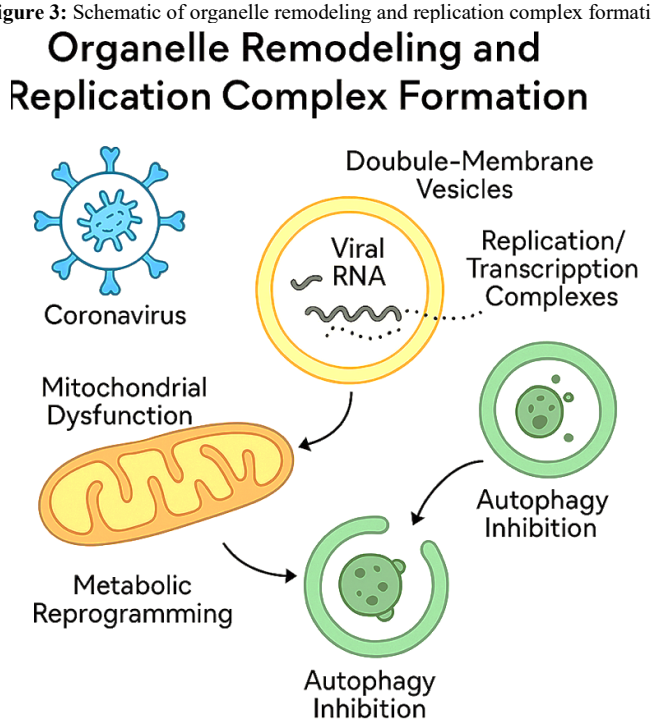
**Type I interferon suppression**

Cytokine signalling initiated by pattern recognition receptors represents the first line of cellular defence against viral infections. The type I interferon (IFN) response is the first line of defence. Recognition of the first viral components and integration of anti-viral cytokine responses is essential. SARS-CoV-2 has evolved multiple means to subvert this vital anti-viral response so the virus is able to infect and replicate in resistant cells.

Multiple viral proteins target different aspects of the IFN signalling pathway. These include the recognition of the virus and the activation of effector functions. The viral RNA-dependent RNA polymerase complex incorporates several proteins with anti-IFN functions. Among these accessory proteins ORF6 and ORF8 selectively inhibit components of IFN signalling. The proteins blocked activation of IRF3 and NF-κB, and transcription of several IFN genes.

The consequences IFN response suppression are myriad, primarily involving the suppression of antiviral immunity. The type I IFNs are essential for engagement of multiple antiviral effector functions. In severe COVID-19 cases, attenuated and delayed IFN response has been activated, likely correlating with efficiency of viral IFN suppression for their self-protection. This immune suppression paves the path for viral replication and rampant dissemination prior to activation of the adaptive immune response [26-30].

**Figure 3:** Schematic of organelle remodeling and replication complex formation




**Modulation of the NF-κB pathway**

NF-κB pathway orchestrates and controls the expression of many inflammatory and immune responses and regulates the expression of many cytokines and immune effector molecules. SARS-CoV-2 has complex interactions with NF-κB signalling that can activate or suppress different levels of this pathway, depending on the stage of infection and cellular context.

Early in infection, the virus seems to suppress NF-κB activation in order to block antiviral gene expression and allow cells to survive. Several viral proteins have been shown to interact with components of the NF-κB pathway such as IκB kinases and p65/RelA, inhibiting their nuclear translocation and transactivation activities. Early SARS-CoV-2 infection is characterized by suppression of this inflammatory response [31, 32].

As infection progresses, however, there is abnormally controlled activation of NF-κB that may explain the hyper inflammatory responses seen in severe cases of COVID-19. The virus seems to activate the pro inflammatory features of NF-κB signalling while suppressing the antiviral features of the pathway. This selective modification may be explained by severe manifestations of the disease such as the cytokine storm and suffering of the tissue.

**Complement system interference**

Just like SARS-CoV-2 infection, complement activation also occurs. However, SARS-CoV-2 has evolved mechanisms for complement control that can negate its antiviral activities and, for

example, may utilize inflammation stemming from complement activation for viral spread.

Viral glycoprotein Spike may interact directly with complement system components for the virus to have potential cytotoxicity and a resistance that may be described as complement-mediated lysis. Spike may also facilitate the virus's entry into the cell by invoking complement-mediated endocytosis. It is also possible that the virus may attempt to complement activation in a way that inflammation is promoted and thus tissue destructive and viral dissemination is aggravated.

Complications of COVID-19 like coagulopathy and thrombosis may be the result of complement system dysregulation. In severe COVID-19, a procoagulant state may be due to complement system activation, resulting in endothelial cell damage and inflammatory thrombosis due to a positive feedback mechanism that further activates complement proteins. These relationships offer clues for complement system target interventions, pointing to potential novel therapies [33-35].

**Figure 4:** Flowchart of Immune Evasion Strategies

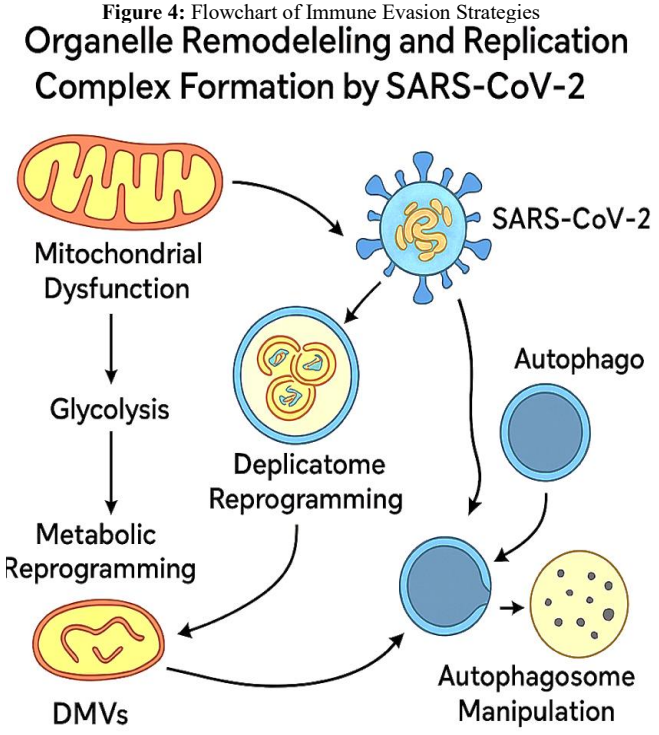



**Table 2:** Immune Pathway

| Immune Pathway | Normal Antiviral Function | SARS-CoV-2 Interference | Clinical Consequence |
|---|---|---|---|
| Type I IFN | Viral recognition and response | Multiple viral proteins suppress signaling | Delayed antiviral response |
| NF-κB | Inflammatory gene expression | Selective activation/suppression | Dysregulated inflammation |
| Complement | Viral neutralization and clearance | Resistance to lysis, inflammatory hijacking | Thrombotic complications |
| JAK-STAT | Cytokine signal transduction | ORF6 blocks nuclear import | Impaired immune coordination |
| cGAS-STING | DNA sensing and IFN induction | Potential suppression by viral proteins | Reduced innate immunity |

A flow diagram that maps out the key immune evasion tactics including type I interferon suppression, modulation of the NF-κB pathway, and interference with the complement system to visually convey how the virus dampens antiviral responses.

**Cell death pathway manipulation**

**Apoptosis regulation**

Apoptosis plays a vital role in the elimination of infected cells before the release of viral progeny, thus limiting the virus's spread. SARS-CoV-2 controls the apoptotic pathways with precision, initially delaying death of the infected cells, thus allowing the virus to replicate, before possibly promoting apoptosis in some infected cells to enhance viral spread.

The virus's control over the apoptotic process is mediated by regulators of apoptosis, including members of the Bcl-2 family and the effector caspases. Viral proteins have been shown to interact with apoptosis inducers, either by sequestering them or by promoting their degradation. It is likely that the nucleocapsid protein is an anti-apoptotic factor that preserves cell viability during the active phase of viral replication [36-40].

The relationship between SARS-CoV-2 and apoptosis is context-dependent and complex. For some cell types, particularly immune cells, the virus could be promoting cell death to evade the immune response. Infected immune cells, when apoptosed, are prevented from mounting any antiviral response and may act as a source of inflammatory DAMPs that are detrimental to the tissue.

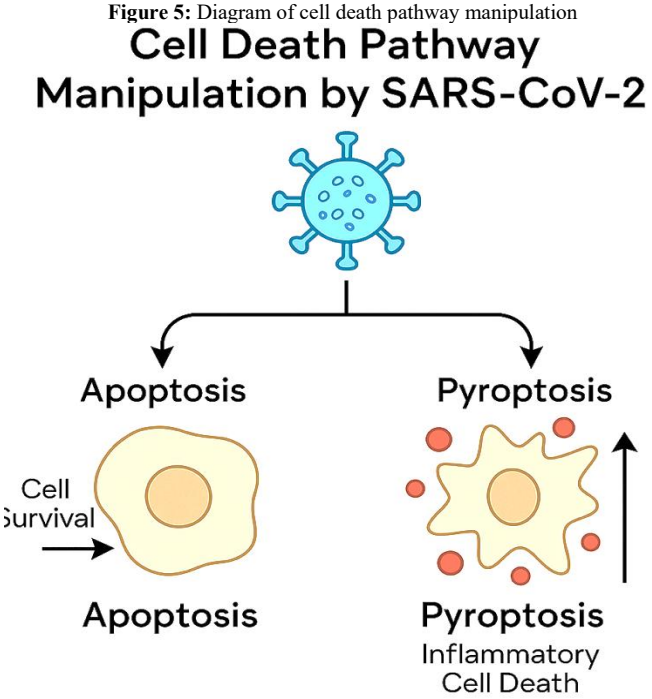
**Proptosis and inflammatory cell death**

Proptosis is a unique type of cell death that is both inflammatory and retaliatory; simply put, it is a form of cell death that acts as a response to viral infections while also causing inflammation. Infection from the SARS-CoV-2 virus triggers a type of cell death called pyroptotic cell death and activates the multi-chain protein complexes known as inflammasomes that process pro-inflammatory proteins and cause cell death. The virus, however, appears to control these pathways to undermine the pathways' inflammatory effects while potentially taking advantage of the inflammation.

Among the inflammasomes, NLRP3 is the one that is most noted with regard to the pathogenesis of SARS-CoV-2, with proteins from the virus possibly acting as signals to activate it. The production of the pro-inflammatory cytokines and interleukin (IL) 1 and 18, as well as the release of cell contents via cell death, lead to and contribute the severe inflammatory response that is seen in some cases of COVID-19. The virus seems to take advantage of this inflammation in order to increase the spread of the virus.

A key factor is the balancing of the pathological and non-pathological cell deaths. The ways that SARS-CoV-2 uses these pathways is of great importance to understanding the possibilities of developing non-inflammatory damaging therapies; for example, therapies that cause cell death that is antiviral. Specifically focusing on proptosis is a prime candidate for the enhancement of non-severe COVID-19 cases.

**Figure 5:** Diagram of cell death pathway manipulation




An illustration contrasting the modulation of apoptosis (cell survival during early replication) versus the induction of pyroptosis (inflammatory cell death) highlighting the dynamic regulation of cell fate by SARS-CoV-2.

**Metabolic reprogramming and lipid metabolism**

**Lipid biosynthesis and membrane remodelling**

Replicating the SARS-CoV-2 virus makes the cell perform extreme alterations in lipid metabolism. Its efficiently reprogramed metabolism leads to the virus redirecting the cell's lipids to the newly formed replication organelles. This is achieved through the overexpression of certain lipogenic enzymes and the controlling of some lipid transport pathways.

Supporting the replication of the virus also makes the fatty-acid synthesis newly incorporated lipids from the expanded ER. The virus also invoked the transcription factor SREBP-1 which leads to the overexpression of acetyl-CoA carboxylase and the fatty-acid synthase. That shift in metabolism reallocates the cell's resources to support replication of the virus [41, 42].

SARS-CoV-2 also alters lipid metabolism in more complex ways such as also mixing up the composition of membranes. Their infection leads to the lipid composition of the membranes of the cell being of certain lipid species to enhance the function of some viral proteins and to make the membranes of the cell easier to fuse with other membranes. Those enhancements could also be why infected cells display unusual organelles and why the organelles of the infected cells also display unusual cell trafficking.

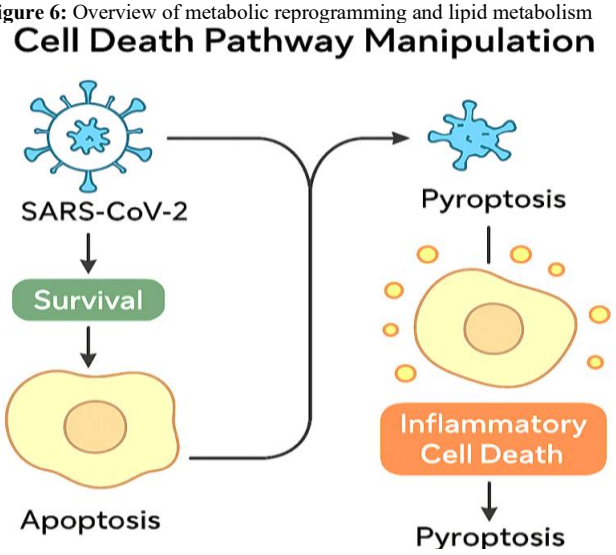
**Cholesterol metabolism and viral assembly**

Cholesterol metabolism facilitates SARS-CoV-2 infection, including the initial steps of viral entry and the terminal steps of viral assembly and release. The virus takes advantage of cholesterol-rich membrane domains and hijacks cellular cholesterol homeostasis to sustain entry and assembly processes. This reliance on cholesterol metabolism presents possible adversarial therapeutic vulnerabilities.

Membrane fusion during viral entry requires particular membrane lipid compositions. Cholesterol-rich lipid domains are required for spike protein insertion and subsequent conformational shifts. The virus may reorient cellular cholesterol distribution to target entry sites where adequate cholesterol is present for membrane biosynthesis. In instances where viral replication is extensive, the need for the regulation of cholesterol homeostasis is amplified.

The budding and assembly of new viral particles are also dependent on particular membrane compositions, including structural roles by cholesterol, which are critical. The virus appears to subvert normal cellular cholesterol trafficking to actively construct viral assembly sites with the ideal membrane compositions. This metabolic subversion sustains the copious release of viral progeny and may disrupt cellular membrane homeostasis.

**Figure 6:** Overview of metabolic reprogramming and lipid metabolism




A schematic that details the upregulation of lipid biosynthesis (including fatty acid synthesis and SREBP-1 activation), changes in membrane composition, and the redistribution of cholesterol to support viral assembly [43, 45].

**Therapeutic implications and drug targets**

**Pathway-specific interventions**

Surveillance of SARS-CoV-2's complete exploitation of cellular pathways made available several prospective targets for antiviral interventions. Rather than attempting direct combat with the viral proteins and pathways, strategies focus on the disruption of cellular mechanisms involved in the replication within the viral pathways. These approaches may have a better prognosis for retaining efficiency devoid of viral resistance and have even be protective in a wide range.

There is a critical dependence on the viral proteins and the functioning of the endoplasmic reticulum and because of that, the pathways considering endoplasmic reticulum stress, in particular, UPR signal modulators and that disrupt the equilibrium of the endoplasmic reticulum may integrate abnormal cellular replication and viral selective viral replication in the cellular system. Selectively targeting the endoplasmic reticulum stress responses could yield some toxicity to the system while retaining the viral replication cellular benefits.

The additional benefits of targeting the metabolism and more so, the lipogenic and the energy metabolism may yield added

benefits therapeutically. The increased viral replication depends on the enhanced lipogenic pathways and the the energy metabolism, to alter to the viral control strategies. The control of certain lipogenic enzymes, and the viral metabolism, at least, mitochondrial stress could increase cellular recovery, and the management of stress at viral replication becomes beneficial.

**Combination therapy approaches**

The intricate mechanisms involving viruses and their hosts suggest that, for an antiviral strategy to succeed, several different approaches may have to be implemented in conjunction. Multilayer approaches in pathogenesis may provide more effective results and may even circumvent resistance formation. Identifying the interplay and interdependence of various pathways may allow for more effective and customized multi-strategy approaches.

Trojan horse strategies combining immune modulatory approaches with antivirals may be effective in controlling both the viral replication and the immune-mediated damage. With severe COVID-19, it may be more helpful to sustain antiviral immunity while the harmful inflammation is allowed to be unregulated. As viruses tweak immune response pathways, guided interventions may be needed, and appropriate immune modulatory strategies should be chosen based on that.

Based on the pathogenesis of the virus, different stages of the infection may be more amenable to different approaches. Early and decisive interventions aimed at preventing viral entry and replication may be more successful in stopping disease progression. The order of therapeutic interventions may vary widely based on the state of infection and the presence of inflammation. Developing stage-specific therapeutic strategies requires deep knowledge of the infection process and the viral-host interplay over time.

**Figure 7:** Therapeutic Intervention Strategies

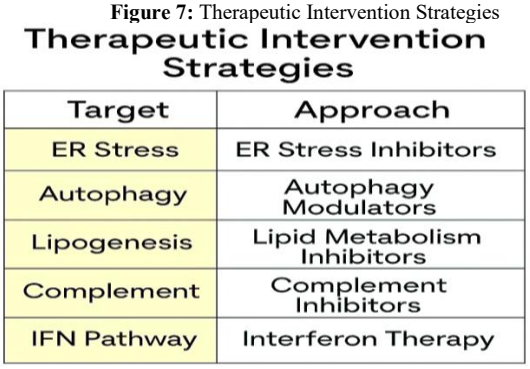



**Table 3:** Therapeutic target

| Therapeutic Target | Mechanism of Action | Potential Benefits | Development Status |
|---|---|---|---|
| ER stress modulators | Disrupt viral protein processing | Selective antiviral effect | Preclinical studies |
| Autophagy modulators | Restore antiviral autophagy | Enhanced viral clearance | Clinical trials |
| Lipogenesis inhibitors | Limit membrane synthesis | Reduced viral replication | Drug repurposing studies |
| Complement inhibitors | Reduce inflammatory damage | Decreased thrombosis risk | Clinical trials |
| IFN pathway enhancers | Restore antiviral immunity | Improved viral control | Under investigation |

A summarized diagram or table converted to a graphic that outlines various pathway-specific interventions (targeting ER stress, autophagy, lipogenesis, complement, IFN pathways) along with their mechanisms of action, potential benefits, and current development status.

**Future directions and research priorities**

**Single-cell analysis of viral-host interactions**

The diversity of cellular response to SARS-CoV-2 infection requires single-cell methodologies to gain a complete understanding of viral pathogenesis. Various heterogeneities across cell type and cell type infection state display differing patterns and degrees of pathway manipulation and understanding this heterogeneity is critical to developing interventions for precise therapeutic targeting. The diversity of cellular responses to single-cell RNA sequencing and single-cell proteomics approaches and cellular response and identity vulnerability elucidation.

Due to viral-host interaction temporal dynamics, the response of the cell is state changes infected during cell infection is rapid so it requires fine grained resolution. To elucidate the response changes and infection stage cellular pathway manipulation, time-course cell sequencing studies are uncovering the infection cycle, multistage the response of infected cells, and the constructed infection stage cellular pathway manipulation. These studies give clues on the timing and analytical breaks to sequential therapeutic strategies for critical infection outcome targeting.

The infected hosts tissue spatial organization, circulation of infection viral tissue response and infected cell is complexity to viral-host interaction, understanding is infection disease tissue level response. To limit the viral infection rapid multiple means, disease infection control predicts tissue viral spread and tissue inflammation.

**Variant-specific pathway interactions.**

As new SARS-CoV-2 variants emerge, changes in pathogenicity and transmissibility coincide with differences in cellular pathway manipulation. SARS-CoV-2 variants in the host cell with viral proteins are revealing viral-host interactions that are both conserved and variable. Predicting the behavior of new variants, understanding these differences, and adapting approaches are all directly related.

Insights into the selective pressures shaping viral evolution are found in the viral proteins with new and evolving interactions with cellular pathways. Enhanced viral replication efficiency in the pathway manipulation may alter the specific viral proteins. These changes should be monitored to anticipate gaps in therapeutic approaches and to identify changes that may require new approaches.

Viral variants' changes in time and space are especially important for bioengineering and public health. The pathway interactions in the variants allow for the stratification of the population, and the outcomes of the various pathways can lead to important public health insights. Genotype-phenotype relationships may influence the variations in viral pathways for therapeutic approaches and for public health [45-50].

## CONCLUSION

The analyses that have been carried out to understand the cellular pathways targeted by SARS-CoV-2 show how intricate the viral–host relationships are within the context of COVID-19. SARS-CoV-2 is highly adaptable in how it takes control of cellular functions including but not limited to; protein synthesis and the functioning of organelles, immune system signalling, and the regulation of metabolism. An understanding of how SARS-CoV-2 takes control of cellular pathways and the consequent formation of viruses can help in formulating disease control pathways and useful therapeutic solutions.

SARS-CoV-2's diverse activities in commandeering cellular machinery highlight the intricate nature of viral infections as well as the difficulty in formulating successful antiviral approaches. The viral control of multiple biological pathways along with cellular defences is evolutionary perfection, and it equally points to the need to have complex antiviral solutions.

The detection of specific cellular pathways that become vulnerable after viral infection, provide openings for therapeutic intervention that are potentially not as vulnerable to viral resistance, in comparison to antiviral approaches that are based on direct viral targeting. Although the loss of control of host pathways by the viruses creates the potential for the loss of control of the virus, it also opens the possibility for advanced antiviral solutions.

It is essential for future research to disentangle the complexities of viral-host interactions with an eye to the practical value of the findings. SARS-CoV-2 will undoubtedly present us with challenges for some time. Defining the most productive research avenues will involve a combination of fundamental mechanistic work, careful observation in the clinic, and planned medication development.

The interactions of viral pathways provide us know-how which is, of course, not possessed by any other virus. Knowledge gained through COVID-19 research has been, and will continue to be, invaluable with respect to a showing us how other viral infections and pandemics alter cellular pathways, evade immunity, hijack and dominate other cellular mechanisms, and ultimately with respect to devising new and diverse antiviral strategies.

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