The Role of cell death on SARS – COV 2

Introduction

A family of enclosed, single-stranded, positive-strand RNA viruses, coronaviruses are categorized under the Nidovirales order. The infections in this coronavirus family affect both people and a variety of animal species. They are mainly disseminated by respiratory droplets and intimate contact, which causes them to spread quickly among human populations. From minor respiratory problems to severe pneumonia and acute respiratory distress syndrome (ARDS), the virus mostly affects the lower respiratory tract. Effective diagnosis, treatment, and prevention efforts of SARS-CoV depend on an understanding of its etiology, transmission dynamics, and clinical symptoms.

SARS-CoV manipulates various cell death pathways such as apoptosis, necrosis, pyroptosis, and autophagy to enhance its survival within host cells, evade the immune system, and induce inflammation, impacting host immune response and requiring further study for therapeutic development:

1)Apoptosis: is a controlled process of programmed cellular death that enables the cell to perish without releasing toxic substances. In order to hinder the immune system's ability to fight against SARS-CoV infections, the virus might trigger cell death in the infected cells. Proteins like the SARS-CoV ORF3a protein that become viral can start apoptotic processes that result in caspase activation, damage to mitochondria, and ultimately cell death. SARS-CoV causes infected cells to die early through apoptosis, possibly decreasing immune detection and facilitating the spread of the virus

2)necrosis:Cell damage is usually the cause of necrosis, a form of cell death. Cells enlarge throughout this process and finally rupture, releasing their contents into surrounding tissues. Tissue death may occasionally result from severe inflammatory reactions brought on by SARS-CoV. Necrosis, as opposed to apoptosis, can exacerbate tissue damage by releasing cell components that attract immune cells and produce inflammation. Cell death from tissue necrosis in severe SARS cases can exacerbate the disease's associated breathing problems.

3)Pyroptosis:is a type of inflammatory programmed cell death that is usually brought on by infection. Pro-inflammatory chemicals like IL-1β and IL-18 are released as cells enlarge, membrane pores form, and eventually lyse. By destroying infected cells, pyroptosis, which is a component of the innate immune response to infection, can be produced in SARS-CoV infections and aid in limiting viral propagation. Excessive pyroptosis, on the other hand, might cause inflammation and exacerbate lung tissue damage by contributing to the cytokine storm.

4)Autophagy: Cellular recycling helps eliminate damaged cellular parts. By breaking down viral parts, it can act as a protective mechanism. However, SARS-CoV has the ability to enhance its own replication by altering autophagy. SARS-CoV has the ability to extend the length of infection in cells by altering autophagic pathways to inhibit the breakdown of its viral particles. Autophagy in SARS-CoV infection can have a dual effect by either promoting viral survival or triggering defense mechanisms against the virus.

The factors that contributes to cell death in SARS- COV :
Viral proteins : SARS –COV infection will result in the release of different proteins that enhances the cell death , for example :

M protein , S protein and neclocapsid protein that activates the apoptosis and pyroptosis .

ORF3a, ORF3b and ORF6 :play an important role on the activation of necroptosis and apoptotic pathways due to activation of inflamosome and caspases .

BAX and BAK proteins : causes activation to caspase -9 which will activate the intrinsic apoptotic pathway .

Host immune response against this virus can induce the cell death by two different mechanisms:
The over secretion of cytokines such as : TNF ,INF-Y and IL-1 and IL-6 .
The over activation to the cells of the immune system will cause tissue damage and will contribute to cell death as the final outcome .

Host cell receptors : SARS-COV increases the affinity of binding between several death ligands (TNF ,FAS ligand) to its receptors in which they induce this process .in addition to that one of the pathogenesis patterns to this virus is increasing the expression of receptors that enhances the viral entry and replication to the targeted cell , Such as :ACER2 receptor .
Impaired autophagy this condition will inhibit the autophagy and increase the accumulation of organelles of damaged cell and enhances the apoptosis.
ER stress : the increased viral replication and the secretion for several proteins and cytokines will affect the normal proteins structure making it misfolded so this will induce several signal to be produced to activate apoptotic pathway .
mitochondrial dysfunction : SARS –COV will result on the production of ROS and oxidative stress that distributes the mitochondria and leads to the release of its contents outside to induce the extrinsic pathway of apoptosis .

Mechanisms of Cell Death Induced by SARS-CoV

1. Apoptosis Induction
   Viral Proteins:
   Spike (S) protein binds to ACE2 receptors(is found on many cell types), including lung epithelial cells, endothelial cells, and others., activating apoptotic signaling cascades.
   Envelope (E) protein causes ion imbalance, leading to ER stress and apoptosis.
   Non- stuctural proteins (e.g., NSP1, NSP3) disrupt host proteins synthesis, triggering apoptosis.

   2. Pyroptosis Induction
   Inflammasome Activation
   Viral RNA and proteins activate the NLRP3 inflammasome.
   Activated caspase-1 cleaves gasdermin D, The cleaved gasdermin D forms pores in the cell membrane, resulting in cell swelling and eventual lysis.

   3. Autophagy Manipulation:
   Autophagic Pathway Alteration
   The virus induces autophagy to facilitate viral replication while blocking its late stages, preventing degradation of viral components.

The impact of cell death on the progression of SARS-CoV

Viral Replication and Spread :
Apoptosis: Programmed cell death restricts the replication of viruses as there is no infected cell left to replicate the virus, but increased apoptosis can be detrimental to tissues and organs.
Necrosis: uncontrolled cell death allows release of virus particles hence promoting the spread of the virus.

Immune Response and Inflammation:
Pyroptosis: Inflammatory cell death that plays an important role in immune response but over activation could result in a cytokine storm causing various tissue damage and organ failure.
Cytokine Storm: The main role of pro-inflammatory cytokines is to promote inflammation and in certain instances, result in ARDS a leading cause of death in severe cases of COVID-19.

Tissue Damage and Organ Dysfunction
Lung Damage: The primary cause of lung damage and subsequent respiratory dysfunction is the death of lung epithelial cells mediated by SARS-CoV-2. Multi
Organ Failure: Widespread inflammation and death of cells in extreme cases can commit other body tissues including heart and kidneys.

Therapeutic Implications of Cell Death Pathways in SARS-CoV Infections:
The goal of therapy is to prevent excessive tissue damage and enhance clinical results by reducing or controlling cell death.

1.Therapies Targeting Apoptosis

- Inhibitors of Apoptosis: Certain medications, such as caspase inhibitors, can prevent needless cell death by blocking proteins involved in the apoptotic cascade.

- Immune Modulation to Control Apoptosis: Certain therapies, such corticosteroids, try to lessen immune-driven apoptosis in SARS-CoV infections.

* Such as Dexamethasone, used in severe cases to manage hyperinflammation.

2. Therapies Targeting Necrosis and Pyroptosis:

- Anti-Inflammatory Drugs: these drugs help reduce the tissue damage that necrosis and pyroptosis produces.

- IL-1 and IL-6 Inhibitors: To control severe inflammation, medications that target these inflammatory cytokines (such as tocilizumab and anakinra) have been utilized to disrupt the inflammatory pathways that cause pyroptosis.

3. Autophagy Modulation Therapies:

- Autophagy Inducers: Autophagy induction could aid in removing virus particles from cells before they seriously harm them.

- Drugs such as: Rapamycin

4. Therapies to Preserve Cell Integrity and Reduce Oxidative Stress:

- Antioxidants: Cell death in SARS-CoV infections is a result of oxidative stress. By reducing oxidative damage, antioxidants such as N-acetylcysteine may aid in cell repair and decrease cell death.

- ACE2 Receptor Modulators: SARS-CoV binds to ACE2 receptors, leading to downregulation of ACE2, which can increase oxidative stress and tissue damage.

5. Emerging Therapies and Experimental Approaches:

- Stem Cell Therapy: Mesenchymal stem cells (MSCs) have demonstrated promise in immune response modulation, lung repair, and inflammation reduction. Additionally, these cells can lessen necrosis and apoptosis.

- Gene Therapy: Although this is yet experimental, gene-editing techniques may be able to target particular genes implicated in cell death pathways.