

Spike Protein pathogenicity research library

Abdi A et al., “Biomed Interaction of SARS-CoV-2 with cardiomyocytes: Insight into the underlying molecular mechanisms of cardiac injury and pharmacotherapy.” *Pharmacother.* 2022;146:112518. doi: [10.1016/j.biopha.2021.112518](https://doi.org/10.1016/j.biopha.2021.112518)

Aboudounya MM and RJ Heads, “COVID-19 and Toll-Like Receptor 4 (TLR4): SARS-CoV-2 May Bind and Activate TLR4 to Increase ACE2 Expression, Facilitating Entry and Causing Hyperinflammation.” *Mediators Inflamm.* 2021;2021:8874339. doi: <https://doi.org/10.1155/2021/8874339>

Acevedo-Whitehouse K and R Bruno, “Potential health risks of mRNA-based vaccine therapy: A hypothesis,” *Med. Hypotheses* 2023, 171: 111015. doi: <https://doi.org/10.1016/j.mehy.2023.111015>

Ahn WM et al., “SARS-CoV-2 Spike Protein Stimulates Macropinocytosis in Murine and Human Macrophages via PKC-NADPH Oxidase Signaling,” *Antioxidants* 2024, 13, 2: 175. doi: <https://doi.org/10.3390/antiox13020175>

Ait-Belkacem I et al., “SARS-CoV-2 spike protein induces a differential monocyte activation that may contribute to age bias in COVID-19 severity,” *Sci. Rep.* 2022, 12: 20824. doi: <https://doi.org/10.1038/s41598-022-25259-2>

Aksenova AY et al., “The increased amyloidogenicity of Spike RBD and pH-dependent binding to ACE2 may contribute to the transmissibility and pathogenic properties of SARS-CoV-2 omicron as suggested by in silico study,” *Int J Mol Sci.* 2022, 23(21): 13502. doi: <https://doi.org/10.3390/ijms232113502>

Al-Kuraishy HM et al., “Changes in the Blood Viscosity in Patients With SARS-CoV-2 Infection.” *Front. Med.* 2022, 9:876017. doi: [10.3389/fmed.2022.876017](https://doi.org/10.3389/fmed.2022.876017)

Al-Kuraishy HM et al., “Hemolytic anemia in COVID-19.” *Ann. Hematol.* 2022;101:1887–1895. doi: [10.1007/s00277-022-04907-7](https://doi.org/10.1007/s00277-022-04907-7)

Albornoz EA et al., “SARS-CoV-2 drives NLRP3 inflammasome activation in human microglia through spike protein,” *Mol. Psychiatr.* (2023) 28: 2878–2893. Doi: <https://doi.org/10.1038/s41380-022-01831-0>

Aleem A and Ahmed Nadeem, *Coronavirus (COVID-19) Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)* (Treasure Island, FL: StatPearls, January, 2023)

Almehdhi AM et al., “SARS-CoV-2 Spike Protein: Pathogenesis, Vaccines, and Potential Therapies,” *Infection* 49, no. 5 (October 2021): 855–876, doi: <https://doi.org/10.1007/s15010-021-01677-8>

Angeli F et al., “COVID-19, vaccines and deficiency of ACE2 and other angiotensinases. Closing the loop on the ‘Spike effect’.” *Eur J. Intern. Med.* 2022;103:23–28. doi: [10.1016/j.ejim.2022.06.015](https://doi.org/10.1016/j.ejim.2022.06.015)

Angeli F et al., “The spike effect of acute respiratory syndrome coronavirus 2 and coronavirus disease 2019 vaccines on blood pressure,” *Eur J Intern Med.* 2023 Mar;109:12-21. doi: [10.1016/j.ejim.2022.12.004](https://doi.org/10.1016/j.ejim.2022.12.004)

Ao Z et al., “SARS-CoV-2 Delta spike protein enhances the viral fusogenicity and inflammatory cytokine production.” *iScience* 2022, 25, 8: 104759. doi: [10.1016/j.isci.2022.104759](https://doi.org/10.1016/j.isci.2022.104759)

Appelbaum K et al., “SARS-CoV-2 spike-dependent platelet activation in COVID-19 vaccine-induced thrombocytopenia.” *Blood Adv.* 2022 no. 6: 2250–2253. doi: [10.1182/bloodadvances.2021005050](https://doi.org/10.1182/bloodadvances.2021005050)

Arjsri P et al., “Hesperetin from root extract of *Clerodendrum petasites* S. Moore inhibits SARS-CoV-2 spike protein S1 subunit-induced Nlrp3 inflammasome in A549 lung cells via modulation of the Akt/Mapk/Ap-1 pathway,” *Int. J. Mol. Sci.* 2022, 23, 18: 10346. doi: <https://doi.org/10.3390/ijms231810346>

Asandei A et al., “Non-Receptor-Mediated Lipid Membrane Permeabilization by the SARS-CoV-2 Spike Protein S1 Subunit.” *ACS Appl. Mater. Interfaces* 2020, 12, 50: 55649–55658. doi: <https://doi.org/10.1021/acsami.0c17044>

Avolio E et al., “The SARS-CoV-2 Spike Protein Disrupts Human Cardiac Pericytes Function through CD147 Receptor-Mediated Signalling: A Potential Non-infective Mechanism of COVID-19 Microvascular Disease,” *Clinical Science* 135, no. 24. (December 22, 2021): 2667–2689, doi: <https://doi.org/10.1042/CS20210735>

Baldari CT et al., “Emerging Roles of SARS-CoV-2 Spike-ACE2 in Immune Evasion and Pathogenesis,” *Trends in Immunology* 44 no. 6 (June 2023), doi: <https://doi.org/10.1016/j.it.2023.04.001>

Balzanelli MG et al., “The Role of SARS-CoV-2 Spike Protein in Long-term Damage of Tissues and Organs, the Underestimated Role of Retrotransposons and Stem Cells, a Working Hypothesis,” *Endocr Metab Immune Disord Drug Targets* 2025, 25, 2: 85-98. doi: [10.2174/0118715303283480240227113401](https://doi.org/10.2174/0118715303283480240227113401)

Barhoumi T et al., “SARS-CoV-2 coronavirus Spike protein-induced apoptosis, inflammatory, and oxidative stress responses in THP-1-like-macrophages: potential role of angiotensin-converting enzyme inhibitor (perindopril),” *Front Immunol.* 2021, 12: 728896. doi: <https://doi.org/10.3389/fimmu.2021.728896>

Barreda D et al., “SARS-CoV-2 Spike Protein and Its Receptor Binding Domain Promote a Proinflammatory Activation Profile on Human Dendritic Cells,” *Cells* (2021) 10, 12: 3279. doi: <https://doi.org/10.3390/cells10123279>

Baumeier C et al., “Intramyocardial Inflammation after COVID-19 Vaccination: An Endomyocardial Biopsy-Proven Case Series.” *Int. J. Mol. Sci.* 2022;23:6940. doi: <https://doi.org/10.3390/ijms23136940>

Bellavite P et al., “Immune response and molecular mechanisms of cardiovascular adverse effects of spike proteins from SARS-coV-2 and mRNA vaccines,” *Biomedicines* 2023, 11, 2: 451. doi: <https://doi.org/10.3390/biomedicines11020451>

Bhargavan B and GD Kanmogne, “SARS-CoV-2 spike proteins and cell–cell communication inhibits TFPI and induces thrombogenic factors in human lung microvascular endothelial cells and neutrophils: implications for COVID-19 coagulopathy pathogenesis,” *Int. J. Mol. Sci.* 2022, 23, 18: 10436. doi: <https://doi.org/10.3390/ijms231810436>

Bhattacharyya S and JK Tobacman, “SARS-CoV-2 spike protein-ACE2 interaction increases carbohydrate sulfotransferases and reduces N-acetylgalactosamine-4-sulfatase by p38 MAPK,” *Signal Transduct Target Ther* 2024, 9, 39. doi: <https://doi.org/10.1038/s41392-024-01741-3>

Biancatelli RMLC, et al. “The SARS-CoV-2 spike protein subunit S1 induces COVID-19-like acute lung injury in Kappa18-hACE2 transgenic mice and barrier dysfunction in human endothelial cells.” *Am. J. Physiol. Lung Cell. Mol. Physiol.* 2021, 321, L477–L484. doi: <https://doi.org/10.1152/ajplung.00223.2021>

Biering SB et al., “SARS-CoV-2 Spike Triggers Barrier Dysfunction and Vascular Leak via Integrins and TGF- β Signaling,” *Nat. Commun.* 2022, 13: 7630. doi: <https://doi.org/10.1038/s41467-022-34910-5>

Bocquet-Garcon A, “Impact of the SARS-CoV-2 Spike Protein on the Innate Immune System: A Review,” *Cureus* 2024, 16(3): e57008. doi: [10.7759/cureus.57008](https://doi.org/10.7759/cureus.57008)

- Boretti A. "PQQ Supplementation and SARS-CoV-2 Spike Protein-Induced Heart Inflammation," *Nat. Prod. Commun.* 2022, 17, 1934578x221080929. doi: <https://doi.org/10.1177/1934578X221080929>
- Bortolotti D et al., "SARS-CoV-2 Spike 1 Protein Controls Natural Killer Cell Activation via the HLA-E/NKG2A Pathway," *Cells* 2020, 9(9), 1975. doi: <https://doi.org/10.3390/cells9091975>
- Boschi C et al., "SARS-CoV-2 Spike Protein Induces Hemagglutination: Implications for COVID-19 Morbidities and Therapeutics and for Vaccine Adverse Effects," *International Journal of Biological Macromolecules* 23, no. 24 (2022): 15480, doi: <https://doi.org/10.3390/ijms232415480>
- Braga L et al., "Drugs that inhibit TMEM16 proteins block SARS-CoV-2 spike-induced syncytia," *Nature* 2021, 594:88–93. doi: <https://doi.org/10.1038/s41586-021-03491-6>
- Buoninfante A et al., "Myocarditis associated with COVID-19 vaccination," *npj Vaccines* 2024, 122. doi: <https://doi.org/10.1038/s41541-024-00893-1>
- Burkhardt A. "Pathology Conference: Vaccine-Induced Spike Protein Production in the Brain, Organs etc., now Proven." Report24.news. 2022, <https://report24.news/pathologie-konferenz-impfinduzierte-spike-produktion-in-gehirn-u-a-organen-nun-erwiesen/>
- Burnett FN et al., "SARS-CoV-2 Spike Protein Intensifies Cerebrovascular Complications in Diabetic hACE2 Mice through RAAS and TLR Signaling Activation," *Int. J. Mol. Sci.* 2023, 24(22): 16394. doi: <https://doi.org/10.3390/ijms242216394>
- Buzhdygan TP et al., "The SARS-CoV-2 Spike Protein Alters Barrier Function in 2D Static and 3D Microfluidic in-Vitro Models of the Human Blood-Brain Barrier," *Neurobiol. Dis.* 2020, 146, 105131. doi: <https://doi.org/10.1016/j.nbd.2020.105131>
- Bye AP et al., "Aberrant glycosylation of anti-SARS-CoV-2 spike IgG is a prothrombotic stimulus for platelets," *Blood* 2021, 138, 6: 1481–9. doi: <https://doi.org/10.1182/blood.2021011871>
- Cao JB et al., "Mast cell degranulation-triggered by SARS-CoV-2 induces tracheal-bronchial epithelial inflammation and injury," *Virolog. Sin.* 2024, 39, 2: 309-318. doi: <https://doi.org/10.1016/j.virs.2024.03.001>
- Cao S et al., "Spike Protein Fragments Promote Alzheimer's Amyloidogenesis," *ACS Appl. Mater. Interfaces* (2023), 15, 34: 40317-40329. doi: <https://doi.org/10.1021/acsami.3c09815>
- Cao X et al., "Spike protein of SARS-CoV-2 activates macrophages and contributes to induction of acute lung inflammation in male mice," *FASEB J.* 2021, 35, e21801. doi: <https://doi.org/10.1096/fj.202002742RR>
- Cao X et al., "The SARS-CoV-2 spike protein induces long-term transcriptional perturbations of mitochondrial metabolic genes, causes cardiac fibrosis, and reduces myocardial contractile in obese mice." *Mol. Metab.* (2023) 74, 101756. doi: <https://doi.org/10.1016/j.molmet.2023.101756>
- Caohuy H et al., "Inflammation in the COVID-19 airway is due to inhibition of CFTR signaling by the SARS-CoV-2 spike protein," *Sci. Rep.* 2024, 14: 16895. doi: <https://doi.org/10.1038/s41598-024-66473-4>
- Carnevale R et al., "Toll-Like Receptor 4-Dependent Platelet-Related Thrombosis in SARS-CoV-2 Infection," *Circulation Research* 132, no. 3 (2023): 290– 305, doi: <https://doi.org/10.1161/CIRCRESAHA.122.321541>

Cattin-Ortolá J et al., "Sequences in the cytoplasmic tail of SARS-CoV-2 Spike facilitate expression at the cell surface and syncytia formation." *Nat Commun* 2021, 12, 1: 5333. doi: <https://doi.org/10.1038/s41467-021-25589-1>

Chang MH et al., "SARS-CoV-2 Spike Protein 1 Causes Aggregation of α -Synuclein via Microglia-Induced Inflammation and Production of Mitochondrial ROS: Potential Therapeutic Applications of Metformin," *Biomedicines* 2024 May 31;12(6):1223. doi: <https://doi.org/10.3390/biomedicines12061223>

Chaves JCS et al., "Differential Cytokine Responses of APOE3 and APOE4 Blood-brain Barrier Cell Types to SARS-CoV-2 Spike Proteins," *J. Neuroimmune Pharmacol.* 2024, 19, 22. doi: <https://doi.org/10.1007/s11481-024-10127-9>

Cheng MH et al., "Superantigenic character of an insert unique to SARS-CoV-2 spike supported by skewed TCR repertoire in patients with hyperinflammation," *Proc Natl Acad Sci* 2020, 117: 25254–25262. doi: <https://doi.org/10.1073/pnas.201072211>

Chiok K et al., "Proinflammatory Responses in SARS-CoV-2 and Soluble Spike Glycoprotein S1 Subunit Activated Human Macrophages," *Viruses* 2023, 15, 3: 754. doi: <https://doi.org/10.3390/v15030754>

Chittasupho C et al., "Inhibition of SARS-CoV-2-Induced NLRP3 Inflammasome-Mediated Lung Cell Inflammation by Triphala-Loaded Nanoparticle Targeting Spike Glycoprotein S1," *Pharmaceutics* 2024, 16, 6: 751. <https://doi.org/10.3390/pharmaceutics16060751>

Chittasupho C et al., "Targeting spike glycoprotein S1 mediated by NLRP3 inflammasome machinery and the cytokine releases in A549 lung epithelial cells by nanocurcumin," *Pharmaceuticals (Basel)* 2023, 16, 6: 862. doi: <https://doi.org/10.3390/ph16060862>

Choi JY et al., "SARS-CoV-2 spike S1 subunit protein-mediated increase of beta-secretase 1 (BACE1) impairs human brain vessel cells," *Biochem. Biophys. Res. Commun.* 2022, 625, 20: 66-71. doi: <https://doi.org/10.1016/j.bbrc.2022.07.113>

Clemens DJ et al., "SARS-CoV-2 spike protein-mediated cardiomyocyte fusion may contribute to increased arrhythmic risk in COVID-19," *PLoS One* 2023, 18(3): e0282151. doi: <https://doi.org/10.1371/journal.pone.0282151>

Clough E et al., "Mitochondrial Dynamics in SARS-COV2 Spike Protein Treated Human Microglia: Implications for Neuro-COVID," *Journal of Neuroimmune Pharmacology* 16, no. 4 (December 2021): 770–784, doi: <https://doi.org/10.1007/s11481-021-10015-6>

Correa Y et al., "SARS-CoV-2 spike protein removes lipids from model membranes and interferes with the capacity of high-density lipoprotein to exchange lipids," *J. Colloid Interface Sci.* (2021) 602: 732-739. doi: <https://doi.org/10.1016/j.jcis.2021.06.056>

"Coronavirus Spike Protein Activated Natural Immune Response, Damaged Heart Muscle Cells," *DAIC*, July 27, 2022, <https://www.dicardiology.com/content/coronavirus-spike-protein-activated-natural-immune-response-damaged-heart-muscle-cells>

Corpetti C et al., "Cannabidiol inhibits SARS-Cov-2 spike (S) protein-induced cytotoxicity and inflammation through a PPAR γ -dependent TLR4/NLRP3/Caspase-1 signaling suppression in Caco-2 cell line." *Phytother. Res.* 2021, 35, 12: 6893–6903. doi: <https://doi.org/10.1002/ptr.7302>

Cory TJ et al., "Metformin Suppresses Monocyte Immunometabolic Activation by SARS-CoV-2 Spike Protein Subunit 1," *Front. Immunol. Sec. Cytokines and Soluble Mediators in Immunity*, 2021, 12: 733921. doi: <https://doi.org/10.3389/fimmu.2021.733921>

Cosentino M and Franca Marino, "Understanding the Pharmacology of COVID- 19 mRNA Vaccines: Playing Dice with the Spike?" *International Journal of Molecular Sciences* 23, no. 18 (September 17, 2022): 10881, doi: <https://doi.org/10.3390/ijms231810881>

Cossenza LC et al., "Inhibitory effects of SARS-CoV-2 spike protein and BNT162b2 vaccine on erythropoietin-induced globin gene expression in erythroid precursor cells from patients with β -thalassemia," *Exp. Hematol.* 2024, 129, 104128. doi: <https://doi.org/10.1016/j.exphem.2023.11.002>

Craddock V et al., "Persistent circulation of soluble and extracellular vesicle-linked Spike protein in individuals with postacute sequelae of COVID-19." *J Med. Virol.* 2023 Feb;95(2):e28568. doi: <https://doi.org/10.1002/jmv.28568>

Das T et al., "N-glycosylation of the SARS-CoV-2 spike protein at Asn331 and Asn343 is involved in spike-ACE2 binding, virus entry, and regulation of IL-6," *Microbiol. Immunol.* 2024, 68, 5: 165-178. doi: <https://doi.org/10.1111/1348-0421.13121>

De Michele M et al., "Evidence of SARS-CoV-2 Spike Protein on Retrieved Thrombi from COVID-19 Patients," *Journal of Hematology Oncology* 2022, 15, 108, doi: <https://doi.org/10.1186/s13045-022-01329-w>

De Michele M et al., "Vaccine-induced immune thrombotic thrombocytopenia: a possible pathogenic role of ChAdOx1 nCoV-19 vaccine-encoded soluble SARS-CoV-2 spike protein," *Haematologica* 2022, 107, 7: 1687–92. <https://doi.org/10.3324/haematol.2021.280180>

De Sousa PMB et al., "Fatal Myocarditis following COVID-19 mRNA Immunization: A Case Report and Differential Diagnosis Review," *Vaccines* 2024, 12, 2: 194. doi: <https://doi.org/10.3390/vaccines12020194>

Del Re A et al., "Intranasal delivery of PEA-producing *Lactobacillus paracasei* F19 alleviates SARS-CoV-2 spike protein-induced lung injury in mice," *Transl. Med. Commun.* 2024, 9, 9. doi: <https://doi.org/10.1186/s41231-024-00167-x>

Del Re A et al., "Ultramicronized Palmitoylethanolamide Inhibits NLRP3 Inflammasome Expression and Pro-Inflammatory Response Activated by SARS-CoV-2 Spike Protein in Cultured Murine Alveolar Macrophages." *Metabolites* 2021, 11, 9: 592. doi: <https://doi.org/10.3390/metabo11090592>

DeOre BJ et al., "SARS-CoV-2 Spike Protein Disrupts Blood-Brain Barrier Integrity via RhoA Activation," *J Neuroimmune Pharmacol.* 2021 Dec;16(4):722-728. Doi: <https://doi.org/10.1007/s11481-021-10029-0>

Devaux CA and L. Camoin-Jau, "Molecular mimicry of the viral spike in the SARS-CoV-2 vaccine possibly triggers transient dysregulation of ACE2, leading to vascular and coagulation dysfunction similar to SARS-CoV-2 infection," *Viruses* 2023, 15, 5: 1045. doi: <https://doi.org/10.3390/v15051045>

Dissook S et al., "Luteolin-rich fraction from *Perilla frutescens* seed meal inhibits spike glycoprotein S1 of SARS-CoV-2-induced NLRP3 inflammasome lung cell inflammation via regulation of JAK1/STAT3 pathway: A potential anti-inflammatory compound against inflammation-induced long-COVID," *Front. Med.* 2023, 9: 1072056. doi: <https://doi.org/10.3389/fmed.2022.1072056>

Duarte C., "Age-dependent effects of the recombinant spike protein/SARS-CoV-2 on the M-CSF- and IL-34-differentiated macrophages in vitro." *Biochem. Biophys. Res. Commun.* 2021, 546: 97–102. doi: <https://doi.org/10.1016/j.bbrc.2021.01.104>

Erdogan MA, "Prenatal SARS-CoV-2 Spike Protein Exposure Induces Autism-Like Neurobehavioral Changes in Male Neonatal Rats," *J Neuroimmune Pharmacol.* 2023 Dec;18(4):573-591. doi: [10.1007/s11481-023-10089-4](https://doi.org/10.1007/s11481-023-10089-4)

Fajloun Z et al., "SARS-CoV-2 or Vaccinal Spike Protein can Induce Mast Cell Activation Syndrome (MCAS)," *Infect Disord Drug Targets*, 2025, 25, 1: e300424229561. doi: [10.2174/0118715265319896240427045026](https://doi.org/10.2174/0118715265319896240427045026)

Ferrer MD et al., "Nitrite Attenuates the In Vitro Inflammatory Response of Immune Cells to the SARS-CoV-2 S Protein without Interfering in the Antioxidant Enzyme Activation," *Int. J. Mol. Sci.* 2024, 25, 5: 3001. <https://doi.org/10.3390/ijms25053001>

Fontes-Dantas FL, "SARS-CoV-2 Spike Protein Induces TLR4-Mediated Long-Term Cognitive Dysfunction Recapitulating Post-COVID-19 Syndrome in Mice," *Cell Reports* 42, no. 3 (March 2023):112189, doi: <https://doi.org/10.1016/j.celrep.2023.112189>

Forsyth CB et al., "The SARS-CoV-2 S1 spike protein promotes MAPK and NF- κ B activation in human lung cells and inflammatory cytokine production in human lung and intestinal epithelial cells," *Microorganisms* 2022, 10, 10: 1996. doi: <https://doi.org/10.3390/microorganisms10101996>

Forte E, "Circulating spike protein may contribute to myocarditis after COVID-19 vaccination," *Nat. Cardiovasc. Res.* 2023, 2: 100. doi: <https://doi.org/10.1038/s44161-023-00222-0>

Frank MG et al., "SARS-CoV-2 S1 subunit produces a protracted priming of the neuroinflammatory, physiological, and behavioral responses to a remote immune challenge: A role for corticosteroids," *Brain Behav. Immun.* (October 2024) 121: 87-103. doi: <https://doi.org/10.1016/j.bbi.2024.07.034>

Frank MG et al., "SARS-CoV-2 Spike S1 Subunit Induces Neuroinflammatory, Microglial and Behavioral Sickness Responses: Evidence of PAMP-Like Properties," *Brain Behav. Immun.* 100 (February 2022): 267277, doi: <https://doi.org/10.1016/j.bbi.2021.12.007>

Freeborn J, "Misfolded Spike Protein Could Explain Complicated COVID-19 Symptoms," *Medical News Today*, May 26, 2022, <https://www.medicalnewstoday.com/articles/misfolded-spike-protein-could-explain-complicated-covid-19-symptoms>

Freitas RS et al., "SARS-CoV-2 Spike antagonizes innate antiviral immunity by targeting interferon regulatory factor 3," *Front Cell Infect Microbiol.* 2021, 11: 789462. doi: <https://doi.org/10.3389/fcimb.2021.789462>

Frühbeck G et al., "FNDC4 and FNDC5 reduce SARS-CoV-2 entry points and spike glycoprotein S1-induced pyroptosis, apoptosis, and necroptosis in human adipocytes." *Cell Mol Immunol.* 2021;18(10):2457–9. doi: <https://doi.org/10.1038/s41423-021-00762-0>

Gamblicher T et al., "SARS-CoV-2 spike protein is present in both endothelial and eccrine cells of a chilblain-like skin lesion," *J Eur Acad Dermatol Venereol.* 2020, 1, 10: e187-e189. doi: <https://doi.org/10.1111/jdv.16970>

Gao X et al., "Spike-Mediated ACE2 Down-Regulation Was Involved in the Pathogenesis of SARS-CoV-2 Infection," *Journal of Infection* 85, no. 4 (October 2022), 418–427, doi: [10.1016/j.jinf.2022.06.030](https://doi.org/10.1016/j.jinf.2022.06.030)

Gasparello J et al., "Sulforaphane inhibits the expression of interleukin-6 and interleukin-8 induced in bronchial epithelial IB3-1 cells by exposure to the SARS-CoV-2 Spike protein," *Phytomedicine* 2021, 87: 153583. doi: <https://doi.org/10.1016/j.phymed.2021.153583>

Gawaz A et al., "SARS-CoV-2-Induced Vasculitic Skin Lesions Are Associated with Massive Spike Protein Depositions in Autophagosomes," *J Invest Dermatol.* 2024, 144, 2: 369-377.e4. doi: <https://doi.org/10.1016/j.jid.2023.07.018>

Ghazanfari D et al., "Mechanistic insights into SARS-CoV-2 spike protein induction of the chemokine CXCL10," *Sci. Rep.* 2024, 14: 11179. doi: <https://doi.org/10.1038/s41598-024-61906-6>

Golob-Schwarzl N et al., "SARS-CoV-2 spike protein functionally interacts with primary human conjunctival epithelial cells to induce a pro-inflammatory response," *Eye* 2022, 36: 2353–5. doi: <https://doi.org/10.1038/s41433-022-02066-7>

Gracie NP et al., "Cellular signalling by SARS-CoV-2 spike protein," *Microbiology Australia* 2024, 45, 1: 13-17. doi: <https://doi.org/10.1071/MA24005>

Greenberger JS et al., "SARS-CoV-2 Spike Protein Induces Oxidative Stress and Senescence in Mouse and Human Lung," *In Vivo* 2024, 38, 4: 1546-1556; doi: <https://doi.org/10.21873/invivo.13605>

Grishma K and Das Sarma, "The Role of Coronavirus Spike Protein in Inducing Optic Neuritis in Mice: Parallels to the SARS-CoV-2 Virus," *J Neuroophthalmol* 2024, 44, 3: 319-329. Doi: [10.1097/WNO.0000000000002234](https://doi.org/10.1097/WNO.0000000000002234)

Grobbelaar LM et al., "SARS-CoV-2 Spike Protein S1 Induces Fibrin(ogen) Resistant to Fibrinolysis: Implications for Microclot Formation in COVID-19," *Bioscience Reports* 41, no. 8 (August 27, 2021): BSR20210611, doi: <https://doi.org/10.1042/BSR20210611>

Gu T et al., "Cytokine Signature Induced by SARS-CoV-2 Spike Protein in a Mouse Model." *Front. Immunol.*, 27 January 2021 Sec. Inflammation. doi: <https://doi.org/10.3389/fimmu.2020.621441>

Guo X et al., "Regulation of proinflammatory molecules and tissue factor by SARS-CoV-2 spike protein in human placental cells: implications for SARS-CoV-2 pathogenesis in pregnant women." *Front Immunol* 2022, 13: 876555–876555. <https://doi.org/10.3389/fimmu.2022.876555>

Guo Y and V Kanamarlapudi, "Molecular Analysis of SARS-CoV-2 Spike Protein-Induced Endothelial Cell Permeability and vWF Secretion," *Int. J. Mol. Sci.* 2023, 24(6): 5664. <https://doi.org/10.3390/ijms24065664>

Gussow AB et al., "Genomic Determinants of Pathogenicity in SARS-CoV-2 and Other Human Coronaviruses," *PNAS* 117, no. 26 (June 10, 2020): 15193–15199, <https://doi.org/10.1073/pnas.2008176117>

Halma MTJ et al., "Exploring autophagy in treating SARS-CoV-2 spike protein-related pathology," *Endocrinol Metab (EnM)* 2024, 14: 100163. doi: <https://doi.org/10.1016/j.endmts.2024.100163>

Halma MTJ et al., "Strategies for the Management of Spike Protein-Related Pathology," *Microorganisms* 11, no. 5 (May 20, 2023): 1308, doi: <https://doi.org/10.3390/microorganisms11051308>

Heath SP et al., "SARS-CoV-2 Spike Protein Exacerbates Thromboembolic Cerebrovascular Complications in Humanized ACE2 Mouse Model," *Transl Stroke Res.* (2024) doi: <https://doi.org/10.1007/s12975-024-01301-5>

Heil M, "Self-DNA driven inflammation in COVID-19 and after mRNA-based vaccination: lessons for non-COVID-19 pathologies," *Front. Immunol.*, 2023, 14. doi: <https://doi.org/10.3389/fimmu.2023.1259879>

Huang X et al., "Sars-Cov-2 Spike Protein-Induced Damage of hiPSC-Derived Cardiomyocytes." *Adv. Biol.* 2022, 6, 7: e2101327. doi: <https://doi.org/10.1002/adbi.202101327>

Hulscher N et al., "Autopsy findings in cases of fatal COVID-19 vaccine-induced myocarditis," *ESC Heart Failure* 2024. doi: <https://doi.org/10.1002/ehf2.14680>

Huynh TV et al., "Spike Protein Impairs Mitochondrial Function in Human Cardiomyocytes: Mechanisms Underlying Cardiac Injury in COVID-19." *Cells* 2023, 12, 877. doi: <https://doi.org/10.3390/cells12060877>

Huynh TV et al., "Spike Protein of SARS-CoV-2 Activates Cardiac Fibrogenesis through NLRP3 Inflammasomes and NF- κ B Signaling," *Cells* 2024, 13, 16: 1331: <https://doi.org/10.3390/cells13161331>

Iba T and JH Levy, "The roles of platelets in COVID-19-associated coagulopathy and vaccine-induced immune thrombotic thrombocytopenia," *Trends Cardiovasc Med.* 2022, 32, 1: 1-9. doi: <https://doi.org/10.1016/j.tcm.2021.08.012>

Idrees D and Vijay Kumar, "SARS-CoV-2 Spike Protein Interactions with Amyloidogenic Proteins: Potential Clues to Neurodegeneration," *Biochemical and Biophysical Research Communications* 2021, 554 : 94–98, doi: <https://doi.org/10.1016/j.bbrc.2021.03.100>

Imig JD, "SARS-CoV-2 spike protein causes cardiovascular disease independent of viral infection," *Clin Sci (Lond)* (2022) 136 (6): 431–434. doi: <https://doi.org/10.1042/CS20220028>

Jana S et al., "Cell-free hemoglobin does not attenuate the effects of SARS-CoV-2 spike protein S1 subunit in pulmonary endothelial cells," *Int. J. Mol. Sci.* 2021, 22, 16: 9041. doi: <https://doi.org/10.3390/ijms22169041>

Jiang Q et al., "SARS-CoV-2 spike S1 protein induces microglial NLRP3-dependent neuroinflammation and cognitive impairment in mice," *Exp. Neurol.* 2025, 383: 115020. doi: <https://doi.org/10.1016/j.expneurol.2024.115020>

Johnson EL et al., "The S1 spike protein of SARS-CoV-2 upregulates the ERK/MAPK signaling pathway in DC-SIGN-expressing THP-1 cells," *Cell Stress Chaperones* 2024, 29, 2: 227-234. doi: <https://doi.org/10.1016/j.cstres.2024.03.002>

Jugler C et al, "SARS-CoV-2 Spike Protein-Induced Interleukin 6 Signaling Is Blocked by a Plant-Produced Anti-Interleukin 6 Receptor Monoclonal Antibody," *Vaccines* 2021, 9, 11): 1365. <https://doi.org/10.3390/vaccines9111365>

Kammala AK et al., "In vitro mRNA-S maternal vaccination induced altered immune regulation at the maternal-fetal interface," *Am. J. Reprod. Immunol.* 2024, 91, 5: e13861. doi: <https://doi.org/10.1111/aji.13861>

Karwaciak I et al., "Nucleocapsid and Spike Proteins of the Coronavirus Sars-Cov-2 Induce Il6 in Monocytes and Macrophages—Potential Implications for Cytokine Storm Syndrome." *Vaccines* 2021, 9(1), 54: 1–10. doi: <https://doi.org/10.3390/vaccines9010054>

Kato Y et al., "TRPC3-Nox2 Protein Complex Formation Increases the Risk of SARS-CoV-2 Spike Protein-Induced Cardiomyocyte Dysfunction through ACE2 Upregulation." *Int. J. Mol. Sci.* 2023, 24, 1: 102. doi: <https://doi.org/10.3390/ijms24010102>

Ken W et al., "Low dose radiation therapy attenuates ACE2 depression and inflammatory cytokines induction by COVID-19 viral spike protein in human bronchial epithelial cells," *Int J Radiat Biol.* 2022, 98, 10:1532-1541. doi: <https://doi.org/10.1080/09553002.2022.2055806>

Khaddaj-Mallat R et al., "SARS-CoV-2 deregulates the vascular and immune functions of brain pericytes via Spike protein." *Neurobiol. Dis.* 2021, 161, 105561. doi: <https://doi.org/10.1016/j.nbd.2021.105561>

Khan S et al., "SARS-CoV-2 Spike Protein Induces Inflammation via TLR2-Dependent Activation of the NF- κ B Pathway," *eLife* 10 (December 6, 2021): e68563, doi: <https://doi.org/10.7554/elife.68563>

Kim ES et al., "Spike Proteins of SARS-CoV-2 Induce Pathological Changes in Molecular Delivery and Metabolic Function in the Brain Endothelial Cells," *Viruses*, 2021, 13(10):2021. doi: <https://doi.org/10.3390/v13102021>

Kim MJ et al., "The SARS-CoV-2 spike protein induces lung cancer migration and invasion in a TLR2-dependent manner," *Cancer Commun* (London), 2023, 44, 2: 273–277. doi: <https://doi.org/10.1002/cac2.12485>

Kim SY et al., "Characterization of heparin and severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) spike glycoprotein binding interactions," *Antivir Res.* 2020, 181: 104873. doi: <https://doi.org/10.1016/j.antiviral.2020.104873>

Kircheis R, "Coagulopathies after Vaccination against SARS-CoV-2 May Be Derived from a Combined Effect of SARS-CoV-2 Spike Protein and Adenovirus Vector-Triggered Signaling Pathways," *Int J Mol Sci* 2021, 22(19): 10791. <https://doi.org/10.3390/ijms221910791>

Kircheis R and O Planz, "Could a Lower Toll-like Receptor (TLR) and NF- κ B Activation Due to a Changed Charge Distribution in the Spike Protein Be the Reason for the Lower Pathogenicity of Omicron?" *Int. J. Mol. Sci.* 2022, 23, 11: 5966. doi: <https://doi.org/10.3390/ijms23115966>

Ko CJ et al., "Discordant anti-SARS-CoV-2 spike protein and RNA staining in cutaneous pernioic lesions suggests endothelial deposition of cleaved spike protein," *J. Cutan Pathol* 2021, 48 (1): 47–52. doi: <https://doi.org/10.1111/cup.13866>

Kowarz E et al., "Vaccine-induced COVID-19 mimicry syndrome," *eLife* (Feb 15 2022), 11:e74974. doi: <https://doi.org/10.7554/eLife.74974>

Kucia M et al. "An evidence that SARS-Cov-2/COVID-19 spike protein (SP) damages hematopoietic stem/progenitor cells in the mechanism of pyroptosis in Nlrp3 inflammasome-dependent manner," *Leukemia* 2021, 35: 3026-3029. doi: <https://doi.org/10.1038/s41375-021-01332-z>

Kuhn CC et al. "Direct Cryo-ET observation of platelet deformation induced by SARS-CoV-2 spike protein," *Nat. Commun.* (2023) 14, 620. doi: <https://doi.org/10.1038/s41467-023-36279-5>

Kulkoviene G et al., "Differential Mitochondrial, Oxidative Stress and Inflammatory Responses to SARS-CoV-2 Spike Protein Receptor Binding Domain in Human Lung Microvascular, Coronary Artery Endothelial and Bronchial Epithelial Cells," *Int. J. Mol. Sci.* 2024, 25, 6: 3188. doi: <https://doi.org/10.3390/ijms25063188>

Kumar N et al., "SARS-CoV-2 spike protein S1-mediated endothelial injury and pro-inflammatory state is amplified by dihydrotestosterone and prevented by mineralocorticoid antagonism". *Viruses* 2021, 13, 11: 2209. Doi: <https://doi.org/10.3390/v13112209>

Kyriakopoulos AM et al., "Mitogen Activated Protein Kinase (MAPK) Activation, p53, and Autophagy Inhibition Characterize the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Spike Protein Induced Neurotoxicity." *Cureus* 2022, 14, 12: e32361. doi: [10.7759/cureus.32361](https://doi.org/10.7759/cureus.32361)

Lazebnik Y, "Cell fusion as a link between the SARS-CoV-2 spike protein, COVID-19 complications, and vaccine side effects," *Oncotarget* 2021, 12(25): 2476-2488. doi: <https://doi.org/10.18632/oncotarget.28088>

Lehmann KJ, "Impact of SARS-CoV-2 Spikes on Safety of Spike-Based COVID-19 Vaccinations," *Immunome Res.* 2024, 20, 2: 1000267. doi: [10.35248/1745-7580.24.20.267](https://doi.org/10.35248/1745-7580.24.20.267)

Lehmann KJ, "SARS-CoV-2-Spike Interactions with the Renin-Angiotensin-Aldosterone System – Consequences of Adverse Reactions of Vaccination." *J Biol Today's World* 2023, 12/4: 001-013. <https://doi.org/10.31219/osf.io/27g5h>

Lehmann KJ, "Suspected Causes of the Specific Intolerance Profile of Spike-Based Covid-19 Vaccines," *Med. Res. Arch* 2024, 12, 9. doi: [10.18103/mra.v12i9.5704](https://doi.org/10.18103/mra.v12i9.5704)

Lei Y et al., "SARS-CoV-2 Spike Protein Impairs Endothelial Function via Downregulation of ACE 2," *Circulation Research* 128, no. 9 (2021): 1323–1326, doi: <https://doi.org/10.1161/CIRCRESAHA.121.318902>

Lesgard JF et al., "Toxicity of SARS-CoV-2 Spike Protein from the Virus and Produced from COVID-19 mRNA or Adenoviral DNA Vaccines." *Arch Microbiol Immun* 2023, 7, 3: 121- 138. doi: [10.26502/ami.936500110](https://doi.org/10.26502/ami.936500110)

Letarov AV et al., "Free SARS-CoV-2 Spike Protein S1 Particles May Play a Role in the Pathogenesis of COVID-19 Infection." *Biochemistry (Moscow)* 2021, 86, 257–261. doi: <https://doi.org/10.1134/S0006297921030032>

Li F et al., "SARS-CoV-2 Spike Promotes Inflammation and Apoptosis Through Autophagy by ROS-Suppressed PI3K/AKT/mTOR Signaling." *Biochim Biophys Acta BBA - Mol Basis Dis* (2021) 1867:166260. doi: 10.1016/j.bbadis.2021.166260. doi: <https://doi.org/10.1016/j.bbadis.2021.166260>

Li K et al., "SARS-CoV-2 Spike protein promotes vWF secretion and thrombosis via endothelial cytoskeleton-associated protein 4 (CKAP4)," *Signal Transduct Targ Ther* (2022) 7, 332. doi: <https://doi.org/10.1038/s41392-022-01183-9>

Li T et al., "Platelets Mediate Inflammatory Monocyte Activation by SARS-CoV-2 Spike Protein," *Journal of Clinical Investigation* 132, no. 4 (February 15, 2022): e150101. doi: [10.1172/JCI150101](https://doi.org/10.1172/JCI150101)

Li Z et al., "SARS-CoV-2 pathogenesis in the gastrointestinal tract mediated by Spike-induced intestinal inflammation," *Precis. Clin. Med.* 2024, 7, 1: pbad034. doi: <https://doi.org/10.1093/pcmedi/pbad034>

Liang S et al., "SARS-CoV-2 spike protein induces IL-18-mediated cardiopulmonary inflammation via reduced mitophagy," *Signal Transduct Target Ther* (2023) 8, 103. doi: <https://doi.org/10.1038/s41392-023-01368-w>

Lin Z, "More than a key—the pathological roles of SARS-CoV-2 spike protein in COVID-19 related cardiac injury." *Sports Med Health Sci* 2023, 6, 3: 209-220. <https://doi.org/10.1016/j.smhs.2023.03.004>

Liu T et al., "RS-5645 attenuates inflammatory cytokine storm induced by SARS-CoV-2 spike protein and LPS by modulating pulmonary microbiota," *Int J Biol Sci.* 2021, 17, 13: 3305–3319. doi: [10.7150/ijbs.63329](https://doi.org/10.7150/ijbs.63329)

Liu X et al., "SARS-CoV-2 spike protein-induced cell fusion activates the cGAS-STING pathway and the interferon response," *Sci Signal.* 2022, 15(729): eabg8744. doi: [10.1126/scisignal.abg8744](https://doi.org/10.1126/scisignal.abg8744)

Loh D, "The potential of melatonin in the prevention and attenuation of oxidative hemolysis and myocardial injury from cd147 SARS-CoV-2 spike protein receptor binding." *Melatonin Research.* 3, 3 (June 2020), 380-416. doi: <https://doi.org/10.32794/mr11250069>

Loh JT et al., "Dok3 restrains neutrophil production of calprotectin during TLR4 sensing of SARS-CoV-2 spike protein," *Front. Immunol.* 2022, 13, Sec. Molecular Innate Immunity. doi: <https://doi.org/10.3389/fimmu.2022.996637>

Lu J and PD Sun, "High affinity binding of SARS-CoV-2 spike protein enhances ACE2 carboxypeptidase activity," *J. Biol. Chem* (December 2020) 295, 52: p18579-18588. doi: [10.1074/jbc.RA120.015303](https://doi.org/10.1074/jbc.RA120.015303)

Luchini A et al., "Lipid bilayer degradation induced by SARS-CoV-2 spike protein as revealed by neutron reflectometry," *Sci. Rep.* (2021) 11: 14867. doi: <https://doi.org/10.1038/s41598-021-93996-x>

Luo Y et al., "SARS-Cov-2 spike induces intestinal barrier dysfunction through the interaction between CEACAM5 and Galectin-9," *Front. Immunol.*, 2024, 15. doi: <https://doi.org/10.3389/fimmu.2024.1303356>

Lykhmus O et al., "Immunization with 674–685 fragment of SARS-Cov-2 spike protein induces neuroinflammation and impairs episodic memory of mice." *Biochem. Biophys. Res. Commun.* 2022, 622: 57–63. doi: <https://doi.org/10.1016/j.bbrc.2022.07.016>

Ma G et al., "SARS-CoV-2 Spike protein S2 subunit modulates γ -secretase and enhances amyloid- β production in COVID-19 neuropathy," *Cell Discov* 8, 99 (2022). doi: <https://doi.org/10.1038/s41421-022-00458-3>

Maeda Y et al., "Differential Ability of Spike Protein of SARS-CoV-2 Variants to Downregulate ACE2," *Int. J. Mol. Sci.* 2024, 25, 2: 1353, <https://doi.org/10.3390/ijms25021353>

Magen E et al., "Clinical and Molecular Characterization of a Rare Case of BNT162b2 mRNA COVID-19 Vaccine-Associated Myositis." *Vaccines*. 2022;10:1135. doi: <https://doi.org/10.3390/vaccines10071135>

Magro N et al., "Disruption of the blood-brain barrier is correlated with spike endocytosis by ACE2 + endothelia in the CNS microvasculature in fatal COVID-19. Scientific commentary on 'Detection of blood-brain barrier disruption in brains of patients with COVID-19, but no evidence of brain penetration by SARS-CoV-2,'" *Acta Neuropathol.* 2024 Feb 27;147(1):47. doi: <https://doi.org/10.1007/s00401-023-02681-y>

Marrone L et al., "Tirofiban prevents the effects of SARS-CoV-2 spike protein on macrophage activation and endothelial cell death," *Heliyon*, (2024) 10, 15: e35341. doi: [10.1016/j.heliyon.2024.e35341](https://doi.org/10.1016/j.heliyon.2024.e35341)

Martinez-Marmol R et al., "SARS-CoV-2 infection and viral fusogens cause neuronal and glial fusion that compromises neuronal activity," *Sci. Adv.* 2023, 9, 23. doi: [10.1126/sciadv.adg2248](https://doi.org/10.1126/sciadv.adg2248)

Matsuzawa Y et al., "Impact of Renin–Angiotensin–Aldosterone System Inhibitors on COVID-19," *Hypertension Research* 45, no. 7 (2022): 1147–1153, doi: <https://doi.org/10.1038/s41440-022-00922-3>

Maugeri N et al., "Unconventional CD147-Dependent Platelet Activation Elicited by SARS-CoV-2 in COVID-19," *Journal of Thrombosis and Haemostasis* 20, no. 2. (October 28, 2021): 434–448, doi: <https://doi.org/10.1111/jth.15575>

Mercado-Gómez M et al., "The spike of SARS-CoV-2 promotes metabolic rewiring in hepatocytes." *Commun. Biol.* 2022, 5, 827. doi: <https://doi.org/10.1038/s42003-022-03789-9>

Meyer K et al., "SARS-CoV-2 Spike Protein Induces Paracrine Senescence and Leukocyte Adhesion in Endothelial Cells," *J. Virol.* 2021, 95, e0079421. doi: <https://doi.org/10.1128/jvi.00794-21>

Miller GM et al., "SARS-CoV-2 and SARS-CoV-2 Spike protein S1 subunit Trigger Proinflammatory Response in Macrophages in the Absence of Productive Infection," *J. Immunol.* 2023, 210 (1_Supplement): 71.30. doi: <https://doi.org/10.4049/jimmunol.210.Supp.71.30>

Mishra R and AC Banerjea, "SARS-CoV-2 Spike targets USP33-IRF9 axis via exosomal miR-148a to activate human microglia." *Front. Immunol.* 2021, 12: 656700. <https://doi.org/10.3389/fimmu.2021.656700>

Mörz M, "A Case Report: Multifocal Necrotizing Encephalitis and Myocarditis after BNT162b2 mRNA Vaccination against COVID-19," *Vaccines* 2022, 10, 10: 1651. doi: <https://doi.org/10.3390/vaccines10101651>

Moutal A et al., "SARS-CoV-2 Spike protein co-opts VEGF-A/Neuropilin-1 receptor signaling to induce analgesia," *Pain* (2020) 162, 1: 243–252. doi: [10.1097/j.pain.0000000000002097](https://doi.org/10.1097/j.pain.0000000000002097)

Munavilli GG et al., "COVID-19/SARS-CoV-2 virus spike protein-related delayed inflammatory reaction to hyaluronic acid dermal fillers: a challenging clinical conundrum in diagnosis and treatment," *Arch. Dermatol. Res.* 2022, 314: 1-15. doi: <https://doi.org/10.1007/s00403-021-02190-6>

Nahalka J, "1-L Transcription of SARS-CoV-2 Spike Protein S1 Subunit," *Int. J. Mol. Sci.* 2024, 25, 8: 4440. doi: <https://doi.org/10.3390/ijms25084440>

Nascimento RR et al., "SARS-CoV-2 Spike protein triggers gut impairment since mucosal barrier to innermost layers: From basic science to clinical relevance," *Mucosal Immunol.* 2024, 17, 4: 565-583. doi: <https://doi.org/10.1016/j.mucimm.2024.03.00>

Nguyen V, "The Spike Protein of SARS-CoV-2 Impairs Lipid Metabolism and Increases Susceptibility to Lipotoxicity: Implication for a Role of Nrf2," *Cells* (2022) 11, 12: 1916. doi: <https://doi.org/10.3390/cells11121916>

Niu C et al., "SARS-CoV-2 spike protein induces the cytokine release syndrome by stimulating T cells to produce more IL-2," *Front. Immunol.* 2024, 15: 1444643. doi: <https://doi.org/10.3389/fimmu.2024.1444643>

Norris B et al., "Evaluation of Glutathione in Spike Protein of SARS-CoV-2 Induced Immunothrombosis and Cytokine Dysregulation," *Antioxidants* 2024, 13, 3: 271. doi: <https://doi.org/10.3390/antiox13030271>

Nunez-Castilla J et al., "Potential autoimmunity resulting from molecular mimicry between SARS-CoV-2 spike and human proteins," *Viruses* 2022, 14 (7): 1415. <https://doi.org/10.3390/v14071415>

Nuovo JG et al., "Endothelial Cell Damage Is the Central Part of COVID-19 and a Mouse Model Induced by Injection of the S1 Subunit of the Spike Protein." *Ann. Diagn. Pathol.* 2021, 51, 151682. doi: <https://doi.org/10.1016/j.anndiagpath.2020.151682>

Nyström S, "Amyloidogenesis of SARS-CoV-2 Spike Protein," *J. Am. Chem. Soc.* 2022, 144, 8945–8950. doi: <https://doi.org/10.1021/jacs.2c03925>

Oh J et al., "SARS-CoV-2 Spike Protein Induces Cognitive Deficit and Anxiety-Like Behavior in Mouse via Non-cell Autonomous Hippocampal Neuronal Death," *Scientific Reports* 12, no. 5496 (2022), doi: <https://doi.org/10.1038/s41598-022-09410-7>

Olajide OA et al., "Induction of Exaggerated Cytokine Production in Human Peripheral Blood Mononuclear Cells by a Recombinant SARS-CoV-2 Spike Glycoprotein S1 and Its Inhibition by Dexamethasone," *Inflammation* (2021) 44: 1865–1877. doi: <https://doi.org/10.1007/s10753-021-01464-5>

Olajide OA et al., "SARS-CoV-2 spike glycoprotein S1 induces neuroinflammation in BV-2 microglia," *Mol. Neurobiol.* 2022; 59:445-458. doi: <https://doi.org/10.1007/s12035-021-02593-6>

Onnis A et al., "SARS-CoV-2 Spike protein suppresses CTL-mediated killing by inhibiting immune synapse assembly," *J Exp Med* (2023) 220 (2): e20220906. doi: <https://doi.org/10.1084/jem.20220906>

Palestra F et al. "SARS-CoV-2 Spike Protein Activates Human Lung Macrophages," *Int. J. Mol. Sci.* 2023, 24, 3: 3036. doi: <https://doi.org/10.3390/ijms24033036>

Pallas RM, "Innate and adaptative immune mechanisms of COVID-19 vaccines. Serious adverse events associated with SARS-CoV-2 vaccination: A systematic review," *Vacunas* (English ed.) 2024, 25, 2: 285.e1-285.e94. doi: <https://doi.org/10.1016/j.vacune.2024.05.002>

Panigrahi S et al., "SARS-CoV-2 Spike Protein Destabilizes Microvascular Homeostasis," *Microbiol Spectr.* 2021 Dec 22;9(3):e0073521. doi: <https://doi.org/10.1128/Spectrum.00735-21>

Park C et al., "Murine alveolar Macrophages Rapidly Accumulate intranasally Administered SARS-CoV-2 Spike Protein leading to neutrophil Recruitment and Damage," *Elife* 12 (2024), p. RP86764. doi: <https://doi.org/10.7554/eLife.86764.3>

Park YJ et al., "D-dimer and CoV-2 spike-immune complexes contribute to the production of PGE2 and proinflammatory cytokines in monocytes," *PLoS Pathog.*, 2022, 18, 4: e1010468. doi: <https://doi.org/10.1371/journal.ppat.1010468>

Park YJ et al., "Pyrogenic and inflammatory mediators are produced by polarized M1 and M2 macrophages activated with D-dimer and SARS-CoV-2 spike immune complexes," *Cytokine* 2024, 173: 156447. doi: <https://doi.org/10.1016/j.cyto.2023.156447>

Parry PL et al., "'Spikeopathy': COVID-19 Spike Protein Is Pathogenic, from Both Virus and Vaccine mRNA," *Biomedicine* 11, no. 8 (August 17, 2023): 2287, doi: <https://doi.org/10.3390/biomedicines11082287>

Passariello M et al., "Interactions of Spike-RBD of SARS-CoV-2 and Platelet Factor 4: New Insights in the Etiopathogenesis of Thrombosis," *Int. J. Mol. Sci.* 2021, 22, 16: 8562. doi: <https://doi.org/10.3390/ijms22168562>

Patra T et al., "SARS-CoV-2 spike protein promotes IL-6 trans-signaling by activation of angiotensin II receptor signaling in epithelial cells." *PLoS Pathog.* 2020;16:e1009128. doi: <https://doi.org/10.1371/journal.ppat.1009128>

Patterson BK et al., "Persistence of SARS CoV-2 S1 Protein in CD16+ Monocytes in Post-Acute Sequelae of COVID-19 (PASC) up to 15 Months Post-Infection," *Front. Immunol.* 12 (Sec. Viral Immunology). doi: <https://doi.org/10.3389/fimmu.2021.746021>

Pence B, "Recombinant SARS-CoV-2 Spike Protein Mediates Glycolytic and Inflammatory Activation in Human Monocytes," *Innov Aging* 2020, 4, sp. 1: 955. doi: <https://doi.org/10.1093/geroni/igaa057.3493>

Perico L et al., "SARS-CoV-2 and the spike protein in endotheliopathy," *Trends Microbiol.* 2024, 32, 1: 53-67. doi: [10.1016/j.tim.2023.06.004](https://doi.org/10.1016/j.tim.2023.06.004)

Perico L et al., "SARS-CoV-2 Spike Protein 1 Activates Microvascular Endothelial Cells and Complement System Leading to Platelet Aggregation." *Front. Immunol.* 2022, 13, 827146. doi: <https://doi.org/10.3389/fimmu.2022.827146>

Petrlova J et al., "SARS-CoV-2 spike protein aggregation is triggered by bacterial lipopolysaccharide," *FEBS Lett.* 2022, 596:2566–2575. doi: <https://doi.org/10.1002/1873-3468.14490>

Petrosino S and N Matende, "Elimination/Neutralization of COVID-19 Vaccine-Produced Spike Protein: Scoping Review," *Mathews Journal of Nutrition & Dietetics* 2024, 7, 2. doi: <https://doi.org/10.30654/MJND.10034>

Petrovski D et al., "Penetration of the SARS-CoV-2 Spike Protein across the Blood-Brain Barrier, as Revealed by a Combination of a Human Cell Culture Model System and Optical Biosensing." *Biomedicines* 2022, 10, 1: 188. doi: <https://doi.org/10.3390/biomedicines10010188>

Petruk G et al., "SARS-CoV-2 spike protein binds to bacterial lipopolysaccharide and boosts proinflammatory activity," *J. Mol. Cell Biol.* (2020) 12: 916-932. doi: <https://doi.org/10.1093/jmcb/mjaa067>

Prieto-Villalobos J et al., "SARS-CoV-2 spike protein S1 activates Cx43 hemichannels and disturbs intracellular Ca²⁺ dynamics," *Biol Res.* 2023 Oct 25;56(1):56. doi: <https://doi.org/10.1186/s40659-023-00468-9>

Puthia MTL et al., "Experimental model of pulmonary inflammation induced by SARS-CoV-2 spike protein and endotoxin." *ACS Pharmacol Transl Sci.* 2022, 5, 3: 141–8. doi: <https://doi.org/10.1021/acsptsci.1c00219>

Raghavan S et al., "SARS-CoV-2 Spike Protein Induces Degradation of Junctional Proteins That Maintain Endothelial Barrier Integrity." *Front. Cardiovasc. Med.* 2021, 8, 687783. doi: <https://doi.org/10.3389/fcvm.2021.687783>

Rahman M et al., "Differential Effect of SARS-CoV-2 Spike Glycoprotein 1 on Human Bronchial and Alveolar Lung Mucosa Models: Implications for Pathogenicity." *Viruses* 2021, 13, 12: 2537. doi: <https://doi.org/10.3390/v13122537>

Rajah MM et al., "SARS-CoV-2 Alpha, Beta, and Delta variants display enhanced spike-mediated syncytia formation," *EMBO J.* 2021, 40: e108944. doi: <https://doi.org/10.15252/emboj.2021108944>

Ratajczak MZ et al., "SARS-CoV-2 Entry Receptor ACE2 Is Expressed on Very Small CD45⁺ Precursors of Hematopoietic and Endothelial Cells and in Response to Virus Spike Protein Activates the Nlrp3 Inflammasome," *Stem Cell Rev Rep.* 2021 Feb;17(1):266-277. doi: <https://doi.org/10.1007/s12015-020-10010-z>

Robles JP et al., "The Spike Protein of SARS-CoV-2 Induces Endothelial Inflammation through Integrin $\alpha 5\beta 1$ and NF- κ B Signaling," *J. Biol. Chem.* 2022, 298, 3: 101695, <https://doi.org/10.1016/j.jbc.2022.101695>

Ropa J et al., "Human Hematopoietic Stem, Progenitor, and Immune Cells Respond Ex Vivo to SARS-CoV-2 Spike Protein," *Stem Cell Rev Rep.* 2021, 17, 1:253-265. doi: <https://doi.org/10.1007/s12015-020-10056-z>

Rotoli BM et al., "Endothelial cell activation by SARS-CoV-2 spike S1 protein: A crosstalk between endothelium and innate immune cells," *Biomedicines* 2021, 9, 9: 1220. doi: <https://doi.org/10.3390/biomedicines9091220>

Roytenberg R et al., "Thymidine phosphorylase mediates SARS-CoV-2 spike protein enhanced thrombosis in K18-hACE2TG mice," *Thromb. Res.* 2024, 244, 8: 109195. doi: [10.1016/j.thromres.2024.109195](https://doi.org/10.1016/j.thromres.2024.109195)

Ruben ML et al., "The SARS-CoV-2 spike protein subunit S1 induces COVID-19-like acute lung injury in K18-hACE2 transgenic mice and barrier dysfunction in human endothelial cells." *Am J Physiol Lung Cell Mol Physiol.* 2021, 321, 2: L477-L484. doi: <https://doi.org/10.1152/ajplung.00223.2021>

Russo A, et al., "Implication of COVID-19 on Erythrocytes Functionality: Red Blood Cell Biochemical Implications and Morpho-Functional Aspects," *Int. J. Mol. Sci.* 2022, 23, 4: 2171; <https://doi.org/10.3390/ijms23042171>

Ryu JK et al., "Fibrin drives thromboinflammation and neuropathology in COVID-19," *Nature* 2024, 633: 905-913. doi: <https://doi.org/10.1038/s41586-024-07873-4>

Saadi F et al., "Spike glycoprotein is central to coronavirus pathogenesis-parallel between m-CoV and SARS-CoV-2," *Ann Neurosci.* 2021, 28 (3-4): 201–218. doi: <https://doi.org/10.1177/09727531211023755>

Samsudin S et al., "SARS-CoV-2 spike protein as a bacterial lipopolysaccharide delivery system in an overzealous inflammatory cascade," *J. Mol. Biol.* 2022, 14, 9: mjac058. <https://doi.org/10.1093/jmcb/mjac058>

Sano H et al., "A case of persistent, confluent maculopapular erythema following a COVID-19 mRNA vaccination is possibly associated with the intralesional spike protein expressed by vascular endothelial cells and eccrine glands in the deep dermis," *J. Dermatol.* (2023) 50: 1208–1212. doi: <https://doi.org/10.1111/1346-8138.16816>

Sano S et al., "SARS-CoV-2 spike protein found in the acrosyringium and eccrine gland of repetitive miliaria-like lesions in a woman following mRNA vaccination." *J. Dermatol.* (2024) 51, 9: e293-e295. doi: <https://doi.org/10.1111/1346-8138.17204>

Santonja C et al., "COVID-19 chilblain-like lesion: immunohistochemical demonstration of SARS-CoV-2 spike protein in blood vessel endothelium and sweat gland epithelium in a polymerase chain reaction-negative patient." *Br J Dermatol.* 2020, 183(4): 778-780. doi: <https://doi.org/10.1111/bjd.19338>

Satta S et al., "An engineered nano-liposome-human ACE2 decoy neutralizes SARS-CoV-2 Spike protein-induced inflammation in both murine and human macrophages," *Theranostics* 2022, 12, 6: 2639–2657. doi: [10.7150/thno.66831](https://doi.org/10.7150/thno.66831)

Schein, DE. "A Deadly Embrace: Hemagglutination Mediated by SARS-CoV-2 Spike Protein at its 22 N-Glycosylation Sites, Red Blood Cell Surface Sialoglycoproteins, and Antibody." *Int. J. Mol. Sci.* 2022, 23(5), 2558. doi: <https://doi.org/10.3390/ijms23052558>

Schein DE et al., "Sialylated Glycan Bindings from SARS-CoV-2 Spike Protein to Blood and Endothelial Cells Govern the Severe Morbidities of COVID-19," *Int. J. Mol. Sci.* 2023 Dec 1;24(23):17039. doi: <https://doi.org/10.3390/ijms242317039>

Schroeder JT and AP Bieneman, "The S1 Subunit of the SARS-CoV-2 Spike protein activates human monocytes to produce cytokines linked to COVID-19: relevance to galectin-3," *Front Immunol.* 2022, 13: 831763. doi: <https://doi.org/10.3389/fimmu.2022.831763>

Segura-Villalobos D et al., "Jacareubin inhibits TLR4-induced lung inflammatory response caused by the RBD domain of SARS-CoV-2 Spike protein." *Pharmacol. Rep.* 2022, 74: 1315–1325. doi: <https://doi.org/10.1007/s43440-022-00398-5>

Semmarath W et al., "Cyanidin-3-O-glucoside and Peonidin-3-O-glucoside-Rich Fraction of Black Rice Germ and Bran Suppresses Inflammatory Responses from SARS-CoV-2 Spike Glycoprotein S1-Induction In Vitro in A549 Lung Cells and THP-1 Macrophages via Inhibition of the NLRP3 Inflammasome Pathway," *Nutrients* 2022, 14, 13: 2738. doi: <https://doi.org/10.3390/nu14132738>

Sharma VK et al., "Nanocurcumin Potently Inhibits SARS-CoV-2 Spike Protein-Induced Cytokine Storm by Deactivation of MAPK/NF- κ B Signaling in Epithelial Cells." *ACS Appl. Bio Mater.* 2022, 5, 2: 483–491. doi: <https://doi.org/10.1021/acsabm.1c00874>

Shirato K and Takako Kizaki, "SARS-CoV-2 Spike Protein S1 Subunit Induces Pro-inflammatory Responses via Toll-Like Receptor 4 Signaling in Murine and Human Macrophages," *Heliyon* 7, no. 2 (February 2, 2021):e06187, doi: <https://doi.org/10.1016/j.heliyon.2021.e06187>

Singh N and Anuradha Bharara Singh, "S2 Subunit of SARS-nCoV-2 Interacts with Tumor Suppressor Protein p53 and BRCA: An in Silico Study," *Translational Oncology* 13, no. 10 (October 2020): 100814, doi: <https://doi.org/10.1016/j.tranon.2020.100814>

Singh RD, "The spike protein of sars-cov-2 induces heme oxygenase-1: pathophysiologic implications," *Biochim Biophys Acta, Mol Basis Dis* (2022) 1868, 3: 166322. doi: <https://doi.org/10.1016/j.bbadis.2021.166322>

Sirsendu J et al., "Cell-Free Hemoglobin Does Not Attenuate the Effects of SARS-CoV-2 Spike Protein S1 Subunit in Pulmonary Endothelial Cells," *Int J Mol Sci*, 2021 Aug 22;22(16):9041. doi: <https://doi.org/10.3390/ijms22169041>

Soares CD et al., "Oral vesiculobullous lesions as an early sign of COVID-19: immunohistochemical detection of SARS-CoV-2 spike protein," *Br. J. Dermatol.* 2021, 184, 1: e6. doi: <https://doi.org/10.1111/bjd.19569>

Solis O et al., "The SARS-CoV-2 spike protein binds and modulates estrogen receptors," *Sci. Adv.* 2022, 8, 48: eadd4150. doi: [10.1126/sciadv.add4150](https://doi.org/10.1126/sciadv.add4150)

Stern B et al., "SARS-CoV-2 spike protein induces endothelial dysfunction in 3D engineered vascular networks." *J. Biomed. Mater. Res. A.* 2023, 112, 4: 524-533. doi: <https://doi.org/10.1002/jbm.a.37543>

Sui Y et al., "SARS-CoV-2 Spike Protein Suppresses ACE2 and Type I Interferon Expression in Primary Cells From Macaque Lung Bronchoalveolar Lavage," *Frontiers in Immunology* (June 4, 2021), 12. doi: <https://doi.org/10.3389/fimmu.2021.658428>

Sun Q et al., "SARS-coV-2 spike protein S1 exposure increases susceptibility to angiotensin II-induced hypertension in rats by promoting central neuroinflammation and oxidative stress," *Neurochem. Res.* 2023, 48, 3016–3026. doi: <https://doi.org/10.1007/s11064-023-03949-1>

Sung PS et al., "CLEC5A and TLR2 Are Critical in SARS-CoV-2-Induced NET Formation and Lung Inflammation," *Journal of Biomedical Science* 29, 2002, 52. doi: <https://doi.org/10.1186/s12929-022-00832-z>

Suprewicz L et al., "Blood-brain barrier function in response to SARS-CoV-2 and its spike protein," *Neurol. Neurochir Pol.* 2023, 57: 14–25. doi: [10.5603/PJNNS.a2023.0014](https://doi.org/10.5603/PJNNS.a2023.0014)

Suprewicz L et al., "Recombinant human plasma gelsolin reverses increased permeability of the blood-brain barrier induced by the spike protein of the SARS-CoV-2 virus," *J Neuroinflammation* 2022, 19, 1: 282, doi: <https://doi.org/10.1186/s12974-022-02642-4>

Suzuki YJ et al., "SARS-CoV-2 spike protein-mediated cell signaling in lung vascular cells." *Vascul. Pharmacol.* 2021;137:106823. doi: <https://doi.org/10.1016/j.vph.2020.106823>

Suzuki YJ and SG Gychka, "SARS-CoV-2 Spike Protein Elicits Cell Signaling in Human Host Cells: Implications for Possible Consequences of COVID-19 Vaccines," *Vaccines* 2021, 9, 1, 36. doi: <https://doi.org/10.3390/vaccines9010036>

Swank Z, et al. "Persistent Circulating Severe Acute Respiratory Syndrome Coronavirus 2 Spike Is Associated With Post-acute Coronavirus Disease 2019 Sequelae," *Clin. Infect. Dis* 2023, 76, 3: e487–e490. doi: <https://doi.org/10.1093/cid/ciac722>

Tetz G and Victor Tetz, "Prion-Like Domains in Spike Protein of SARS-CoV-2 Differ across Its Variants and Enable Changes in Affinity to ACE2," *Microorganisms* 10, no. 2 (January 25, 2022): 280, doi: <https://doi.org/10.3390/microorganisms10020280>

Theobald SJ et al., "Long-lived macrophage reprogramming drives spike protein-mediated inflammasome activation in COVID-19." *EMBO Mol. Med.* (2021) 13:e14150. doi: <https://doi.org/10.15252/emmm.202114150>

Theoharides TC, "Could SARS-CoV-2 Spike Protein Be Responsible for Long-COVID Syndrome?" *Molecular Neurobiology* 59, no. 3 (March 2022): 1850–1861, doi: <https://doi.org/10.1007/s12035-021-02696-0>

Theoharides TC and P. Conti, "Be Aware of SARS-CoV-2 Spike Protein: There Is More Than Meets the Eye," *Journal of Biological Regulators and Homeostatic Agents* 35, no. 3 (May–June 2021): 833–838 doi: [10.23812/THEO_EDIT_3_21](https://doi.org/10.23812/THEO_EDIT_3_21)

Theuerkauf SA et al., "Quantitative assays reveal cell fusion at minimal levels of SARS-CoV-2 spike protein and fusion from without." *iScience* 2021, 24, 3: 102170. <https://doi.org/10.1016/j.isci.2021.102170>

Tillman TS et al., "SARS-CoV-2 Spike Protein Downregulates Cell Surface alpha7nAChR through a Helical Motif in the Spike Neck." *ACS Chem. Neurosci.* (2023) 14, 4: 689–698. doi: <https://doi.org/10.1021/acscchemneuro.2c00610>

Trougakos IP et al., "Adverse Effects of COVID-19 mRNA Vaccines: The Spike Hypothesis," *Trends in Molecular Medicine* 28, no. 7 (July 2022): 542–554. doi: [10.1016/j.molmed.2022.04.007](https://doi.org/10.1016/j.molmed.2022.04.007)

Tyrkalska SD et al., "Differential proinflammatory activities of spike proteins of SARS-CoV-2 variants of concern," *Sci. Adv.* 2022, 8, 37: eabo0732. doi: [10.1126/sciadv.abo0732](https://doi.org/10.1126/sciadv.abo0732)

Vargas-Castro R et al., "Calcitriol prevents SARS-CoV spike-induced inflammation in human trophoblasts through downregulating ACE2 and TMPRSS2 expression," *J Steroid Biochem Mol Biol* 2025, 245: 106625. doi: <https://doi.org/10.1016/j.jsbmb.2024.106625>

Vettori M et al., "Effects of Different Types of Recombinant SARS-CoV-2 Spike Protein on Circulating Monocytes' Structure," *Int. J. Mol. Sci.* 2023, 24, 11, 9373. doi: <https://doi.org/10.3390/ijms24119373>

Villacampa A et al., "SARS-CoV-2 S protein activates NLRP3 inflammasome and deregulates coagulation factors in endothelial and immune cells," *Cell Commun. Signal.* 2024, 22, 38. doi: <https://doi.org/10.1186/s12964-023-01397-6>

Wang J et al., "SARS-CoV-2 Spike Protein S1 Domain Accelerates α -Synuclein Phosphorylation and Aggregation in Cellular Models of Synucleinopathy," *Mol Neurobiol.* 2024 Apr;61(4):2446-2458. doi: <https://doi.org/10.1007/s12035-023-03726-9>

Wu ML et al., "Mast cell activation triggered by SARS-CoV-2 causes inflammation in brain microvascular endothelial cells and microglia," *Front. Cell. Infect. Microbiol.*, 2024, 14. doi: <https://doi.org/10.3389/fcimb.2024.1358873>

Yamamoto M et al., "Persistent varicella zoster virus infection following mRNA COVID-19 vaccination was associated with the presence of encoded spike protein in the lesion." *J. Cutan Immunol. Allergy.* 2022:1–6. doi: <https://doi.org/10.1002/cia2.12278>

- Yilmaz A et al., "Differential proinflammatory responses of colon epithelial cells to SARS-CoV-2 spike protein and *Pseudomonas aeruginosa* lipopolysaccharide," *Turk J Biochem.* 2024. doi: <https://doi.org/10.1515/tjb-2024-0144>
- Yonker LM et al., "Circulating Spike Protein Detected in Post-COVID-19 mRNA Vaccine Myocarditis," *Circulation* 147, no. 11 (2023), <https://doi.org/10.1161/CIRCULATIONAHA.122.061025>
- Youn JY et al., "Therapeutic application of estrogen for COVID-19: Attenuation of SARS-CoV-2 spike protein and IL-6 stimulated, ACE2-dependent NOX2 activation, ROS production and MCP-1 upregulation in endothelial cells," *Redox Biol.* 2021, 46: 102099. doi: <https://doi.org/10.1016/j.redox.2021.102099>
- Youn YJ et al., "Nucleocapsid and spike proteins of SARS-CoV-2 drive neutrophil extracellular trap formation." *Immune Netw.* (2021) 21, 2: e16. doi: <https://doi.org/10.4110/in.2021.21.e16>
- Yu J et al., "Direct activation of the alternative complement pathway by SARS-CoV-2 spike proteins is blocked by factor D inhibition," *Blood* 2020, 136 (18): 2080–2089. doi: <https://doi.org/10.1182/blood.2020008248>
- Zaki H and S Khan, "SARS-CoV-2 spike protein induces inflammatory molecules through TLR2 in macrophages and monocytes." *J. Immunol.* 2021, 206 (1_supplement): 62.07. doi: <https://doi.org/10.4049/jimmunol.206.Supp.62.07>
- Zaki H and S Khan, "TLR2 senses spike protein of SARS-CoV-2 to trigger inflammation," *J. Immunol.* 2022, 208 (1_Supplement): 125.30. doi: <https://doi.org/10.4049/jimmunol.208.Supp.125.30>
- Zekri-Nechar K et al., "Spike Protein Subunits of SARS-CoV-2 Alter Mitochondrial Metabolism in Human Pulmonary Microvascular Endothelial Cells: Involvement of Factor Xa." *Dis. Markers* (2022): 1118195. doi: <https://doi.org/10.1155/2022/1118195>
- Zeng FM et al., "SARS-CoV-2 spike spurs intestinal inflammation via VEGF production in enterocytes," *EMBO Mol Med.* 2022, 14: e14844. doi: <https://doi.org/10.15252/emmm.202114844>
- Zhang Q et al., "Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) membrane (M) and spike (S) proteins antagonize host type I interferon response," 2021, *Front Cell Infect Microbiol* 11: 766922. doi: <https://doi.org/10.3389/fcimb.2021.766922>
- Zhang RG et al., "SARS-CoV-2 spike protein receptor binding domain promotes IL-6 and IL-8 release via ATP/P2Y₂ and ERK1/2 signaling pathways in human bronchial epithelia," *Mol. Immunol.* 2024, 167: 53-61. doi: <https://doi.org/10.1016/j.molimm.2024.02.005>
- Zhang S et al., "SARS-CoV-2 Binds Platelet ACE2 to Enhance Thrombosis in COVID-19," *Journal of Hematology & Oncology* 13 no. 120 (2020): 120, doi: <https://doi.org/10.1186/s13045-020-00954-7>
- Zhang Z et al., "SARS-CoV-2 spike protein dictates syncytium-mediated lymphocyte elimination." *Cell Death Differ.* 2021, 28, 2765–2777. doi: <https://doi.org/10.1038/s41418-021-00782-3>
- Zhao Y et al., "SARS-CoV-2 spike protein interacts with and activates TLR4." *Cell Res.* 2021;31:818–820. doi: <https://doi.org/10.1038/s41422-021-00495-9>
- Zheng Y et al., "SARS-CoV-2 Spike Protein Causes Blood Coagulation and Thrombosis by Competitive Binding to Heparan Sulfate," *International Journal of Biological Macromolecules* 193 (December 15, 2021): 1124–1129, doi: <https://doi.org/10.1016/j.ijbiomac.2021.10.112>

Zhu G et al., "SARS-CoV-2 spike protein-induced host inflammatory response signature in human corneal epithelial cells," *Mol. Med. Rep.* (2021) 24: 584. doi: <https://doi.org/10.3892/mmr.2021.12223>

CATEGORIES

- A. General/Overview**
- B. ACE2**
- C. Amyloid, prion-like properties**
- D. Autoimmune**
- E. Blood pressure/hypertension**
- F. CD147**
- G. Cell membrane permeability, barrier dysfunction**
- H. Cerebral, cerebrovascular, blood-brain barrier, cognitive**
- I. Clinical pathology**
- J. Clotting, platelets, hemoglobin**
- K. Cytokines, chemokines, inteferon, interleukins**
- L. Endothelial**
- M. Gastrointestinal**
- N. Immune dysfunction**
- O. Macrophages, monocytes, neutrophils**
- P. MAPK/NF-kB**
- Q. Mast cells**
- R. Microglia**
- S. Microvascular**
- T. Mitochondria/metabolism**
- U. Myocarditis/cardiomyopathy**
- V. NLRP3**
- W. Ocular, ophthalmic, conjunctival**
- X. Other cell signaling**
- Y. Pregnancy**
- Z. Pulmonary, respiratory**
- AA. Renin-Angiotensin-Aldosterone System**
- BB. Senescence/aging**
- CC. Stem cells**
- DD. Syncytia/cell fusion**
- EE. Therapies**
- FF. Toll-like receptors (TLRs)**

A. General/Overview

Acevedo-Whitehouse K and R Bruno, "Potential health risks of mRNA-based vaccine therapy: A hypothesis," *Med. Hypotheses* 2023, 171: 111015. doi: <https://doi.org/10.1016/j.mehy.2023.111015>

Almehdi AM et al., "SARS-CoV-2 Spike Protein: Pathogenesis, Vaccines, and Potential Therapies," *Infection* 49, no. 5 (October 2021): 855–876, doi: <https://doi.org/10.1007/s15010-021-01677-8>

Baldari CT et al., "Emerging Roles of SARS-CoV-2 Spike-ACE2 in Immune Evasion and Pathogenesis," *Trends in Immunology* 44 no. 6 (June 2023), doi: <https://doi.org/10.1016/j.it.2023.04.001>

Cosentino M and Franca Marino, "Understanding the Pharmacology of COVID- 19 mRNA Vaccines: Playing Dice with the Spike?" *International Journal of Molecular Sciences* 23, no. 18 (September 17, 2022): 10881, doi: <https://doi.org/10.3390/ijms231810881>

Gussow AB et al., "Genomic Determinants of Pathogenicity in SARS-CoV-2 and Other Human Coronaviruses," *PNAS* 117, no. 26 (June 10, 2020): 15193–15199, <https://doi.org/10.1073/pnas.2008176117>

Halma MTJ et al., "Strategies for the Management of Spike Protein-Related Pathology," *Microorganisms* 11, no. 5 (May 20, 2023): 1308, doi: <https://doi.org/10.3390/microorganisms11051308>

Kowarz E et al., "Vaccine-induced COVID-19 mimicry syndrome," *eLife* (Feb 15 2022), 11:e74974. doi: <https://doi.org/10.7554/eLife.74974>

Lehmann KJ, "Impact of SARS-CoV-2 Spikes on Safety of Spike-Based COVID-19 Vaccinations," *Immunome Res.* 2024, 20, 2: 1000267. doi: [10.35248/1745-7580.24.20.267](https://doi.org/10.35248/1745-7580.24.20.267)

Lehmann KJ, "Suspected Causes of the Specific Intolerance Profile of Spike-Based Covid-19 Vaccines," *Med. Res. Arch* 2024, 12, 9. doi: [10.18103/mra.v12i9.5704](https://doi.org/10.18103/mra.v12i9.5704)

Lesgard JF et al., "Toxicity of SARS-CoV-2 Spike Protein from the Virus and Produced from COVID-19 mRNA or Adenoviral DNA Vaccines." *Arch Microbiol Immun* 2023, 7, 3: 121- 138. doi: [10.26502/ami.936500110](https://doi.org/10.26502/ami.936500110)

Letarov AV et al., "Free SARS-CoV-2 Spike Protein S1 Particles May Play a Role in the Pathogenesis of COVID-19 Infection." *Biochemistry* (Moscow) 2021, 86, 257–261. doi: <https://doi.org/10.1134/S0006297921030032>

Nuovo JG et al., "Endothelial Cell Damage Is the Central Part of COVID-19 and a Mouse Model Induced by Injection of the S1 Subunit of the Spike Protein." *Ann. Diagn. Pathol.* 2021, 51, 151682. doi: <https://doi.org/10.1016/j.anndiagpath.2020.151682>

Pallas RM, "Innate and adaptative immune mechanisms of COVID-19 vaccines. Serious adverse events associated with SARS-CoV-2 vaccination: A systematic review," *Vacunas* (English ed.) 2024, 25, 2: 285.e1-285.e94. doi: <https://doi.org/10.1016/j.vacune.2024.05.002>

Parry PL et al., "'Spikeopathy': COVID-19 Spike Protein Is Pathogenic, from Both Virus and Vaccine mRNA," *Biomedicine* 11, no. 8 (August 17, 2023): 2287, doi: <https://doi.org/10.3390/biomedicines11082287>

Saadi F et al., "Spike glycoprotein is central to coronavirus pathogenesis-parallel between m-CoV and SARS-CoV-2," *Ann Neurosci.* 2021, 28 (3-4): 201–218. doi: <https://doi.org/10.1177/09727531211023755>

Swank Z, et al. "Persistent Circulating Severe Acute Respiratory Syndrome Coronavirus 2 Spike Is Associated With Post-acute Coronavirus Disease 2019 Sequelae," *Clin. Infect. Dis* 2023, 76, 3: e487–e490. doi: <https://doi.org/10.1093/cid/ciac722>

Theoharides TC, "Could SARS-CoV-2 Spike Protein Be Responsible for Long-COVID Syndrome?" *Molecular Neurobiology* 59, no. 3 (March 2022): 1850–1861, doi: <https://doi.org/10.1007/s12035-021-02696-0>

Theoharides TC and P. Conti, "Be Aware of SARS-CoV-2 Spike Protein: There Is More Than Meets the Eye," *Journal of Biological Regulators and Homeostatic Agents* 35, no. 3 (May–June 2021): 833–838 doi: [10.23812/THEO_EDIT_3_21](https://doi.org/10.23812/THEO_EDIT_3_21)

Trougakos IP et al., "Adverse Effects of COVID-19 mRNA Vaccines: The Spike Hypothesis," *Trends in Molecular Medicine* 28, no. 7 (July 2022): 542–554. doi: [10.1016/j.molmed.2022.04.007](https://doi.org/10.1016/j.molmed.2022.04.007)

Tyrkalska SD et al., “Differential proinflammatory activities of spike proteins of SARS-CoV-2 variants of concern,” *Sci. Adv.* 2022, 8, 37: eabo0732. doi: [10.1126/sciadv.abo0732](https://doi.org/10.1126/sciadv.abo0732)

B. ACE2

Aboudounya MM and RJ Heads, “COVID-19 and Toll-Like Receptor 4 (TLR4): SARS-CoV-2 May Bind and Activate TLR4 to Increase ACE2 Expression, Facilitating Entry and Causing Hyperinflammation.” *Mediators Inflamm.* 2021;2021:8874339. doi: <https://doi.org/10.1155/2021/8874339>

Aksenova AY et al., “The increased amyloidogenicity of Spike RBD and pH-dependent binding to ACE2 may contribute to the transmissibility and pathogenic properties of SARS-CoV-2 omicron as suggested by in silico study,” *Int J Mol Sci.* 2022, 23(21): 13502. doi: <https://doi.org/10.3390/ijms232113502>

Angeli F et al., “COVID-19, vaccines and deficiency of ACE2 and other angiotensinases. Closing the loop on the ‘Spike effect’.” *Eur J. Intern. Med.* 2022;103:23–28. doi: [10.1016/j.ejim.2022.06.015](https://doi.org/10.1016/j.ejim.2022.06.015)

Baldari CT et al., “Emerging Roles of SARS-CoV-2 Spike-ACE2 in Immune Evasion and Pathogenesis,” *Trends in Immunology* 44 no. 6 (June 2023), doi: <https://doi.org/10.1016/j.it.2023.04.001>

Devaux CA and L. Camoin-Jau, “Molecular mimicry of the viral spike in the SARS-CoV-2 vaccine possibly triggers transient dysregulation of ACE2, leading to vascular and coagulation dysfunction similar to SARS-CoV-2 infection,” *Viruses* 2023, 15, 5: 1045. doi: <https://doi.org/10.3390/v15051045>

Gao X et al., “Spike-Mediated ACE2 Down-Regulation Was Involved in the Pathogenesis of SARS-CoV-2 Infection,” *Journal of Infection* 85, no. 4 (October 2022), 418–427, doi: [10.1016/j.jinf.2022.06.030](https://doi.org/10.1016/j.jinf.2022.06.030)

Kato Y et al., “TRPC3-Nox2 Protein Complex Formation Increases the Risk of SARS-CoV-2 Spike Protein-Induced Cardiomyocyte Dysfunction through ACE2 Upregulation.” *Int. J. Mol. Sci.* 2023, 24, 1: 102. doi: <https://doi.org/10.3390/ijms24010102>

Ken W et al., “Low dose radiation therapy attenuates ACE2 depression and inflammatory cytokines induction by COVID-19 viral spike protein in human bronchial epithelial cells,” *Int J Radiat Biol.* 2022, 98, 10:1532-1541. doi: <https://doi.org/10.1080/09553002.2022.2055806>

Lei Y et al., “SARS-CoV-2 Spike Protein Impairs Endothelial Function via Downregulation of ACE 2,” *Circulation Research* 128, no. 9 (2021): 1323–1326, doi: <https://doi.org/10.1161/CIRCRESAHA.121.318902>

Lu J and PD Sun, “High affinity binding of SARS-CoV-2 spike protein enhances ACE2 carboxypeptidase activity,” *J. Biol. Chem* (December 2020) 295, 52: p18579-18588. doi: [10.1074/jbc.RA120.015303](https://doi.org/10.1074/jbc.RA120.015303)

Maeda Y et al., “Differential Ability of Spike Protein of SARS-CoV-2 Variants to Downregulate ACE2,” *Int. J. Mol. Sci.* 2024, 25, 2: 1353, <https://doi.org/10.3390/ijms25021353>

Magro N et al., “Disruption of the blood-brain barrier is correlated with spike endocytosis by ACE2 + endothelia in the CNS microvasculature in fatal COVID-19. Scientific commentary on ‘Detection of blood-brain barrier disruption in brains of patients with COVID-19, but no evidence of brain penetration by SARS-CoV-2’,” *Acta Neuropathol.* 2024 Feb 27;147(1):47. doi: <https://doi.org/10.1007/s00401-023-02681-y>

Satta S et al., “An engineered nano-liposome-human ACE2 decoy neutralizes SARS-CoV-2 Spike protein-induced inflammation in both murine and human macrophages,” *Theranostics* 2022, 12, 6: 2639–2657. doi: [10.7150/thno.66831](https://doi.org/10.7150/thno.66831)

Sui Y et al., "SARS-CoV-2 Spike Protein Suppresses ACE2 and Type I Interferon Expression in Primary Cells From Macaque Lung Bronchoalveolar Lavage," *Frontiers in Immunology* (June 4, 2021), 12. doi: <https://doi.org/10.3389/fimmu.2021.658428>

Tetz G and Victor Tetz, "Prion-Like Domains in Spike Protein of SARS-CoV-2 Differ across Its Variants and Enable Changes in Affinity to ACE2," *Microorganisms* 10, no. 2 (January 25, 2022): 280, doi: <https://doi.org/10.3390/microorganisms10020280>

Vargas-Castro R et al., "Calcitriol prevents SARS-CoV spike-induced inflammation in human trophoblasts through downregulating ACE2 and TMPRSS2 expression," *J Steroid Biochem Mol Biol* 2025, 245: 106625. doi: <https://doi.org/10.1016/j.jsbmb.2024.106625>

Youn JY et al., "Therapeutic application of estrogen for COVID-19: Attenuation of SARS-CoV-2 spike protein and IL-6 stimulated, ACE2-dependent NOX2 activation, ROS production and MCP-1 upregulation in endothelial cells," *Redox Biol.* 2021, 46: 102099. doi: <https://doi.org/10.1016/j.redox.2021.102099>

Zhang S et al., "SARS-CoV-2 Binds Platelet ACE2 to Enhance Thrombosis in COVID-19," *Journal of Hematology & Oncology* 13 no. 120 (2020): 120, doi: <https://doi.org/10.1186/s13045-020-00954-7>

C. Amyloid, prion-like properties

Aksenova AY et al., "The increased amyloidogenicity of Spike RBD and pH-dependent binding to ACE2 may contribute to the transmissibility and pathogenic properties of SARS-CoV-2 omicron as suggested by in silico study," *Int J Mol Sci.* 2022, 23(21): 13502. doi: <https://doi.org/10.3390/ijms232113502>

Cao S et al., "Spike Protein Fragments Promote Alzheimer's Amyloidogenesis," *ACS Appl. Mater. Interfaces* (2023), 15, 34: 40317-40329. doi: <https://doi.org/10.1021/acsami.3c09815>

Freeborn J, "Misfolded Spike Protein Could Explain Complicated COVID-19 Symptoms," *Medical News Today*, May 26, 2022, <https://www.medicalnewstoday.com/articles/misfolded-spike-protein-could-explain-complicated-covid-19-symptoms>

Idrees D and Vijay Kumar, "SARS-CoV-2 Spike Protein Interactions with Amyloidogenic Proteins: Potential Clues to Neurodegeneration," *Biochemical and Biophysical Research Communications* 2021, 554 : 94–98, doi: <https://doi.org/10.1016/j.bbrc.2021.03.100>

Ma G et al., "SARS-CoV-2 Spike protein S2 subunit modulates γ -secretase and enhances amyloid- β production in COVID-19 neuropathy," *Cell Discov* 8, 99 (2022). doi: <https://doi.org/10.1038/s41421-022-00458-3>

Nahalka J, "1-L Transcription of SARS-CoV-2 Spike Protein S1 Subunit," *Int. J. Mol. Sci.* 2024, 25, 8: 4440. doi: <https://doi.org/10.3390/ijms25084440>

Nyström S, "Amyloidogenesis of SARS-CoV-2 Spike Protein," *J. Am. Chem. Soc.* 2022, 144, 8945–8950. doi: <https://doi.org/10.1021/jacs.2c03925>

Petrlova J et al., "SARS-CoV-2 spike protein aggregation is triggered by bacterial lipopolysaccharide," *FEBS Lett.* 2022, 596:2566–2575. doi: <https://doi.org/10.1002/1873-3468.14490>

Petruk G et al., "SARS-CoV-2 spike protein binds to bacterial lipopolysaccharide and boosts proinflammatory activity," *J. Mol. Cell Biol.* (2020) 12: 916-932. doi: <https://doi.org/10.1093/jmcb/mjaa067>

Tetz G and Victor Tetz, "Prion-Like Domains in Spike Protein of SARS-CoV-2 Differ across Its Variants and Enable Changes in Affinity to ACE2," *Microorganisms* 10, no. 2 (January 25, 2022): 280, doi: <https://doi.org/10.3390/microorganisms10020280>

Wang J et al., "SARS-CoV-2 Spike Protein S1 Domain Accelerates α -Synuclein Phosphorylation and Aggregation in Cellular Models of Synucleinopathy," *Mol Neurobiol.* 2024 Apr;61(4):2446-2458. doi: <https://doi.org/10.1007/s12035-023-03726-9>

D. Autoimmune

Heil M, "Self-DNA driven inflammation in COVID-19 and after mRNA-based vaccination: lessons for non-COVID-19 pathologies," *Front. Immunol.*, 2023, 14. doi: <https://doi.org/10.3389/fimmu.2023.1259879>

Nunez-Castilla J et al., "Potential autoimmunity resulting from molecular mimicry between SARS-CoV-2 spike and human proteins," *Viruses* 2022, 14 (7): 1415. <https://doi.org/10.3390/v14071415>

E. Blood pressure/hypertension

Angeli F et al., "The spike effect of acute respiratory syndrome coronavirus 2 and coronavirus disease 2019 vaccines on blood pressure," *Eur J Intern Med.* 2023 Mar;109:12-21. doi: [10.1016/j.ejim.2022.12.004](https://doi.org/10.1016/j.ejim.2022.12.004)

Sun Q et al., "SARS-coV-2 spike protein S1 exposure increases susceptibility to angiotensin II-induced hypertension in rats by promoting central neuroinflammation and oxidative stress," *Neurochem. Res.* 2023, 48, 3016–3026. doi: <https://doi.org/10.1007/s11064-023-03949-1>

F. CD147

Avolio E et al., "The SARS-CoV-2 Spike Protein Disrupts Human Cardiac Pericytes Function through CD147 Receptor-Mediated Signalling: A Potential Non-infective Mechanism of COVID-19 Microvascular Disease," *Clinical Science* 135, no. 24. (December 22, 2021): 2667–2689, doi: <https://doi.org/10.1042/CS20210735>

Loh D, "The potential of melatonin in the prevention and attenuation of oxidative hemolysis and myocardial injury from cd147 SARS-CoV-2 spike protein receptor binding." *Melatonin Research.* 3, 3 (June 2020), 380-416. doi: <https://doi.org/10.32794/mr11250069>

Maugeri N et al., "Unconventional CD147-Dependent Platelet Activation Elicited by SARS-CoV-2 in COVID-19," *Journal of Thrombosis and Haemostasis* 20, no. 2. (October 28, 2021): 434–448, doi: <https://doi.org/10.1111/jth.15575>

G. Cell membrane permeability, barrier dysfunction

Asandei A et al., "Non-Receptor-Mediated Lipid Membrane Permeabilization by the SARS-CoV-2 Spike Protein S1 Subunit." *ACS Appl. Mater. Interfaces* 2020, 12, 50: 55649–55658. doi: <https://doi.org/10.1021/acsami.0c17044>

Biancatelli RMLC, et al. "The SARS-CoV-2 spike protein subunit S1 induces COVID-19-like acute lung injury in Kappa18-hACE2 transgenic mice and barrier dysfunction in human endothelial cells." *Am. J. Physiol. Lung Cell. Mol. Physiol.* 2021, 321, L477–L484. doi: <https://doi.org/10.1152/ajplung.00223.2021>

Biering SB et al., "SARS-CoV-2 Spike Triggers Barrier Dysfunction and Vascular Leak via Integrins and TGF- β Signaling," *Nat. Commun.* 2022, 13: 7630. doi: <https://doi.org/10.1038/s41467-022-34910-5>

Buzhdygan TP et al., "The SARS-CoV-2 Spike Protein Alters Barrier Function in 2D Static and 3D Microfluidic in-Vitro Models of the Human Blood-Brain Barrier," *Neurobiol. Dis.* 2020, 146, 105131. doi: <https://doi.org/10.1016/j.nbd.2020.105131>

Chaves JCS et al., "Differential Cytokine Responses of APOE3 and APOE4 Blood-brain Barrier Cell Types to SARS-CoV-2 Spike Proteins," *J. Neuroimmune Pharmacol.* 2024, 19, 22. doi: <https://doi.org/10.1007/s11481-024-10127-9>

Correa Y et al., "SARS-CoV-2 spike protein removes lipids from model membranes and interferes with the capacity of high-density lipoprotein to exchange lipids," *J. Colloid Interface Sci.* (2021) 602: 732-739. doi: <https://doi.org/10.1016/j.jcis.2021.06.056>

DeOre BJ et al., "SARS-CoV-2 Spike Protein Disrupts Blood-Brain Barrier Integrity via RhoA Activation," *J Neuroimmune Pharmacol.* 2021 Dec;16(4):722-728. Doi: <https://doi.org/10.1007/s11481-021-10029-0>

Guo Y and V Kanamarlapudi, "Molecular Analysis of SARS-CoV-2 Spike Protein-Induced Endothelial Cell Permeability and vWF Secretion," *Int. J. Mol. Sci.* 2023, 24(6): 5664. <https://doi.org/10.3390/ijms24065664>

Luchini A et al., "Lipid bilayer degradation induced by SARS-CoV-2 spike protein as revealed by neutron reflectometry," *Sci. Rep.* (2021) 11: 14867. doi: <https://doi.org/10.1038/s41598-021-93996-x>

Luo Y et al., "SARS-Cov-2 spike induces intestinal barrier dysfunction through the interaction between CEACAM5 and Galectin-9," *Front. Immunol.*, 2024, 15. doi: <https://doi.org/10.3389/fimmu.2024.1303356>

Magro N et al., "Disruption of the blood-brain barrier is correlated with spike endocytosis by ACE2 + endothelia in the CNS microvasculature in fatal COVID-19. Scientific commentary on 'Detection of blood-brain barrier disruption in brains of patients with COVID-19, but no evidence of brain penetration by SARS-CoV-2'," *Acta Neuropathol.* 2024 Feb 27;147(1):47. doi: <https://doi.org/10.1007/s00401-023-02681-y>

Raghavan S et al., "SARS-CoV-2 Spike Protein Induces Degradation of Junctional Proteins That Maintain Endothelial Barrier Integrity." *Front. Cardiovasc. Med.* 2021, 8, 687783. doi: <https://doi.org/10.3389/fcvm.2021.687783>

Ruben ML et al., "The SARS-CoV-2 spike protein subunit S1 induces COVID-19-like acute lung injury in K18-hACE2 transgenic mice and barrier dysfunction in human endothelial cells." *Am J Physiol Lung Cell Mol Physiol.* 2021, 321, 2: L477-L484. doi: <https://doi.org/10.1152/ajplung.00223.2021>

H. Cerebral, cerebrovascular, blood-brain barrier, cognitive

Burnett FN et al., "SARS-CoV-2 Spike Protein Intensifies Cerebrovascular Complications in Diabetic hACE2 Mice through RAAS and TLR Signaling Activation," *Int. J. Mol. Sci.* 2023, 24(22): 16394. doi: <https://doi.org/10.3390/ijms242216394>

Choi JY et al., "SARS-CoV-2 spike S1 subunit protein-mediated increase of beta-secretase 1 (BACE1) impairs human brain vessel cells," *Biochem. Biophys. Res. Commun.* 2022, 625, 20: 66-71. doi: <https://doi.org/10.1016/j.bbrc.2022.07.113>

Clough E et al., "Mitochondrial Dynamics in SARS-COV2 Spike Protein Treated Human Microglia: Implications for Neuro-COVID," *Journal of Neuroimmune Pharmacology* 16, no. 4 (December 2021): 770–784, doi: <https://doi.org/10.1007/s11481-021-10015-6>

DeOre BJ et al., "SARS-CoV-2 Spike Protein Disrupts Blood-Brain Barrier Integrity via RhoA Activation," *J Neuroimmune Pharmacol.* 2021 Dec;16(4):722-728. Doi: <https://doi.org/10.1007/s11481-021-10029-0>

Erdogan MA, "Prenatal SARS-CoV-2 Spike Protein Exposure Induces Autism-Like Neurobehavioral Changes in Male Neonatal Rats," *J Neuroimmune Pharmacol.* 2023 Dec;18(4):573-591. doi: [10.1007/s11481-023-10089-4](https://doi.org/10.1007/s11481-023-10089-4)

Fontes-Dantas FL, "SARS-CoV-2 Spike Protein Induces TLR4-Mediated Long-Term Cognitive Dysfunction Recapitulating Post-COVID-19 Syndrome in Mice," *Cell Reports* 42, no. 3 (March 2023):112189, doi: <https://doi.org/10.1016/j.celrep.2023.112189>

Frank MG et al., "SARS-CoV-2 S1 subunit produces a protracted priming of the neuroinflammatory, physiological, and behavioral responses to a remote immune challenge: A role for corticosteroids," *Brain Behav. Immun.* (October 2024) 121: 87-103. doi: <https://doi.org/10.1016/j.bbi.2024.07.034>

Heath SP et al., "SARS-CoV-2 Spike Protein Exacerbates Thromboembolic Cerebrovascular Complications in Humanized ACE2 Mouse Model," *Transl Stroke Res.* (2024) doi: <https://doi.org/10.1007/s12975-024-01301-5>

Khaddaj-Mallat R et al., "SARS-CoV-2 deregulates the vascular and immune functions of brain pericytes via spike protein." *Neurobiol. Dis.* 2021, 161, 105561. doi: <https://doi.org/10.1016/j.nbd.2021.105561>

Kim ES et al., "Spike Proteins of SARS-CoV-2 Induce Pathological Changes in Molecular Delivery and Metabolic Function in the Brain Endothelial Cells," *Viruses*, 2021, 13(10):2021. doi: <https://doi.org/10.3390/v13102021>

Lykhmus O et al., "Immunization with 674–685 fragment of SARS-Cov-2 spike protein induces neuroinflammation and impairs episodic memory of mice." *Biochem. Biophys. Res. Commun.* 2022, 622: 57–63. doi: <https://doi.org/10.1016/j.bbrc.2022.07.016>

Magro N et al., "Disruption of the blood-brain barrier is correlated with spike endocytosis by ACE2 + endothelia in the CNS microvasculature in fatal COVID-19. Scientific commentary on 'Detection of blood-brain barrier disruption in brains of patients with COVID-19, but no evidence of brain penetration by SARS-CoV-2,'" *Acta Neuropathol.* 2024 Feb 27;147(1):47. doi: <https://doi.org/10.1007/s00401-023-02681-y>

Oh J et al., "SARS-CoV-2 Spike Protein Induces Cognitive Deficit and Anxiety-Like Behavior in Mouse via Non-cell Autonomous Hippocampal Neuronal Death," *Scientific Reports* 12, no. 5496 (2022), doi: <https://doi.org/10.1038/s41598-022-09410-7>

Petrovski D et al., "Penetration of the SARS-CoV-2 Spike Protein across the Blood-Brain Barrier, as Revealed by a Combination of a Human Cell Culture Model System and Optical Biosensing." *Biomedicines* 2022, 10, 1: 188. doi: <https://doi.org/10.3390/biomedicines10010188>

Suprewicz L et al., "Blood-brain barrier function in response to SARS-CoV-2 and its spike protein," *Neurol. Neurochir Pol.* 2023, 57: 14–25. doi: [10.5603/PJNNS.a2023.0014](https://doi.org/10.5603/PJNNS.a2023.0014)

Suprewicz L et al., "Recombinant human plasma gelsolin reverses increased permeability of the blood-brain barrier induced by the spike protein of the SARS-CoV-2 virus," *J Neuroinflammation* 2022, 19, 1: 282, doi: <https://doi.org/10.1186/s12974-022-02642-4>

Wu ML et al., "Mast cell activation triggered by SARS-CoV-2 causes inflammation in brain microvascular endothelial cells and microglia," *Front. Cell. Infect. Microbiol.*, 2024, 14. doi: <https://doi.org/10.3389/fcimb.2024.1358873>

I. Clinical pathology

Baumeier C et al., "Intramyocardial Inflammation after COVID-19 Vaccination: An Endomyocardial Biopsy-Proven Case Series." *Int. J. Mol. Sci.* 2022;23:6940. doi: <https://doi.org/10.3390/ijms23136940>

Burkhardt A. "Pathology Conference: Vaccine-Induced Spike Protein Production in the Brain, Organs etc., now Proven." Report24.news. 2022, <https://report24.news/pathologie-konferenz-impfinduzierte-spike-produktion-in-gehirn-u-a-organen-nun-erwiesen/>

Craddock V et al., "Persistent circulation of soluble and extracellular vesicle-linked Spike protein in individuals with postacute sequelae of COVID-19." *J Med. Virol.* 2023 Feb;95(2):e28568. doi: <https://doi.org/10.1002/jmv.28568>

De Michele M et al., "Evidence of SARS-CoV-2 Spike Protein on Retrieved Thrombi from COVID-19 Patients," *Journal of Hematology Oncology* 2022, 15, 108, doi: <https://doi.org/10.1186/s13045-022-01329-w>

De Sousa PMB et al., "Fatal Myocarditis following COVID-19 mRNA Immunization: A Case Report and Differential Diagnosis Review," *Vaccines* 2024, 12, 2: 194. doi: <https://doi.org/10.3390/vaccines12020194>

Gamblicher T et al., "SARS-CoV-2 spike protein is present in both endothelial and eccrine cells of a chilblain-like skin lesion," *J Eur Acad Dermatol Venereol.* 2020, 1, 10: e187-e189. doi: <https://doi.org/10.1111/jdv.16970>

Gawaz A et al., "SARS-CoV-2-Induced Vasculitic Skin Lesions Are Associated with Massive Spike Protein Depositions in Autophagosomes," *J Invest Dermatol.* 2024, 144, 2: 369-377.e4. doi: <https://doi.org/10.1016/j.jid.2023.07.018>

Hulscher N et al., "Autopsy findings in cases of fatal COVID-19 vaccine-induced myocarditis," *ESC Heart Failure* 2024. doi: <https://doi.org/10.1002/ehf2.14680>

Ko CJ et al., "Discordant anti-SARS-CoV-2 spike protein and RNA staining in cutaneous pernioitic lesions suggests endothelial deposition of cleaved spike protein," *J. Cutan Pathol* 2021, 48 (1): 47–52. doi: <https://doi.org/10.1111/cup.13866>

Magen E et al., "Clinical and Molecular Characterization of a Rare Case of BNT162b2 mRNA COVID-19 Vaccine-Associated Myositis." *Vaccines.* 2022;10:1135. doi: <https://doi.org/10.3390/vaccines10071135>

Magro N et al., "Disruption of the blood-brain barrier is correlated with spike endocytosis by ACE2 + endothelia in the CNS microvasculature in fatal COVID-19. Scientific commentary on 'Detection of blood-brain barrier disruption in brains of patients with COVID-19, but no evidence of brain penetration by SARS-CoV-2,'" *Acta Neuropathol.* 2024 Feb 27;147(1):47. doi: <https://doi.org/10.1007/s00401-023-02681-y>

Mörz M, "A Case Report: Multifocal Necrotizing Encephalitis and Myocarditis after BNT162b2 mRNA Vaccination against COVID-19," *Vaccines* 2022, 10, 10: 1651. doi: <https://doi.org/10.3390/vaccines10101651>

Sano H et al., "A case of persistent, confluent maculopapular erythema following a COVID-19 mRNA vaccination is possibly associated with the intralesional spike protein expressed by vascular endothelial cells and eccrine glands in the deep dermis," *J. Dermatol.* (2023) 50: 1208–1212. doi: <https://doi.org/10.1111/1346-8138.16816>

Sano S et al., "SARS-CoV-2 spike protein found in the acrosyringium and eccrine gland of repetitive miliaria-like lesions in a woman following mRNA vaccination." *J. Dermatol.* (2024) 51, 9: e293-e295. doi: <https://doi.org/10.1111/1346-8138.17204>

Santonja C et al., "COVID-19 chilblain-like lesion: immunohistochemical demonstration of SARS-CoV-2 spike protein in blood vessel endothelium and sweat gland epithelium in a polymerase chain reaction-negative patient." *Br J Dermatol.* 2020, 183(4): 778-780. doi: <https://doi.org/10.1111/bjd.19338>

Soares CD et al., "Oral vesiculobullous lesions as an early sign of COVID-19: immunohistochemical detection of SARS-CoV-2 spike protein," *Br. J. Dermatol.* 2021, 184, 1: e6. doi: <https://doi.org/10.1111/bjd.19569>

Yamamoto M et al., "Persistent varicella zoster virus infection following mRNA COVID-19 vaccination was associated with the presence of encoded spike protein in the lesion." *J. Cutan Immunol. Allergy.* 2022:1-6. doi: <https://doi.org/10.1002/cia2.12278>

Yonker LM et al., "Circulating Spike Protein Detected in Post-COVID-19 mRNA Vaccine Myocarditis," *Circulation* 147, no. 11 (2023), <https://doi.org/10.1161/CIRCULATIONAHA.122.061025>

J. Clotting, platelets, hemoglobin

Al-Kuraishy HM et al., "Changes in the Blood Viscosity in Patients With SARS-CoV-2 Infection." *Front. Med.* 2022, 9:876017. doi: [10.3389/fmed.2022.876017](https://doi.org/10.3389/fmed.2022.876017)

Al-Kuraishy HM et al., "Hemolytic anemia in COVID-19." *Ann. Hematol.* 2022;101:1887-1895. doi: [10.1007/s00277-022-04907-7](https://doi.org/10.1007/s00277-022-04907-7)

Aleem A and Ahmed Nadeem, *Coronavirus (COVID-19) Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)* (Treasure Island, FL: StatPearls, January, 2023)

Appelbaum K et al., "SARS-CoV-2 spike-dependent platelet activation in COVID-19 vaccine-induced thrombocytopenia." *Blood Adv.* 2022 no. 6: 2250-2253. doi: [10.1182/bloodadvances.2021005050](https://doi.org/10.1182/bloodadvances.2021005050)

Boschi C et al., "SARS-CoV-2 Spike Protein Induces Hemagglutination: Implications for COVID-19 Morbidities and Therapeutics and for Vaccine Adverse Effects," *International Journal of Biological Macromolecules* 23, no. 24 (2022): 15480, doi: <https://doi.org/10.3390/ijms232415480>

Bye AP et al., "Aberrant glycosylation of anti-SARS-CoV-2 spike IgG is a prothrombotic stimulus for platelets," *Blood* 2021, 138, 6: 1481-9. doi: <https://doi.org/10.1182/blood.2021011871>

Carnevale R et al., "Toll-Like Receptor 4-Dependent Platelet-Related Thrombosis in SARS-CoV-2 Infection," *Circulation Research* 132, no. 3 (2023): 290-305, doi: <https://doi.org/10.1161/CIRCRESAHA.122.321541>

Cossenza LC et al., "Inhibitory effects of SARS-CoV-2 spike protein and BNT162b2 vaccine on erythropoietin-induced globin gene expression in erythroid precursor cells from patients with β -thalassemia," *Exp. Hematol.* 2024, 129, 104128. doi: <https://doi.org/10.1016/j.exphem.2023.11.002>

De Michele M et al., "Vaccine-induced immune thrombotic thrombocytopenia: a possible pathogenic role of ChAdOx1 nCoV-19 vaccine-encoded soluble SARS-CoV-2 spike protein," *Haematologica* 2022, 107, 7: 1687-92. <https://doi.org/10.3324/haematol.2021.280180>

Grobbelaar LM et al., "SARS-CoV-2 Spike Protein S1 Induces Fibrin(ogen) Resistant to Fibrinolysis: Implications for Microclot Formation in COVID-19," *Bioscience Reports* 41, no. 8 (August 27, 2021): BSR20210611, doi: <https://doi.org/10.1042/BSR20210611>

Heath SP et al., "SARS-CoV-2 Spike Protein Exacerbates Thromboembolic Cerebrovascular Complications in Humanized ACE2 Mouse Model," *Transl Stroke Res.* (2024) doi: <https://doi.org/10.1007/s12975-024-01301-5>

Iba T and JH Levy, "The roles of platelets in COVID-19-associated coagulopathy and vaccine-induced immune thrombotic thrombocytopenia," *Trends Cardiovasc Med.* 2022, 32, 1: 1-9. doi: <https://doi.org/10.1016/j.tcm.2021.08.012>

Huynh TV et al., "Spike Protein of SARS-CoV-2 Activates Cardiac Fibrogenesis through NLRP3 Inflammasomes and NF- κ B Signaling," *Cells* 2024, 13, 16: 1331: <https://doi.org/10.3390/cells13161331>

Iba T and JH Levy, "The roles of platelets in COVID-19-associated coagulopathy and vaccine-induced immune thrombotic thrombocytopenia," *Trends Cardiovasc Med.* 2022, 32, 1: 1-9. doi: <https://doi.org/10.1016/j.tcm.2021.08.012>

Jana S et al., "Cell-free hemoglobin does not attenuate the effects of SARS-CoV-2 spike protein S1 subunit in pulmonary endothelial cells," *Int. J. Mol. Sci.* 2021, 22, 16: 9041. doi: <https://doi.org/10.3390/ijms22169041>

Kim SY et al., "Characterization of heparin and severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) spike glycoprotein binding interactions," *Antivir Res.* 2020, 181: 104873. doi: <https://doi.org/10.1016/j.antiviral.2020.104873>

Kircheis R, "Coagulopathies after Vaccination against SARS-CoV-2 May Be Derived from a Combined Effect of SARS-CoV-2 Spike Protein and Adenovirus Vector-Triggered Signaling Pathways," *Int J Mol Sci* 2021, 22(19): 10791. <https://doi.org/10.3390/ijms221910791>

Kuhn CC et al. "Direct Cryo-ET observation of platelet deformation induced by SARS-CoV-2 spike protein," *Nat. Commun.* (2023) 14, 620. doi: <https://doi.org/10.1038/s41467-023-36279-5>

Li T et al., "Platelets Mediate Inflammatory Monocyte Activation by SARS-CoV-2 Spike Protein," *Journal of Clinical Investigation* 132, no. 4 (February 15, 2022): e150101. doi: [10.1172/JCI150101](https://doi.org/10.1172/JCI150101)

Maugeri N et al., "Unconventional CD147-Dependent Platelet Activation Elicited by SARS-CoV-2 in COVID-19," *Journal of Thrombosis and Haemostasis* 20, no. 2. (October 28, 2021): 434–448, doi: <https://doi.org/10.1111/jth.15575>

Passariello M et al., "Interactions of Spike-RBD of SARS-CoV-2 and Platelet Factor 4: New Insights in the Etiopathogenesis of Thrombosis," *Int. J. Mol. Sci.* 2021, 22, 16: 8562. doi: <https://doi.org/10.3390/ijms22168562>

Perico L et al., "SARS-CoV-2 Spike Protein 1 Activates Microvascular Endothelial Cells and Complement System Leading to Platelet Aggregation." *Front. Immunol.* 2022, 13, 827146. doi: <https://doi.org/10.3389/fimmu.2022.827146>

Roytenberg R et al., "Thymidine phosphorylase mediates SARS-CoV-2 spike protein enhanced thrombosis in K18-hACE2TG mice," *Thromb. Res.* 2024, 244, 8: 109195. doi: [10.1016/j.thromres.2024.109195](https://doi.org/10.1016/j.thromres.2024.109195)

Russo A, et al., "Implication of COVID-19 on Erythrocytes Functionality: Red Blood Cell Biochemical Implications and Morpho-Functional Aspects," *Int. J. Mol. Sci.* 2022, 23, 4: 2171; <https://doi.org/10.3390/ijms23042171>

Ryu JK et al., "Fibrin drives thromboinflammation and neuropathology in COVID-19," *Nature* 2024, 633: 905-913. doi: <https://doi.org/10.1038/s41586-024-07873-4>

Scheim, DE. "A Deadly Embrace: Hemagglutination Mediated by SARS-CoV-2 Spike Protein at its 22 N-Glycosylation Sites, Red Blood Cell Surface Sialoglycoproteins, and Antibody." *Int. J. Mol. Sci.* 2022, 23(5), 2558. doi: <https://doi.org/10.3390/ijms23052558>

Scheim DE et al., "Sialylated Glycan Bindings from SARS-CoV-2 Spike Protein to Blood and Endothelial Cells Govern the Severe Morbidities of COVID-19," *Int. J. Mol. Sci.* 2023 Dec 1;24(23):17039. doi: <https://doi.org/10.3390/ijms242317039>

Sirsendu J et al., "Cell-Free Hemoglobin Does Not Attenuate the Effects of SARS-CoV-2 Spike Protein S1 Subunit in Pulmonary Endothelial Cells," *Int J Mol Sci*, 2021 Aug 22;22(16):9041. doi: <https://doi.org/10.3390/ijms22169041>

Zhang S et al., "SARS-CoV-2 Binds Platelet ACE2 to Enhance Thrombosis in COVID-19," *Journal of Hematology & Oncology* 13 no. 120 (2020): 120, doi: <https://doi.org/10.1186/s13045-020-00954-7>

Zhang Z et al., "SARS-CoV-2 spike protein dictates syncytium-mediated lymphocyte elimination." *Cell Death Differ.* 2021, 28, 2765–2777. doi: <https://doi.org/10.1038/s41418-021-00782-3>

Zheng Y et al., "SARS-CoV-2 Spike Protein Causes Blood Coagulation and Thrombosis by Competitive Binding to Heparan Sulfate," *International Journal of Biological Macromolecules* 193 (December 15, 2021): 1124–1129, doi: <https://doi.org/10.1016/j.ijbiomac.2021.10.112>

K. Cytokines, chemokines, inteferon, interleukins

Ao Z et al., "SARS-CoV-2 Delta spike protein enhances the viral fusogenicity and inflammatory cytokine production." *iScience* 2022, 25, 8: 104759. doi: [10.1016/j.isci.2022.104759](https://doi.org/10.1016/j.isci.2022.104759)

Chaves JCS et al., "Differential Cytokine Responses of APOE3 and APOE4 Blood-brain Barrier Cell Types to SARS-CoV-2 Spike Proteins," *J. Neuroimmune Pharmacol.* 2024, 19, 22. doi: <https://doi.org/10.1007/s11481-024-10127-9>

Chittasupho C et al., "Targeting spike glycoprotein S1 mediated by NLRP3 inflammasome machinery and the cytokine releases in A549 lung epithelial cells by nanocurcumin," *Pharmaceuticals* (Basel) 2023, 16, 6: 862. doi: <https://doi.org/10.3390/ph16060862>

Das T et al., "N-glycosylation of the SARS-CoV-2 spike protein at Asn331 and Asn343 is involved in spike-ACE2 binding, virus entry, and regulation of IL-6," *Microbiol. Immunol.* 2024, 68, 5: 165-178. doi: <https://doi.org/10.1111/1348-0421.13121>

Duarte C., "Age-dependent effects of the recombinant spike protein/SARS-CoV-2 on the M-CSF- and IL-34-differentiated macrophages in vitro." *Biochem. Biophys. Res. Commun.* 2021, 546: 97–102. doi: <https://doi.org/10.1016/j.bbrc.2021.01.104>

Forsyth CB et al., "The SARS-CoV-2 S1 spike protein promotes MAPK and NF-κB activation in human lung cells and inflammatory cytokine production in human lung and intestinal epithelial cells," *Microorganisms* 2022, 10, 10: 1996. doi: <https://doi.org/10.3390/microorganisms10101996>

Freitas RS et al., "SARS-CoV-2 Spike antagonizes innate antiviral immunity by targeting interferon regulatory factor 3," *Front Cell Infect Microbiol.* 2021, 11: 789462. doi: <https://doi.org/10.3389/fcimb.2021.789462>

Gasparello J et al., "Sulforaphane inhibits the expression of interleukin-6 and interleukin-8 induced in bronchial epithelial IB3-1 cells by exposure to the SARS-CoV-2 Spike protein," *Phytomedicine* 2021, 87: 153583. doi: <https://doi.org/10.1016/j.phymed.2021.153583>

Ghazanfari D et al., "Mechanistic insights into SARS-CoV-2 spike protein induction of the chemokine CXCL10," *Sci. Rep.* 2024, 14: 11179. doi: <https://doi.org/10.1038/s41598-024-61906-6>

Gracie NP et al., "Cellular signalling by SARS-CoV-2 spike protein," *Microbiology Australia* 2024, 45, 1: 13-17. doi: <https://doi.org/10.1071/MA24005>

Gu T et al., "Cytokine Signature Induced by SARS-CoV-2 Spike Protein in a Mouse Model." *Front. Immunol.*, 27 January 2021 Sec. Inflammation. doi: <https://doi.org/10.3389/fimmu.2020.621441>

Jugler C et al, "SARS-CoV-2 Spike Protein-Induced Interleukin 6 Signaling Is Blocked by a Plant-Produced Anti-Interleukin 6 Receptor Monoclonal Antibody," *Vaccines* 2021, 9, 11): 1365. <https://doi.org/10.3390/vaccines9111365>

Liang S et al., "SARS-CoV-2 spike protein induces IL-18-mediated cardiopulmonary inflammation via reduced mitophagy," *Signal Transduct Target Ther* (2023) 8, 103. doi: <https://doi.org/10.1038/s41392-023-01368-w>

Liu T et al., "RS-5645 attenuates inflammatory cytokine storm induced by SARS-CoV-2 spike protein and LPS by modulating pulmonary microbiota," *Int J Biol Sci.* 2021, 17, 13: 3305–3319. doi: [10.7150/ijbs.63329](https://doi.org/10.7150/ijbs.63329)

Liu X et al., "SARS-CoV-2 spike protein-induced cell fusion activates the cGAS-STING pathway and the interferon response," *Sci Signal.* 2022, 15(729): eabg8744. doi: [10.1126/scisignal.abg8744](https://doi.org/10.1126/scisignal.abg8744)

Niu C et al., "SARS-CoV-2 spike protein induces the cytokine release syndrome by stimulating T cells to produce more IL-2," *Front. Immunol.* 2024, 15: 1444643. doi: <https://doi.org/10.3389/fimmu.2024.1444643>

Norris B et al., "Evaluation of Glutathione in Spike Protein of SARS-CoV-2 Induced Immunothrombosis and Cytokine Dysregulation," *Antioxidants* 2024, 13, 3: 271. doi: <https://doi.org/10.3390/antiox13030271>

Olajide OA et al., "Induction of Exaggerated Cytokine Production in Human Peripheral Blood Mononuclear Cells by a Recombinant SARS-CoV-2 Spike Glycoprotein S1 and Its Inhibition by Dexamethasone," *Inflammation* (2021) 44: 1865–1877. doi: <https://doi.org/10.1007/s10753-021-01464-5>

Park YJ et al., "D-dimer and CoV-2 spike-immune complexes contribute to the production of PGE2 and proinflammatory cytokines in monocytes," *PLoS Pathog.*, 2022, 18, 4: e1010468. doi: <https://doi.org/10.1371/journal.ppat.1010468>

Patra T et al., "SARS-CoV-2 spike protein promotes IL-6 trans-signaling by activation of angiotensin II receptor signaling in epithelial cells." *PLoS Pathog.* 2020;16:e1009128. doi: <https://doi.org/10.1371/journal.ppat.1009128>

Samsudin S et al., "SARS-CoV-2 spike protein as a bacterial lipopolysaccharide delivery system in an overzealous inflammatory cascade," *J. Mol. Biol.* 2022, 14, 9: mjac058. <https://doi.org/10.1093/jmcb/mjac058>

Schroeder JT and AP Bieneman, "The S1 Subunit of the SARS-CoV-2 Spike protein activates human monocytes to produce cytokines linked to COVID-19: relevance to galectin-3," *Front Immunol.* 2022, 13: 831763. doi: <https://doi.org/10.3389/fimmu.2022.831763>

Sharma VK et al., “Nanocurcumin Potently Inhibits SARS-CoV-2 Spike Protein-Induced Cytokine Storm by Deactivation of MAPK/NF- κ B Signaling in Epithelial Cells.” *ACS Appl. Bio Mater.* 2022, 5, 2: 483–491. doi: <https://doi.org/10.1021/acsabm.1c00874>

Sui Y et al., “SARS-CoV-2 Spike Protein Suppresses ACE2 and Type I Interferon Expression in Primary Cells From Macaque Lung Bronchoalveolar Lavage,” *Frontiers in Immunology* (June 4, 2021), 12. doi: <https://doi.org/10.3389/fimmu.2021.658428>

Youn JY et al., “Therapeutic application of estrogen for COVID-19: Attenuation of SARS-CoV-2 spike protein and IL-6 stimulated, ACE2-dependent NOX2 activation, ROS production and MCP-1 upregulation in endothelial cells,” *Redox Biol.* 2021, 46: 102099. doi: <https://doi.org/10.1016/j.redox.2021.102099>

Zhang Q et al., “Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) membrane (M) and spike (S) proteins antagonize host type I interferon response,” 2021, *Front Cell Infect Microbiol* 11: 766922. doi: <https://doi.org/10.3389/fcimb.2021.766922>

Zhang RG et al., “SARS-CoV-2 spike protein receptor binding domain promotes IL-6 and IL-8 release via ATP/P2Y₂ and ERK1/2 signaling pathways in human bronchial epithelia,” *Mol. Immunol.* 2024, 167: 53-61. doi: <https://doi.org/10.1016/j.molimm.2024.02.005>

L. Endothelial

Bhargavan B and GD Kanmogne, “SARS-CoV-2 spike proteins and cell–cell communication inhibits TFPI and induces thrombogenic factors in human lung microvascular endothelial cells and neutrophils: implications for COVID-19 coagulopathy pathogenesis,” *Int. J. Mol. Sci.* 2022, 23, 18: 10436. doi: <https://doi.org/10.3390/ijms231810436>

Biancatelli RMLC, et al. “The SARS-CoV-2 spike protein subunit S1 induces COVID-19-like acute lung injury in Kappa18-hACE2 transgenic mice and barrier dysfunction in human endothelial cells.” *Am. J. Physiol. Lung Cell. Mol. Physiol.* 2021, 321, L477–L484. doi: <https://doi.org/10.1152/ajplung.00223.2021>

Gamblicher T et al., “SARS-CoV-2 spike protein is present in both endothelial and eccrine cells of a chilblain-like skin lesion,” *J Eur Acad Dermatol Venereol.* 2020, 1, 10: e187-e189. doi: <https://doi.org/10.1111/jdv.16970>

Guo Y and V Kanamarlapudi, “Molecular Analysis of SARS-CoV-2 Spike Protein-Induced Endothelial Cell Permeability and vWF Secretion,” *Int. J. Mol. Sci.* 2023, 24(6): 5664. <https://doi.org/10.3390/ijms24065664>

Jana S et al., “Cell-free hemoglobin does not attenuate the effects of SARS-CoV-2 spike protein S1 subunit in pulmonary endothelial cells,” *Int. J. Mol. Sci.* 2021, 22, 16: 9041. doi: <https://doi.org/10.3390/ijms22169041>

Kulkoviene G et al., “Differential Mitochondrial, Oxidative Stress and Inflammatory Responses to SARS-CoV-2 Spike Protein Receptor Binding Domain in Human Lung Microvascular, Coronary Artery Endothelial and Bronchial Epithelial Cells,” *Int. J. Mol. Sci.* 2024, 25, 6: 3188. doi: <https://doi.org/10.3390/ijms25063188>

Marrone L et al., “Tirofiban prevents the effects of SARS-CoV-2 spike protein on macrophage activation and endothelial cell death,” *Heliyon*, (2024) 10, 15: e35341. doi: [10.1016/j.heliyon.2024.e35341](https://doi.org/10.1016/j.heliyon.2024.e35341)

Meyer K et al., “SARS-CoV-2 Spike Protein Induces Paracrine Senescence and Leukocyte Adhesion in Endothelial Cells,” *J. Virol.* 2021, 95, e0079421. doi: <https://doi.org/10.1128/jvi.00794-21>

Nuovo JG et al., "Endothelial Cell Damage Is the Central Part of COVID-19 and a Mouse Model Induced by Injection of the S1 Subunit of the Spike Protein." *Ann. Diagn. Pathol.* 2021, 51, 151682. doi: <https://doi.org/10.1016/j.anndiagpath.2020.151682>

Perico L et al., "SARS-CoV-2 and the spike protein in endotheliopathy," *Trends Microbiol.* 2024, 32, 1: 53-67. doi: [10.1016/j.tim.2023.06.004](https://doi.org/10.1016/j.tim.2023.06.004)

Perico L et al., "SARS-CoV-2 Spike Protein 1 Activates Microvascular Endothelial Cells and Complement System Leading to Platelet Aggregation." *Front. Immunol.* 2022, 13, 827146. doi: <https://doi.org/10.3389/fimmu.2022.827146>

Raghavan S et al., "SARS-CoV-2 Spike Protein Induces Degradation of Junctional Proteins That Maintain Endothelial Barrier Integrity." *Front. Cardiovasc. Med.* 2021, 8, 687783. doi: <https://doi.org/10.3389/fcvm.2021.687783>

Ratajczak MZ et al., "SARS-CoV-2 Entry Receptor ACE2 Is Expressed on Very Small CD45⁺ Precursors of Hematopoietic and Endothelial Cells and in Response to Virus Spike Protein Activates the Nlrp3 Inflammasome," *Stem Cell Rev Rep.* 2021 Feb;17(1):266-277. doi: <https://doi.org/10.1007/s12015-020-10010-z>

Robles JP et al., "The Spike Protein of SARS-CoV-2 Induces Endothelial Inflammation through Integrin $\alpha 5\beta 1$ and NF- κ B Signaling," *J. Biol. Chem.* 2022, 298, 3: 101695, <https://doi.org/10.1016/j.jbc.2022.101695>

Rotoli BM et al., "Endothelial cell activation by SARS-CoV-2 spike S1 protein: A crosstalk between endothelium and innate immune cells," *Biomedicines* 2021, 9, 9: 1220. doi: <https://doi.org/10.3390/biomedicines9091220>

Ruben ML et al., "The SARS-CoV-2 spike protein subunit S1 induces COVID-19-like acute lung injury in K18-hACE2 transgenic mice and barrier dysfunction in human endothelial cells." *Am J Physiol Lung Cell Mol Physiol.* 2021, 321, 2: L477-L484. doi: <https://doi.org/10.1152/ajplung.00223.2021>

Sano H et al., "A case of persistent, confluent maculopapular erythema following a COVID-19 mRNA vaccination is possibly associated with the intralesional spike protein expressed by vascular endothelial cells and eccrine glands in the deep dermis," *J. Dermatol.* (2023) 50: 1208–1212. doi: <https://doi.org/10.1111/1346-8138.16816>

Santonja C et al., "COVID-19 chilblain-like lesion: immunohistochemical demonstration of SARS-CoV-2 spike protein in blood vessel endothelium and sweat gland epithelium in a polymerase chain reaction-negative patient." *Br J Dermatol.* 2020, 183(4): 778-780. doi: <https://doi.org/10.1111/bjd.19338>

Scheim DE et al., "Sialylated Glycan Bindings from SARS-CoV-2 Spike Protein to Blood and Endothelial Cells Govern the Severe Morbidities of COVID-19," *Int. J. Mol. Sci.* 2023 Dec 1;24(23):17039. doi: <https://doi.org/10.3390/ijms242317039>

Sirsendu J et al., "Cell-Free Hemoglobin Does Not Attenuate the Effects of SARS-CoV-2 Spike Protein S1 Subunit in Pulmonary Endothelial Cells," *Int J Mol Sci.* 2021 Aug 22;22(16):9041. doi: <https://doi.org/10.3390/ijms22169041>

Stern B et al., "SARS-CoV-2 spike protein induces endothelial dysfunction in 3D engineered vascular networks." *J. Biomed. Mater. Res. A.* 2023, 112, 4: 524-533. doi: <https://doi.org/10.1002/jbm.a.37543>

Villacampa A et al., "SARS-CoV-2 S protein activates NLRP3 inflammasome and deregulates coagulation factors in endothelial and immune cells," *Cell Commun. Signal.* 2024, 22, 38. doi: <https://doi.org/10.1186/s12964-023-01397-6>

Wu ML et al., "Mast cell activation triggered by SARS-CoV-2 causes inflammation in brain microvascular endothelial cells and microglia," *Front. Cell. Infect. Microbiol.*, 2024, 14. doi: <https://doi.org/10.3389/fcimb.2024.1358873>

Youn JY et al., "Therapeutic application of estrogen for COVID-19: Attenuation of SARS-CoV-2 spike protein and IL-6 stimulated, ACE2-dependent NOX2 activation, ROS production and MCP-1 upregulation in endothelial cells," *Redox Biol.* 2021, 46: 102099. doi: <https://doi.org/10.1016/j.redox.2021.102099>

Zekri-Nechar K et al., "Spike Protein Subunits of SARS-CoV-2 Alter Mitochondrial Metabolism in Human Pulmonary Microvascular Endothelial Cells: Involvement of Factor Xa." *Dis. Markers* (2022): 1118195. doi: <https://doi.org/10.1155/2022/1118195>

M. Gastrointestinal

Forsyth CB et al., "The SARS-CoV-2 S1 spike protein promotes MAPK and NF-κB activation in human lung cells and inflammatory cytokine production in human lung and intestinal epithelial cells," *Microorganisms* 2022, 10, 10: 1996. doi: <https://doi.org/10.3390/microorganisms10101996>

Li Z et al., "SARS-CoV-2 pathogenesis in the gastrointestinal tract mediated by Spike-induced intestinal inflammation," *Precis. Clin. Med.* 2024, 7, 1: pbad034. doi: <https://doi.org/10.1093/pcmedi/pbad034>

Luo Y et al., "SARS-Cov-2 spike induces intestinal barrier dysfunction through the interaction between CEACAM5 and Galectin-9," *Front. Immunol.*, 2024, 15. doi: <https://doi.org/10.3389/fimmu.2024.1303356>

Nascimento RR et al., "SARS-CoV-2 Spike protein triggers gut impairment since mucosal barrier to innermost layers: From basic science to clinical relevance," *Mucosal Immunol.* 2024, 17, 4: 565-583. doi: <https://doi.org/10.1016/j.mucimm.2024.03.00>

Yilmaz A et al., "Differential proinflammatory responses of colon epithelial cells to SARS-CoV-2 spike protein and *Pseudomonas aeruginosa* lipopolysaccharide," *Turk J Biochem.* 2024. doi: <https://doi.org/10.1515/tjb-2024-0144>

Zeng FM et al., "SARS-CoV-2 spike spurs intestinal inflammation via VEGF production in enterocytes," *EMBO Mol Med.* 2022, 14: e14844. doi: <https://doi.org/10.15252/emmm.202114844>

N. Immune dysfunction

Baldari CT et al., "Emerging Roles of SARS-CoV-2 Spike-ACE2 in Immune Evasion and Pathogenesis," *Trends in Immunology* 44 no. 6 (June 2023), doi: <https://doi.org/10.1016/j.it.2023.04.001>

Bocquet-Garcon A, "Impact of the SARS-CoV-2 Spike Protein on the Innate Immune System: A Review," *Cureus* 2024, 16(3): e57008. doi: [10.7759/cureus.57008](https://doi.org/10.7759/cureus.57008)

Kim MJ et al., "The SARS-CoV-2 spike protein induces lung cancer migration and invasion in a TLR2-dependent manner," *Cancer Commun (London)*, 2023, 44, 2: 273-277. doi: <https://doi.org/10.1002/cac2.12485>

Onnis A et al., “SARS-CoV-2 Spike protein suppresses CTL-mediated killing by inhibiting immune synapse assembly,” *J Exp Med* (2023) 220 (2): e20220906. doi: <https://doi.org/10.1084/jem.20220906>

O. Macrophages, monocytes, neutrophils

Ahn WM et al., “SARS-CoV-2 Spike Protein Stimulates Macropinocytosis in Murine and Human Macrophages via PKC-NADPH Oxidase Signaling,” *Antioxidants* 2024, 13, 2: 175.
doi: <https://doi.org/10.3390/antiox13020175>

Ait-Belkacem I et al., “SARS-CoV-2 spike protein induces a differential monocyte activation that may contribute to age bias in COVID-19 severity,” *Sci. Rep.* 2022, 12: 20824. doi: <https://doi.org/10.1038/s41598-022-25259-2>

Barhoumi T et al., “SARS-CoV-2 coronavirus Spike protein-induced apoptosis, inflammatory, and oxidative stress responses in THP-1-like-macrophages: potential role of angiotensin-converting enzyme inhibitor (perindopril),” *Front Immunol.* 2021, 12: 728896. doi: <https://doi.org/10.3389/fimmu.2021.728896>

Bortolotti D et al., “SARS-CoV-2 Spike 1 Protein Controls Natural Killer Cell Activation via the HLA-E/NKG2A Pathway,” *Cells* 2020, 9(9), 1975. doi: <https://doi.org/10.3390/cells9091975>

Cao X et al., “Spike protein of SARS-CoV-2 activates macrophages and contributes to induction of acute lung inflammation in male mice,” *FASEB J.* 2021, 35, e21801. doi: <https://doi.org/10.1096/fj.202002742RR>

Chiok K et al., “Proinflammatory Responses in SARS-CoV-2 and Soluble Spike Glycoprotein S1 Subunit Activated Human Macrophages,” *Viruses* 2023, 15, 3: 754. doi: <https://doi.org/10.3390/v15030754>

Cory TJ et al., “Metformin Suppresses Monocyte Immunometabolic Activation by SARS-CoV-2 Spike Protein Subunit 1,” *Front. Immunol. Sec. Cytokines and Soluble Mediators in Immunity*, 2021, 12: 733921. doi: <https://doi.org/10.3389/fimmu.2021.733921>

Del Re A et al., “Ultramicronized Palmitoylethanolamide Inhibits NLRP3 Inflammasome Expression and Pro-Inflammatory Response Activated by SARS-CoV-2 Spike Protein in Cultured Murine Alveolar Macrophages.” *Metabolites* 2021, 11, 9: 592. doi: <https://doi.org/10.3390/metabo11090592>

Duarte C., “Age-dependent effects of the recombinant spike protein/SARS-CoV-2 on the M-CSF- and IL-34-differentiated macrophages in vitro.” *Biochem. Biophys. Res. Commun.* 2021, 546: 97–102. doi: <https://doi.org/10.1016/j.bbrc.2021.01.104>

Karwaciak I et al., “Nucleocapsid and Spike Proteins of the Coronavirus Sars-Cov-2 Induce Il6 in Monocytes and Macrophages—Potential Implications for Cytokine Storm Syndrome.” *Vaccines* 2021, 9(1), 54: 1–10. doi: <https://doi.org/10.3390/vaccines9010054>

Li T et al., “Platelets Mediate Inflammatory Monocyte Activation by SARS-CoV-2 Spike Protein,” *Journal of Clinical Investigation* 132, no. 4 (February 15, 2022): e150101. doi: [10.1172/JCI150101](https://doi.org/10.1172/JCI150101)

Loh JT et al., “Dok3 restrains neutrophil production of calprotectin during TLR4 sensing of SARS-CoV-2 spike protein,” *Front. Immunol.* 2022, 13, Sec. Molecular Innate Immunity. doi: <https://doi.org/10.3389/fimmu.2022.996637>

Marrone L et al., “Tirofiban prevents the effects of SARS-CoV-2 spike protein on macrophage activation and endothelial cell death,” *Heliyon*, (2024) 10, 15: e35341. doi: [10.1016/j.heliyon.2024.e35341](https://doi.org/10.1016/j.heliyon.2024.e35341)

Miller GM et al., "SARS-CoV-2 and SARS-CoV-2 Spike protein S1 subunit Trigger Proinflammatory Response in Macrophages in the Absence of Productive Infection," *J. Immunol.* 2023, 210 (1_Supplement): 71.30. doi: <https://doi.org/10.4049/jimmunol.210.Supp.71.30>

Onnis A et al., "SARS-CoV-2 Spike protein suppresses CTL-mediated killing by inhibiting immune synapse assembly," *J Exp Med* (2023) 220 (2): e20220906. doi: <https://doi.org/10.1084/jem.20220906>

Palestra F et al. "SARS-CoV-2 Spike Protein Activates Human Lung Macrophages," *Int. J. Mol. Sci.* 2023, 24, 3: 3036. doi: <https://doi.org/10.3390/ijms24033036>

Park C et al., "Murine alveolar Macrophages Rapidly Accumulate intranasally Administered SARS-CoV-2 Spike Protein leading to neutrophil Recruitment and Damage," *Elife* 12 (2024), p. RP86764. doi: <https://doi.org/10.7554/eLife.86764.3>

Park YJ et al., "D-dimer and CoV-2 spike-immune complexes contribute to the production of PGE2 and proinflammatory cytokines in monocytes," *PLoS Pathog.*, 2022, 18, 4: e1010468. doi: <https://doi.org/10.1371/journal.ppat.1010468>

Park YJ et al., "Pyrogenic and inflammatory mediators are produced by polarized M1 and M2 macrophages activated with D-dimer and SARS-CoV-2 spike immune complexes," *Cytokine* 2024, 173: 156447. doi: <https://doi.org/10.1016/j.cyto.2023.156447>

Patterson BK et al., "Persistence of SARS CoV-2 S1 Protein in CD16+ Monocytes in Post-Acute Sequelae of COVID-19 (PASC) up to 15 Months Post-Infection," *Front. Immunol.* 12 (Sec. Viral Immunology). doi: <https://doi.org/10.3389/fimmu.2021.746021>

Pence B, "Recombinant SARS-CoV-2 Spike Protein Mediates Glycolytic and Inflammatory Activation in Human Monocytes," *Innov Aging* 2020, 4, sp. 1: 955. doi: <https://doi.org/10.1093/geroni/igaa057.3493>

Satta S et al., "An engineered nano-liposome-human ACE2 decoy neutralizes SARS-CoV-2 Spike protein-induced inflammation in both murine and human macrophages," *Theranostics* 2022, 12, 6: 2639–2657. doi: [10.7150/thno.66831](https://doi.org/10.7150/thno.66831)

Schroeder JT and AP Bieneman, "The S1 Subunit of the SARS-CoV-2 Spike protein activates human monocytes to produce cytokines linked to COVID-19: relevance to galectin-3," *Front Immunol.* 2022, 13: 831763. doi: <https://doi.org/10.3389/fimmu.2022.831763>

Shirato K and Takako Kizaki, "SARS-CoV-2 Spike Protein S1 Subunit Induces Pro- inflammatory Responses via Toll-Like Receptor 4 Signaling in Murine and Human Macrophages," *Heliyon* 7, no. 2 (February 2, 2021):e06187, doi: <https://doi.org/10.1016/j.heliyon.2021.e06187>

Theobald SJ et al., "Long-lived macrophage reprogramming drives spike protein-mediated inflammasome activation in COVID-19." *EMBO Mol. Med.* (2021) 13:e14150. doi: <https://doi.org/10.15252/emmm.202114150>

Vettori M et al., "Effects of Different Types of Recombinant SARS-CoV-2 Spike Protein on Circulating Monocytes' Structure," *Int. J. Mol. Sci.* 2023, 24, 11, 9373. doi: <https://doi.org/10.3390/ijms24119373>

Youn YJ et al., "Nucleocapsid and spike proteins of SARS-CoV-2 drive neutrophil extracellular trap formation." *Immune Netw.* (2021) 21, 2: e16. doi: <https://doi.org/10.4110/in.2021.21.e16>

Zaki H and S Khan, "SARS-CoV-2 spike protein induces inflammatory molecules through TLR2 in macrophages and monocytes." *J. Immunol.* 2021, 206 (1_supplement): 62.07. doi: <https://doi.org/10.4049/jimmunol.206.Supp.62.07>

P. MAPK/NF- κ B

Arjsri P et al., "Hesperetin from root extract of *Clerodendrum petasites* S. Moore inhibits SARS-CoV-2 spike protein S1 subunit-induced Nlrp3 inflammasome in A549 lung cells via modulation of the Akt/Mapk/Ap-1 pathway," *Int. J. Mol. Sci.* 2022, 23, 18: 10346. doi: <https://doi.org/10.3390/ijms231810346>

Bhattacharyya S and JK Tobacman, "SARS-CoV-2 spike protein-ACE2 interaction increases carbohydrate sulfotransferases and reduces N-acetylgalactosamine-4-sulfatase by p38 MAPK," *Signal Transduct Target Ther* 2024, 9, 39. doi: <https://doi.org/10.1038/s41392-024-01741-3>

Forsyth CB et al., "The SARS-CoV-2 S1 spike protein promotes MAPK and NF- κ B activation in human lung cells and inflammatory cytokine production in human lung and intestinal epithelial cells," *Microorganisms* 2022, 10, 10: 1996. doi: <https://doi.org/10.3390/microorganisms10101996>

Johnson EL et al., "The S1 spike protein of SARS-CoV-2 upregulates the ERK/MAPK signaling pathway in DC-SIGN-expressing THP-1 cells," *Cell Stress Chaperones* 2024, 29, 2: 227-234. doi: <https://doi.org/10.1016/j.cstres.2024.03.002>

Khan S et al., "SARS-CoV-2 Spike Protein Induces Inflammation via TLR2-Dependent Activation of the NF- κ B Pathway," *eLife* 10 (December 6, 2021): e68563, doi: <https://doi.org/10.7554/eLife.68563>

Kircheis R and O Planz, "Could a Lower Toll-like Receptor (TLR) and NF- κ B Activation Due to a Changed Charge Distribution in the Spike Protein Be the Reason for the Lower Pathogenicity of Omicron?" *Int. J. Mol. Sci.* 2022, 23, 11: 5966. doi: <https://doi.org/10.3390/ijms23115966>

Kyriakopoulos AM et al., "Mitogen Activated Protein Kinase (MAPK) Activation, p53, and Autophagy Inhibition Characterize the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Spike Protein Induced Neurotoxicity." *Cureus* 2022, 14, 12: e32361. doi: [10.7759/cureus.32361](https://doi.org/10.7759/cureus.32361)

Robles JP et al., "The Spike Protein of SARS-CoV-2 Induces Endothelial Inflammation through Integrin α 5 β 1 and NF- κ B Signaling," *J. Biol. Chem.* 2022, 298, 3: 101695, <https://doi.org/10.1016/j.jbc.2022.101695>

Sharma VK et al., "Nanocurcumin Potently Inhibits SARS-CoV-2 Spike Protein-Induced Cytokine Storm by Deactivation of MAPK/NF- κ B Signaling in Epithelial Cells." *ACS Appl. Bio Mater.* 2022, 5, 2: 483–491. doi: <https://doi.org/10.1021/acsabm.1c00874>

Bhattacharyya S and JK Tobacman, "SARS-CoV-2 spike protein-ACE2 interaction increases carbohydrate sulfotransferases and reduces N-acetylgalactosamine-4-sulfatase by p38 MAPK," *Signal Transduct Target Ther* 2024, 9, 39. doi: <https://doi.org/10.1038/s41392-024-01741-3>

Q. Mast cells

Cao JB et al., "Mast cell degranulation-triggered by SARS-CoV-2 induces tracheal-bronchial epithelial inflammation and injury," *Virol. Sin.* 2024, 39, 2: 309-318. doi: <https://doi.org/10.1016/j.virs.2024.03.001>

Fajloun Z et al., "SARS-CoV-2 or Vaccinal Spike Protein can Induce Mast Cell Activation Syndrome (MCAS)," *Infect Disord Drug Targets*, 2025, 25, 1: e300424229561. doi: [10.2174/0118715265319896240427045026](https://doi.org/10.2174/0118715265319896240427045026)

Wu ML et al., "Mast cell activation triggered by SARS-CoV-2 causes inflammation in brain microvascular endothelial cells and microglia," *Front. Cell. Infect. Microbiol.*, 2024, 14. doi: <https://doi.org/10.3389/fcimb.2024.1358873>

R. Microglia

Chang MH et al., "SARS-CoV-2 Spike Protein 1 Causes Aggregation of α -Synuclein via Microglia-Induced Inflammation and Production of Mitochondrial ROS: Potential Therapeutic Applications of Metformin," *Biomedicines* 2024 May 31;12(6):1223. doi: <https://doi.org/10.3390/biomedicines12061223>

Clough E et al., "Mitochondrial Dynamics in SARS-COV2 Spike Protein Treated Human Microglia: Implications for Neuro-COVID," *Journal of Neuroimmune Pharmacology* 16, no. 4 (December 2021): 770–784, doi: <https://doi.org/10.1007/s11481-021-10015-6>

Frank MG et al., "SARS-CoV-2 Spike S1 Subunit Induces Neuroinflammatory, Microglial and Behavioral Sickness Responses: Evidence of PAMP-Like Properties," *Brain Behav. Immun.* 100 (February 2022): 267277, doi: <https://doi.org/10.1016/j.bbi.2021.12.007>

Mishra R and AC Banerjea, "SARS-CoV-2 Spike targets USP33-IRF9 axis via exosomal miR-148a to activate human microglia." *Front. Immunol.* 2021, 12: 656700. <https://doi.org/10.3389/fimmu.2021.656700>

Olajide OA et al., "SARS-CoV-2 spike glycoprotein S1 induces neuroinflammation in BV-2 microglia," *Mol. Neurobiol.* 2022; 59:445-458. doi: <https://doi.org/10.1007/s12035-021-02593-6>

Wu ML et al., "Mast cell activation triggered by SARS-CoV-2 causes inflammation in brain microvascular endothelial cells and microglia," *Front. Cell. Infect. Microbiol.*, 2024, 14. doi: <https://doi.org/10.3389/fcimb.2024.1358873>

S. Microvascular

Avolio E et al., "The SARS-CoV-2 Spike Protein Disrupts Human Cardiac Pericytes Function through CD147 Receptor-Mediated Signalling: A Potential Non-infective Mechanism of COVID-19 Microvascular Disease," *Clinical Science* 135, no. 24. (December 22, 2021): 2667–2689, doi: <https://doi.org/10.1042/CS20210735>

Bhargavan B and GD Kanmogne, "SARS-CoV-2 spike proteins and cell–cell communication inhibits TFPI and induces thrombogenic factors in human lung microvascular endothelial cells and neutrophils: implications for COVID-19 coagulopathy pathogenesis," *Int. J. Mol. Sci.* 2022, 23, 18: 10436. doi: <https://doi.org/10.3390/ijms231810436>

Kulkoviene G et al., "Differential Mitochondrial, Oxidative Stress and Inflammatory Responses to SARS-CoV-2 Spike Protein Receptor Binding Domain in Human Lung Microvascular, Coronary Artery Endothelial and Bronchial Epithelial Cells," *Int. J. Mol. Sci.* 2024, 25, 6: 3188. doi: <https://doi.org/10.3390/ijms25063188>

Magro N et al., "Disruption of the blood-brain barrier is correlated with spike endocytosis by ACE2 + endothelia in the CNS microvasculature in fatal COVID-19. Scientific commentary on 'Detection of blood-brain barrier disruption in brains of patients with COVID-19, but no evidence of brain penetration by SARS-CoV-2,'" *Acta Neuropathol.* 2024 Feb 27;147(1):47. doi: <https://doi.org/10.1007/s00401-023-02681-y>

Panigrahi S et al., "SARS-CoV-2 Spike Protein Destabilizes Microvascular Homeostasis," *Microbiol Spectr.* 2021 Dec 22;9(3):e0073521. doi: <https://doi.org/10.1128/Spectrum.00735-21>

Perico L et al., “SARS-CoV-2 Spike Protein 1 Activates Microvascular Endothelial Cells and Complement System Leading to Platelet Aggregation.” *Front. Immunol.* 2022, 13, 827146. doi: <https://doi.org/10.3389/fimmu.2022.827146>

Wu ML et al., “Mast cell activation triggered by SARS-CoV-2 causes inflammation in brain microvascular endothelial cells and microglia,” *Front. Cell. Infect. Microbiol.*, 2024, 14. doi: <https://doi.org/10.3389/fcimb.2024.1358873>

Zekri-Nechar K et al., “Spike Protein Subunits of SARS-CoV-2 Alter Mitochondrial Metabolism in Human Pulmonary Microvascular Endothelial Cells: Involvement of Factor Xa.” *Dis. Markers* (2022): 1118195. doi: <https://doi.org/10.1155/2022/1118195>

T. Mitochondria/metabolism

Cao X et al., “The SARS-CoV-2 spike protein induces long-term transcriptional perturbations of mitochondrial metabolic genes, causes cardiac fibrosis, and reduces myocardial contractile in obese mice.” *Mol. Metab.* (2023) 74, 101756. doi: <https://doi.org/10.1016/j.molmet.2023.101756>

Chang MH et al., “SARS-CoV-2 Spike Protein 1 Causes Aggregation of α -Synuclein via Microglia-Induced Inflammation and Production of Mitochondrial ROS: Potential Therapeutic Applications of Metformin,” *Biomedicines* 2024 May 31;12(6):1223. doi: <https://doi.org/10.3390/biomedicines12061223>

Clough E et al., “Mitochondrial Dynamics in SARS-COV2 Spike Protein Treated Human Microglia: Implications for Neuro-COVID,” *Journal of Neuroimmune Pharmacology* 16, no. 4 (December 2021): 770–784, doi: <https://doi.org/10.1007/s11481-021-10015-6>

Huynh TV et al., “Spike Protein Impairs Mitochondrial Function in Human Cardiomyocytes: Mechanisms Underlying Cardiac Injury in COVID-19.” *Cells* 2023, 12, 877. doi: <https://doi.org/10.3390/cells12060877>

Kulkoviene G et al., “Differential Mitochondrial, Oxidative Stress and Inflammatory Responses to SARS-CoV-2 Spike Protein Receptor Binding Domain in Human Lung Microvascular, Coronary Artery Endothelial and Bronchial Epithelial Cells,” *Int. J. Mol. Sci.* 2024, 25, 6: 3188. doi: <https://doi.org/10.3390/ijms25063188>

Mercado-Gómez M et al., “The spike of SARS-CoV-2 promotes metabolic rewiring in hepatocytes.” *Commun. Biol.* 2022, 5, 827. doi: <https://doi.org/10.1038/s42003-022-03789-9>

Nguyen V, “The Spike Protein of SARS-CoV-2 Impairs Lipid Metabolism and Increases Susceptibility to Lipotoxicity: Implication for a Role of Nrf2,” *Cells* (2022) 11, 12: 1916. doi: <https://doi.org/10.3390/cells11121916>

Zekri-Nechar K et al., “Spike Protein Subunits of SARS-CoV-2 Alter Mitochondrial Metabolism in Human Pulmonary Microvascular Endothelial Cells: Involvement of Factor Xa.” *Dis. Markers* (2022): 1118195. doi: <https://doi.org/10.1155/2022/1118195>

U. Myocarditis/cardiomyopathy

Avolio E et al., “The SARS-CoV-2 Spike Protein Disrupts Human Cardiac Pericytes Function through CD147 Receptor-Mediated Signalling: A Potential Non-infective Mechanism of COVID-19 Microvascular Disease,” *Clinical Science* 135, no. 24. (December 22, 2021): 2667–2689, doi: <https://doi.org/10.1042/CS20210735>

Baumeier C et al., "Intramyocardial Inflammation after COVID-19 Vaccination: An Endomyocardial Biopsy-Proven Case Series." *Int. J. Mol. Sci.* 2022;23:6940. doi: <https://doi.org/10.3390/ijms23136940>

Bellavite P et al., "Immune response and molecular mechanisms of cardiovascular adverse effects of spike proteins from SARS-coV-2 and mRNA vaccines," *Biomedicines* 2023, 11, 2: 451. doi: <https://doi.org/10.3390/biomedicines11020451>

Boretti A. "PQQ Supplementation and SARS-CoV-2 Spike Protein-Induced Heart Inflammation," *Nat. Prod. Commun.* 2022, 17, 1934578x221080929. doi: <https://doi.org/10.1177/1934578X221080929>

Buoninfante A et al., "Myocarditis associated with COVID-19 vaccination," *npj Vaccines* 2024, 122. doi: <https://doi.org/10.1038/s41541-024-00893-1>

Cao X et al., "The SARS-CoV-2 spike protein induces long-term transcriptional perturbations of mitochondrial metabolic genes, causes cardiac fibrosis, and reduces myocardial contractile in obese mice." *Mol. Metab.* (2023) 74, 101756. doi: <https://doi.org/10.1016/j.molmet.2023.101756>

Clemens DJ et al., "SARS-CoV-2 spike protein-mediated cardiomyocyte fusion may contribute to increased arrhythmic risk in COVID-19," *PLoS One* 2023, 18(3): e0282151. doi: <https://doi.org/10.1371/journal.pone.0282151>

"Coronavirus Spike Protein Activated Natural Immune Response, Damaged Heart Muscle Cells," *DAIC*, July 27, 2022, <https://www.dicardiology.com/content/coronavirus-spike-protein-activated-natural-immune-response-damaged-heart-muscle-cells>

De Sousa PMB et al., "Fatal Myocarditis following COVID-19 mRNA Immunization: A Case Report and Differential Diagnosis Review," *Vaccines* 2024, 12, 2: 194. doi: <https://doi.org/10.3390/vaccines12020194>

Forte E, "Circulating spike protein may contribute to myocarditis after COVID-19 vaccination," *Nat. Cardiovasc. Res.* 2023, 2: 100. doi: <https://doi.org/10.1038/s44161-023-00222-0>

Huang X et al., "Sars-Cov-2 Spike Protein-Induced Damage of hiPSC-Derived Cardiomyocytes." *Adv. Biol.* 2022, 6, 7: e2101327. doi: <https://doi.org/10.1002/adbi.202101327>

Hulscher N et al., "Autopsy findings in cases of fatal COVID-19 vaccine-induced myocarditis," *ESC Heart Failure* 2024. doi: <https://doi.org/10.1002/ehf2.14680>

Huynh TV et al., "Spike Protein Impairs Mitochondrial Function in Human Cardiomyocytes: Mechanisms Underlying Cardiac Injury in COVID-19." *Cells* 2023, 12, 877. doi: <https://doi.org/10.3390/cells12060877>

Huynh TV et al., "Spike Protein of SARS-CoV-2 Activates Cardiac Fibrogenesis through NLRP3 Inflammasomes and NF-κB Signaling," *Cells* 2024, 13, 16: 1331: <https://doi.org/10.3390/cells13161331>

Imig JD, "SARS-CoV-2 spike protein causes cardiovascular disease independent of viral infection," *Clin Sci (Lond)* (2022) 136 (6): 431–434. doi: <https://doi.org/10.1042/CS20220028>

Kato Y et al., "TRPC3-Nox2 Protein Complex Formation Increases the Risk of SARS-CoV-2 Spike Protein-Induced Cardiomyocyte Dysfunction through ACE2 Upregulation." *Int. J. Mol. Sci.* 2023, 24, 1: 102. doi: <https://doi.org/10.3390/ijms24010102>

Lin Z, "More than a key—the pathological roles of SARS-CoV-2 spike protein in COVID-19 related cardiac injury." *Sports Med Health Sci* 2023, 6, 3: 209-220. <https://doi.org/10.1016/j.smhs.2023.03.004>

Yonker LM et al., “Circulating Spike Protein Detected in Post–COVID-19 mRNA Vaccine Myocarditis,” *Circulation* 147, no. 11 (2023), <https://doi.org/10.1161/CIRCULATIONAHA.122.061025>

V. NLRP3

Albornoz EA et al., “SARS-CoV-2 drives NLRP3 inflammasome activation in human microglia through spike protein,” *Mol. Psychiatr.* (2023) 28: 2878–2893. Doi: <https://doi.org/10.1038/s41380-022-01831-0>

Arjsri P et al., “Hesperetin from root extract of *Clerodendrum petasites* S. Moore inhibits SARS-CoV-2 spike protein S1 subunit-induced Nlrp3 inflammasome in A549 lung cells via modulation of the Akt/Mapk/Ap-1 pathway,” *Int. J. Mol. Sci.* 2022, 23, 18: 10346. doi: <https://doi.org/10.3390/ijms231810346>

Chittasupho C et al., “Inhibition of SARS-CoV-2-Induced NLRP3 Inflammasome-Mediated Lung Cell Inflammation by Triphala-Loaded Nanoparticle Targeting Spike Glycoprotein S1,” *Pharmaceutics* 2024, 16, 6: 751. <https://doi.org/10.3390/pharmaceutics16060751>

Chittasupho C et al., “Targeting spike glycoprotein S1 mediated by NLRP3 inflammasome machinery and the cytokine releases in A549 lung epithelial cells by nanocurcumin,” *Pharmaceuticals* (Basel) 2023, 16, 6: 862. doi: <https://doi.org/10.3390/ph16060862>

Corpetti C et al., “Cannabidiol inhibits SARS-Cov-2 spike (S) protein-induced cytotoxicity and inflammation through a PPAR γ -dependent TLR4/NLRP3/Caspase-1 signaling suppression in Caco-2 cell line.” *Phytother. Res.* 2021, 35, 12: 6893–6903. doi: <https://doi.org/10.1002/ptr.7302>

Del Re A et al., “Ultramicronized Palmitoylethanolamide Inhibits NLRP3 Inflammasome Expression and Pro-Inflammatory Response Activated by SARS-CoV-2 Spike Protein in Cultured Murine Alveolar Macrophages.” *Metabolites* 2021, 11, 9: 592. doi: <https://doi.org/10.3390/metabo11090592>

Dissook S et al., “Luteolin-rich fraction from *Perilla frutescens* seed meal inhibits spike glycoprotein S1 of SARS-CoV-2-induced NLRP3 inflammasome lung cell inflammation via regulation of JAK1/STAT3 pathway: A potential anti-inflammatory compound against inflammation-induced long-COVID,” *Front. Med.* 2023, 9: 1072056. doi: <https://doi.org/10.3389/fmed.2022.1072056>

Huynh TV et al., “Spike Protein of SARS-CoV-2 Activates Cardiac Fibrogenesis through NLRP3 Inflammasomes and NF- κ B Signaling,” *Cells* 2024, 13, 16: 1331: <https://doi.org/10.3390/cells13161331>

Jiang Q et al., “SARS-CoV-2 spike S1 protein induces microglial NLRP3-dependent neuroinflammation and cognitive impairment in mice,” *Exp. Neurol.* 2025, 383: 115020. doi: <https://doi.org/10.1016/j.expneurol.2024.115020>

Kucia M et al. “An evidence that SARS-Cov-2/COVID-19 spike protein (SP) damages hematopoietic stem/progenitor cells in the mechanism of pyroptosis in Nlrp3 inflammasome-dependent manner,” *Leukemia* 2021, 35: 3026-3029. doi: <https://doi.org/10.1038/s41375-021-01332-z>

Ratajczak MZ et al., “SARS-CoV-2 Entry Receptor ACE2 Is Expressed on Very Small CD45⁺ Precursors of Hematopoietic and Endothelial Cells and in Response to Virus Spike Protein Activates the Nlrp3 Inflammasome,” *Stem Cell Rev Rep.* 2021 Feb;17(1):266-277. doi: <https://doi.org/10.1007/s12015-020-10010-z>

Semmarath W et al., “Cyanidin-3-O-glucoside and Peonidin-3-O-glucoside-Rich Fraction of Black Rice Germ and Bran Suppresses Inflammatory Responses from SARS-CoV-2 Spike Glycoprotein S1-Induction In Vitro in

A549 Lung Cells and THP-1 Macrophages via Inhibition of the NLRP3 Inflammasome Pathway,” *Nutrients* 2022, 14, 13: 2738. doi: <https://doi.org/10.3390/nu14132738>

Villacampa A et al., “SARS-CoV-2 S protein activates NLRP3 inflammasome and deregulates coagulation factors in endothelial and immune cells,” *Cell Commun. Signal.* 2024, 22, 38. doi: <https://doi.org/10.1186/s12964-023-01397-6>

W. Ocular, ophthalmic, conjunctival

Golob-Schwarzl N et al., “SARS-CoV-2 spike protein functionally interacts with primary human conjunctival epithelial cells to induce a pro-inflammatory response,” *Eye* 2022, 36: 2353–5. doi: <https://doi.org/10.1038/s41433-022-02066-7>

Grishma K and Das Sarma, “The Role of Coronavirus Spike Protein in Inducing Optic Neuritis in Mice: Parallels to the SARS-CoV-2 Virus,” *J Neuroophthalmol* 2024, 44, 3: 319-329. Doi: [10.1097/WNO.0000000000002234](https://doi.org/10.1097/WNO.0000000000002234)

Zhu G et al., “SARS-CoV-2 spike protein-induced host inflammatory response signature in human corneal epithelial cells,” *Mol. Med. Rep.* (2021) 24: 584. doi: <https://doi.org/10.3892/mmr.2021.12223>

X. Other cell signaling

Caohuy H et al., “Inflammation in the COVID-19 airway is due to inhibition of CFTR signaling by the SARS-CoV-2 spike protein,” *Sci. Rep.* 2024, 14: 16895. doi: <https://doi.org/10.1038/s41598-024-66473-4>

Choi JY et al., “SARS-CoV-2 spike S1 subunit protein-mediated increase of beta-secretase 1 (BACE1) impairs human brain vessel cells,” *Biochem. Biophys. Res. Commun.* 2022, 625, 20: 66-71. doi: <https://doi.org/10.1016/j.bbrc.2022.07.113>

Corpetti C et al., “Cannabidiol inhibits SARS-Cov-2 spike (S) protein-induced cytotoxicity and inflammation through a PPAR γ -dependent TLR4/NLRP3/Caspase-1 signaling suppression in Caco-2 cell line.” *Phytother. Res.* 2021, 35, 12: 6893–6903. doi: <https://doi.org/10.1002/ptr.7302>

Gracie NP et al., “Cellular signalling by SARS-CoV-2 spike protein,” *Microbiology Australia* 2024, 45, 1: 13-17. doi: <https://doi.org/10.1071/MA24005>

Li F et al., “SARS-CoV-2 Spike Promotes Inflammation and Apoptosis Through Autophagy by ROS-Suppressed PI3K/AKT/mTOR Signaling.” *Biochim Biophys Acta BBA - Mol Basis Dis* (2021) 1867:166260. doi: [10.1016/j.bbadis.2021.166260](https://doi.org/10.1016/j.bbadis.2021.166260). doi: <https://doi.org/10.1016/j.bbadis.2021.166260>

Li K et al., “SARS-CoV-2 Spike protein promotes vWF secretion and thrombosis via endothelial cytoskeleton-associated protein 4 (CKAP4),” *Signal Transduct Targ Ther* (2022) 7, 332. doi: <https://doi.org/10.1038/s41392-022-01183-9>

Moutal A et al., “SARS-CoV-2 Spike protein co-opts VEGF-A/Neuropilin-1 receptor signaling to induce analgesia,” *Pain* (2020) 162, 1: 243–252. doi: [10.1097/j.pain.0000000000002097](https://doi.org/10.1097/j.pain.0000000000002097)

Munavilli GG et al., “COVID-19/SARS-CoV-2 virus spike protein-related delayed inflammatory reaction to hyaluronic acid dermal fillers: a challenging clinical conundrum in diagnosis and treatment,” *Arch. Dermatol. Res.* 2022, 314: 1-15. doi: <https://doi.org/10.1007/s00403-021-02190-6>

Prieto-Villalobos J et al., "SARS-CoV-2 spike protein S1 activates Cx43 hemichannels and disturbs intracellular Ca²⁺ dynamics," *Biol Res.* 2023 Oct 25;56(1):56. doi: <https://doi.org/10.1186/s40659-023-00468-9>

Rotoli BM et al., "Endothelial cell activation by SARS-CoV-2 spike S1 protein: A crosstalk between endothelium and innate immune cells," *Biomedicines* 2021, 9, 9: 1220. doi: <https://doi.org/10.3390/biomedicines9091220>

Singh N and Anuradha Bharara Singh, "S2 Subunit of SARS-nCoV-2 Interacts with Tumor Suppressor Protein p53 and BRCA: An in Silico Study," *Translational Oncology* 13, no. 10 (October 2020): 100814, doi: <https://doi.org/10.1016/j.tranon.2020.100814>

Singh RD, "The spike protein of sars-cov-2 induces heme oxygenase-1: pathophysiologic implications," *Biochim Biophys Acta, Mol Basis Dis* (2022) 1868, 3: 166322. doi: <https://doi.org/10.1016/j.bbadis.2021.166322>

Solis O et al., "The SARS-CoV-2 spike protein binds and modulates estrogen receptors," *Sci. Adv.* 2022, 8, 48: eadd4150. doi: [10.1126/sciadv.add4150](https://doi.org/10.1126/sciadv.add4150)

Suzuki YJ et al., "SARS-CoV-2 spike protein-mediated cell signaling in lung vascular cells." *Vascul. Pharmacol.* 2021;137:106823. doi: <https://doi.org/10.1016/j.vph.2020.106823>

Suzuki YJ and SG Gychka, "SARS-CoV-2 Spike Protein Elicits Cell Signaling in Human Host Cells: Implications for Possible Consequences of COVID-19 Vaccines," *Vaccines* 2021, 9, 1, 36. doi: <https://doi.org/10.3390/vaccines9010036>

Tillman TS et al., "SARS-CoV-2 Spike Protein Downregulates Cell Surface alpha7nAChR through a Helical Motif in the Spike Neck." *ACS Chem. Neurosci.* (2023) 14, 4: 689–698. doi: <https://doi.org/10.1021/acscchemneuro.2c00610>

Y. Pregnancy

Erdogan MA, "Prenatal SARS-CoV-2 Spike Protein Exposure Induces Autism-Like Neurobehavioral Changes in Male Neonatal Rats," *J Neuroimmune Pharmacol.* 2023 Dec;18(4):573-591. doi: [10.1007/s11481-023-10089-4](https://doi.org/10.1007/s11481-023-10089-4)

Guo X et al., "Regulation of proinflammatory molecules and tissue factor by SARS-CoV-2 spike protein in human placental cells: implications for SARS-CoV-2 pathogenesis in pregnant women." *Front Immunol* 2022, 13: 876555–876555. <https://doi.org/10.3389/fimmu.2022.876555>

Kammala AK et al., "In vitro mRNA-S maternal vaccination induced altered immune regulation at the maternal-fetal interface," *Am. J. Reprod. Immunol.* 2024, 91, 5: e13861. doi: <https://doi.org/10.1111/aji.13861>

Z. Pulmonary, respiratory

Bhargavan B and GD Kanmogne, "SARS-CoV-2 spike proteins and cell-cell communication inhibits TFPI and induces thrombogenic factors in human lung microvascular endothelial cells and neutrophils: implications for COVID-19 coagulopathy pathogenesis," *Int. J. Mol. Sci.* 2022, 23, 18: 10436. doi: <https://doi.org/10.3390/ijms231810436>

Biancatelli RMLC, et al. "The SARS-CoV-2 spike protein subunit S1 induces COVID-19-like acute lung injury in Kappa18-hACE2 transgenic mice and barrier dysfunction in human endothelial cells." *Am. J. Physiol. Lung Cell. Mol. Physiol.* 2021, 321, L477–L484. doi: <https://doi.org/10.1152/ajplung.00223.2021>

Cao JB et al., "Mast cell degranulation-triggered by SARS-CoV-2 induces tracheal-bronchial epithelial inflammation and injury," *Virol. Sin.* 2024, 39, 2: 309-318. doi: <https://doi.org/10.1016/j.virs.2024.03.001>

Cao X et al., "Spike protein of SARS-CoV-2 activates macrophages and contributes to induction of acute lung inflammation in male mice," *FASEB J.* 2021, 35, e21801. doi: <https://doi.org/10.1096/fj.202002742RR>

Caohuy H et al., "Inflammation in the COVID-19 airway is due to inhibition of CFTR signaling by the SARS-CoV-2 spike protein," *Sci. Rep.* 2024, 14: 16895. doi: <https://doi.org/10.1038/s41598-024-66473-4>

Chittasupho C et al., "Inhibition of SARS-CoV-2-Induced NLRP3 Inflammasome-Mediated Lung Cell Inflammation by Triphala-Loaded Nanoparticle Targeting Spike Glycoprotein S1," *Pharmaceutics* 2024, 16, 6: 751. <https://doi.org/10.3390/pharmaceutics16060751>

Chittasupho C et al., "Targeting spike glycoprotein S1 mediated by NLRP3 inflammasome machinery and the cytokine releases in A549 lung epithelial cells by nanocurcumin," *Pharmaceutics* (Basel) 2023, 16, 6: 862. doi: <https://doi.org/10.3390/ph16060862>

Del Re A et al., "Intranasal delivery of PEA-producing *Lactobacillus paracasei* F19 alleviates SARS-CoV-2 spike protein-induced lung injury in mice," *Transl. Med. Commun.* 2024, 9, 9. doi: <https://doi.org/10.1186/s41231-024-00167-x>

Forsyth CB et al., "The SARS-CoV-2 S1 spike protein promotes MAPK and NF-κB activation in human lung cells and inflammatory cytokine production in human lung and intestinal epithelial cells," *Microorganisms* 2022, 10, 10: 1996. doi: <https://doi.org/10.3390/microorganisms10101996>

Greenberger JS et al., "SARS-CoV-2 Spike Protein Induces Oxidative Stress and Senescence in Mouse and Human Lung," *In Vivo* 2024, 38, 4: 1546-1556; doi: <https://doi.org/10.21873/invivo.13605>

Jana S et al., "Cell-free hemoglobin does not attenuate the effects of SARS-CoV-2 spike protein S1 subunit in pulmonary endothelial cells," *Int. J. Mol. Sci.* 2021, 22, 16: 9041. doi: <https://doi.org/10.3390/ijms22169041>

Kulkoviene G et al., "Differential Mitochondrial, Oxidative Stress and Inflammatory Responses to SARS-CoV-2 Spike Protein Receptor Binding Domain in Human Lung Microvascular, Coronary Artery Endothelial and Bronchial Epithelial Cells," *Int. J. Mol. Sci.* 2024, 25, 6: 3188. doi: <https://doi.org/10.3390/ijms25063188>

Liang S et al., "SARS-CoV-2 spike protein induces IL-18-mediated cardiopulmonary inflammation via reduced mitophagy," *Signal Transduct Target Ther* (2023) 8, 103. doi: <https://doi.org/10.1038/s41392-023-01368-w>

Liu T et al., "RS-5645 attenuates inflammatory cytokine storm induced by SARS-CoV-2 spike protein and LPS by modulating pulmonary microbiota," *Int J Biol Sci.* 2021, 17, 13: 3305–3319. doi: [10.7150/ijbs.63329](https://doi.org/10.7150/ijbs.63329)

Palestra F et al. "SARS-CoV-2 Spike Protein Activates Human Lung Macrophages," *Int. J. Mol. Sci.* 2023, 24, 3: 3036. doi: <https://doi.org/10.3390/ijms24033036>

Park C et al., "Murine alveolar Macrophages Rapidly Accumulate intranasally Administered SARS-CoV-2 Spike Protein leading to neutrophil Recruitment and Damage," *Elife* 12 (2024), p. RP86764. doi: <https://doi.org/10.7554/eLife.86764.3>

Puthia MTL et al., “Experimental model of pulmonary inflammation induced by SARS-CoV-2 spike protein and endotoxin.” *ACS Pharmacol Transl Sci.* 2022, 5, 3: 141–8. doi: <https://doi.org/10.1021/acsptsci.1c00219>

Rahman M et al., “Differential Effect of SARS-CoV-2 Spike Glycoprotein 1 on Human Bronchial and Alveolar Lung Mucosa Models: Implications for Pathogenicity.” *Viruses* 2021, 13, 12: 2537. doi: <https://doi.org/10.3390/v13122537>

Ruben ML et al., “The SARS-CoV-2 spike protein subunit S1 induces COVID-19-like acute lung injury in K18-hACE2 transgenic mice and barrier dysfunction in human endothelial cells.” *Am J Physiol Lung Cell Mol Physiol.* 2021, 321, 2: L477-L484. doi: <https://doi.org/10.1152/ajplung.00223.2021>

Segura-Villalobos D et al., “Jacareubin inhibits TLR4-induced lung inflammatory response caused by the RBD domain of SARS-CoV-2 Spike protein.” *Pharmacol. Rep.* 2022, 74: 1315–1325. doi: <https://doi.org/10.1007/s43440-022-00398-5>

Semmarath W et al., “Cyanidin-3-O-glucoside and Peonidin-3-O-glucoside-Rich Fraction of Black Rice Germ and Bran Suppresses Inflammatory Responses from SARS-CoV-2 Spike Glycoprotein S1-Induction In Vitro in A549 Lung Cells and THP-1 Macrophages via Inhibition of the NLRP3 Inflammasome Pathway,” *Nutrients* 2022, 14, 13: 2738. doi: <https://doi.org/10.3390/nu14132738>

Sirsendu J et al., “Cell-Free Hemoglobin Does Not Attenuate the Effects of SARS-CoV-2 Spike Protein S1 Subunit in Pulmonary Endothelial Cells,” *Int J Mol Sci.* 2021 Aug 22;22(16):9041. doi: <https://doi.org/10.3390/ijms22169041>

Sui Y et al., “SARS-CoV-2 Spike Protein Suppresses ACE2 and Type I Interferon Expression in Primary Cells From Macaque Lung Bronchoalveolar Lavage,” *Frontiers in Immunology* (June 4, 2021), 12. doi: <https://doi.org/10.3389/fimmu.2021.658428>

Sung PS et al., “CLEC5A and TLR2 Are Critical in SARS-CoV-2-Induced NET Formation and Lung Inflammation,” *Journal of Biomedical Science* 29, no. 52 (2022), doi: <https://doi.org/10.1186/s12929-022-00832-z>

Suzuki YJ et al., “SARS-CoV-2 spike protein-mediated cell signaling in lung vascular cells.” *Vascul. Pharmacol.* 2021;137:106823. doi: <https://doi.org/10.1016/j.vph.2020.106823>

Zekri-Nechar K et al., “Spike Protein Subunits of SARS-CoV-2 Alter Mitochondrial Metabolism in Human Pulmonary Microvascular Endothelial Cells: Involvement of Factor Xa.” *Dis. Markers* (2022): 1118195. doi: <https://doi.org/10.1155/2022/1118195>

AA. Renin-Angiotensin-Aldosterone System

Lehmann KJ, “SARS-CoV-2-Spike Interactions with the Renin-Angiotensin-Aldosterone System – Consequences of Adverse Reactions of Vaccination.” *J Biol Today’s World* 2023, 12/4: 001-013. <https://doi.org/10.31219/osf.io/27g5h>

Matsuzawa Y et al., “Impact of Renin–Angiotensin–Aldosterone System Inhibitors on COVID-19,” *Hypertension Research* 45, no. 7 (2022): 1147–1153, doi: <https://doi.org/10.1038/s41440-022-00922-3>

BB. Senescence/aging

Duarte C., "Age-dependent effects of the recombinant spike protein/SARS-CoV-2 on the M-CSF- and IL-34-differentiated macrophages in vitro." *Biochem. Biophys. Res. Commun.* 2021, 546: 97–102. doi: <https://doi.org/10.1016/j.bbrc.2021.01.104>

Greenberger JS et al., "SARS-CoV-2 Spike Protein Induces Oxidative Stress and Senescence in Mouse and Human Lung," *In Vivo* 2024, 38, 4: 1546-1556; doi: <https://doi.org/10.21873/invivo.13605>

Meyer K et al., "SARS-CoV-2 Spike Protein Induces Paracrine Senescence and Leukocyte Adhesion in Endothelial Cells," *J. Virol.* 2021, 95, e0079421. doi: <https://doi.org/10.1128/jvi.00794-21>

CC. Stem cells

Balzanelli MG et al., "The Role of SARS-CoV-2 Spike Protein in Long-term Damage of Tissues and Organs, the Underestimated Role of Retrotransposons and Stem Cells, a Working Hypothesis," *Endocr Metab Immune Disord Drug Targets* 2025, 25, 2: 85-98. doi: [10.2174/0118715303283480240227113401](https://doi.org/10.2174/0118715303283480240227113401)

Kucia M et al. "An evidence that SARS-Cov-2/COVID-19 spike protein (SP) damages hematopoietic stem/progenitor cells in the mechanism of pyroptosis in Nlrp3 inflammasome-dependent manner," *Leukemia* 2021, 35: 3026-3029. doi: <https://doi.org/10.1038/s41375-021-01332-z>

Ropa J et al., "Human Hematopoietic Stem, Progenitor, and Immune Cells Respond Ex Vivo to SARS-CoV-2 Spike Protein," *Stem Cell Rev Rep.* 2021, 17, 1:253-265. doi: <https://doi.org/10.1007/s12015-020-10056-z>

DD. Syncytia/cell fusion

Braga L et al., "Drugs that inhibit TMEM16 proteins block SARS-CoV-2 spike-induced syncytia," *Nature* 2021, 594:88–93. doi: <https://doi.org/10.1038/s41586-021-03491-6>

Cattin-Ortolá J et al., "Sequences in the cytoplasmic tail of SARS-CoV-2 Spike facilitate expression at the cell surface and syncytia formation." *Nat Commun* 2021, 12, 1: 5333. doi: <https://doi.org/10.1038/s41467-021-25589-1>

Clemens DJ et al., "SARS-CoV-2 spike protein-mediated cardiomyocyte fusion may contribute to increased arrhythmic risk in COVID-19," *PLoS One* 2023, 18(3): e0282151. doi: <https://doi.org/10.1371/journal.pone.0282151>

Lazebnik Y, "Cell fusion as a link between the SARS-CoV-2 spike protein, COVID-19 complications, and vaccine side effects," *Oncotarget* 2021, 12(25): 2476-2488. doi: <https://doi.org/10.18632/oncotarget.28088>

Liu X et al., "SARS-CoV-2 spike protein-induced cell fusion activates the cGAS-STING pathway and the interferon response," *Sci Signal.* 2022, 15(729): eabg8744. doi: [10.1126/scisignal.abg8744](https://doi.org/10.1126/scisignal.abg8744)

Martinez-Marmol R et al., "SARS-CoV-2 infection and viral fusogens cause neuronal and glial fusion that compromises neuronal activity," *Sci. Adv.* 2023, 9, 23. doi: [10.1126/sciadv.adg2248](https://doi.org/10.1126/sciadv.adg2248)

Rajah MM et al., "SARS-CoV-2 Alpha, Beta, and Delta variants display enhanced spike-mediated syncytia formation," *EMBO J.* 2021, 40: e108944. doi: <https://doi.org/10.15252/emboj.2021108944>

Shirato K and Takako Kizaki, "SARS-CoV-2 Spike Protein S1 Subunit Induces Pro-inflammatory Responses via Toll-Like Receptor 4 Signaling in Murine and Human Macrophages," *Heliyon* 7, no. 2 (February 2, 2021):e06187, doi: <https://doi.org/10.1016/j.heliyon.2021.e06187>

Theuerkauf SA et al., “Quantitative assays reveal cell fusion at minimal levels of SARS-CoV-2 spike protein and fusion from without.” *iScience* 2021, 24, 3: 102170. <https://doi.org/10.1016/j.isci.2021.102170>

Zhang Z et al., “SARS-CoV-2 spike protein dictates syncytium-mediated lymphocyte elimination.” *Cell Death Differ.* 2021, 28, 2765–2777. doi: <https://doi.org/10.1038/s41418-021-00782-3>

EE. Therapies

Almehdi AM et al., “SARS-CoV-2 Spike Protein: Pathogenesis, Vaccines, and Potential Therapies,” *Infection* 49, no. 5 (October 2021): 855–876, doi: <https://doi.org/10.1007/s15010-021-01677-8>

Boretti A. “PQQ Supplementation and SARS-CoV-2 Spike Protein-Induced Heart Inflammation,” *Nat. Prod. Commun.* 2022, 17, 1934578x221080929. doi: <https://doi.org/10.1177/1934578X221080929>

Boschi C et al., “SARS-CoV-2 Spike Protein Induces Hemagglutination: Implications for COVID-19 Morbidities and Therapeutics and for Vaccine Adverse Effects,” *International Journal of Biological Macromolecules* 23, no. 24 (2022): 15480, doi: <https://doi.org/10.3390/ijms232415480>

Braga L et al., “Drugs that inhibit TMEM16 proteins block SARS-CoV-2 spike-induced syncytia,” *Nature* 2021, 594:88–93. doi: <https://doi.org/10.1038/s41586-021-03491-6>

Chang MH et al., “SARS-CoV-2 Spike Protein 1 Causes Aggregation of α -Synuclein via Microglia-Induced Inflammation and Production of Mitochondrial ROS: Potential Therapeutic Applications of Metformin,” *Biomedicines* 2024 May 31;12(6):1223. doi: <https://doi.org/10.3390/biomedicines12061223>

Chittasupho C et al., “Inhibition of SARS-CoV-2-Induced NLRP3 Inflammasome-Mediated Lung Cell Inflammation by Triphala-Loaded Nanoparticle Targeting Spike Glycoprotein S1,” *Pharmaceutics* 2024, 16, 6: 751. <https://doi.org/10.3390/pharmaceutics16060751>

Chittasupho C et al., “Targeting spike glycoprotein S1 mediated by NLRP3 inflammasome machinery and the cytokine releases in A549 lung epithelial cells by nanocurcumin,” *Pharmaceutics* (Basel) 2023, 16, 6: 862. doi: <https://doi.org/10.3390/ph16060862>

Corpetti C et al., “Cannabidiol inhibits SARS-Cov-2 spike (S) protein-induced cytotoxicity and inflammation through a PPAR γ -dependent TLR4/NLRP3/Caspase-1 signaling suppression in Caco-2 cell line.” *Phytother. Res.* 2021, 35, 12: 6893–6903. doi: <https://doi.org/10.1002/ptr.7302>

Cory TJ et al., “Metformin Suppresses Monocyte Immunometabolic Activation by SARS-CoV-2 Spike Protein Subunit 1,” *Front. Immunol. Sec. Cytokines and Soluble Mediators in Immunity*, 2021, 12: 733921. doi: <https://doi.org/10.3389/fimmu.2021.733921>

Del Re A et al., “Intranasal delivery of PEA-producing *Lactobacillus paracasei* F19 alleviates SARS-CoV-2 spike protein-induced lung injury in mice,” *Transl. Med. Commun.* 2024, 9, 9. doi: <https://doi.org/10.1186/s41231-024-00167-x>

Del Re A et al., “Ultramicronized Palmitoylethanolamide Inhibits NLRP3 Inflammasome Expression and Pro-Inflammatory Response Activated by SARS-CoV-2 Spike Protein in Cultured Murine Alveolar Macrophages.” *Metabolites* 2021, 11, 9: 592. doi: <https://doi.org/10.3390/metabo11090592>

Ferrer MD et al., "Nitrite Attenuates the In Vitro Inflammatory Response of Immune Cells to the SARS-CoV-2 S Protein without Interfering in the Antioxidant Enzyme Activation," *Int. J. Mol. Sci.* 2024, 25, 5: 3001. <https://doi.org/10.3390/ijms25053001>

Frank MG et al., "SARS-CoV-2 S1 subunit produces a protracted priming of the neuroinflammatory, physiological, and behavioral responses to a remote immune challenge: A role for corticosteroids," *Brain Behav. Immun.* (October 2024) 121: 87-103. doi: <https://doi.org/10.1016/j.bbi.2024.07.034>

Frühbeck G et al., "FNDC4 and FNDC5 reduce SARS-CoV-2 entry points and spike glycoprotein S1-induced pyroptosis, apoptosis, and necroptosis in human adipocytes." *Cell Mol Immunol.* 2021;18(10):2457–9. doi: <https://doi.org/10.1038/s41423-021-00762-0>

Gasparello J et al., "Sulforaphane inhibits the expression of interleukin-6 and interleukin-8 induced in bronchial epithelial IB3-1 cells by exposure to the SARS-CoV-2 Spike protein," *Phytomedicine* 2021, 87: 153583. doi: <https://doi.org/10.1016/j.phymed.2021.153583>

Halma MTJ et al., "Exploring autophagy in treating SARS-CoV-2 spike protein-related pathology," *Endocrinol Metab (EnM)* 2024, 14: 100163. doi: <https://doi.org/10.1016/j.endmts.2024.100163>

Halma MTJ et al., "Strategies for the Management of Spike Protein-Related Pathology," *Microorganisms* 11, no. 5 (May 20, 2023): 1308, doi: <https://doi.org/10.3390/microorganisms11051308>

Jana S et al., "Cell-free hemoglobin does not attenuate the effects of SARS-CoV-2 spike protein S1 subunit in pulmonary endothelial cells," *Int. J. Mol. Sci.* 2021, 22, 16: 9041. doi: <https://doi.org/10.3390/ijms22169041>

Jugler C et al, "SARS-CoV-2 Spike Protein-Induced Interleukin 6 Signaling Is Blocked by a Plant-Produced Anti-Interleukin 6 Receptor Monoclonal Antibody," *Vaccines* 2021, 9, 11): 1365. <https://doi.org/10.3390/vaccines9111365>

Ken W et al., "Low dose radiation therapy attenuates ACE2 depression and inflammatory cytokines induction by COVID-19 viral spike protein in human bronchial epithelial cells," *Int J Radiat Biol.* 2022, 98, 10:1532-1541. doi: <https://doi.org/10.1080/09553002.2022.2055806>

Kumar N et al., "SARS-CoV-2 spike protein S1-mediated endothelial injury and pro-inflammatory state Is amplified by dihydrotestosterone and prevented by mineralocorticoid antagonism". *Viruses* 2021, 13, 11: 2209. Doi: <https://doi.org/10.3390/v13112209>

Liu T et al., "RS-5645 attenuates inflammatory cytokine storm induced by SARS-CoV-2 spike protein and LPS by modulating pulmonary microbiota," *Int J Biol Sci.* 2021, 17, 13: 3305–3319. doi: [10.7150/ijbs.63329](https://doi.org/10.7150/ijbs.63329)

Loh D, "The potential of melatonin in the prevention and attenuation of oxidative hemolysis and myocardial injury from cd147 SARS-CoV-2 spike protein receptor binding." *Melatonin Research.* 3, 3 (June 2020), 380-416. doi: <https://doi.org/10.32794/mr11250069>

Loh JT et al., "Dok3 restrains neutrophil production of calprotectin during TLR4 sensing of SARS-CoV-2 spike protein," *Front. Immunol.* 2022, 13, Sec. Molecular Innate Immunity. doi: <https://doi.org/10.3389/fimmu.2022.996637>

Marrone L et al., "Tirofiban prevents the effects of SARS-CoV-2 spike protein on macrophage activation and endothelial cell death," *Heliyon*, (2024) 10, 15: e35341. doi: [10.1016/j.heliyon.2024.e35341](https://doi.org/10.1016/j.heliyon.2024.e35341)

Norris B et al., "Evaluation of Glutathione in Spike Protein of SARS-CoV-2 Induced Immunothrombosis and Cytokine Dysregulation," *Antioxidants* 2024, 13, 3: 271. doi: <https://doi.org/10.3390/antiox13030271>

Olajide OA et al., “Induction of Exaggerated Cytokine Production in Human Peripheral Blood Mononuclear Cells by a Recombinant SARS-CoV-2 Spike Glycoprotein S1 and Its Inhibition by Dexamethasone,” *Inflammation* (2021) 44: 1865–1877. doi: <https://doi.org/10.1007/s10753-021-01464-5>

Petrosino S and N Matende, “Elimination/Neutralization of COVID-19 Vaccine-Produced Spike Protein: Scoping Review,” *Mathews Journal of Nutrition & Dietetics* 2024, 7, 2. doi: <https://doi.org/10.30654/MJND.10034>

Satta S et al., “An engineered nano-liposome-human ACE2 decoy neutralizes SARS-CoV-2 Spike protein-induced inflammation in both murine and human macrophages,” *Theranostics* 2022, 12, 6: 2639–2657. doi: [10.7150/thno.66831](https://doi.org/10.7150/thno.66831)

Segura-Villalobos D et al., “Jacareubin inhibits TLR4-induced lung inflammatory response caused by the RBD domain of SARS-CoV-2 Spike protein.” *Pharmacol. Rep.* 2022, 74: 1315–1325. doi: <https://doi.org/10.1007/s43440-022-00398-5>

Semmarath W et al., “Cyanidin-3-O-glucoside and Peonidin-3-O-glucoside-Rich Fraction of Black Rice Germ and Bran Suppresses Inflammatory Responses from SARS-CoV-2 Spike Glycoprotein S1-Induction In Vitro in A549 Lung Cells and THP-1 Macrophages via Inhibition of the NLRP3 Inflammasome Pathway,” *Nutrients* 2022, 14, 13: 2738. doi: <https://doi.org/10.3390/nu14132738>

Suprewicz L et al., “Recombinant human plasma gelsolin reverses increased permeability of the blood-brain barrier induced by the spike protein of the SARS-CoV-2 virus,” *J Neuroinflammation* 2022, 19, 1: 282, doi: <https://doi.org/10.1186/s12974-022-02642-4>

Vargas-Castro R et al., “Calcitriol prevents SARS-CoV spike-induced inflammation in human trophoblasts through downregulating ACE2 and TMPRSS2 expression,” *J Steroid Biochem Mol Biol* 2025, 245: 106625. doi: <https://doi.org/10.1016/j.jsbmb.2024.106625>

Youn JY et al., “Therapeutic application of estrogen for COVID-19: Attenuation of SARS-CoV-2 spike protein and IL-6 stimulated, ACE2-dependent NOX2 activation, ROS production and MCP-1 upregulation in endothelial cells,” *Redox Biol.* 2021, 46: 102099. doi: <https://doi.org/10.1016/j.redox.2021.102099>

Yu J et al., “Direct activation of the alternative complement pathway by SARS-CoV-2 spike proteins is blocked by factor D inhibition,” *Blood* 2020, 136 (18): 2080–2089. doi: <https://doi.org/10.1182/blood.2020008248>

Toll-like receptors (TLRs)

Aboudounya MM and RJ Heads, “COVID-19 and Toll-Like Receptor 4 (TLR4): SARS-CoV-2 May Bind and Activate TLR4 to Increase ACE2 Expression, Facilitating Entry and Causing Hyperinflammation.” *Mediators Inflamm.* 2021;2021:8874339. doi: <https://doi.org/10.1155/2021/8874339>

Burnett FN et al., “SARS-CoV-2 Spike Protein Intensifies Cerebrovascular Complications in Diabetic hACE2 Mice through RAAS and TLR Signaling Activation,” *Int. J. Mol. Sci.* 2023, 24(22): 16394. doi: <https://doi.org/10.3390/ijms242216394>

Carnevale R et al., “Toll-Like Receptor 4-Dependent Platelet-Related Thrombosis in SARS-CoV-2 Infection,” *Circulation Research* 132, no. 3 (2023): 290–305, doi: <https://doi.org/10.1161/CIRCRESAHA.122.321541>

Corpetti C et al., “Cannabidiol inhibits SARS-Cov-2 spike (S) protein-induced cytotoxicity and inflammation through a PPAR γ -dependent TLR4/NLRP3/Caspase-1 signaling suppression in Caco-2 cell line.” *Phytother. Res.* 2021, 35, 12: 6893–6903. doi: <https://doi.org/10.1002/ptr.7302>

Fontes-Dantas FL, “SARS-CoV-2 Spike Protein Induces TLR4-Mediated Long- Term Cognitive Dysfunction Recapitulating Post-COVID-19 Syndrome in Mice,” *Cell Reports* 42, no. 3 (March 2023):112189, doi: <https://doi.org/10.1016/j.celrep.2023.112189>

Khan S et al., “SARS-CoV-2 Spike Protein Induces Inflammation via TLR2-Dependent Activation of the NF- κ B Pathway,” *eLife* 10 (December 6, 2021): e68563, doi: <https://doi.org/10.7554/elife.68563>

Kim MJ et al., “The SARS-CoV-2 spike protein induces lung cancer migration and invasion in a TLR2-dependent manner,” *Cancer Commun* (London), 2023, 44, 2: 273–277. doi: <https://doi.org/10.1002/cac2.12485>

Kircheis R and O Planz, “Could a Lower Toll-like Receptor (TLR) and NF- κ B Activation Due to a Changed Charge Distribution in the Spike Protein Be the Reason for the Lower Pathogenicity of Omicron?” *Int. J. Mol. Sci.* 2022, 23, 11: 5966. doi: <https://doi.org/10.3390/ijms23115966>

Loh JT et al., “Dok3 restrains neutrophil production of calprotectin during TLR4 sensing of SARS-CoV-2 spike protein,” *Front. Immunol.* 2022, 13, Sec. Molecular Innate Immunity. doi: <https://doi.org/10.3389/fimmu.2022.996637>

Segura-Villalobos D et al., “Jacareubin inhibits TLR4-induced lung inflammatory response caused by the RBD domain of SARS-CoV-2 Spike protein.” *Pharmacol. Rep.* 2022, 74: 1315–1325. doi: <https://doi.org/10.1007/s43440-022-00398-5>

Sirsendu J et al., “Cell-Free Hemoglobin Does Not Attenuate the Effects of SARS-CoV-2 Spike Protein S1 Subunit in Pulmonary Endothelial Cells,” *Int J Mol Sci*, 2021 Aug 22;22(16):9041. doi: <https://doi.org/10.3390/ijms22169041>

Sung PS et al., “CLEC5A and TLR2 Are Critical in SARS-CoV-2-Induced NET Formation and Lung Inflammation,” *Journal of Biomedical Science* 29, no. 52 (2022), doi: <https://doi.org/10.1186/s12929-022-00832-z>

Zaki H and S Khan, “SARS-CoV-2 spike protein induces inflammatory molecules through TLR2 in macrophages and monocytes.” *J. Immunol.* 2021, 206 (1_supplement): 62.07. doi: <https://doi.org/10.4049/jimmunol.206.Supp.62.07>

Zaki H and S Khan, “TLR2 senses spike protein of SARS-CoV-2 to trigger inflammation,” *J. Immunol.* 2022, 208 (1_Supplement): 125.30. doi: <https://doi.org/10.4049/jimmunol.208.Supp.125.30>

Zhao Y et al., “SARS-CoV-2 spike protein interacts with and activates TLR4.” *Cell Res.* 2021;31:818–820. doi: <https://doi.org/10.1038/s41422-021-00495-9>