Mechanisms of Immune Evasion Utilized by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

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Introduction

Over time, the human immune system has evolved to fight viruses and virally infected cells. However, to survive, viruses have also developed sophisticated biological strategies to avoid recognition and destruction by the immune system. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen responsible for the COVID-19 pandemic, has demonstrated profound ability to escape antibody neutralization through various mechanisms of immune evasion, compromising vaccine effectiveness and creating an urgent need for the development of intervention strategies to lessen disease severity and prevent death (see figure 3) (Rubio-Casillas et al., 2022; Zhang et al., 2021).

Pathogenesis of Disease

Understanding the structure of SARS-CoV-2 is important for developing effective vaccines and pharmacological therapies. The trimeric spike (S) protein of the virus covers the viral surface and is a relevant target for the development of diagnostic tools, therapies, and vaccines (see figure 1) (Zhang et al., 2021). All current vaccine strategies employed the spike protein's genetic sequence, which would allow the immune system to recognize the SARS-CoV-2 spike as a foreign antigen. In turn, this would initiate the formation of specific antibodies against it, creating a defense against infection. Generally, antibodies will attach to the spike's specific receptor-binding domain (RBD), impeding the pathogen from infecting host cells (Jackson et al., 2022; Rubio-Casillas et al., 2022).

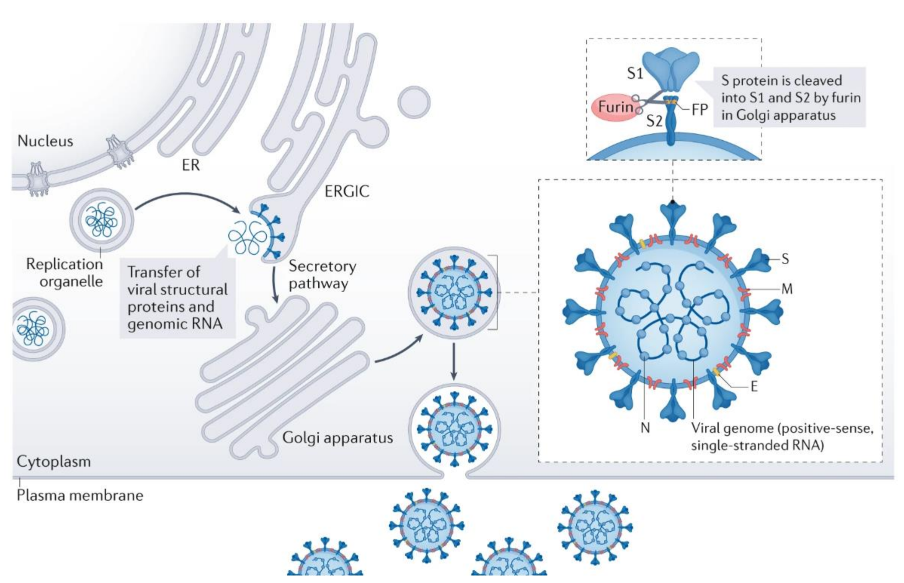

Figure 1. Coronavirus structure and maturation

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Epitope Masking: Spike camouflage uses glycan molecules

Multiple viruses have used an epitope masking strategy to escape recognition by the immune defense system. Epitope masking occurs when a virus coats their envelope glycoproteins with glycans produced by the host to prevent or minimize antibody detection. Viruses other than SARS-CoV-2 that have successfully used this evasion strategy include hepatitis C virus, HIV-1, hepatitis B virus, herpes simplex virus, and coronaviruses. The glycan barrier not only plays a critical role in epitope camouflage, but also enhances viral bonding, entrance, and membrane fusion. SARS-CoV-2 spike protein has been found to contain fewer glycans in comparison with other glycoproteins (see figure 2), inferring the formation of a weaker protective barrier that may be conducive to the attachment of the neutralizing antibodies (Rubio-Casillas et al., 2022).

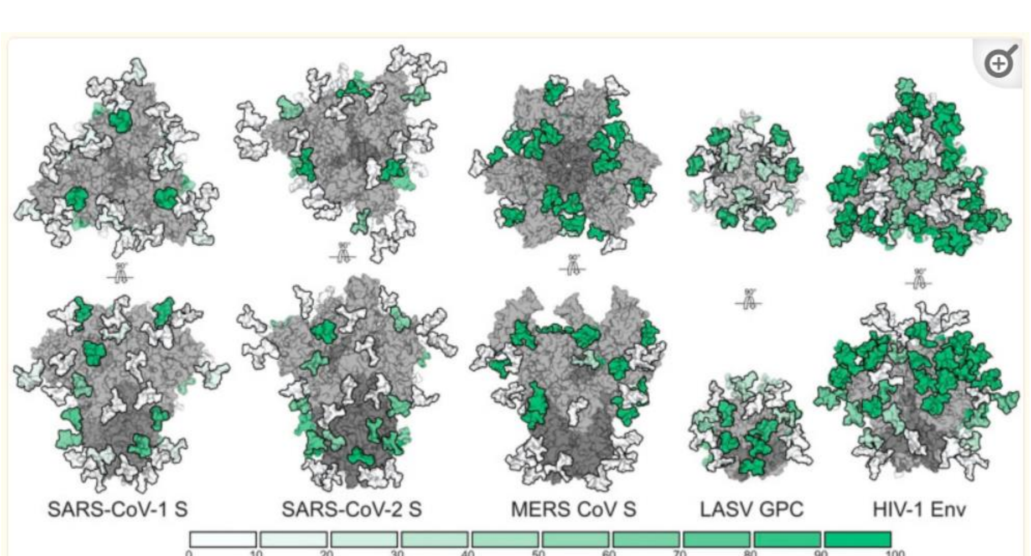

Figure 2. Glycan shields from different viruses. The number of glycans in SARS-CoV-2 is lower compared with the other viruses as evidenced in the figure above.

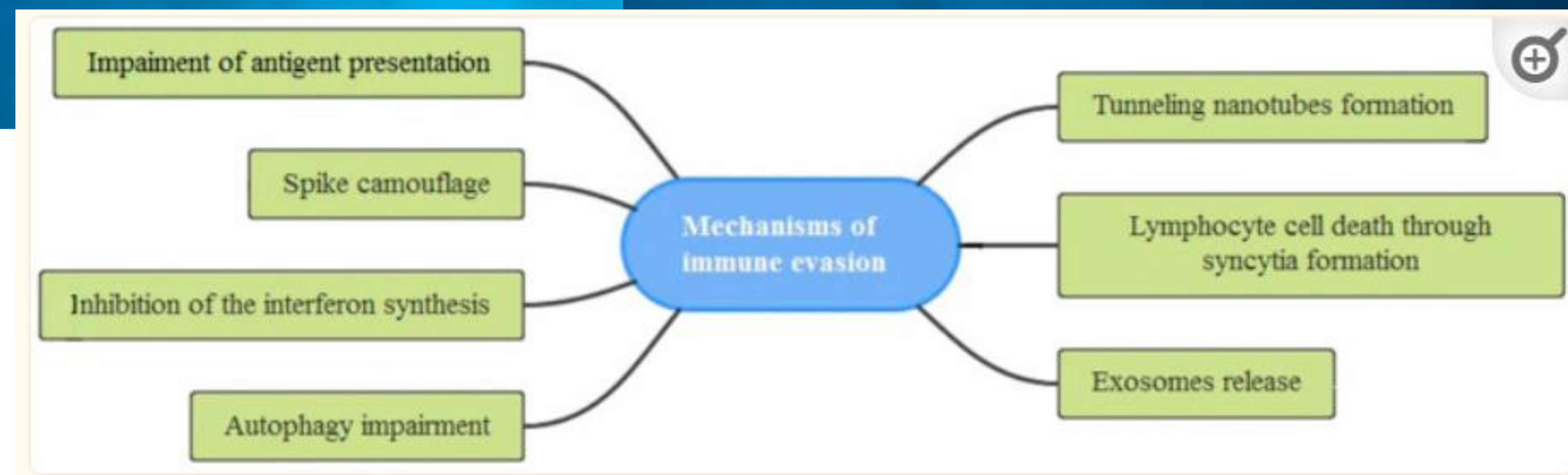

Figure 3. Various evasion mechanisms developed by SARS-CoV-2 to avoid immune surveillance and attack by the immune system.

Differential impairment of MHC-I-mediated antigen presentation by SARS-CoV-2 variants

Viruses that cause long-term infections, such as HIV-1 and the Kaposi Sarcoma associated Herpes virus (KSHV), may manage to escape immune detection by disrupting antigen presentation, which is needed for immune activation. Interference with antigen presentation can decrease production of major histocompatibility complex I (MHC-I) molecules bound to the cellular membrane. The open reading frame 8 (ORF8) of SARS-CoV-2 creates a polypeptide that engages with MHC-I molecules, resulting in reduced antigen expression (Rubio-Casillas et al., 2022).

Interference with interferon synthesis

The natural interferon (IFN) response is one of the first mechanisms against viral infection. However, coronaviruses escape host immune response by using varying mechanisms, including inhibition of IFN communication, antagonizing IFN synthesis, and boosting IFN tolerance. SARS-CoV-2 specifically renders an insufficient and delayed IFN-1 response that contributes to disease severity. Multiple proteins of this pathogen can inhibit the IFN defensive response, leading to alterations in IFN-I generation and impaired signal transduction (Rubio-Casillas et al., 2022; Sievers et al., 2023).

Increase viral replication and prevent apoptosis of infected cells through induction of incomplete mitophagy

SARS-CoV-2 activates both the induction and inhibition of apoptosis. SARS-CoV-2 controls the nuclear factor kappa B (NF-κB) pathway and inhibitors of apoptosis are increased when NF-κB is induced. This viral strategy is essential for viral infection, survival, and inflammation. In addition, the SARS-CoV-2 ORF3a protein causes mitochondrial damage and mitochondrial reactive oxygen species (mtROS) liberation which fosters hypoxia-inducible factor 1 (HIF1-α) production. This results in the enhancement of SARS-CoV-2 infection and cytokine release (Rubio-Casillas et al., 2022).

Cell to cell infection and lymphocyte cell death through syncytia formation

SARS-CoV-2 infection is associated with syncytia (fused cells) production. A recent study showed that SARS-CoV-2-infected Vero E6 cells can produce groups of many syncytia 24 hours after infection. This does not occur in uninfected cells. It is proposed that virus-mediated cell fusion may increase viral genome transmission to neighboring cells via shared cytoplasm (Rubio-Casillas et al., 2022).

Cell to cell infection and immune evasion through cytoplasmic nanotubes

SARS-CoV-2 are thought to spread and produce infection among host cells through tunneling nanotubes (TNTs). TNTs are nanometer-to-micrometer diameter cylindrical formations that connect adjacent or remote cells and foster communication between connected cells (see Figure 4). This allows for the sharing and transport of biomolecules intra-cytoplasmically. TNTs are transitory in nature and emerge and dissipate within minutes (Rubio-Casillas et al., 2022).

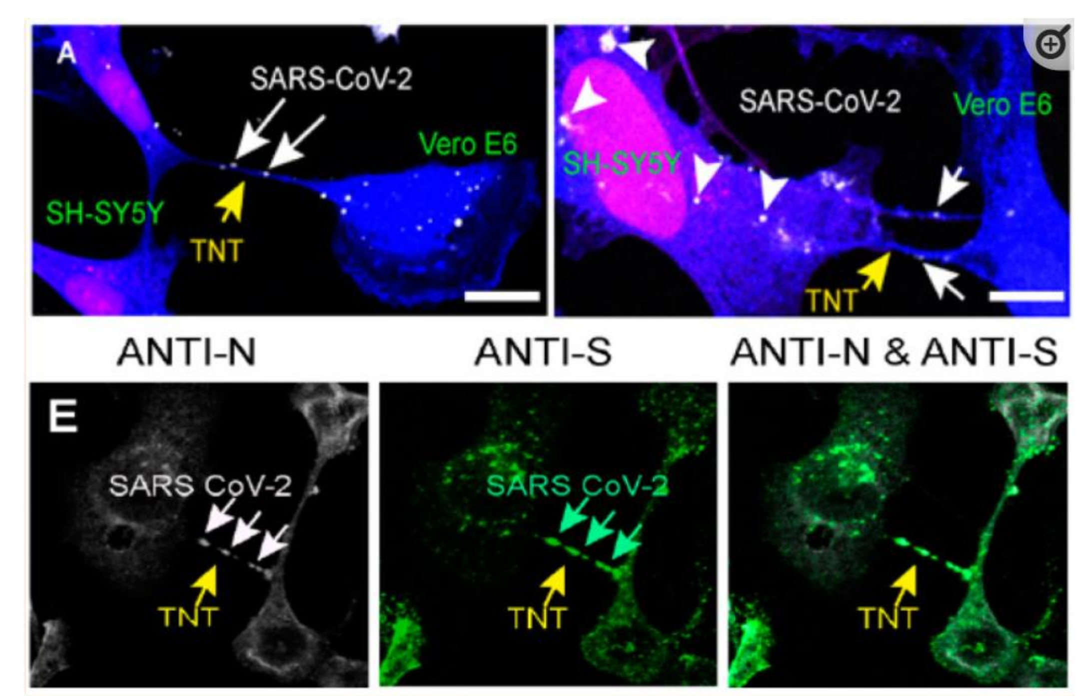

Figure 4. Cell to cell infection and immune evasion through cytoplasmic nanotubes

Immune evasion through exosome release

Exosome packaging has been shown to protect virus antibody defense systems by shielding them from inactivation and allowing virus integration within cells that are generally immune to pathogens. These exosomes can also pose as fake targets, thereby evading immune response. Exosomes that behave as Trojan horses may be responsible for reemerging virus RNA in individuals with COVID-19 (Horn & MacLean, 2021; Rubio-Casillas et al., 2022).

Recovery Outcomes and Treatments

No specific targeted antiviral treatment for SARS-CoV-2 infection exists. However, clinical trials are underway to develop novel therapeutic approaches and vaccines. Extracellular vesicles like exosomes have been identified as future therapeutic targets for development of therapeutic agents. Current treatments for COVID-19 that have been evidenced to reduce mortality include systemic corticosteroids (particularly dexamethasone), interleukin-6 receptor antagonists (such as tocilizumab), and Janus kinase inhibitors (such as baricitinib). They have also been noted to reduce length of hospital stay and time needed on a ventilator for patients with severe disease. Antivirals such as molnupiravir, nirmatrelvir/ritonavir, and remdesivir, have also been effective against COVID-19 infection that is not severe (Looi, 2023; Sbarigia et al., 2022).

Prevention Strategies

Various prevention strategies used in tandem can help to reduce virus transmission and severe disease including:

- Following strict hygiene measures like frequent handwashing with soap, avoiding touching the face and the eyes, using hand sanitizer, and wearing a face mask
- Covering coughs and sneezes with disposable tissues
- Staying home when sick and practicing social distancing
- Frequently disinfecting household or office items
- Optimizing nutrition and rest
- Staying updated on COVID vaccinations (Krittanawong et al., 2022)

Conclusions

To effectively combat SARS-CoV-2, the mechanisms by which the virus evades immune detection and destruction need to be fully explored and understood. These mechanisms will inform the development of effective vaccines, treatments, and help to optimize management of the disease, especially in those with underlying conditions.

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