Important Replication Cofactors for SARS-CoV-2, Including Delta Variant are IFITM Proteins

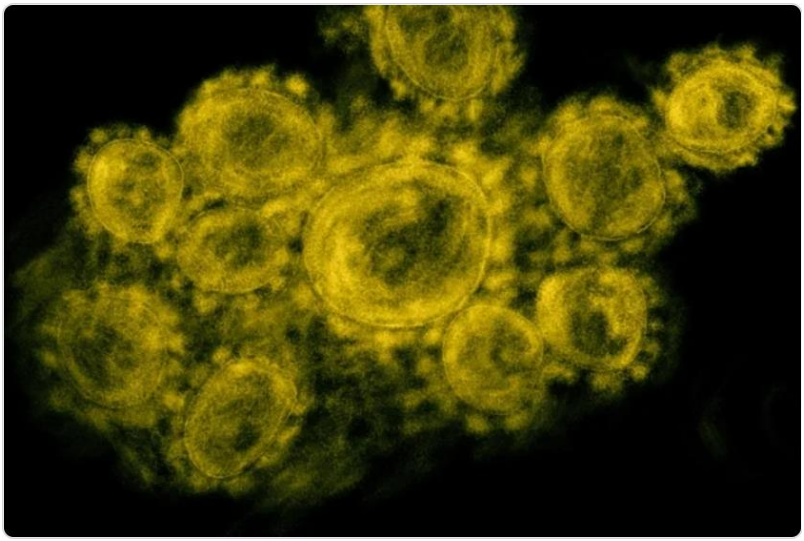
The causative agent responsible for the unprecedented coronavirus disease 2019 (COVID-19) pandemic is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The mechanism of entry of SARS-CoV-2 involves the binding of the viral spike (S) protein to the cellular angiotensin-converting enzyme (ACE) 2 receptor that leads to proteolytic processing of the S precursor into the active S1 and S2 subunits. However, there are other factors responsible for SARS-CoV-2 entry, propagation, and pathogenesis.

In a previous study, researchers have shown that a variant of SARS-CoV-2 isolated in the Netherlands on 12 February 2020 seizes interferon-induced transmembrane (IFITM) proteins, especially IFITM2, as entry cofactors during infection.

The World Health Organization (WHO) has classified four SARS-CoV-2 variants as variants of concern (VOCs): B.1.1.7, B.1.351, P.1, and B.1.617.2. These are also known as alpha, beta, gamma, and delta variants, respectively.

In a study recently published, researchers investigated the IFITM2 dependency of SARS-CoV-2 VOCs, including the delta variant for efficient infection.

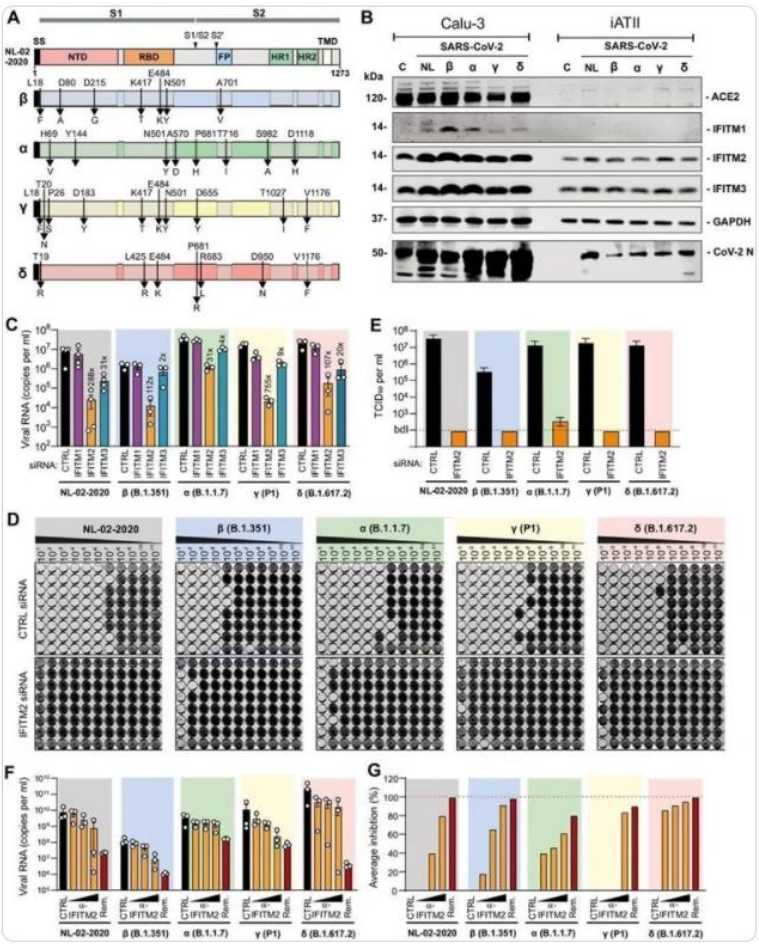


Interferon-Induced Transmembrane Proteins for Efficient SARS-CoV-2 Infection

IFITMs are a family of IFN stimulated genes (ISGs) known to protect cells against infection by many viruses, such as human immunodeficiency viruses, influenza A, rhabdo, and highly pathogenic coronaviruses, including SARS-CoV-2.

In this study, the researchers used the human epithelial lung cancer cell line Calu-3 due to its ability for siRNA knockdown (KD) of IFITM expression and iPSC-derived alveolar epithelial type II (iATII) cells as a model for the primary target cells of SARS-CoV-2 infection in the distal lung.

The Western blot analysis could not detect the ACE2 expression by iATII cells; however, it was easily detectable using fluorescence-activated cell sorting.



Outcomes

The results showed that the SARS-CoV-2 Delta variant of concern in comparison to NL-02-2020 in Calu-3 cells generated 3-fold higher levels of viral RNA.

The outcomes of the study showed that there was a reduction of viral RNA production from 31- (Alpha) to 754-fold (Gamma) on depletion of endogenous IFITM2 expression in Calu-3 cells.

Further, it was noted that KD of IFITM1 had a small effect; however, silencing of IFITM3 resulted in 2- to 31-fold depletion of viral RNA production.

Interestingly, the production of infectious SARS-CoV-2 particles in Calu-3 cells reduced to near background levels upon silencing of IFITM2. Furthermore, the replication of SARS-CoV-2 VOC in iATII was reduced by the antibody targeting the N-terminus of IFITM2 in a dose-dependent manner.

"*IFITMs (especially IFITM2) are also critical cofactors for efficient replication of current SARS-CoV-2 VOCs including the dominant Delta variant*."

Conclusion

The study's findings suggest that endogenous IFITMs (especially IFITM2) are important cofactors for the effective replication of SARS-CoV-2 VOCs, including the dominant Delta variant. It was noted that the SARS-CoV-2 Delta variant replicated at a 30-times higher rate in comparison to the early NL-02-2020 isolate in iATII cells. Thus, the dependency of IFITM2 maintained by VOCs can be further explored as a target for therapeutic or preventive approaches.

Efficient inhibition of the SARS-CoV-2 Delta VOC by an a-IFITM2 antibody illustrates that IFITM2 may have a crucial role in SARS-CoV-2 transmission as well as pathogenesis.

Source:

https://www.news-medical.net/news/20211122/IFITM-proteins-are-important-replication-cofactors-for-SARS-CoV-2-including-Delta-variant.aspx