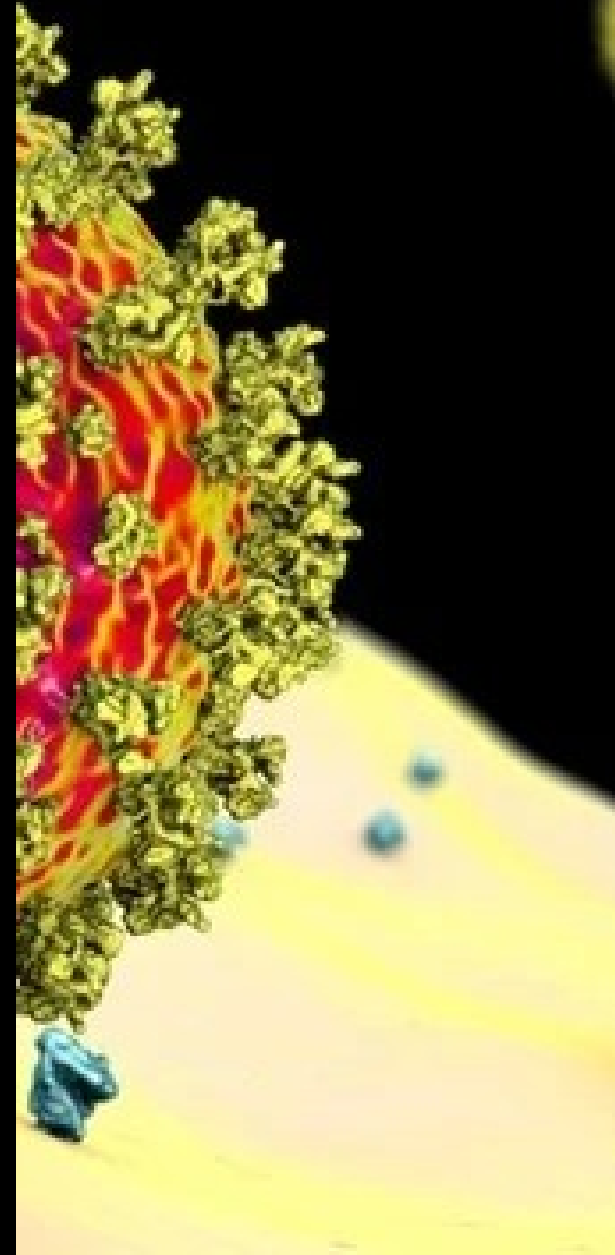




SARS-CoV-2 pathophysiology



1. Renin-angiotensin-aldosteron systém (RAS)

- Receptor ACE2
- Pathologic regulation of RAS and covid 19



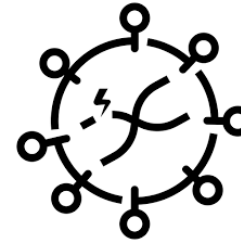
1. Renin-angiotensin-aldosteron systém (RAS)

- Receptor ACE2
- Pathologic regulation of RAS and covid 19



2. Non-specific (innate) immunity a mutagenesis

- Mechanisms of innate immunity
- Mutations raised by host cell



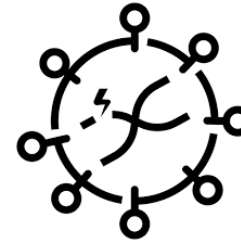
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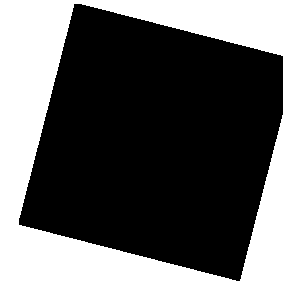
2. Non-specific (innate) immunity a mutagenesis

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3. Specific immune reaction and complement activation

- Antibody response
- Inflammation



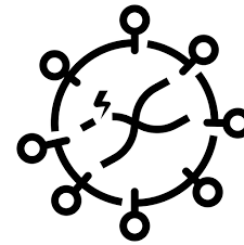
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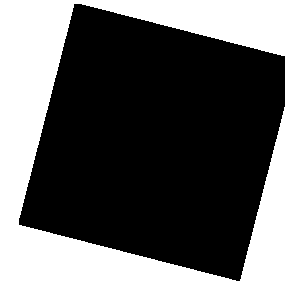
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3. Specific immune reaction and complement activation

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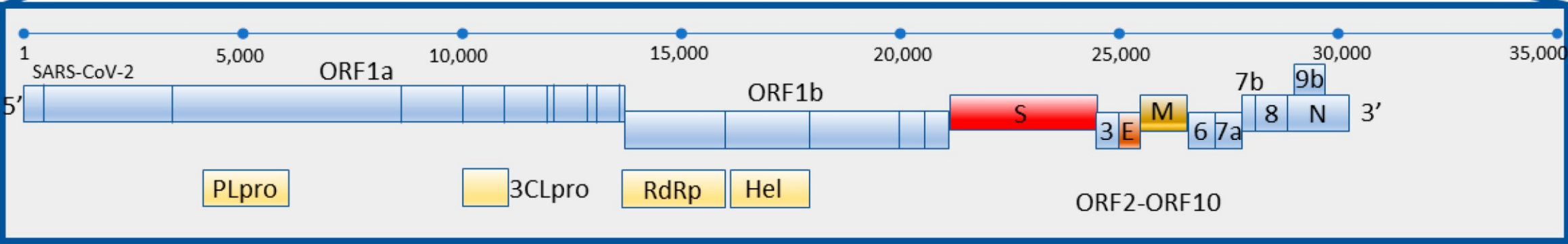
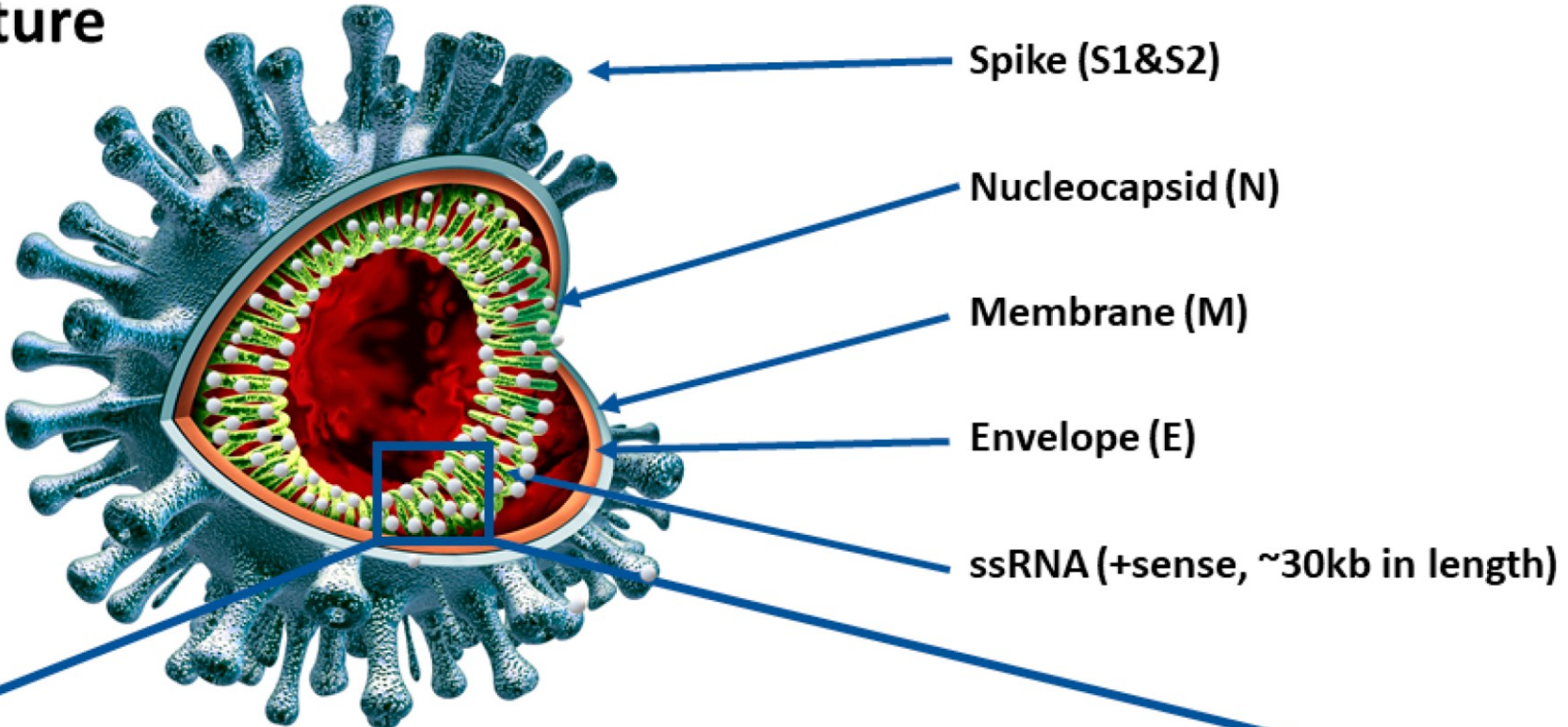


4. Mechanisms of endothelial injury

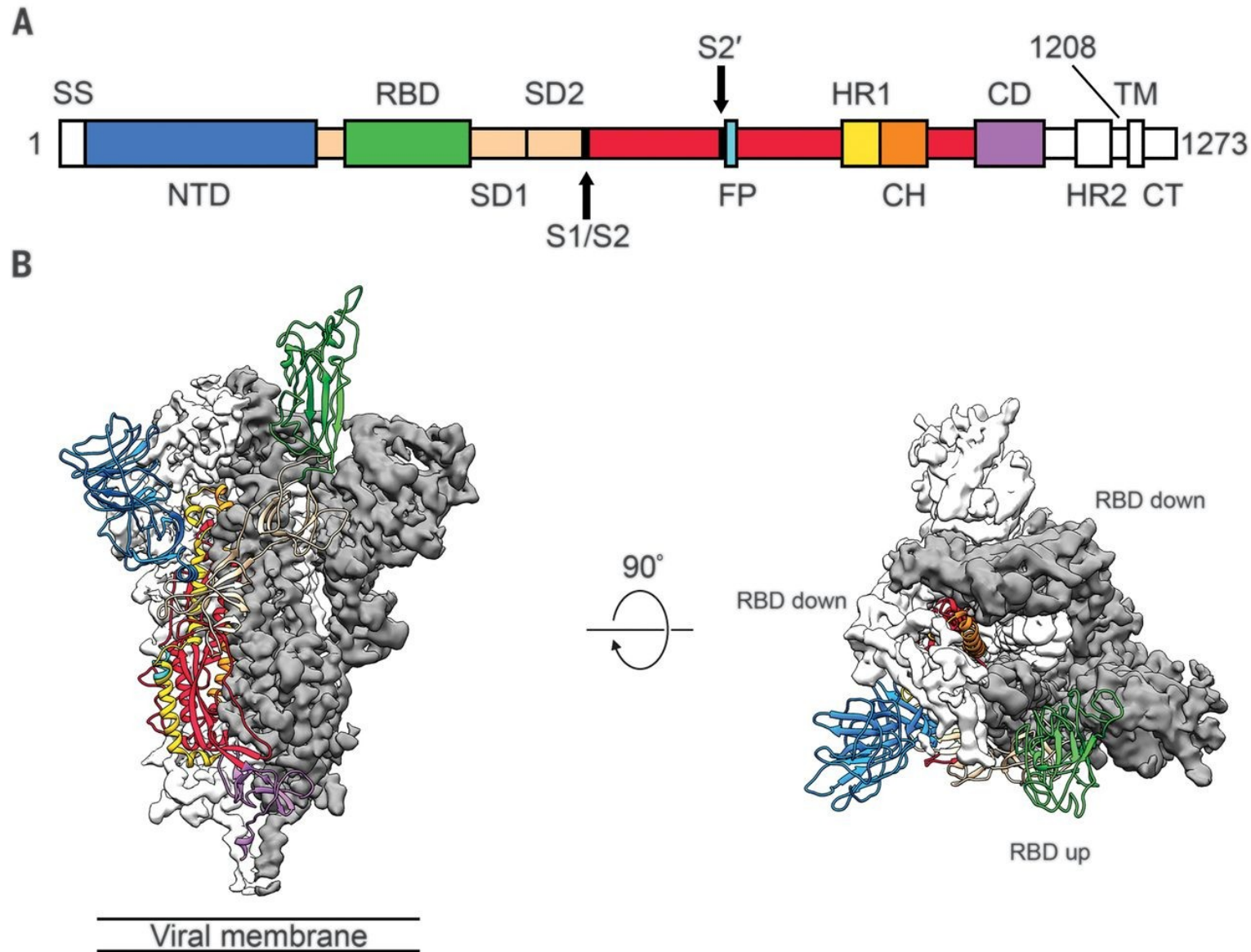
- Cytokine storm, ARDS



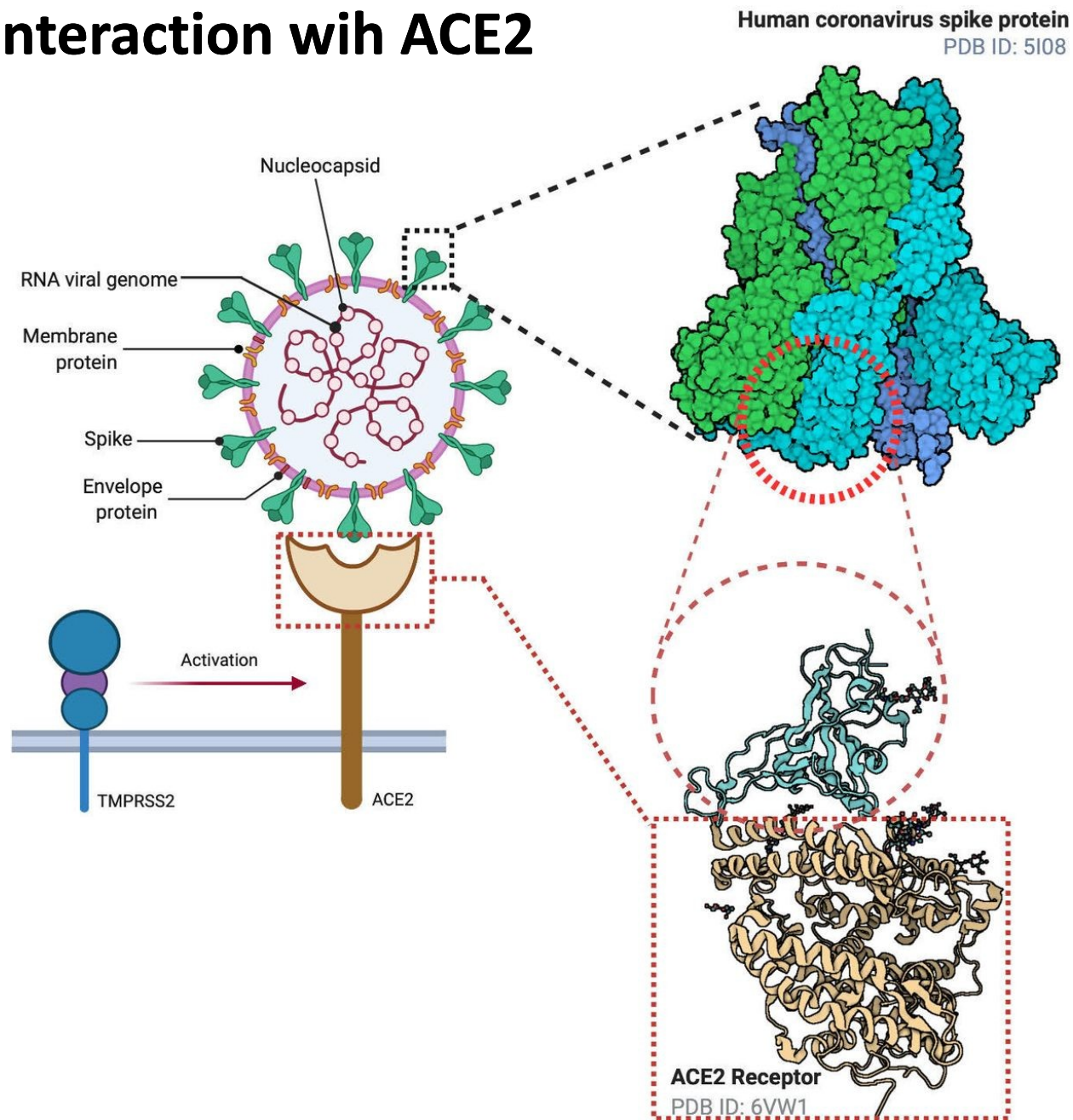
SARS-CoV-2 Structure



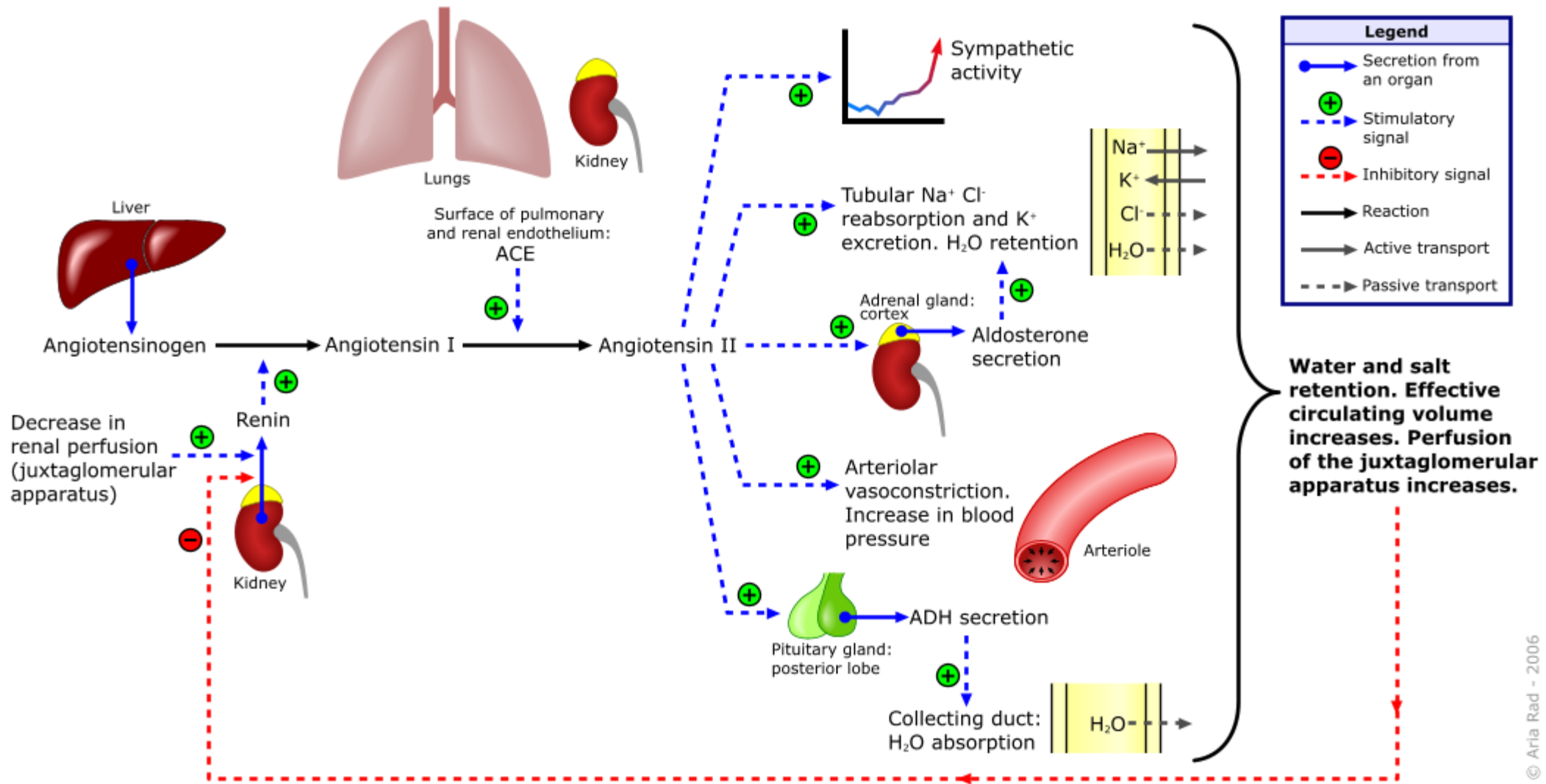
S-protein structure



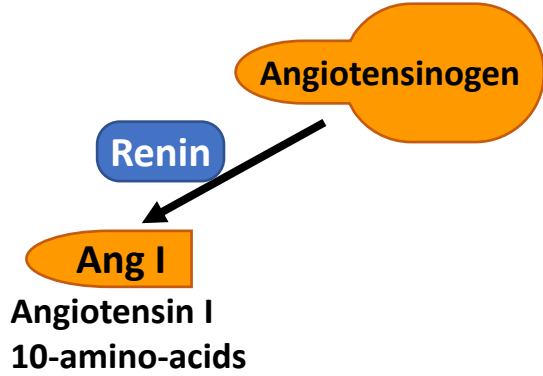
S-protein structure and interaction with ACE2



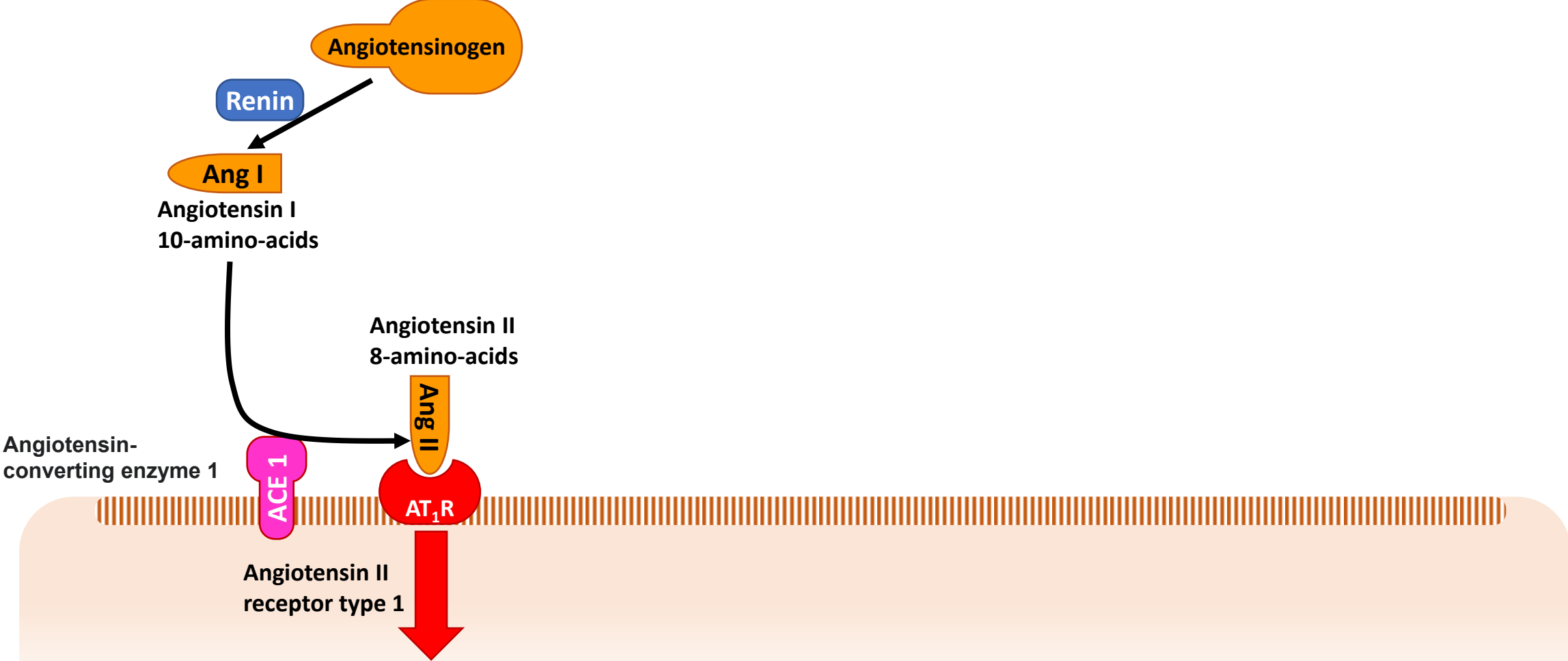
Renin-angiotensin-aldosterone system



The role of RAS in SARS-Cov-2 infection

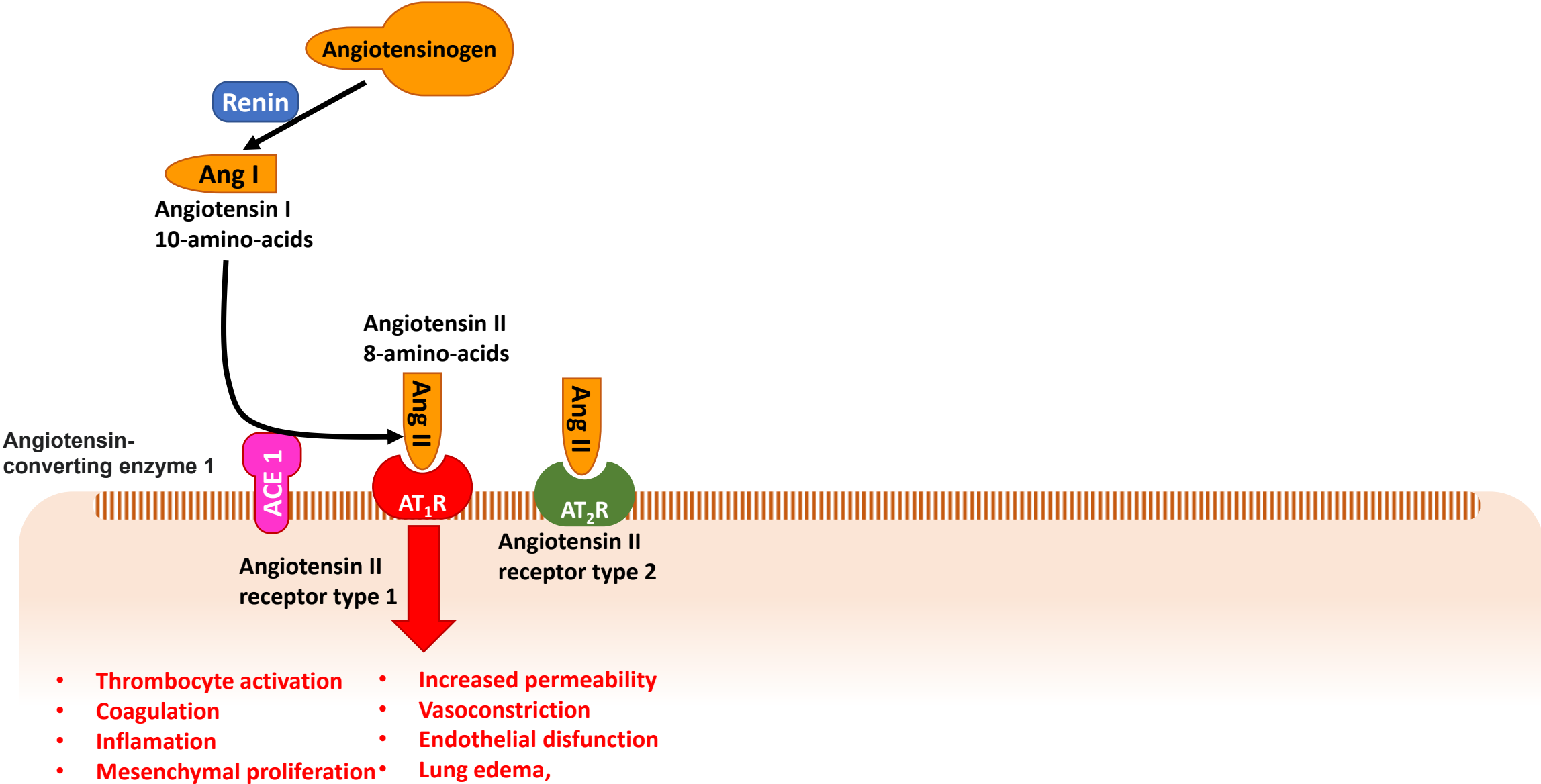


The role of RAS in SARS-Cov-2 infection

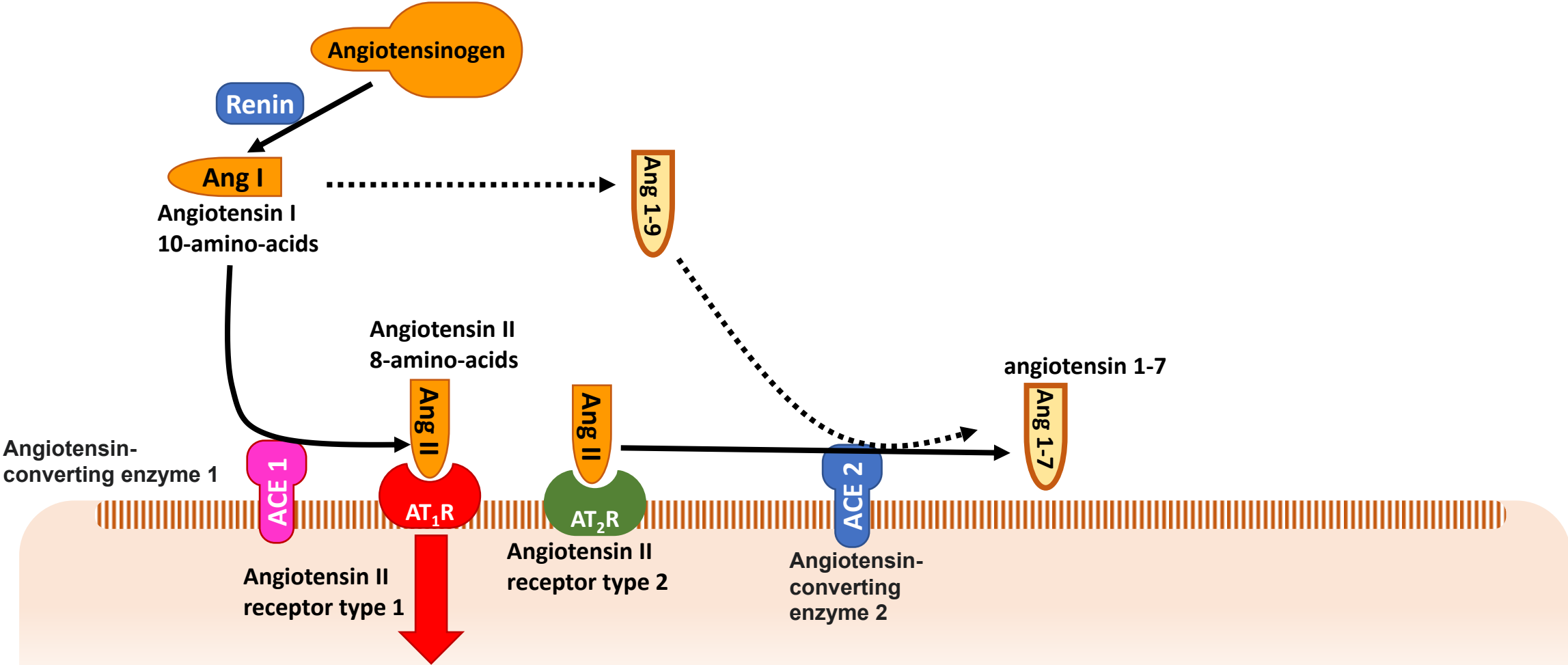


- Thrombocyte activation
- Coagulation
- Inflammation
- Mesenchymal proliferation
- Increased permeability
- Vasoconstriction
- Endothelial dysfunction
- Lung edema,

The role of RAS in SARS-Cov-2 infection

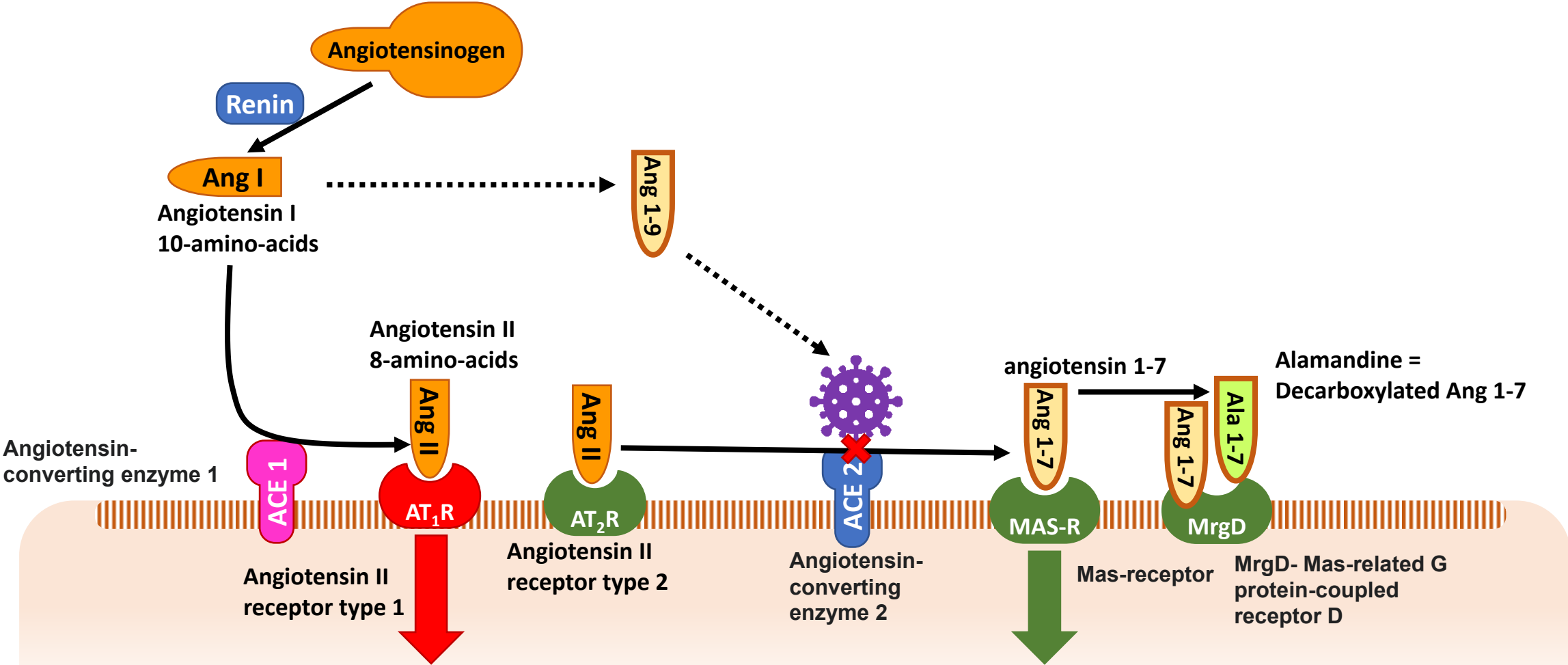


The role of RAS in SARS-Cov-2 infection



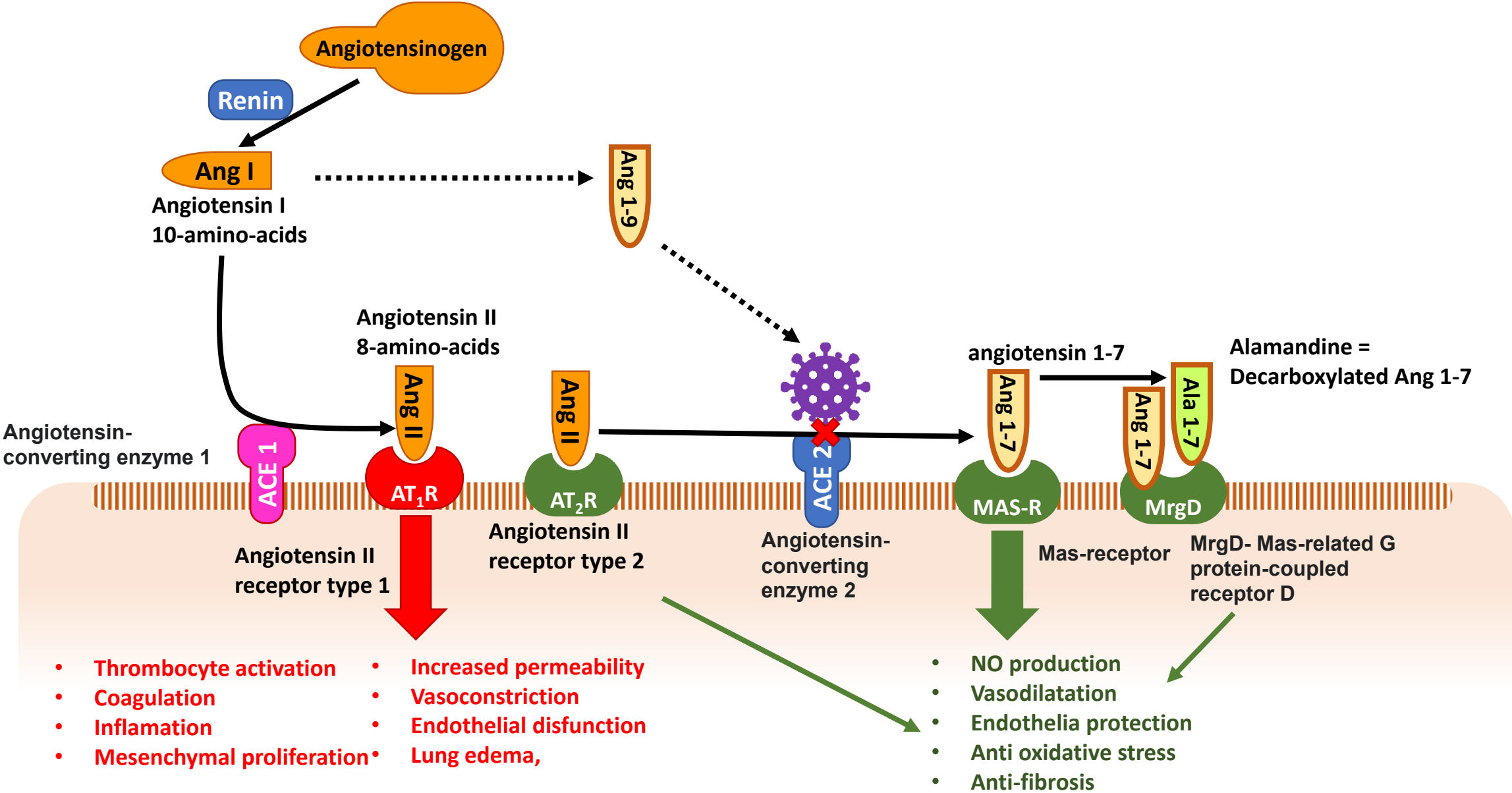
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The role of RAS in SARS-Cov-2 infection

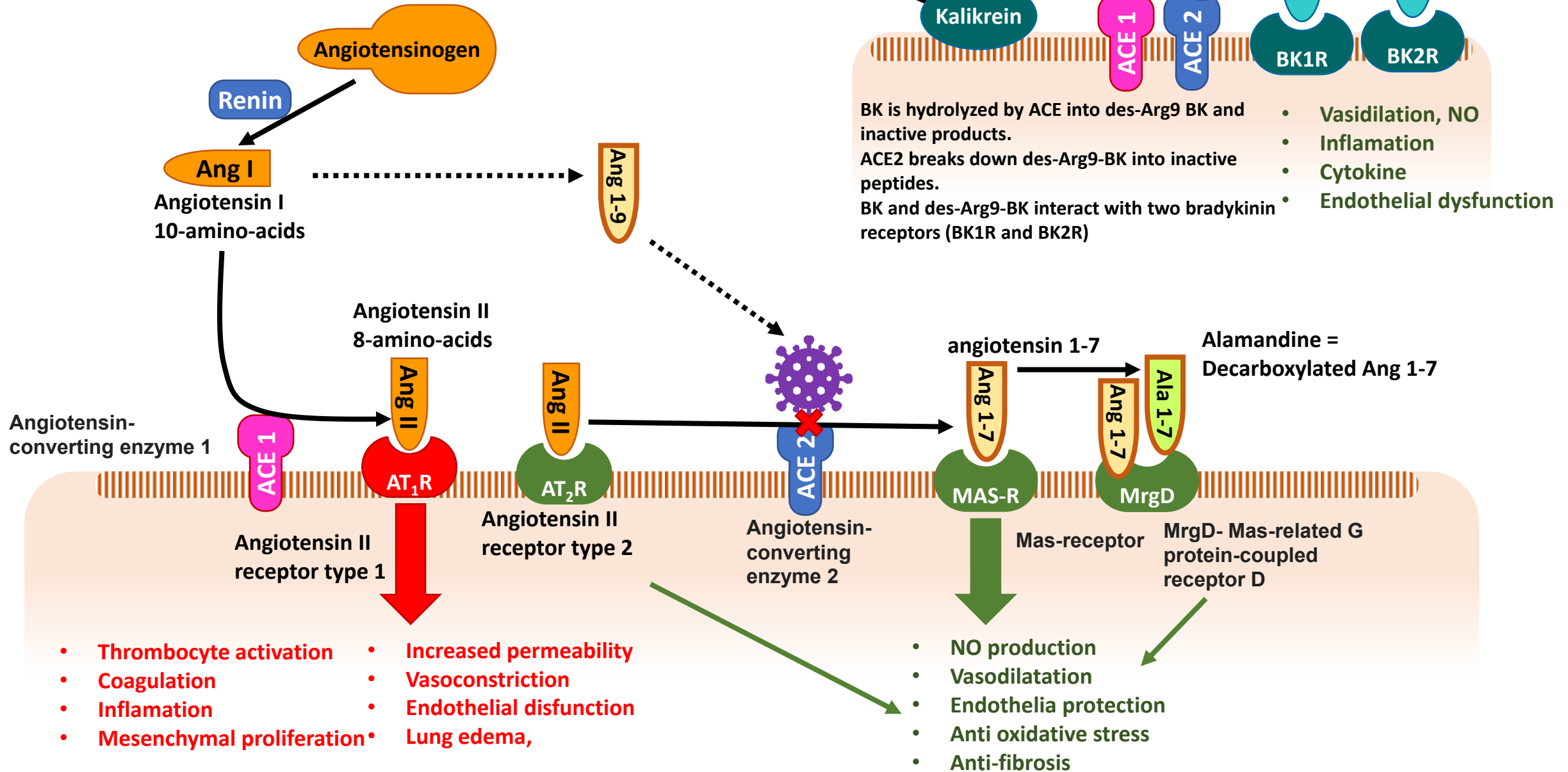


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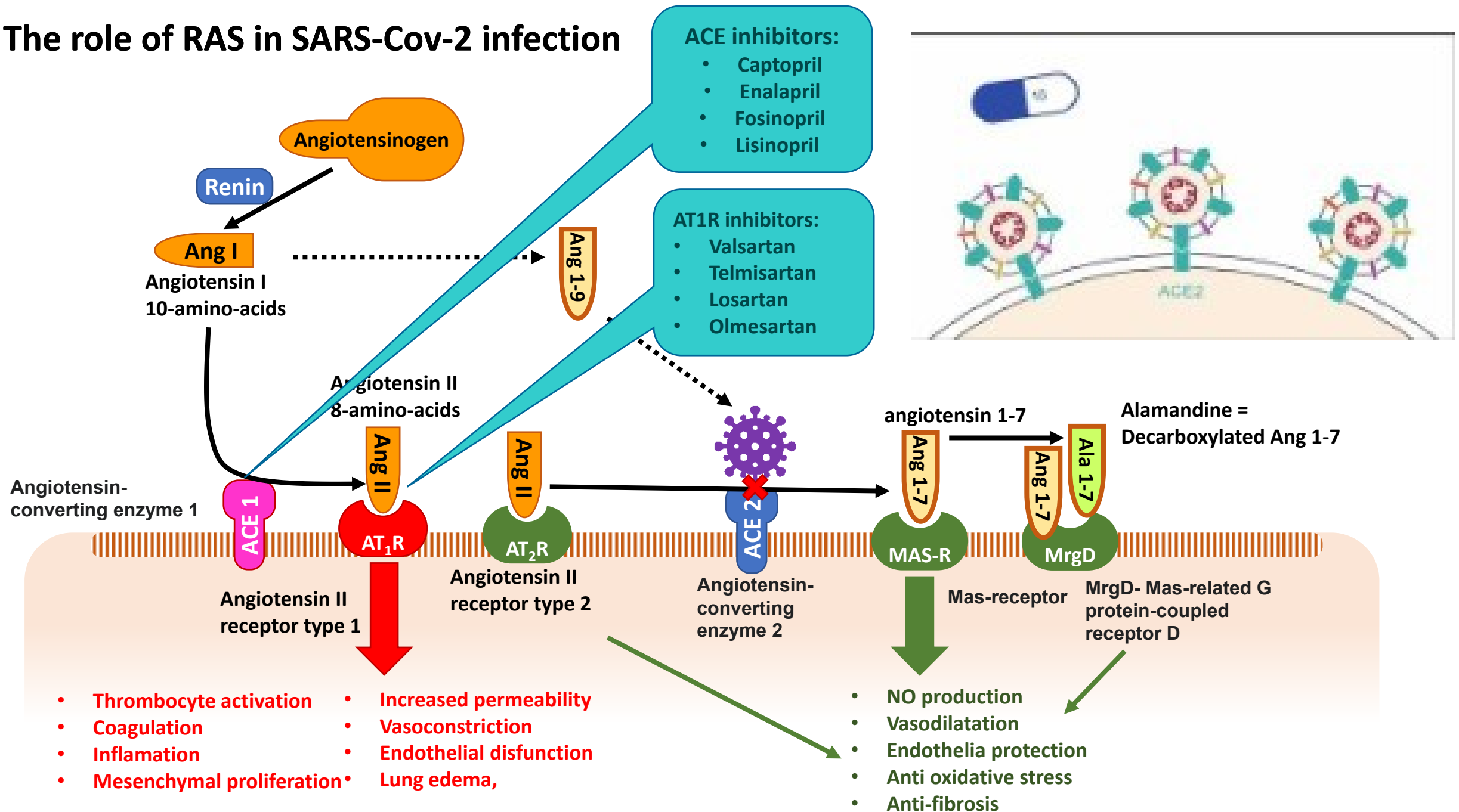
The role of RAS in SARS-Cov-2 infection



The role of RAS in SARS-Cov-2 infection



The role of RAS in SARS-Cov-2 infection



Mechanisms of innate immunity

(fast but non-specific response)

Detection of pathogenic microorganisms

- Membrane receptors
- Intracellular receptors of foreign nucleic acids
- Cytokine signalling

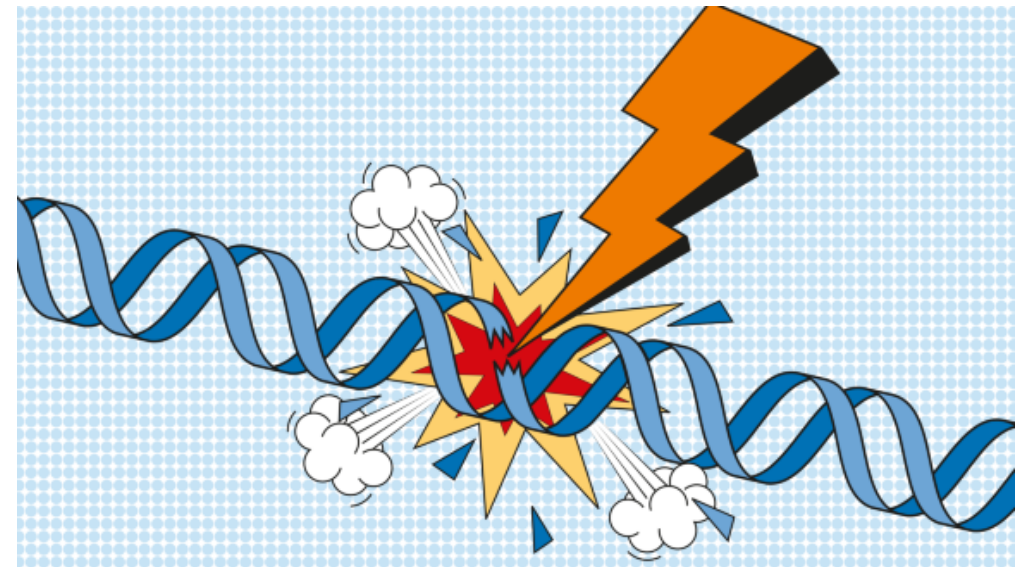


Intracellular signalling pathways

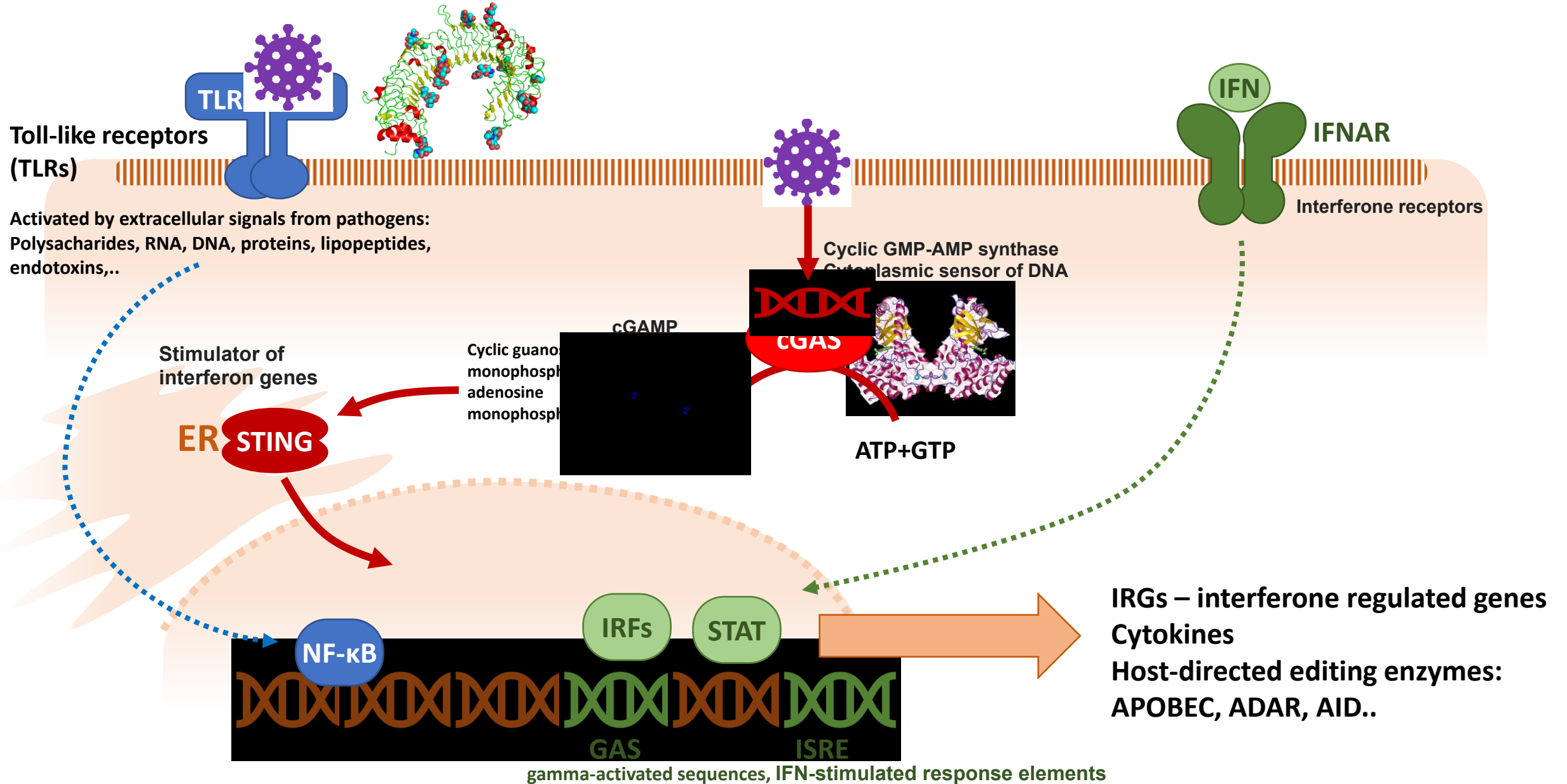


Activation of transcription / gene expression

- Expression of cytokines
- Activation of specific immune response
- Elimination of microorganisms
- Use of gene

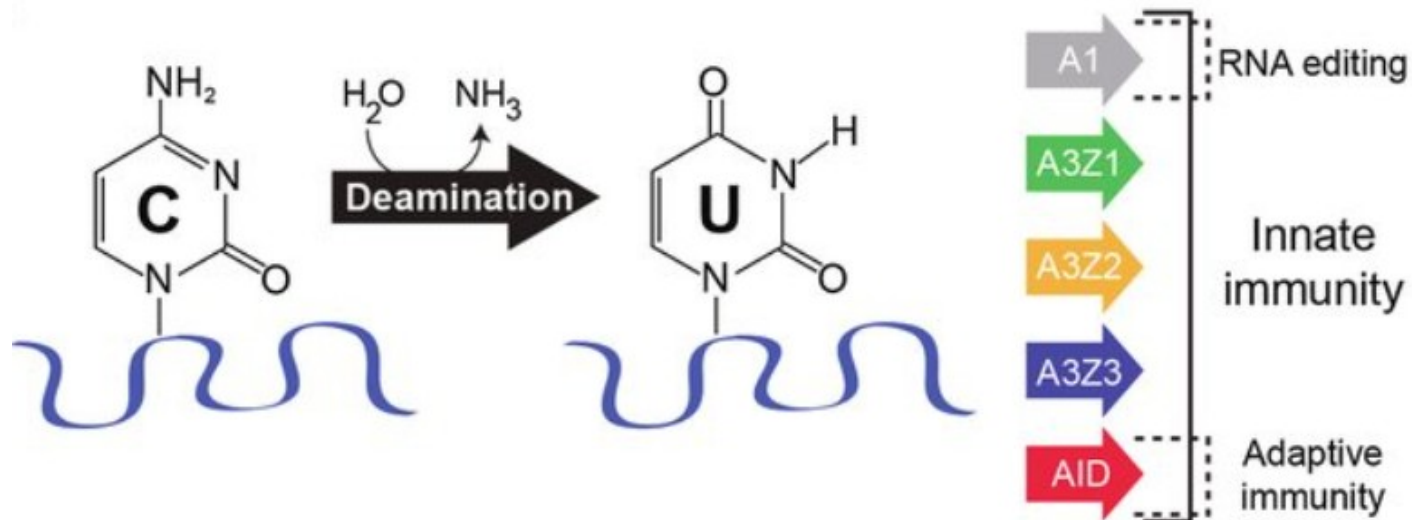


Mechanisms of innate immunity



APOBEC family members

- APOBEC ("apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like") is a family of evolutionarily conserved cytidine deaminases.
- Discovered due to their ability to eliminate HIV infection
- When misregulated, are a major source of mutation in numerous cancer types.
- AID is a part of adaptive immunity; it is responsible for hypermutation of variable immunoglobulin regions in lymphocytes



APOBEC1

APOBEC2

APOBEC3A

APOBEC3B

APOBEC3C

APOBEC3D

APOBEC3F

APOBEC3G

APOBEC3H

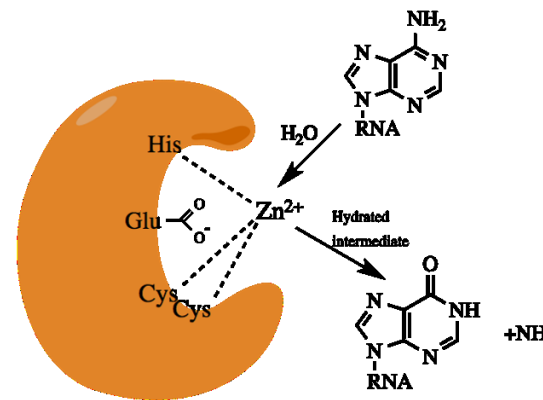
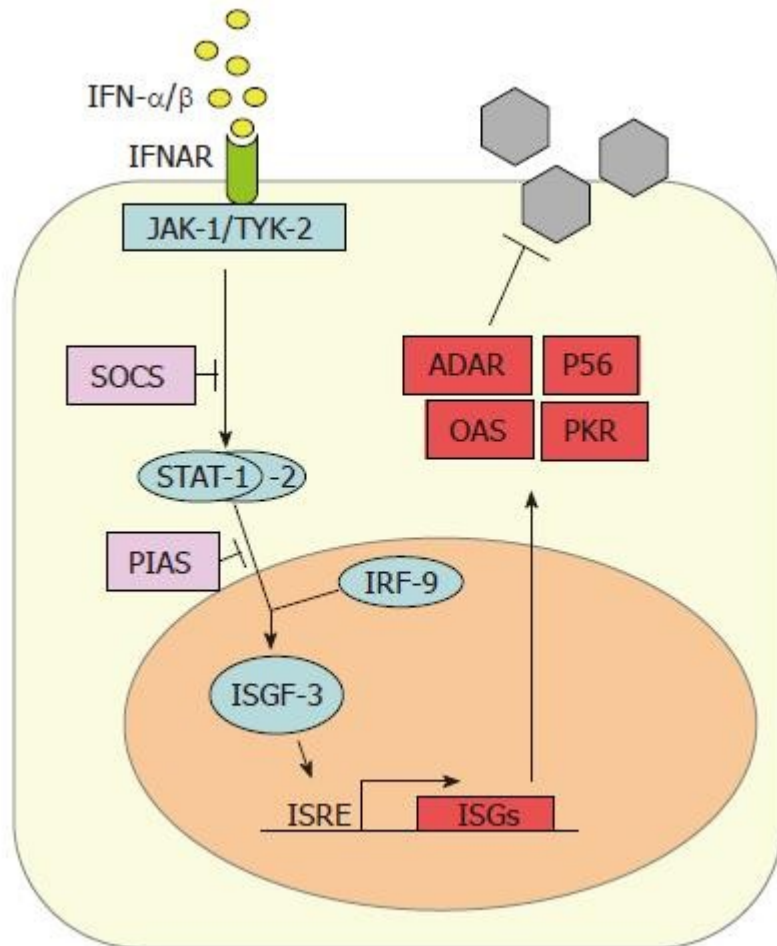
APOBEC4

AID (activation induced deaminase)

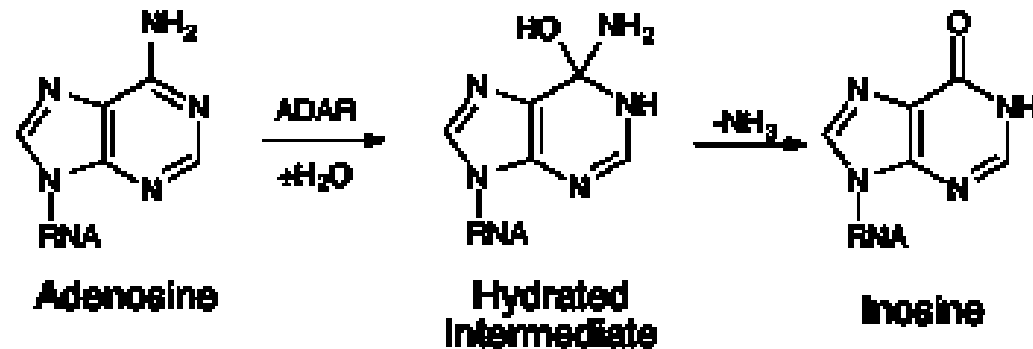
ADAR - adenosine deaminase acting on RNA

responsible for binding to double stranded RNA (dsRNA) and converting adenosine (A) to inosine (I) by deamination. ADAR protein is a RNA-binding protein, which functions in RNA-editing through post-transcriptional modification of mRNA transcripts by changing the nucleotide content of the RNA

Dysregulation associated with: Aicardi–Goutières syndrome and Bilateral Striatal Necrosis/Dystonia, cancer (HCC)



Mechanism of action:
Deamination of adenosine to inosine
Destabilize RNA
Mismatch pairing when replicated

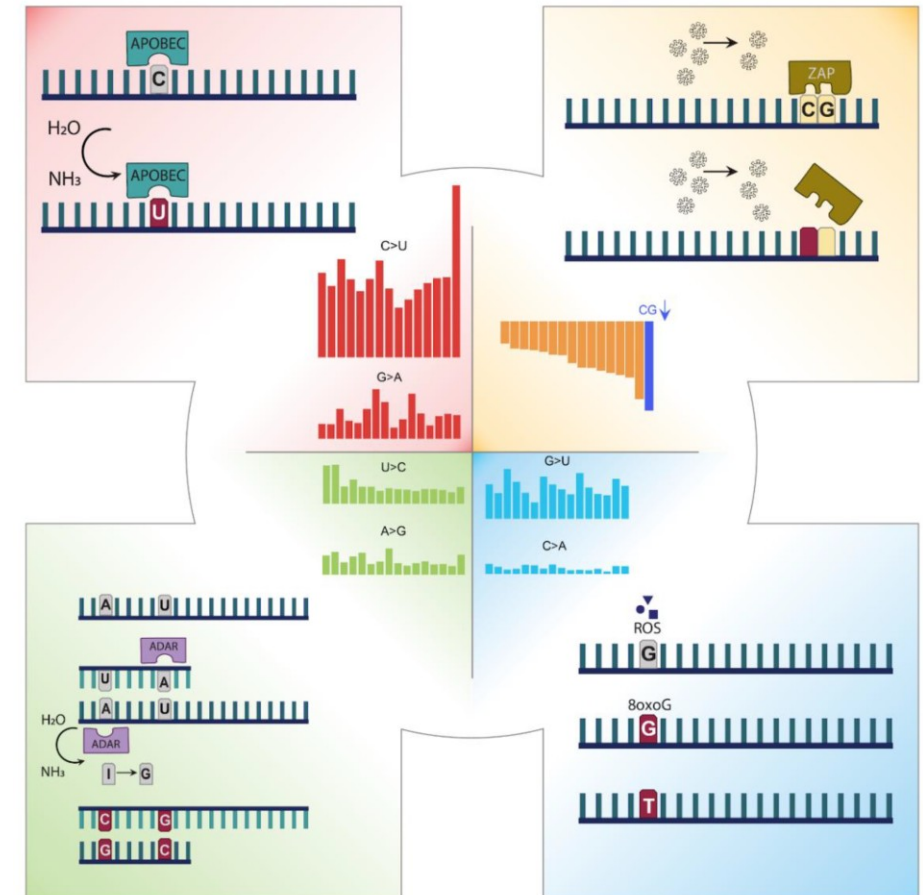
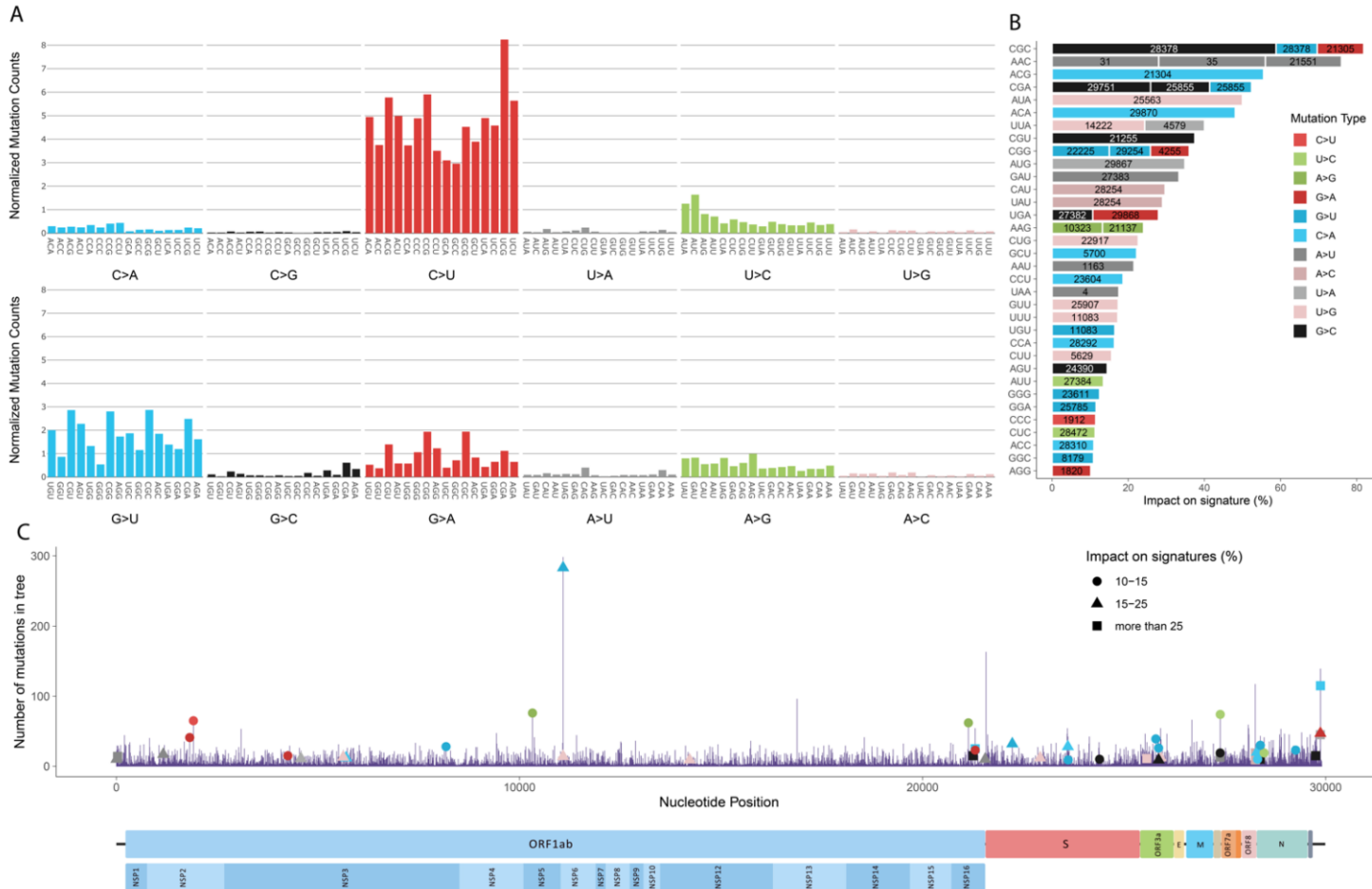


Article

The Mutation Profile of SARS-CoV-2 Is Primarily Shaped by the Host Antiviral Defense

Cem Azgari ¹, Zeynep Kilinc ¹, Berk Turhan ¹, Defne Cerci ¹ and Ogun Adebali ¹*

The results suggest that the heterogeneous mutation patterns are mainly reflections of host (i) antiviral mechanisms that are achieved through APOBEC, ADAR, and ZAP proteins, and (ii) probable adaptation against reactive oxygen species.





Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc



Host-directed editing of the SARS-CoV-2 genome

Tobias Mourier ^{a, **, 1}, Mukhtar Sadykov ^{a, 1}, Michael J. Carr ^{b, c}, Gabriel Gonzalez ^{b, c}, William W. Hall ^{b, c, d}, Arnab Pain ^{a, c, *}

^a King Abdullah University of Science and Technology (KAUST), Pathogen Genomics Laboratory, Biological and Environmental Science and Engineering (BESE), Thuwal-Jeddah, 23955-6900, Saudi Arabia

^b National Virus Reference Laboratory (NVRL), School of Medicine, University College Dublin, Belfield, D04 V1W8, Dublin, Ireland

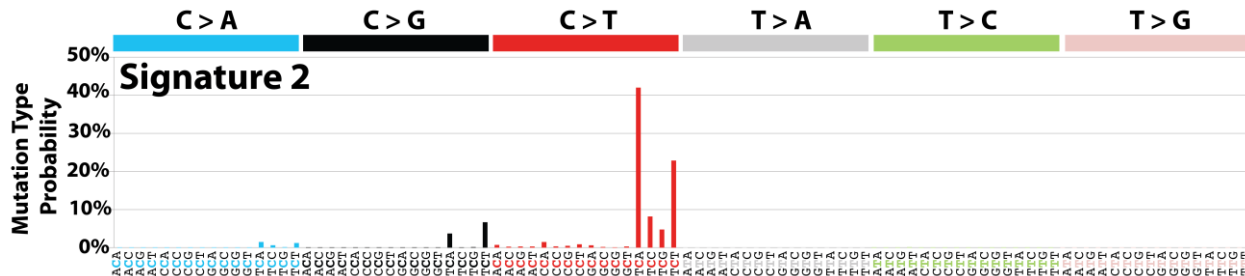
^c Research Center for Zoonosis Control, Global Institution for Collaborative Research and Education (GI-CoRE), Hokkaido University, N20 W10 Kita-ku, Sapporo, 001-0020, Japan

^d Global Virus Network (GVN), 801 W. Baltimore St., Baltimore, MD, 21201, USA



Signatures of Mutational Processes in Human Cancer

Signature 2 has been attributed to activity of the AID/APOBEC family of cytidine deaminases.



SARS-CoV-2 genome



	2.6%	10.6%	1.4%	A
1.6%		1.6%	12.6%	C
10.9%	0.3%		1.5%	G
2.4%	36.9%	17.6%		U

changed to

ROS can oxidize guanine to oxoguanine, which pairs with A, leading to G-to-U changes.

Valyi-Nagy and Dermody (2005); Smith (2017); Graudenzi et al. (2020)

APOBEC can deaminate cytosine to uracil, leading to C-to-U changes

When: After replication, before packaging
Salter et al. (2016); Di Giorgio et al. (2020)

ADAR can deaminate adenine to inosine (I), which pairs with cytosine, leading to A-to-G changes

When: During replication
Placido et al. (2007); Bass (2002)

Article

Six reference-quality genomes reveal evolution of bat adaptations

<https://doi.org/10.1038/s41586-020-2486-3>

Received: 14 October 2019

Accepted: 9 June 2020

Published online: 22 July 2020

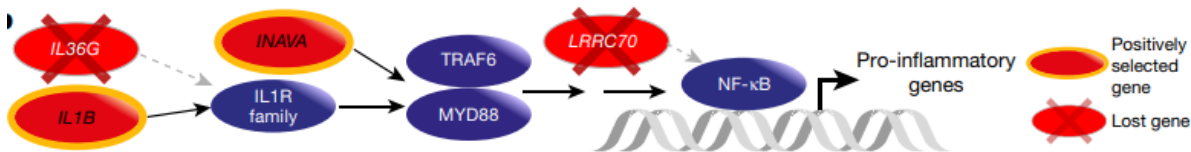
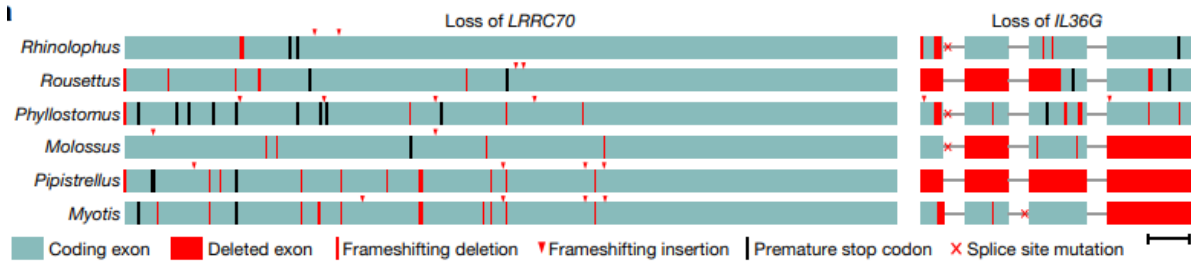
Open access

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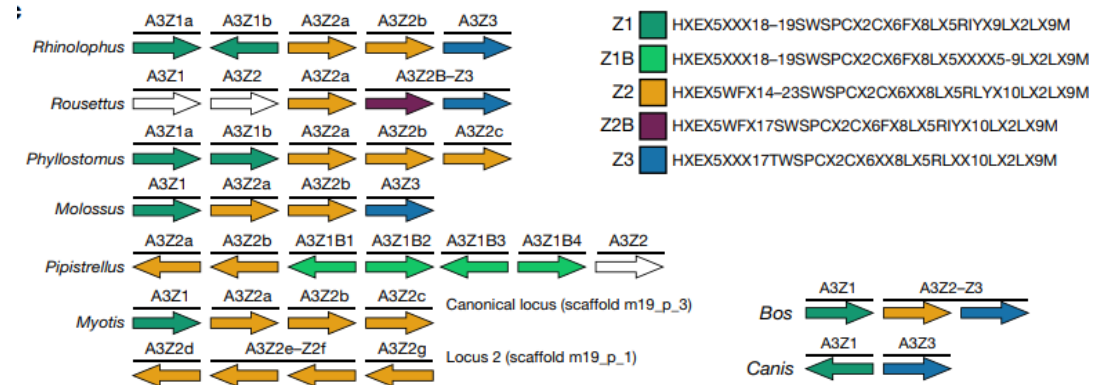
David Jebb^{1,2,3,25}, Zixia Huang^{4,25}, Martin Pippel^{1,3,25}, Graham M. Hughes⁴, Ksenia Lavrichenko⁵, Paolo Devanna⁵, Sylke Winkler¹, Lars S. Jermiin^{4,6,7}, Emilia C. Skirmuntt⁸, Aris Katzourakis⁸, Lucy Burkitt-Gray⁹, David A. Ray¹⁰, Kevin A. M. Sullivan¹⁰, Juliana G. Roscito^{1,2,3}, Bogdan M. Kirilenko^{1,2,3}, Liliana M. Dávalos^{11,12}, Angélique P. Corthals¹³, Megan L. Power⁴, Gareth Jones¹⁴, Roger D. Ransome¹⁴, Dina K. N. Dechmann^{15,16,17}, Andrea G. Locatelli⁴, Sébastien J. Puechmaille^{18,19}, Olivier Fedrigo²⁰, Erich D. Jarvis^{20,21,22}, Michael Hiller^{1,2,3,26}, Sonja C. Vernes^{5,23,26}, Eugene W. Myers^{1,3,24,26} & Emma C. Teeling^{4,26}



Loss of genes in NF-κB signalling pathway



Expansion of the APOBEC3 gene locus



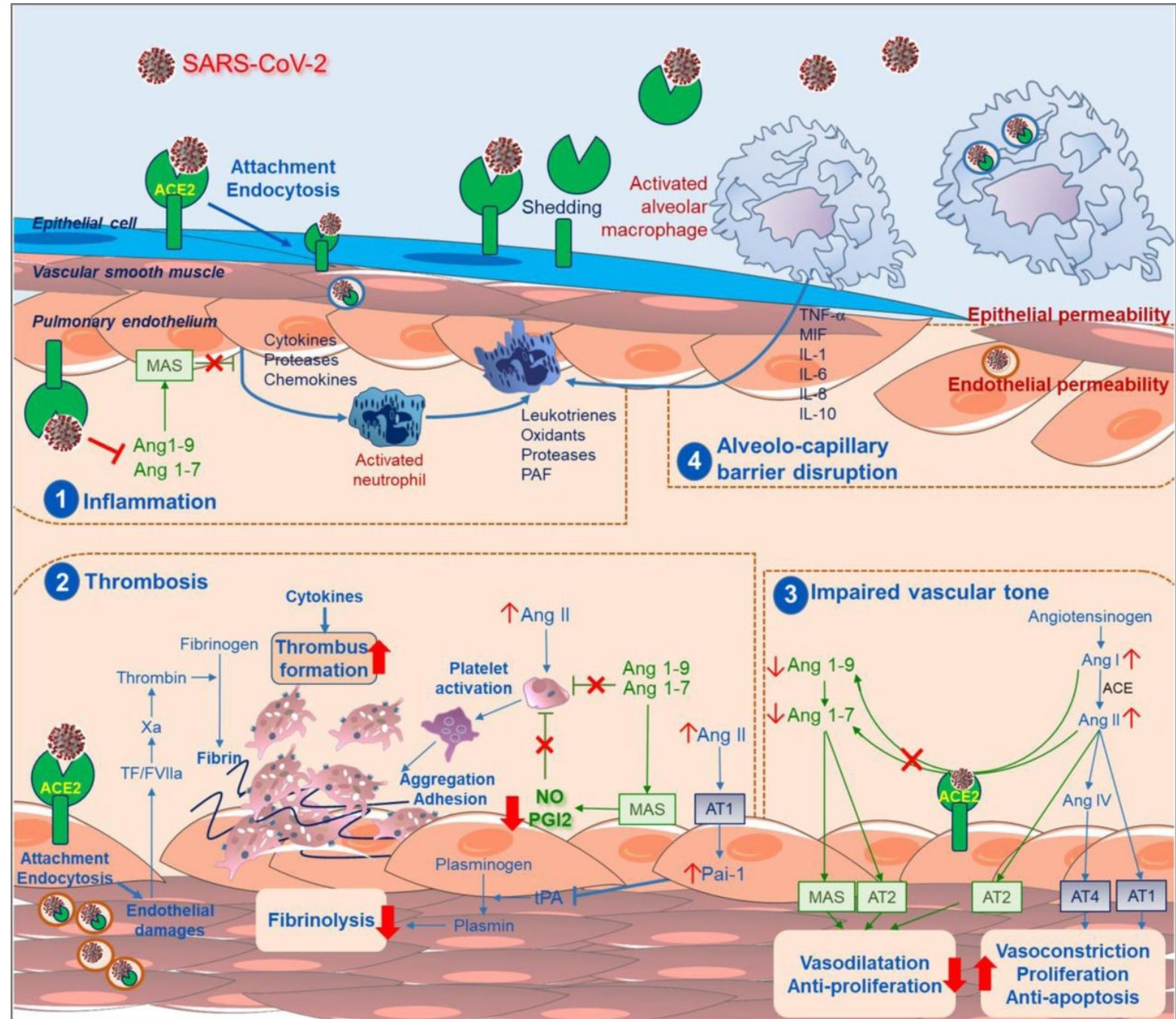
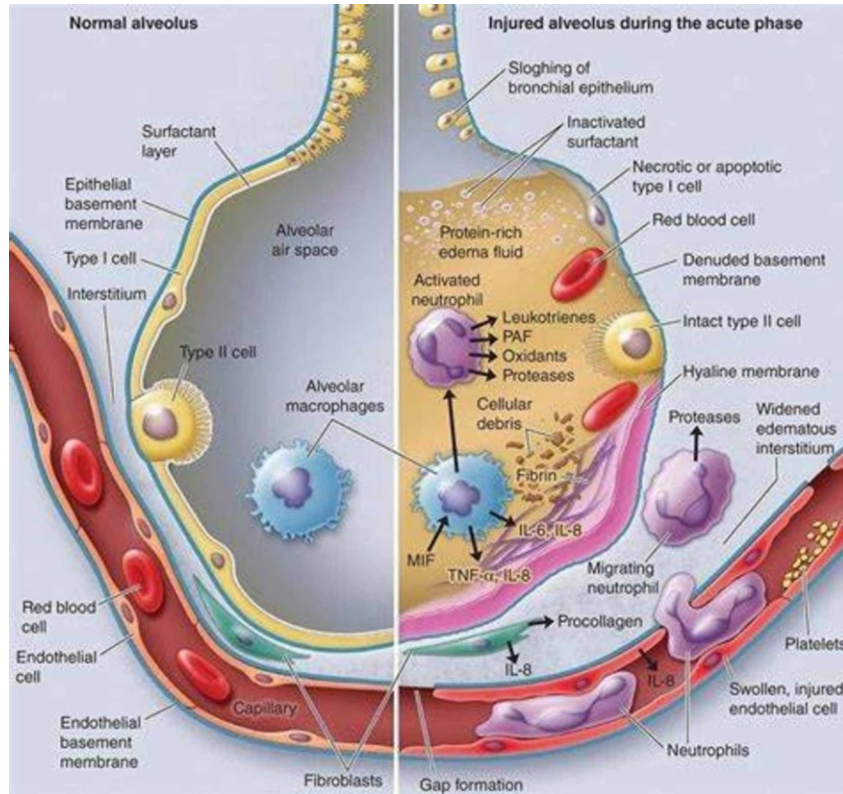


Early View

Editorial

Endothelial cell dysfunction: a major player in SARS-CoV-2 infection (COVID-19)?

Alice Huertas, David Montani, Laurent Savale, Jérémie Pichon, Ly Tu, Florence Parent, Christophe Guignabert, Marc Humbert



Mechanisms of endothelial damage by SARS-CoV2

THE LANCET

Vol 395 May 2, 2020



EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Endothelial cell infection and endotheliitis in COVID-19

Cardiovascular complications are rapidly emerging as a key threat in coronavirus disease 2019 (COVID-19) in addition to respiratory disease. The mechanisms underlying the disproportionate effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on patients with cardiovascular comorbidities, however, remain incompletely understood.^{1,2}

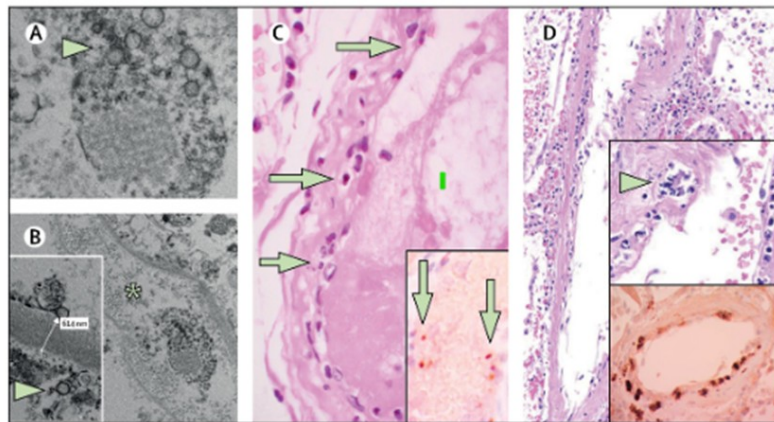


Figure: Pathology of endothelial cell dysfunction in COVID-19
(A, B) Electron microscopy of kidney tissue shows viral inclusion bodies in a peritubular space and viral particles in endothelial cells of the glomerular capillary loops. Aggregates of viral particles (arrow) appear with



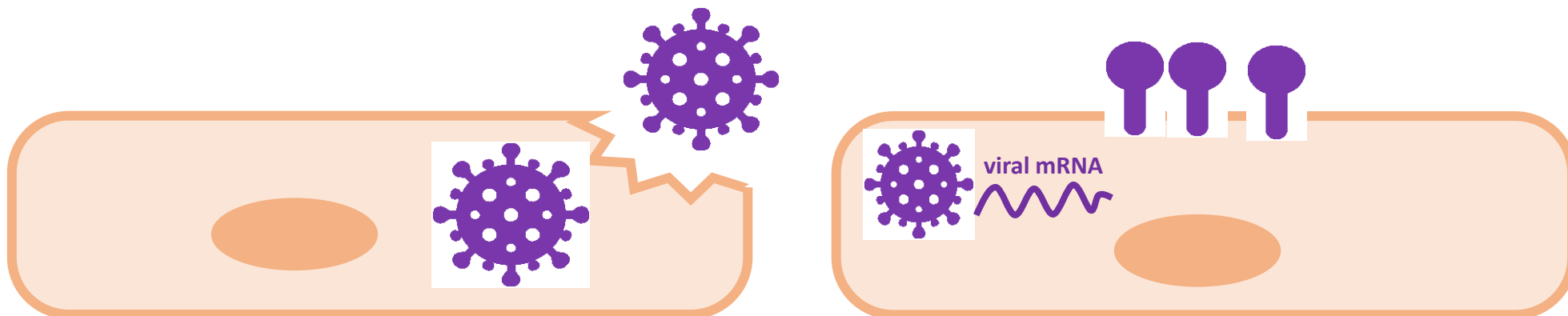
Published Online
April 17, 2020
[https://doi.org/10.1016/S0140-6736\(20\)30937-5](https://doi.org/10.1016/S0140-6736(20)30937-5)

Early View

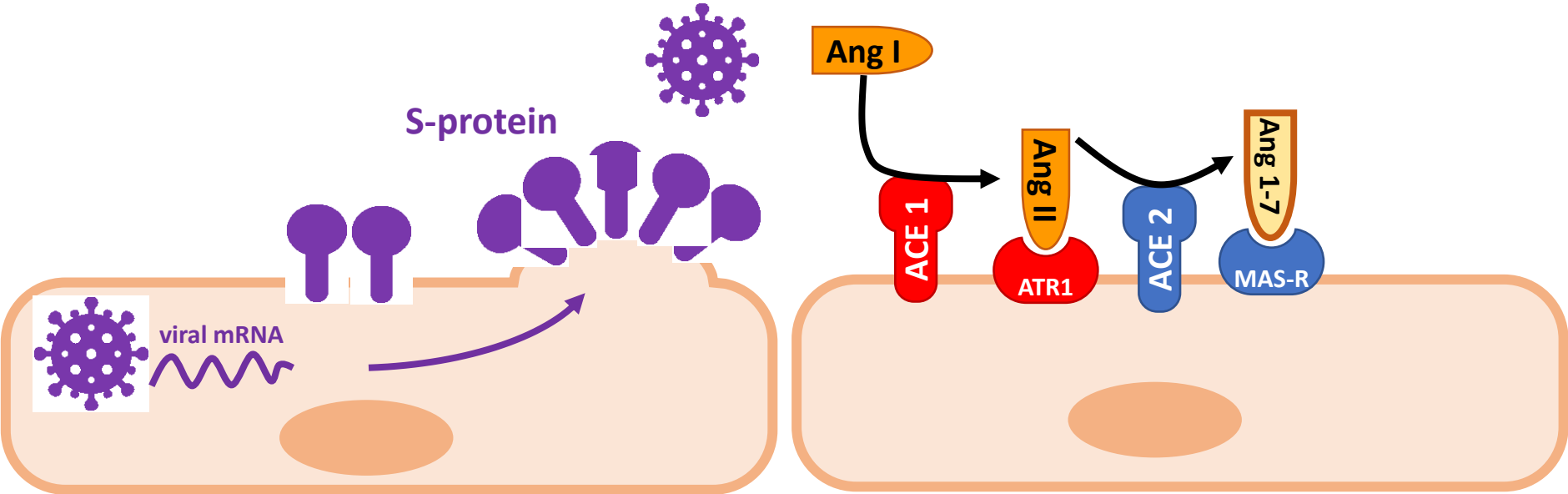
Editorial

Endothelial cell dysfunction: a major player in SARS-CoV-2 infection (COVID-19)?

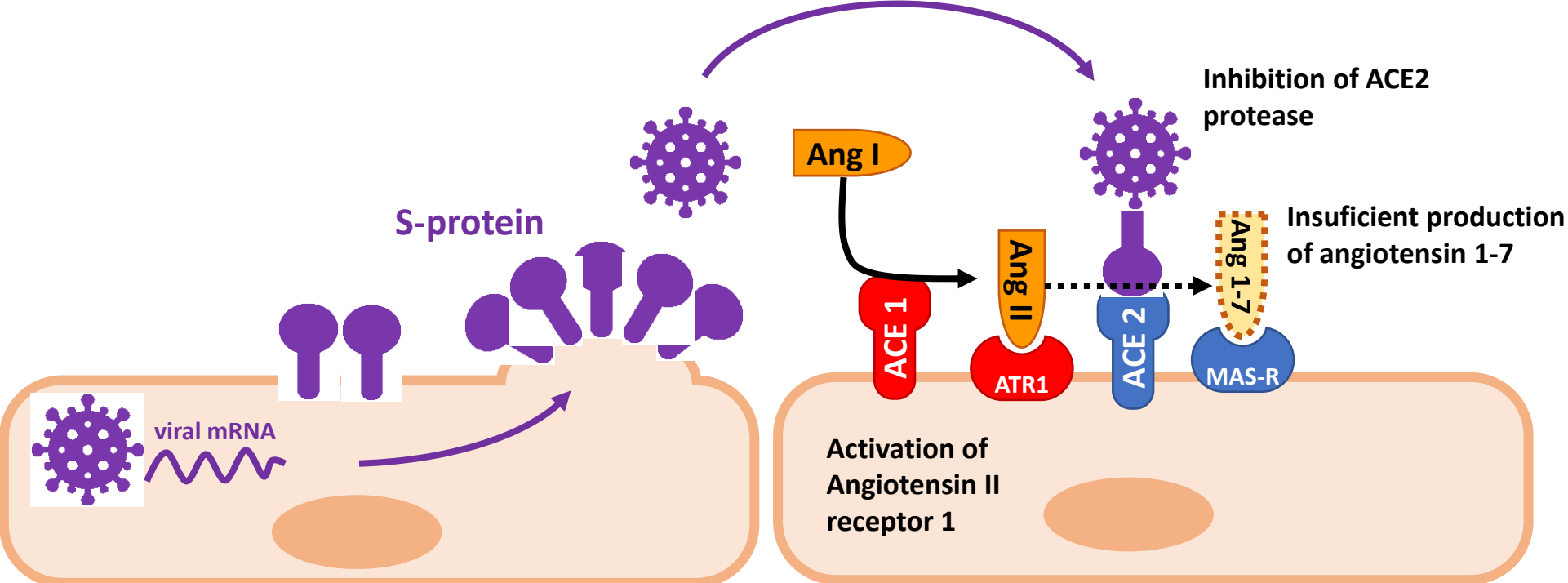
Alice Huertas, David Montani, Laurent Savale, Jérémie Pichon, Ly Tu, Florence Parent, Christophe Guignabert, Marc Humbert



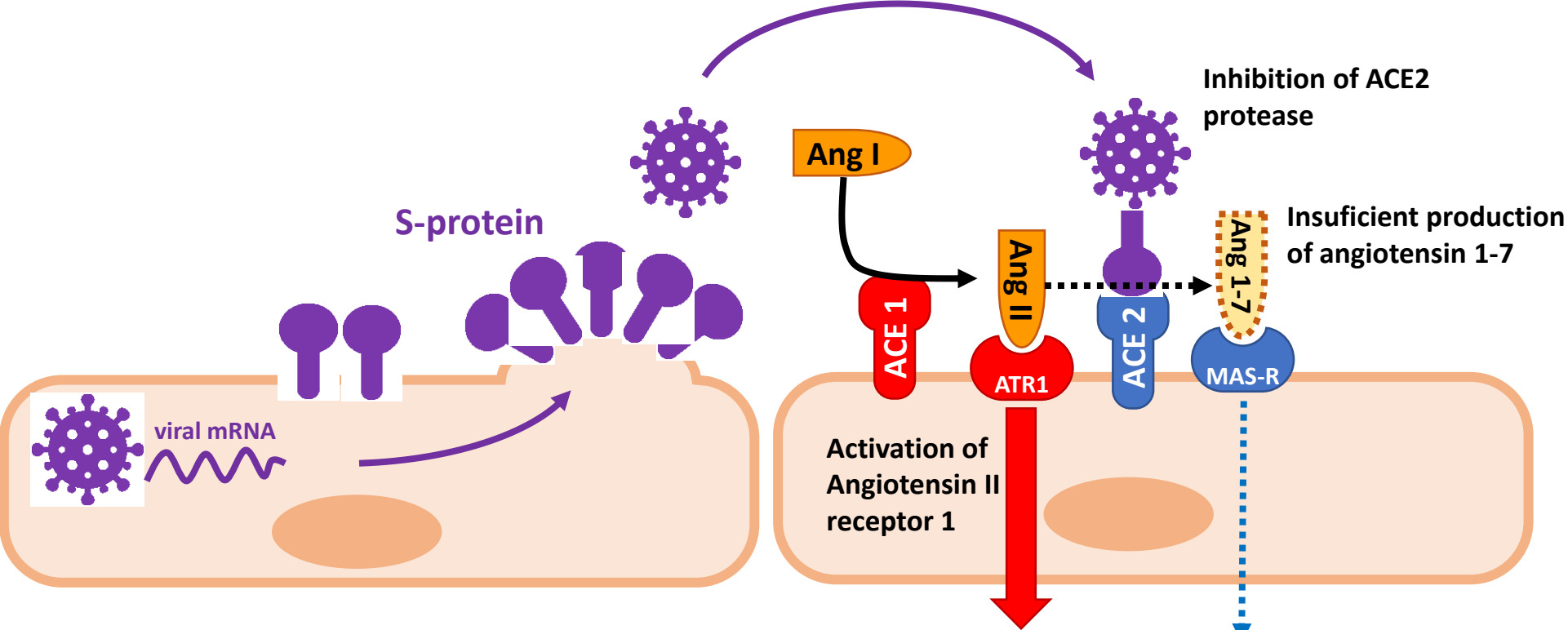
Mechanisms of endothelial damage by SARS-CoV2



Mechanisms of endothelial damage by SARS-CoV2



Mechanisms of endothelial damage by SARS-CoV2



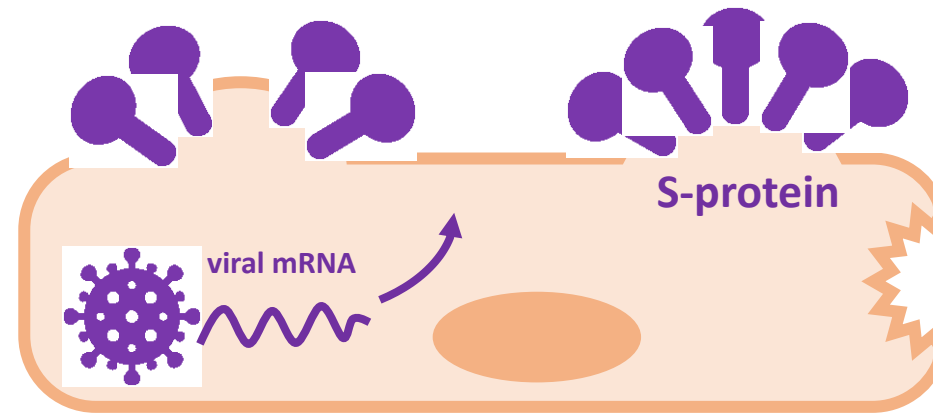
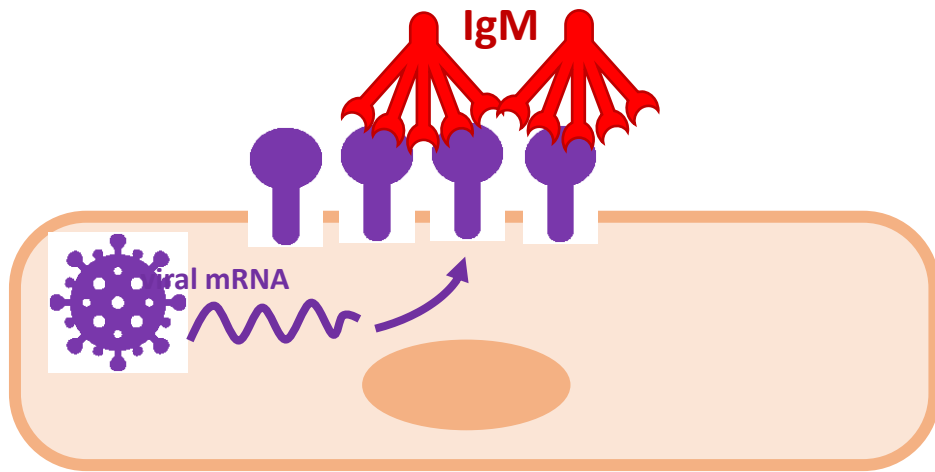
Lung edema
ARDS



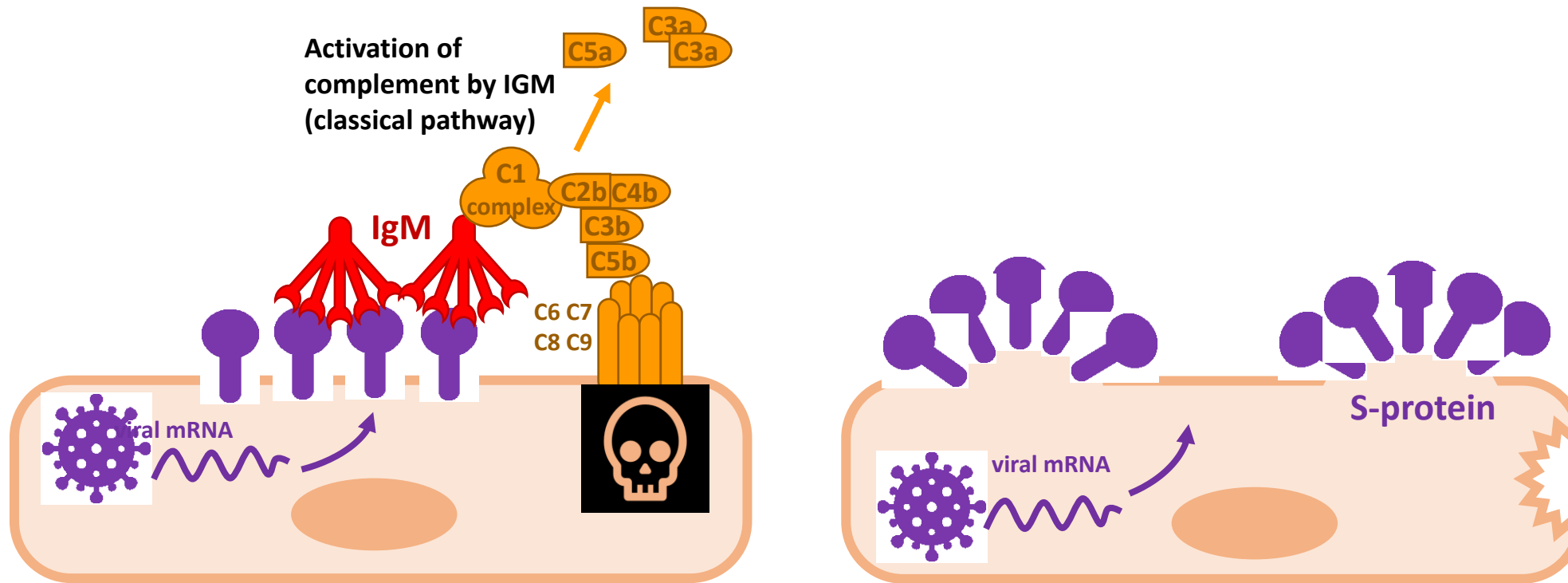
- Increased permeability
- Vasoconstriction
- Endothelial dysfunction
- Thrombocyte activation
- Coagulation
- Inflammation
- Mesenchymal proliferation

- NO production
- Vasodilatation
- Endothelia protection
- Anti oxidative stress
- Anti-fibrosis

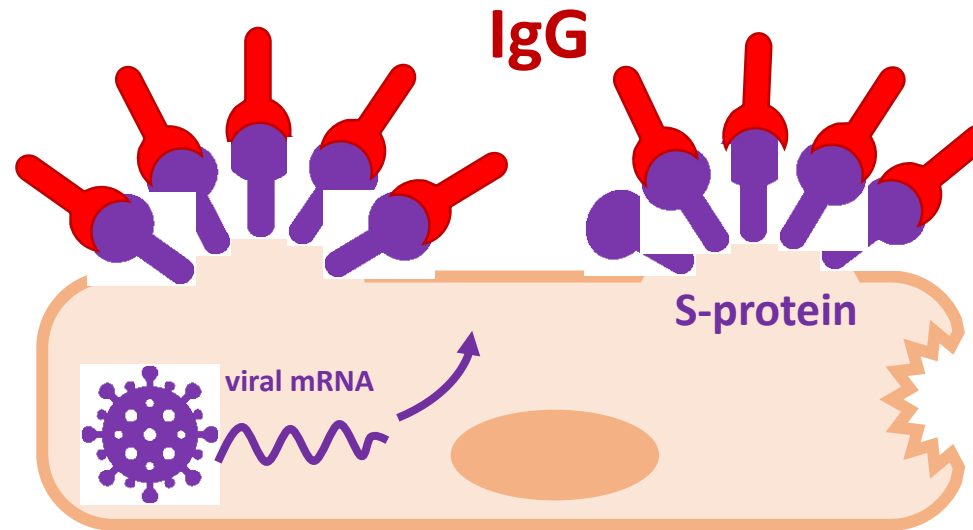
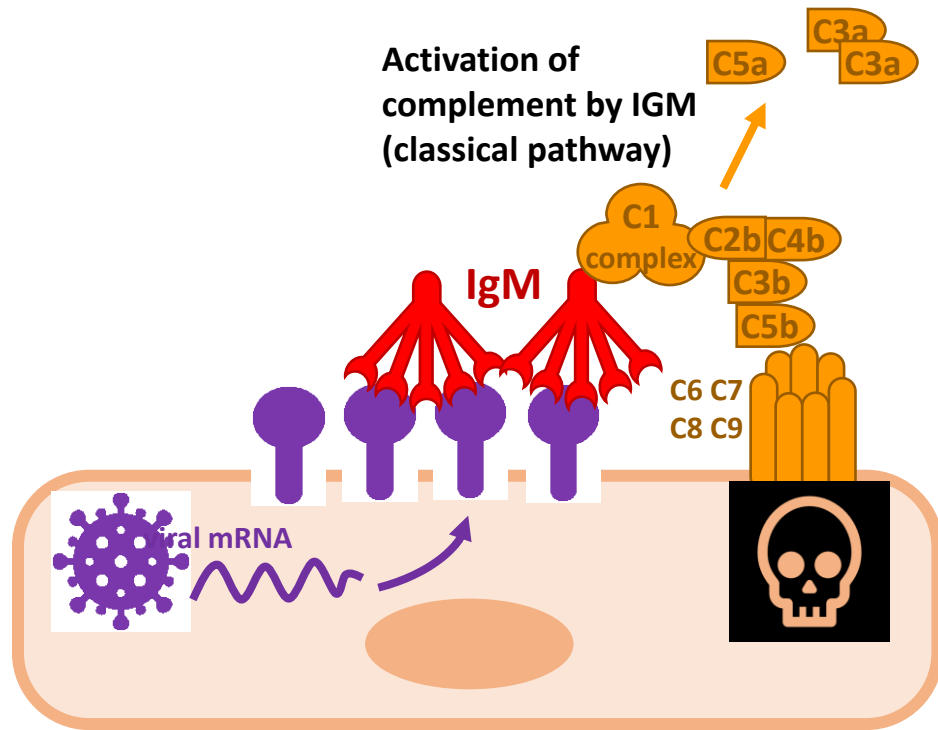
Mechanisms of endothelial damage by SARS-CoV2



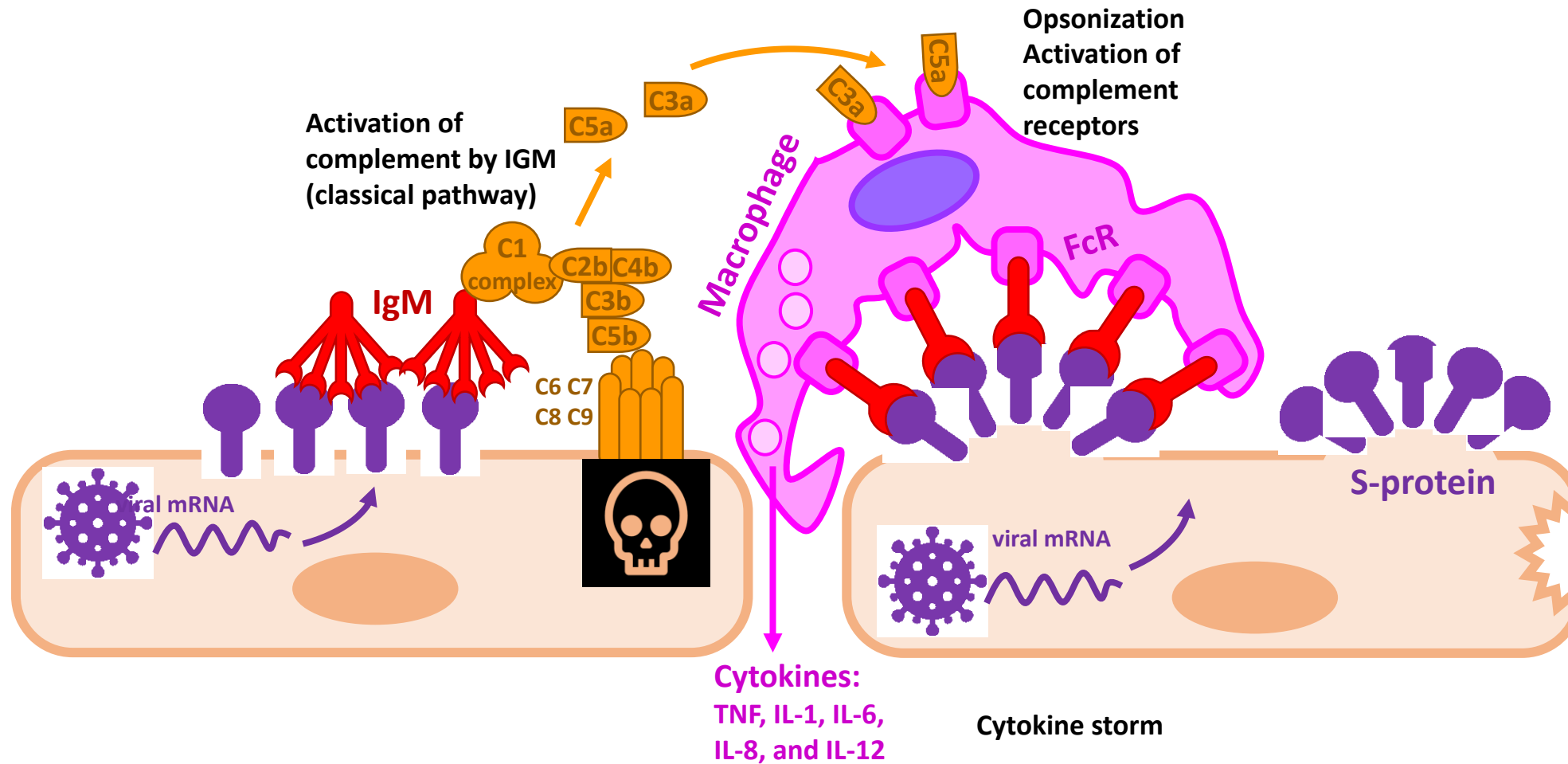
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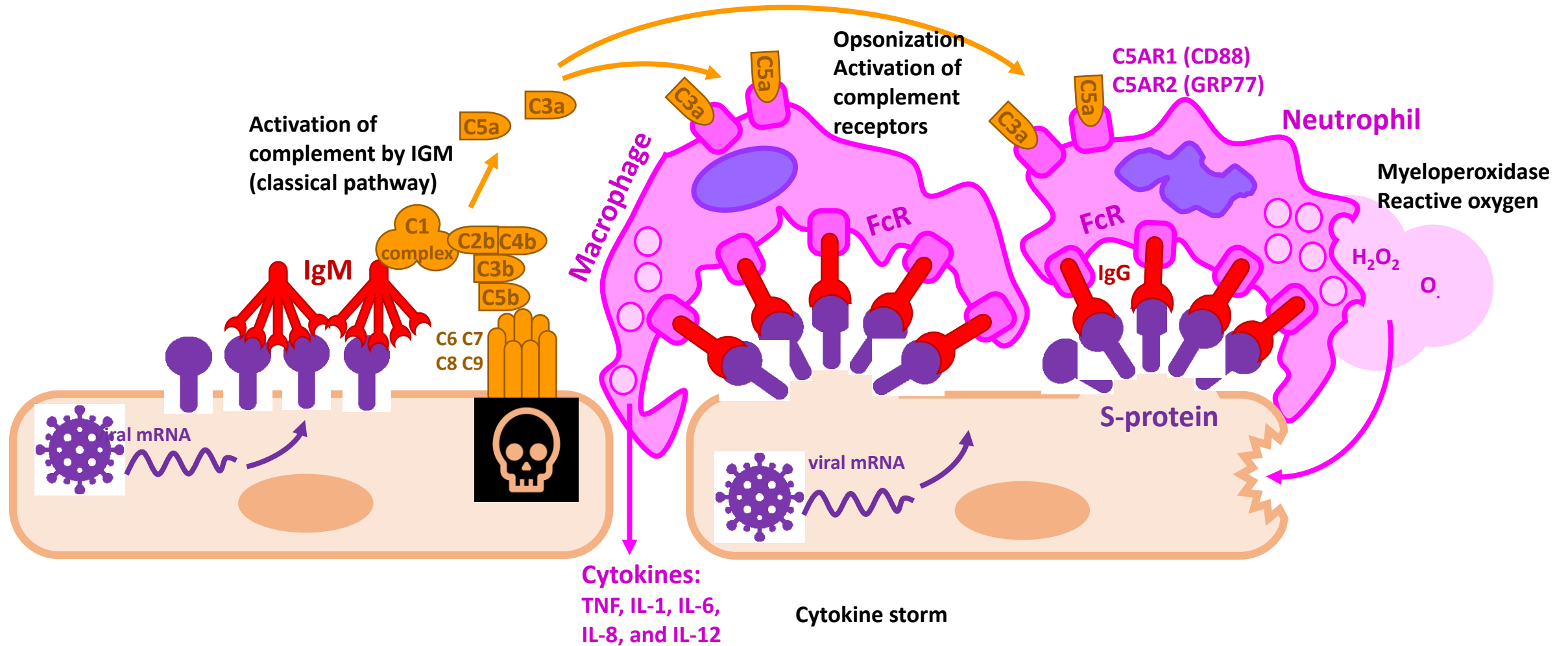
Mechanisms of endothelial damage by SARS-CoV2



Mechanisms of endothelial damage by SARS-CoV2

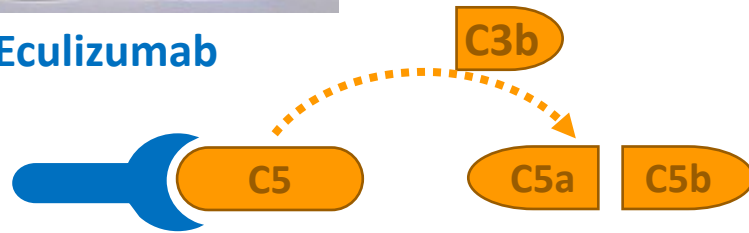


Mechanisms of endothelial damage by SARS-CoV2





Ecuzumab



Eculizumab is humanized therapeutic antibody that binds C5 complement and prevents its cleavage by C3b. It is used to treat paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), and neuromyelitis optica.

Received: 10 April 2020 | Revised: 16 April 2020 | Accepted: 17 April 2020

DOI: 10.1111/pai.13263

ORIGINAL ARTICLE

Two X-linked agammaglobulinemia patients develop pneumonia as COVID-19 manifestation but recover

Annarosa Soresina¹ | Daniele Moratto² | Marco Chiarini² | Ciro Paolillo³ | Giulia Baresi^{4,5} | Emanuele Focà⁶ | Michela Bezzi⁷ | Barbara Baronio⁸ | Mauro Giacomelli^{4,5} | Raffaele Badolato^{4,5}



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EClinicalMedicine

journal homepage: <https://www.journals.elsevier.com/eclinicalmedicine>



Research Paper

Eculizumab as an emergency treatment for adult patients with severe COVID-19 in the intensive care unit: A proof-of-concept study

Djillali Annane^{a,*}, Nicholas Heming^b, Lamiae Grimaldi-Bensouda^c,
Véronique Frémeaux-Bacchi^d, Marie Vigan^e, Anne-Laure Roux^f, Armance Marchal^g,
Hugues Michelon^h, Martin Rottman^f, Pierre Moine^{b,1}, for the Garches COVID 19 Collaborative Group



ORIGINAL RESEARCH
published: 14 January 2021
doi: 10.3389/fimmu.2020.614086

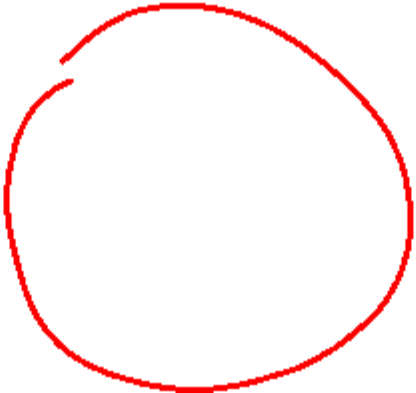
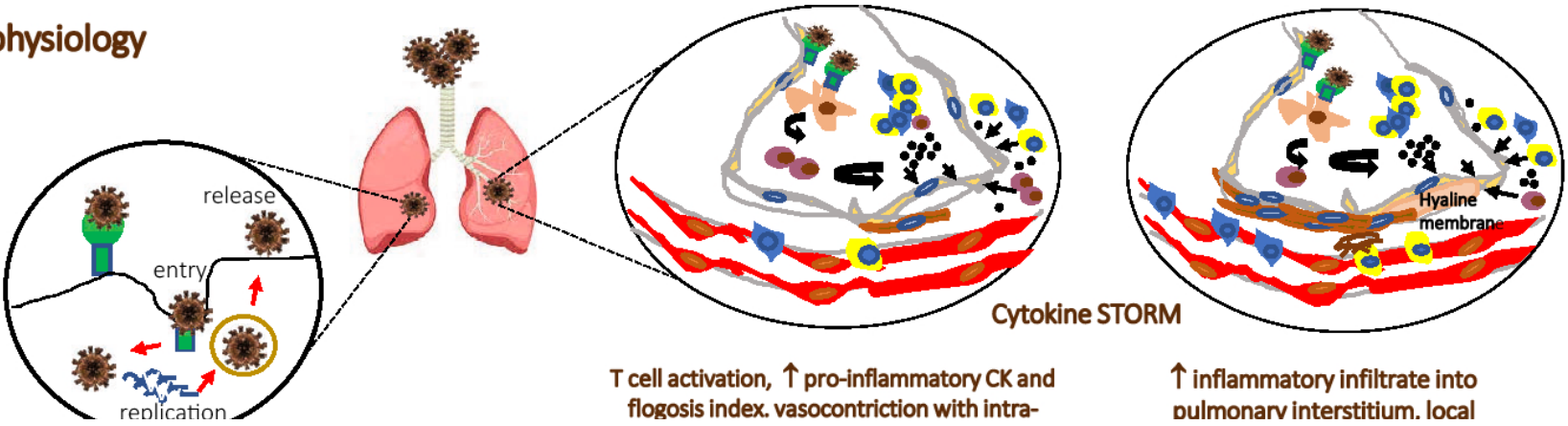


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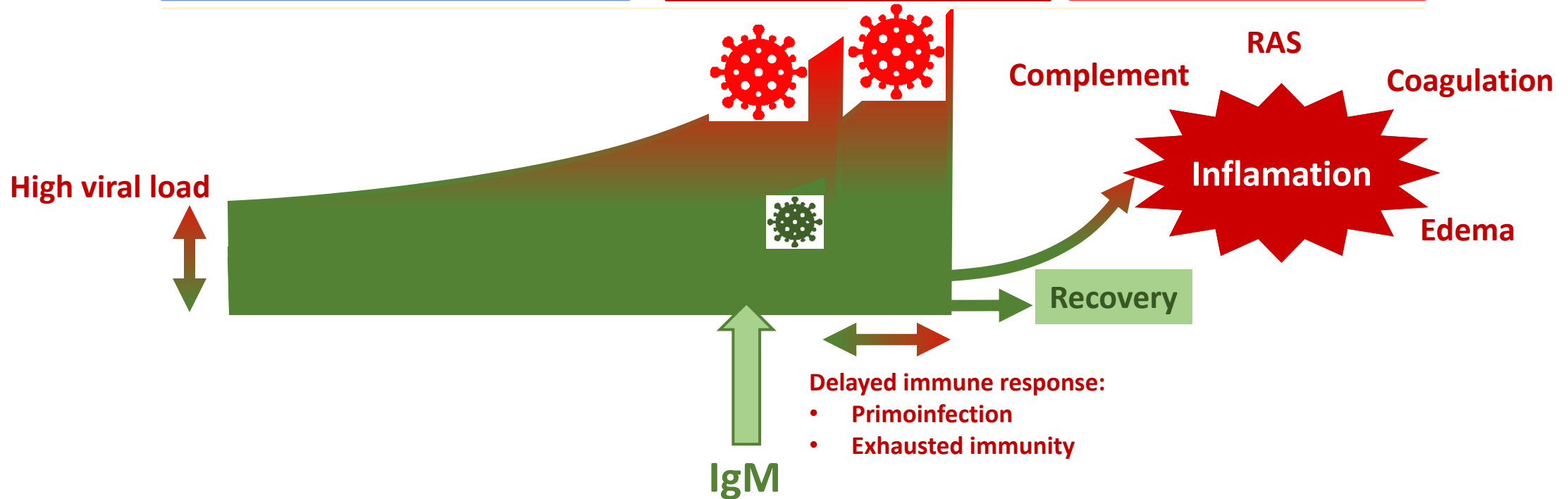
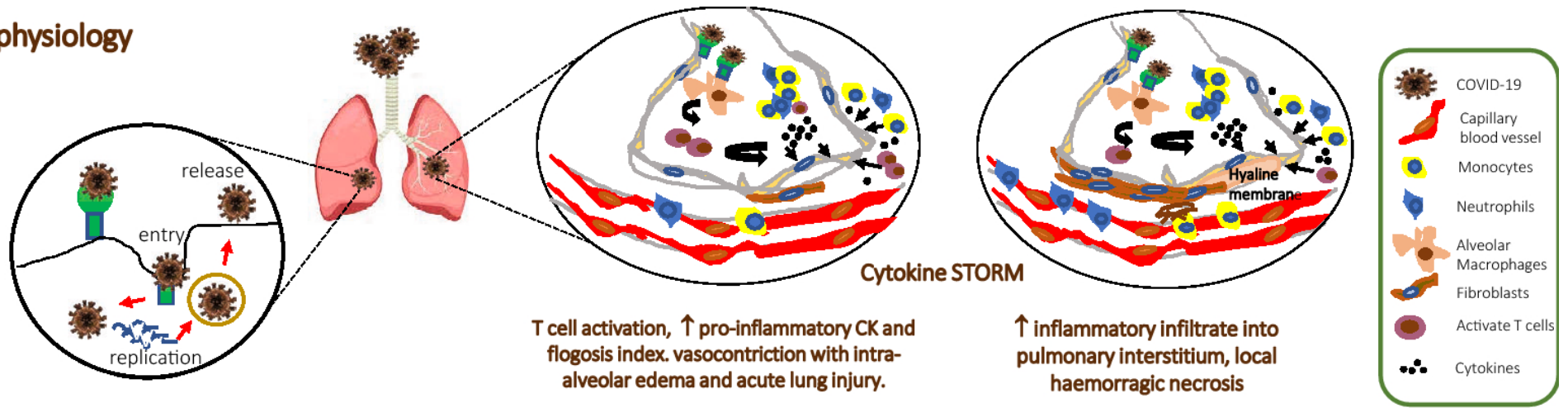
Minor Clinical Impact of COVID-19 Pandemic on Patients With Primary Immunodeficiency in Israel

Nufar Marcus^{1,2,3†}, Shirly Frizinsky^{2,3,4,5,6†}, David Hagin^{2,3,7}, Adi Ovadia^{3,8,9},
Suhair Hanna^{3,10}, Michael Farkash^{1,2,3}, Ramit Maoz-Segal^{2,5,6}, Nancy Agmon-Levin^{2,5,6},
Aron Broides^{3,11}, Amit Nahum^{3,11}, Elli Rosenberg^{3,11}, Amir Asher Kuperman^{12,13},
Yael Dinur-Schejter^{3,14}, Yackov Berkun^{3,15}, Ori Toker^{3,16,17}, Shmuel Goldberg^{16,18},
Ronit Confino-Cohen^{2,19}, Oded Scheuerman²⁰, Basel Badameh^{1,21}, Na'ama Epstein-Rigbi²²,
Amos Etzioni^{3,10}, Ilan Dalal^{2,3,8,9} and Raz Somech^{3,4*}

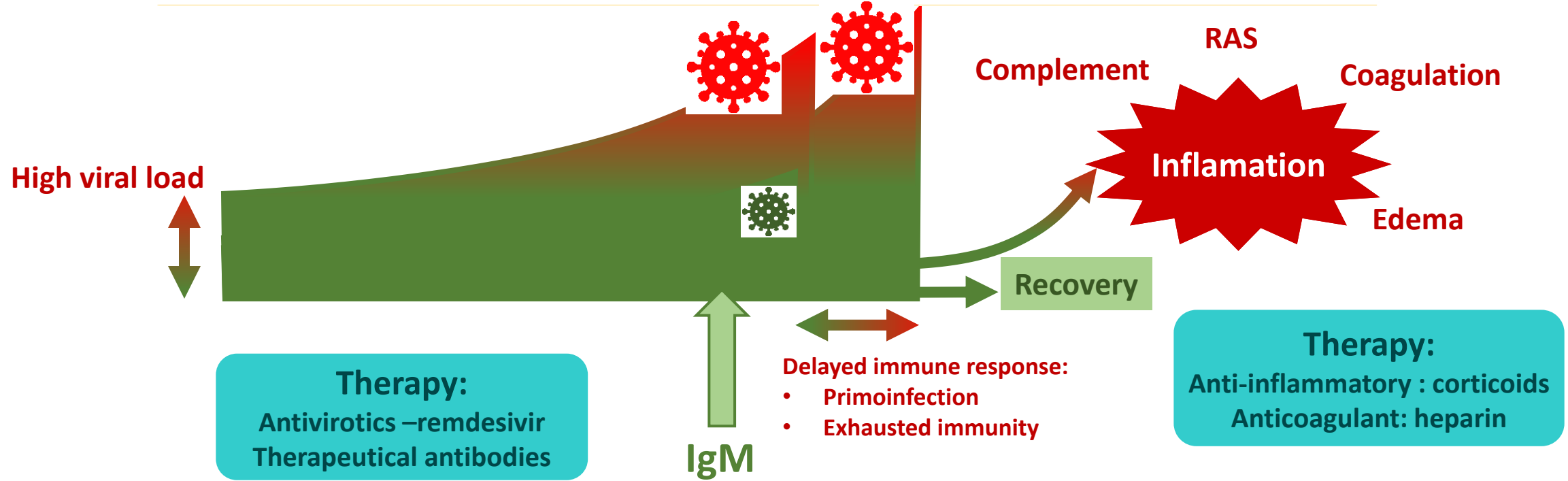
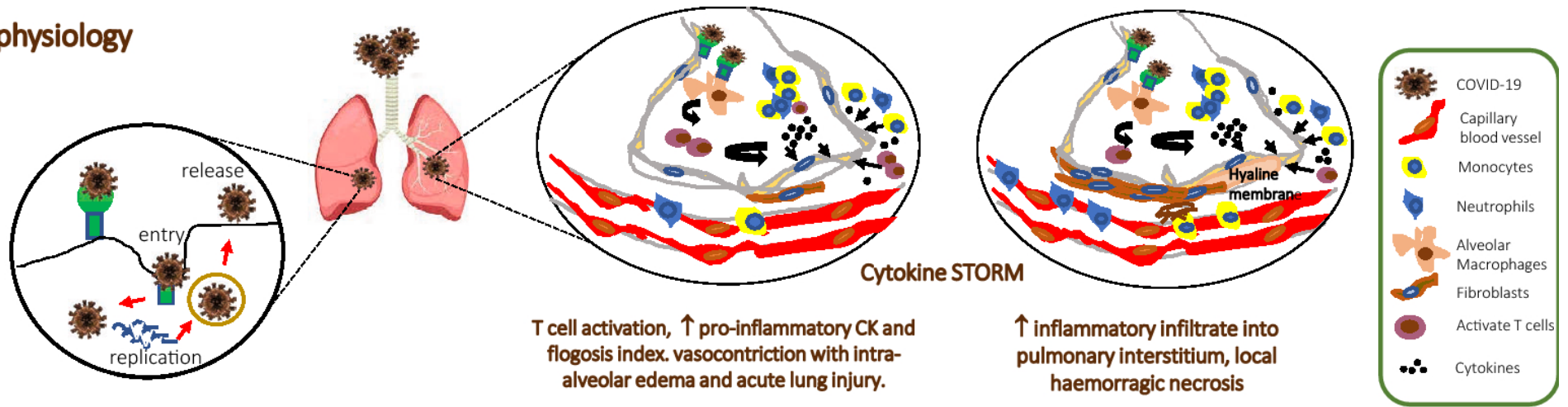
COVID-19 – Pathophysiology



COVID-19 – Pathophysiology



COVID-19 – Pathophysiology

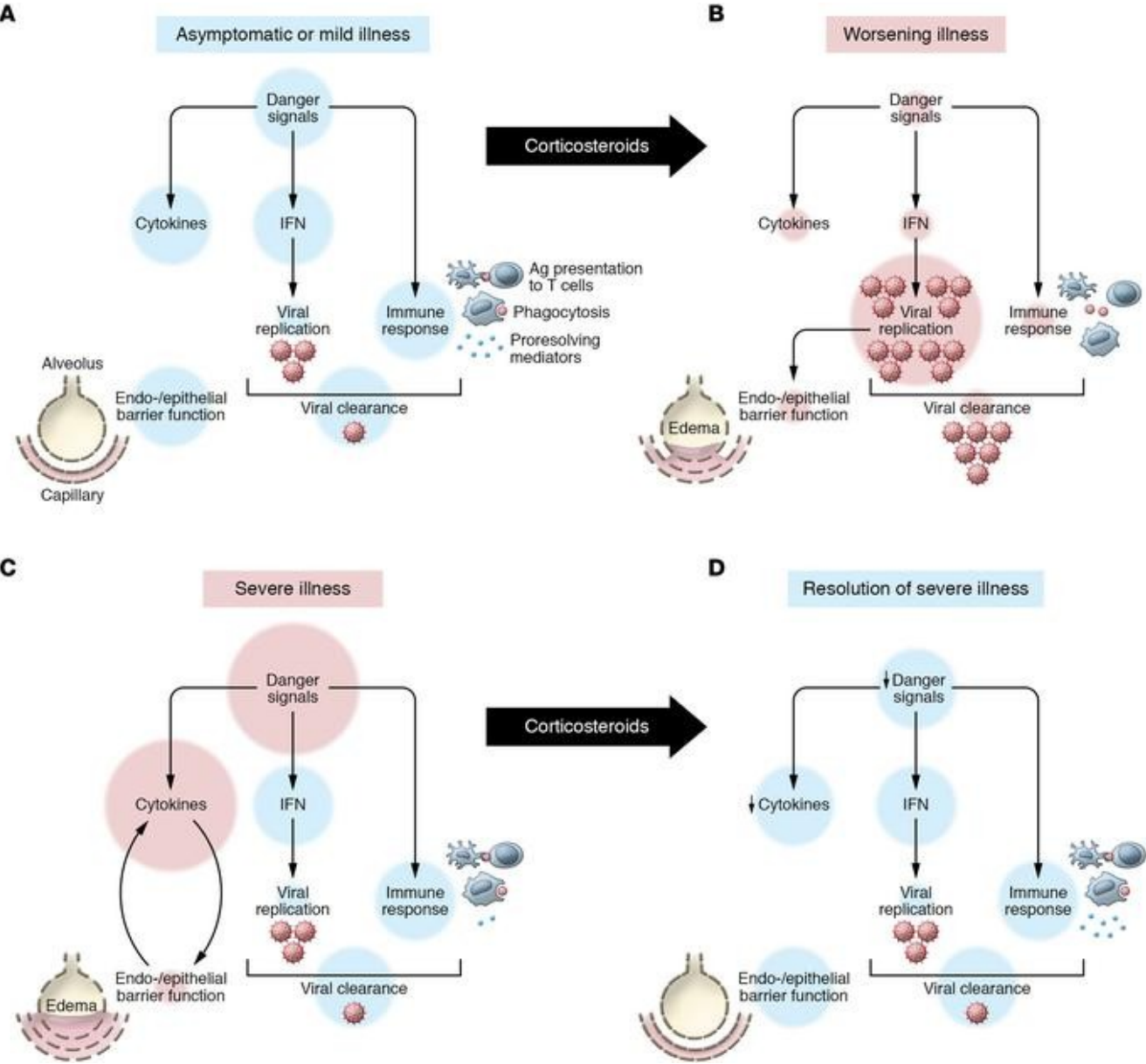


Model for deleterious or beneficial effects of corticosteroids in the treatment of COVID-19.

Corticosteroids, COVID-19 pneumonia, and acute respiratory distress syndrome

Michael A. Matthay^{1,2,3} and Katherine D. Wick^{1,3}

¹Cardiovascular Research Institute, ²Department of Medicine, and ³Department of Anesthesia, UCSF, San Francisco, California, USA.

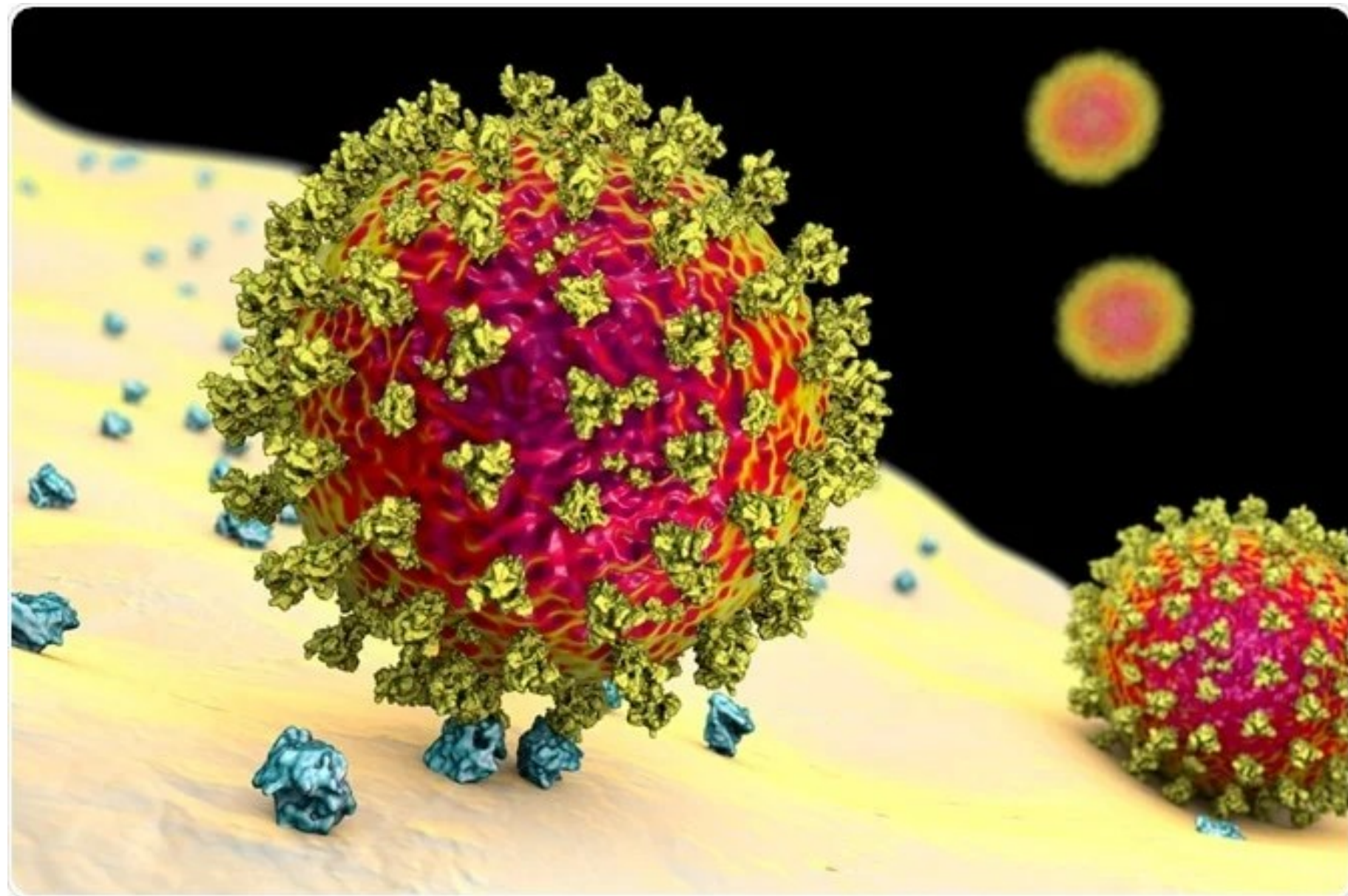


(A) In asymptomatic or mild cases and in the absence of treatment, SARS-CoV-2 induces transcriptional upregulation of interferons (IFNs) and NF-κB activation, which promote cytokine production and activation of macrophages as well as demargination of PMNs. Antigens are presented to T cells and a targeted cytotoxic response ensues.

(B) In worsening illness, corticosteroid treatment can delay pathogen recognition and control. Dampened danger signaling leads to impaired IFN release, unchecked viral replication, and consequent alveolar and lung damage.

(C) In severe illness with COVID-19 without corticosteroid treatment, viral propagation to the alveoli amplifies danger signals and worsens alveolar epithelial and endothelial damage. Persistent damage leads to exuberant NF-κB activation and inflammation worsens even as viral load decreases.

(D) In severe cases of COVID-19 corticosteroid treatment may decrease proinflammatory cytokine burden and help resolution. Corticosteroids promote a proresolving macrophage phenotype that can clear cellular debris. Corticosteroids also reduce capillary permeability and increase alveolar edema fluid clearance, resulting in improved barrier function.



Endothelial cell infection and endotheliitis in COVID-19

Cardiovascular complications are rapidly emerging as a key threat in coronavirus disease 2019 (COVID-19) in addition to respiratory disease. The mechanisms underlying the disproportionate effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on patients with cardiovascular comorbidities, however, remain incompletely understood.^{1,2}

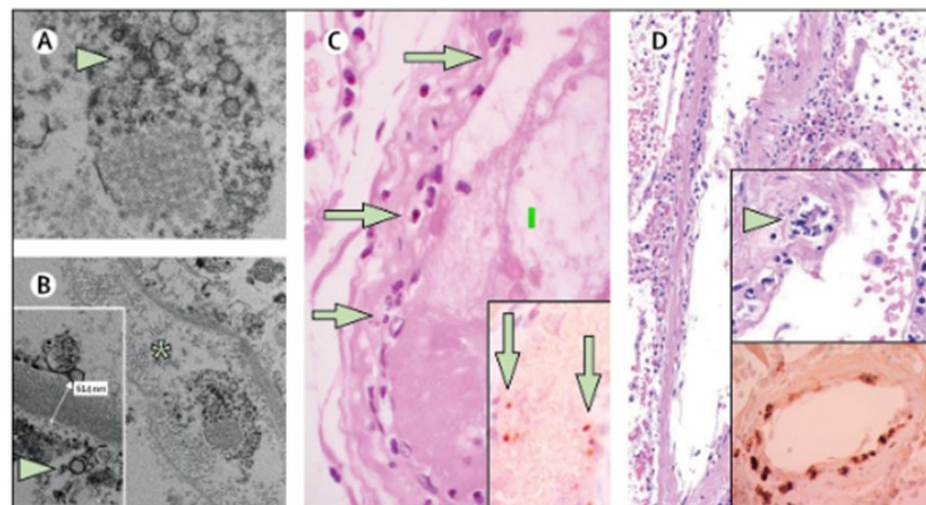


Figure: Pathology of endothelial cell dysfunction in COVID-19

(A, B) Electron microscopy of kidney tissue shows viral inclusion bodies in a peritubular space and viral particles in endothelial cells of the glomerular capillary loops. Aggregates of viral particles (arrow) appear with



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Mechanismy poškození endotelu při infekci SARS-CoV2

