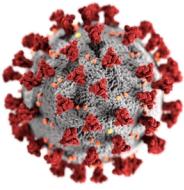


# CIAO COVID AOP

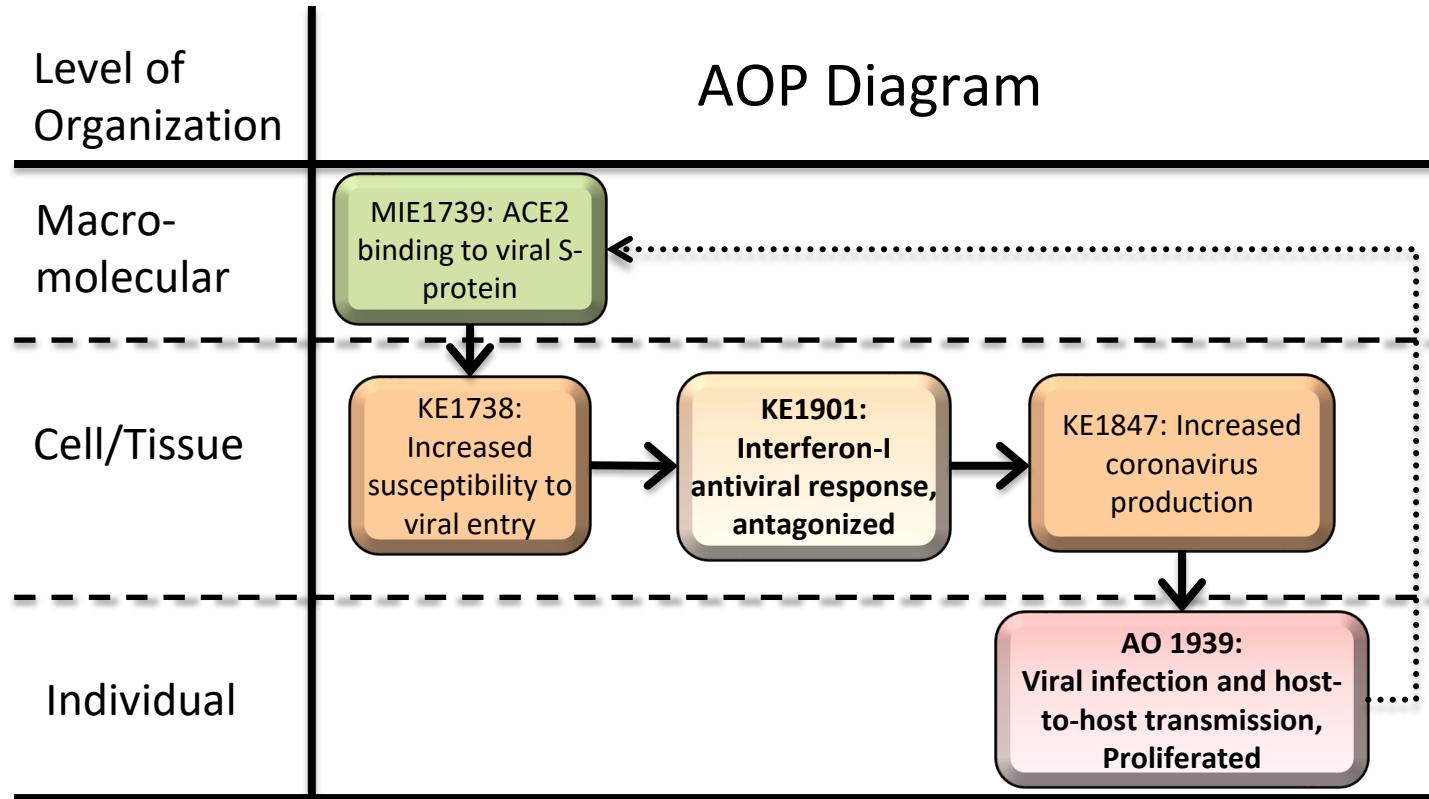
## Early KE harmonization: SARS-CoV-2 entry and antagonism of Interferon (IFN)-I antiviral response leading to replication

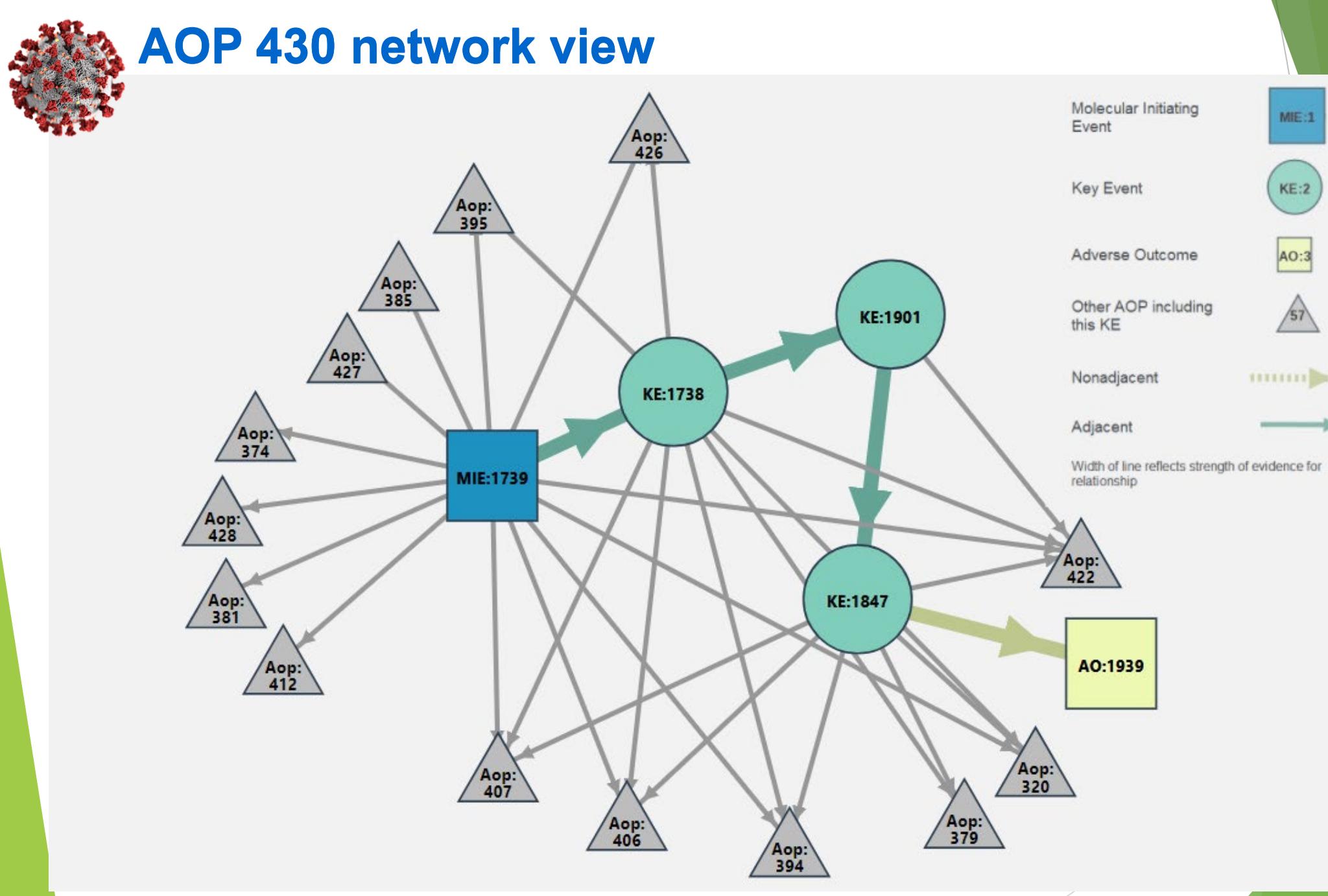
Sally Mayasich, Maria João Amorim, Laure-Alix Clerbaux,  
Penny Nymark

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

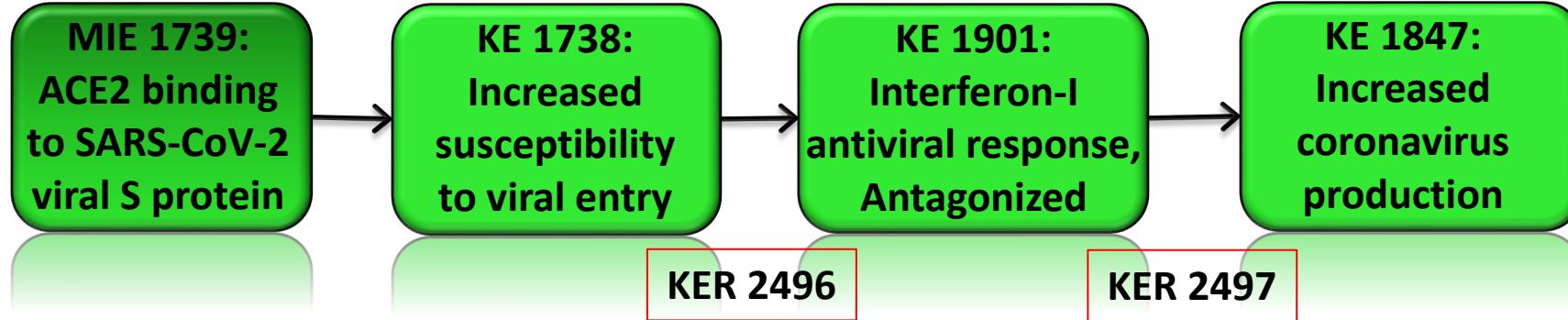


# AOP 430: Sars-CoV-2 Interferon-I antiviral response antagonism and increased viral production leading to viral infection proliferation



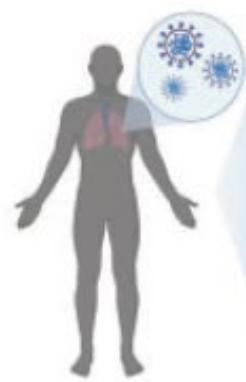


# Early Key Event Hub Module



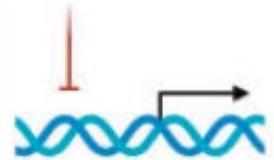
**KER 2496:** Increased susceptibility to viral entry *leads to* IFN-I response, antagonized

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



SARS-CoV-2  
infection

## Failed viral detection



Virus inhibition  
of immune  
sensing



Virus targeting of  
host restriction  
factors



Viral suppression  
of IFN



Inborn errors in  
innate sensing

Part 1 - Viral entry and evasion

## Immune driven pathology



C3a      C5a  
Unsupervised  
complement  
activation



Neutrophil  
activation



NK cell  
dysfunction



Myeloid cytokines

Part 2 - Dysregulated innate immunity



Severe COVID-19  
Tissue damage  
Thrombosis  
Organ failure

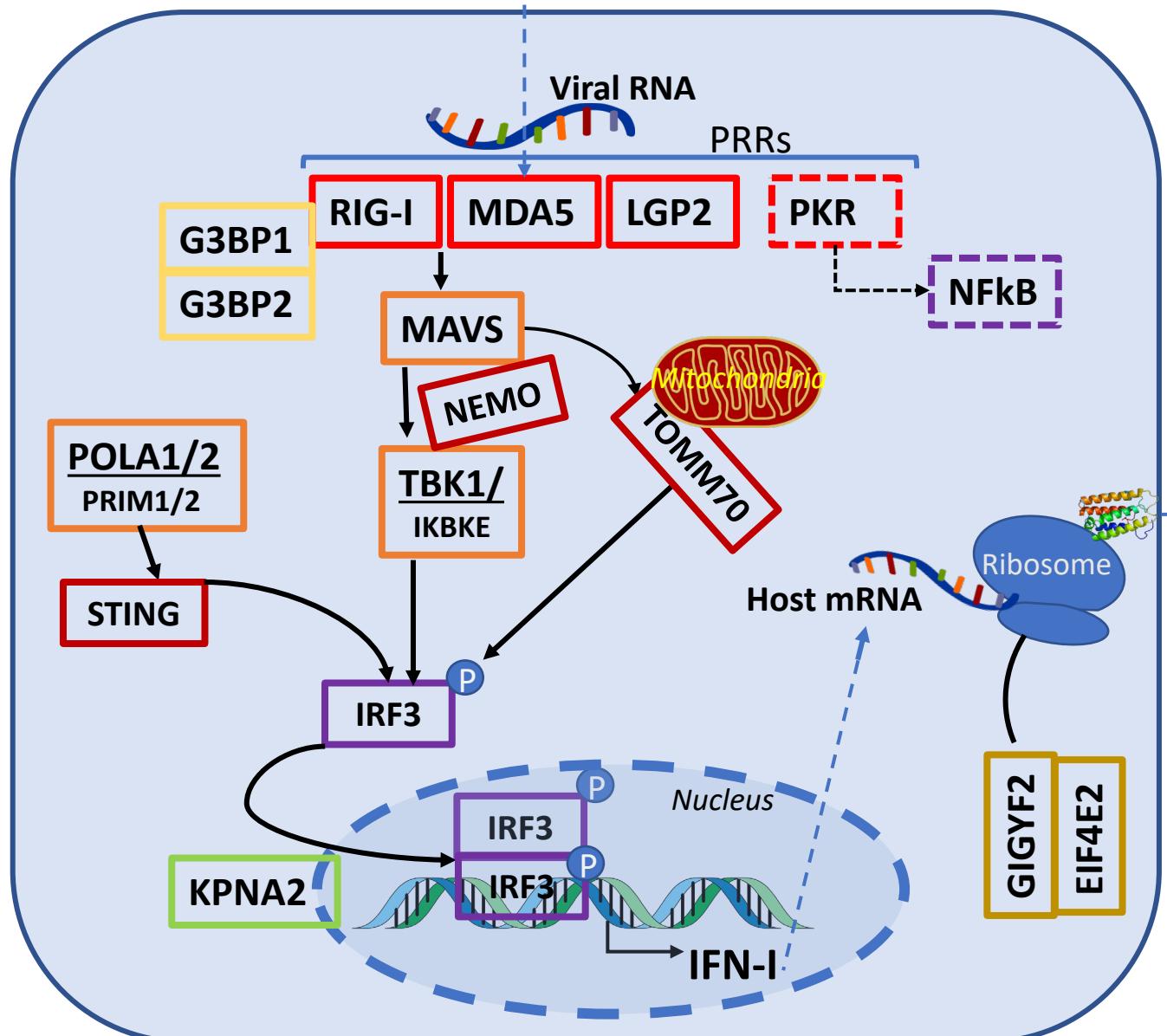
Innate immunology in COVID-19—a living review.

Part I: viral entry, sensing and evasion

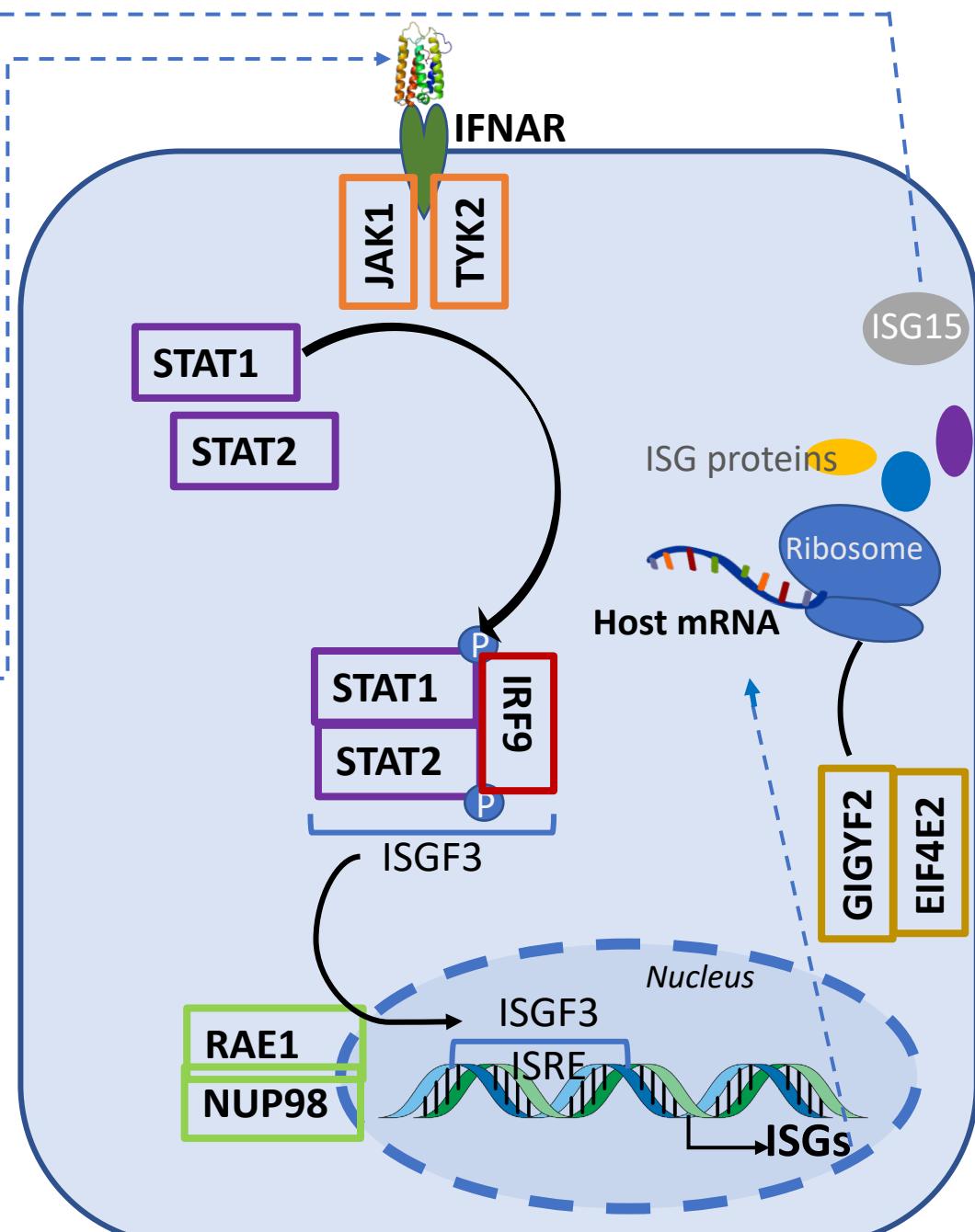
Coveney et al. 2020 doi:

10.1093/oxfimm/iqaa004

## Host antiviral interferon (IFN-I) response



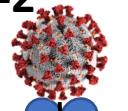
IFNAR



PLEASE DO NOT CITE OR SHARE

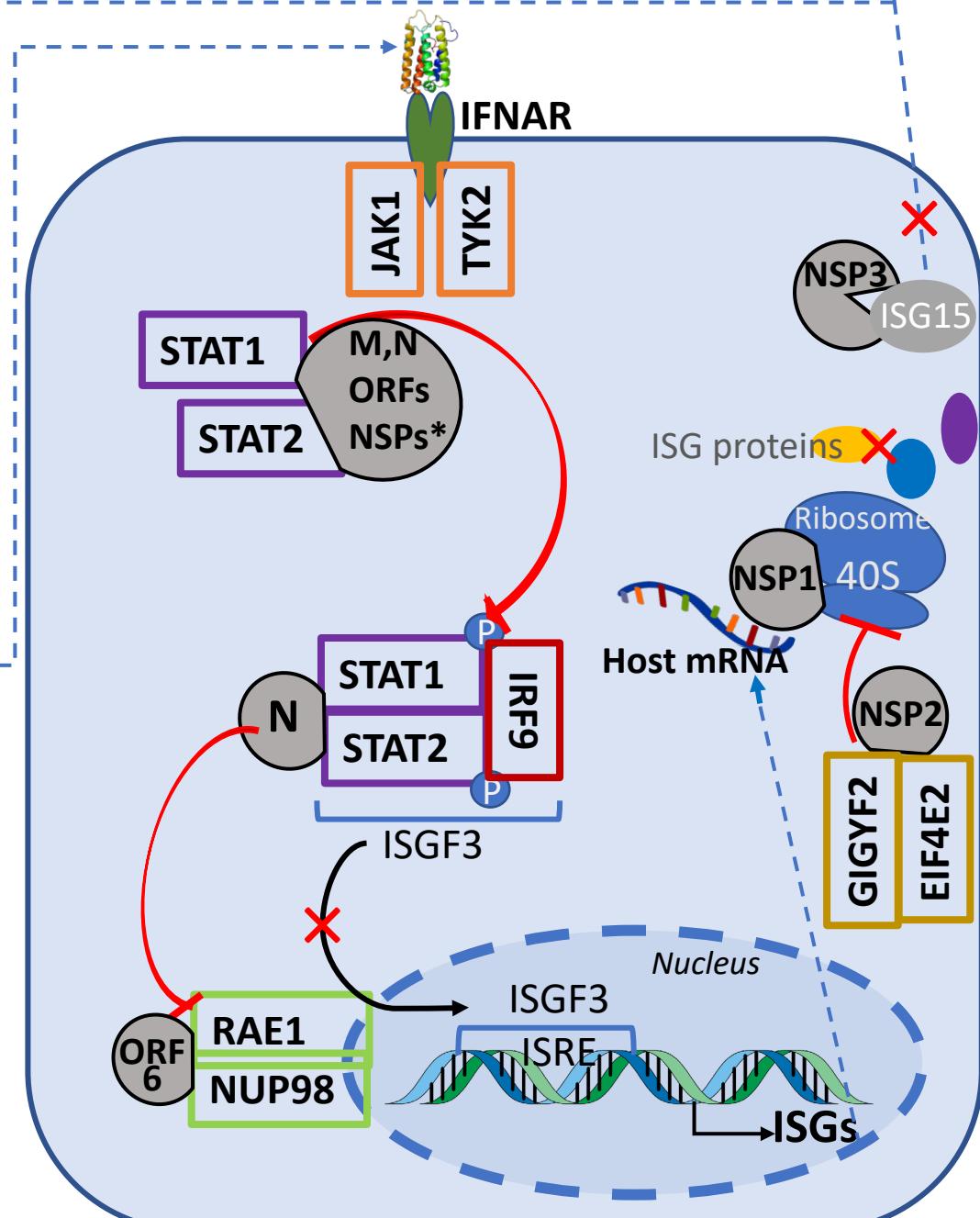
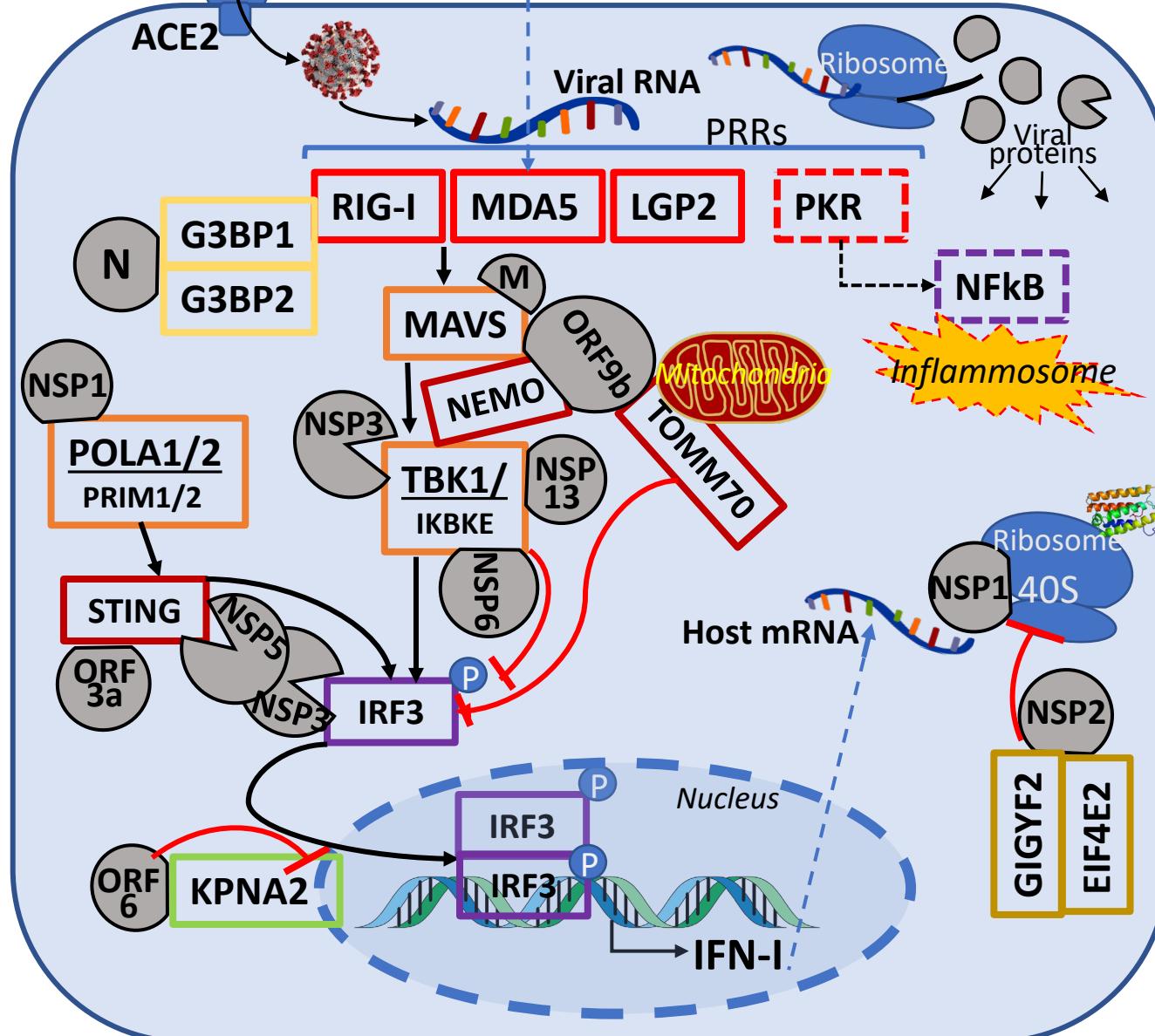
SARS-CoV-2

virus

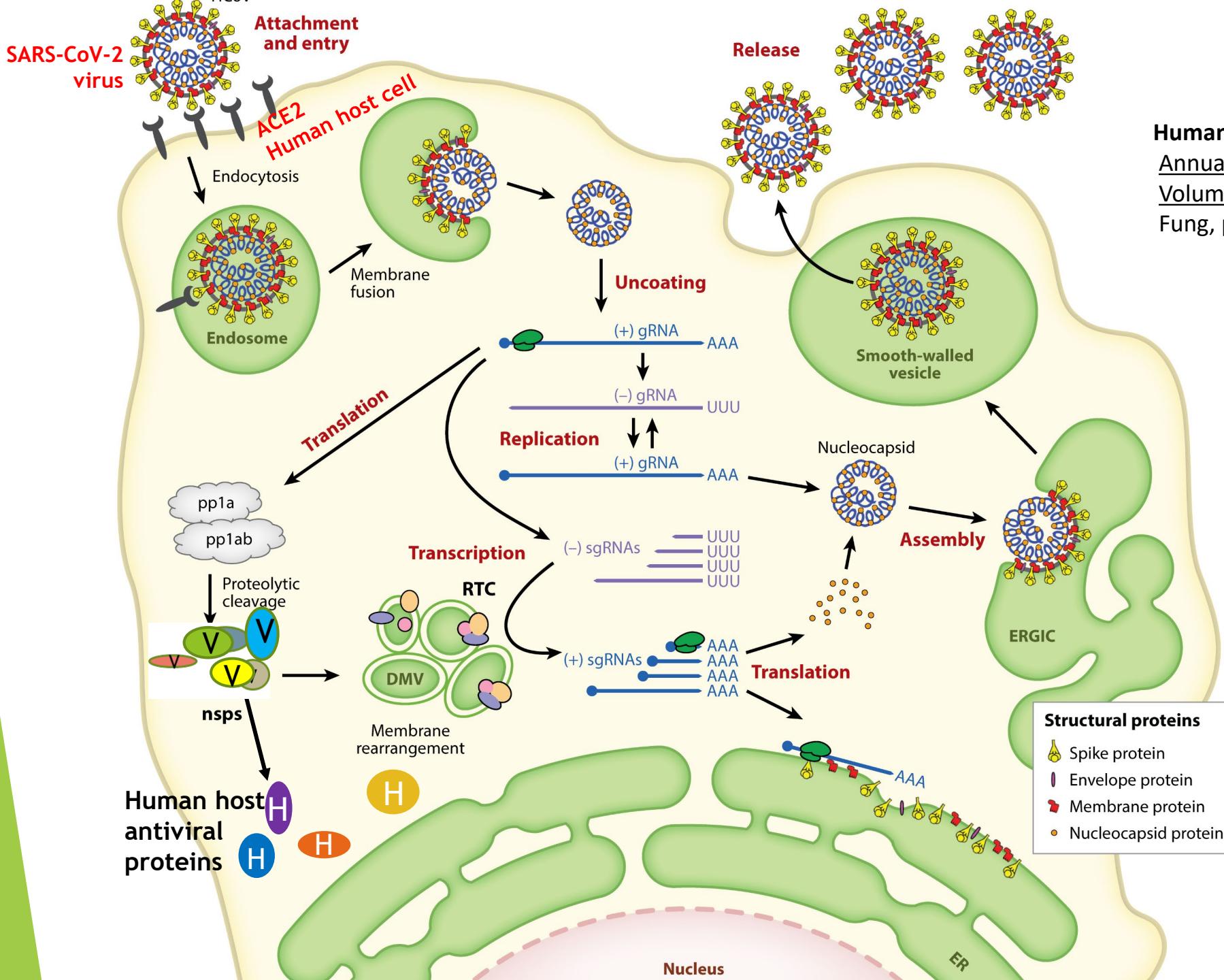


ACE2

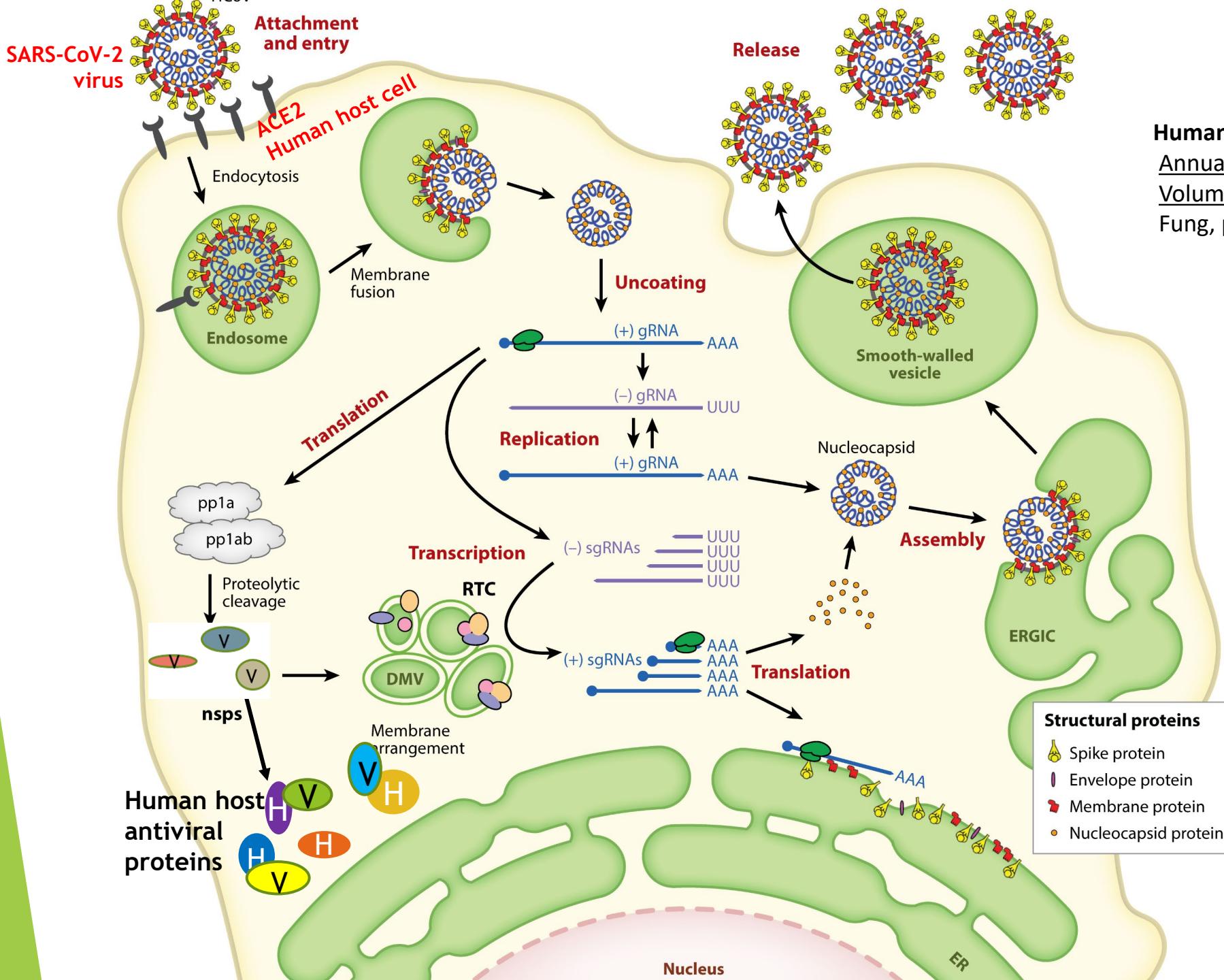
## Host antiviral interferon (IFN-I) response antagonized (HOW)



PLEASE DO NOT CITE OR SHARE



**Human Coronavirus: Host-Pathogen Interaction**  
Annual Review of Microbiology  
**Volume 73, 2019**  
**Fung, pp 529-557**



**Human Coronavirus: Host-Pathogen Interaction**  
Annual Review of Microbiology  
**Volume 73, 2019**  
**Fung, pp 529-557**

# 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

Pericytes possess a key role in the heart injury by COVID-19.

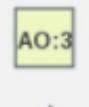
426



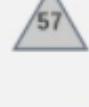
MIE:1



KE:2



AO:3



57



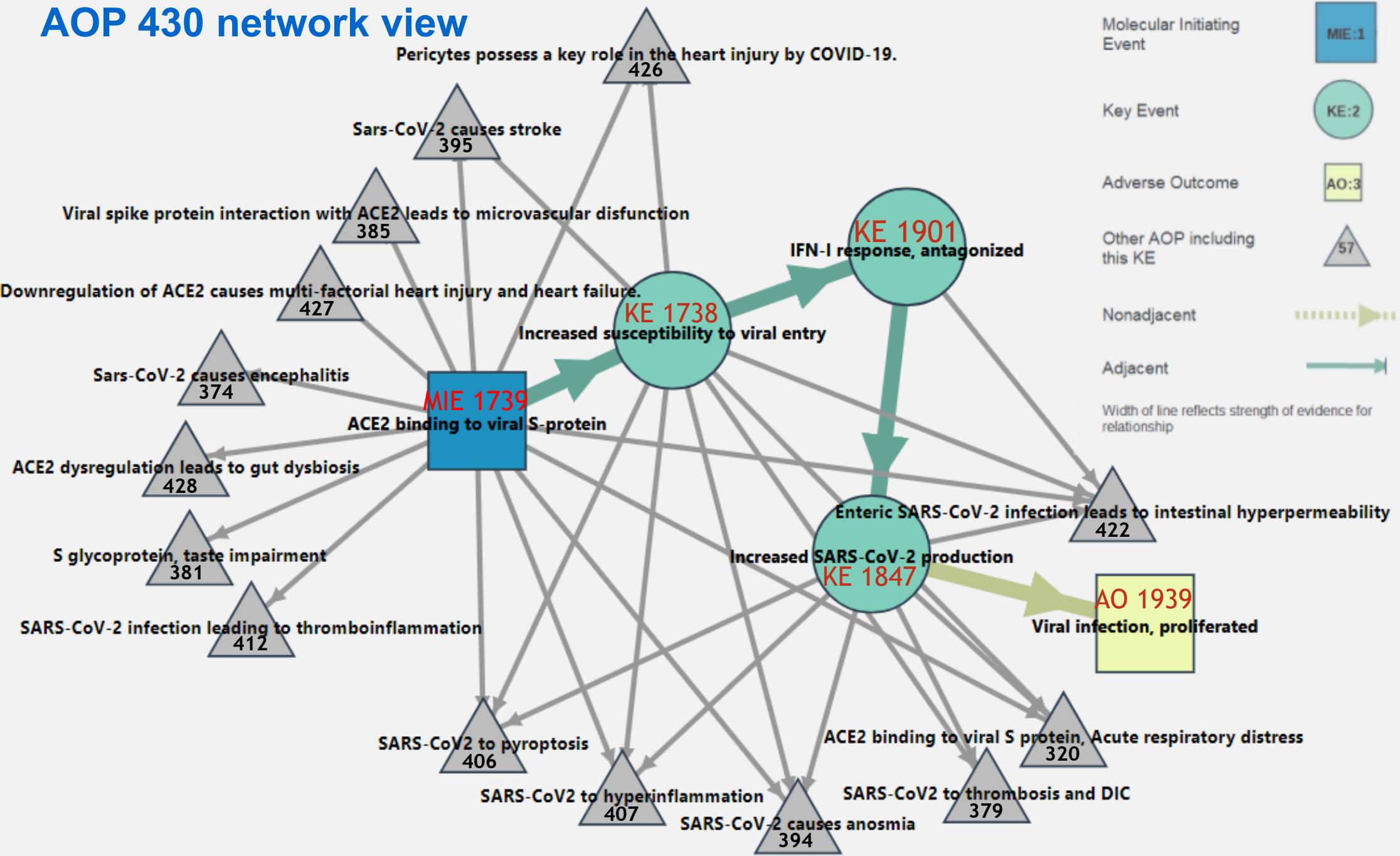
Nonadjacent



Adjacent



Width of line reflects strength of evidence for relationship



# 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 neuroinflammation
- ▶ 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

- ▶ Thanks to Julija Filipovska and Brigitte Landesmann for input on weight of evidence and AOP development.