vaccines

Perspective

The Immunologic Downsides Associated with the Powerful Translation of Current COVID-19 Vaccine mRNA Can Be Overcome by Mucosal Vaccines

Maurizio Federico

Special Issue
Efficacy, Immunogenicity and Safety of COVID-19 Vaccines and COVID-19 Vaccination Strategies
Edited by
Dr. Pedro Plans-Rubió

MDPI

https://doi.org/10.3390/vaccines12111281

- ***Spike mRNA persists in lymph nodes up to 60 days after the second injection***

- ***The inoculation of anti-SARS-CoV-2 mRNA immunogens results in an abundant production of Spike protein:***
  - ***Free and measurable (up to 174 pg/mL in plasma 1-2 days after the first injection);***

(Roltgen et al. Cell, 2022)

mRNA vaccine persists in lymph nodes up to 60 days after the second jab

Cell

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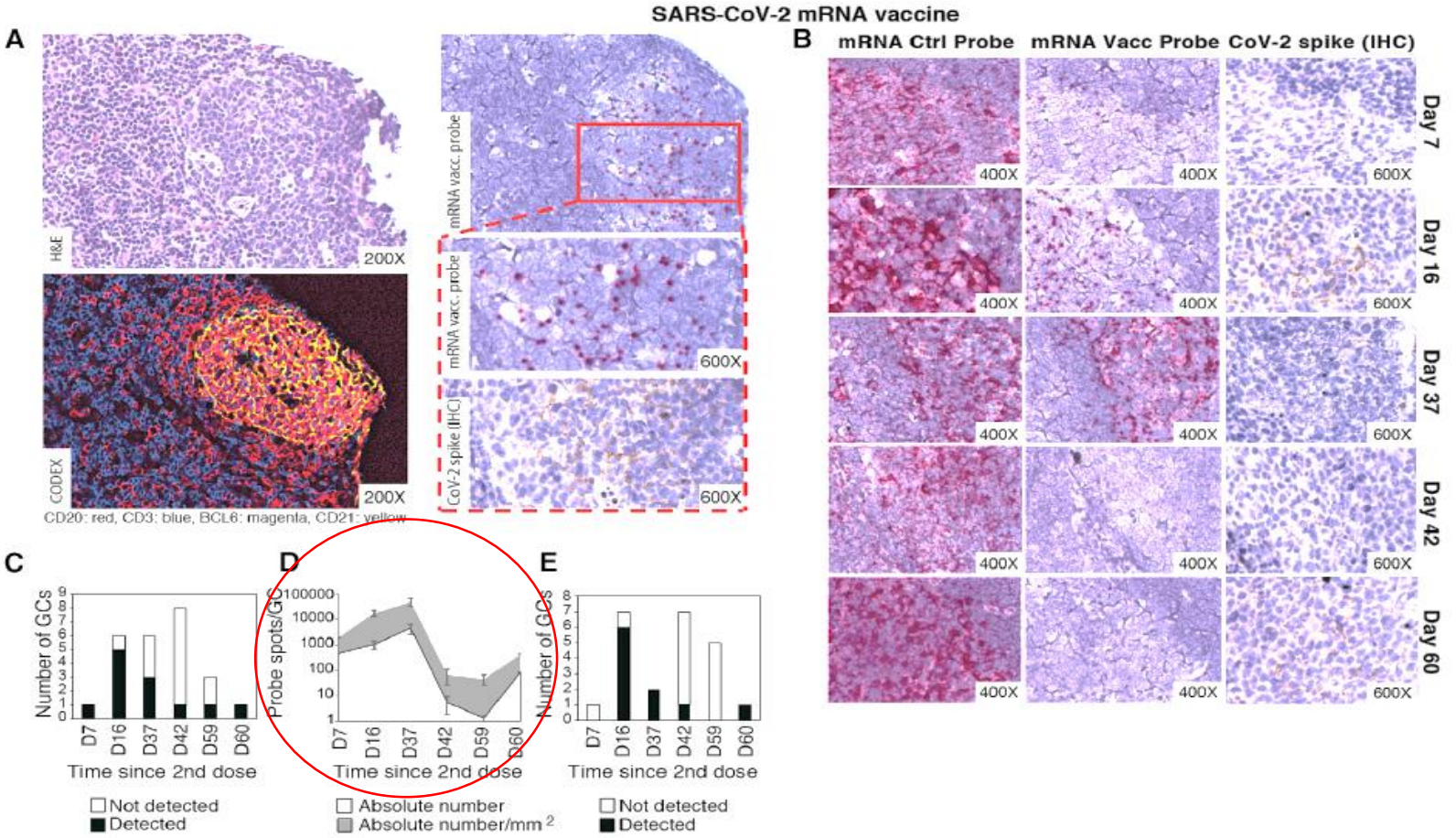
Article

Immune imprinting, breadth of variant recognition, and germinal center response in human SARS-CoV-2 infection and vaccination

Katharina Röltgen,[1,14] Sandra C.A. Nielsen,[1,14] Oscar Silva,[1,14] Sheren F. Younes,[1,14] Maxim Zaslavsky,[1] Cristina Costales,[1] Fan Yang,[1] Oliver F. Wirz,[1] Daniel Solis,[1] Ramona A. Hoh,[1] Aihui Wang,[1] Prabhu S. Arunachalam,[2] Deana Colburg,[1] Shuchun Zhao,[1] Emily Haraguchi,[1] Alexandra S. Lee,[3] Mihir M. Shah,[3] Monali Manohar,[3] Iris Chang,[3] Fei Gao,[2] Vamsee Mallajosyula,[2] Chunfeng Li,[2] James Liu,[4] Massa J. Shoura,[1] Sayantani B. Sindher,[1] Ella Parsons,[1] Naranjargal J. Dashdorj,[5,6] Naranbaatar D. Dashdorj,[5] Robert Monroe,[7] Geidy E. Serrano,[8] Thomas G. Beach,[8] R. Sharon Chinthrajah,[3,9] Gregory W. Charville,[1] James L. Wilbur,[10] Jacob N. Wohlstadter,[10] Mark M. Davis,[2,11,12] Bali Pulendran,[1,2,11] Megan L. Troxell,[1] George B. Sigal,[10] Yasodha Natkunam,[1] Benjamin A. Pinsky,[1,13]



The interaction between SARS-CoV-2 Spike and ACE-2 leads to the production of the cytokine TGF-β by:

- ***Both tissue and alveolar macrophages;***
- ***Lung epithelial cells;***
- ***Endothelial cells***
- ***B lymphocytes***

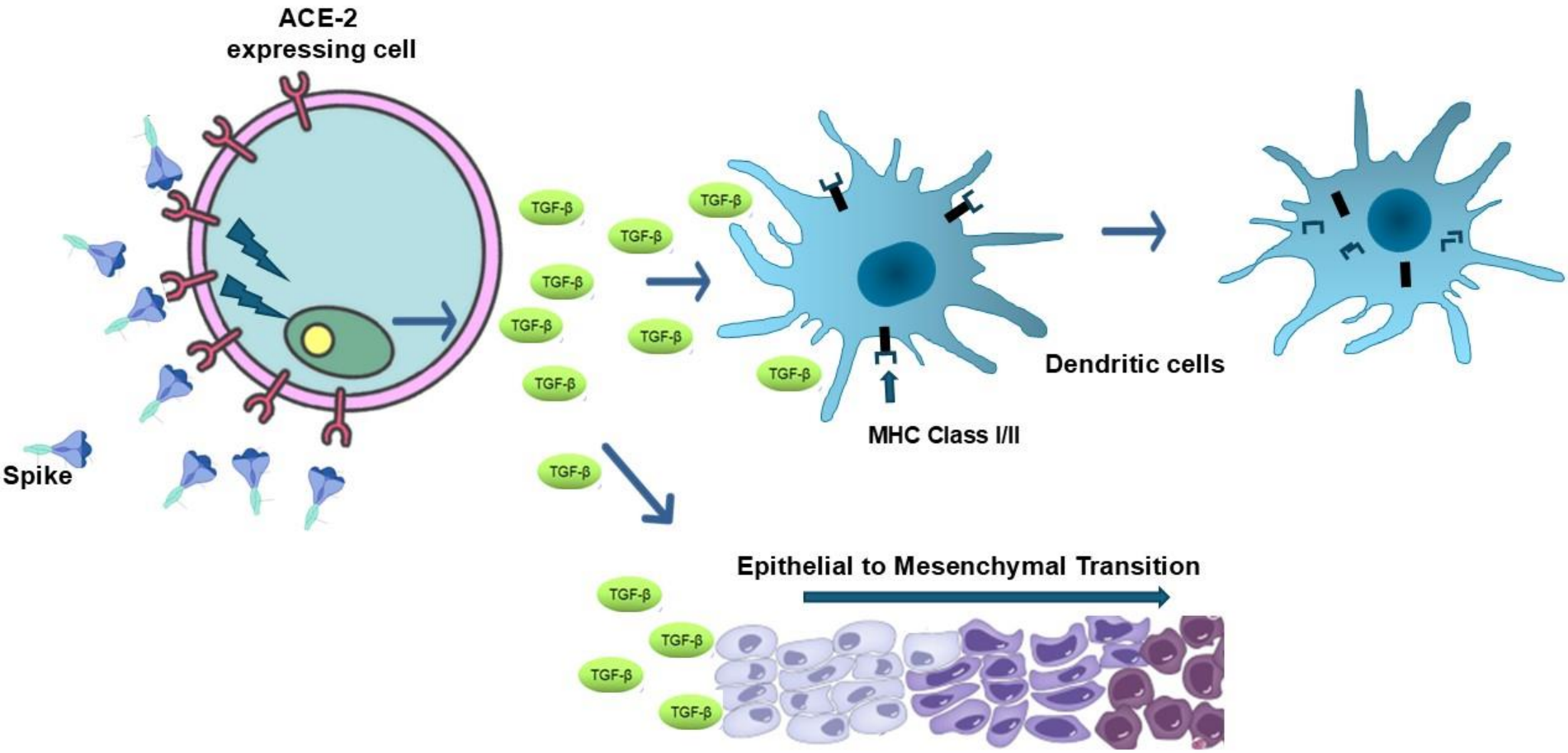
- *Ferreira-Gomes, M. et al. SARS-CoV-2 in Severe COVID-19 Induces a TGF-β-Dominated Chronic Immune Response That Does Not Target Itself. Nat Commun **2021**, 12 (1), 1961.*
- *Biering, S. B. et al. SARS-CoV-2 Spike Triggers Barrier Dysfunction and Vascular Leak via Integrins and TGF-β Signaling. bioRxiv **2021**, 2021.12.10.472112.*

TGF-β renders alveolar macrophages functionally inert, suppressing their production of inflammatory cytokines, and thus counteracting the «cytokine storm»:

- *Yu, X. et al. The Cytokine TGF-β Promotes the Development and Homeostasis of Alveolar Macrophages. Immunity **2017**, 47 (5), 903-912.e4.*
- *Grunwell, et al., TGF-B1 Suppresses the Type I IFN Response and Induces Mitochondrial Dysfunction in Alveolar Macrophages. The Journal of Immunology **2018**, 200 (6), 2115–2128.*

- ***Anti-SARS-CoV-2 vaccines may inhibit cytokine storm as a consequence of functional inhibition of alveolar macrophages***

Bystander effects of the Spike/ACE-2 binding



SARS-CoV-2 Spike can favor both EMT and metastases

Am J Cancer Res 2021;11(5):2278-2290
www.ajcr.us /ISSN:2156-6976/ajcr0130047

Original Article

Epithelial-mesenchymal transition induced by SARS-CoV-2 required transcriptional upregulation of Snail

Yun-Ju Lai[1,2*], Chi-Hong Chao[3,4,5*], Chun-Che Liao[1], Te-An Lee[1], Jung-Mao Hsu[6], Wen-Cheng Chou[1], Jyun Wang[1], Hsiang-Chi Huang[1], Shing-Jyh Chang[7], Yi-Ling Lin[1,8], Chia-Wei Li[1]

Abstract: The engagement of human angiotensin-converting enzyme 2 (hACE2) and SARS-CoV-2 spike protein facilitate virus spread. Thus far, ACE2 and TMPRSS2 expression is correlated with the epithelial-mesenchymal transition (EMT) gene signature in lung cancer. However, the mechanism for SARS-CoV-2-induced EMT has not been thoroughly explored. Here, we showed that SARS-CoV-2 induces EMT phenotypic change and stemness in breast cancer cell model and subsequently identified Snail as a modulator for this regulation. The in-depth analysis identifies the spike protein (S), but not envelope (E), nucleocapsid (N), or membrane protein (M), of SARS-CoV-2 induces EMT marker changes. Suppression of Snail expression in these cells abrogates S protein-induced invasion, migration, stemness, and lung metastasis, suggesting that Snail is required for SARS-CoV-2-mediated aggressive phenotype in cancer. This study reveals an important oncogenic role of SARS-CoV-2 in triggering breast cancer metastasis through Snail upregulation.

Keywords: SARS-CoV-2, ACE2, TMPRSS2, epithelial-mesenchymal transition, EMT, spike, Snail

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MOLECULAR BASIS OF CELL AND DEVELOPMENTAL BIOLOGY · Volume 278, Issue 23, P21113-21123, June 2003 · *Open Access*

Transforming Growth Factor β-1 Induces Snail Transcription Factor in Epithelial Cell Lines

MECHANISMS FOR EPITHELIAL MESENCHYMAL TRANSITIONS*

Hector Peinado · Miguel Quintanilla · Amparo Cano

ELSEVIER

Biochemical and Biophysical Research Communications

Volume 353, Issue 2, 9 February 2007, Pages 337-343

Snail is required for transforming growth factor-β-induced epithelial–mesenchymal transition by activating PI3 kinase/Akt signal pathway

Hee Jun Cho [a], Kyoung Eun Baek [a b], Shizuya Saika [c], Moon-Jin Jeong [d], Jiyun Yoo [a b]

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Yun-Ju Lai[1,2*], Chi-Hong Chao[3,4,5*], Chun-Che Liao[1], Te-An Lee[1], Jung-Mao Hsu[6], Wen-Cheng Chou[1], Jyun Wang[1], Hsiang-Chi Huang[1], Shing-Jyh Chang[7], Yi-Ling Lin[1,8], Chia-Wei Li[1]

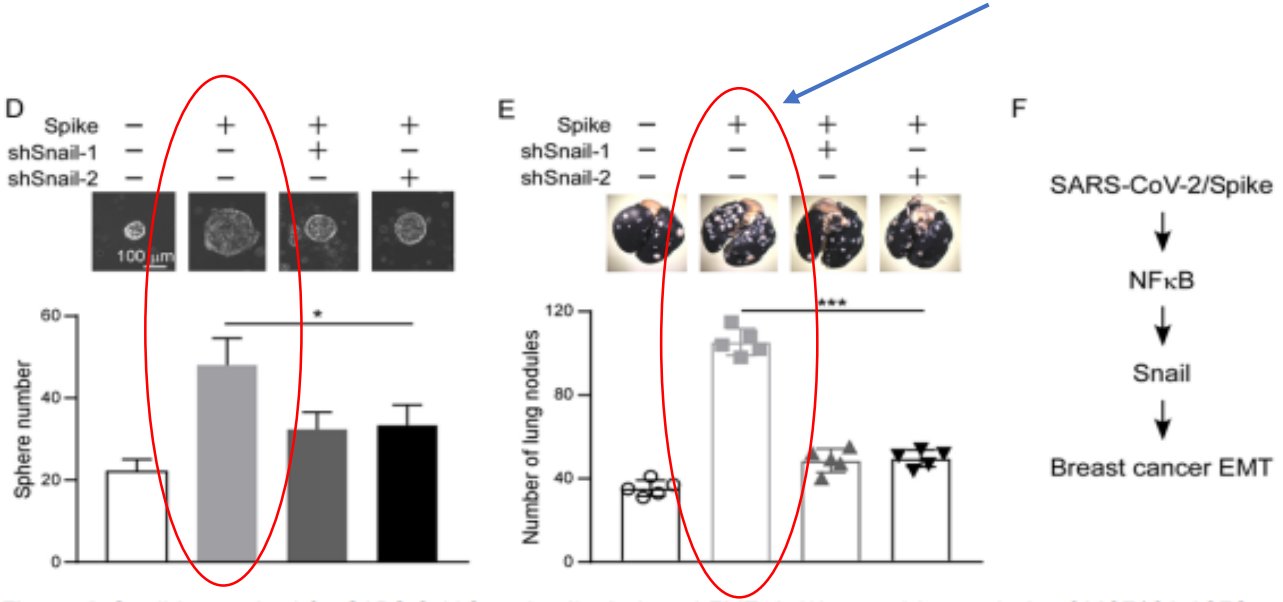


Figure 4. Snail is required for SARS-CoV-2 and spike-induced EMT. A. Western blot analysis of MCF10A-ACE2 cells upon SARS-CoV-2 infection. B. Quantification of migration activity of MCF7-spike cells. C. Quantification of invasion activity of MCF7-spike cells. D. Tumor initiation ability measured by mammosphere formation. MCF7 cells were transiently transfected with indicated plasmids. E. 4T1-spike cells with shSnail stable clones were injected into female BALB/c mice via the tail vein. Lung nodules were stained by India ink at the experimental endpoint. Error bars represent the mean ± SD of five mice. F. Proposed working model of this study. Statistic method: One-way ANOVA with Tukey's Post Hoc Test. *P < 0.05, **P < 0.01, ***P < 0.001.

SARS-CoV-2 Spike induces the release of TGF-β from endothelial human cells

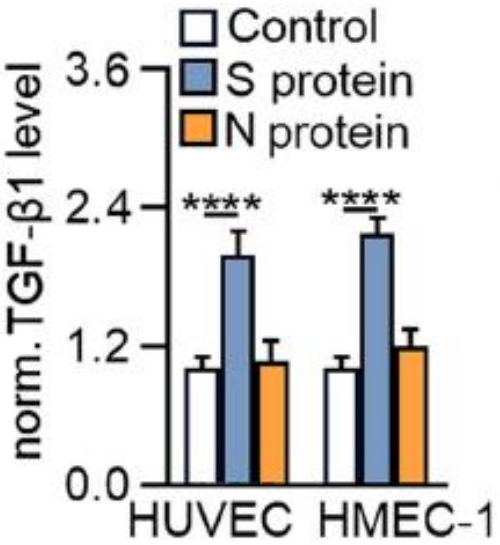
Ciszewski *et al. Cell Communication and Signaling* (2024) 22:296
https://doi.org/10.1186/s12964-024-01665-z

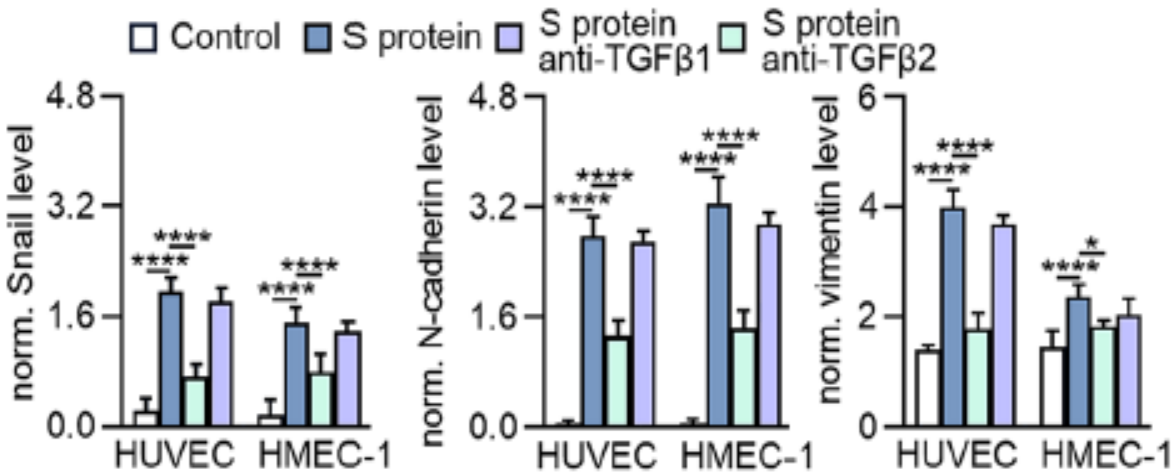
Cell Communication and Signaling

RESEARCH Open Access

Diverse roles of SARS-CoV-2 Spike and Nucleocapsid proteins in EndMT stimulation through the TGF-β-MRTF axis inhibited by aspirin

Wojciech M. Ciszewski[1], Lucyna A. Woźniak[2] and Katarzyna Sobierajska[1*]





COVID-19 vaccine-induced autoimmunity: potential molecular mimicry

viruses

MDPI

Article

Potential Autoimmunity Resulting from Molecular Mimicry between SARS-CoV-2 Spike and Human Proteins

Janelle Nunez-Castilla [1], Vitalii Stebliankin [2], Prabin Baral [3], Christian A. Balbin [1], Masrur Sobhan [4], Trevor Cickovski [2], Ananda Mohan Mondal [2,4,5], Giri Narasimhan [2,5], Prem Chapagain [3,5], Kalai Mathee [5,6] and Jessica Siltberg-Liberles [1,5,*]

Table 1. 3D-mimics found for SARS-CoV-2 Spike.

Motif	Protein	Species	RMSD (Å)	Z-Score	EpiScore	PDB_Chain
TQLPP	Thrombopoietin	Human	0.46	−1.34	10.87	1V7N_X
QLPPA	SMYD3 protein	Human	0.38	−1.42	13.16	5CCL_A
KNLRE	Toll-like receptor 8	Human	0.87	−0.92	5.75	6WML_D
FTVEKG	Pollen allergen Phl p2	*Phleum pratense*	0.76	−1.03	7.89	1WHP_A
GEVFN	Integrin beta 1	Human	0.63	−1.16	7.94	7NWL_B
HAPAT	Activator of 90 kDa heat shock protein ATPase homolog 1	Human	0.74	−1.05	6.76	7DME_A
YSTGS	Argininosuccinate lyase	Human	0.48	−1.31	10.42	1K62_B
EHVNN	Casein kinase 2 alpha isoform	Human	0.29	−1.51	17.24	2ZJW_A
NLLLQ	DNA polymerase subunit gamma 1	Human	0.57	−1.22	8.77	5C51_A
LLQYG	Ankyrin 1	Human	0.20	−1.60	25.00	1N11_A
LPDPS	BRCA1-A complex subunit BRE	Human	0.32	−1.48	15.62	6GVW_C
LPDPS	Semaphorin 7a	Human	0.84	−0.91	5.95	3NVQ_A
DPSKP	60S ribosomal protein L3	Human	0.10	−1.70	50.00	6LU8_B
DPSKP	Alanine and proline-rich secreted protein apa precursor	*Mycobacterium tuberculosis*	0.21	−1.59	23.81	5ZXA_A
IAARD	Talin	*Mus musculus*	0.74	−1.05	6.76	6R9T_A
GNCDV	Tryptophan-tRNA ligase	Human	0.91	−0.88	5.49	1O5T_A
SFKEE	Small subunit processome component 20 homolog	Human	0.32	−1.48	15.62	7MQA_SP
EELDK	Kynureninase	Human	0.22	−1.58	22.73	2HZP_A
ELDKY	Fusion glycoprotein F0	Respiratory syncytial virus	0.12	−1.68	41.67	6EAE_F
DKYFK	Cytoplasmic FMR1-interacting protein 1	Human	0.14	−1.66	35.71	4N78_A

For the 402 human 1D-mimics where no PDB structural representative could be identified for their source sequence, AlphaFold2 3D models were used. Three-dimensional model representatives were found for 102 human 1D-mimics. Of these, 10 are predicted to be AlphaFold2-3D-mimics (termed as "AF-3D-mimics") based on the RMSD (Table 2).

Table 2. Human AF-3D-mimics for SARS-CoV-2 Spike.

Motif	Protein	RMSD (Å)	Z-Score	EpiScore	AlphaFold2 ID
NLLLQ	Ankyrin 3	0.61	−1.18	8.20	AF-Q12955-F1-model_v1_A
LLQYG	Olfactory receptor 10Q1	0.66	−1.13	7.58	AF-Q8NGQ4-F1-model_v1_A
TGIAV	Phosphofructokinase	0.17	−1.63	29.41	AF-P17858-F1-model_v1_A
TGIAV	Low affinity immunoglobulin gamma Fc region receptor II-b	0.17	−1.63	29.41	AF-P31995-F1-model_v1_A
KIQDSL	Phosphorylase b kinase regulatory subunit beta	0.19	−1.61	31.58	AF-Q93100-F1-model_v1_A
KIQDSL	Long-chain-fatty-acid-CoA ligase 5	0.37	−1.43	16.22	AF-Q9ULC5-F1-model_v1_A
VYDPL	Actin-binding protein IPP	0.17	−1.63	29.41	AF-Q9Y573-F1-model_v1_A
EELDK	Tight junction-associated protein 1	0.20	−1.60	25.00	AF-Q5JTD0-F1-model_v1_A
EELDKY	Keratin, type I cytoskeletal 18	0.22	−1.58	27.27	AF-P05783-F1-model_v1_A
ELDKY	Tropomyosin alpha-3 chain	0.18	−1.62	27.78	AF-P06753-F1-model_v1_A

COVID-19 vaccine-induced autoimmunity: auto-antibodies

frontiers | Frontiers in Immunology

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High serum prevalence of autoreactive IgG antibodies against peripheral nerve structures in patients with neurological post-COVID-19 vaccination syndrome

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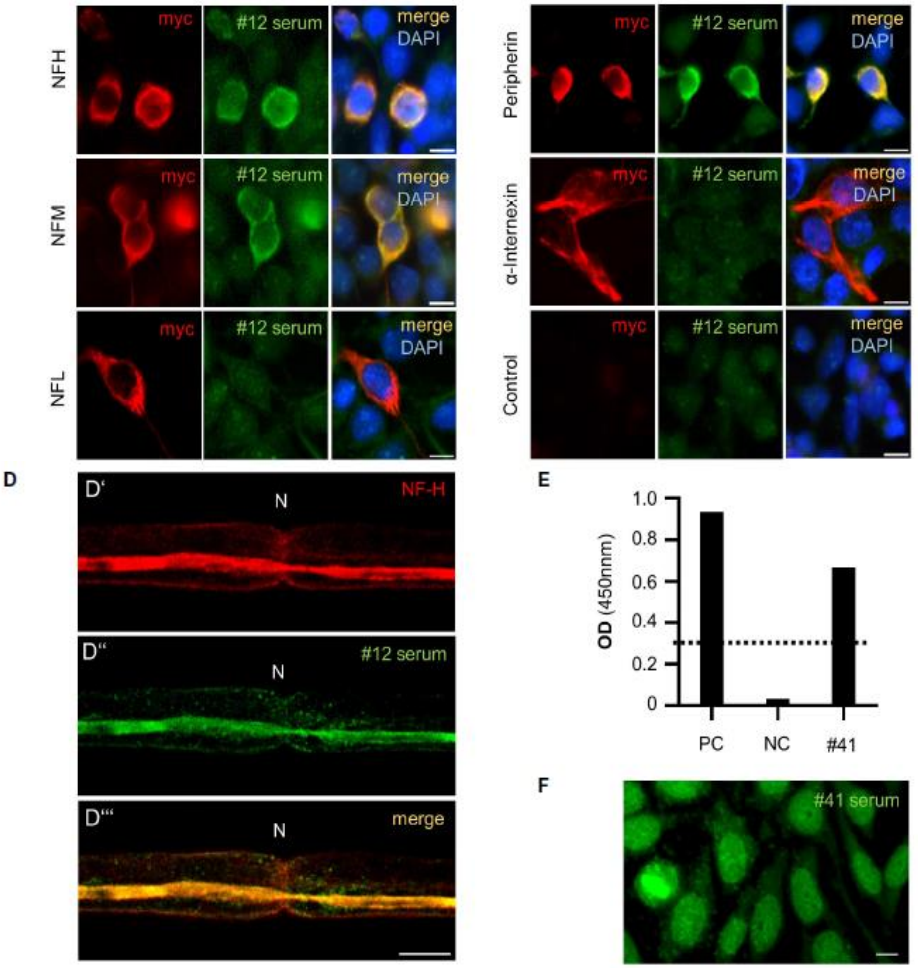
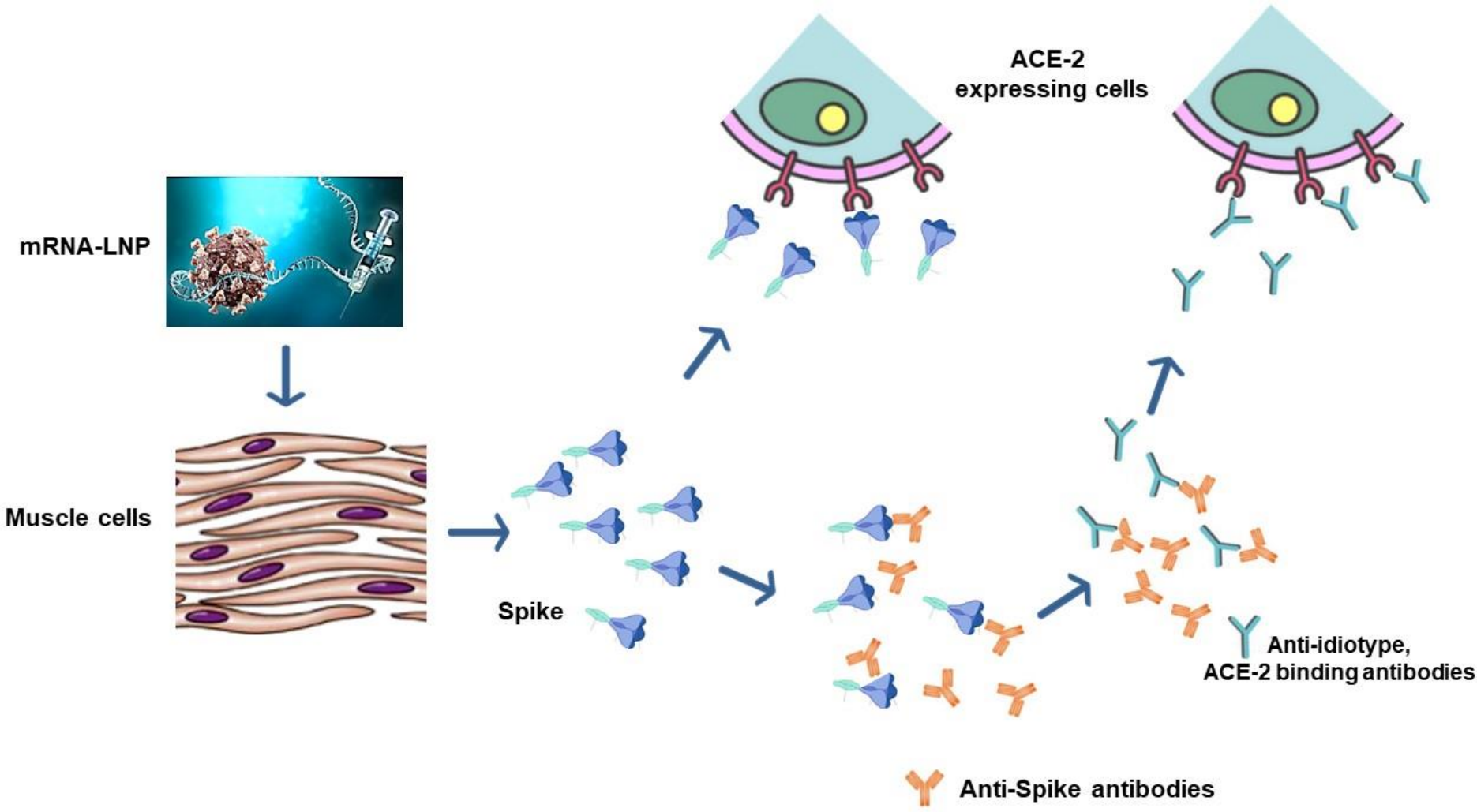


FIGURE 2
Antibody target identification and confirmation in PCVS sera. Volcano plot representing significantly enriched proteins (labeled in red) in patient #12 IgG IP **(A)** and patient #41 IgG IP **(B)** compared to a negative control; in A-B: the x-axis displays the log2-transformed fold change, and the y-axis represents the -log10-transformed p value. **(C)** Cell-based assays with patient #12 serum testing IgG reactivity against neurofilament subunits and control HEK293 cells. **(D)** Costaining of sciatic nerve teased fibers with a commercial NF-H antibody (D') and patient #12 serum (D'') showing clear signal overlap (D'''). **(E)** ELISA analysis of DFS-70 and patient #41 serum. PC: positive control serum. NC: negative control serum. The standard reference serum OD was 0.278 (dotted line). OD: optical density. **(F)** Hep2 staining of patient #41 serum resembling fine speckled nuclear staining typical of DFS-70 IgGs.

Generation of anti-idiotype antibodies after COVID-19 vaccination.



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RECEIVED 08 March 2024

Post-SARS-CoV-2 infection and post-vaccine-related neurological complications share clinical features and the same positivity to anti-ACE2 antibodies

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TABLE 1 Comparison of clinical, instrumental, and laboratory characteristics of patients.

Patient no.	Age and sex	Trigger	Time from the onset of symptoms	CNS or PNS clinical syndrome (diagnosis)	Clinical features	Spine MRI	EDX study	CSF analysis		Anti-ACE2 antibodies (U/mL)[c]	Therapy
								Ly (/μL)[a]	Prot (g/L)[b]		
1	38, F	Anti-SARS-CoV-2 vaccine	7 days after vaccine injection	PNS (immune mediated radiculitis)	Weak DTR in LL, distal burning paresthesia and dysesthesia in LL	CE in the proximal portion of nerve roots D12 to L5 bilaterally	NCS: absent F-waves in deep peroneal nerve bilaterally	11	0.40	37.76	Methylprednisolone
2	60, M	SARS-CoV-2 infection	20 days after negative rRT-PCR assay	PNS (GBS)	Distal weakness in UL and LL, hypoesthesia and paresthesia with stocking-glove distribution, gait ataxia, and global areflexia	NP	NCS: demyelinating sensory-motor polyneuropathy in UL and LL	4	0.85	35.22	PEX
3	80, M	Anti-SARS-CoV-2 vaccine	30 days after vaccine injection	CNS (MRI-negative myelitis)	Neurological examination disclosed exaggerated deep tendon reflexes in the lower limbs, clonus of the right ankle, pyramidal hypertonia in the right lower limb, and spastic-ataxic gait, without sensory levels or Lhermitte's sign	Spine MRI: no spinal cord abnormalities	Normal MEPs and NCS	NP	NP	37.33	Methylprednisolone
4	57, M	SARS-CoV-2 infection	15 days after negative rRT-PCR assay	CNS (MRI-negative myelitis)	Proximal weakness and bilateral pyramidal hypertonia in LL, hyperreflexia in LL, R ankle clonus, and paraparetic–spastic gait	Brain MRI: unremarkable; spine MRI: no spinal cord abnormalities	EMG and NCS: normal; SSEPs and MEPs: impaired central conduction in LL limbs bilaterally (prominent MEPs alteration in the R UL and LL)	3	0.81	37.47	IVIg§

ACE2, angiotensin-converting-enzyme 2; CE, contrast enhancement; CNS, central nervous system; CSF, cerebrospinal fluid; DTR, deep tendon reflexes; EDX, electrodiagnostic; EMG, electromyography; F, female; GBS, Guillain–Barré syndrome; IVIg, intravenous immunoglobulins (§2 g/kg over 5 days); LL, lower limbs; Ly, lymphomonocytes; M, male; MEPs, motor evoked potentials; MRI, magnetic resonance imaging; NCS, nerve conduction studies; NP, not performed; PEX, plasma exchange; PNS, peripheral nervous system; Prot, total proteins; R, right; rRT-PCR, transcription real-time PCR; SSEPs, cortical somatosensory evoked potentials; UL, upper limbs.

[a]Reference range, <5.

[b]Reference range, <0.52.

[c]Cutoff, 30 U/mL.

The ribosomal +1 frameshift

Article

N^1-methylpseudouridylation of mRNA causes +1 ribosomal frameshifting

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Thomas E. Mulroney[1], Tuija Pöyry[1], Juan Carlos Yam-Puc[1], Maria Rust[1], Robert F. Harvey[1], Lajos Kalmar[1], Emily Horner[1], Lucy Booth[1], Alexander P. Ferreira[1], Mark Stoneley[1], Ritwick Sawarkar[1], Alexander J. Mentzer[2], Kathryn S. Lilley[3], C. Mark Smales[4,5], Tobias von der Haar[4], Lance Turtle[6], Susanna Dunachie[7,8,9], Paul Klenerman[7,10], James E. D. Thaventhiran[1,11,12] & Anne E. Willis[1,11,12]

In vitro-transcribed (IVT) mRNAs are modalities that can combat human disease, exemplified by their use as vaccines for severe acute respiratory syndrome coronavirus

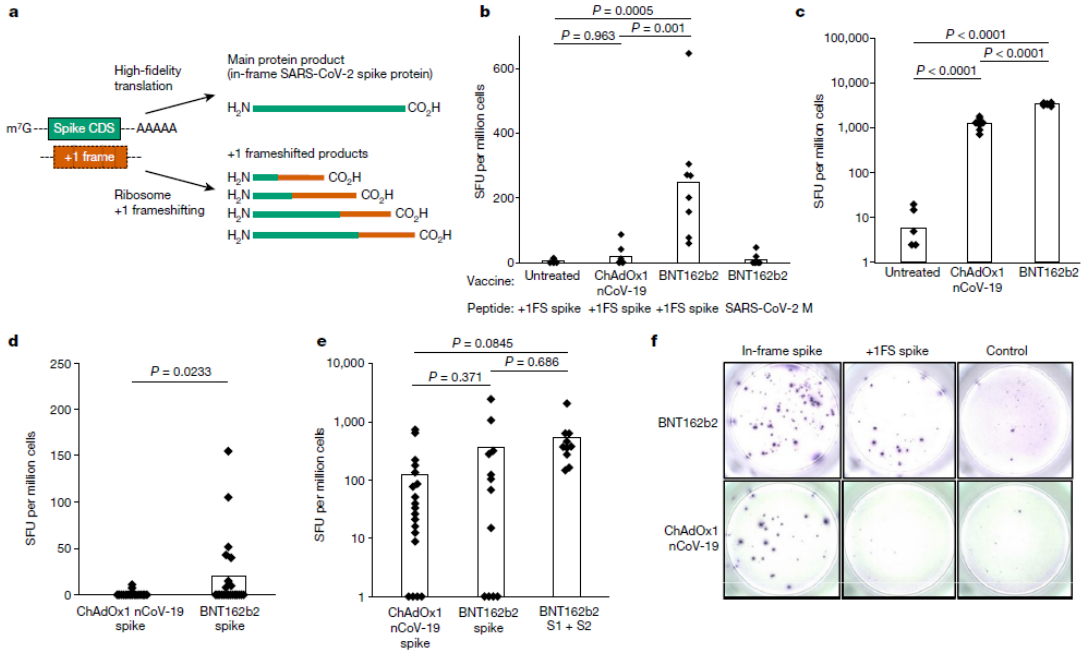

Fig. 2 | +1 frameshifted products elicit off-target cellular immune responses following modified mRNA vaccination. a, Depiction of spike and +1 frameshifted (+1FS) products produced by 1-methylΨ-modified spike mRNA translation. CDS, coding sequence. **b**, Splenocyte IFNγ ELISpot responses from untreated, ChAdOx1 nCoV-19-vaccinated or BNT162b2-vaccinated mice stimulated with +1FS spike peptides. IFNγ ELISpot response from BNT162b2-vaccinated mice stimulated with SARS-CoV-2 M peptides (unrelated control antigen) is included for additional comparison. SFU, spot-forming units. Each group $n = 8$. Untreated versus ChAdOx1 nCoV-19, $P = 0.963$; untreated versus BNT162b2, $P = 0.0005$; ChAdOx1 nCoV-19 versus BNT162b2, $P = 0.001$. **c**, Splenocyte IFNγ ELISpot responses from mice in **b** stimulated with spike peptides. Untreated versus ChAdOx1 nCoV-19, $P = 2.05 \times 10^{-9}$; untreated versus BNT162b2, $P = 4.5 \times 10^{-14}$; ChAdOx1 nCoV-19 versus BNT162b2, $P = 1.88 \times 10^{-13}$. **d**, Peripheral blood mononuclear cells (PBMC) IFNγ ELISpot responses from donors vaccinated with ChAdOx1 nCoV-19 ($n = 20$) or BNT162b2 ($n = 21$) stimulated with +1FS spike peptides. $P = 0.0233$ (Welch's one-tailed t-test). **e**, PBMC IFNγ ELISpot responses from donors in **c** stimulated with in-frame spike peptides: total spike pool or spike S1 + S2 subpools. ChAdOx1 nCoV-19 spike versus BNT162b2 spike, $P = 0.371$; ChAdOx1 nCoV-19 spike versus BNT162b2 S1 + S2, $P = 0.0845$; BNT162b2 spike versus BNT162b2 S1 + S2, $P = 0.686$. **f**, Representative images of PBMC IFNγ ELISpot response wells for two individuals vaccinated with either BNT162b2 responder (top) or ChAdOx1 nCoV-19 (bottom). Left to right: in-frame spike response (spike peptides); +1FS spike response (+1FS spike peptides); no peptide control. P values in **b**,**c**,**e** were determined by one-way ANOVA and Tukey's test.

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Cell Host & Microbe

Perspective

Rethinking next-generation vaccines for coronaviruses, influenzaviruses, and other respiratory viruses

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Table 1. Epidemiologic and immunologic parameters of selected human respiratory viruses and vaccines used to control them

Virus	Incubation period[a]	Marked viremia	Infection elicits long-term protective immunity	Re-infections are rare	Vaccines elicit long-term protective immunity	Vaccine type
Measles (to prodrome)	≈10 days	yes	yes	yes	yes	replicating
Mumps	≈16 days	yes	yes	yes	yes	replicating
Rubella	≈16 days	yes	yes	yes	yes	replicating
Smallpox[b]	≈12 days	yes	yes	yes	yes	replicating
VZV[c]	≈14 days	yes	yes	yes	yes	replicating
Endemic coronaviruses	≈5 days	no	no	no	no	none
Influenza virus	≈2 days	no	no	no	no	replicating, other
Parainfluenzaviruses	≈4 days	no	no	no	no	none
RSV	≈5 days	no	no	no	no	none
SARS-CoV-2	≈4 days	no[d]	no	no	no	non-replicating

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respiratory, lower respiratory tract, and systemic vaccination[44,76,134–141]; or optimized combinations of these. Attempting to control mucosal respiratory viruses with systemically administered non-replicating vaccines has thus far been largely unsuccessful, indicating that new approaches are needed. For example, respiratory disease often reflects host genetic susceptibility factors.[16,51,146,147]

PUBLIC HEALTH CONSIDERATIONS RELATING TO NEXT-GENERATION RESPIRATORY VACCINES MUST

Lack of neutralizing immunity in nasal swabs from COVID-19 mRNA vaccinees

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01318-5

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Sensitivity of infectious SARS-CoV-2 B.1.1.7 and B.1.351 variants to neutralizing antibodies

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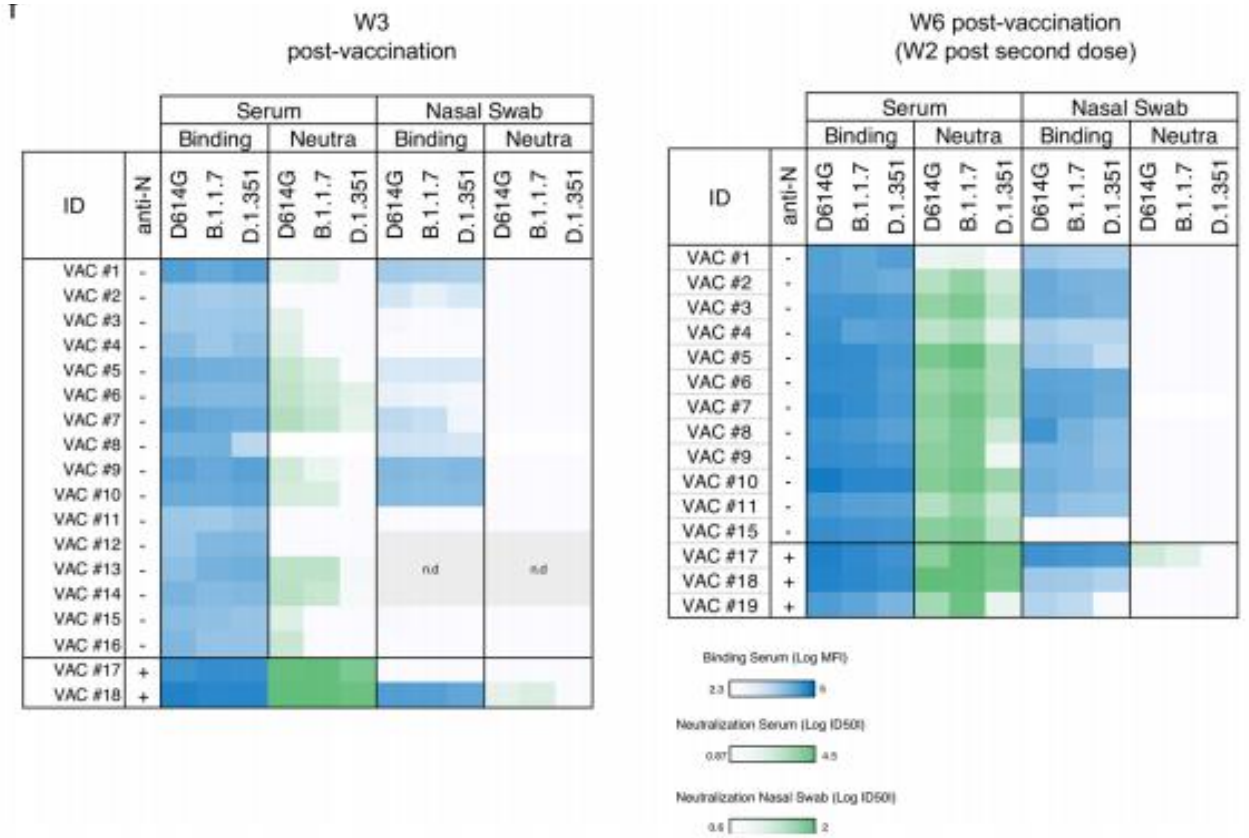

Either low or absent anti-Spike immunity in lungs of vaccinees

July 19, 2022

Science Immunology

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REPORTS | CORONAVIRUS

Respiratory mucosal immunity against SARS-CoV-2 following mRNA vaccination

JINYI TANG, CONG ZENG, THOMAS M. COX, CHAOFAN LI, YOUNG MIN SON, IN SU CHEON, YUE WU, SUPRIYA BEHL, JUSTIN J. TAYLOR, [...] JIE SUN +18 authors Authors Info & Affiliations

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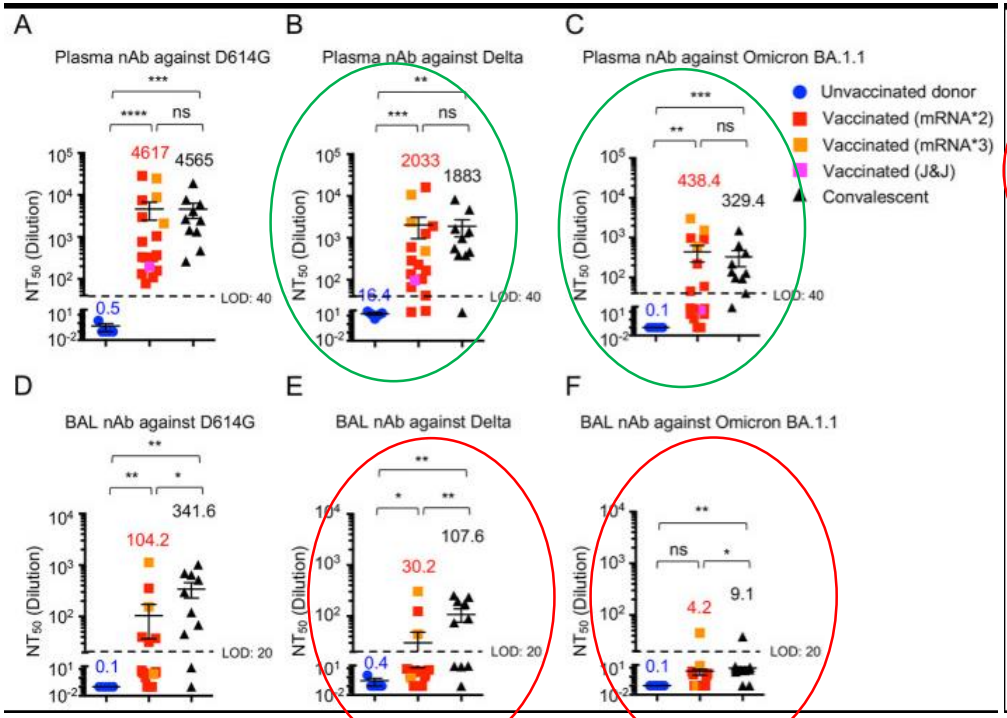

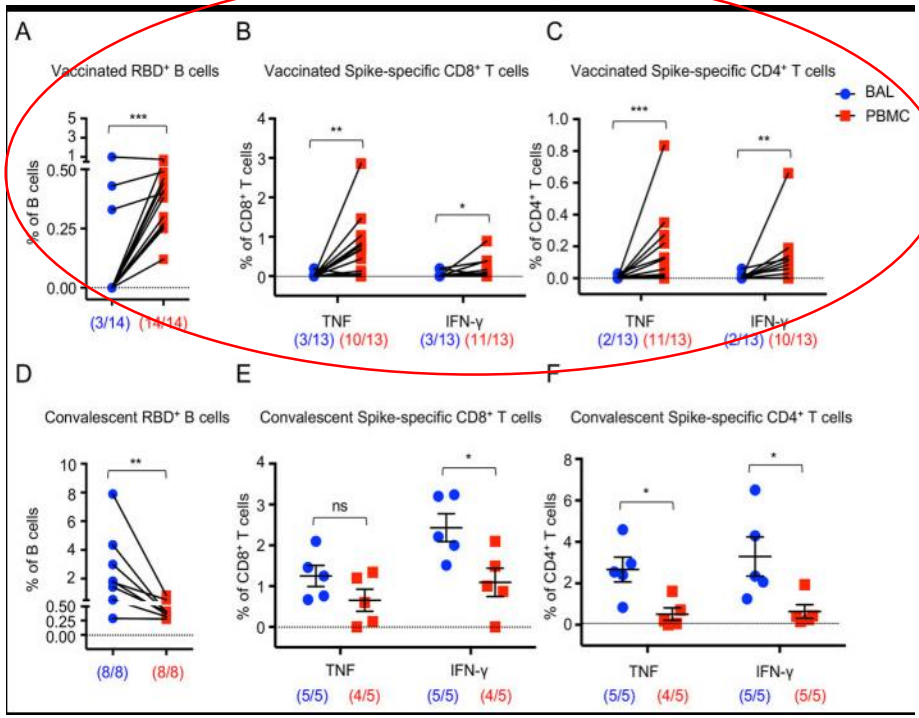

Vaccines designed to elicit respiratory immunity must deliver antigen to the lungs

nature immunology

ARTICLES

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The establishment of resident memory B cells in the lung requires local antigen encounter

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Memory B cells are found in lymphoid and non-lymphoid tissues, suggesting that some may be tissue-resident cells. Here we show that pulmonary influenza infection elicited lung-resident memory B cells (BRM cells) that were phenotypically and functionally distinct from their systemic counterparts. BRM cells were established in the lung early after infection, in part because their placement required local antigen encounter. Lung BRM cells, but not systemic memory B cells, contributed to early plasmablast responses following challenge infection. Following secondary infection, antigen-specific BRM cells differentiated in situ, whereas antigen-non-specific BRM cells were maintained as memory cells. These data demonstrate that BRM cells are an important component of immunity to respiratory viruses such as influenza virus and suggest that vaccines designed to elicit BRM cells must deliver antigen to the lungs.

- The development of lung immune memory is largely not influenced by events occurring in both peripheral circulation and lymphoid organs;

- Lymphocytes in lungs are maintained independently of the pool of circulating lymphocytes, and their continuous loss through intraepithelial migration towards airways is constantly replenished by homeostatic proliferation

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Un grazie e un saluto a tutti