Ruprecht-Karls-Universität Heidelberg

Post COVID Syndrom – Klinik und Pathophysiologie – Januar 2024

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IMD Berlin

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Reproductive and Genetic Hospital of CITIC-Xiangya, Changsha, China

Central South University, Changsha , China

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Post COVID-19

Definition und klinische Aspekte

Post COVID-19 - Pathophysiologie

- Post COVID-19 - Autoimmunerkrankungen
- Post COVID-19 - G-Protein-Rezeptor-AK
- Post COVID-19 – nicht immunologische Gewebeschädigung durch Spike Protein
- Post COVID-19 – Mikrobiom

Post COVID-19Vac-Syndrom

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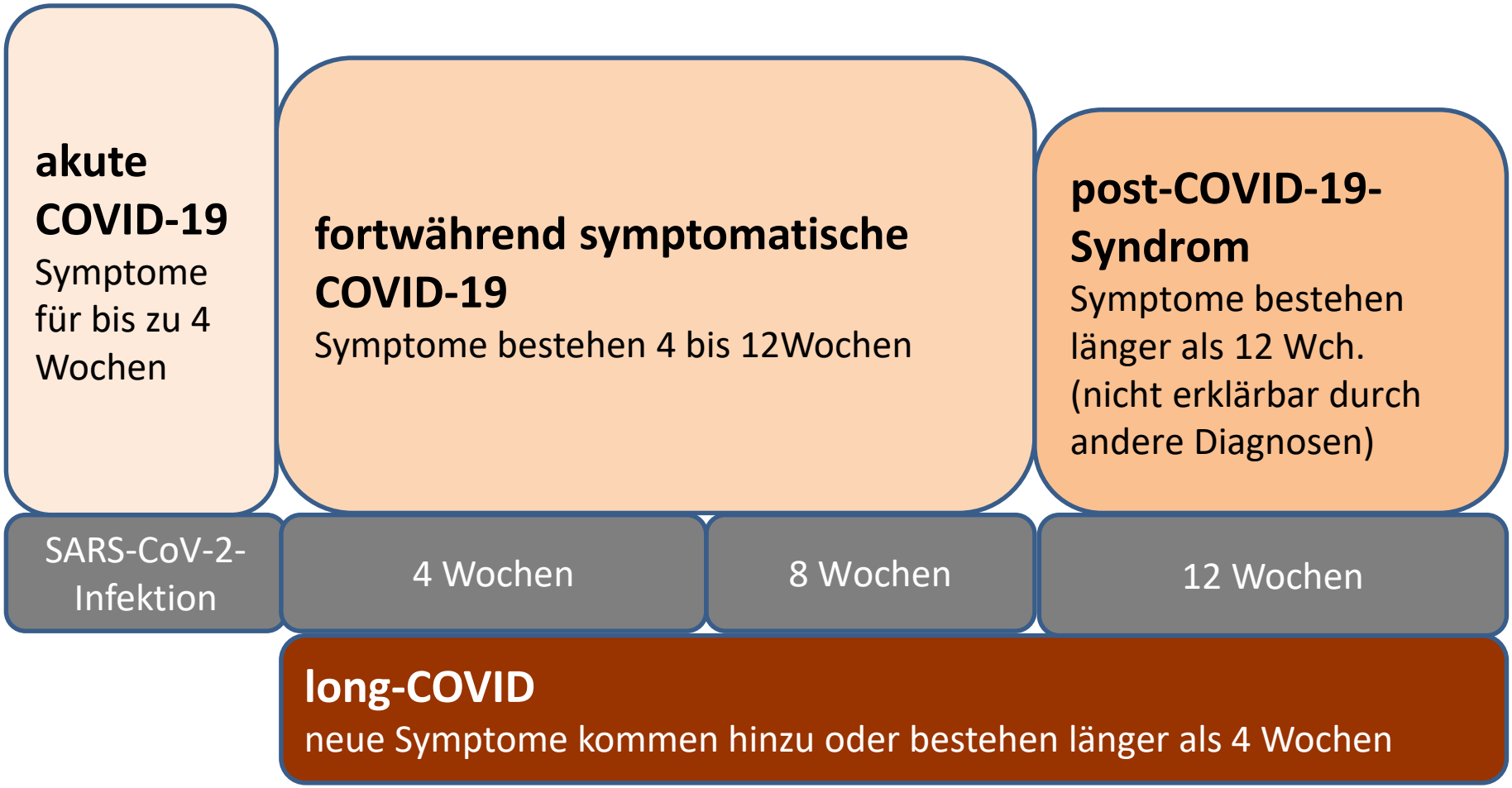
COVID-19 Nomenklatur

- Cave: viele Definitionen



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Post COVID-19 / Long-COVID-19 /

Symptome

Es gibt kein einzelnes Symptom oder Kombinationen von Symptomen, die ein Post Covid-Syndrom beweisen

AWMF S1-Leitlinie Long/ Post-COVID. Stand 17.08.2022

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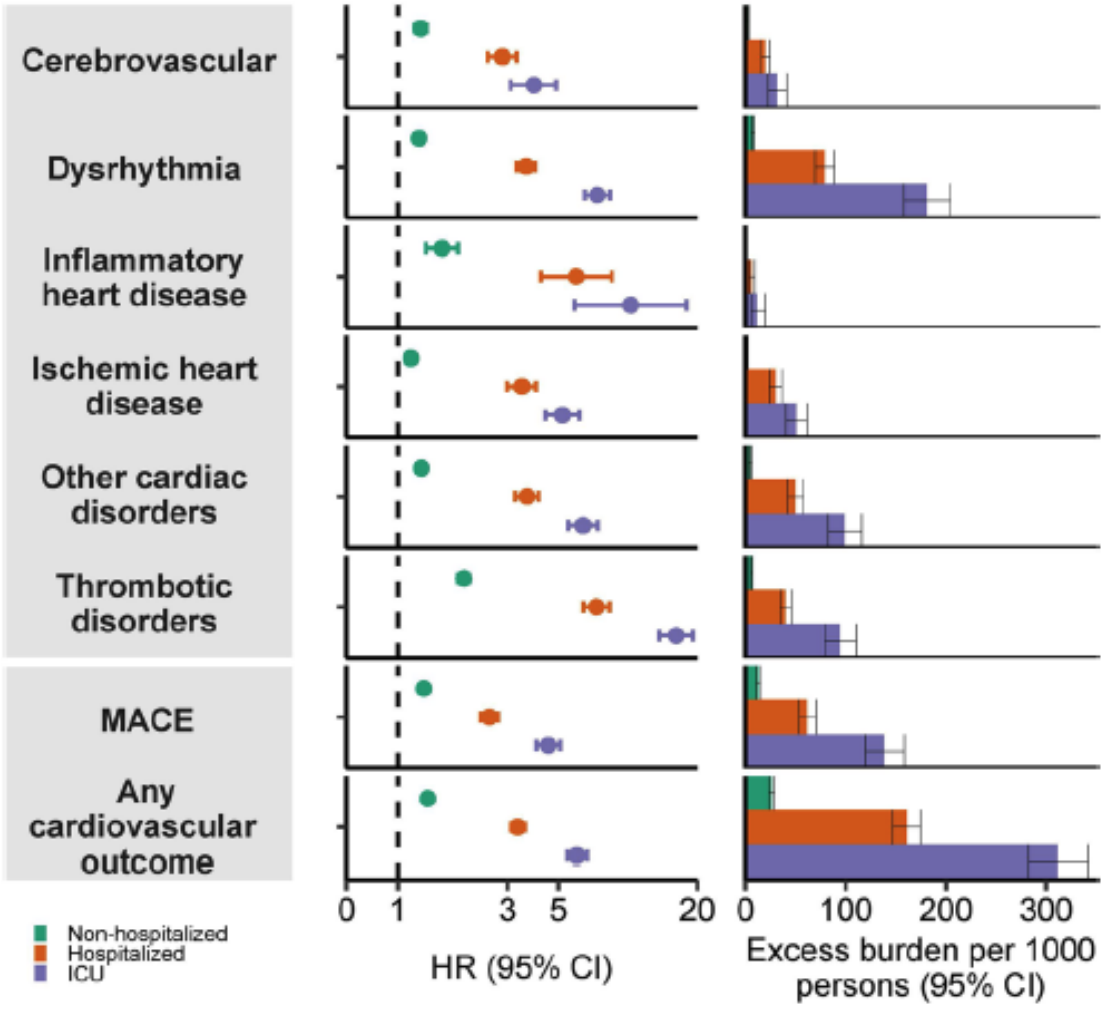
Long-term cardiovascular outcomes of COVID-19.

Nature Med. 2022 Mar;28(3):583-590. doi: 10.1038/s41591-022-01689-3



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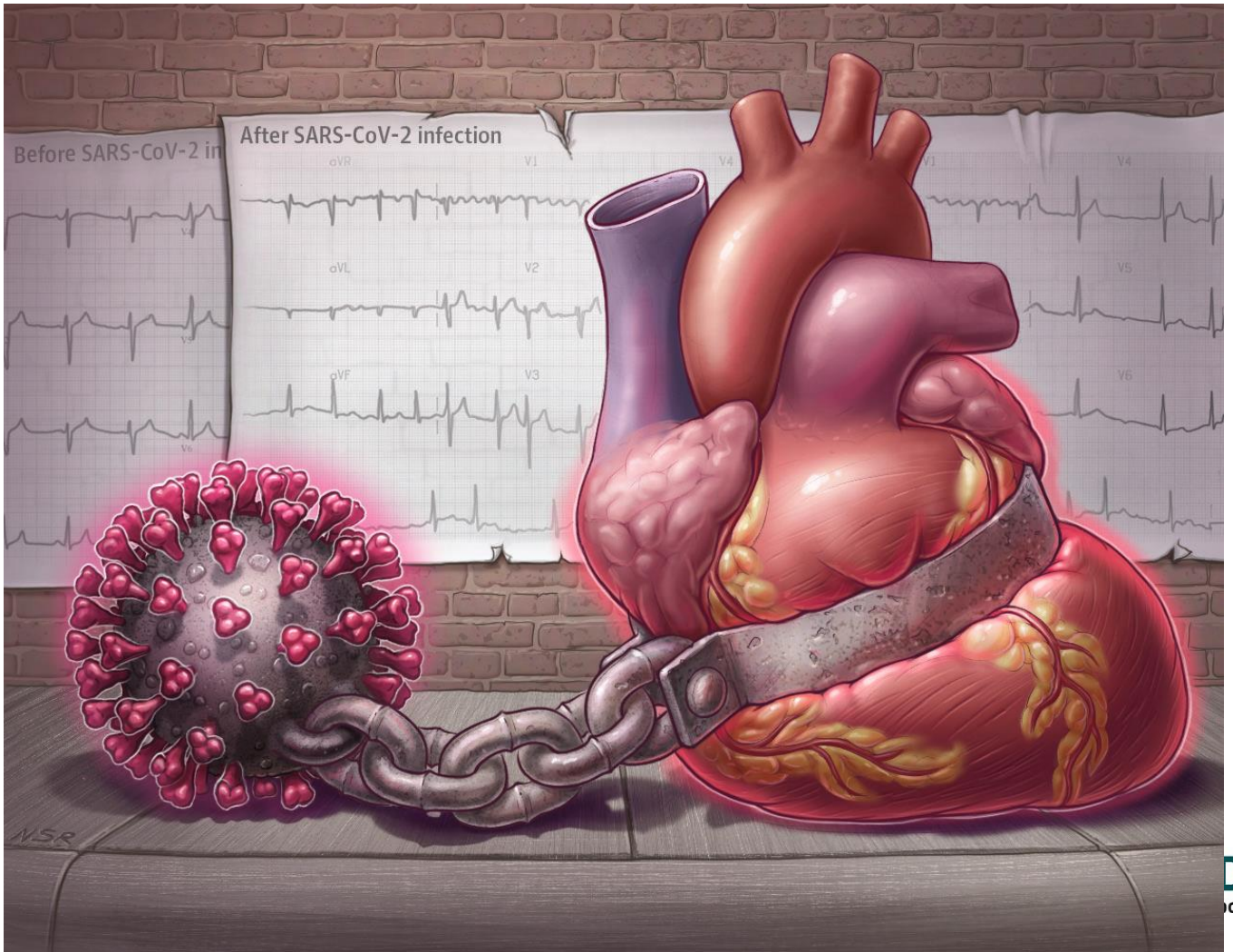
Die Post COVID-Herz-Gefäßerkrankung – Mindsets 1,5 Jahre nach der SARS-CoV-2-Infektion haben die Patienten deutlich erhöhte kardiovaskulärer Risiken



Wer bekommt ein Post COVID Syndrom?

„Post-COVID-Syndrom“ kann auftreten bei

Patienten mit einer

- **schweren**
- **leichten**
- **oder asymptomatischen**

akuten SARS CoV-2 Infektion.

Patienten auch ohne initialen PCR SARS CoV-2 Nachweis
-> hier insbesonders zelluläre Immun-Antwort prüfen

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Wer bekommt ein Post COVID Syndrom?

Risikofaktoren:

- Alter
- Übergewicht/Obesity
- **weibliches Geschlecht**
- Asthma
- Raucher
- Patienten mit schwerem initialen Verlauf
- Vorbestehende neuro-psychatrische Erkrankungen

JAMA Netw. Open 4, e2128568–e2128568 (2021)
Sci. Rep. 11, 13153 (2021).).
JAMA Intern Med. 2023 Jun 1;183(6):566-580

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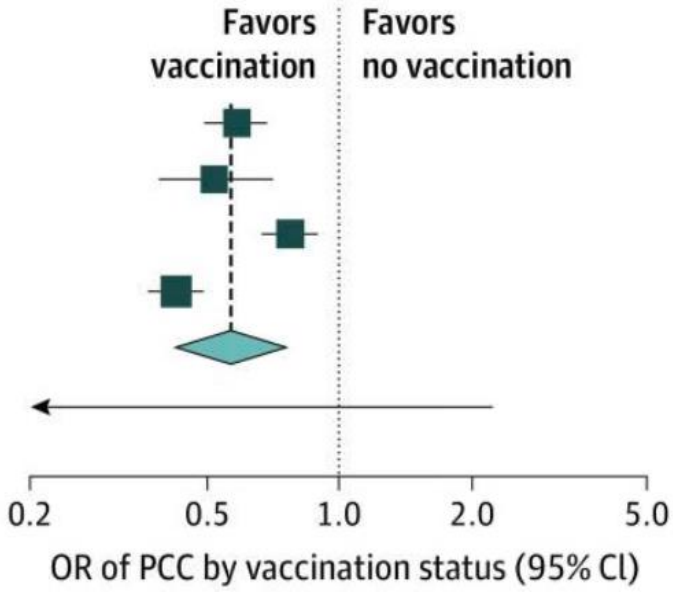
Impfen schützt vor Post COVID

Source	OR (95% CI)
Ayoubkhani et al[18]	0.59 (0.50-0.69)
Emecen et al[26]	0.53 (0.40-0.71)
loannou et al[34]	0.78 (0.68-0.90)
Zisis et al[12]	0.43 (0.37-0.49)
Total (random effects)	0.57 (0.43-0.76)
Prediction interval	(0.15-2.22)
Heterogeneity: $\chi^2_3 = 35.00$ ($P < .001$); $I^2 = 91\%$	



Tsampasian V, Elghazaly H, Chattopadhyay R, Debski M, Naing TKP, Garg P, Clark A, Ntatsaki E, Vassiliou VS. Risk Factors Associated With Post-COVID-19 Condition: A Systematic Review and Meta-analysis. JAMA Intern Med. 2023 Jun 1;183(6):566-580. doi: 10.1001/jamainternmed.2023.0750.

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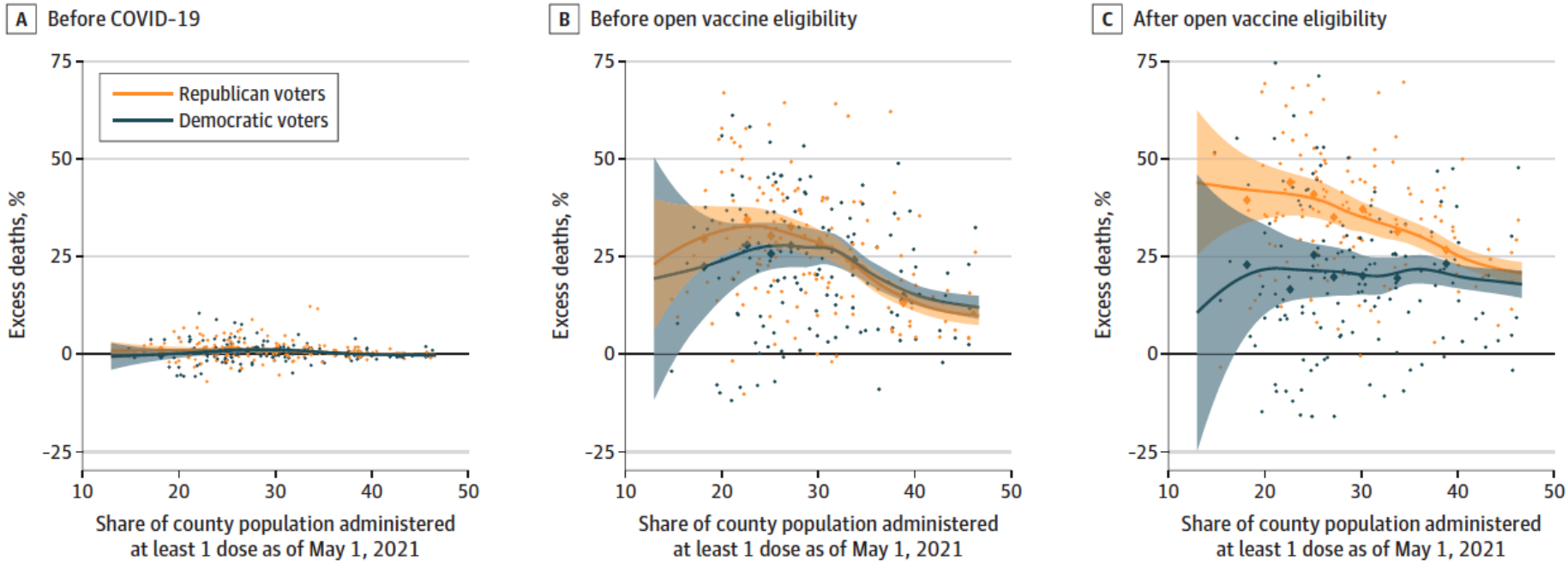
Excess Death Rates for Republican and Democratic Registered Voters in Florida and Ohio During the COVID-19 Pandemic.

JAMA Intern Med. 2023 Sep 1;183(9):916-923.



In der Zeit nach der Ende des Impfppflicht (Dezember 2021) gab es einen deutlichen Unterschied zwischen republikanischen und demokratischen Wählern, wobei sich die höheren Sterberaten bei Republikanern sich hauptsächlich in Bezirke mit niedrigeren Gesamtimpfungsraten fanden, während die Unterschiede in Bezirken mit den höchsten Impfquoten minimal waren.

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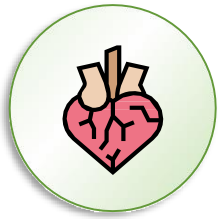
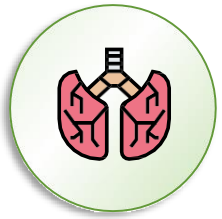
Akute COVID-19 Erkrankung und Langzeit-Schäden

Langzeit-/Spätfolgen von akuten Organ-Maifestationen einer akuten SARS CoV-2 Infektion



CARDIOVASCULAR

COVID-Myokarditis



RESPIRATORY

Lungen-Fibrose

DERMATOLOGIC

Hautausschlag

NEUROLOGIC

Geschmacks- und Geruchsverlust

PSYCHIATRIC

Depression, Angst, und Stimmungs-Störungen

https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/late-sequelae.html
https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2932656-8

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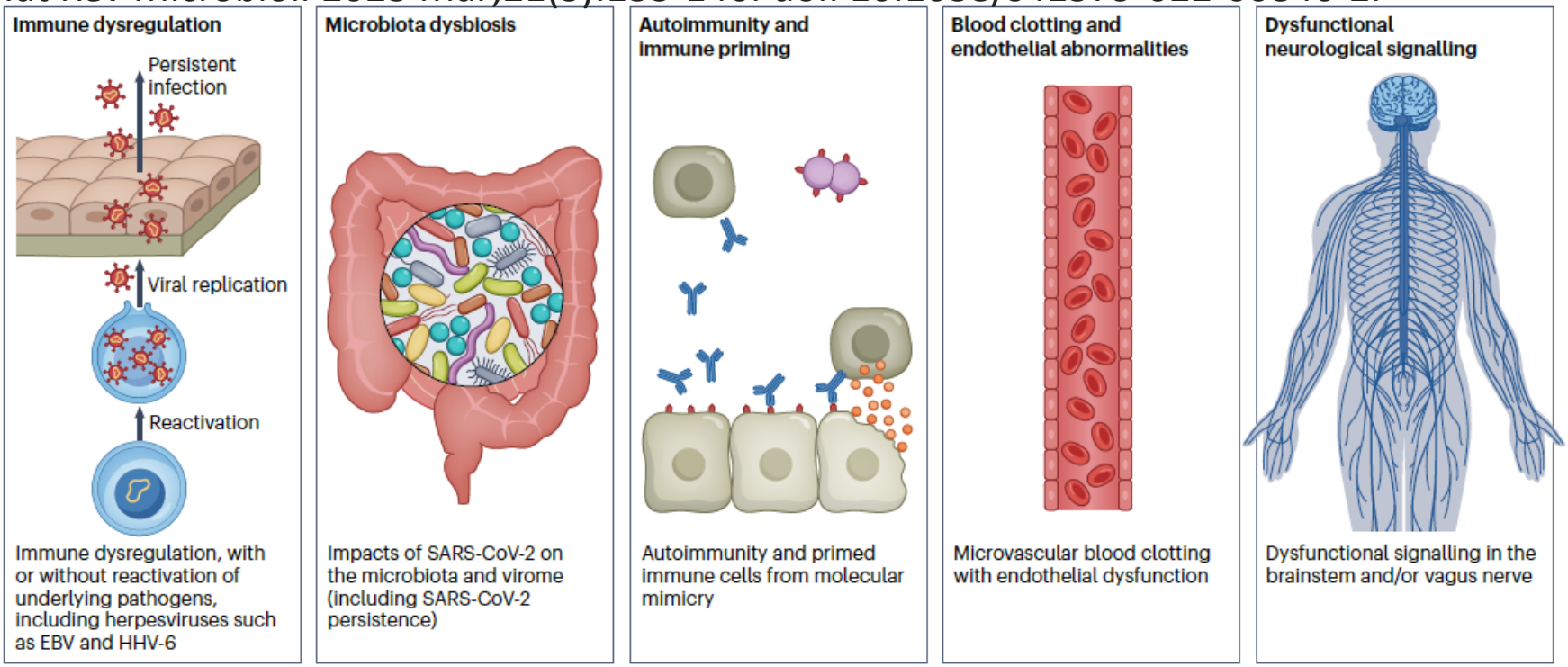
Long COVID: major findings, mechanisms and recommendations.

Nat Rev Microbiol. 2023 Mar;21(3):133-146. doi: 10.1038/s41579-022-00846-2.



Hypothetische Mechanismen der POST COVID-Pathogenese.
Dysregulation des Immunsystems,

- **Störung des MikrobiomsAutoimmunität,**
- **Gerinnung**
- **endotheliale Anomalien sowie**
- **dysfunktionale neurologische Signalübertragung**

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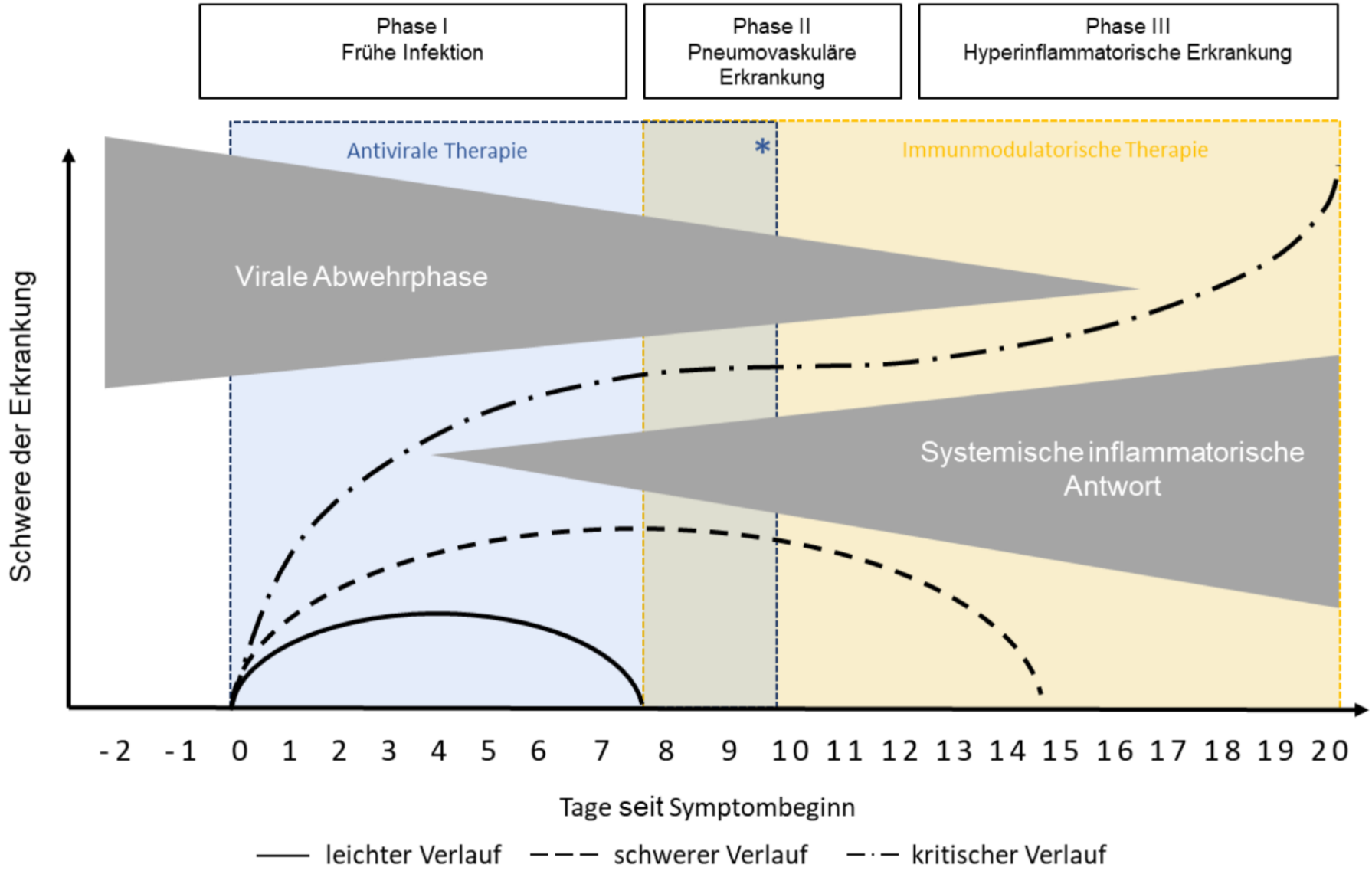

Quelle: RKI, Berlin, 2022

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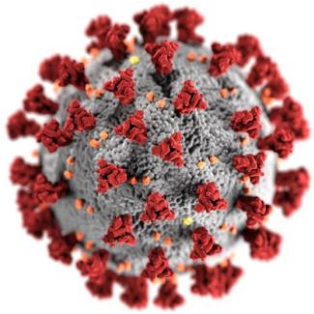
COVID-19 proentzündliches Milieu beeinflusst die Zellkommunikation

COVID-19 assoziierte akute Hyperinflammation



TNF-α
IL-1
INF-g
IL-6

Präsentation von Antigenen; MHC

Gewebsschäden / Zelltod

Ko-stimulatorische Faktoren

Immunzellaktivierung

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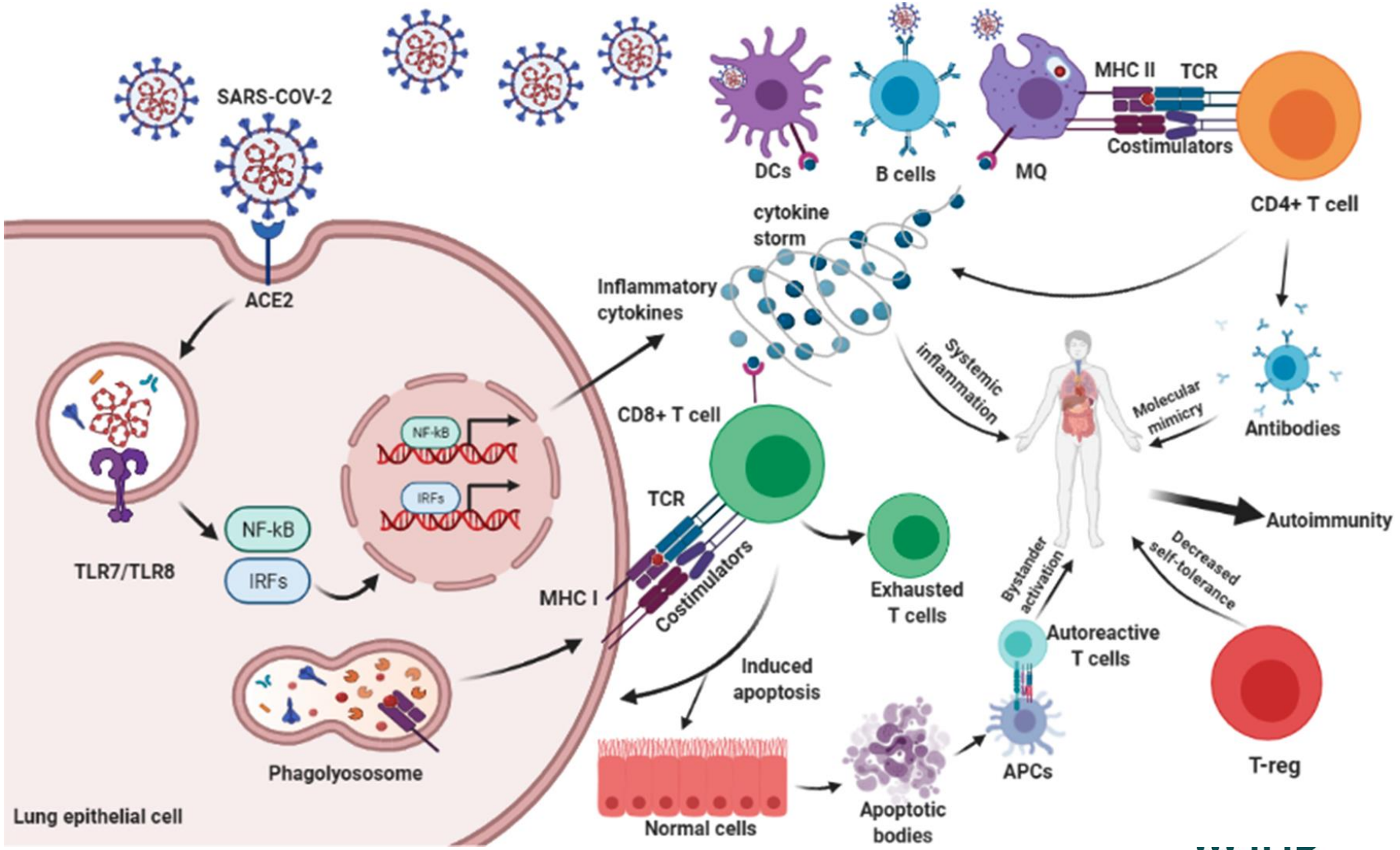
SARS-CoV-2 triggering autoimmune diseases.

Cytokine. 2022 Jun;154:155873. doi: 10.1016/j.cyto.2022.155873.



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nature biotechnology

ARTICLES

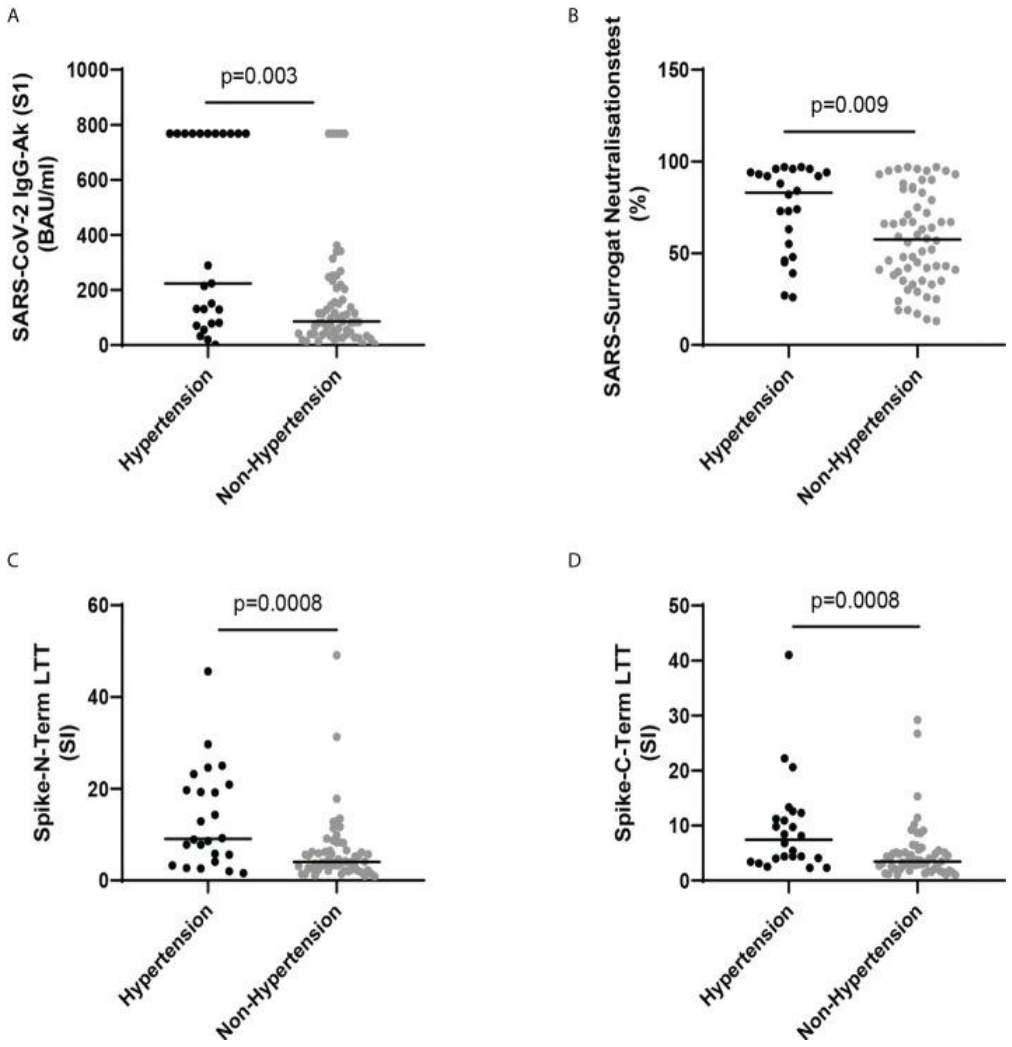
https://doi.org/10.1038/s41587-020-00796-1

Hypertension delays viral clearance and exacerbates airway hyperinflammation in patients with COVID-19

Saskia Trump[1,17], Soeren Lukassen[2,17], Markus S. Anker[3,4,5,6,17], Robert Lorenz Chua[2,17], Johannes Liebig[2,17], Loreen Thürmann[1,17], Victor Max Corman[7,17], Marco Binder[8,17], Jennifer Loske[1], Christina Klasa[9], Teresa Krieger[2], Bianca P. Hennig[2], Marey Messingschlager[1], Fabian Pott[7,10], Julia Kazmierski[7,10], Sven Twardziok[2], Jan Philipp Albrecht[2], Jürgen Eils[2], Sara Hadzibegovic[3,4,5,6], Alessia Lena[3,4,5,6], Bettina Heidecker[3], Thore Bürgel[2], Jakob Steinfeldt[3], Christine Goffinet[7,10], Florian Kurth[11,12], Martin Witzenrath[11], Maria Theresa Völker[13], Sarah Dorothea Müller[13], Uwe Gerd Liebert[14], Naveed Ishaque[2], Lars Kaderali[9], Leif-Erik Sander[11], Christian Drosten[7], Sven Laudi[13,18] ✉, Roland Eils[2,15,16,18] ✉, Christian Conrad[2,18] ✉, Ulf Landmesser[3,18] ✉ and Irina Lehmann[1,15,18] ✉

In coronavirus disease 2019 (COVID-19), hypertension and cardiovascular diseases are major risk factors for critical disease progression. However, the underlying causes and the effects of the main anti-hypertensive therapies—angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs)—remain unclear. Combining clinical data ($n = 144$) and single-cell sequencing data of airway samples ($n = 48$) with in vitro experiments, we observed a distinct inflammatory predisposition of immune cells in patients with hypertension that correlated with critical COVID-19 progression. ACEI treatment was associated with dampened COVID-19-related hyperinflammation and with increased cell intrinsic antiviral responses, whereas ARB treatment related to enhanced epithelial–immune cell interactions. Macrophages and neutrophils of patients with hypertension, in particular under ARB treatment, exhibited higher expression of the pro-inflammatory cytokines *CCL3* and *CCL4* and the chemokine receptor *CCR1*. Although the limited size of our cohort does not allow us to establish clinical efficacy, our data suggest that the clinical benefits of ACEI treatment in patients with COVID-19 who have hypertension warrant further investigation.

Chu C, Schönbrunn A, Klemm K, von Baehr V, Krämer BK, Elitok S, Hocher B. Impact of hypertension on long-term humoral and cellular response to SARS-CoV-2 infection. Front Immunol. 2022 Sep 2;13:915001. doi: 10.3389/fimmu.2022.915001



Verstärkte humorale und zelluläre Immunantwort in Hypertonikern

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Post COVID-19Vac-Syndrom

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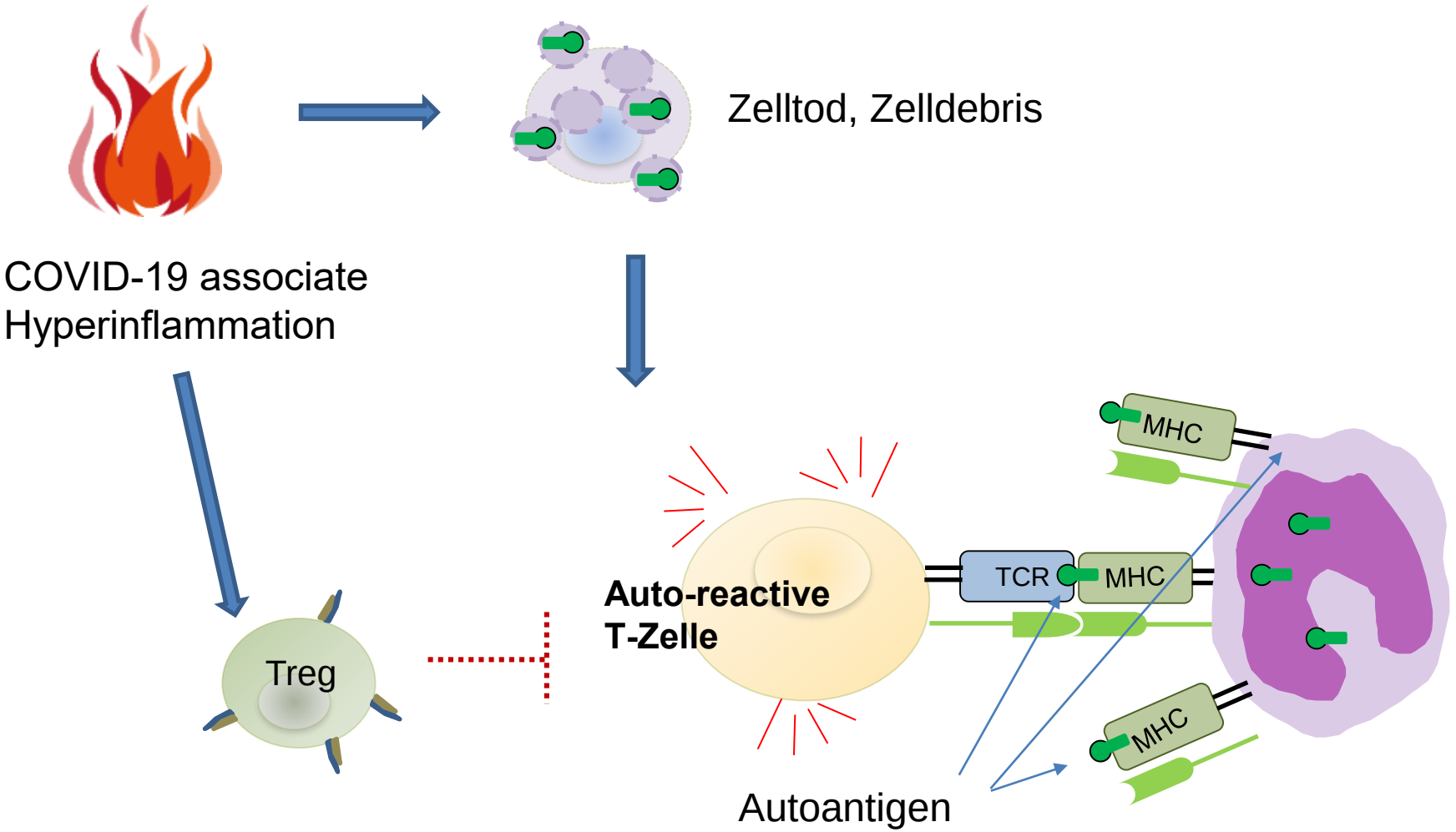
Hyperinflammation und Gewebezerstörung fördern Autoimmunität



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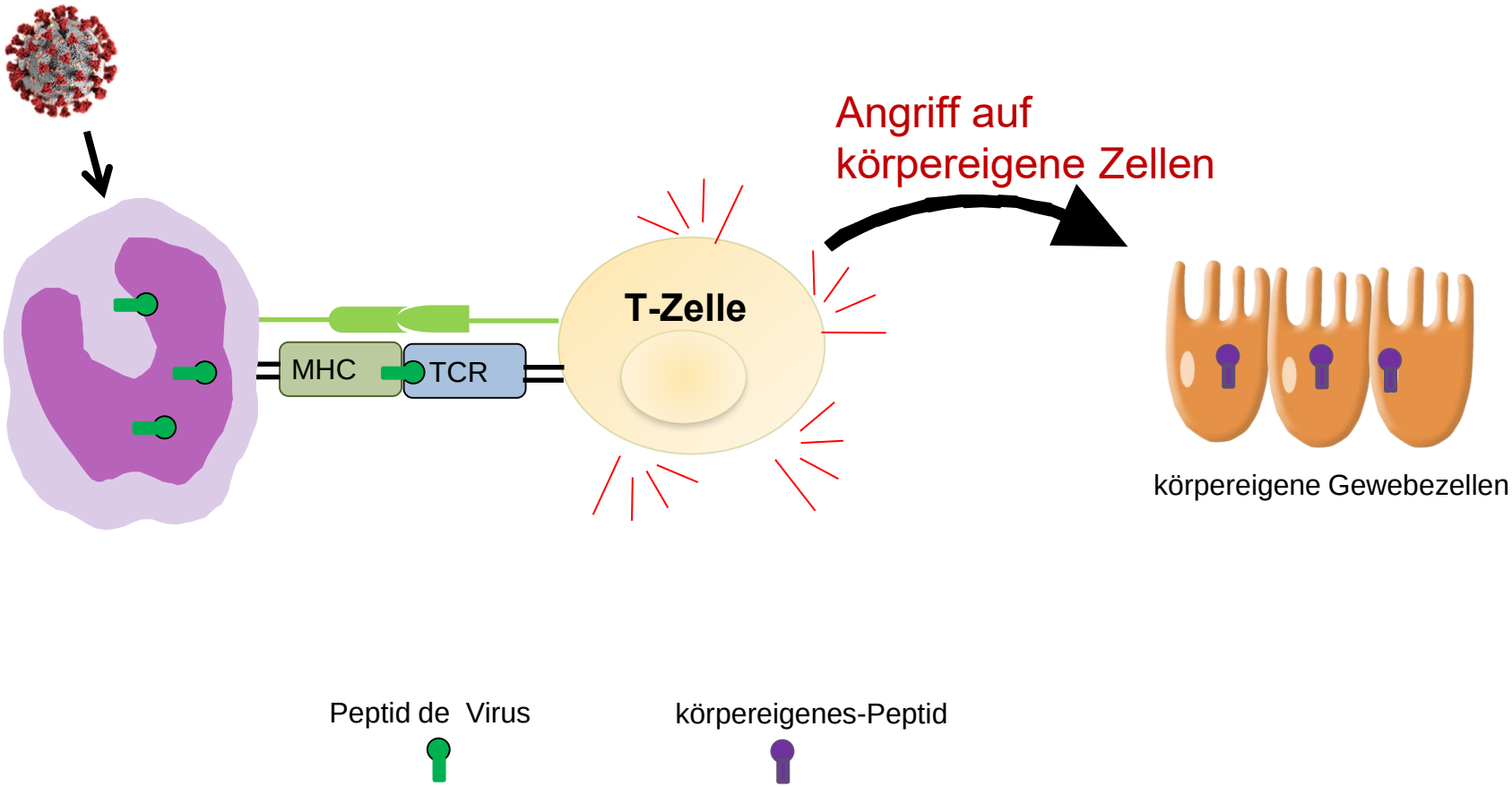
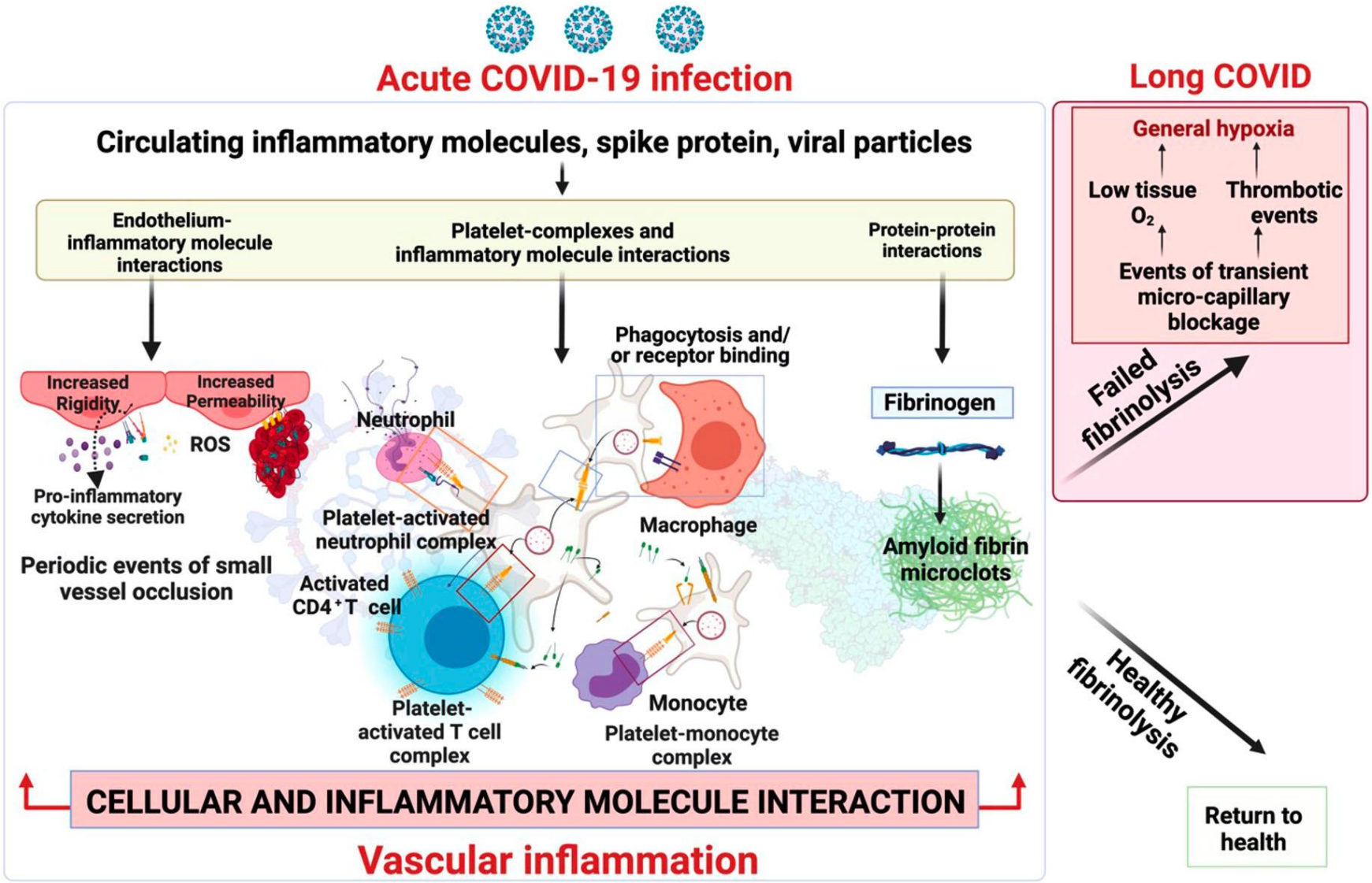
Infektionen → Molekulares Mimikry → Autoimmunität



SARS Cov-2 Antigene (z.B. S1 Protein) kreuz-reagieren oder mimen Autoantigene

Clotting pathologies in post COVID



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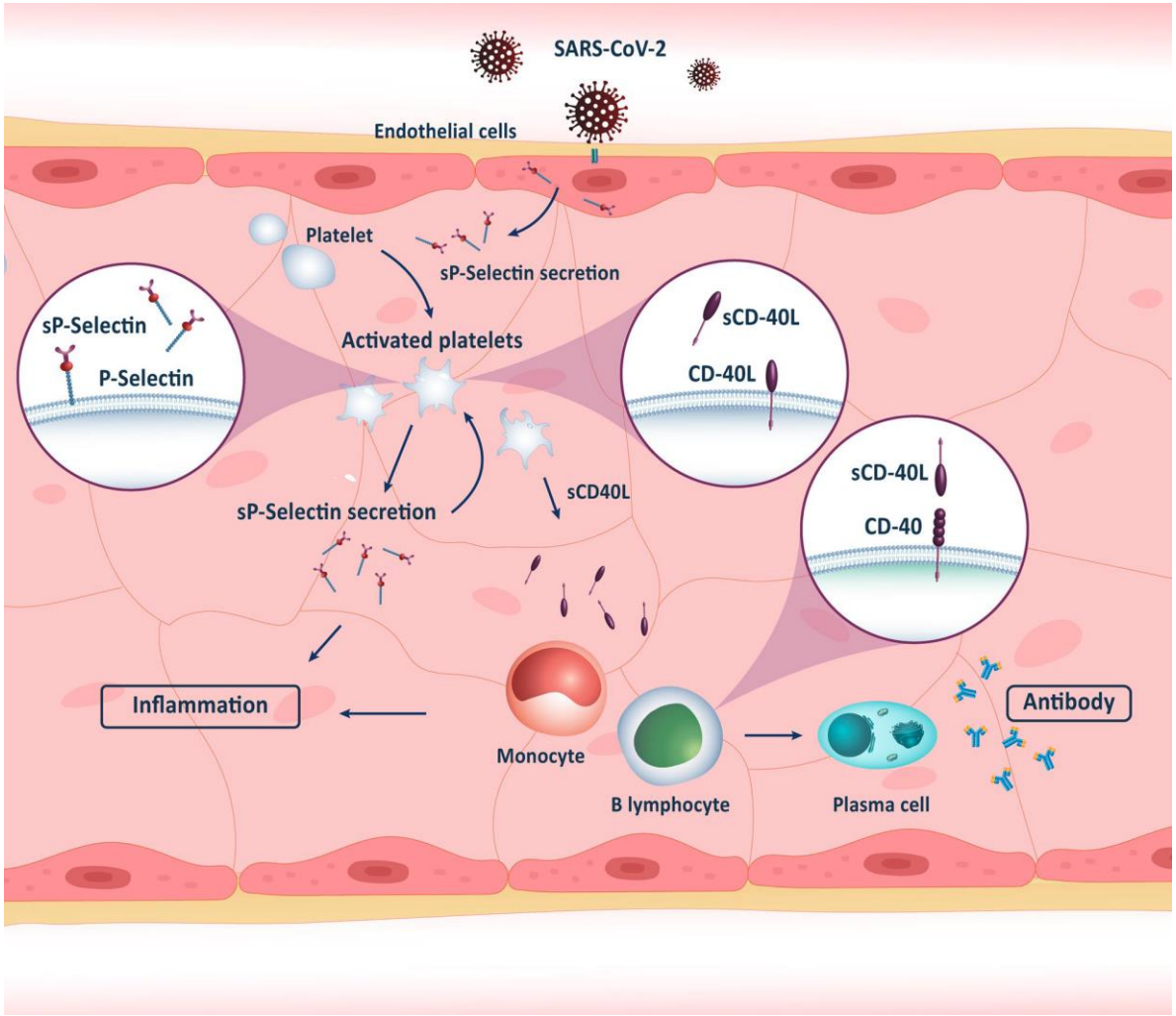
Inflammation mechanism based on the secretion of sP-selectin and **sCD40L** in SARS-CoV-2 infection.



Following infection of the airways of the lungs with the SARS-CoV-2, endothelial cells secrete sP-selectins that cause recruitment and activation of the platelets.

More secretion of sP-selectin and sCD40L by activated platelets cause more activation of platelets and monocytes resulting in unstable plaque formation.

Cell Communication and Signaling (2022) 20:131 https://doi.org/10.1186/s12964-022-00948-7

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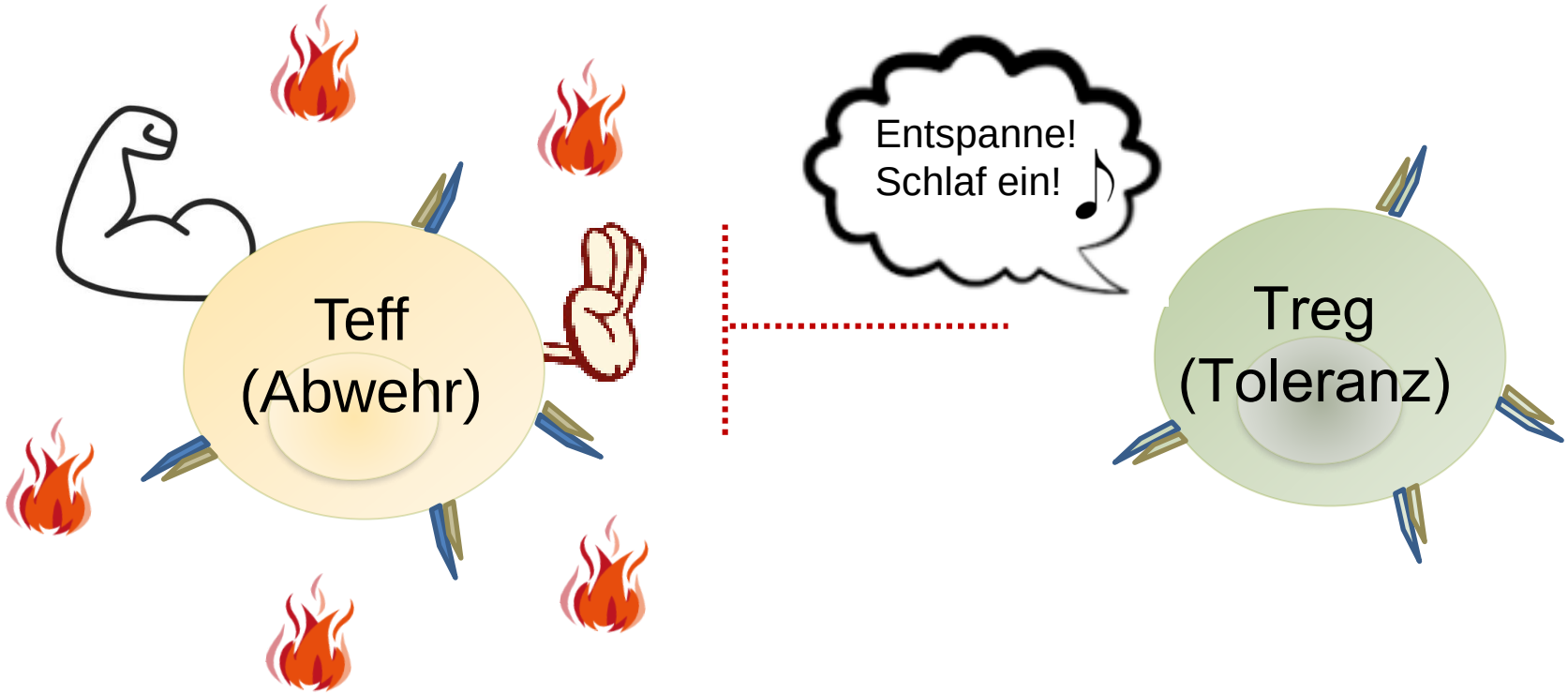
Proentzündliches Milieu beeinflusst die T-Zellantwort

Entzündung reduziert die T-zelluläre Toleranz (T_{reg})



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Alte Bekannte - Infektionen und Autoimmunität

Molekulares Mimikry – Bsp. Rheumatisches Fieber

Symptome: Fieber, Gelenkschmerzen, angegriffenes Herz

Pathologie:

- häufig Infekte mit A-Streptokokken (grampositive, unbewegliche Kettenkokken)
- produzieren „M-Protein“
- AK gegen M-Protein kreuzreagieren mit Molekülen der Herzzellen (Troponin, Myosin…)

-> Endokarditis

S. pyogenes

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ESC European Society of Cardiology

European Heart Journal (2020) **00**, 1–10
doi:10.1093/eurheartj/ehaa697

CLINICAL RESEARCH
Prevention and epidemiology

Angiotensin-converting enzyme 2 (ACE2) levels in relation to risk factors for COVID-19 in two large cohorts of patients with atrial fibrillation

Lars Wallentin [1,2]*, Johan Lindbäck [2], Niclas Eriksson [2], Ziad Hijazi[1,2], John W. Eikelboom[3], Michael D. Ezekowitz [4], Christopher B. Granger[5], Renato D. Lopes[5], Salim Yusuf[3], Jonas Oldgren [1,2], and Agneta Siegbahn[2,6]

[1]Department of Medical Sciences, Cardiology, Uppsala University, Uppsala, Sweden; [2]Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden; [3]Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Canada; [4]Thomas Jefferson Medical College and the Heart Center, Wynnewood, PA, USA; [5]Duke Clinical Research Institute, Duke University Medical Center, Duke Health, Durham, NC, USA; [6]Department of Medical Sciences, Clinical Chemistry, Uppsala University, Uppsala, Sweden

Received 7 May 2020; revised 25 June 2020; editorial decision 4 August 2020; accepted 12 August 2020

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Journal of Autoimmunity 122 (2021) 102683

Contents lists available at ScienceDirect

Journal of Autoimmunity

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

Autoantibodies against ACE2 and angiotensin type-1 receptors increase severity of COVID-19

Ana I. Rodriguez-Perez [a,b,1], Carmen M. Labandeira [a,c,1], Maria A. Pedrosa [a,b], Rita Valenzuela [a,b], Juan A. Suarez-Quintanilla [d], María Cortes-Ayaso [e], Placido Mayán-Conesa [e], Jose L. Labandeira-Garcia [a,b,*]

[a] Research Center for Molecular Medicine and Chronic Diseases (CIMUS), IDIS, University of Santiago de Compostela, Santiago de Compostela, Spain
[b] Networking Research Center on Neurodegenerative Diseases (CIBERNED), Spain
[c] Hospital Alvaro Cunqueiro, University Hospital Complex, Vigo, Spain
[d] Primary Health-Care Unit Fontiñas, IDIS, University of Santiago de Compostela, Santiago de Compostela, Spain
[e] Emergency Department, University Clinical Hospital of Santiago, Santiago de Compostela, Spain

ARTICLE INFO

Keywords:
Autoantibody
Autoimmunity
LIGHT
Outcome prediction
Renin-angiotensin system
SARS-CoV-2

ABSTRACT

The renin-angiotensin system (RAS) plays a major role in COVID-19. Severity of several inflammation-related diseases has been associated with autoantibodies against RAS, particularly agonistic autoantibodies for angiotensin type-1 receptors (AA-AT1) and autoantibodies against ACE2 (AA-ACE2). Disease severity of COVID-19 patients was defined as mild, moderate or severe following the WHO Clinical Progression Scale and determined at medical discharge. Serum AA-AT1 and AA-ACE2 were measured in COVID-19 patients (n = 119) and non-infected controls (n = 23) using specific solid-phase, sandwich enzyme-linked immunosorbent assays. Serum LIGHT (TNFSF14; tumor necrosis factor ligand superfamily member 14) levels were measured with the corresponding assay kit. At diagnosis, AA-AT1 and AA-ACE2 levels were significantly higher in the COVID-19 group relative to controls, and we observed significant association between disease outcome and serum AA-AT1 and AA-ACE2 levels. Mild disease patients had significantly lower levels of AA-AT1 ($p < 0.01$) and AA-ACE2 ($p < 0.001$) than moderate and severe patients. No significant differences were detected between males and females. The increase in autoantibodies was not related to comorbidities potentially affecting COVID-19 severity. There was significant positive correlation between serum levels of AA-AT1 and LIGHT (TNFSF14; $r_{Pearson} = 0.70$, $p < 0.001$). Both AA-AT1 (by agonistic stimulation of AT1 receptors) and AA-ACE2 (by reducing conversion of Angiotensin II into Angiotensin 1-7) may lead to increase in AT1 receptor activity, enhance proinflammatory responses and severity of COVID-19 outcome. Patients with high levels of autoantibodies require more cautious control after diagnosis. Additionally, the results encourage further studies on the possible protective treatment with AT1 receptor blockers in COVID-19.

Cell

CellPress
OPEN ACCESS

Article

Multiple early factors anticipate post-acute COVID-19 sequelae

Yapeng Su,[1,2,3,28,*] Dan Yuan,[1,4,28] Daniel G. Chen,[1,5,28] Rachel H. Ng,[1,4] Kai Wang,[1] Jongchan Choi,[1] Sarah Li,[1] Sunga Hong,[1] Rongyu Zhang,[1,4] Jingyi Xie,[1,6] Sergey A. Kornilov,[1] Kelsey Scherler,[1] Ana Jimena Pavlovitch-Bedzyk,[7] Shen Dong,[8] Christopher Lausted,[1] Inyoul Lee,[1] Shannon Fallen,[1] Chengzhen L. Dai,[1] Priyanka Baloni,[1] Brett Smith,[1] Venkata R. Duvvuri,[1] Kristin G. Anderson,[3,9] Jing Li,[7] Fan Yang,[10] Caroline J. Duncombe,[11] Denise J. McCulloch,[12] Clifford Rostomily,[1] Pamela Troisch,[1] Jing Zhou,[13] Sean Mackay,[13] Quinn DeGottardi,[14] Damon H. May,[14] Ruth Taniguchi,[14] Rachel M. Gittelman,[14] Mark Klinger,[14] Thomas M. Snyder,[14] Ryan Roper,[1] Gladys Wojciechowska,[1,15]

(Author list continued on next page)

ANAs und dsDNA AKs sind prädiktiv für Post COVID-19

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Ein perfektes Immunsystem beherrscht:

Angriff

d.h. die Fähigkeit pathogene Erreger oder Tumorzellen **effektiv und schnell zu eliminieren.**

und

Toleranz

d.h. die Fähigkeit körpereigene Zellen, belanglose Allergene aber auch kommensale Erreger zu **tolerieren und nicht anzugreifen.**

Ein zu schwaches Immunsystem kann zu gestörter Immuntoleranz und zu Autoimmunphänomenen führen

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Post COVID-19Vac-Syndrom

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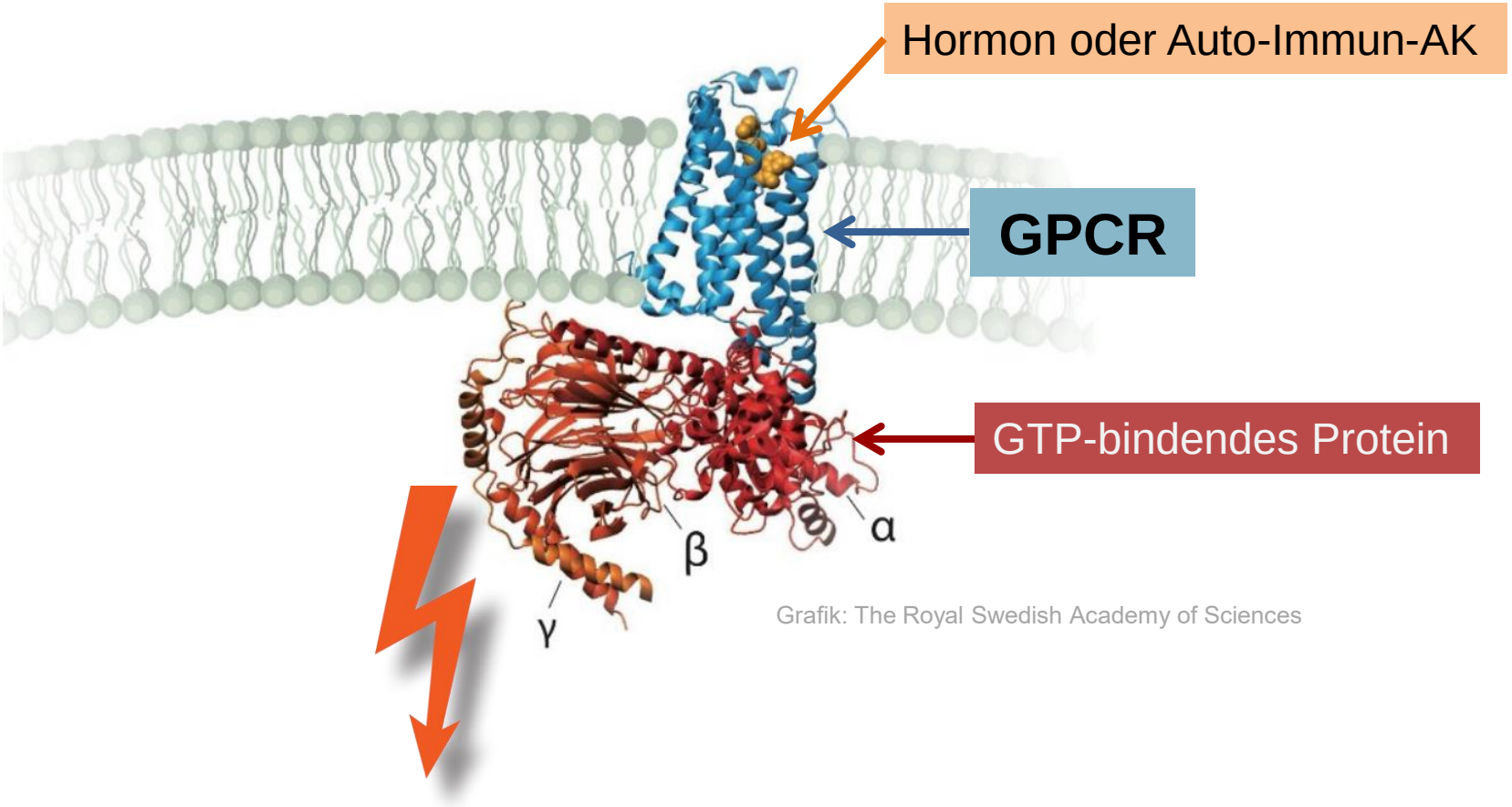
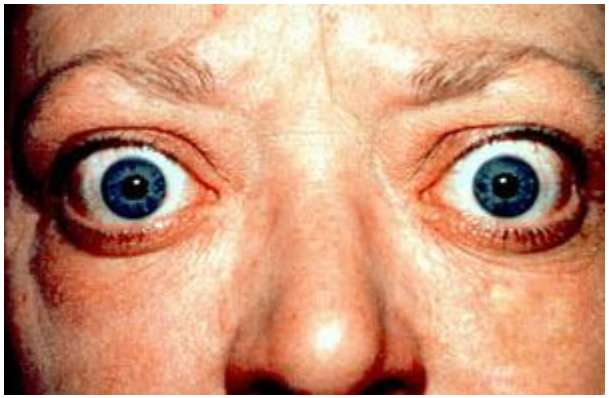
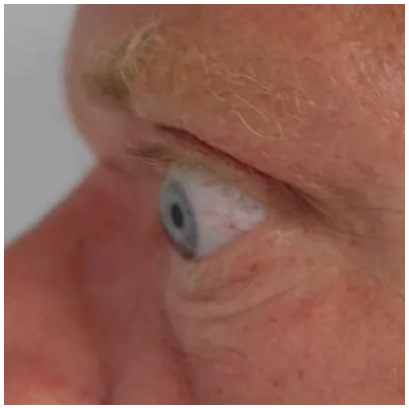
G-Protein-gekoppelte Rezeptoren (GPCR)

- in Zellmembran von Körper- und Immunzellen
- Weiterleitung von Signalen ins Zellinnere
- Beispiele: TSH-Rezeptor, Ang II- Rezeptor, ETA Rezeptor, Acetylcholin-Rezeptor, beta-Rezeptor, Thrombin-Rezeptor, Chemokin-Rezeptoren







Carl Adolph von Basedow

G-Protein-gekoppelte Rezeptorauto-AK (GPCR-AK) Erkrankungen sind alte Bekannte:

Morbus Basedow: TSH-Rezeptor Autoantikörper stimulieren in der Schilddrüse die Synthese von Schilddrüsenhormonen

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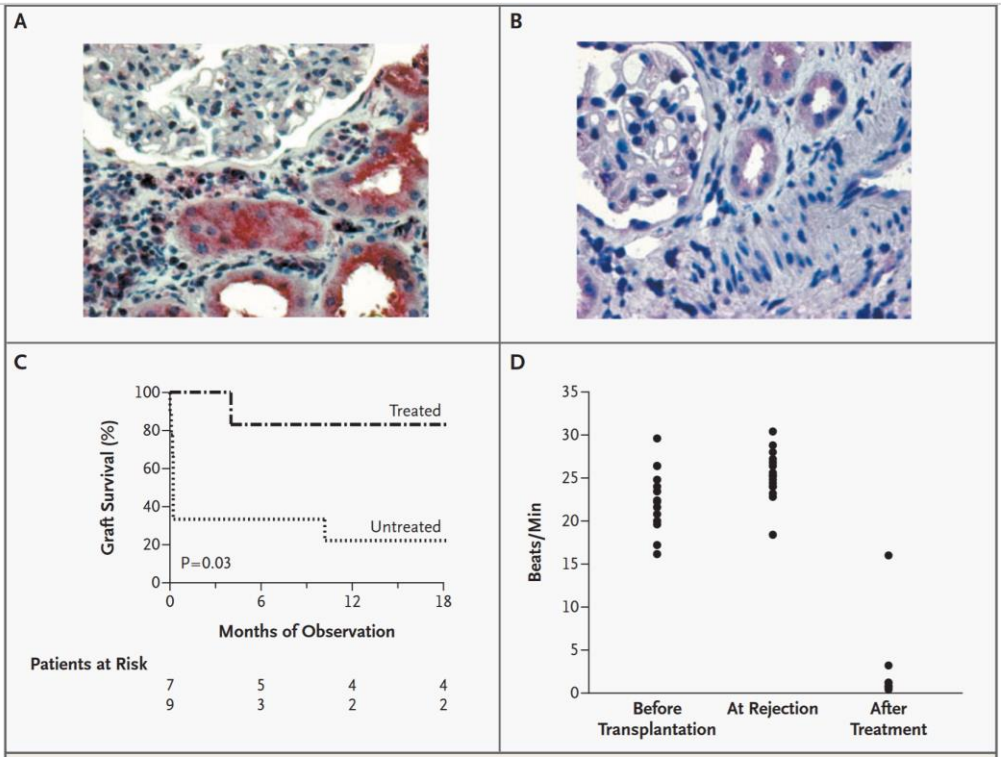
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Angiotensin II Type 1–Receptor Activating Antibodies in Renal-Allograft Rejection

Duska Dragun, M.D., Dominik N. Müller, Ph.D., Jan Hinrich Bräsen, M.D., Lutz Fritsche, M.D., Melina Nieminen-Kelhä, B.S., Ralf Dechend, M.D., Ulrich Kintscher, M.D., Birgit Rudolph, M.D., Johan Hoebeke, Ph.D., Diana Eckert, M.D., Istvan Mazak, M.D., Ralph Plehm, Ph.D., Constanze Schönemann, Ph.D., Thomas Unger, M.D., Klemens Budde, M.D., Hans-Hellmut Neumayer, M.D., Friedrich C. Luft, M.D., and Gerd Wallukat, Ph.D.



Einfluss der Losartan- und Plasmapherese-Behandlung auf die Expression von Gewebefaktoren, das Überleben von Allotransplantatenund AT1-Rezeptor-Antikörper-Aktivität bei AT1-Rezeptor-Antikörper-positiver Abstoßung.

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Involvement of functional autoantibodies against vascular receptors in systemic sclerosis

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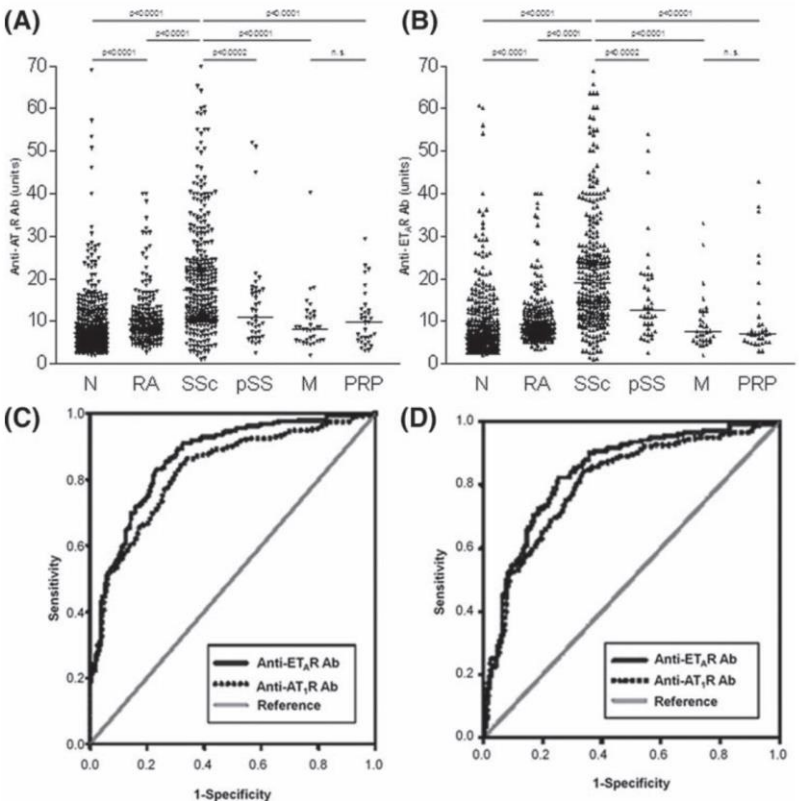

Diagnostischer Wert von Anti-AT 1 R- und Anti-ET A R-Autoantikörpern bei systemischer Sklerose (SSc). (A) Anti-AT 1 R- und (B) Anti-ET A R-Autoantikörper

Receiver-Operating-Characteristics-Analysen für Anti-AT 1 R- und Anti-ET A R-Autoantikörper im Vergleich zu gesunden Kontrollen in (C) nicht angepassten und (D) geschlechts- und altersgleichen Kohorten. AT 1 R, Angiotensin-II-Typ-1-Rezeptor; ET A R, Endothelin-1-Typ-A-Rezeptor.

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Journal of Autoimmunity

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

Autoantibodies against ACE2 and angiotensin type-1 receptors increase severity of COVID-19

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ARTICLE INFO

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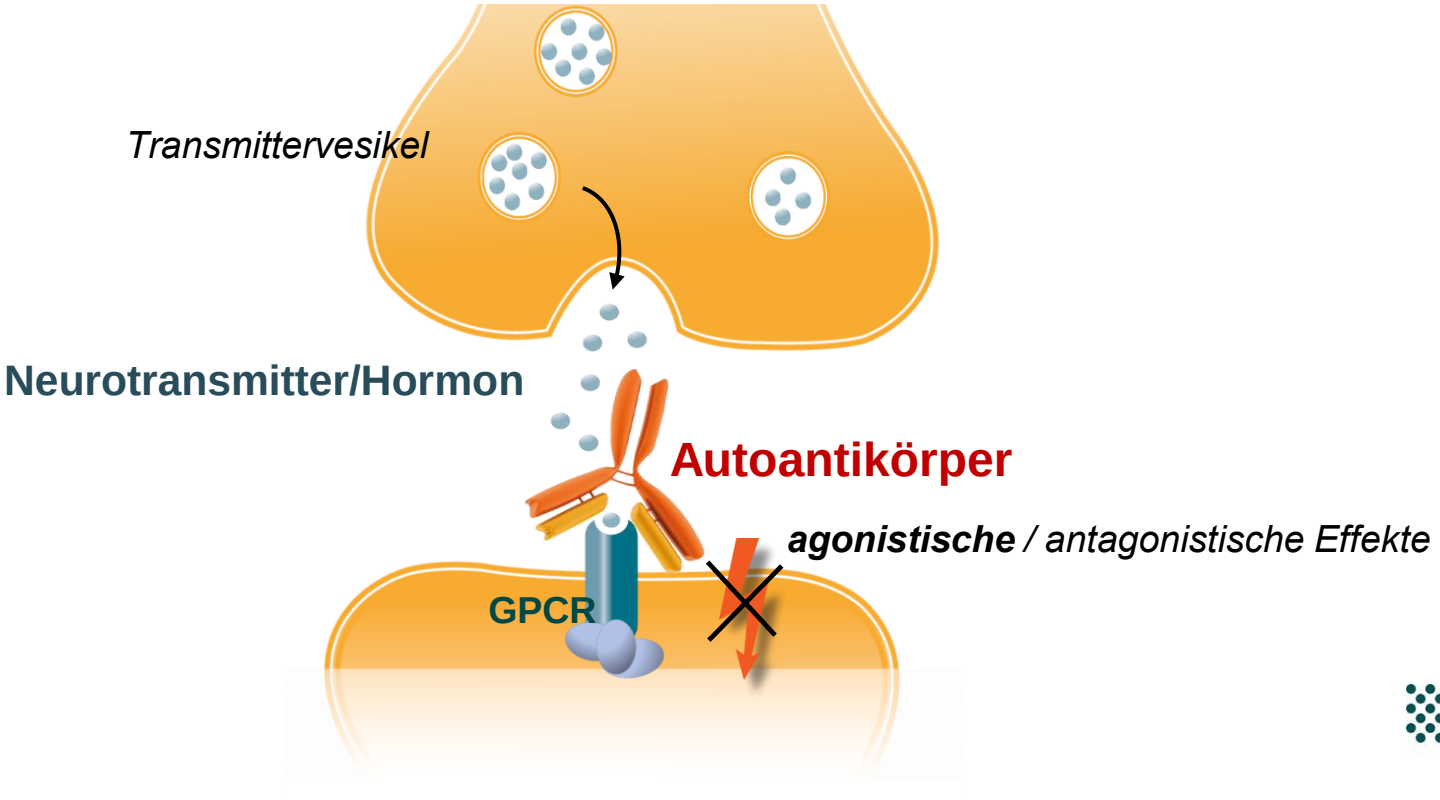
LIGHT
Outcome prediction
Renin-angiotensin system
SARS-CoV-2

ABSTRACT

The renin-angiotensin system (RAS) plays a major role in COVID-19. Severity of several inflammation-related diseases has been associated with autoantibodies against RAS, particularly agonistic autoantibodies for angiotensin type-1 receptors (AA-AT1) and autoantibodies against ACE2 (AA-ACE2). Disease severity of COVID-19 patients was defined as mild, moderate or severe following the WHO Clinical Progression Scale and determined at medical discharge. Serum AA-AT1 and AA-ACE2 were measured in COVID-19 patients ($n = 119$) and non-infected controls ($n = 23$) using specific solid-phase, sandwich enzyme-linked immunosorbent assays. Serum LIGHT (TNFSF14; tumor necrosis factor ligand superfamily member 14) levels were measured with the corresponding assay kit. At diagnosis, AA-AT1 and AA-ACE2 levels were significantly higher in the COVID-19 group relative to controls, and we observed significant association between disease outcome and serum AA-AT1 and AA-ACE2 levels. Mild disease patients had significantly lower levels of AA-AT1 ($p < 0.01$) and AA-ACE2 ($p < 0.001$) than moderate and severe patients. No significant differences were detected between males and females. The increase in autoantibodies was not related to comorbidities potentially affecting COVID-19 severity. There was significant positive correlation between serum levels of AA-AT1 and LIGHT (TNFSF14; $r_{Pearson} = 0.70$, $p < 0.001$). Both AA-AT1 (by agonistic stimulation of AT1 receptors) and AA-ACE2 (by reducing conversion of Angiotensin II into Angiotensin 1-7) may lead to increase in AT1 receptor activity, enhance proinflammatory responses and severity of COVID-19 outcome. Patients with high levels of autoantibodies require more cautious control after diagnosis. Additionally, the results encourage further studies on the possible protective treatment with AT1 receptor blockers in COVID-19.

Pathophysiologie der Auto AK bei neuro-psychiatrischen Störungen:

- führen überwiegend zu einer Aktivierung des Rezeptors an den Synapsen
- unphysiologische Daueraktivierung der Signalkaskade an den Synapsen
- in einigen Fällen auch hemmende Wirkung an Synapsen



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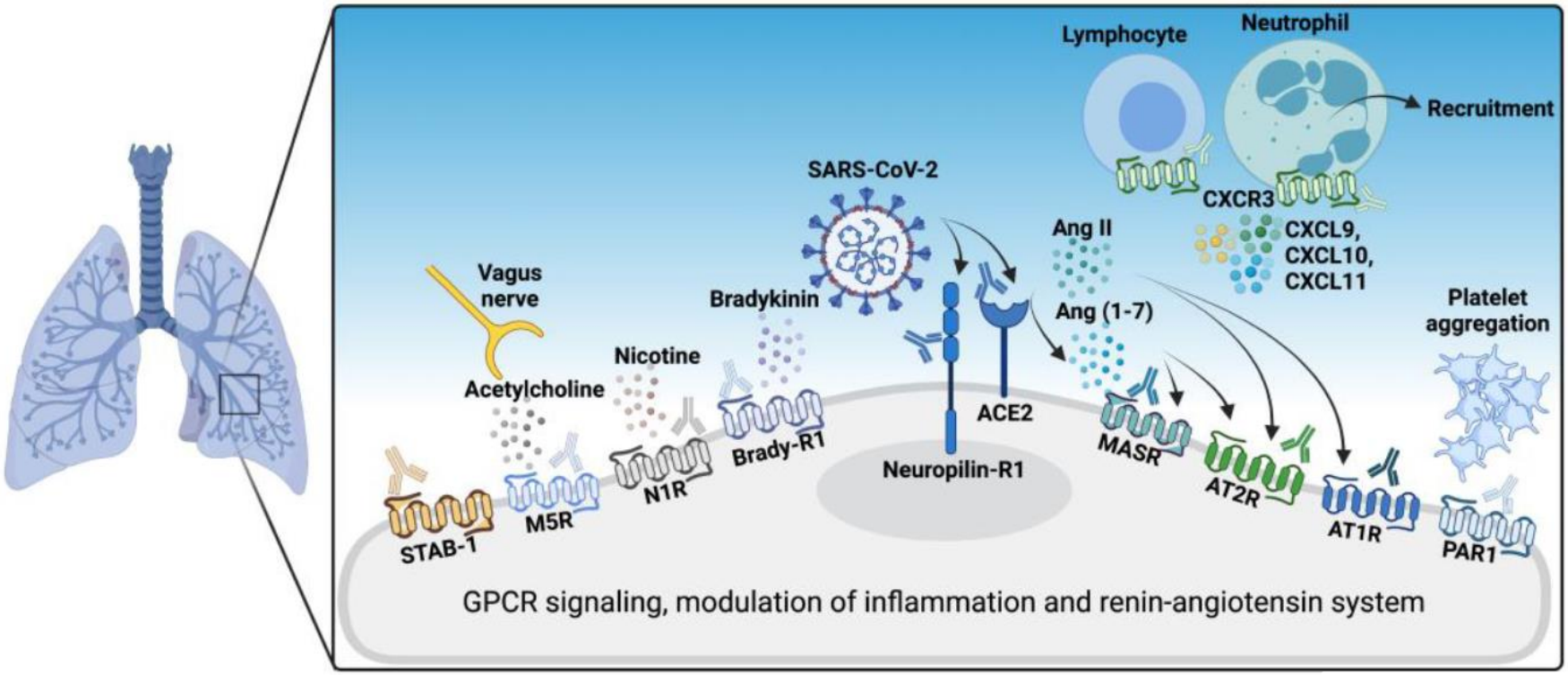
Im Gegensatz zum Morbus Basedow (TSH-R Auto-AK) treten beim Post COVOD Syndrom multiple GPCR-Antikörper auf:

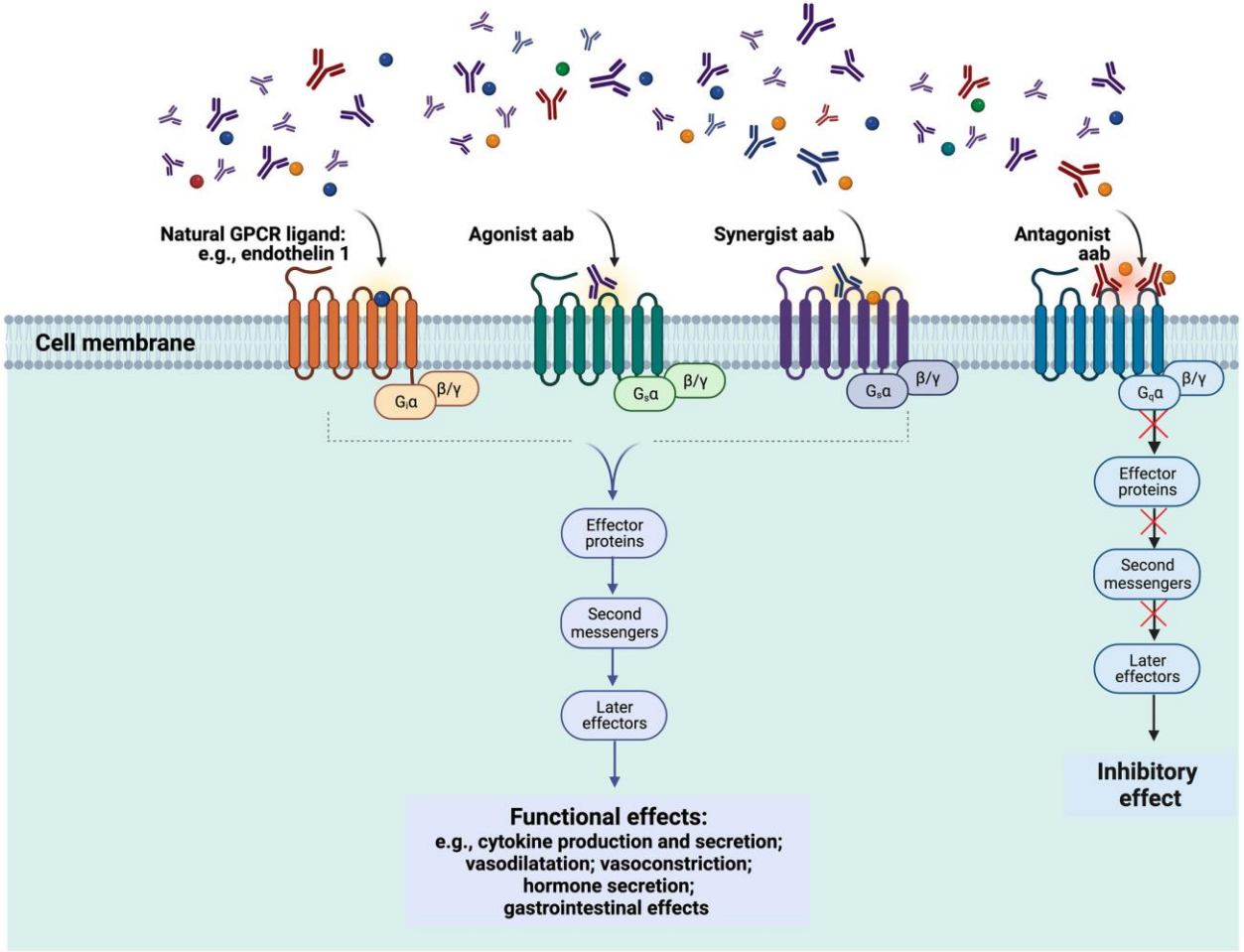
- β1-adrenerge Rez.-Ak
- β2-adrenerge Rez.-Ak
- M3-mAChR-Ak
- M4-mAChR-Ak
- Endothelin-Rezeptor-Ak (ETA)
- PAR1-Ak (PAR1)
- Angiotensin II-Rez. Typ 1-Ak (AT1)
- CXCR3-Rez.-Ak

Unterschiedliche Kombinationen der Auto-AK könnten mit unterschiedlichen klinischen Manifestationen von Post COVID assoziiert sein



Wallukat et al. J Transl Autoimmun. 2021;4:100100. doi: 10.1016/j.jtauto.2021.100100.

Autoantibodies targeting G protein-coupled receptors: An evolving history in autoimmunity. Report of the 4th international symposium. Autoimmun Rev. 2023 May;22(5):103310. doi: 10.1016/j.autrev.2023.103310



Funktionelle Auswirkungen von Anti-GPCR-Autoantikörpern. Diese Auto-Antikörper haben **agonistische, synergistische** oder **antagonistische** Wirkungen auf die Rezeptorbindung

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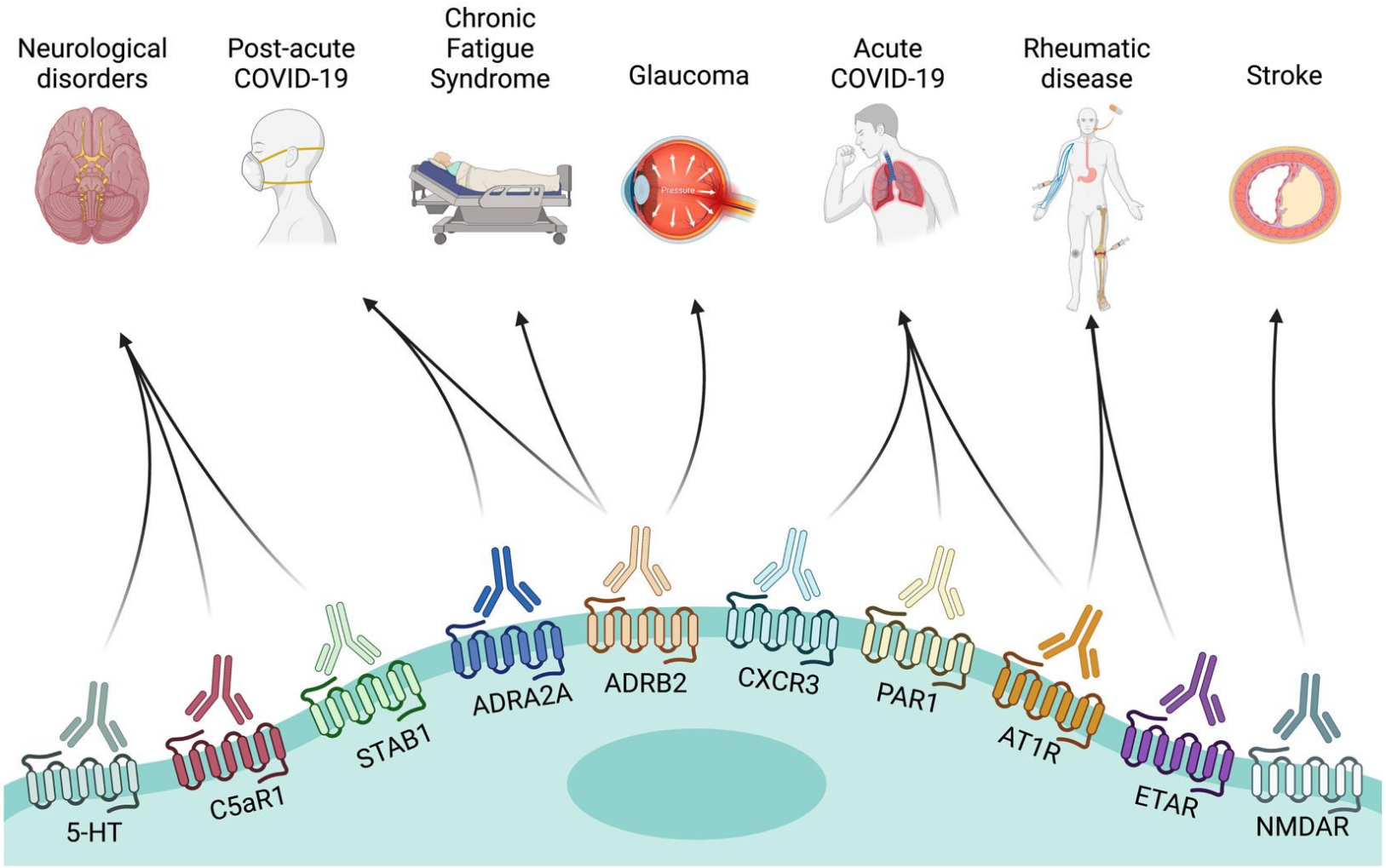
Autoantibodies targeting G protein-coupled receptors: An evolving history in autoimmunity. Report of the 4th international symposium.

Autoimmun Rev. 2023 May;22(5):103310. doi: 10.1016/j.autrev.2023.103310



Die Beteiligung von Anti-GPCR-Auto-Antikörpern an verschiedenen pathologischen Zuständen. Die Krankheiten sind oben und Anti-GPCR aab unten in der Abbildung dargestellt.

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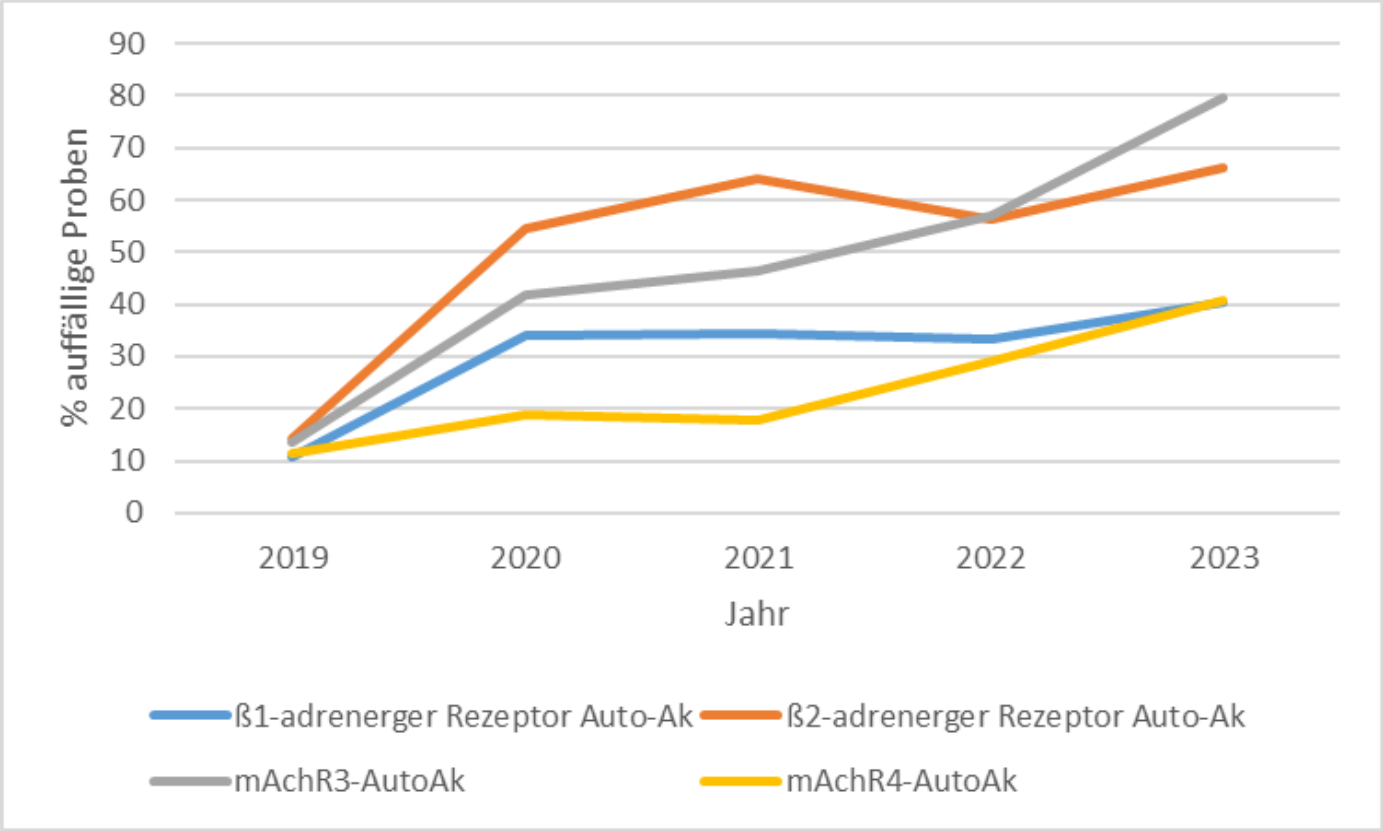
Dysregulierte GPCR-Ak haben nach der Corona-Pandemie zugenommen



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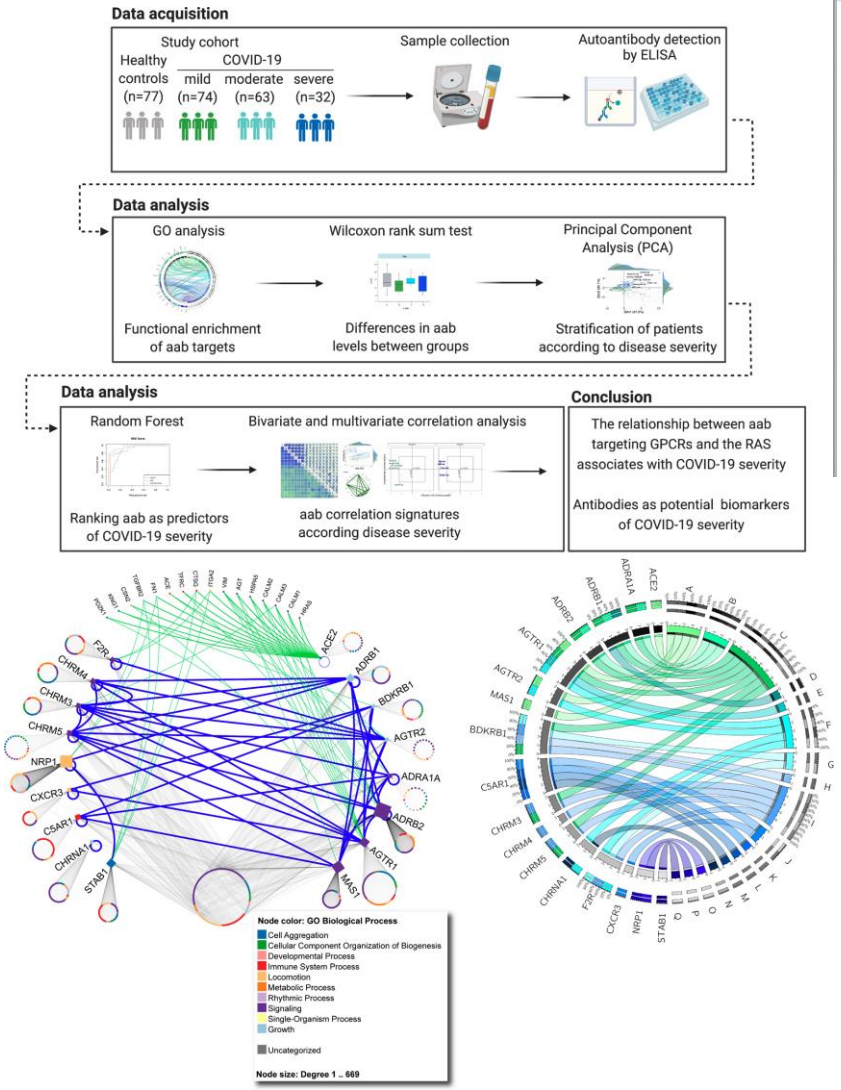

nature COMMUNICATIONS

ARTICLE

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https://doi.org/10.1038/s41467-022-28905-5 OPEN

Autoantibodies targeting GPCRs and RAS-related molecules associate with COVID-19 severity

Otavio Cabral-Marques[1,2,3,25✉], Gilad Halpert[4,5,25], Lena F. Schimke[1,25], Yuri Ostrinski[4,5,6], Aristo Vojdani[7,8], Gabriela Crispim Baiocchi[1], Paula Paccielli Freire[1], Igor Salerno Filgueiras[1], Israel Zyskind[9,10], Miriam T. Lattin[11], Florian Tran[12], Stefan Schreiber[12], Alexandre H. C. Marques[1], Desirée Rodrigues Plaça[2], Dennyson Leandro M. Fonseca[2], Jens Y. Humrich[13], Antje Müller[13], Lasse M. Giil[14], Hanna Graßhoff[13], Anja Schumann[13], Alexander Hackel[13], Juliane Junker[15], Carlotta Meyer[15], Hans D. Ochs[16], Yael Bublil Lavi[17], Carmen Scheibenbogen[18], Ralf Dechend[19], Igor Jurisica[20,21], Kai Schulze-Forster[15], Jonathan I. Silverberg[22], Howard Amital[4,17,23], Jason Zimmerman[10], Harry Heidecke[15], Avi Z. Rosenberg[24], Gabriela Riemekasten[13,25✉] & Yehuda Shoenfeld[4,5,6,25✉]

- **G-Protein gekoppelte Rezeptor Auto AK kommen physiologisch vor und sind Bestandteil physiologischer endokriner Regelkreise**
- **G-Protein gekoppelte Rezeptor Auto AK sind bei Post COVID erhöht**
- **Wichtig ist nicht nur die Höhe der G-Protein gekoppelte Rezeptor Auto AK sondern krankheitssoezifische Muster der Auto AKs**

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Autoantibodies targeting GPCRs and RAS-related molecules associate with COVID-19 severity.
Nat Commun. 2022 Mar 9;13(1):1220. doi: 10.1038/s41467-022-28905-5.

…….. ***Among the anti-GPCR autoantibodies, machine learning classification identifies the chemokine receptor CXCR3 and the RAS-related molecule AGTR1 as targets for antibodies with the strongest association to disease severity*** ……..

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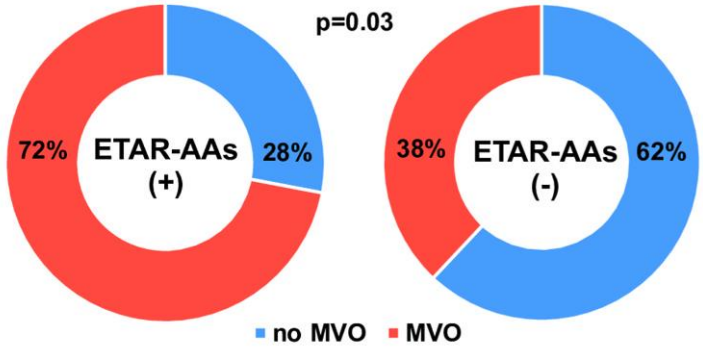
Association of autoantibodies targeting endothelin type-A receptors with no-reflow in ST-elevation myocardial infarction

Atherosclerosis 378 (2023) 117179

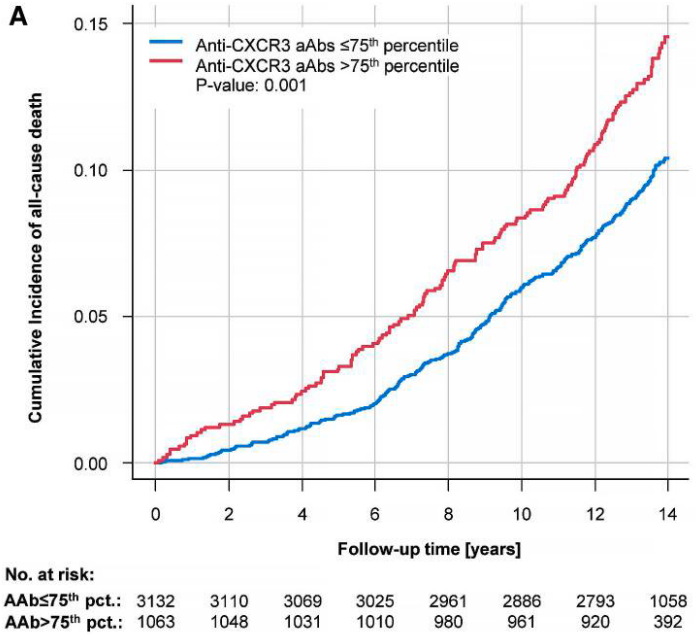
Is the presence of ETAR-AAs associated with no-reflow after STEMI?	
	Prospective single center study
	✓ 50 STEMI patients ✓ PPCI performed within 6 hours after pain onset
	ETAR-AAs measured within 12 hours after PPCI
	Cardiac MR performed within 15 days after PPCI



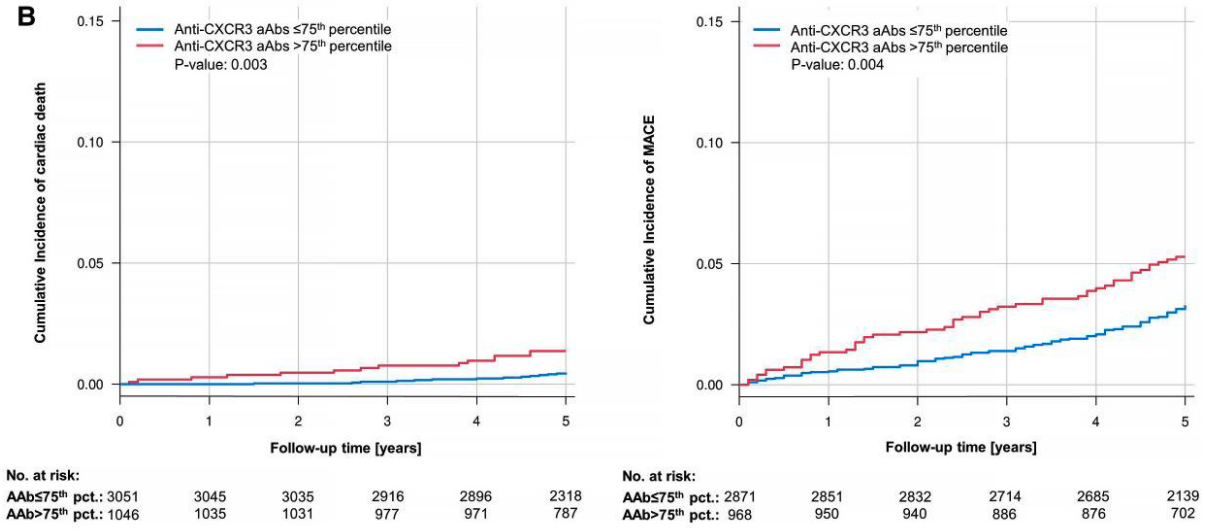
ETAR-AAs (+) is associated with:	
Variable	*p-value*
Peak hs-TnI (ng/L)	0.001
TIMI flow < 3	0.0002

Independent predictors of MVO:		
Variable	*OR (CI 95%)*	*p-value*
ETAR-AAs (+)	3.22 (1.31-7.11)	0.032
Infarct Size	1.06 (1.01-1.12)	0.019

Müller et al., Autoantibodies against the chemokine receptor 3 predict cardiovascular risk. Eur Heart J. 2023 doi: 10.1093/eurheartj/ehad666



Bei Personen ohne Autoimmunerkrankung waren Anti-CXCR3-Aabs nachweisbar und standen in Zusammenhang mit Schädigungen der CV-Endorgane. Sie sind unabhängig assoziiert mit Tod jeglicher Ursache sowie kardialer Morbidität und Mortalität. Tierexperimente weisen auf einen kausalen Zusammenhang zwischen Anti-CXCR3-Aabs und Herz-Kreislauferkrankungen hin.



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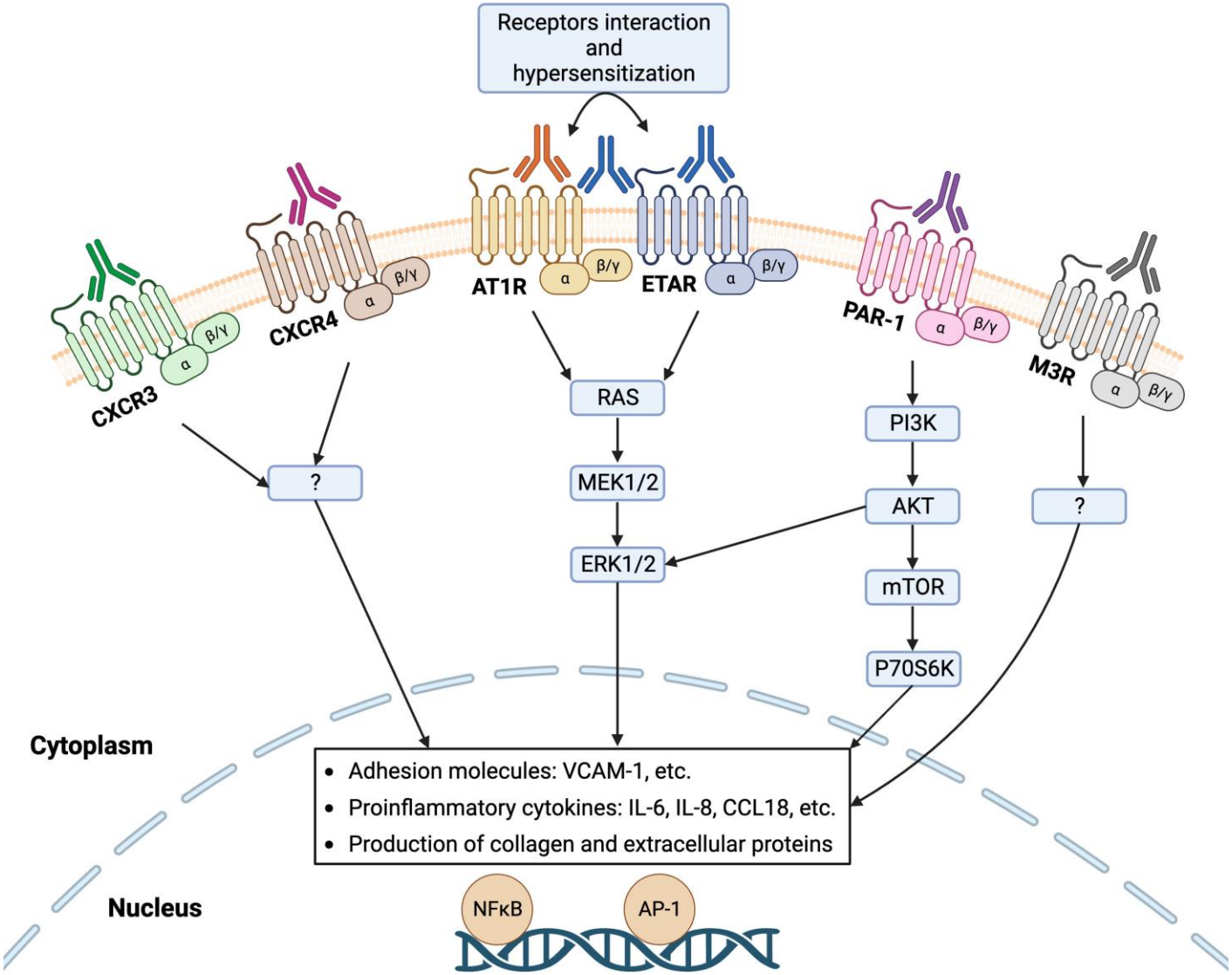

Akbarzadeh R, Müller A, Humrich JY and Riemekasten G (2023) When natural antibodies become pathogenic: autoantibodies targeted against G protein-coupled receptors in the pathogenesis of systemic sclerosis. Front. Immunol. 14:1213804. doi: 10.3389/fimmu.2023.1213804

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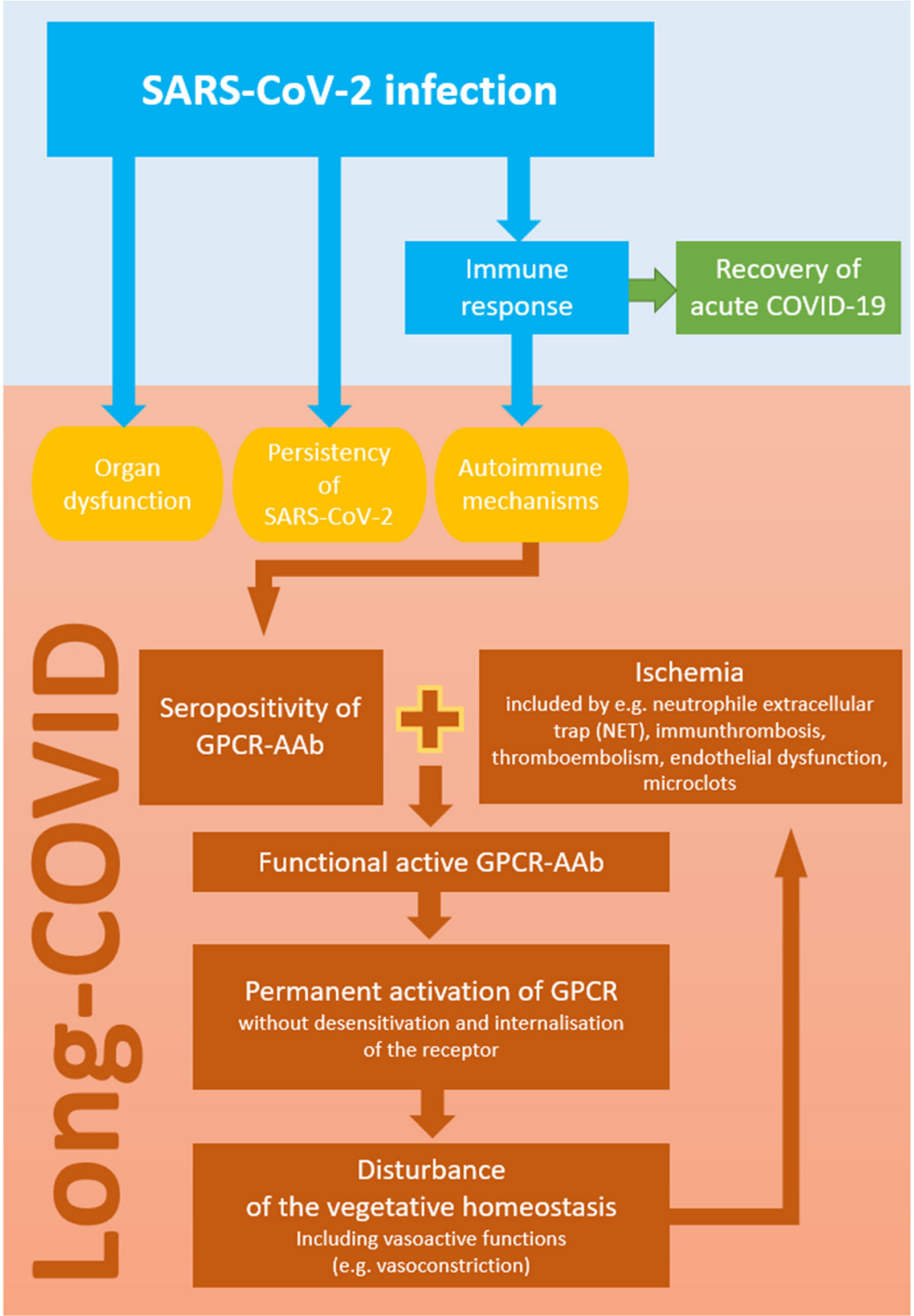

Szewczykowski et al., Association of Functional Autoantibodies against G-Protein-Coupled Receptors with an Impaired Retinal Microcirculation. Int J Mol Sci. 2022 Jun 29;23(13):7209. doi: 10.3390/ijms23137209.

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- Post COVID-19 – Mikrobiom

Post COVID-19Vac-Syndrom

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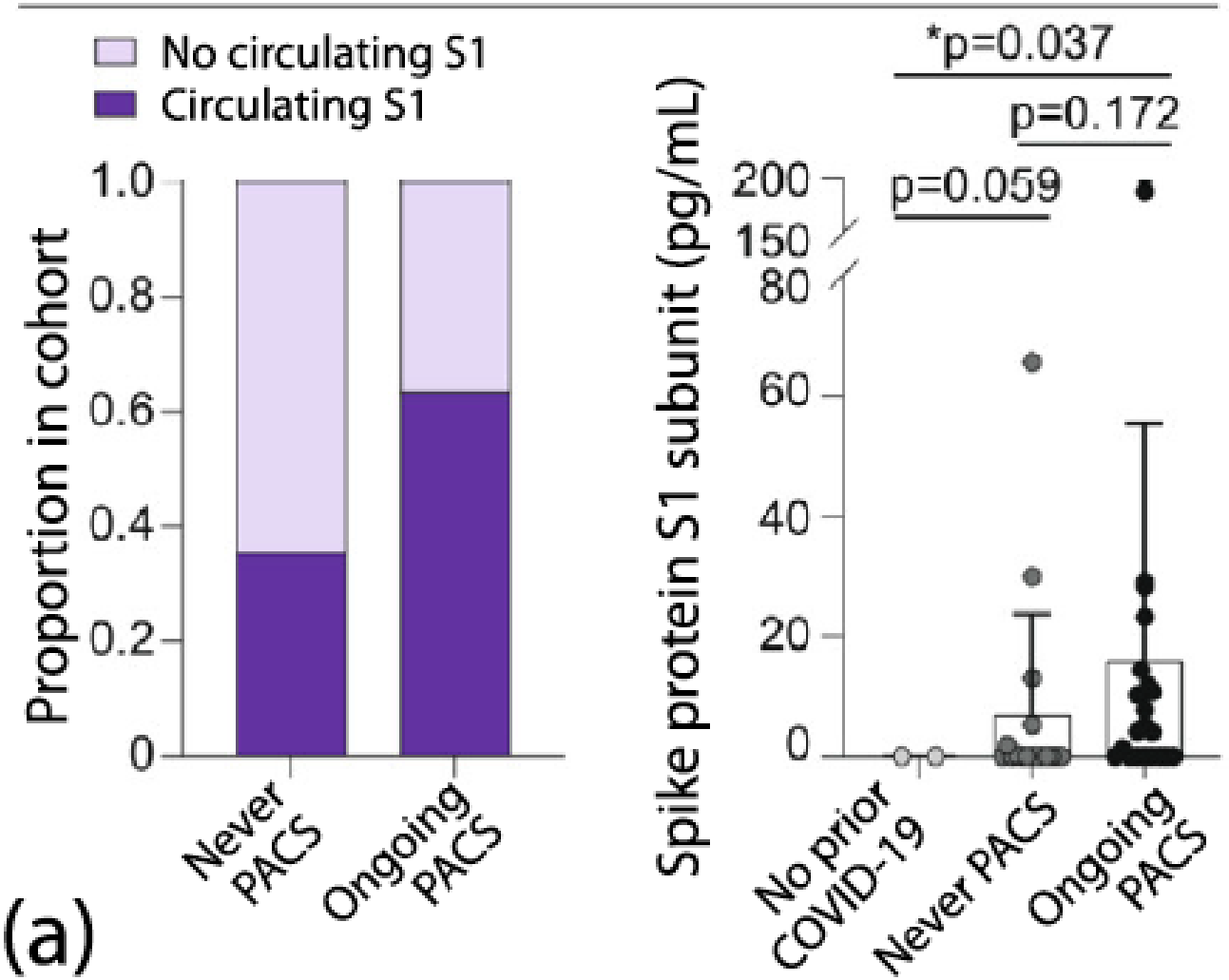
Spike protein concentration in blood plasma

(Schultheiß et al., 2022)



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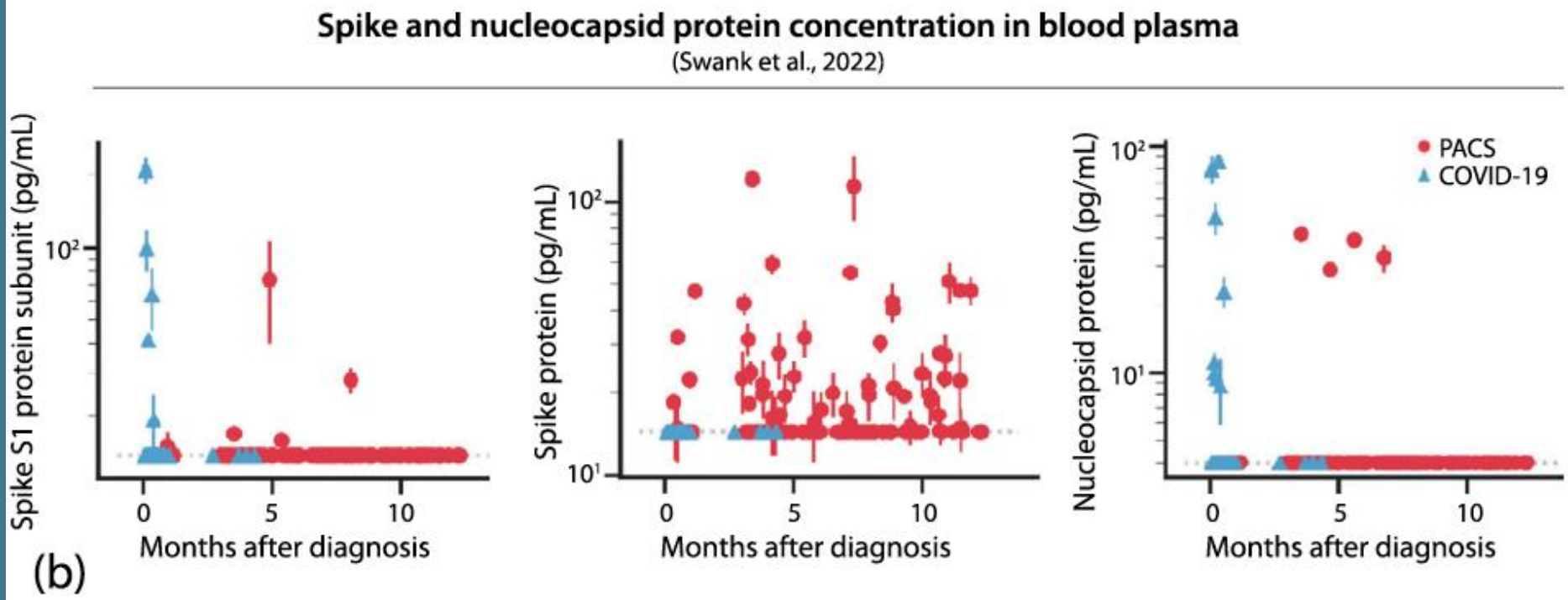

Zeitabhängigkeit von Spike- und Nukleokapsid-Protein-Konzentration im Blutplasma bei Personen mit PACS und COVID-19.

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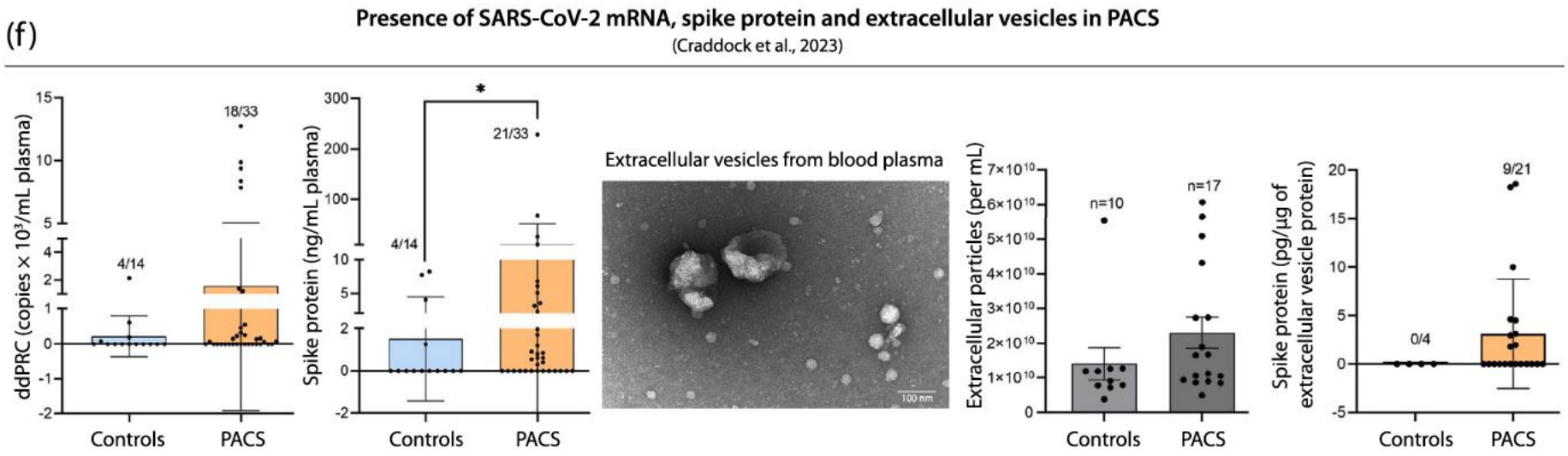

Vorhandensein von SARS-CoV-2-mRNA, Spike-Protein und extrazellulären Vesikeln (EV) mit Spike-Protein im Blutplasma von Personen mit PACS. Eine repräsentative Transmissionselektronenmikroskopie (TEM)-Aufnahme zeigt EVs (50.000fache Vergrößerung). Das Balkendiagramm, das die Unterschiede zwischen EVs in Kontrollen und PACS darstellt, bezieht sich auf kleine EVs

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Ärztlicher Befundbericht

Untersuchung		Ergebnis	Einheit	Referenzbereich
Klinische Immunologie				
Freies Spike-Protein i.S	(ELISA)	84.6	pg/ml	< 4.5

Nachweis von freiem Spike-Protein im Serum.

Zusatzuntersuchung in PBMC: 2,4 pg/ml (kein Nachweis)

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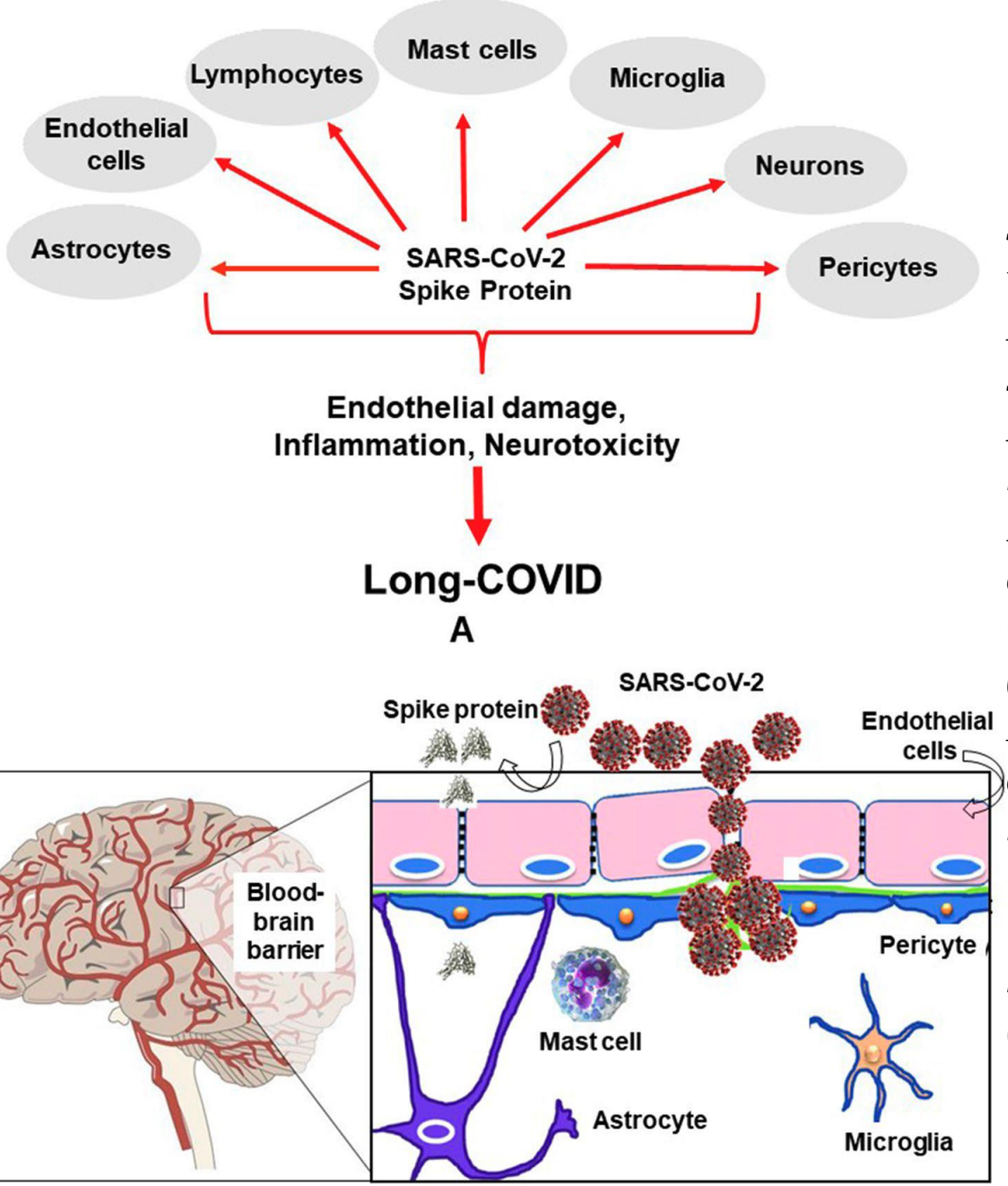

Schematische Darstellung zeigt wie das SARS-CoV-2-Spike-Protein verschiedene Zelltypen stimulieren kann und zur Pathogenese von long-COVID beitragen.
B Schematische Darstellung der Art und Weise, wie SARS-CoV-2 die Blut-Hirn-Schranke (BHS) durch Spalten passiert. Freies Spike-Protein kann auch die Integrität der BHS beeinträchtigen und so in das Gehirn eindringen.

Molecular Neurobiology (2022) 59:1850–1861

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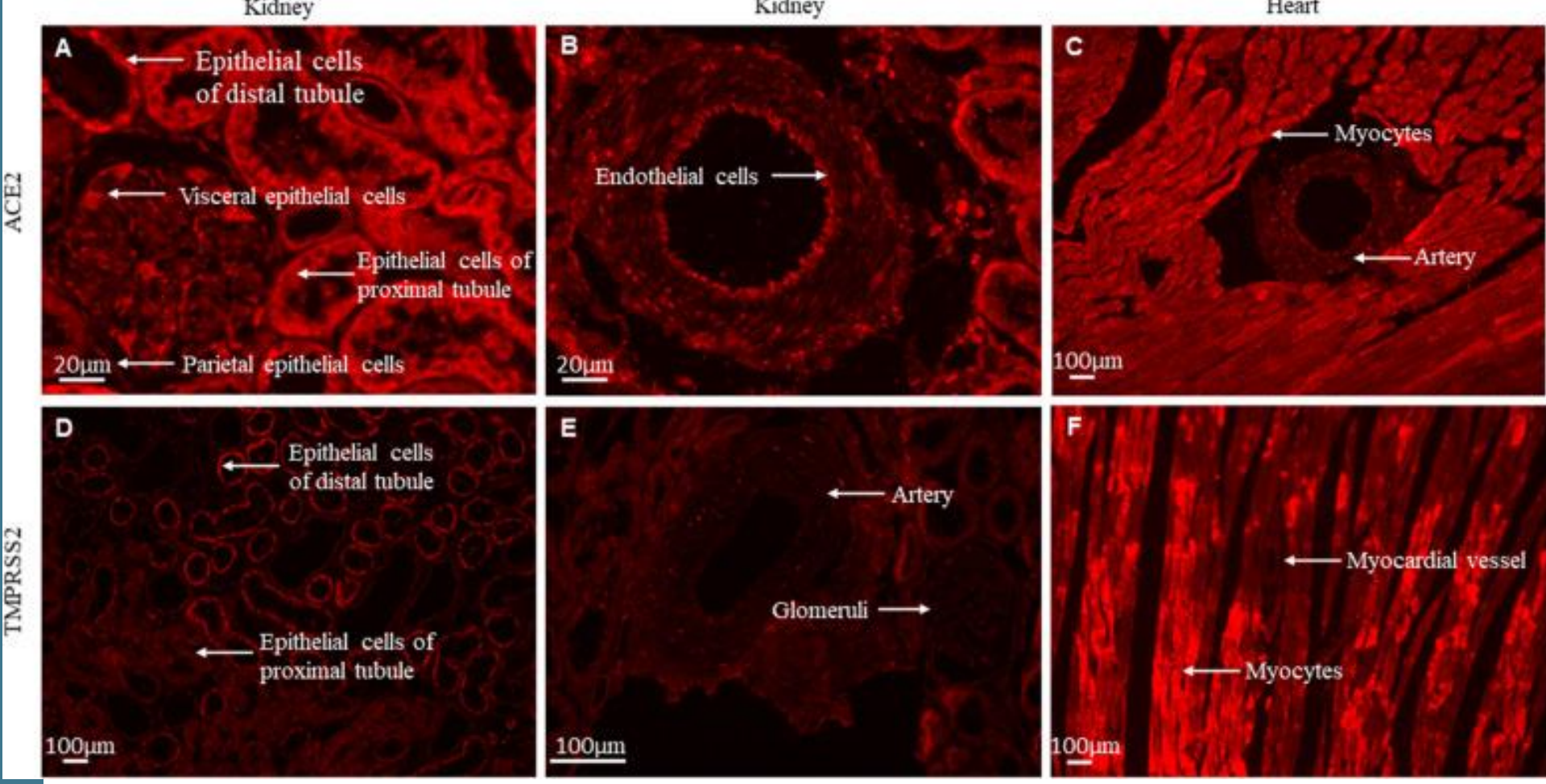

Xiong Y, Delic D, Zeng S, Chen X, Chu C, Hasan AA, Krämer BK, Klein T, Yin L, Hocher B. Regulation of SARS CoV-2 host factors in the kidney and heart in rats with 5/6 nephrectomy-effects of salt, ARB, DPP4 inhibitor and SGLT2 blocker. BMC Nephrol. 2022 Mar 24;23(1):117.

Direkte Aktivierung von ACE2 auf Myocyten durch zirkulierende freie Spike Proteine -> Myokarditis

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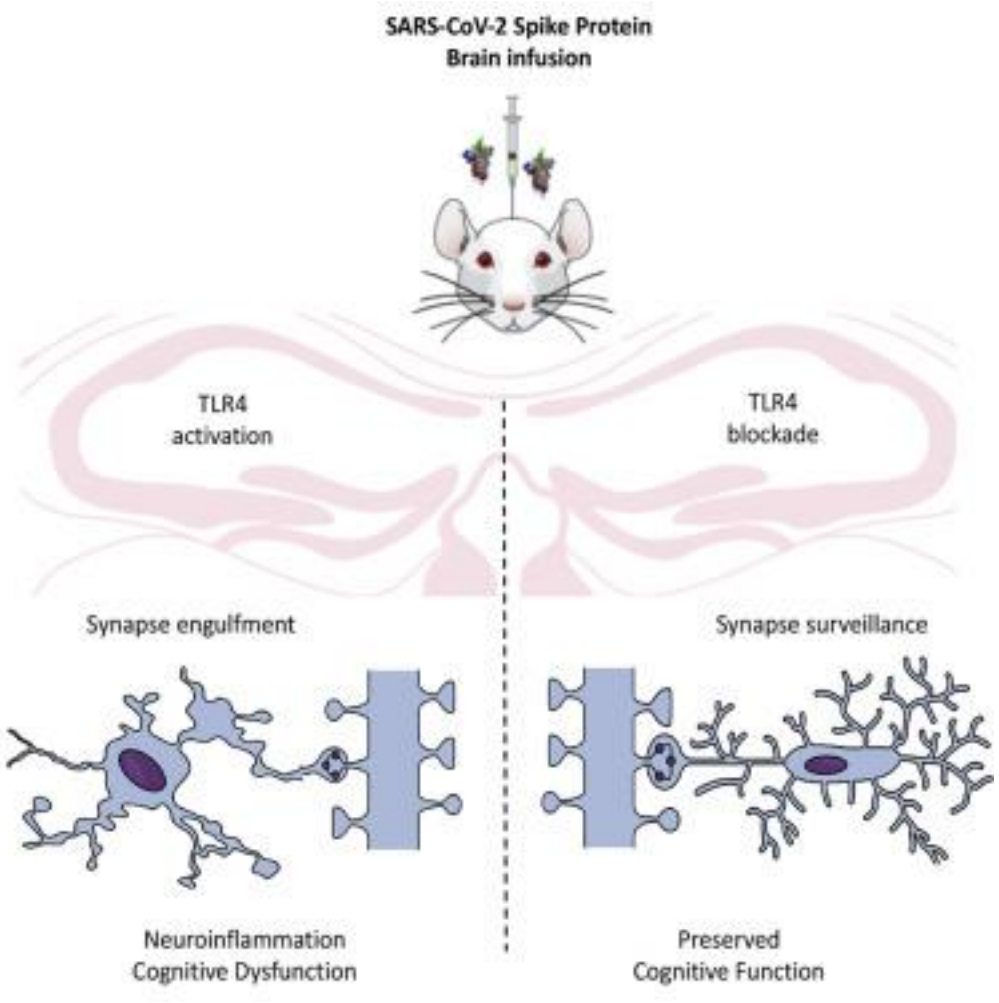
SARS-CoV-2 Spike protein induces TLR4-mediated long-term cognitive dysfunction recapitulating post-COVID-19 syndrome in mice. *Cell reports*, 2023, 42. Jg., Nr. 3, S. 112189.



Highlights

••Spike protein infusion into mouse brain induces late cognitive dysfunction

••Spike protein induces late hippocampal microgliosis and synapse loss

••Blockage of TLR4 renders mice resistant to Spike-induced cognitive dysfunction

••*TLR4*-2604G>A GG genotype was related to poor cognitive outcome in COVID-19 patients

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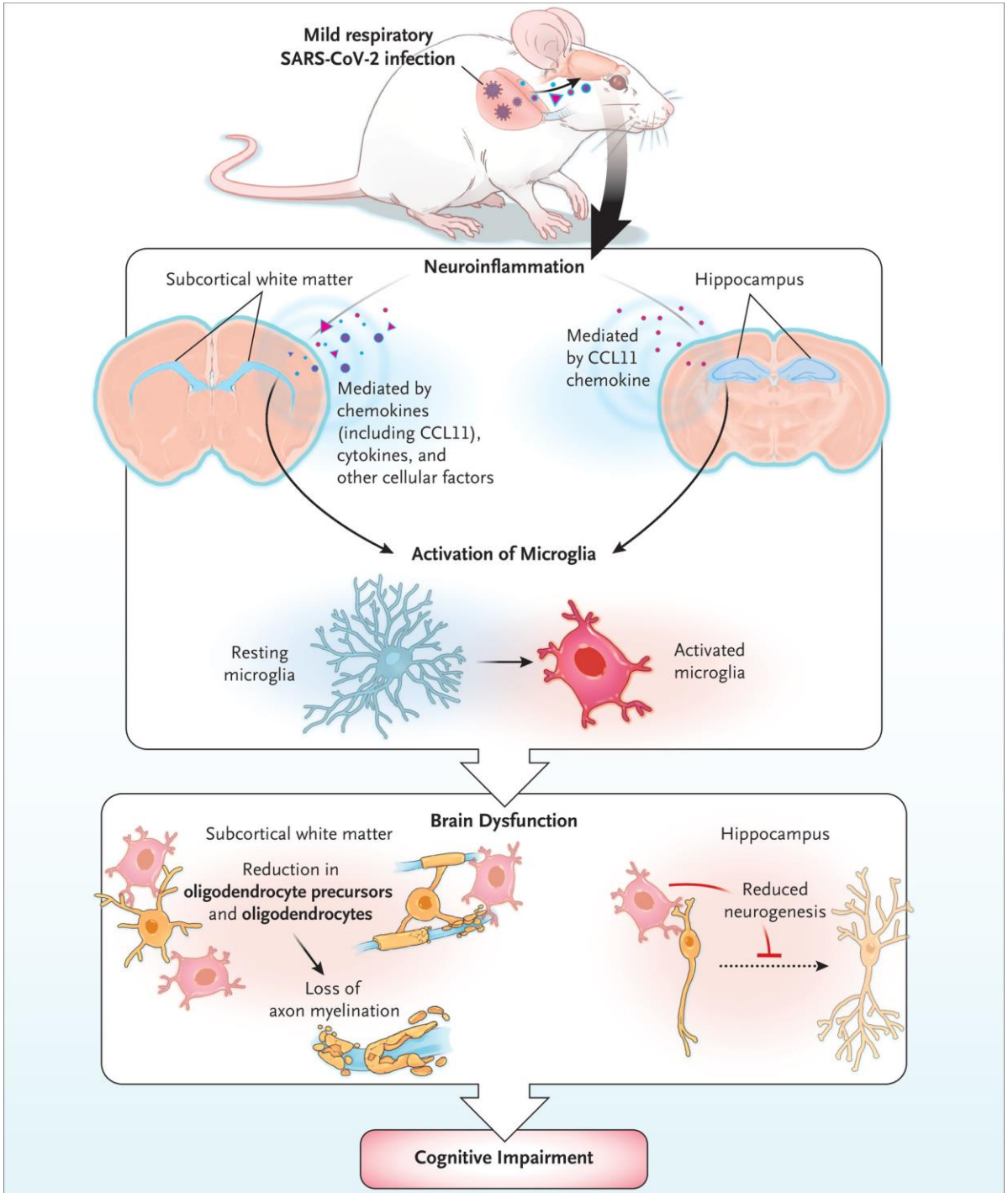

Venkataramani V, Winkler F. Cognitive Deficits in Long Covid-19. N Engl J Med. 2022 Nov 10;387(19):1813-1815. doi: 10.1056/NEJMcibr2210069

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Microorganisms **2022**, *10*, 2067. https://doi.org/10.3390/microorganisms10102067

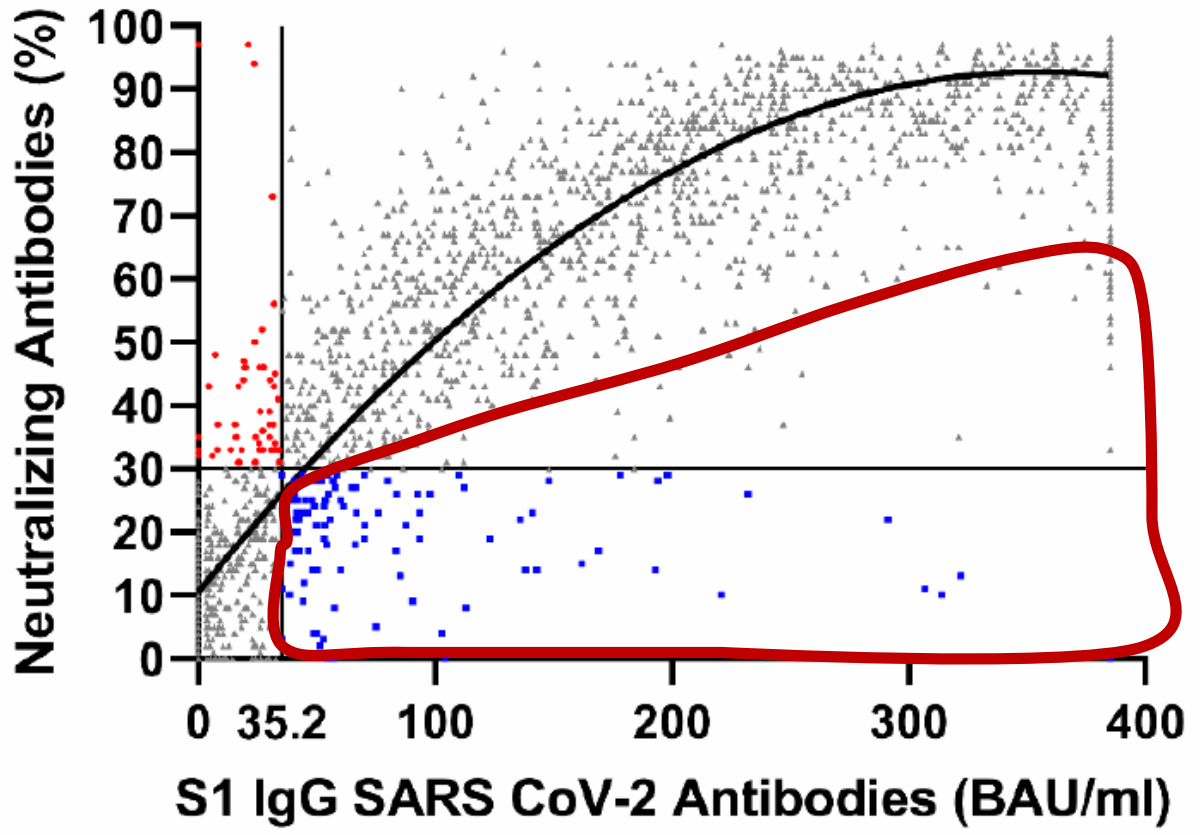
microorganisms

MDPI

Brief Report

Outliers Matter—Correlation between S1 IgG SARS-CoV-2 Antibodies and Neutralizing SARS-CoV-2 Antibodies

Berthold Hocher [1,2,*], Anne Schönbrunn [2], Xin Chen [1], Bernhard K. Krämer [1] and Volker von Baehr [2]



Max. 10%

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- Post COVID-19 – Mikrobiom

Post COVID-19Vac-Syndrom

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frontiers in Microbiology

OPINION
published: 17 September 2021
doi: 10.3389/fmicb.2021.732838

Check for updates

Is There a Connection Between Gut Microbiome Dysbiosis Occurring in COVID-19 Patients and Post-COVID-19 Symptoms?

Kai Hilpert[1] *and Ralf Mikut*[2*]

Abgesehen von diesen Einschränkungen durch relativ kleine Beobachtungsstudien, berichteten jedoch alle Studien über eine signifikante **Abnahme der Diversität** und aber gleichzeitig eine **Anreicherung opportunistischer Erreger** bei Patienten mit Post-COVID-19-Syndrom.

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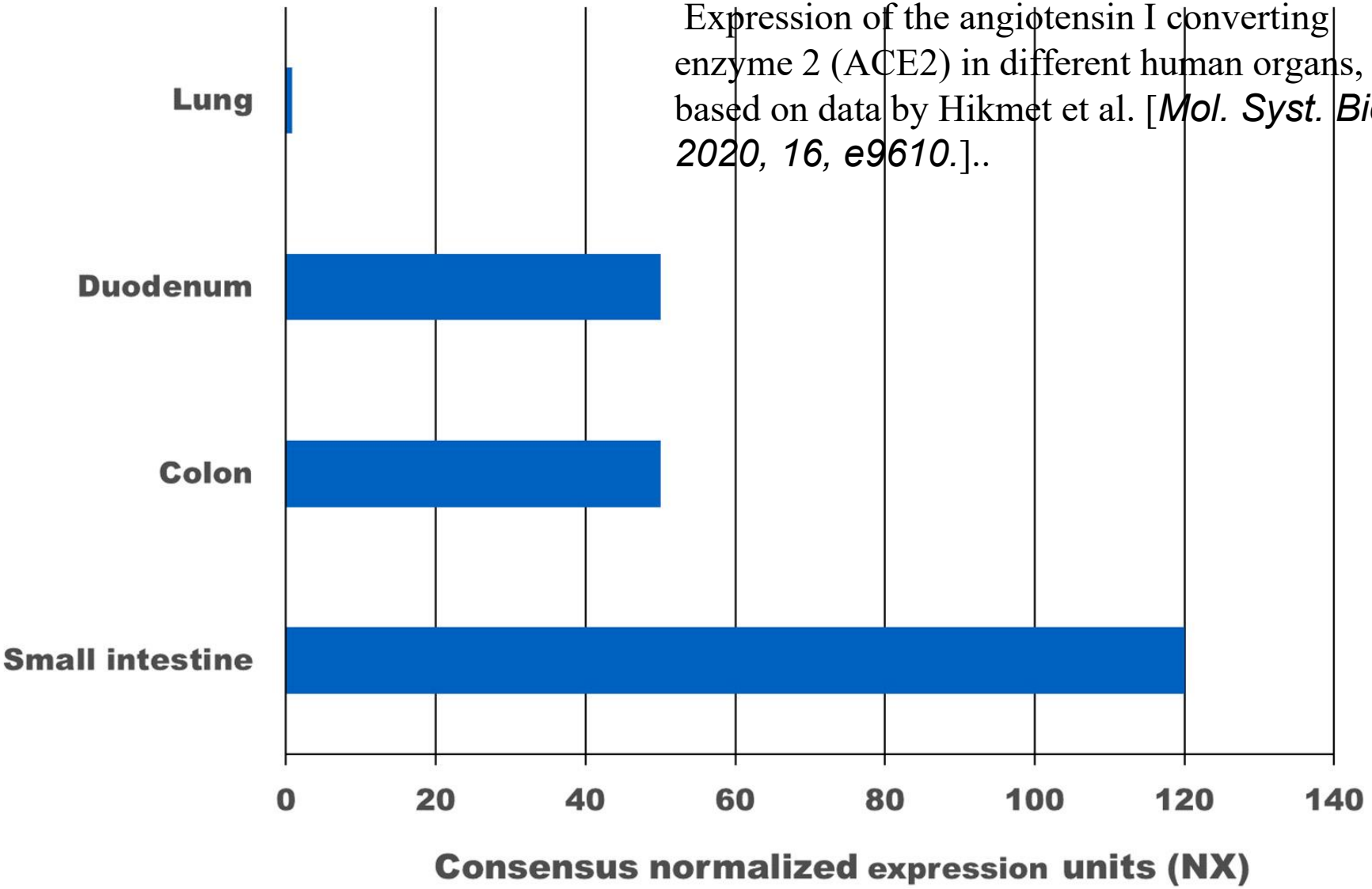
Expression of the angiotensin I converting enzyme 2 (ACE2) in different human organs, based on data by Hikmet et al. [*Mol. Syst. Biol. 2020, 16, e9610.*]..



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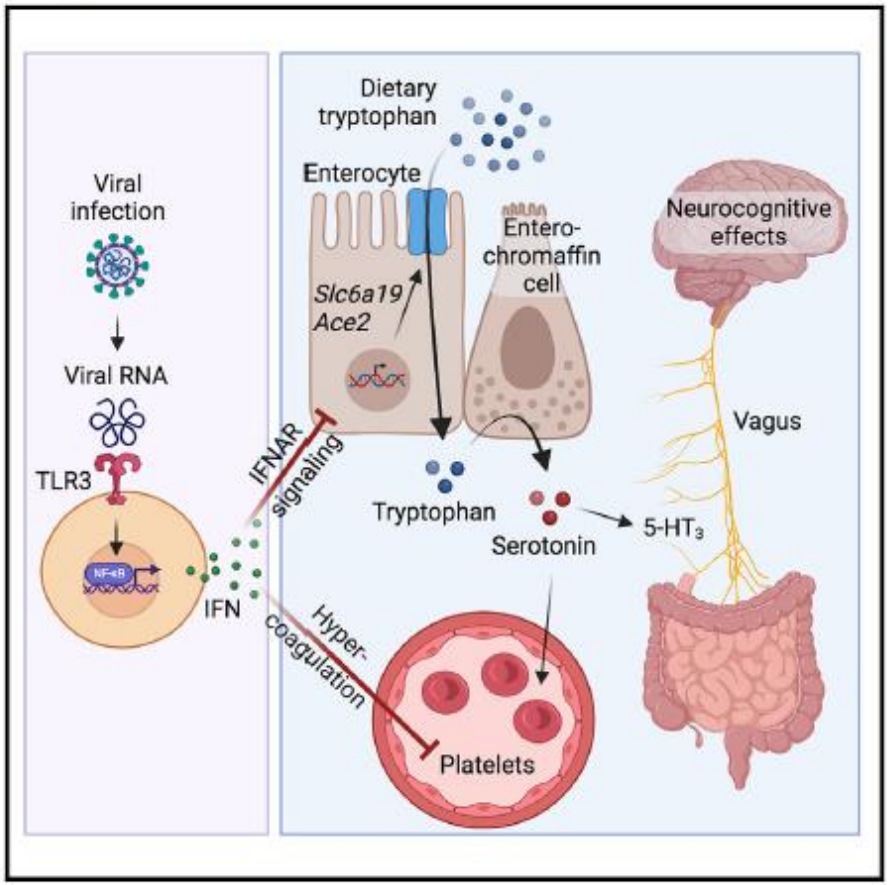
Cell

Serotonin reduction in post-acute sequelae of viral infection

Graphical abstract



Authors

Andrea C. Wong, Ashwarya S. Devason, Iboro C. Umana, ..., Sara Cherry, Christoph A. Thaiss, Maayan Levy

Correspondence

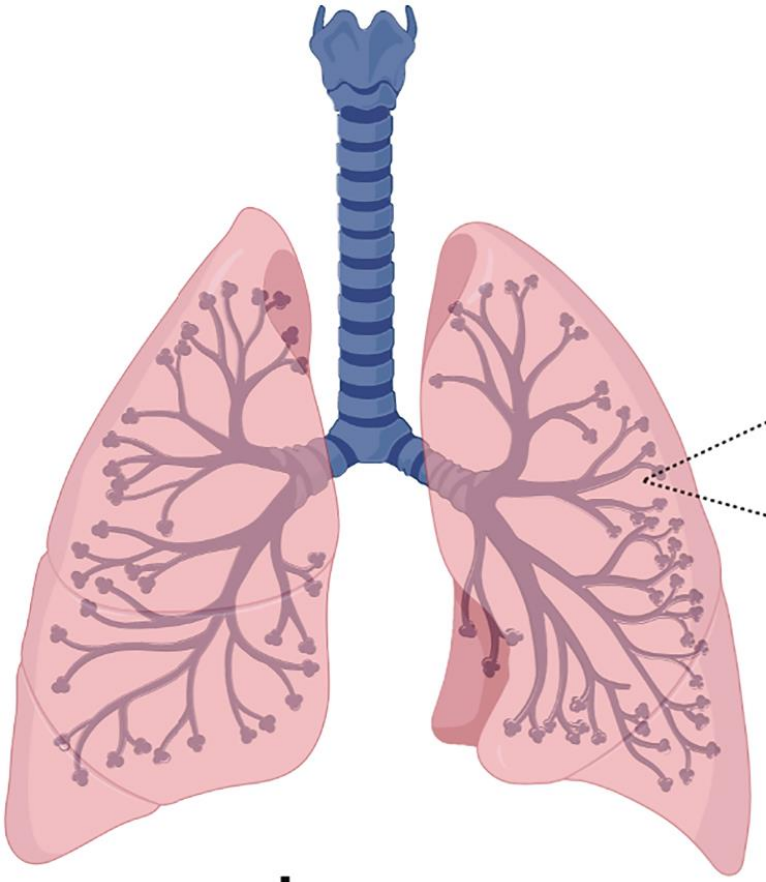
benjamin.abramoff@pennmedicine.upenn.edu (B.A.A.), cherrys@pennmedicine.upenn.edu (S.C.), thaiss@pennmedicine.upenn.edu (C.A.T.), maayanle@pennmedicine.upenn.edu (M.L.)

In brief

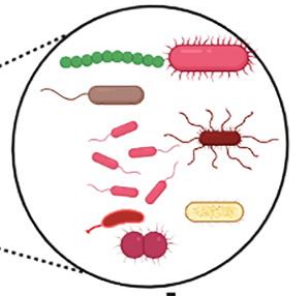
Post-viral syndromes are associated with serotonin reduction, which may contribute to the neurological and cognitive symptoms seen in individuals with Long COVID.

Highlights

- Long COVID is associated with reduced circulating serotonin levels



Lungs



Microbiome

Lung disease
- High microbial density
- Low microbial diversity

Healthy lung
- Low microbial density
- High microbial diversity

Microbiome roles
- Prevents from infection/inflammation
- Immunity development
- Activates immune cells

Lung microbiome and coronavirus disease 2019 (COVID-19): Possible link and implications. Human Microbiome Journal 17 (2020) 100073

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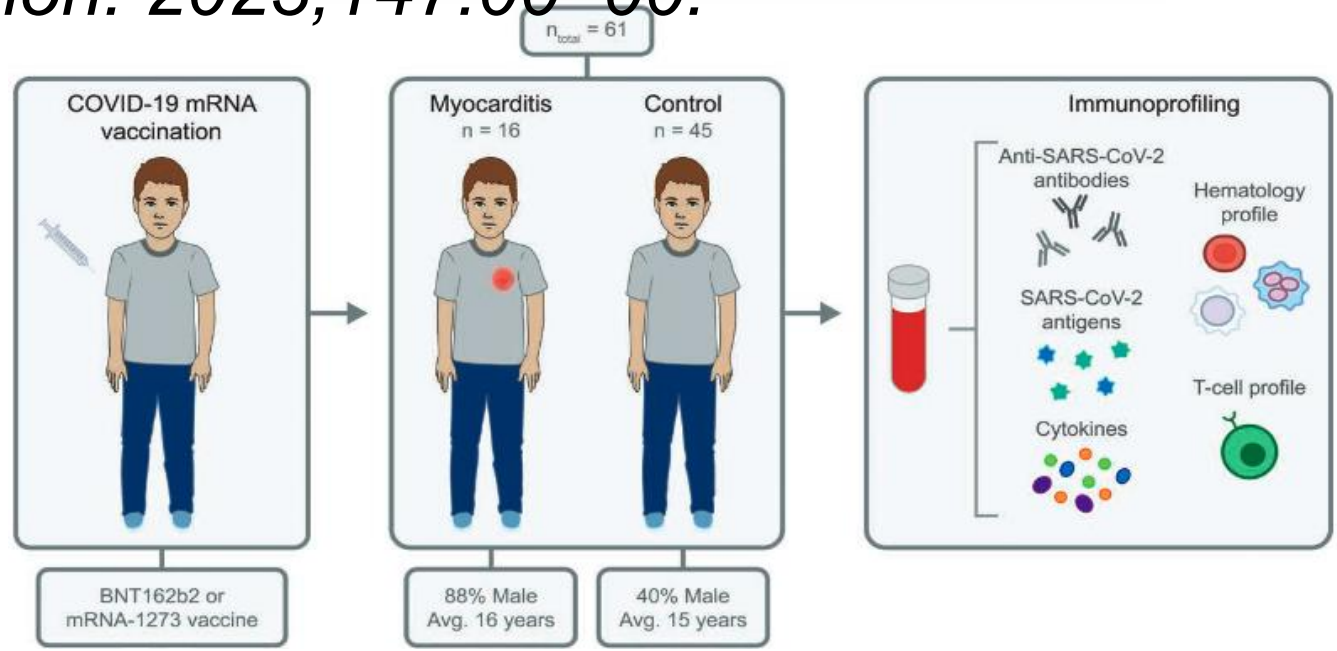
Circulating Spike Protein Detected in Post–COVID-19 mRNA Vaccine Myocarditis

Circulation. 2023;147:00–00.



Das **Immunprofil geimpfter Jugendlicher und junger Erwachsener** zeigte, dass die durch den Impfstoff induzierten **mRNA Immunantworten** zwischen Personen, die eine Myokarditis entwickelten, und Personen, die keine Myokarditis entwickelten, **nicht unterschieden**.

Allerdings wurde freies Spike-Antigen im Blut von Jugendlichen und jungen Erwachsenen nachgewiesen, die nach der mRNA-Impfung eine Myokarditis entwickelten,

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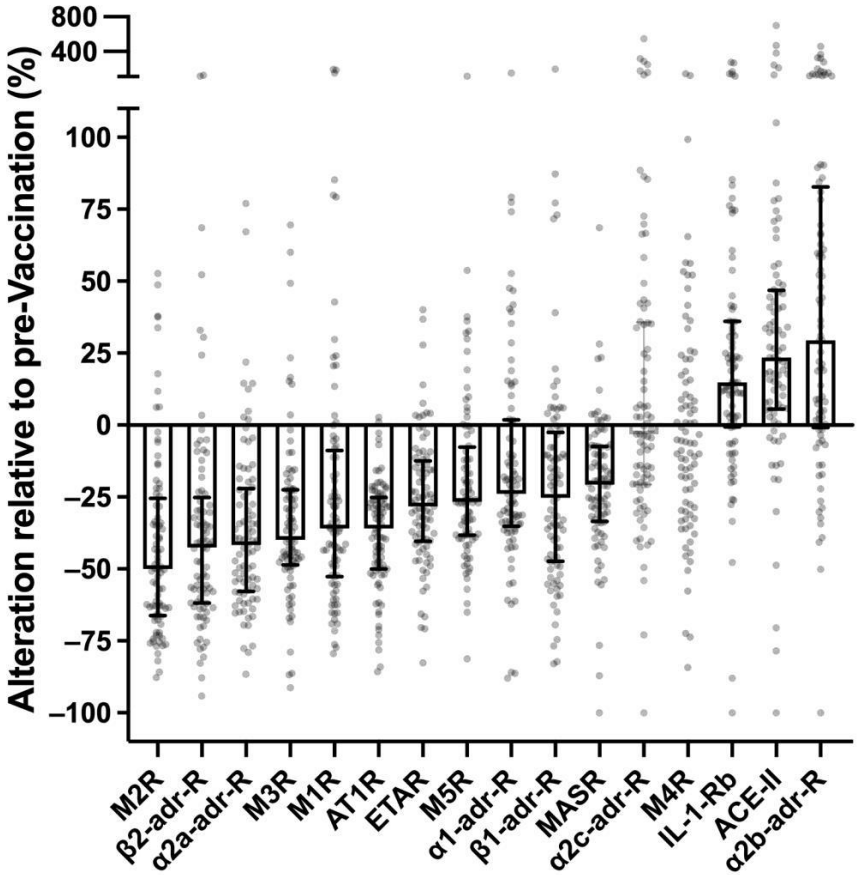

Chronic Fatigue and Dysautonomia following COVID-19 Vaccination Is Distinguished from Normal Vaccination Response by Altered Blood Markers. Vaccines (Basel). 2023 Oct 26;11(11):1642. doi: 10.3390/vaccines11111642.

Bei PACVS schien die serologische Impfantwort signifikant ($p < 0,0001$) verändert zu sein, was eine Unterscheidung vom normalen Zustand nach der Impfung (Sensitivität= 90%, $p < 0,0001$) durch **erhöhte Angiotensin-II-Typ-1-Rezeptor-Antikörper** (Cut-off 10,7 U/mL, ROC-AUC = 0,824 0,027), **verringerte Alpha-2B-Adrenorezeptor-Antikörper** (Cut-off 25,2 U/mL, ROC-AUC = 0,828 0,025) und **erhöhtes IL-6** (Cut-off 2,3 pg/mL, ROC-AUC = 0,850 0,022).

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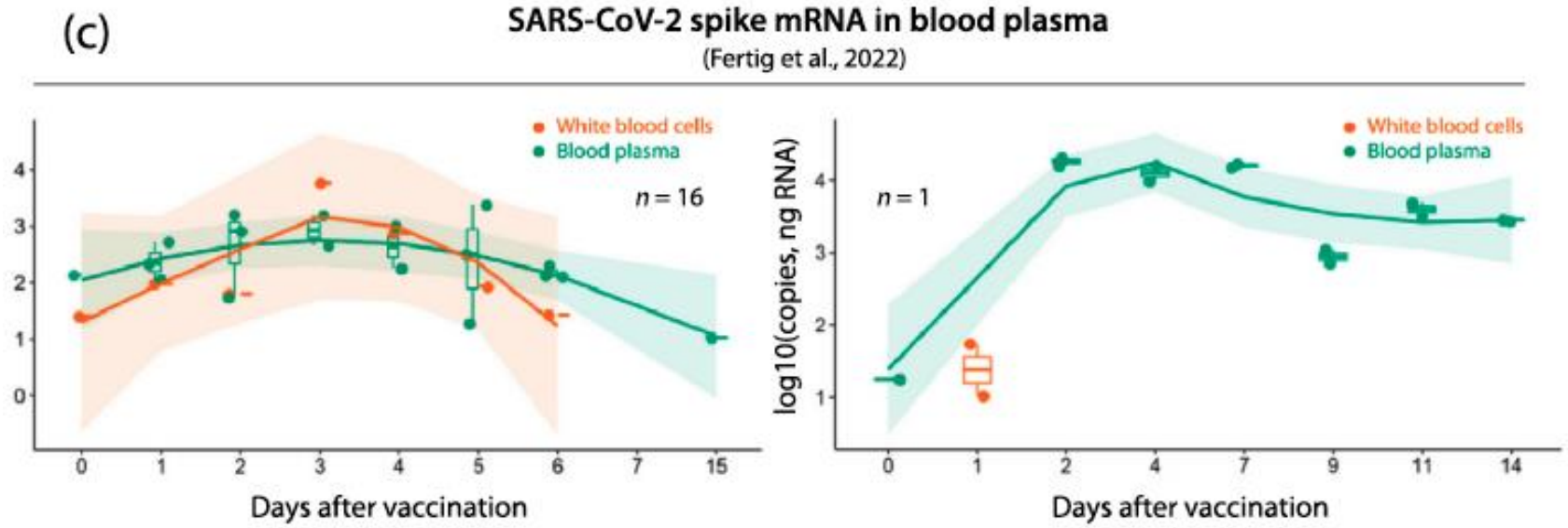

Zirkulierende mRNA im Blut (Plasma und weiße Blutkörperchen) zu verschiedenen Zeitpunkten nach BNT162b2 COVID-19-Impfung. Links ist der Gruppendurchschnitt dargestellt, rechts ein Beispiel von einem einzelnen Individuum.

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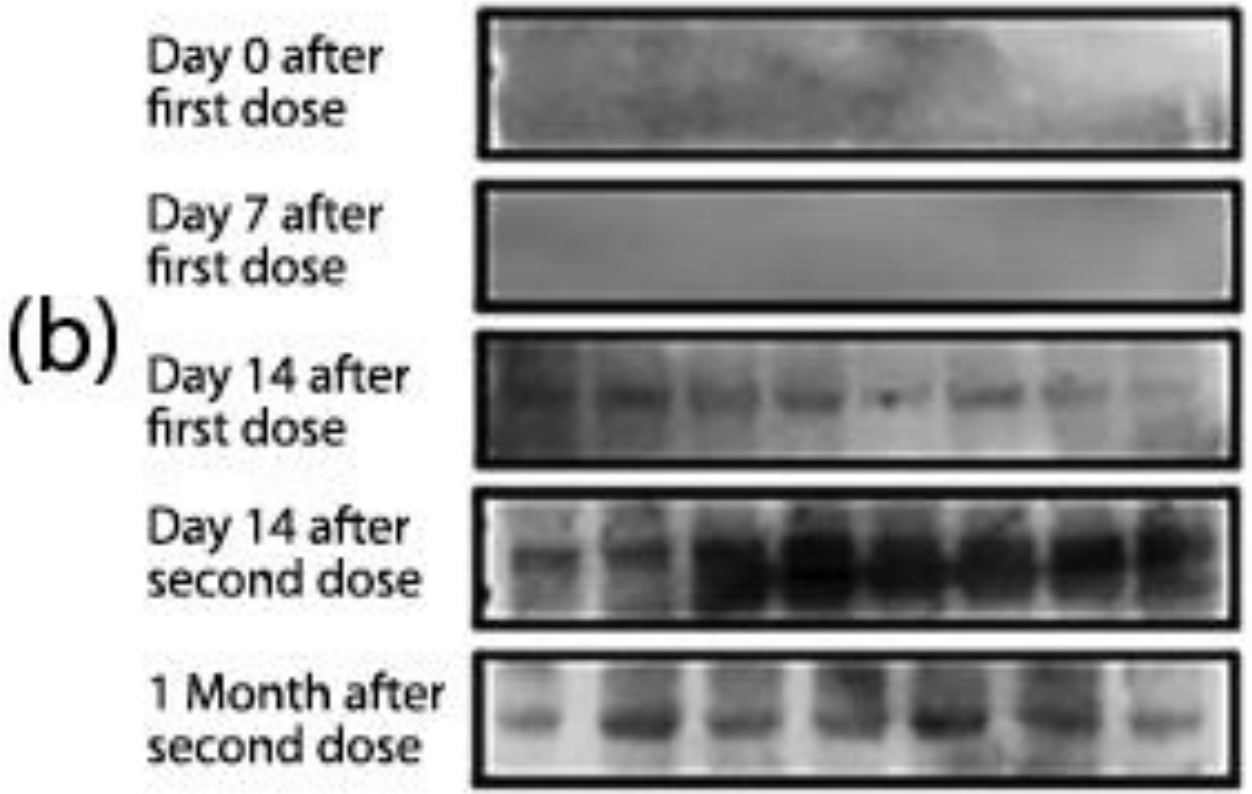
Spike protein S2 subunit in exosomes

(Bansal et al., 2021)



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Was hat Hocher gesagt

- Anders als bei COVID-19 sind bei Post COVID Frauen häufiger betroffen
- Das Post COVID Syndrom betrifft auch das Risiko für ein breites Sprekrtrum von Her-Kreislauferkrankungen
- Es gibt Post COVID Formen mit aktivierten Immunsyste aber auch solche mit inaktivierten Immunsystem
- Beim Post COVID kommr es zum Aufflammen und Neuauftreten von Autoimmunerkrankungen
- Neu aufgetrtene G-Protein-gekoppelte Rezeptor Autoantikörper (GPCR-AAs) spielen eine besondere Rolle in der Pathogenese des Post COVID Syndroms.
- Freies Spike-Protein ist nach Infektion und/oder Impfung lange in Endosomen bei einigen Personen nachweisbar und ist direkt an der Pathogenese von ZNS-Störungen aber auch entzündlichen Reaktionen im Herzen und den Gefäßen beteiligt.

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Covid-Forschung am IMD-Berlin

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SYSTEMATIC REVIEW AND META-ANALYSIS

Comparison of infection risks and clinical outcomes in patients with and without SARS-CoV-2 lung infection under renin–angiotensin–aldosterone system blockade: Systematic review and meta-analysis

Chang Chu[1,2] | Shufei Zeng[1,2] | Ahmed A. Hasan[1,3,4] | Carl-Friedrich Hocher[1] | Bernhard K. Krämer[1,5] | Berthold Hocher[1,6,7,8]

microorganisms

Brief Report

Outliers matter - Correlation between S1 IgG SARS CoV-2 Antibodies and neutralizing SARS CoV-2 Antibodies

Berthold Hocher (MD, PhD)[1,*], Anne Schönbrunn (PhD)[2], Xin Chen (MD)[2], Bernhard K. Krämer(MD, PhD)[1] and Volker von Baehr (MD)[2]

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Impact of hypertension on long-term humoral and cellular response to SARS-CoV-2 infection

Chang Chu[1,2], Anne Schönbrunn[3], Kristin Klemm[1,4], Volker von Baehr[3], Bernhard K. Krämer[1,5,6,7], Saban Elitok[1,4*] and Berthold Hocher[1,3,8,9*]

Clinica Chimica Acta

T-cell proliferation assay for the detection of SARS-CoV-2-specific T-cells

Chang Chu[a,b,1], Anne Schönbrunn[c,1], Saban Elitok[a,d], Florian Kern[e,f], Karsten Schnatbaum[f], Holger Wenschuh[f], Kristin Klemm[a,d], Volker von Baehr[c], Bernhard K. Krämer[a,g,h,i], Berthold Hocher[a,c,j,k,*]

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ABSTRACT

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Vielen Dank!

Fragen ?

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