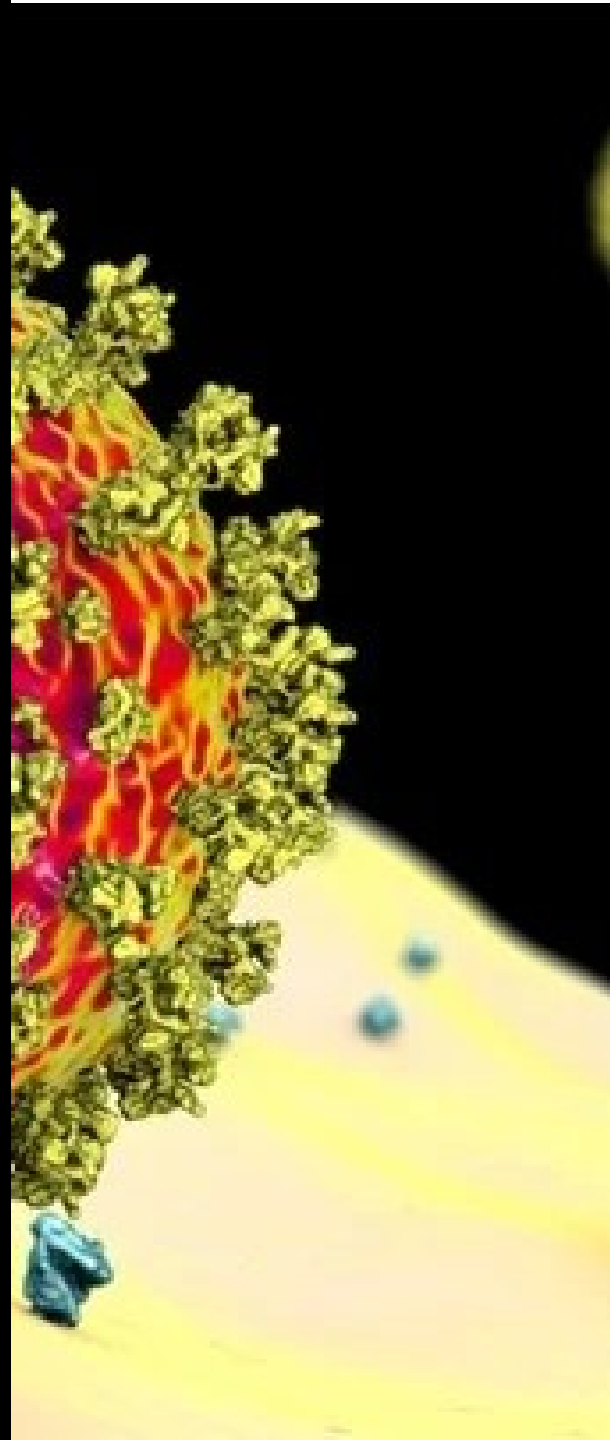
SARS-CoV-2 pathophysiology



1. **Renin-angiotensin-aldosteron systém (RAS)**
    - **Receptor ACE2**
    - **Pathologic regualation of RAS and covid 19**

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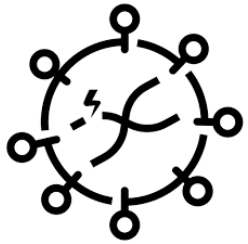
2. **Non-specific (innate) immunity a mutagenesis**
    - **Mechanisms of innate immunity**
    - **Mutations raised by host cell**



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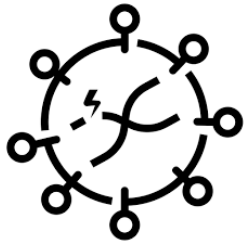
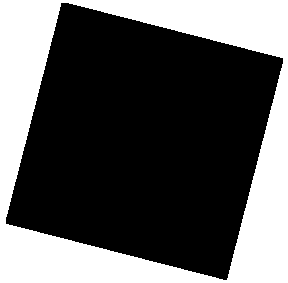


3. **Specific immune reaction and complement activation**
    - **Antibody response**
    - **Inflamation**



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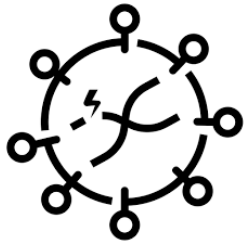

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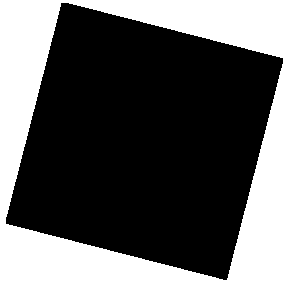
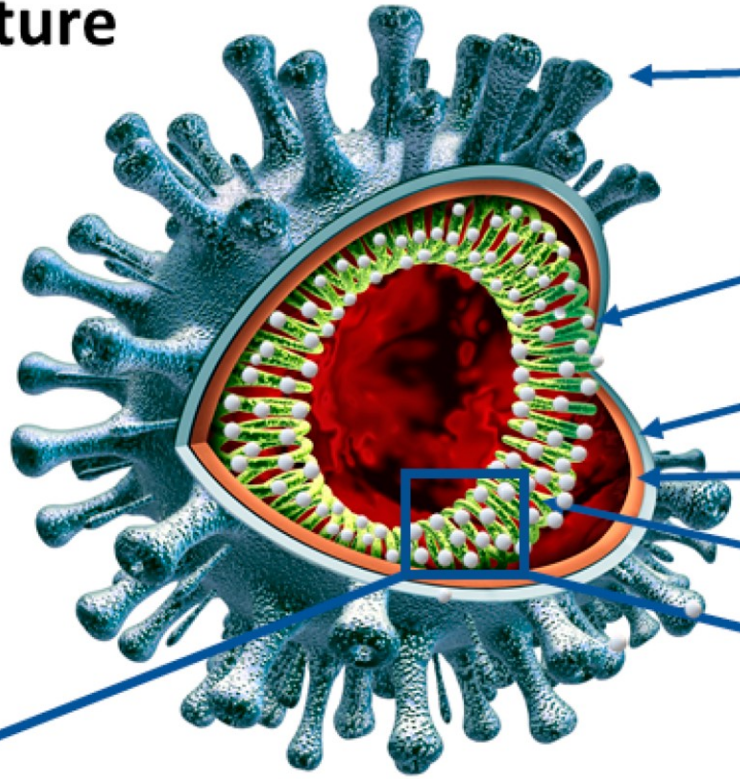


4. **Mechanisms of endothelial injury**
    - **Cytokine storm, ARDS**

SARS-CoV-2 Structure



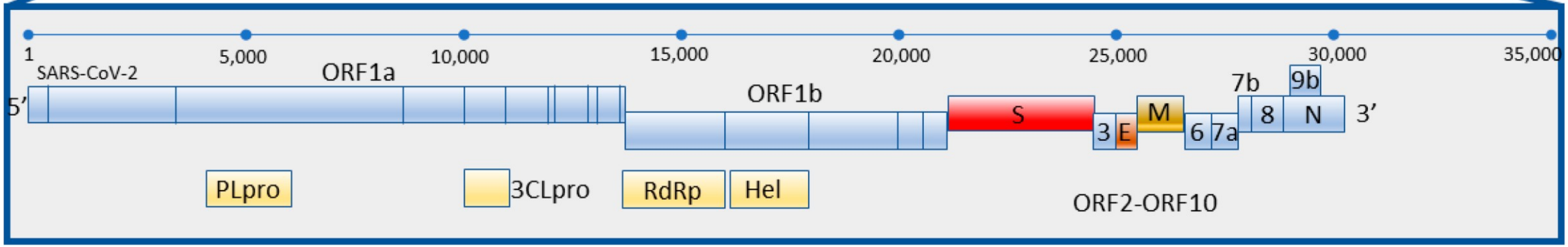
Spike (S1&S2)

Nucleocapsid (N)

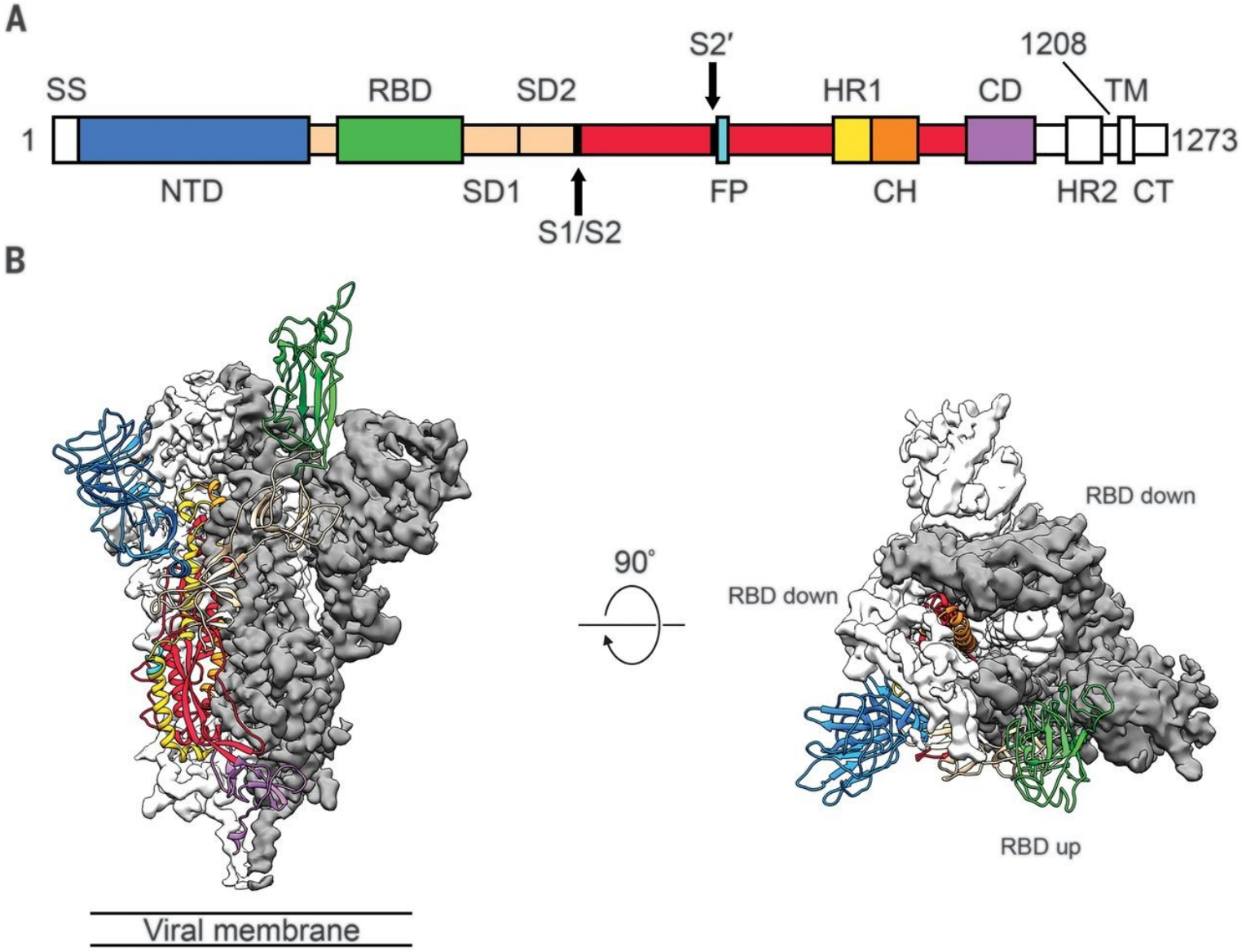
Membrane (M)

Envelope (E)

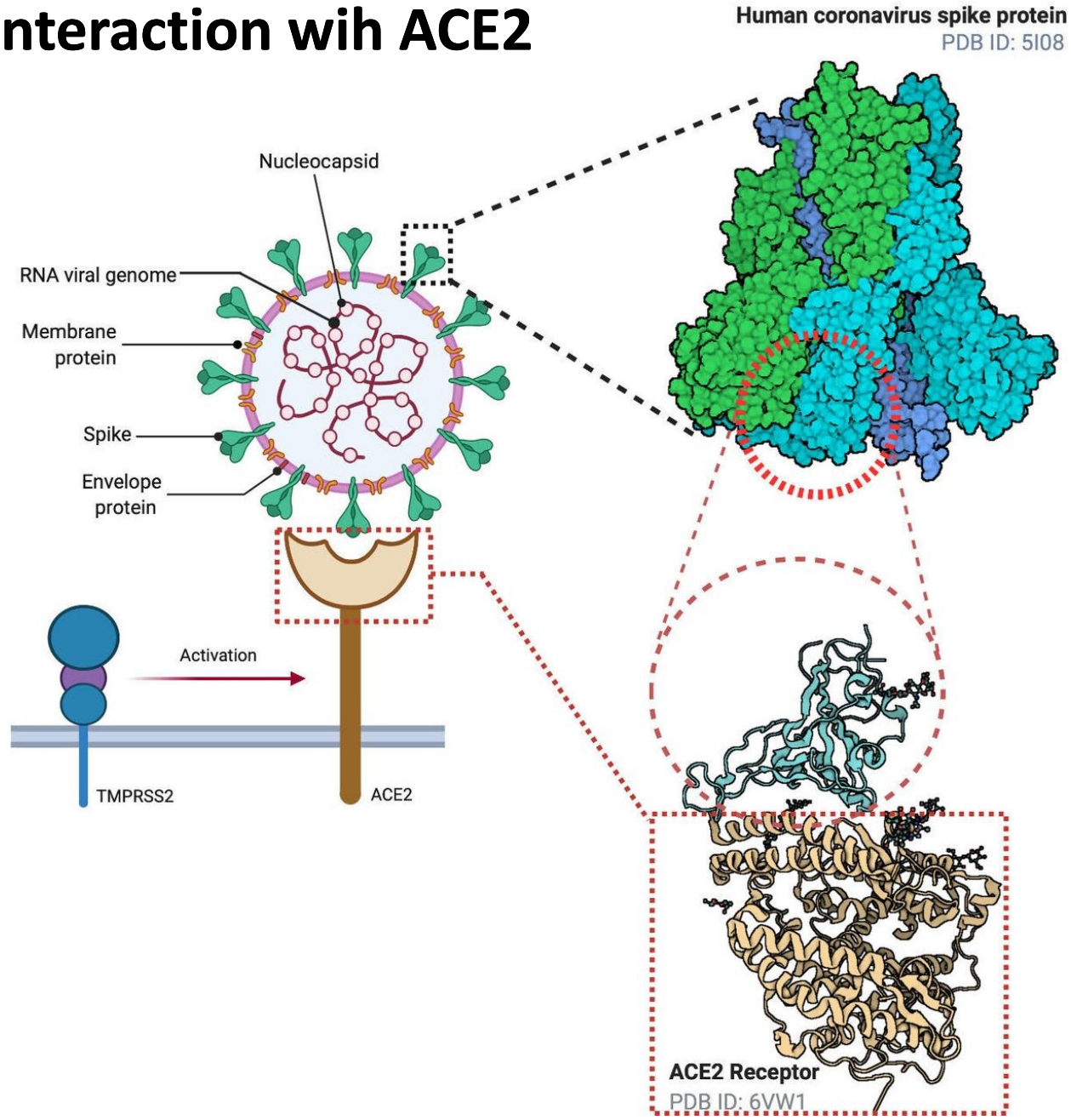
ssRNA (+sense, ~30kb in length)



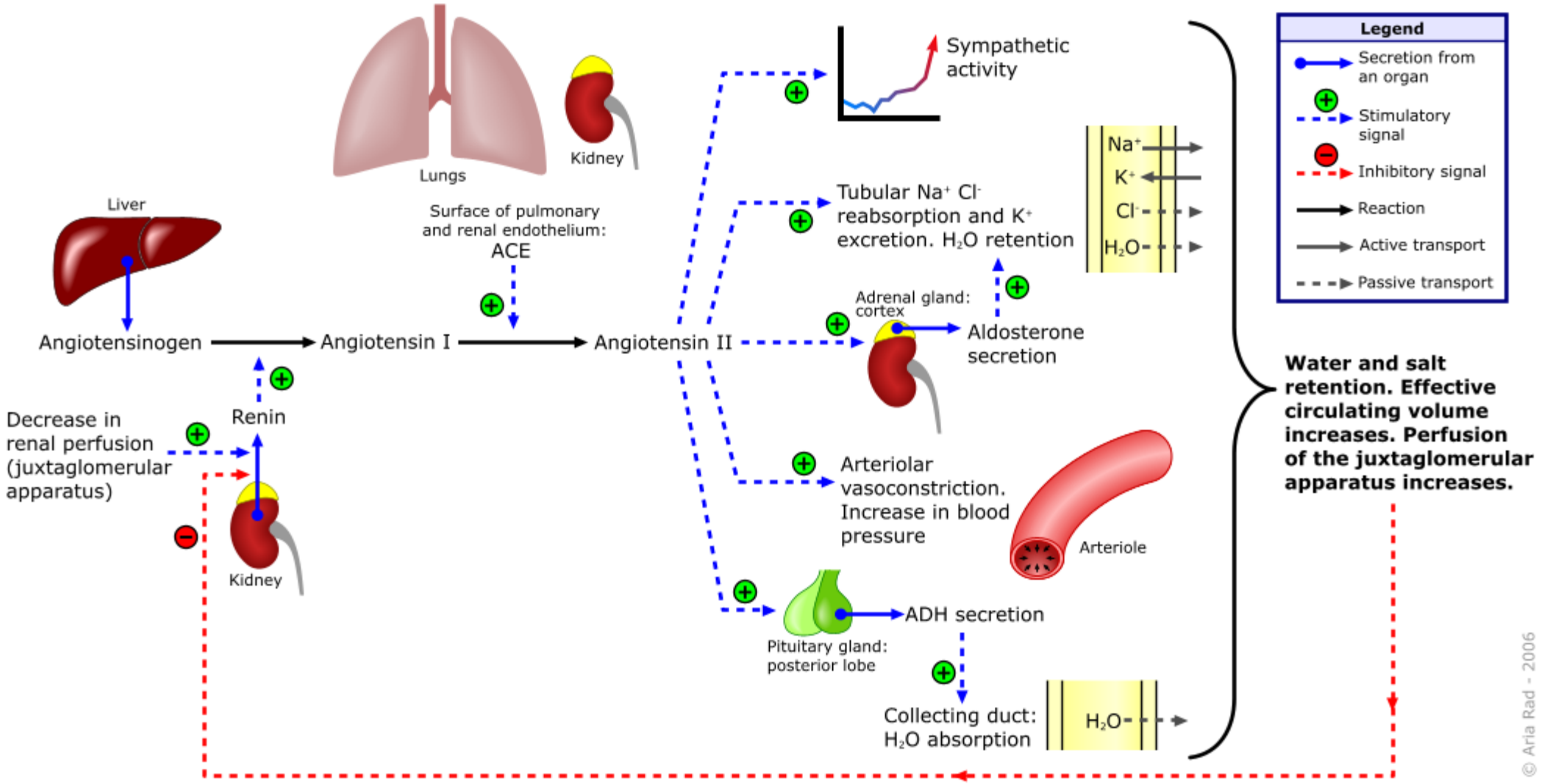
S-protein structure



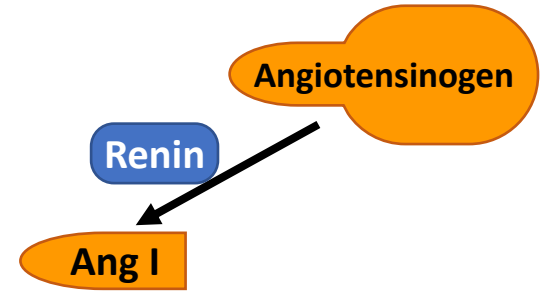
S-protein structure and interaction wih ACE2



Renin-angiotensin-aldosterone system

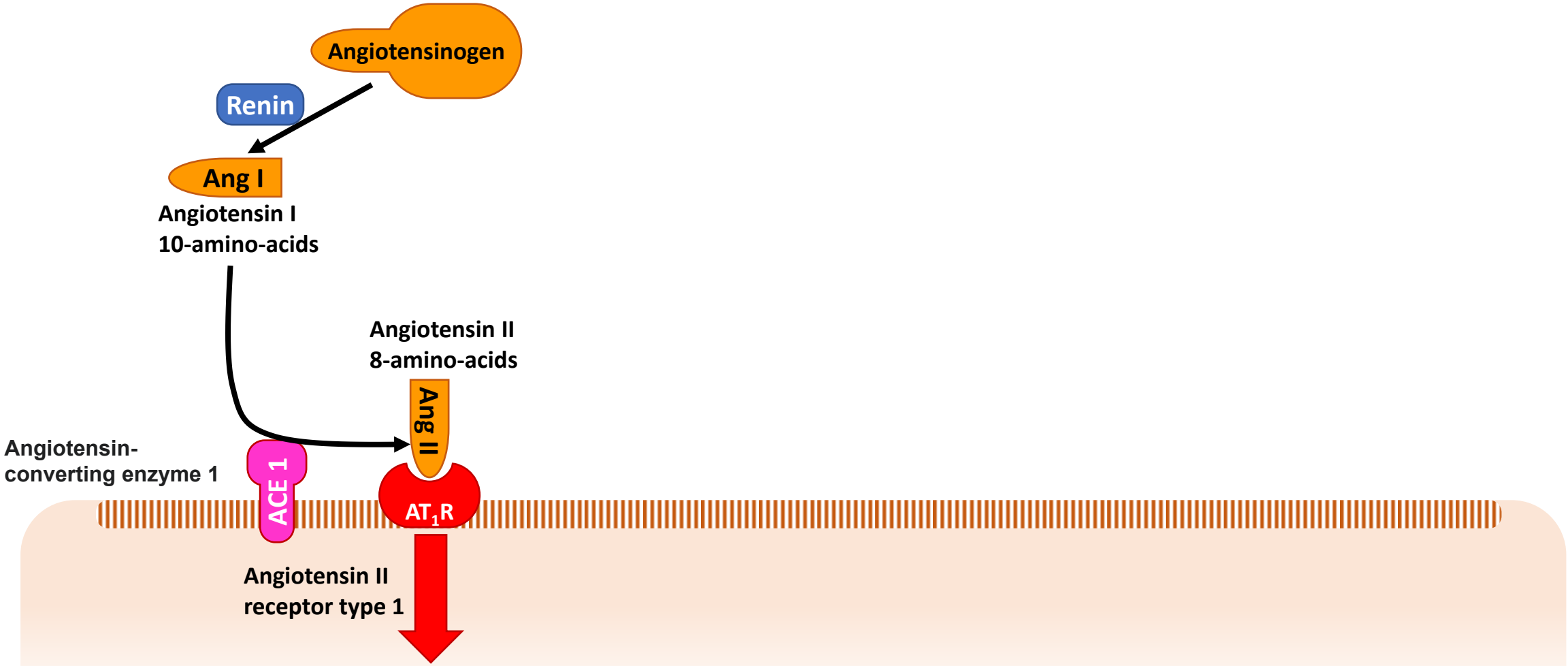


The role of RAS in SARS-Cov-2 infection



Angiotensin I
10-amino-acids

The role of RAS in SARS-Cov-2 infection



- Thrombocyte activation
- Coagulation
- Inflamation
- Mesenchymal proliferation
- Increased permeability
- Vasoconstriction
- Endothelial disfunction
- Lung edema,

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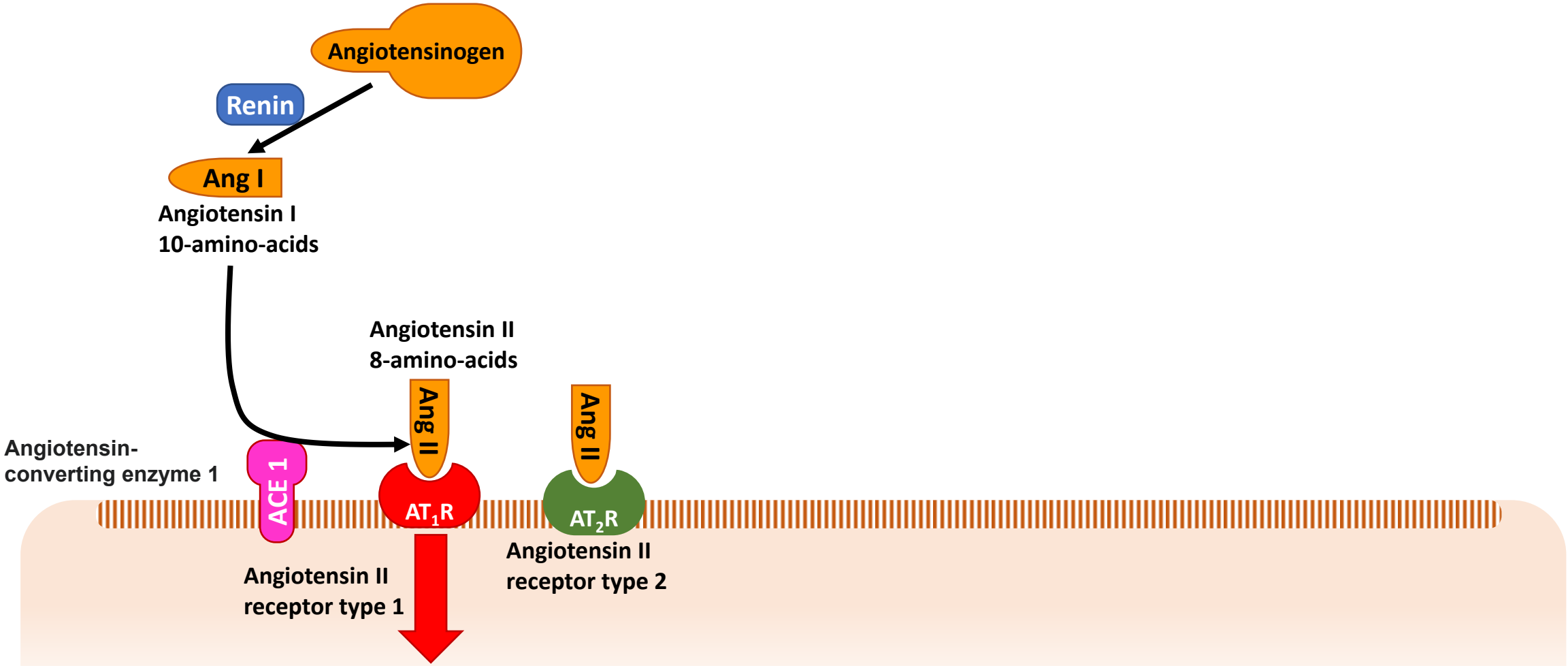

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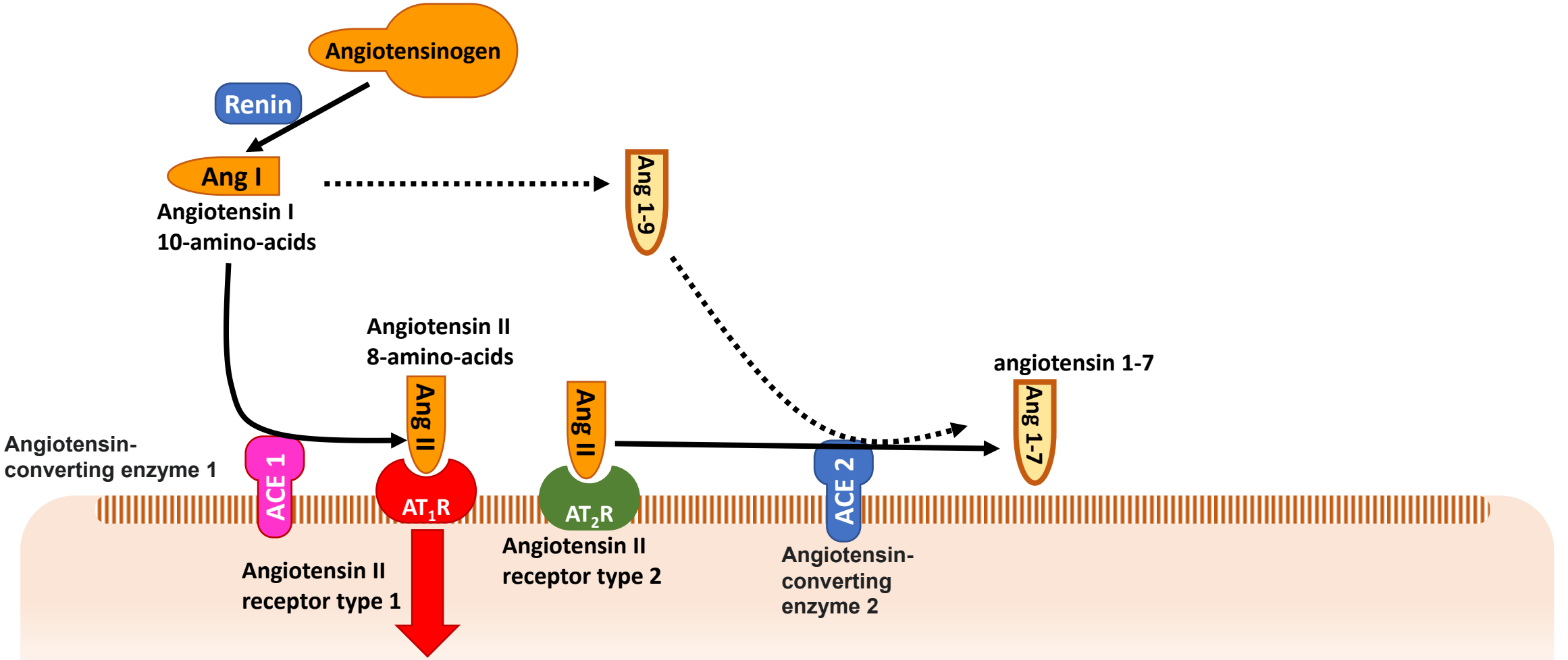

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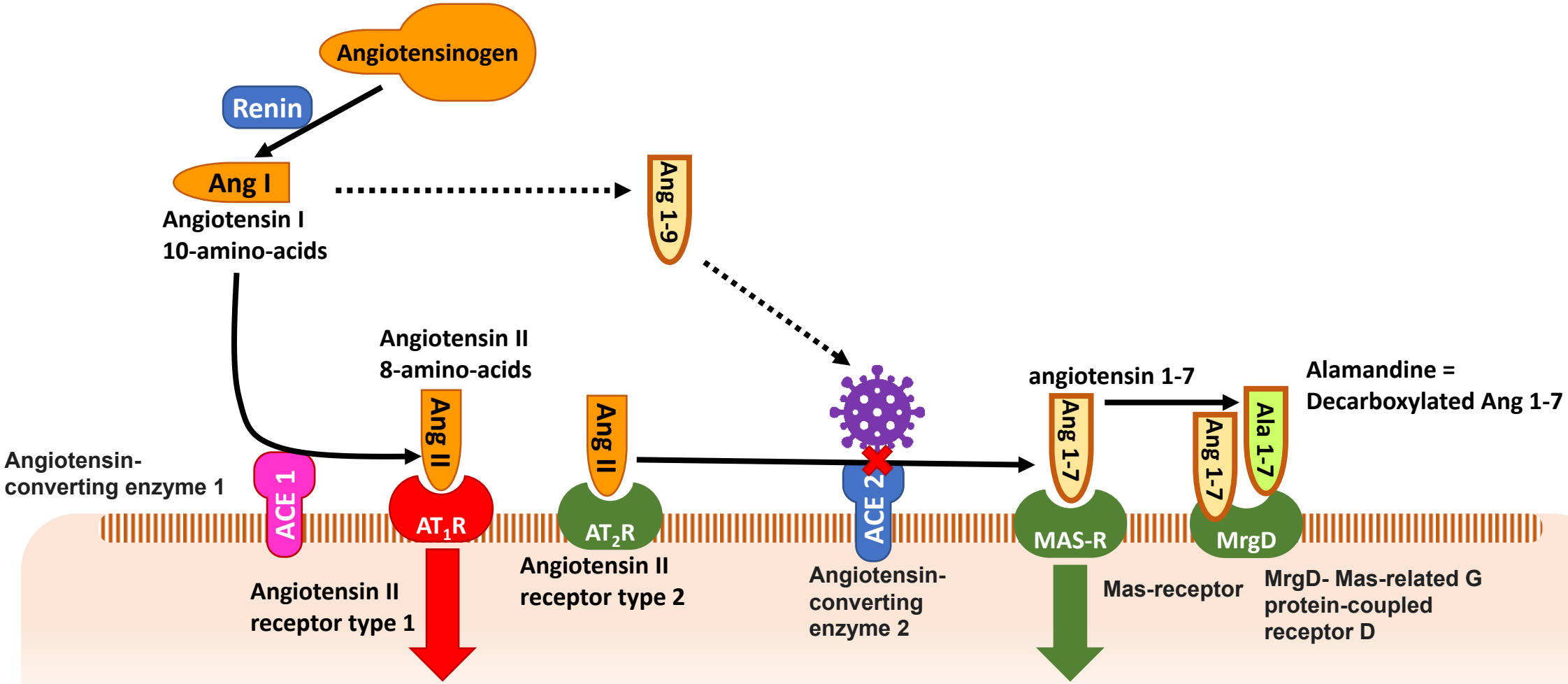

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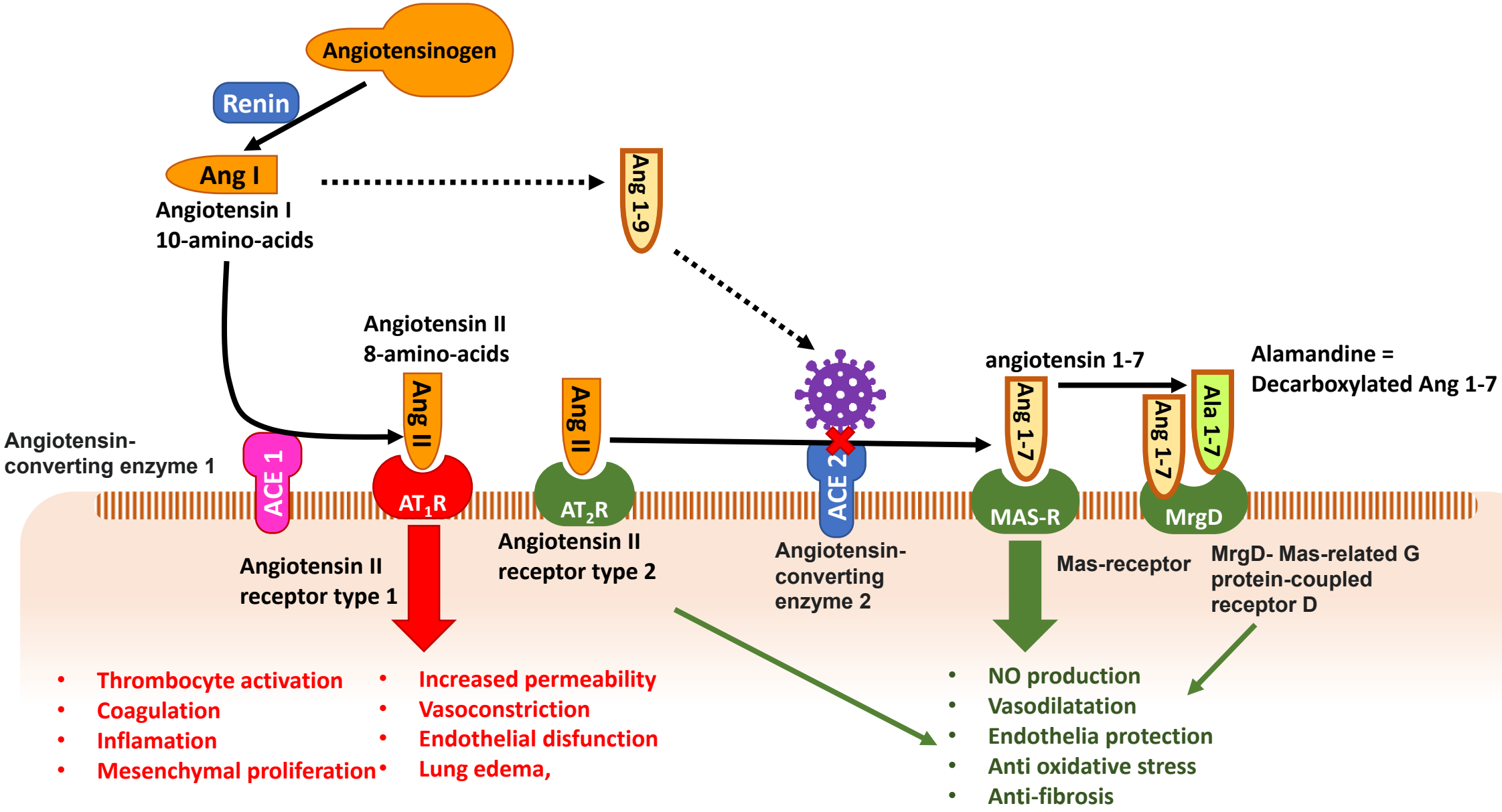

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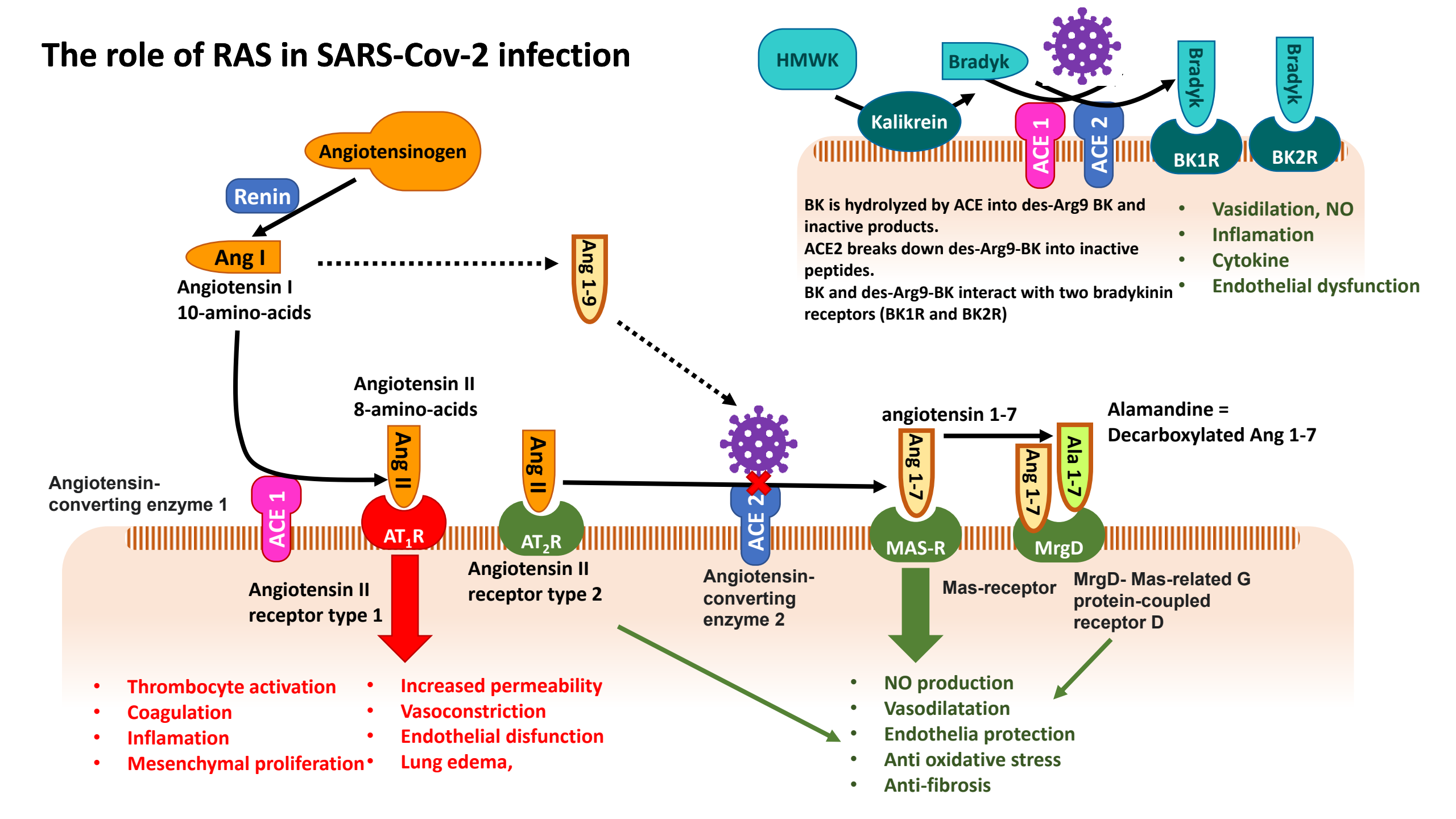

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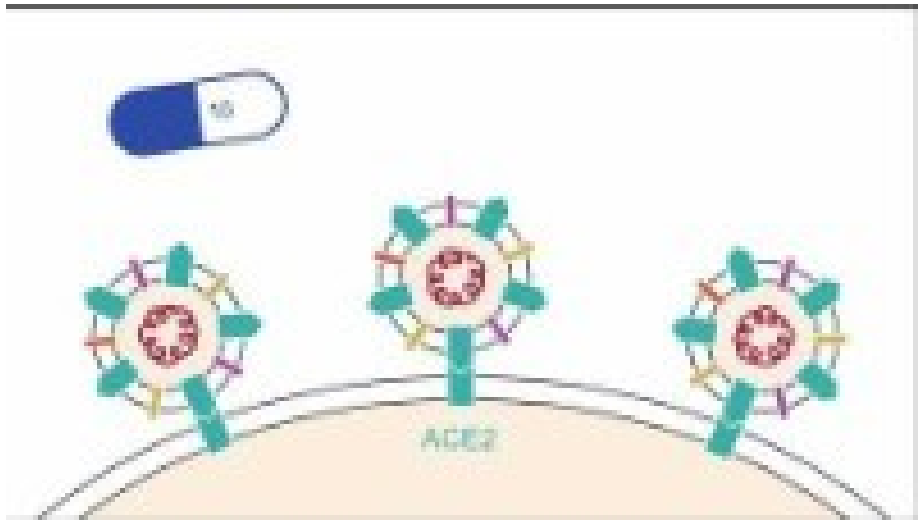

ACE inhibitors:
- Captopril
- Enalapril
- Fosinopril
- Lisinopril

AT1R inhibitors:
- Valsartan
- Telmisartan
- Losartan
- Olmesartan

Angiotensinogen

Renin

Ang I

Angiotensin I
10-amino-acids

Ang 1-9

Angiotensin II
8-amino-acids

Angiotensin-
converting enzyme 1

ACE 1

Ang II

AT_1R

Angiotensin II
receptor type 1

Ang II

AT_2R

Angiotensin II
receptor type 2

ACE 2

Angiotensin-
converting
enzyme 2

angiotensin 1-7

Ang 1-7

MAS-R

Mas-receptor

Ang 1-7

Ala 1-7

MrgD

MrgD- Mas-related G
protein-coupled
receptor D

Alamandine =
Decarboxylated Ang 1-7

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

Mechanisms of innate immunity

(fast but non-specific response)

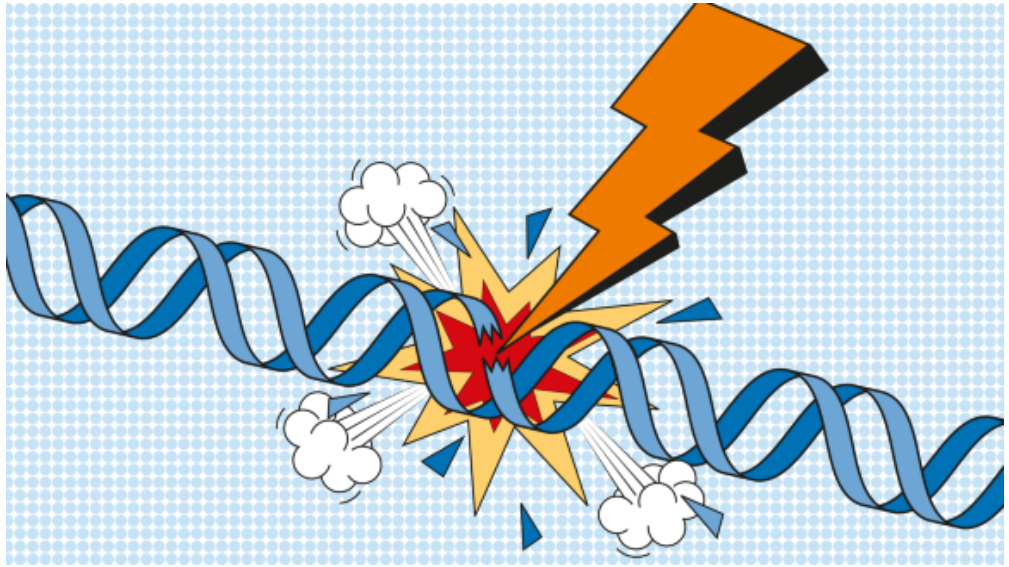
Detection of pathogenic microorganisms

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

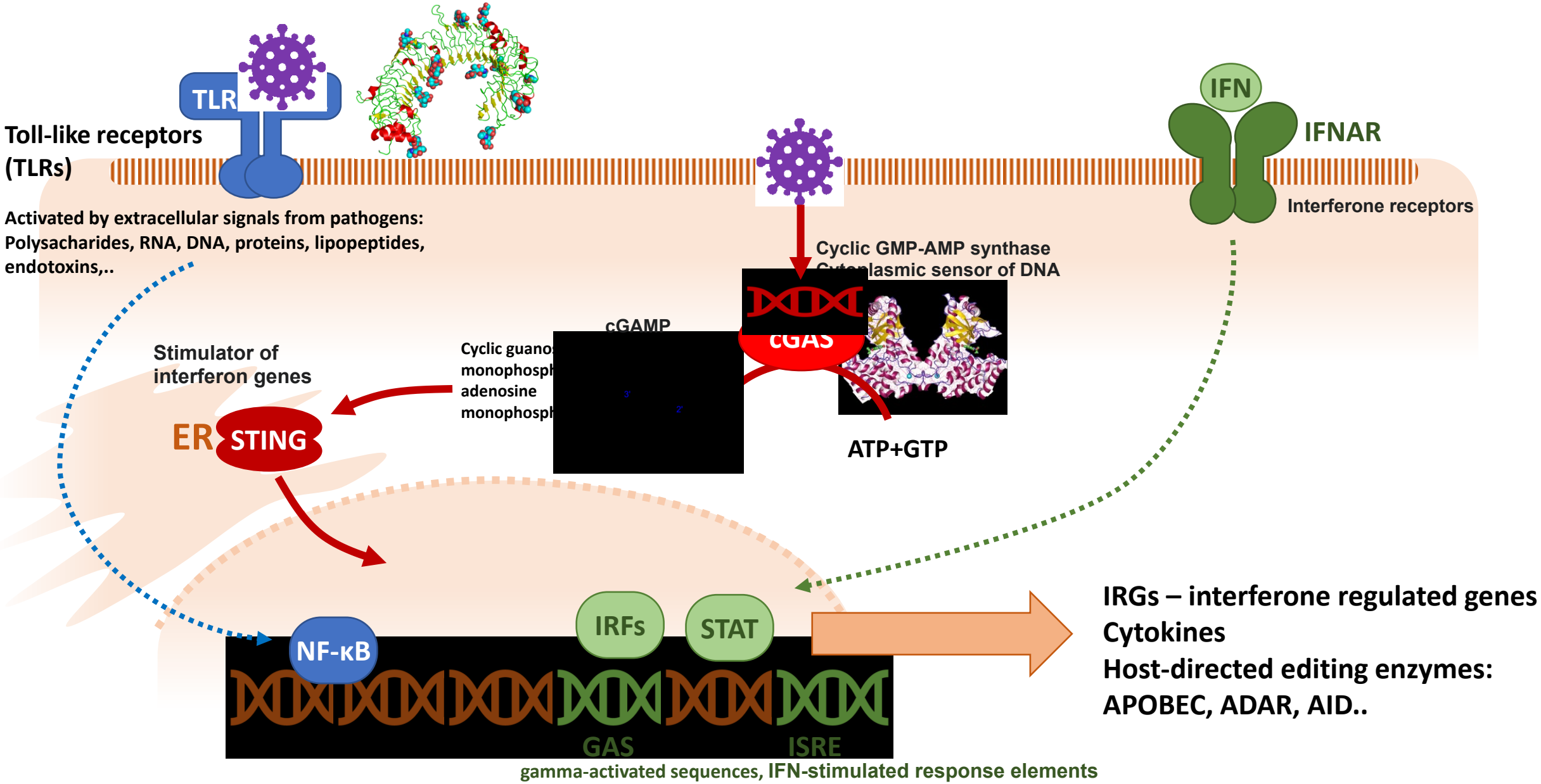
Intracellular signalling pathways

Activation of transcription / gene expression

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

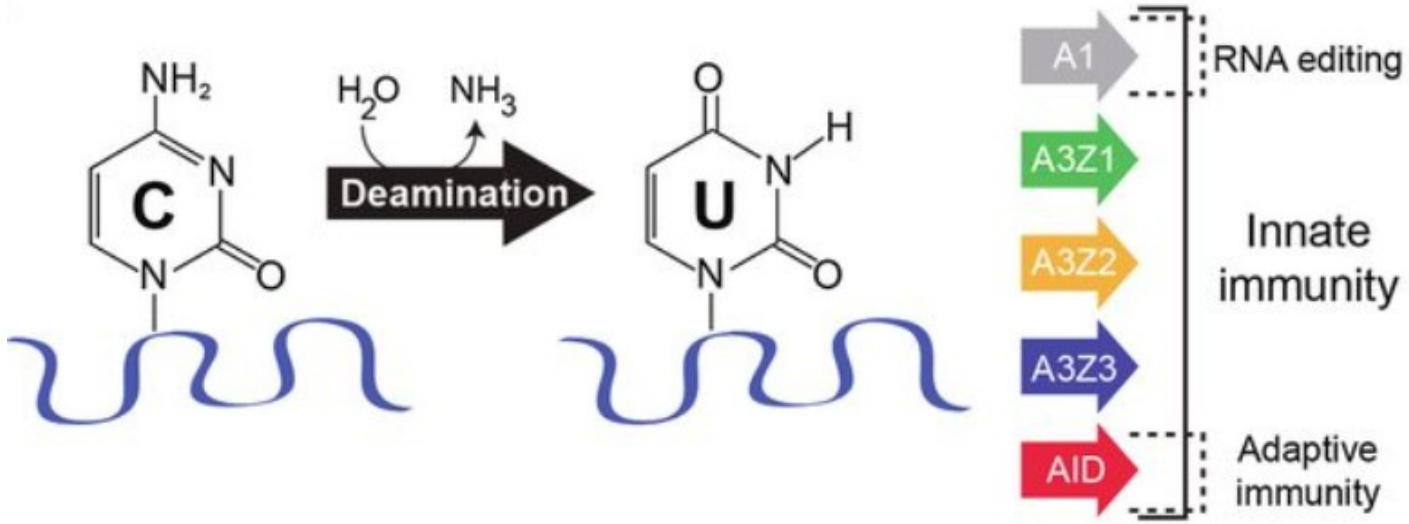


Mechanisms of innate immunity



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

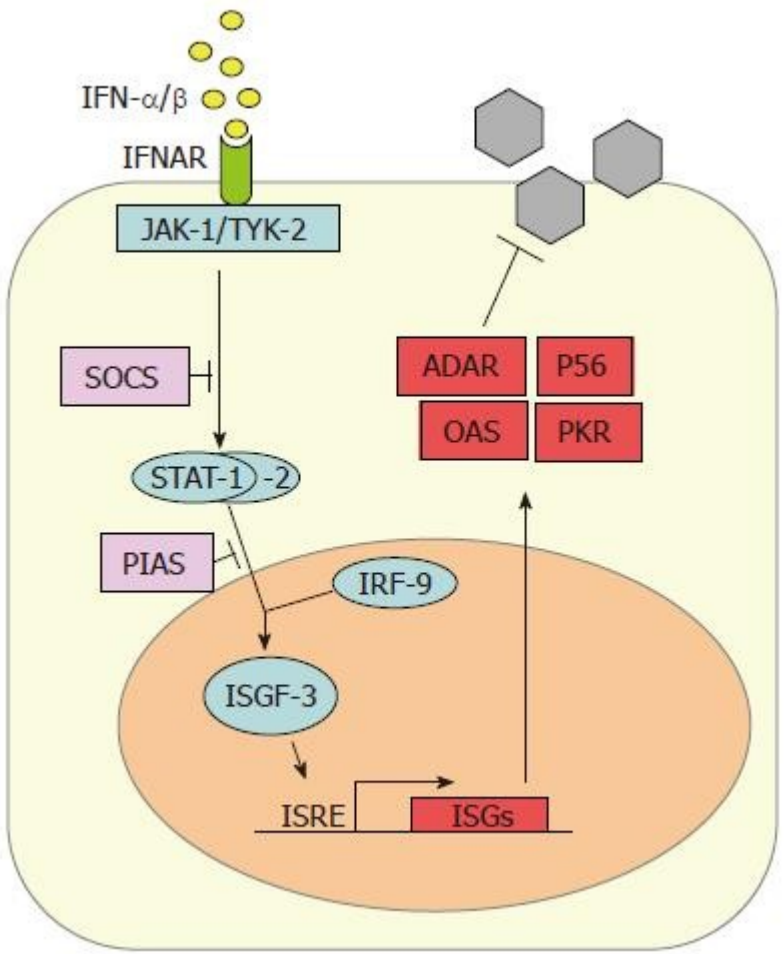


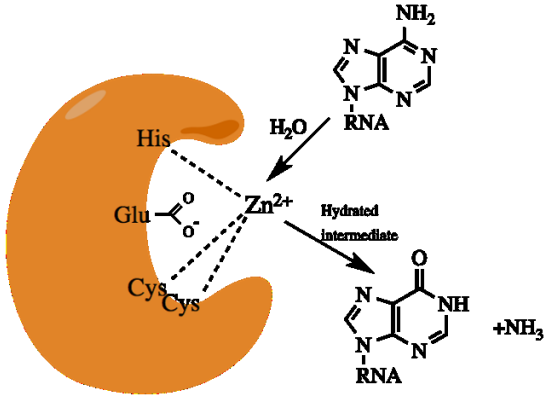
APOBEC1
APOBEC2
APOBEC3A
APOBEC3B
APOBEC3C
APOBEC3D
APOBEC3F
APOBEC3G
APOBEC3H
APOBEC4
AID (activation induced deaminase)

ADAR - adenosine deaminase acting on RNA

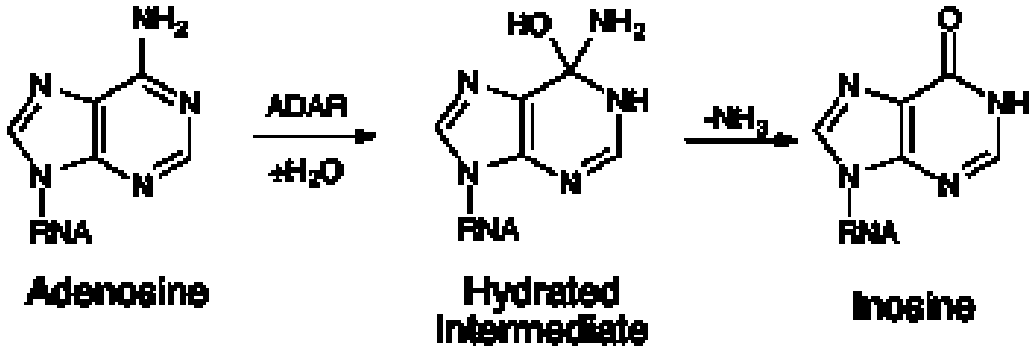
responsible for binding to double stranded RNA (dsRNA) and converting adenosine (A) to inosine (I) by deamination. ADAR protein is a RNA-binding protein, which functions in RNA-editing through post-transcriptional modification of mRNA transcripts by changing the nucleotide content of the RNA

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



viruses

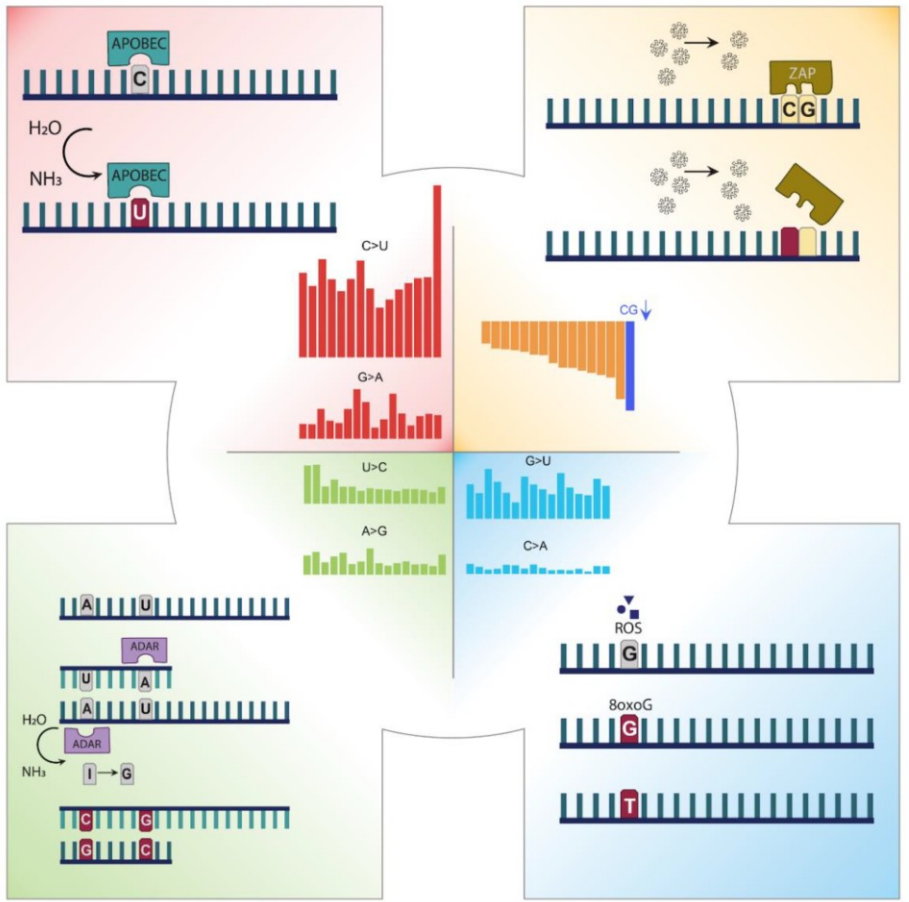
MDPI

Article

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

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

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.



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

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

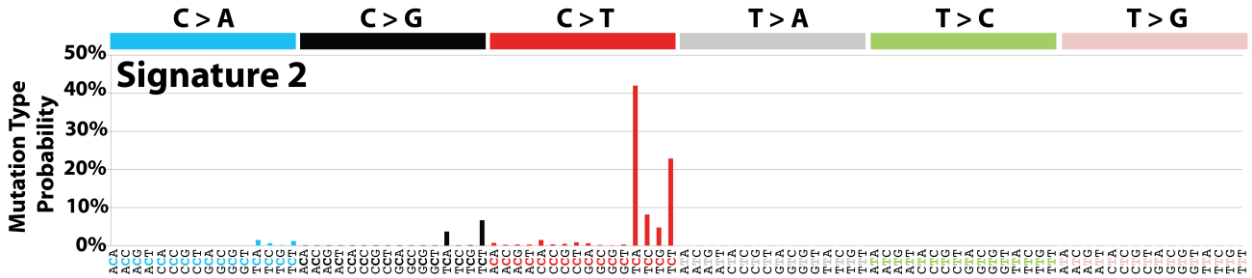
Tobias Mourier [a, **, 1], Mukhtar Sadykov [a, 1], Michael J. Carr [b, c], Gabriel Gonzalez [b, c], William W. Hall [b, c, d], Arnab Pain [a, c, *]

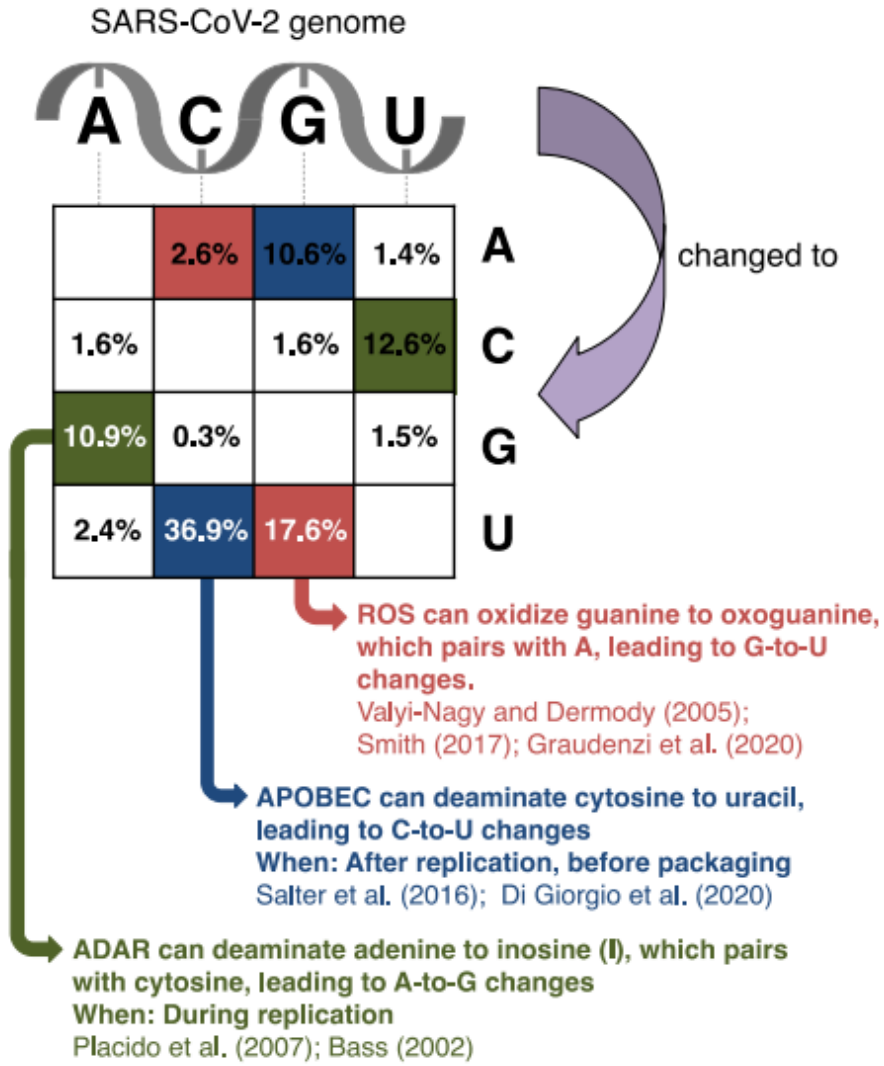
[a] King Abdullah University of Science and Technology (KAUST), Pathogen Genomics Laboratory, Biological and Environmental Science and Engineering (BESE), Thuwal-Jeddah, 23955-6900, Saudi Arabia
[b] National Virus Reference Laboratory (NVRL), School of Medicine, University College Dublin, Belfield, D04 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

COSMIC
Catalogue Of Somatic Mutations In Cancer

Signatures of Mutational Processes in Human Cancer

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





Article

Six reference-quality genomes reveal evolution of bat adaptations

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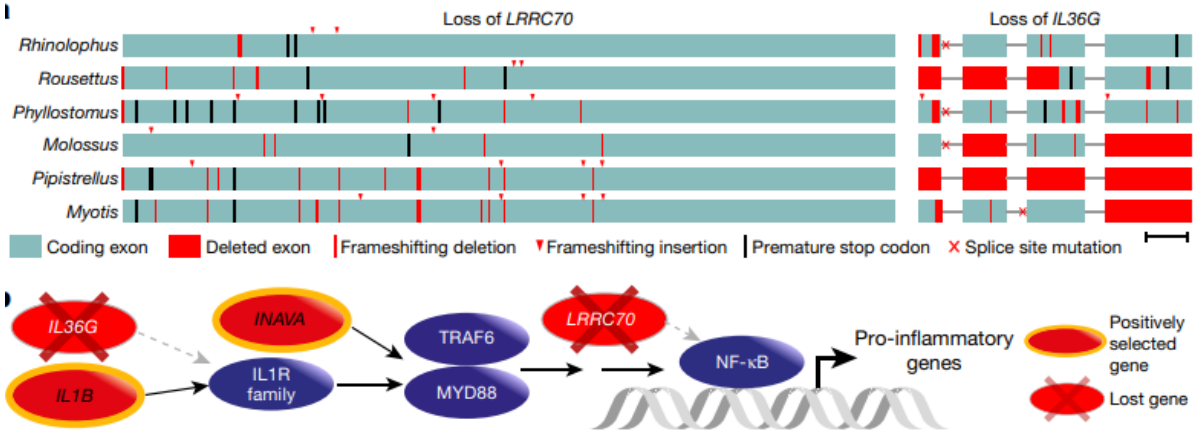
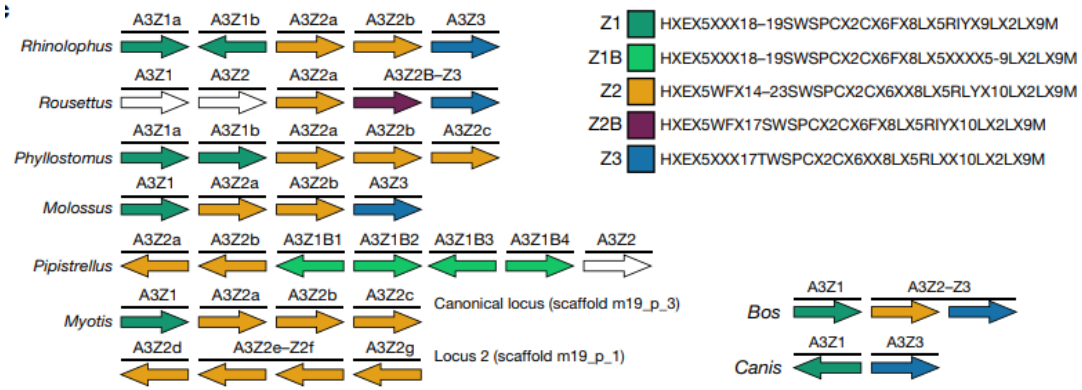
Open access
Check for updates

David Jebb[1,2,3,25], Zixia Huang[4,25], Martin Pippel[1,3,25], Graham M. Hughes[4], Ksenia Lavrichenko[5], Paolo Devanna[5], Sylke Winkler[1], Lars S. Jermiin[4,6,7], Emilia C. Skirmuntt[8], Aris Katzourakis[8], Lucy Burkitt-Gray[9], David A. Ray[10], Kevin A. M. Sullivan[10], Juliana G. Roscito[1,2,3], Bogdan M. Kirilenko[1,2,3], Liliana M. Dávalos[11,12], Angelique P. Corthals[13], Megan L. Power[4], Gareth Jones[14], Roger D. Ransome[14], Dina K. N. Dechmann[15,16,17], Andrea G. Locatelli[4], Sébastien J. Puechmaille[18,19], Olivier Fedrigo[20], 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



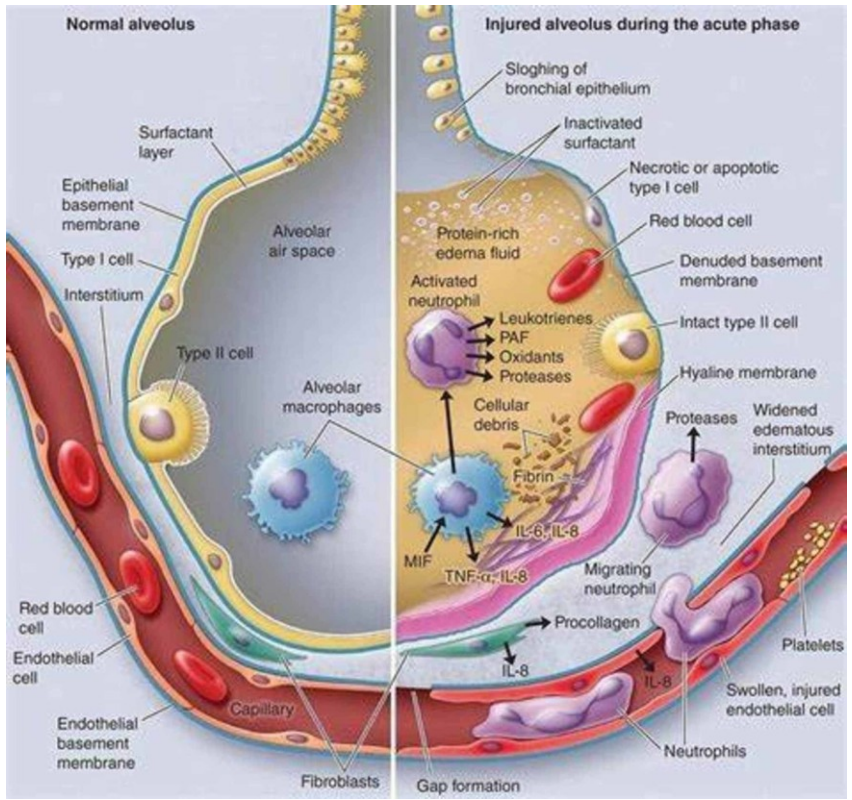
EUROPEAN RESPIRATORY *journal*
FLAGSHIP SCIENTIFIC JOURNAL OF ERS

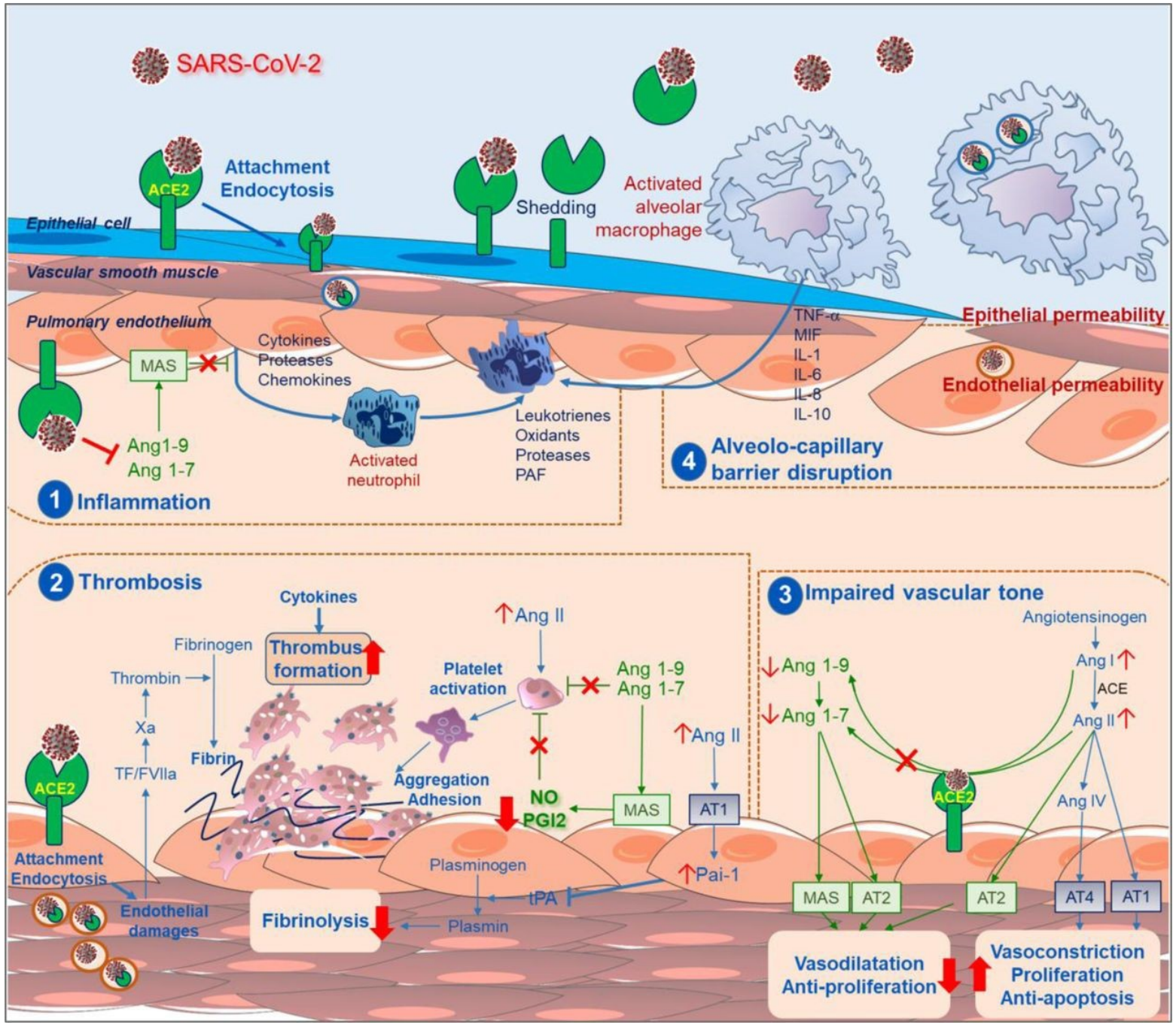
Early View

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

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]

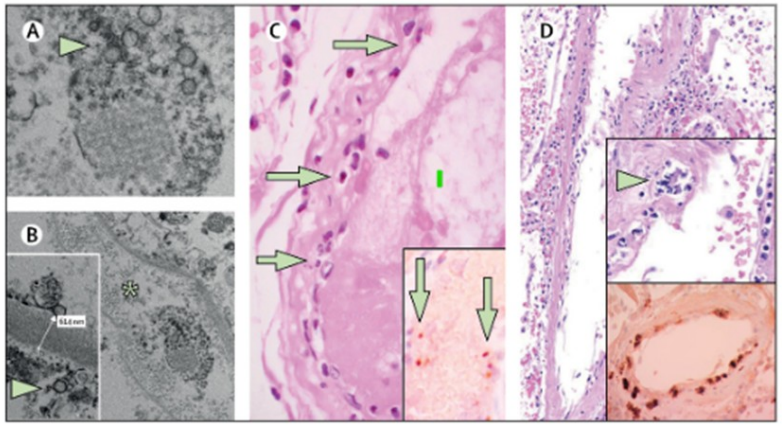


Figure: **Pathology of endothelial cell dysfunction in COVID-19**
(A, B) Electron microscopy of kidney tissue shows viral inclusion bodies in a peritubular space and viral particles in endothelial cells of the glomerular capillary loops. Aggregates of viral particles (arrow) appear with

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S0140-6736(20)30937-5

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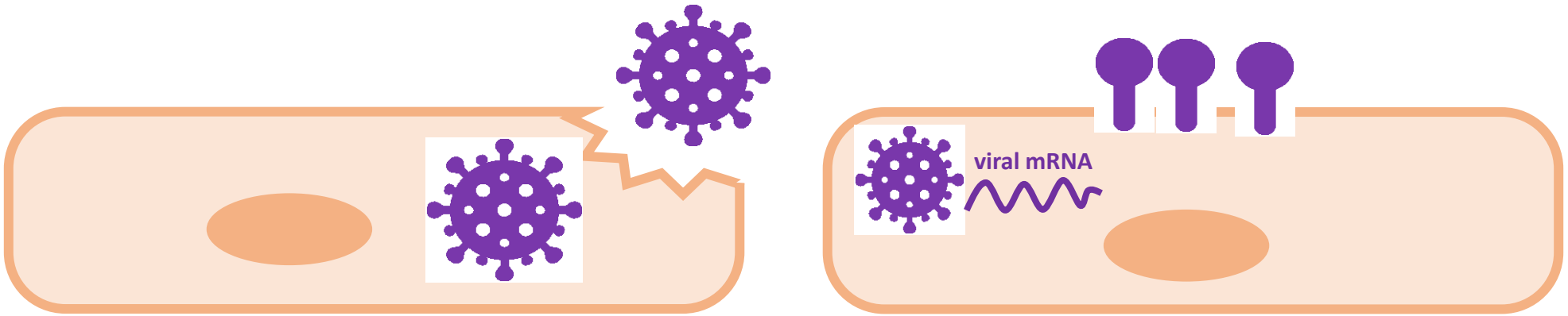
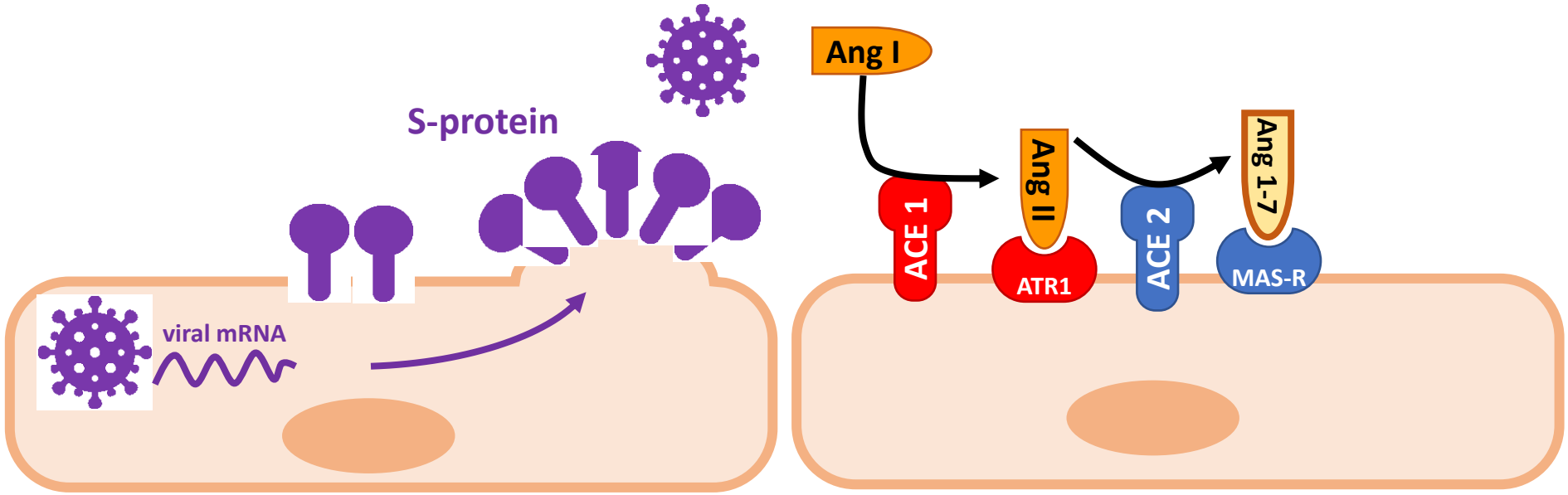


Mechanisms of endothelial damage by SARS-CoV2



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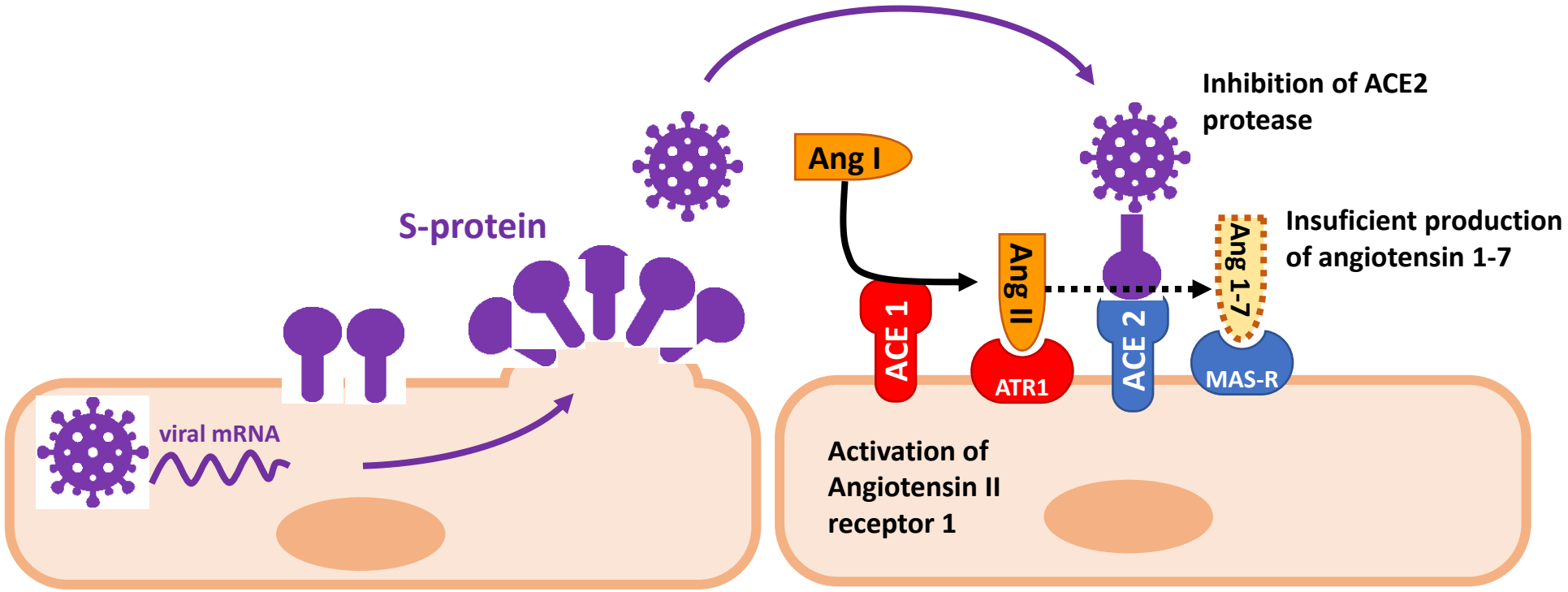

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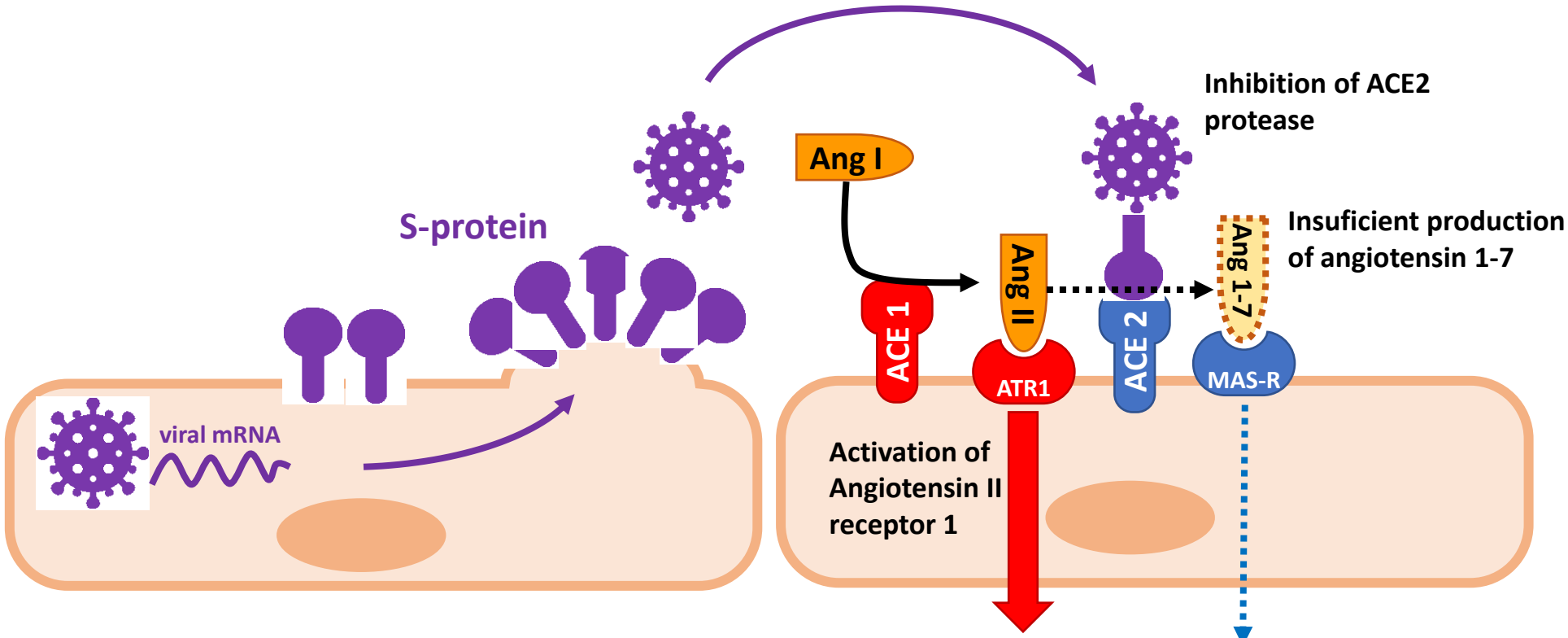

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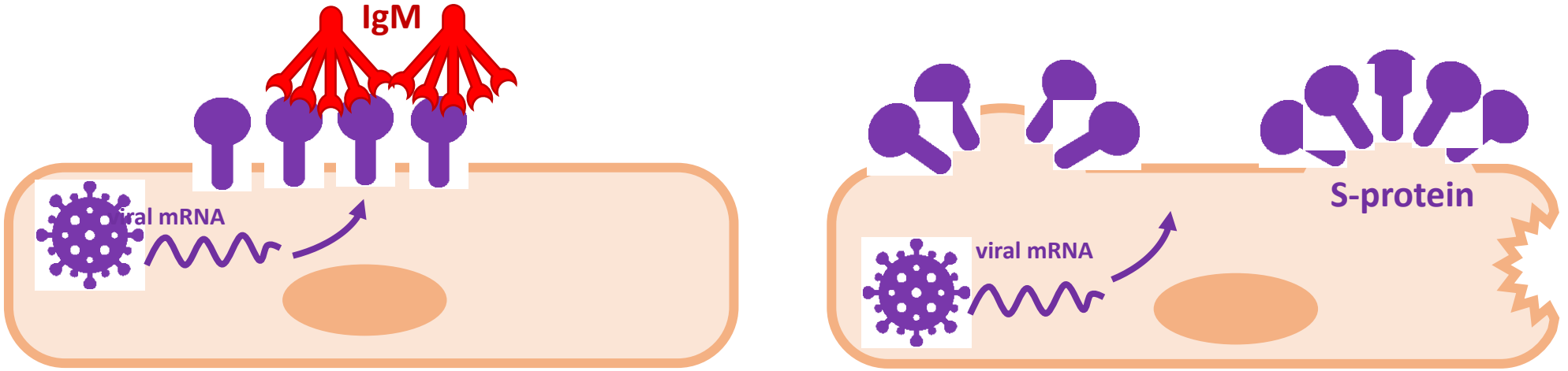
- Vasoconstriction
- Endothelial disfunction
- Thrombocyte activation
- Coagulation
- Inflamation
- Mesenchymal proliferation

Lung edema
ARDS

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

Mechanisms of endothelial damage by SARS-CoV2



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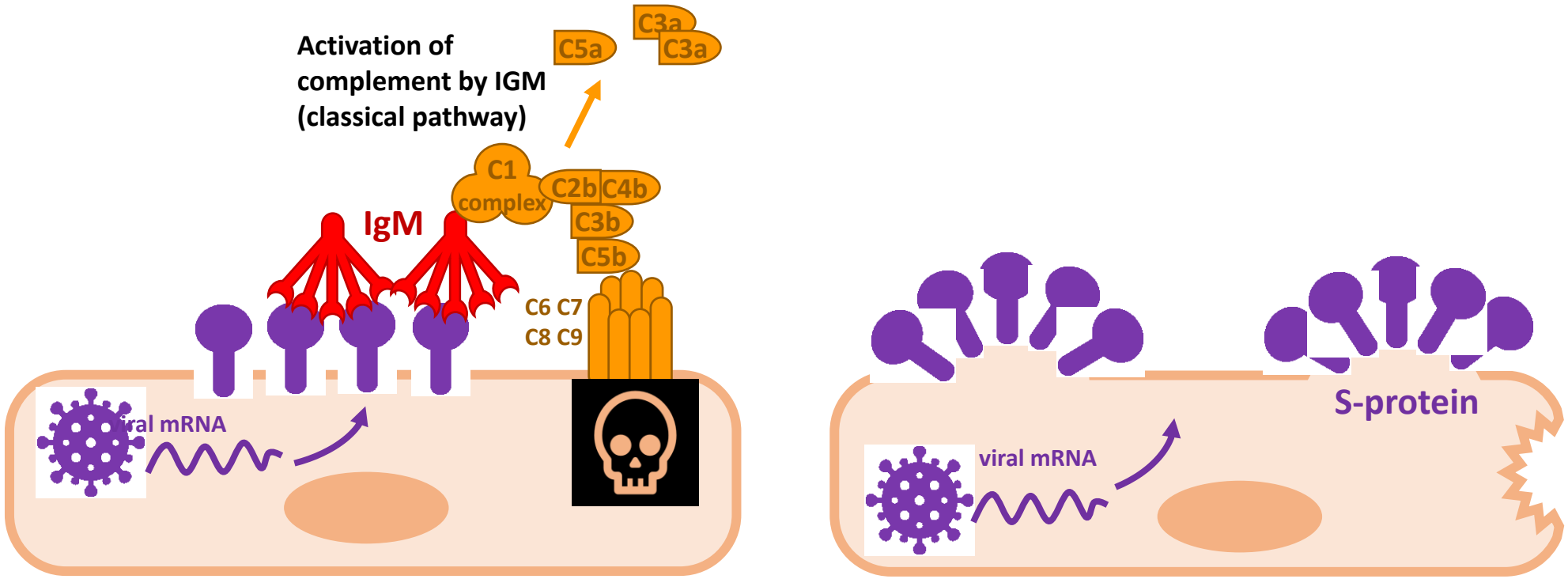
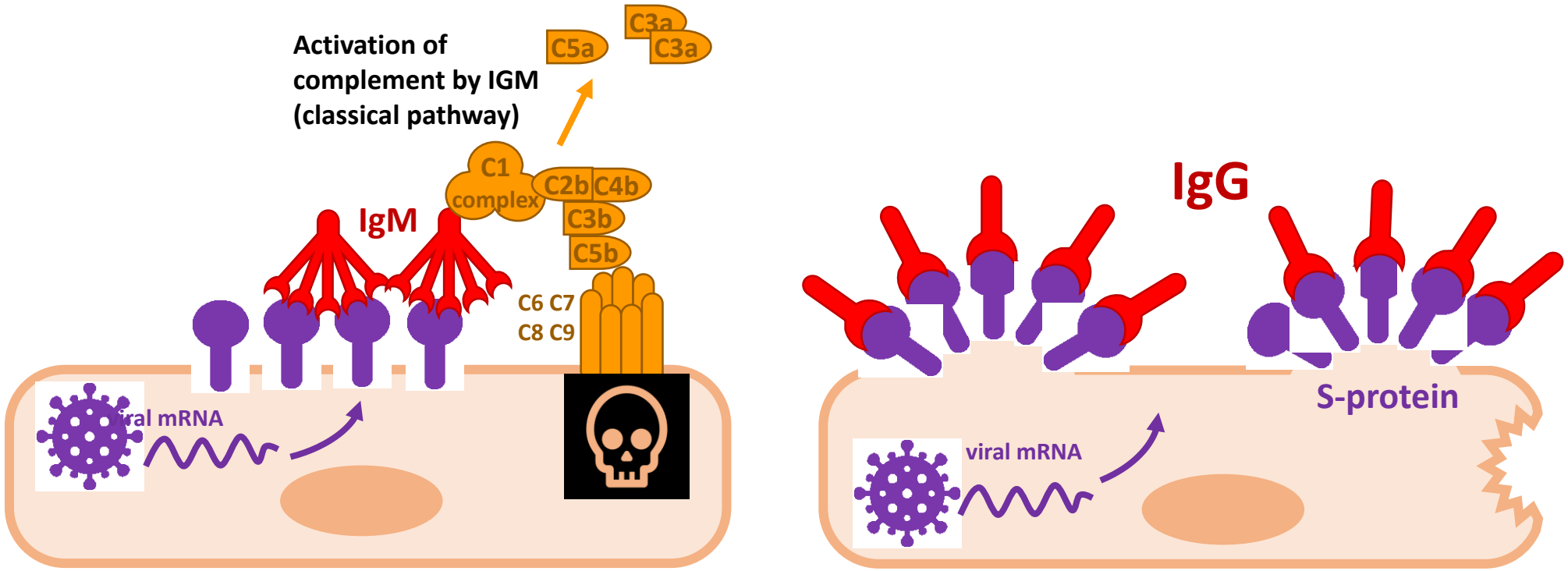


Mechanisms of endothelial damage by SARS-CoV2



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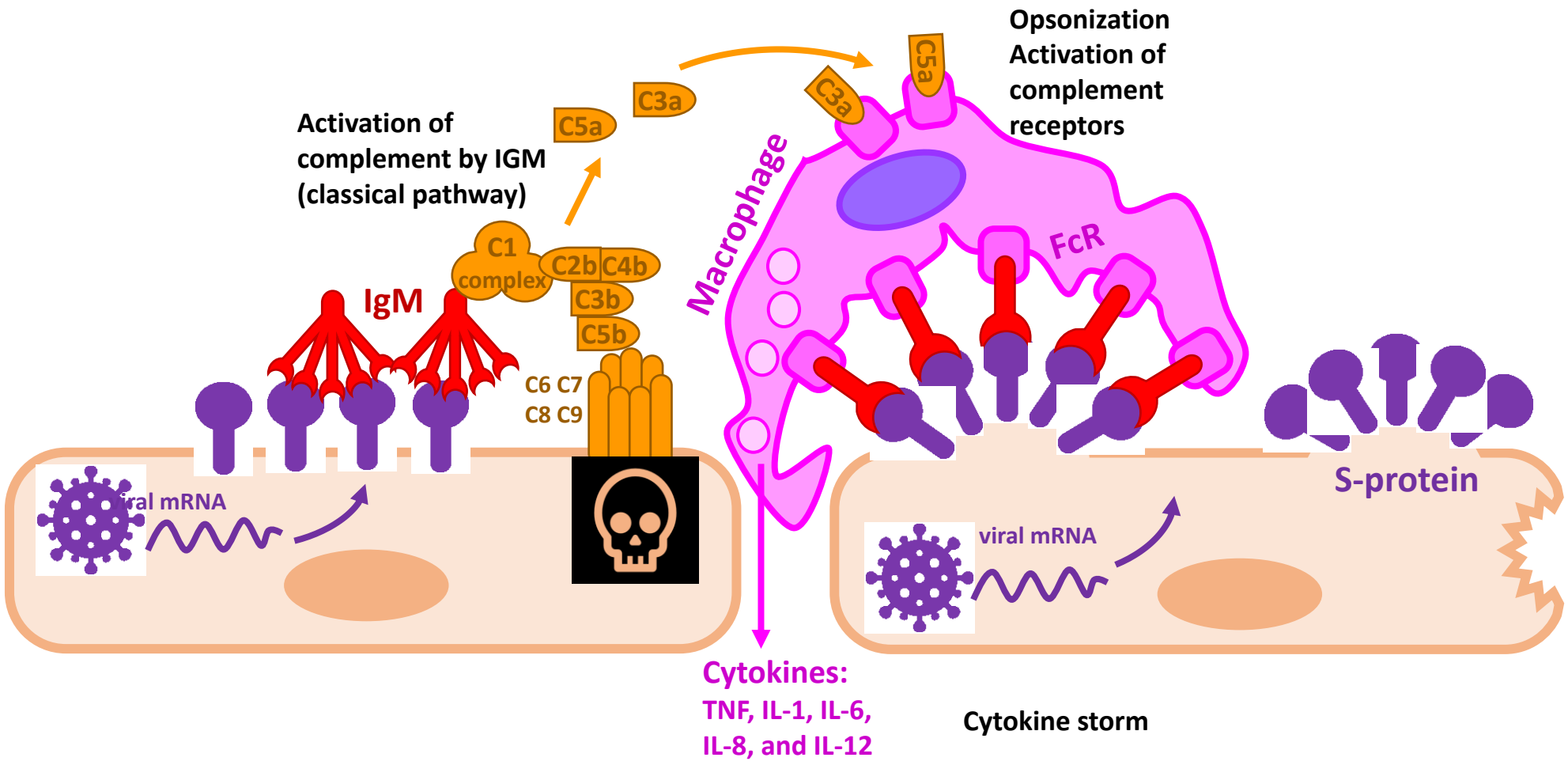
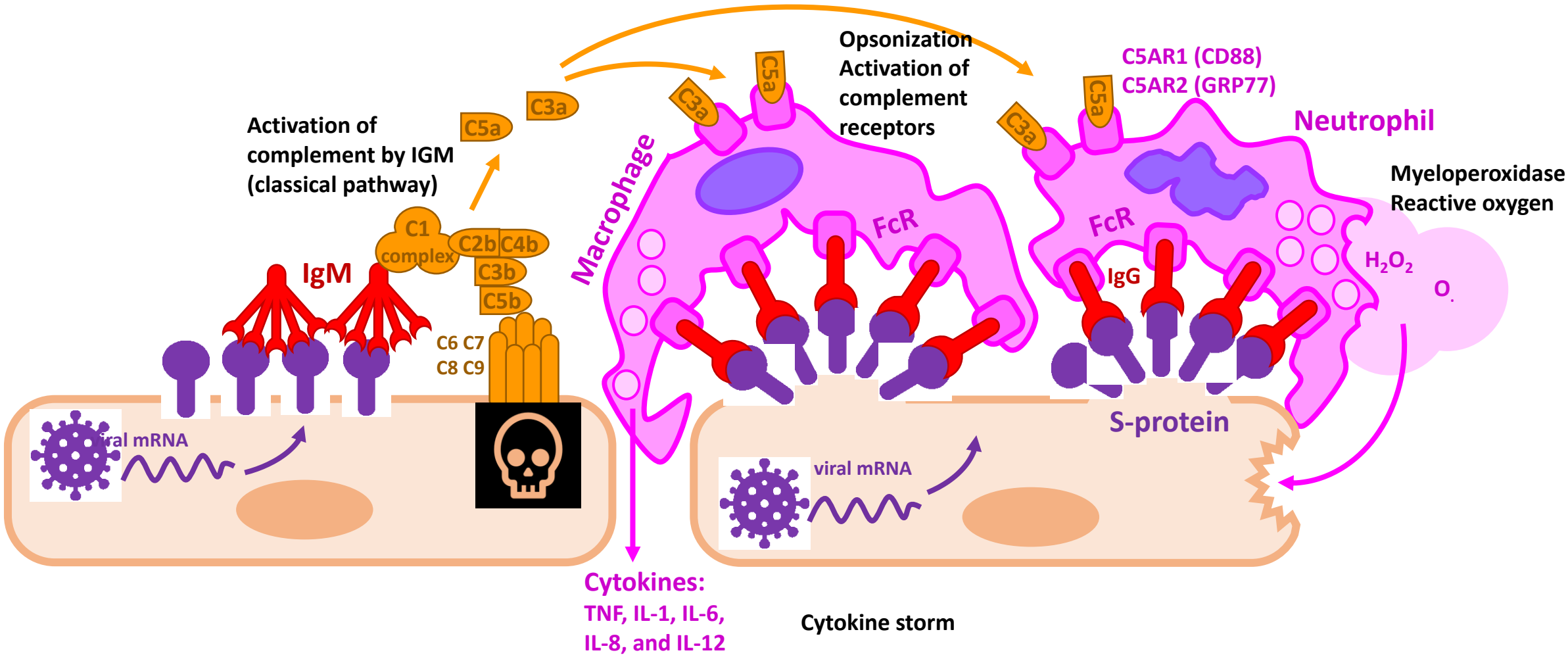
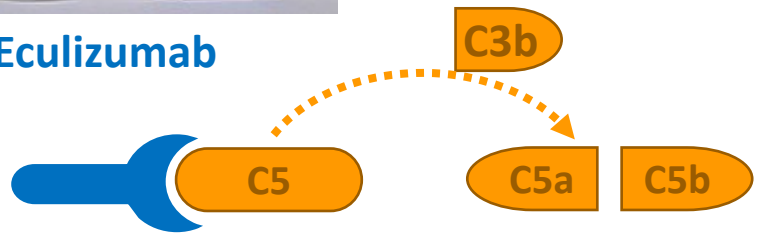


Mechanisms of endothelial damage by SARS-CoV2



Eculizumab



Eculizumab is humanized therapeutical 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.

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Research Paper

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

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ORIGINAL ARTICLE

WILEY

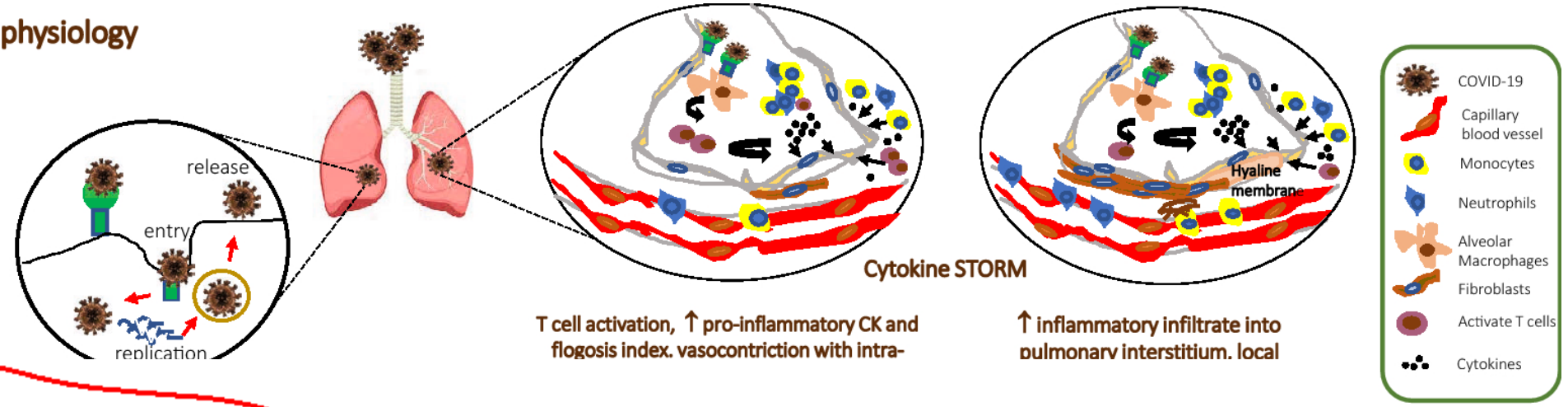
Two X-linked agammaglobulinemia patients develop pneumonia as COVID-19 manifestation but recover

Annarosa Soresina[1] | Daniele Moratto[2] | Marco Chiarini[2] | Ciro Paolillo[3] | Giulia Baresi[4,5] | Emanuele Focà[6] | Michela Bezzi[7] | Barbara Baronio[8] | Mauro Giacomelli[4,5] | Raffaele Badolato[4,5]

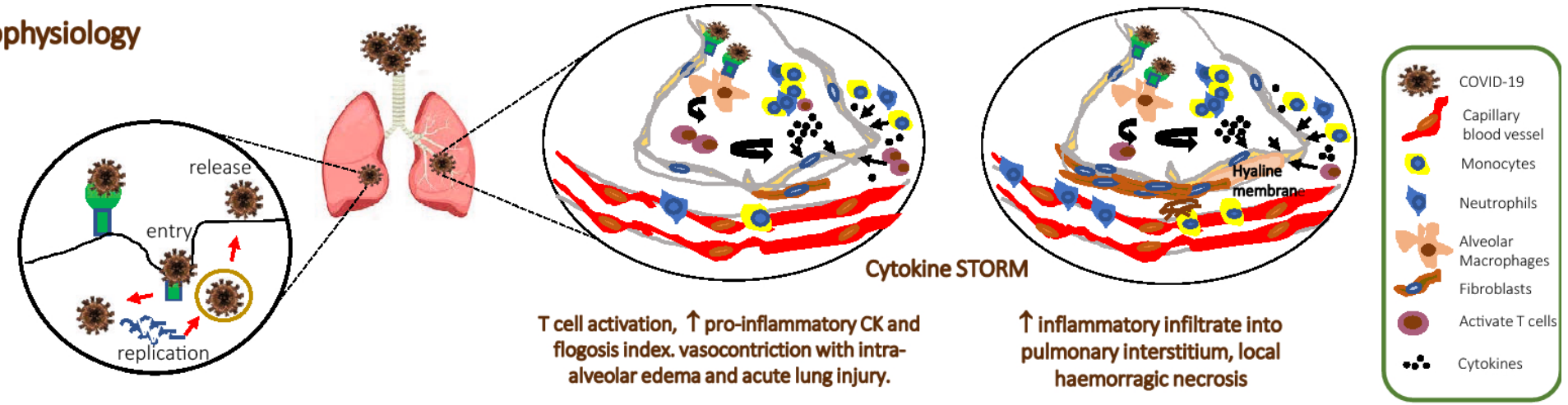
Minor Clinical Impact of COVID-19 Pandemic on Patients With Primary Immunodeficiency in Israel

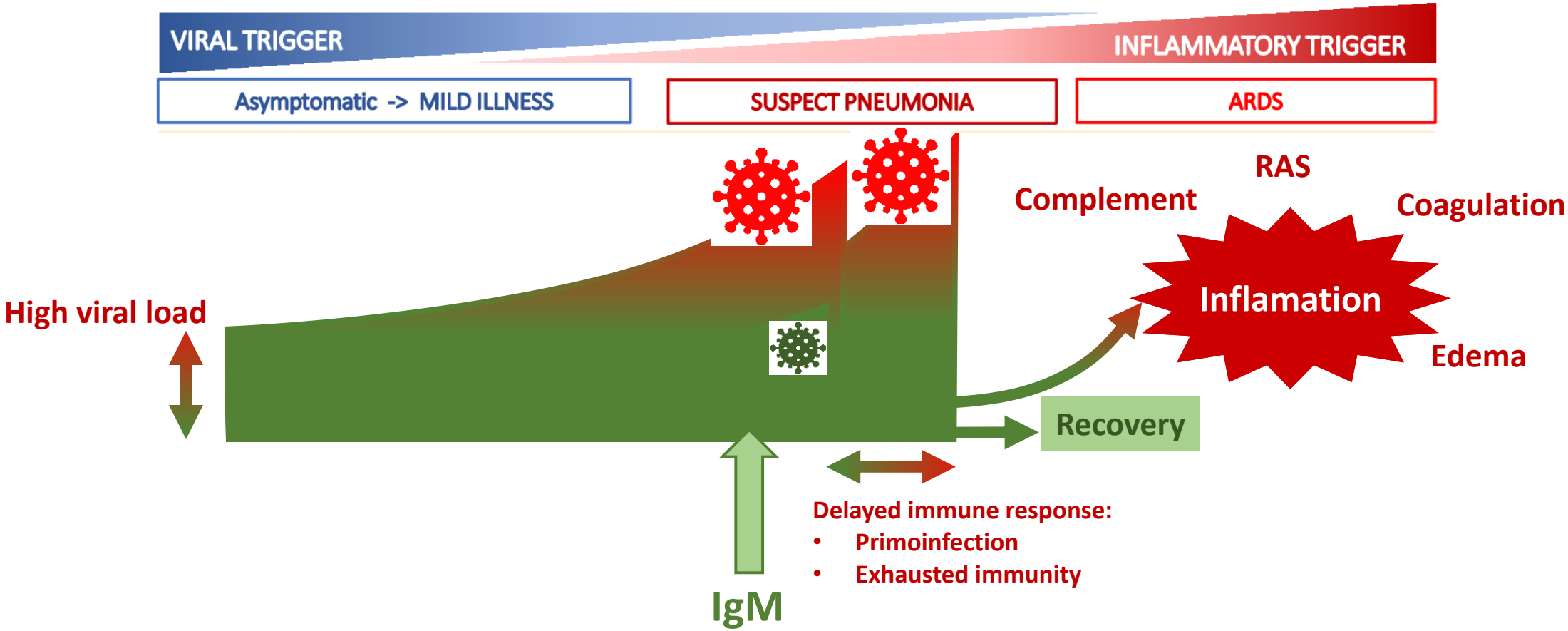
Nufar Marcus[1,2,3†], Shirly Frizinsky[2,3,4,5,6†], David Hagin[2,3,7], Adi Ovadia[3,8,9], Suhair Hanna[3,10], Michael Farkash[1,2,3], Ramit Maoz-Segal[2,5,6], Nancy Agmon-Levin[2,5,6], Arnon Broides[3,11], Amit Nahum[3,11], Elli Rosenberg[3,11], Amir Asher Kuperman[12,13], Yael Dinur-Schejter[3,14], Yackov Berkun[3,15], Ori Toker[3,16,17], Shmuel Goldberg[16,18], Ronit Confino-Cohen[2,19], Oded Scheuerman[20], Basel Badarneh[1,21], Na'ama Epstein-Rigbi[22], Amos Etzioni[3,10], Ilan Dalal[2,3,8,9] and Raz Somech[3,4]*

COVID-19 – Pathophysiology

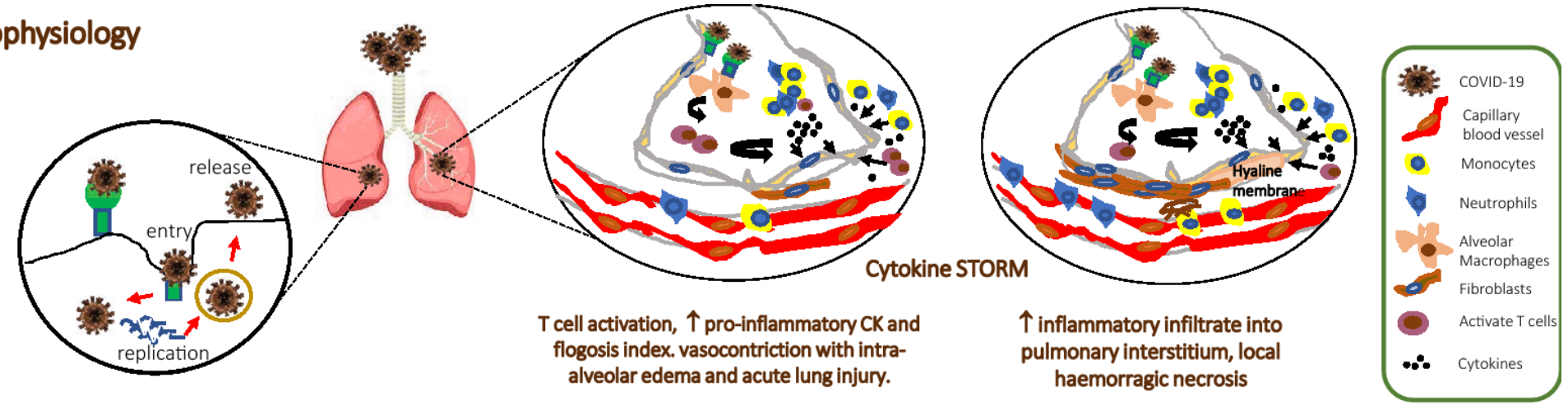


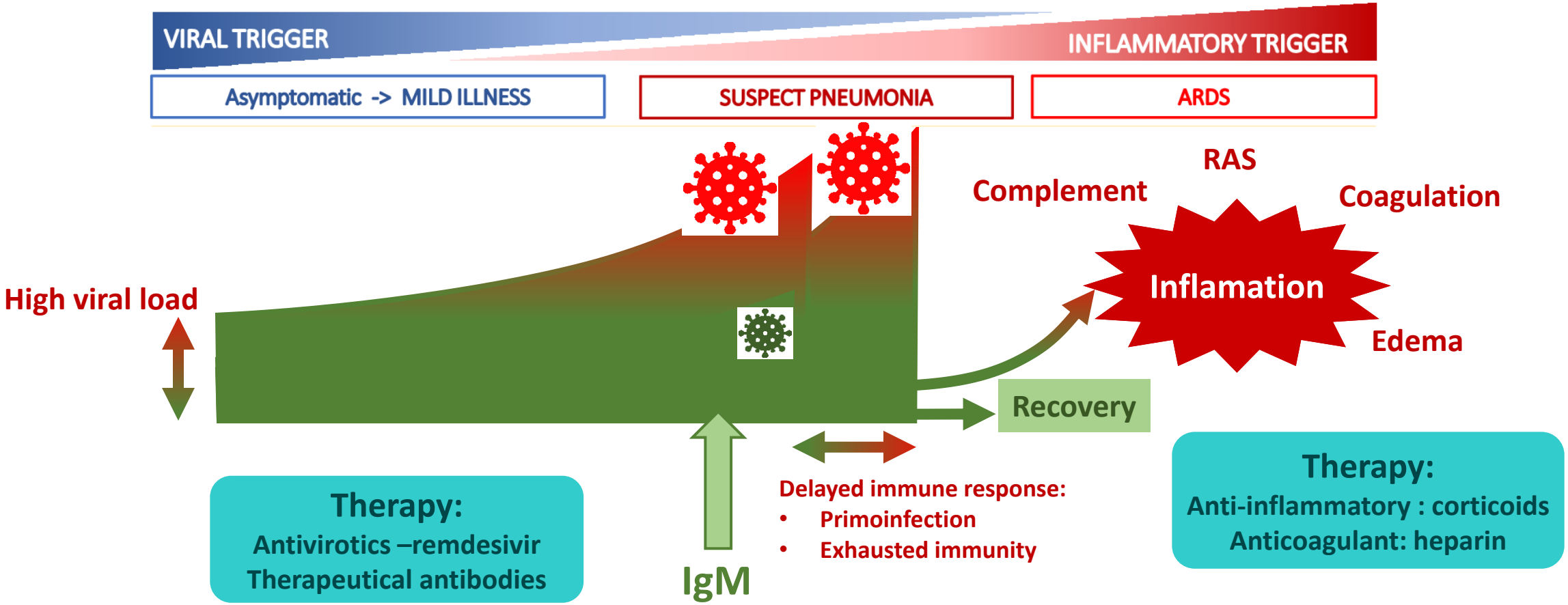
COVID-19 – Pathophysiology



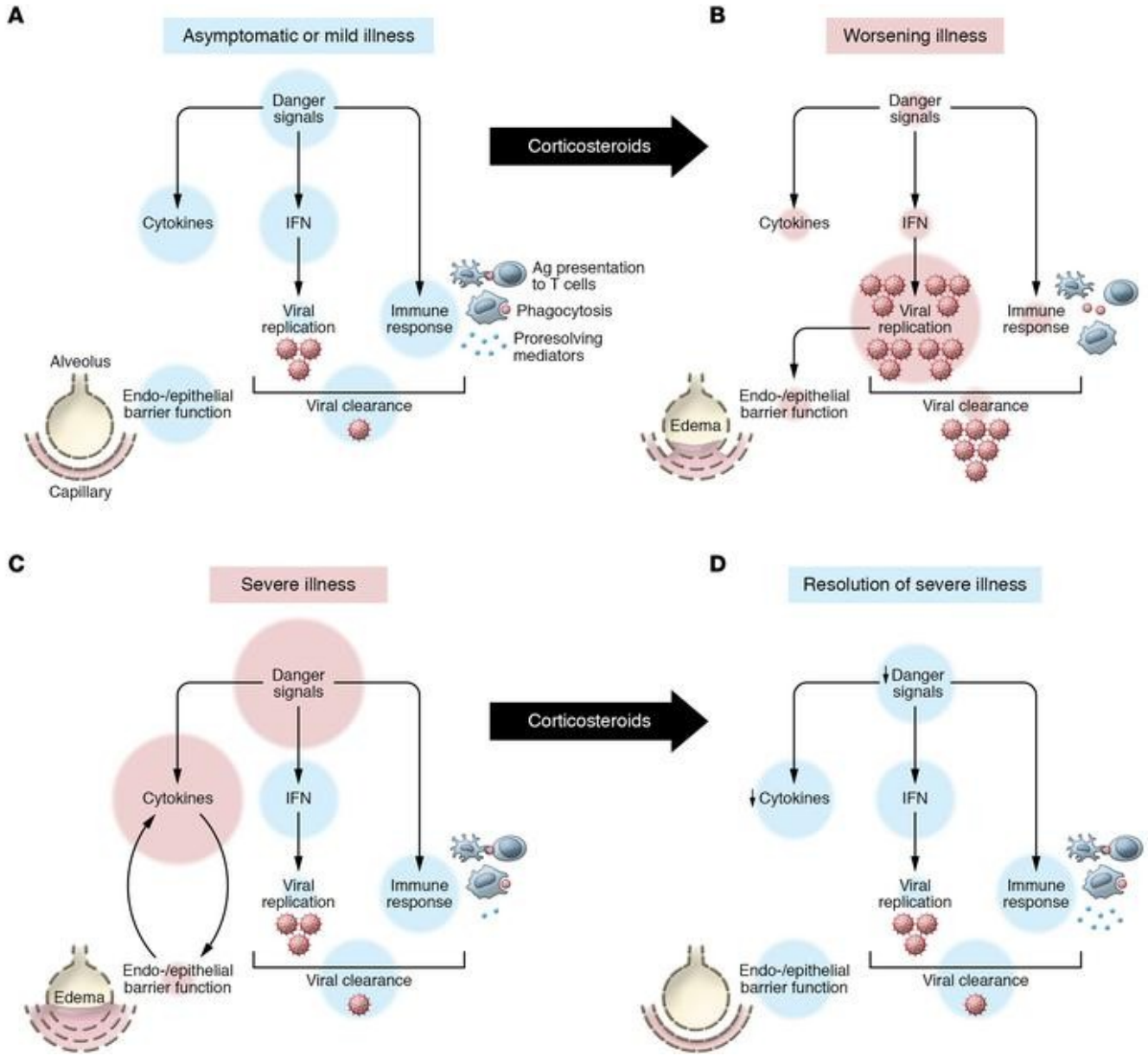


COVID-19 – Pathophysiology





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



COMMENTARY

The Journal of Clinical Investigation

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

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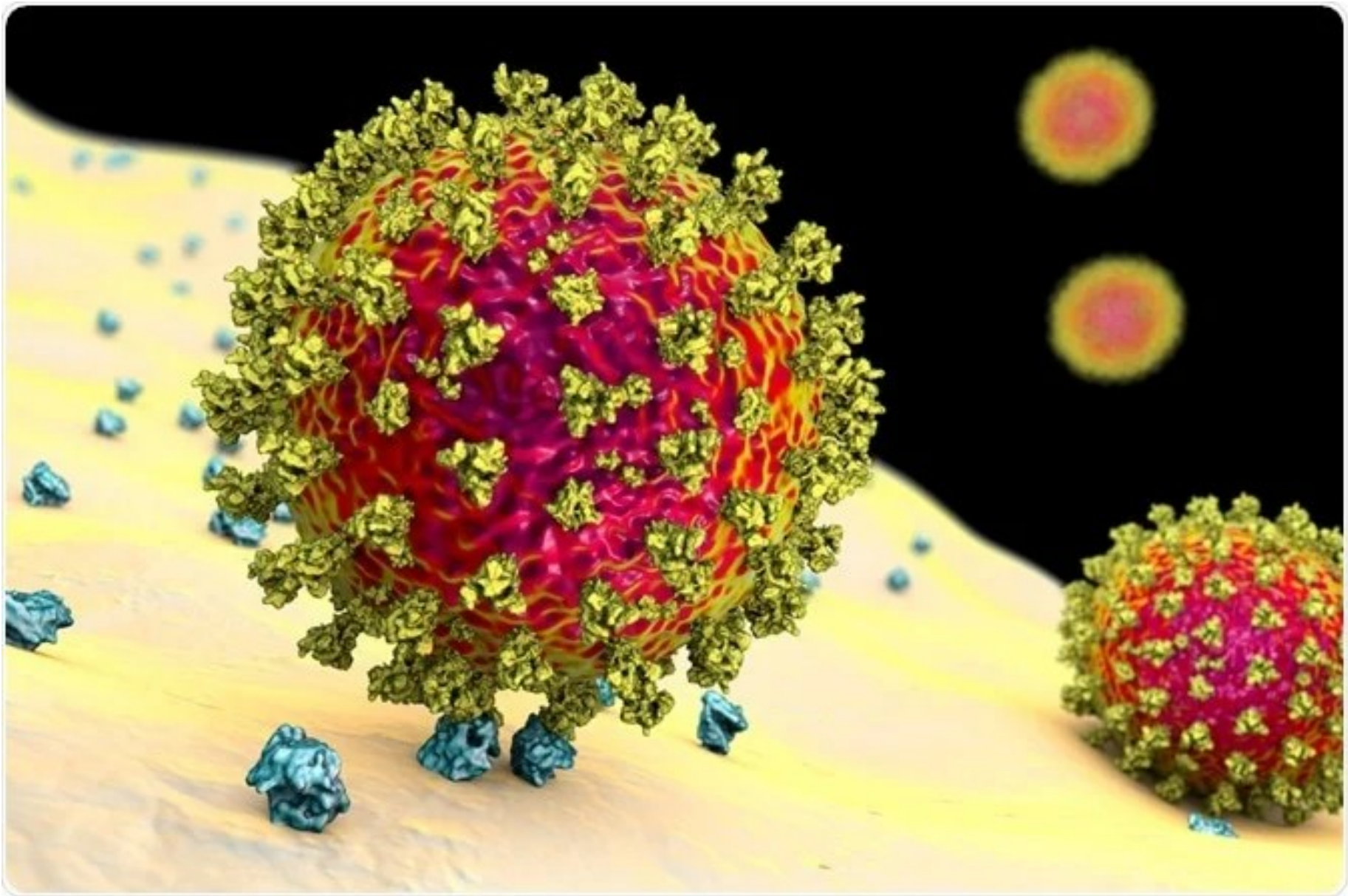
(A) In asymptomatic or mild cases and in the absence of treatment, SARS–CoV-2 induces transcriptional upregulation of interferons (IFNs) and NF-κB activation, which promote cytokine production and activation of macrophages as well as demargination of PMNs. Antigens are presented to T cells and a targeted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



THE LANCET

Vol 395 May 2, 2020

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]

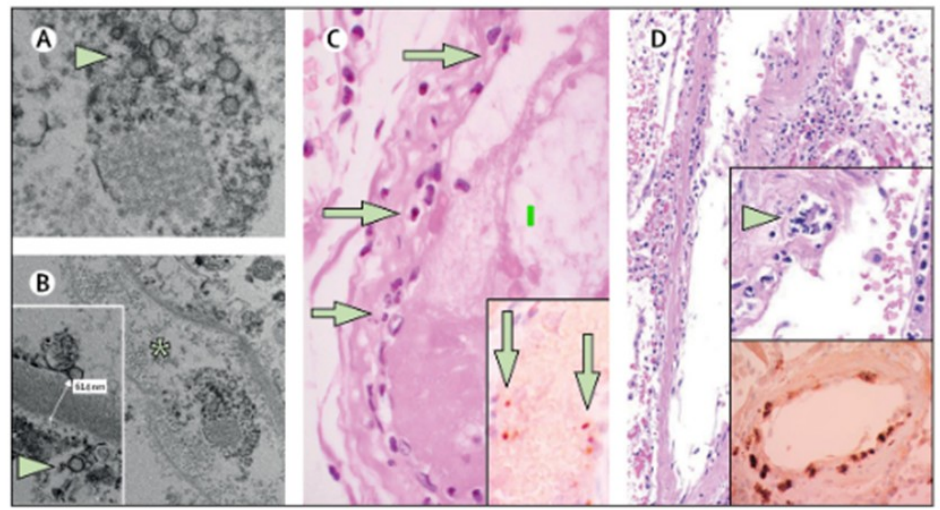


***Figure*: Pathology of endothelial cell dysfunction in COVID-19**
(A, B) Electron microscopy of kidney tissue shows viral inclusion bodies in a peritubular space and viral particles in endothelial cells of the glomerular capillary loops. Aggregates of viral particles (arrow) appear with

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S0140-6736(20)30937-5

Mechanismy poškození endotelu při infekci SARS-CoV2
Mechanisms of endothelial damage by SARS-CoV2