CIAO COVID AOP
Early KE harmonization:
SARS-CoV-2 entry and antagonism of Interferon (IFN)-I antiviral response leading to replication

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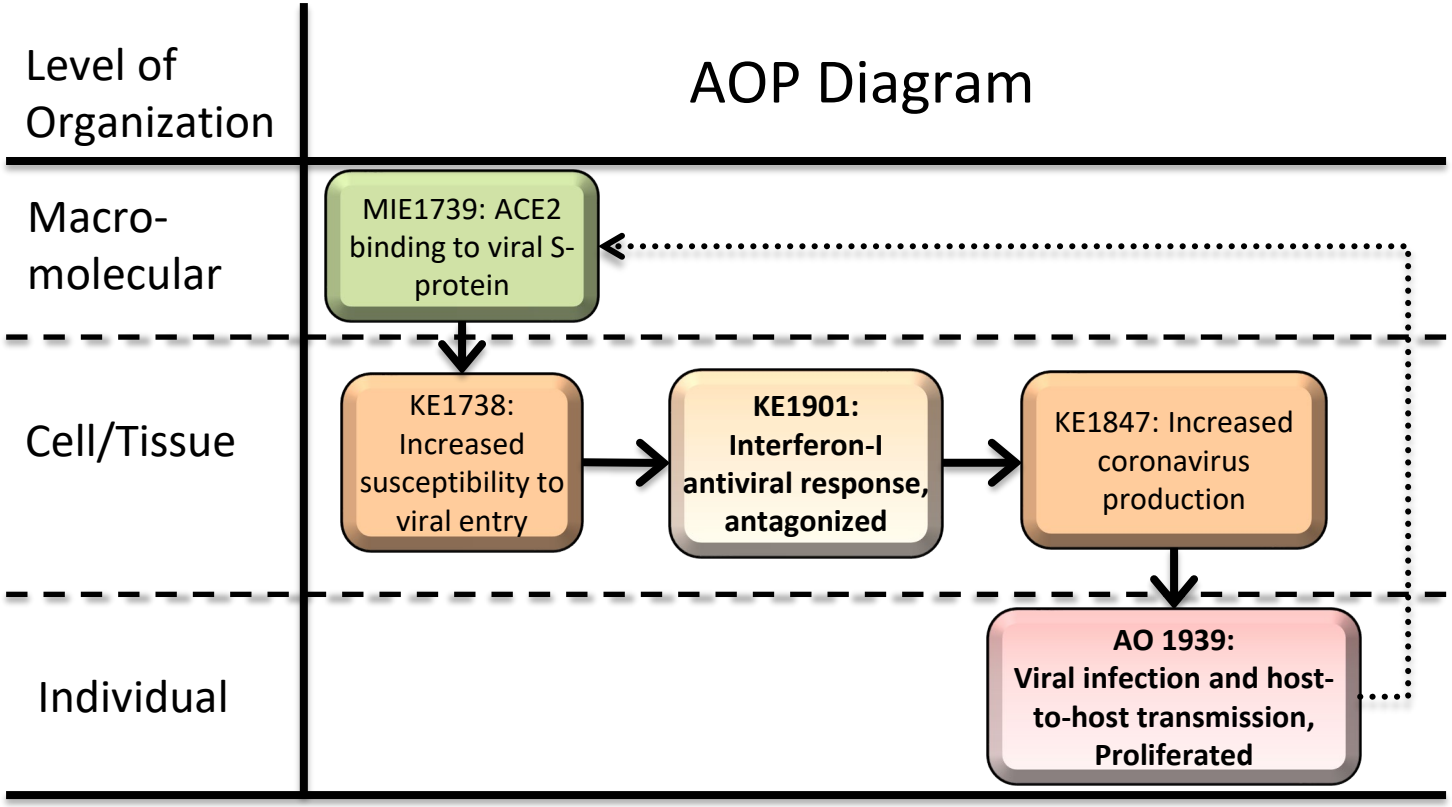
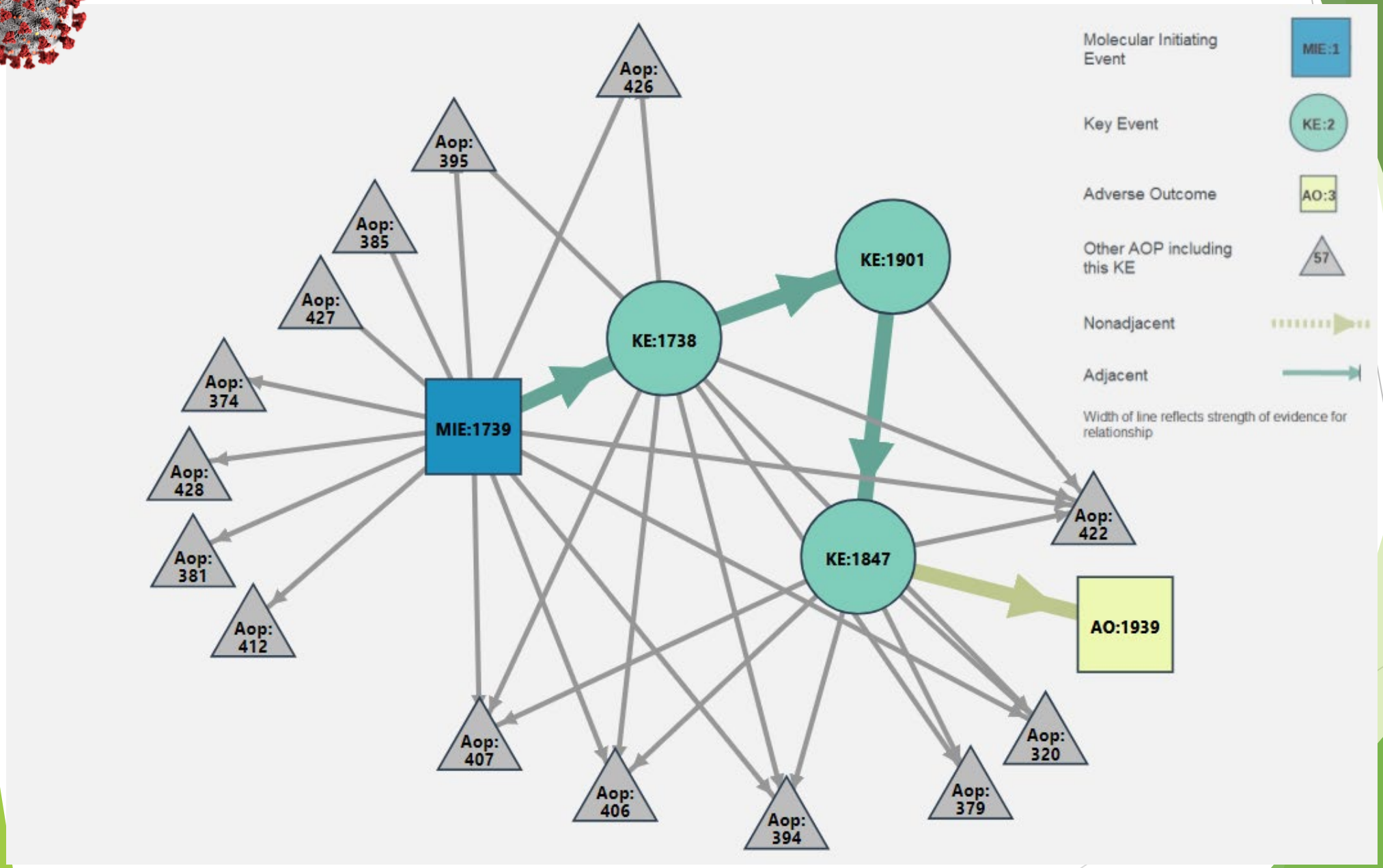
CIAO COVID-19/WikiPathways Joint Workshop, May 9, 2022

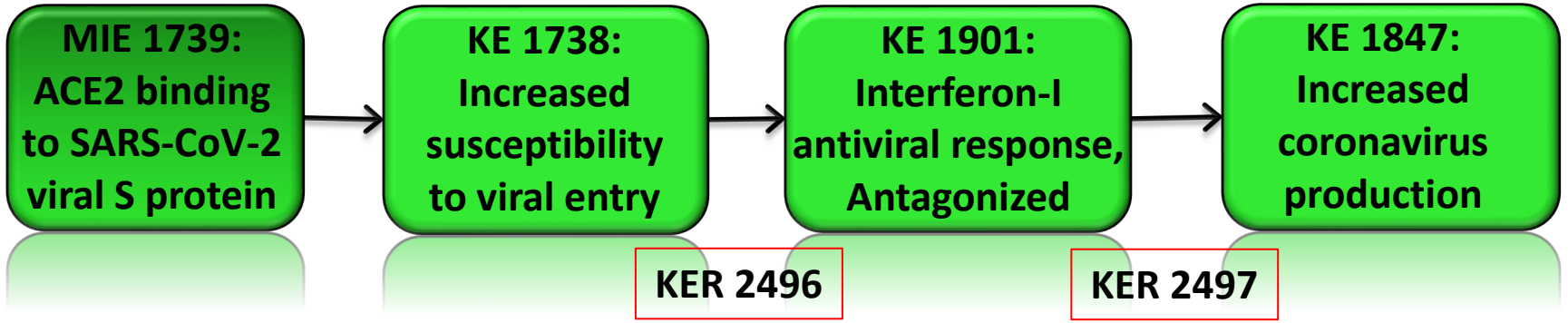
AOP 430: Sars-CoV-2 Interferon-I antiviral response antagonism and increased viral production leading to viral infection proliferation



AOP 430 network view

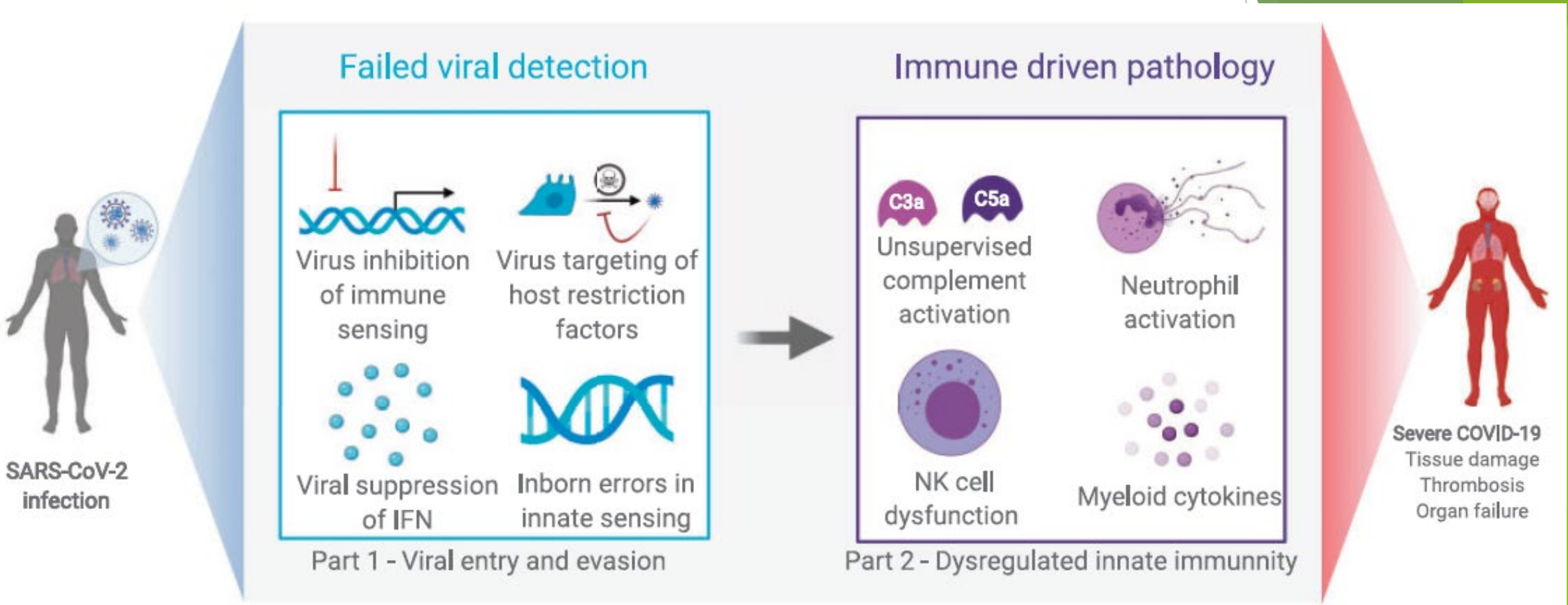


Early Key Event Hub Module

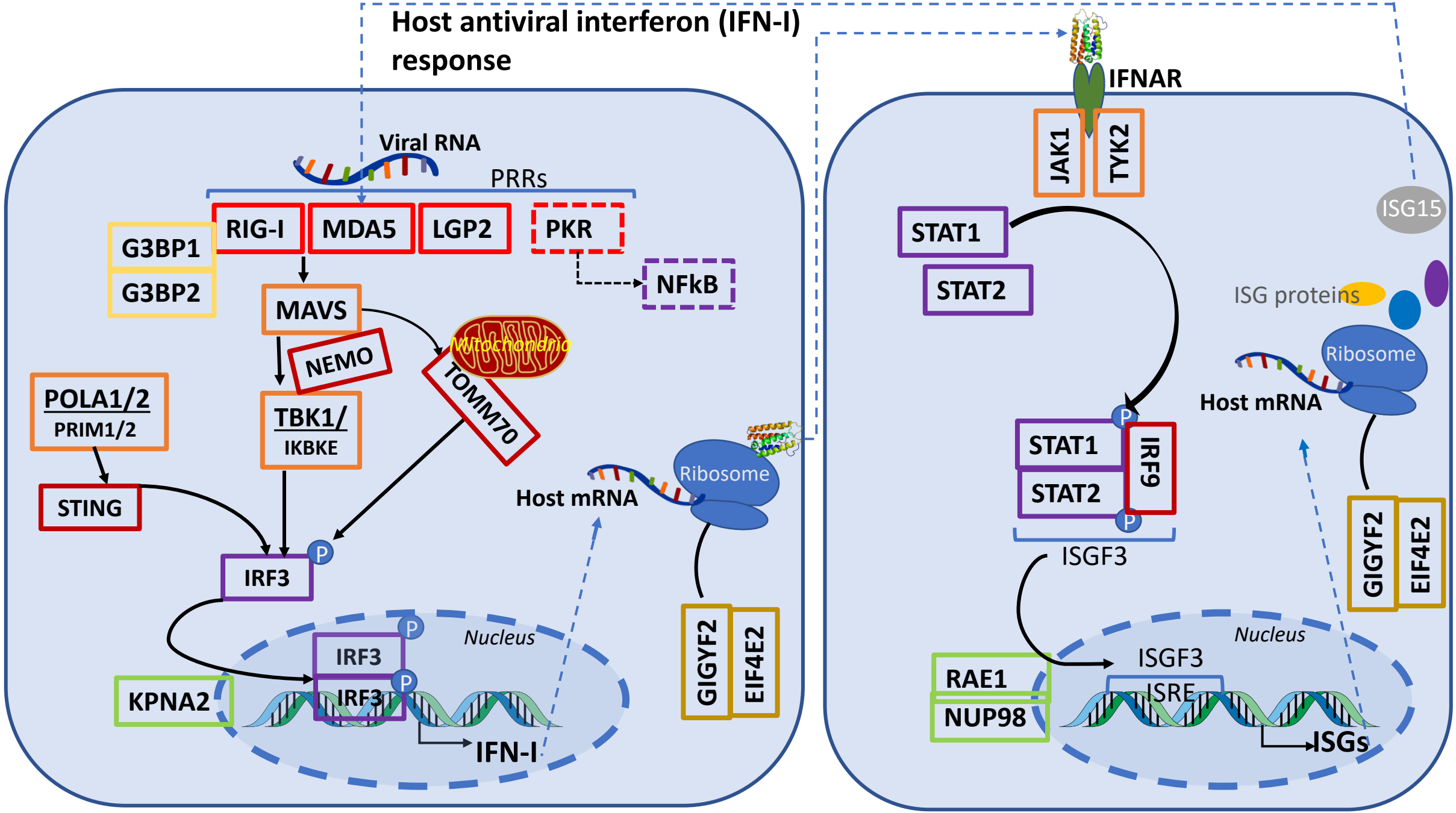


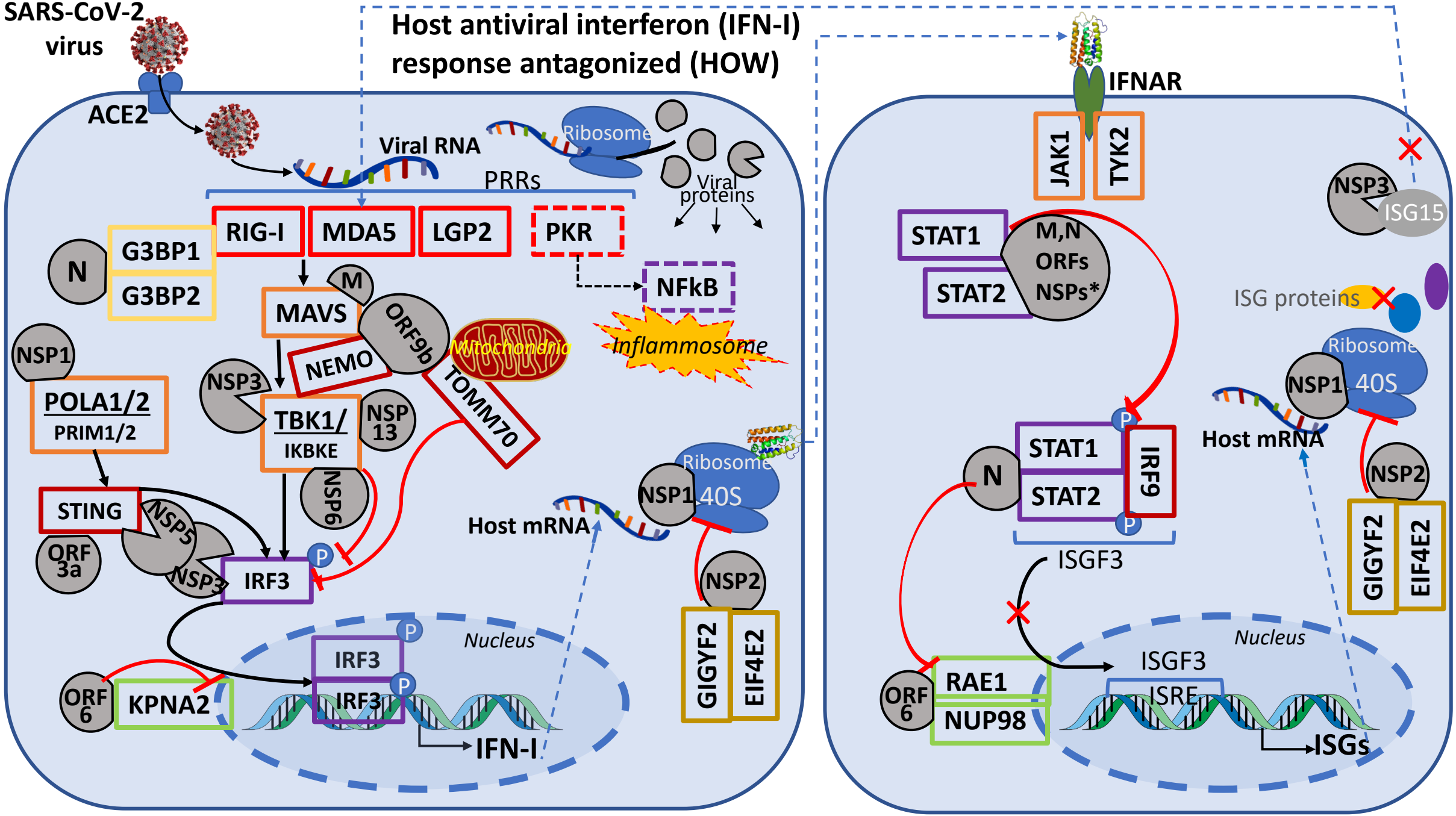
KER 2496: Increased susceptibility to viral entry *leads to* IFN-I response, antagonized

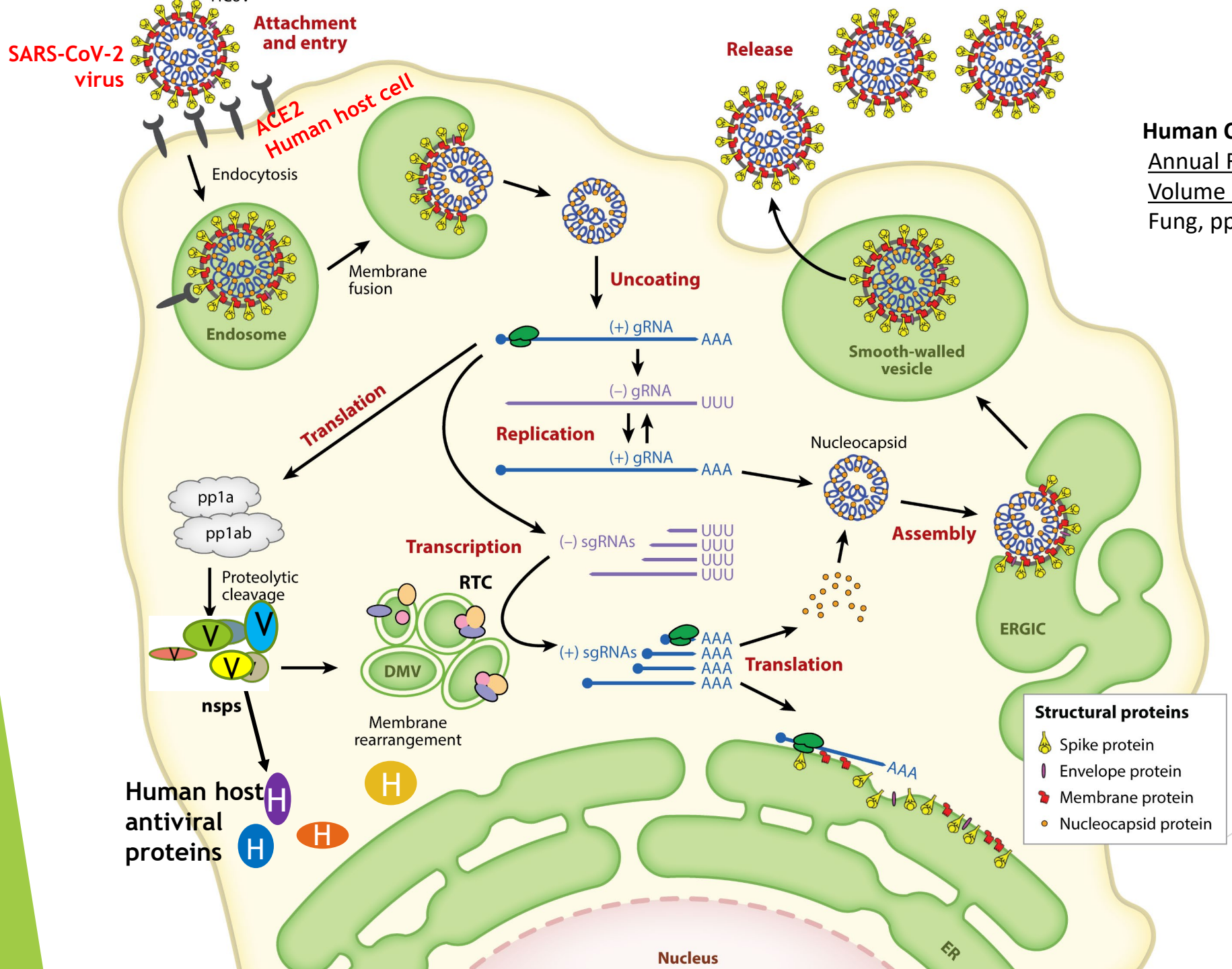
KER 2497: IFN-I response, antagonized leads to Increased SARS-CoV-2 production



Innate immunology in COVID-19—a living review.
Part I: viral entry, sensing and evasion
Coveney et al. 2020 doi:
10.1093/oxfimm/iqaa004





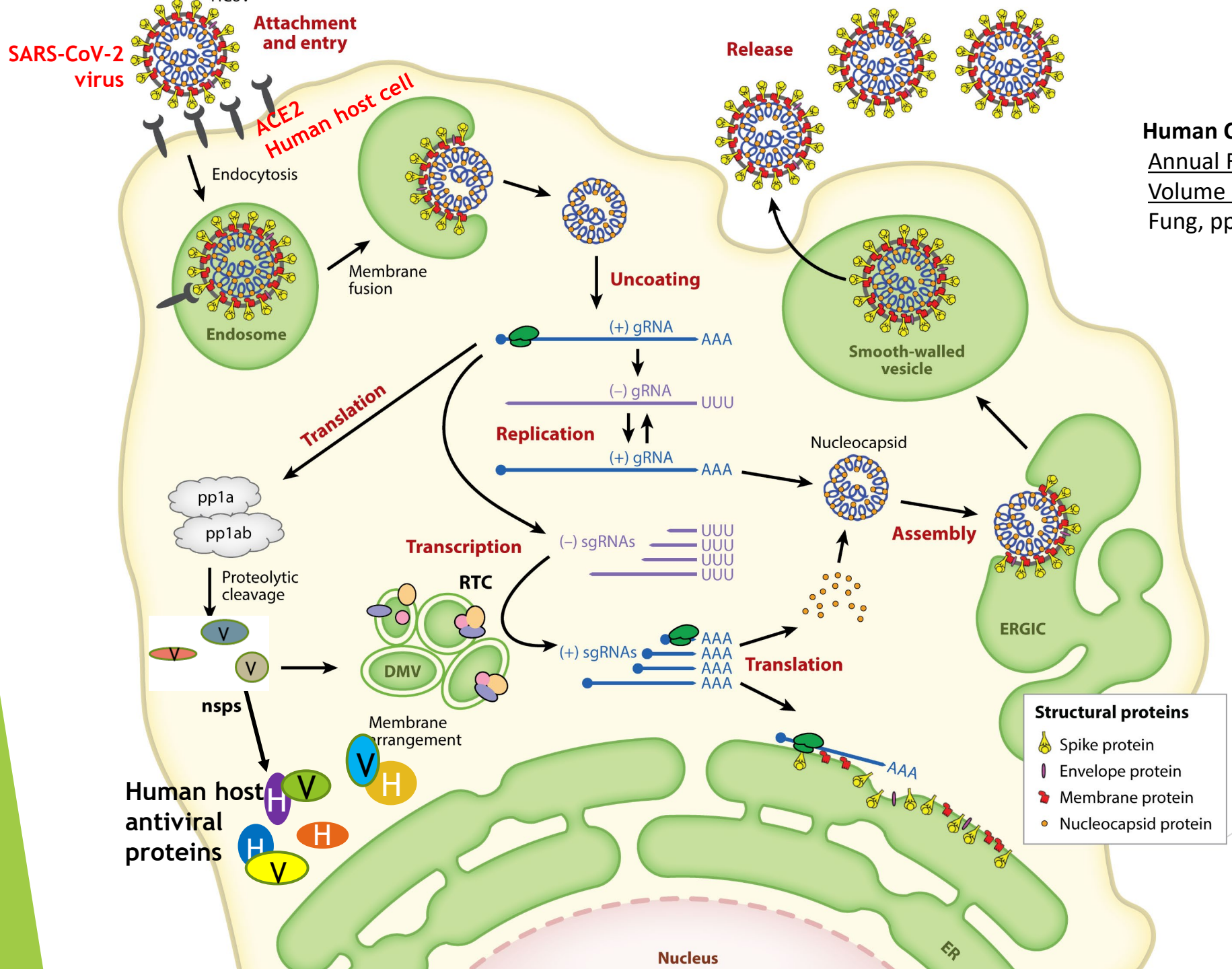


Human Coronavirus: Host-Pathogen Interaction

Annual Review of Microbiology

Volume 73, 2019

Fung, pp 529-557



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Essentiality of IFN anti-viral response antagonism to downstream events

- ACE2 and TMPRSS2 proteins allow viral entry but are not the only determinant of viral replication
- IFNs are a key determinant in the progression of COVID-19.
  - Entry is essential for viral protein expression→ IFN antagonism→ viral replication: viral load → disease/inflammatory responses and/or transmission.
- IFN antagonism and viral replication/production may occur simultaneously but in separate cellular compartments
  - KE 1847 (production) is downstream based on essentiality

IFN and Increased SARS-CoV-2 production

Biological plausibility

- Interferon administered just before or upon exposure abrogates viral production
- IFN autoantibodies in some patients are an underlying factor for more severe disease

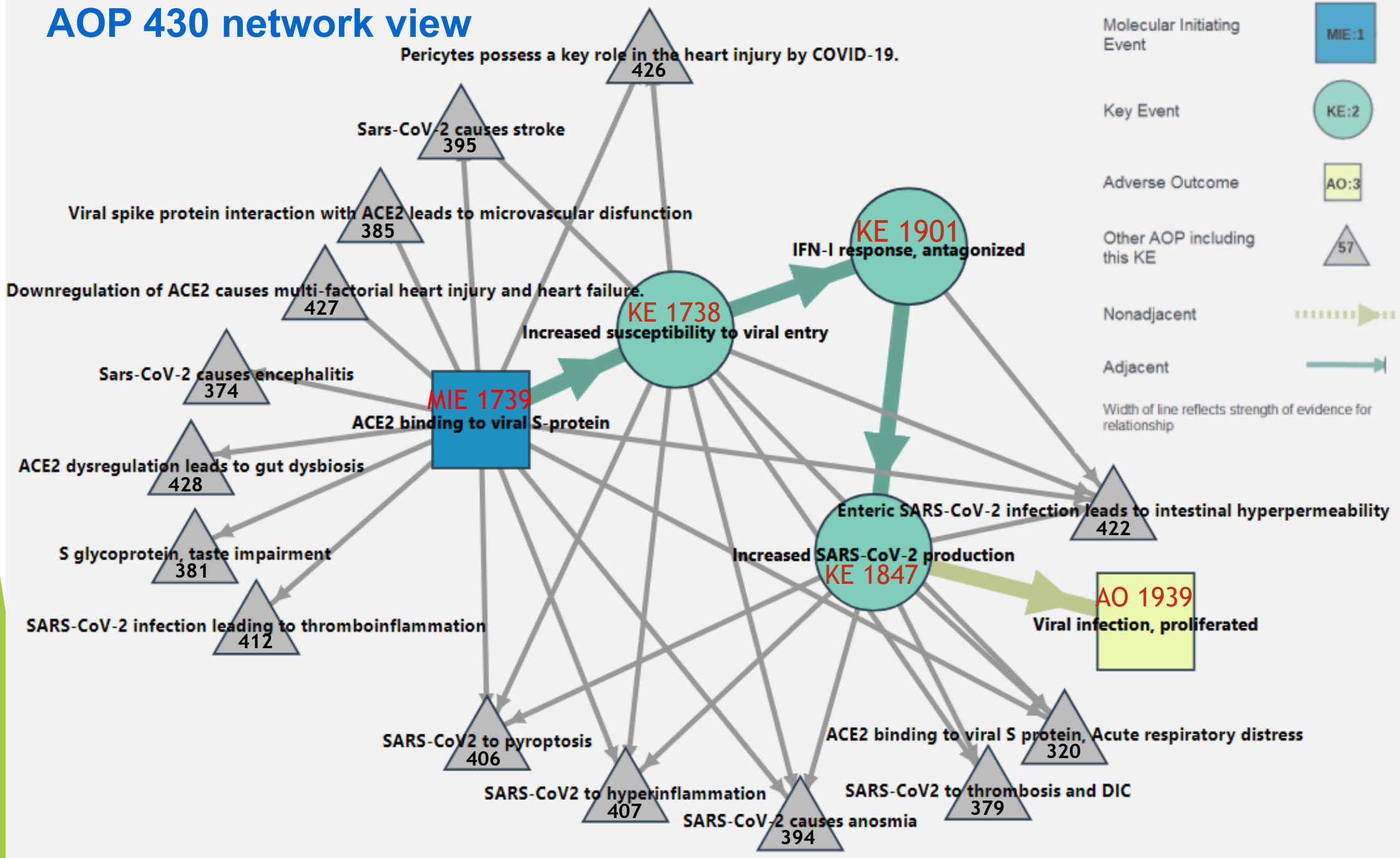
Empirical evidence

- Empirical support for temporal concordance
  - Interferon expression delayed by SARS-CoV-2 vs. other viruses

Cell and Tissue type specificity

- IFN antagonism/viral replication is prevalent in nasal, upper airway, and enteric tissues that provide paths to distal organs and out of the body (to environmental exposure routes).

AOP 430 network view



AOPs using MIE 1739 ACE2 binding to viral S-protein: sorting AOPs requiring replication

Directly leading to adverse KE

- No viral replication required
- AOP 374 Brain cells neuroinflamation
- AOP 381 ACE2 downregulation
- AOP 385 ACE2 dysregulation
- AOP 395 Pericytes 1738→BBB disruption
- AOP 412 ACE2 inhibition
- AOP 426 Heart failure→1738
- AOP 427 ACE2 downregulation
- AOP 428 ACE2 dysregulation

Currently include KE 1738→KE 1847

- Viral replication required for downstream events:
- AOP 320
- AOP 379
- AOP 394
- AOP 406
- AOP 407
- AOP 422
- AOP 430: KE1738-KE1901-KE1847

Acknowledgements

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