COVID19: ¿ENFERMEDAD INFECCIOSA O INMUNITARIA?

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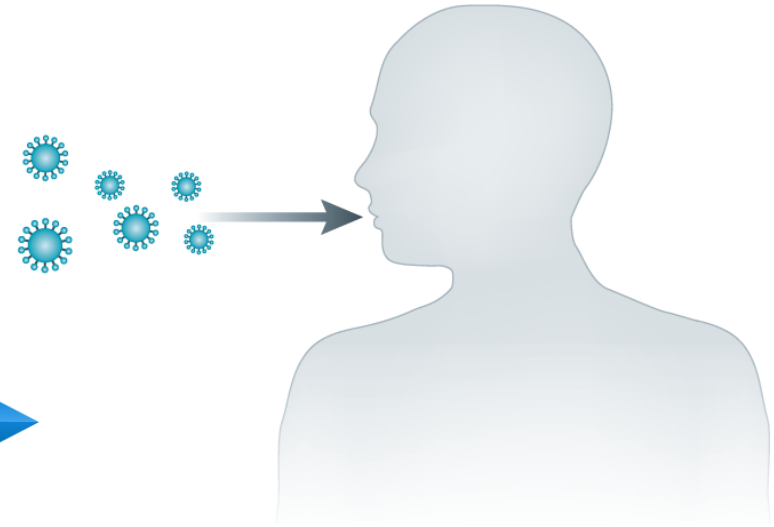
NATURE REVIEWS | IMMUNOLOGY VOLUME 21 | DECEMBER 2021 | 765

PROGRESS

The immunology of asymptomatic SARS-CoV-2 infection: what are the key questions?

Rosemary J. Boyton and Daniel M. Altmann



COVID19: Infección Asintomática Letal

No infection	Asymptomatic infection	Mild symptomatic infection	Severe	Lethal
• Innate resistance? • Pre-existing polymerase-specific T cells?	• Variable T cell response including IFNγ, IL-2, TNF, IL-6 and IL-10 • High neutralizing Ab levels	• Some evidence for greater T cell response than in asymptomatic individuals • High neutralizing Ab levels	• Delayed seroconversion, then high Ab titre • Lymphopenia, especially $CD8^+$ T cell, B cell, NK cell and γδ cell cytopenia • Raised IL-10 and IP10 levels	

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frontiers in Immunology

REVIEW
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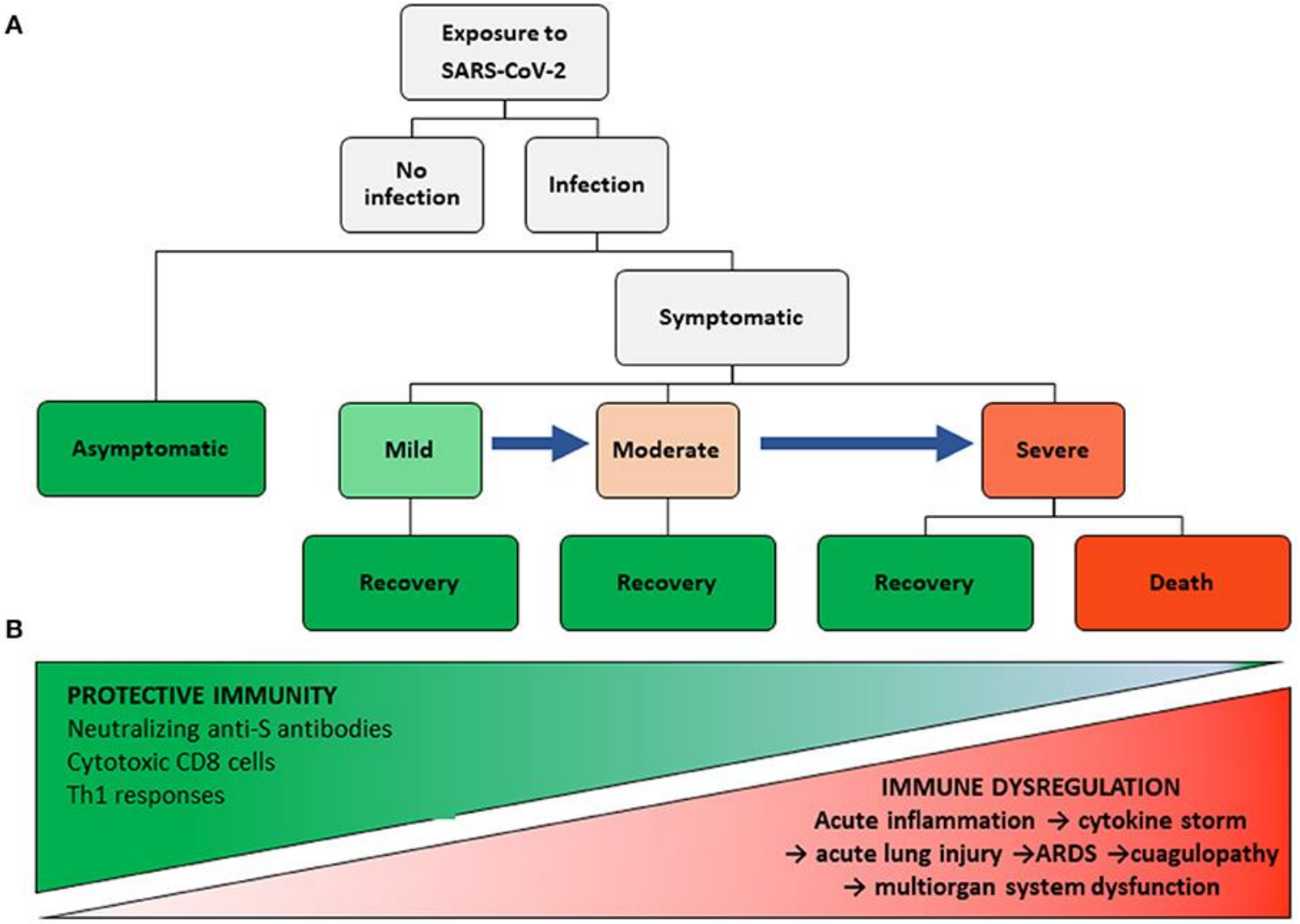
Immune Response, Inflammation, and the Clinical Spectrum of COVID-19

*Luis F. García**



Comportamiento del Sistema Inmunitario del huésped: Factor Determinante

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Review article

Life Sciences 256 (2020) 117900

The immune system and COVID-19: Friend or foe?

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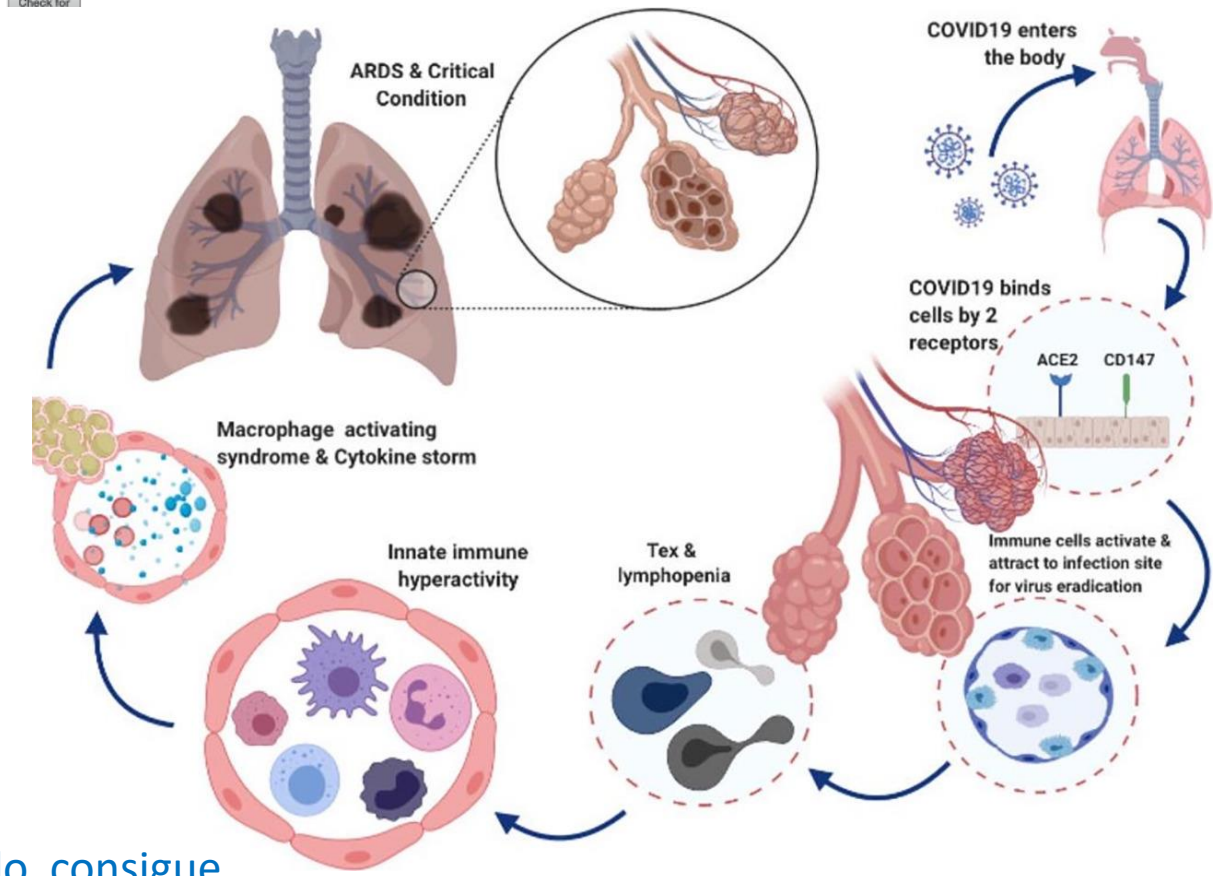
ABSTRACT

Aim: Coronavirus disease 2019 (COVID-19) is a novel highly contagious infection caused by SARS-CoV-2, which has been became a global public health challenge. The pathogenesis of this virus is not yet clearly understood, but there is evidence of a hyper-inflammatory immune response in critically ill patients, which leads to acute respiratory distress syndrome (ARDS) and multi-organ failure.

Material and methods: A literature review was performed to identify relevant articles on COVID-19 published up to April 30, 2020. The search resulted in 361 total articles. After reviewing the titles and abstracts for inclusion, some irrelevant papers were excluded. Additional relevant articles were identified from a review of citations referenced.

Key findings: SARS-CoV-2, directly and indirectly, affects the immune system and avoids being eliminated in early stages. On the other hand, the secretion of inflammatory cytokines creates critical conditions that lead to multi-organ failure.

Significance: The immune system which is affected by the virus tries to respond via a cytokine storm and hyperinflammation, which itself leads to further multi-organ damage and even death.



El sistema inmunitario intenta controlar la infección, si no lo consigue, responde a través de una tormenta de citocinas e hiper-inflamación sistémica **Fallo Multi-orgánico**

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ARTICLES
https://doi.org/10.1038/s41591-020-1051-9

nature medicine

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An inflammatory cytokine signature predicts COVID-19 severity and survival

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Several studies have revealed that the hyper-inflammatory response induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a major cause of disease severity and death. However, predictive biomarkers of pathogenic inflammation to help guide targetable immune pathways are critically lacking. We implemented a rapid multiplex cytokine assay to measure serum interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-α and IL-1β in hospitalized patients with coronavirus disease 2019 (COVID-19) upon admission to the Mount Sinai Health System in New York. Patients ($n = 1,484$) were followed up to 41 d after admission (median, 8 d), and clinical information, laboratory test results and patient outcomes were collected. We found that high serum IL-6, IL-8 and TNF-α levels at the time of hospitalization were strong and independent predictors of patient survival ($P < 0.0001$, $P = 0.0205$ and $P = 0.0140$, respectively). Notably, when adjusting for disease severity, common laboratory inflammation markers, hypoxia and other vitals, demographics, and a range of comorbidities, IL-6 and TNF-α serum levels remained independent and significant predictors of disease severity and death. These findings were validated in a second cohort of patients ($n = 231$). We propose that serum IL-6 and TNF-α levels should be considered in the management and treatment of patients with COVID-19 to stratify prospective clinical trials, guide resource allocation and inform therapeutic options.

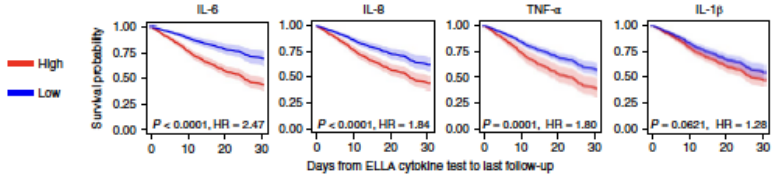

Fig. 3 | Cytokine levels and survival. Survival curves based on each cytokine measured, after multiple variable adjustments for sex, age, race/ethnicity, smoking, CKD, hypertension, asthma and CHF ($n = 1,246$). Cox regression model showing overall survival with CIs for each cytokine based on time from ELLA cytokine test to last follow-up date (discharge, death or still in hospital, whichever comes last), with significance indicated by *P* value and HR. There was worse survival if cytokines were high (red, above cutoffs of 70 pg ml^{-1} for IL-6, 50 pg ml^{-1} for IL-8, 35 pg ml^{-1} for TNF-α and 0.5 pg ml^{-1} for IL-1β) versus low (blue, below cutoffs). Each line indicates the predicted survival probability over follow-up time, with the error band indicating the corresponding two-sided 95% CI.

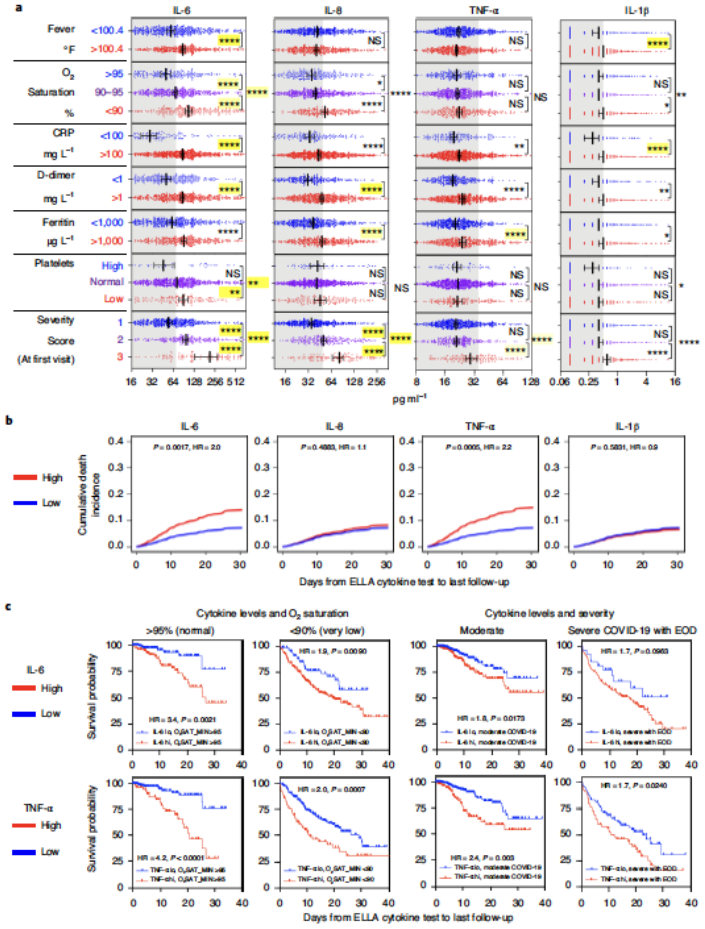

Fig. 4 | Cytokine levels correlate with severity and independently predict survival. Correlation of cytokine levels with established inflammatory and severity measurements. **a**, Correlation of each cytokine with each metric ($n = 1,106$ for fever, $n = 1,112$ for O_2 saturation, $n = 1,023$ for CRP, $n = 926$ for D-dimer, $n = 1,017$ for ferritin, $n = 1,038$ for platelets and $n = 1,023$ for disease severity score), using the same univariate and multivariate analyses as in the Fig. 2 legend. Error bar indicates the median ± 95% CI. **b**, Competing risk analysis ($n = 671$) showing survival differences by IL-6 and TNF-α levels, after adjusting the following variables: IL-6, IL-8, TNF-α, IL-1β, age, sex, race/ethnicity, smoking status, asthma, atrial fibrillation, cancer, CHF, CKD, COPD, diabetes, hypertension, sleep apnea, severity, systolic blood pressure max, O_2 saturation min, D-dimer, albumin, calcium, chloride and platelet count. **c**, Kaplan–Meier univariate analyses of survival by IL-6 and TNF-α levels in patients with normal ($n = 257$), low ($n = 258$) or very low ($n = 287$) O_2 saturation, or in patients with moderate ($n = 588$) versus severe COVID-19 with end organ damage ($n = 136$), as measured at the first available test. EOD, end organ damage.

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Dysregulated Type I Interferon and Inflammatory Monocyte-Macrophage Responses Cause Lethal Pneumonia in SARS-CoV-Infected Mice

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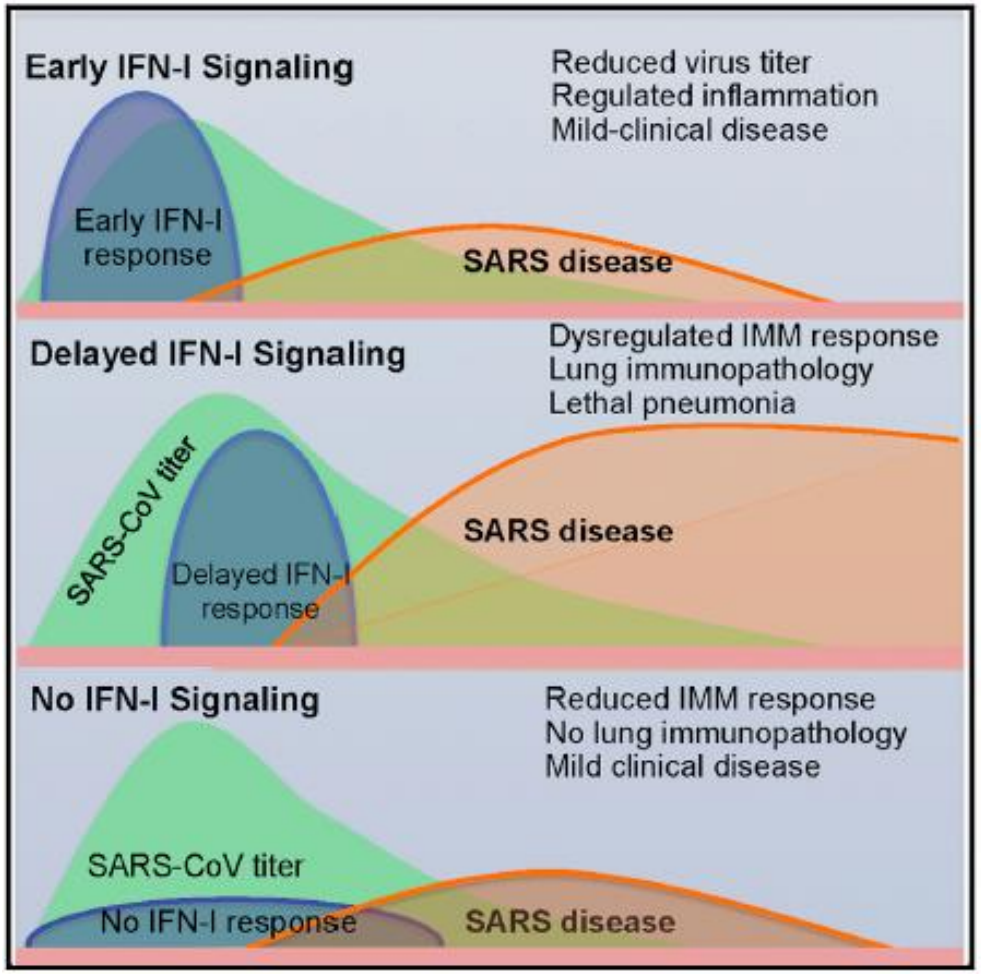
Highlights

- SARS-CoV causes a lethal respiratory infection in BALB/c mice
- Robust SARS-CoV replication and delayed IFN-I signaling promote disease
- IFN-I induces influx of pathogenic inflammatory monocytes and vascular leakage
- Disease severity is ameliorated in the absence of IFN signaling

TIEMPO: FACTOR CLAVE



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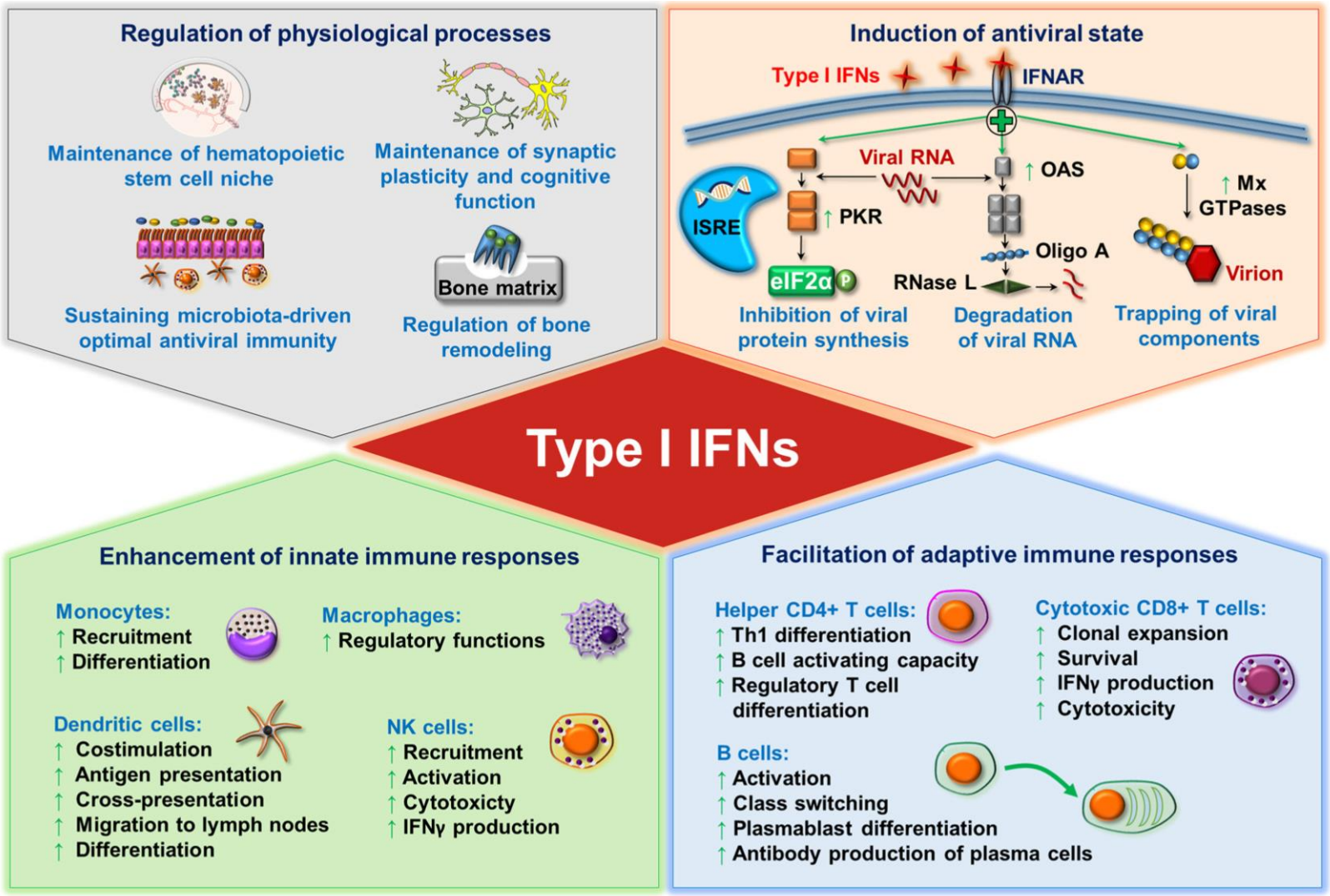
FUNCIONES DEL INTERFERON



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https://doi.org/10.3390/jmp2040019

INMUNODEPRESIÓN ASOCIADA A COVID-19 GRAVE

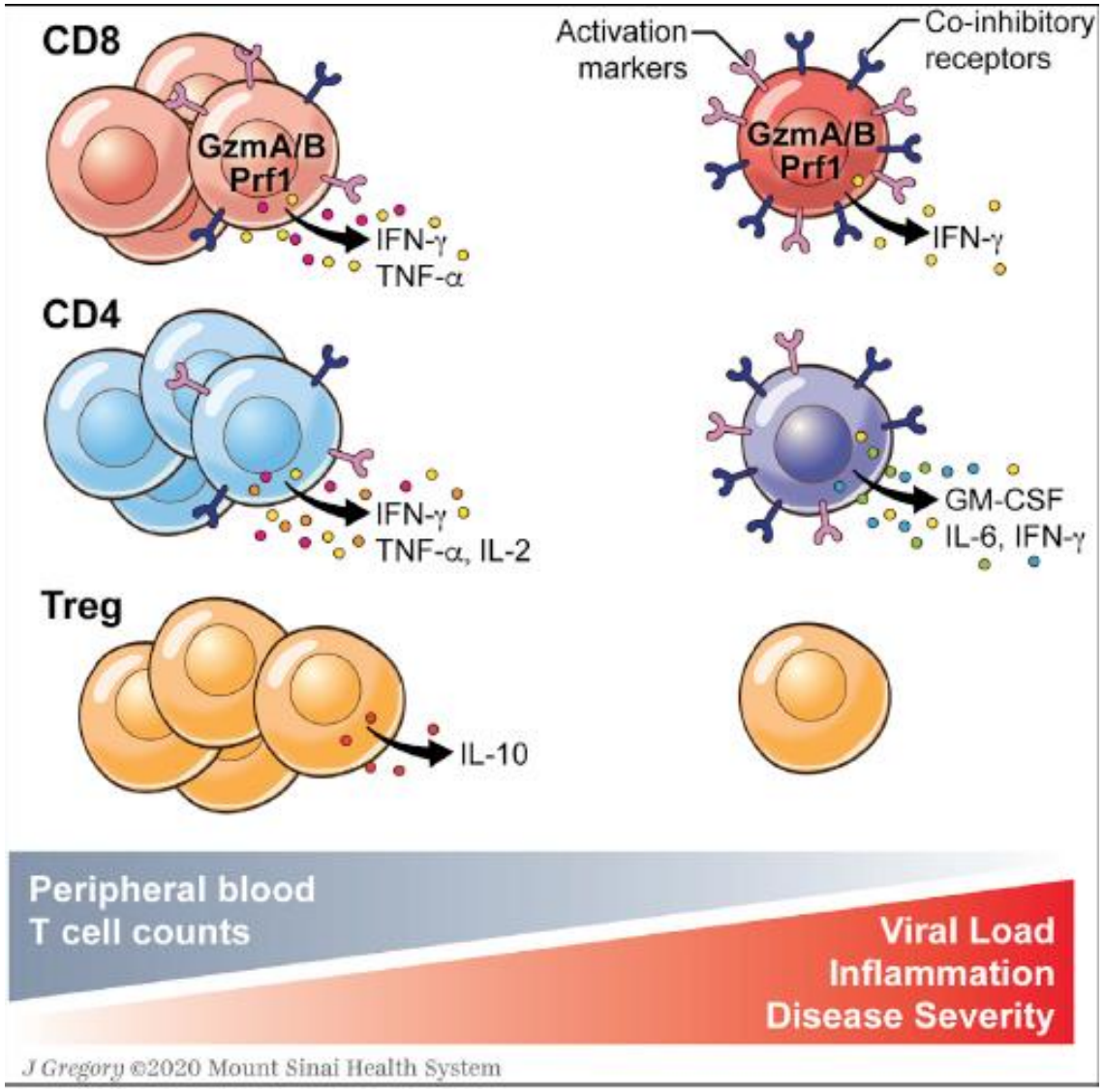

Figure 3. Working Model for T Cell Responses to SARS-CoV-2: Changes in Peripheral Blood T Cell Frequencies and Phenotype

A decrease in peripheral blood T cells associated with disease severity and inflammation is now well documented in COVID-19. Several studies report increased numbers of activated CD4 and CD8 T cells, which display a trend toward an exhausted phenotype in persistent COVID-19, based on continuous and upregulated expression of inhibitory markers as well as potential reduced polyfunctionality and cytotoxicity. In severe disease, production of specific inflammatory cytokines by CD4 T cells has also been reported. This working model needs to be confirmed and expanded on in future studies to assess virus-specific T cell responses both in peripheral blood and in tissues. In addition, larger and more defined patient cohorts with longitudinal data are required to define the relationship between disease severity and T cell phenotype.

IL, interleukin; IFN, interferon; TNF, tumor necrosis factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; GzmA/B, granzyme A/granzyme B; Prf1, perforin.

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PLoS one

Severe Pandemic H1N1 2009 Infection Is Associated with Transient NK and T Deficiency and Aberrant CD8 Responses

Annette Fox[1,2]*, Le Nguyen Minh Hoa[2], Peter Horby[1,2], H. Rogier van Doorn[1,2], Nguyen Vu Trung[3], Nguyen Hong Ha[3], Nguyen Trung Cap[3], Vu Dinh Phu[3], Nguyen Minh Ha[3], Diep Nguyen Thi Ngoc[2], Bich Vu Thi Ngoc[2], Huong Tran Thi Kieu[2], Walter R. Taylor[1,2,4], Jeremy Farrar[1,2], Heiman Wertheim[1,2], Nguyen Van Kinh[3]

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Abstract

Background: It is unclear why the severity of influenza varies in healthy adults or why the burden of severe influenza shifts to young adults when pandemic strains emerge. One possibility is that cross-protective T cell responses wane in this age group in the absence of recent infection. We therefore compared the acute cellular immune response in previously healthy adults with severe versus mild pandemic H1N1 infection.

Methods and Principal Findings: 49 previously healthy adults admitted to the National Hospital of Tropical Diseases, Viet Nam with RT-PCR-confirmed 2009 H1N1 infection were prospectively enrolled. 39 recovered quickly whereas 10 developed severe symptoms requiring supplemental oxygen and prolonged hospitalization. Peripheral blood lymphocyte subset counts and activation (HLADR, CD38) and differentiation (CD27, CD28) marker expression were determined on days 0, 2, 5, 10, 14 and 28 by flow cytometry. NK, CD4 and CD8 lymphopenia developed in 100%, 90% and 60% of severe cases versus 13% ($p<0.001$), 28%, ($p=0.001$) and 18% ($p=0.014$) of mild cases. CD4 and NK counts normalized following recovery. B cell counts were not significantly associated with severity. CD8 activation peaked 6–8 days after mild influenza onset, when 13% (6–22%) were HLADR+CD38+, and was accompanied by a significant loss of resting/CD27+CD28+ cells without accumulation of CD27+CD28− or CD27−CD28− cells. In severe influenza CD8 activation peaked more than 9 days post-onset, and/or was excessive (30–90% HLADR+CD38+) in association with accumulation of CD27+CD28− cells and maintenance of CD8 counts.

Conclusion: Severe influenza is associated with transient T and NK cell deficiency. CD8 phenotype changes during mild influenza are consistent with a rapidly resolving memory response whereas in severe influenza activation is either delayed or excessive, and partially differentiated cells accumulate within blood indicating that recruitment of effector cells to the lung could be impaired.

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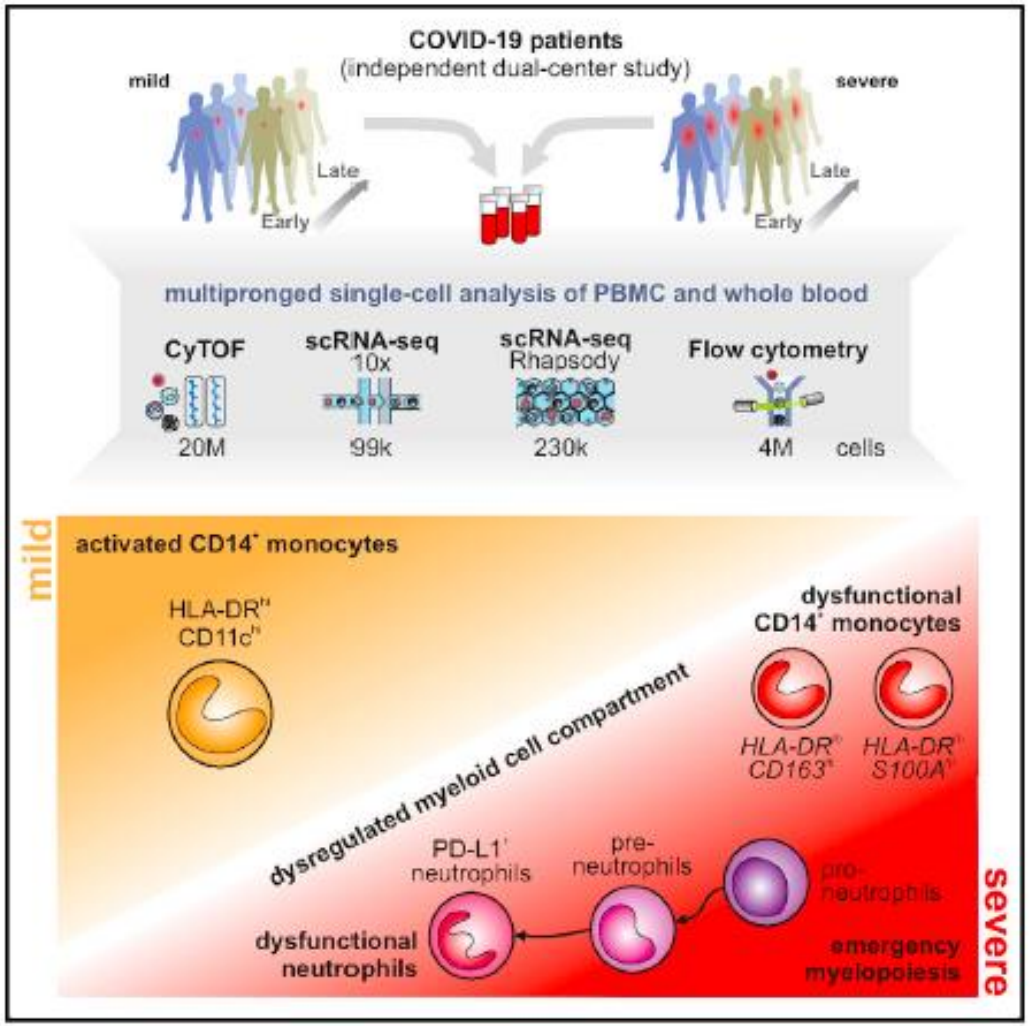
Cell 182, 1419–1440, September 17, 2020

Article

Severe COVID-19 Is Marked by a Dysregulated Myeloid Cell Compartment

Highlights

- SARS-CoV-2 infection induces profound alterations of the myeloid compartment
- Mild COVID-19 is marked by inflammatory *HLA-DR^{hi}CD11c^{hi} CD14^{+}* monocytes
- Dysfunctional HLA-DR^{lo}CD163^{hi} and HLA-DR^{lo}S100A^{hi} CD14^{+} monocytes in severe COVID-19
- Emergency myelopoiesis with immature and dysfunctional neutrophils in severe COVID-19



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Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages

Miriam Merad and Jerome C. Martin

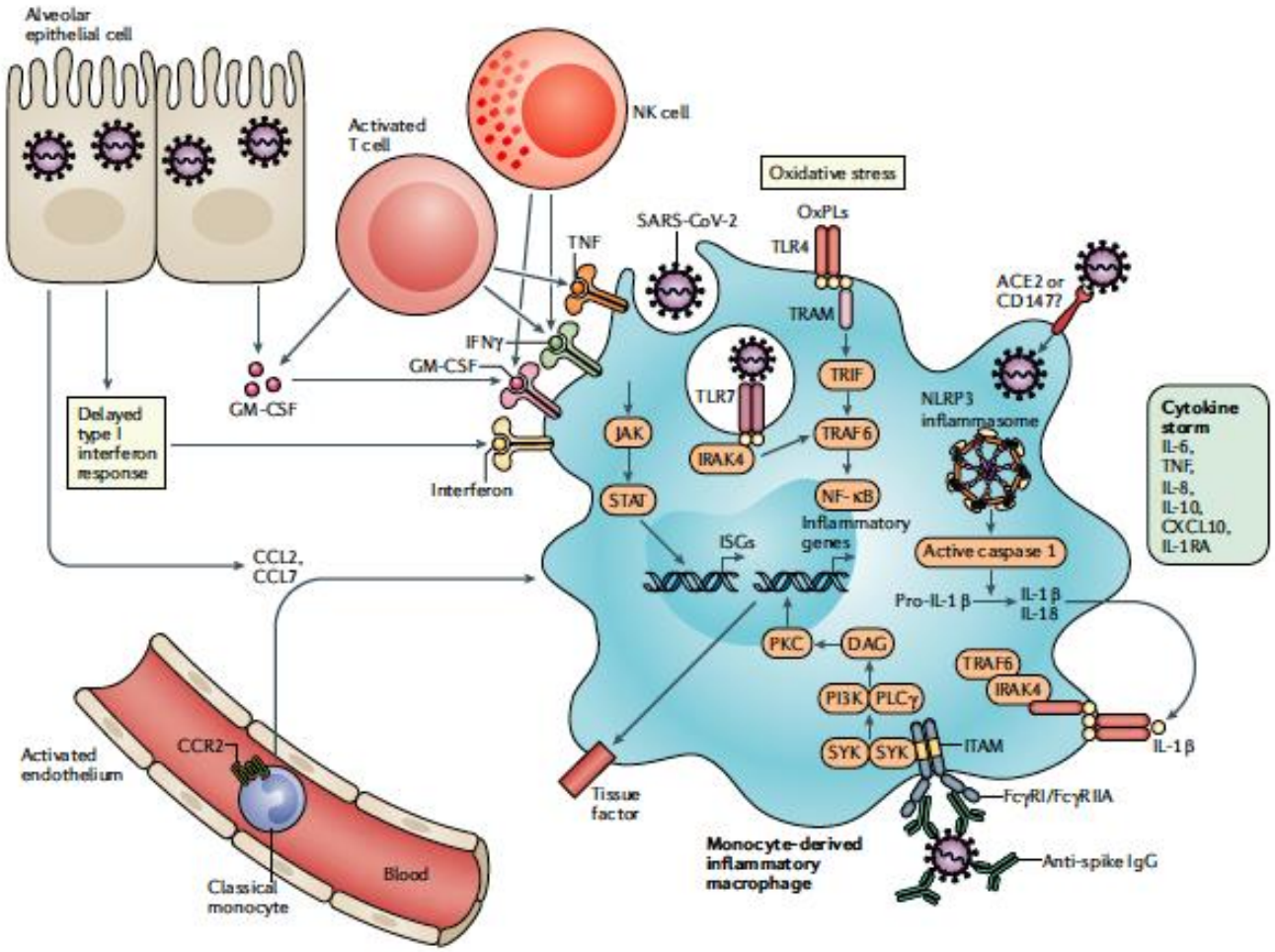

Fig. 1 | **Possible pathways contributing to hyperactivation of monocyte-derived macrophages and hyperinflammation in COVID-19.** Several mechanisms likely contribute to the hyperactivation of monocyte-derived macrophages that is seen in patients with COVID-19. Delayed production of type I interferon leading to enhanced cytopathic effects and increased sensing of microbial threats promotes the enhanced release of monocyte chemoattractants by alveolar epithelial cells (and likely also by macrophages and stromal cells), leading to sustained recruitment of blood monocytes into the lungs. Monocytes differentiate into pro-inflammatory macrophages though activation of Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathways. Activated natural killer (NK) cells and T cells further promote the recruitment and activation of monocyte-derived macrophages through the production of granulocyte–macrophage colony-stimulating factor (GM-CSF), tumour necrosis factor (TNF) and interferon-γ (IFNγ). Oxidized phospholipids (OxPLs) accumulate in infected lungs and activate monocyte-derived macrophages through the Toll-like receptor 4 (TLR4)–TRAF6–NF-κB pathway. Virus sensing can trigger TLR7 activation through viral single-stranded RNA recognition. It is possible that type I interferons induce the expression of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry receptors, enabling the virus to gain access to the cytoplasm of macrophages and to activate the NLRP3 inflammasome, leading to the secretion of mature IL-1β and/or IL-18. IL-1β can amplify activation of monocyte-derived macrophages in an autocrine or paracrine way, but it can also reduce type I interferon production in infected lungs. The engagement of Fcγ receptors (FcγRs) by anti-spike protein IgG immune complexes can contribute to increased inflammatory activation of monocyte-derived macrophages. Activated monocyte-derived macrophages contribute to the COVID-19 cytokine storm by releasing massive amounts of pro-inflammatory cytokines. CCL, CC-chemokine ligand; CXCL10, CXC-chemokine ligand 10; ISG, interferon-stimulated gene; ITAM, immunoreceptor tyrosine-based activation motif; TRAM, TRIF-related adaptor molecule.

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TRASTORNOS DE LA COAGULACIÓN EN LA COVID-19

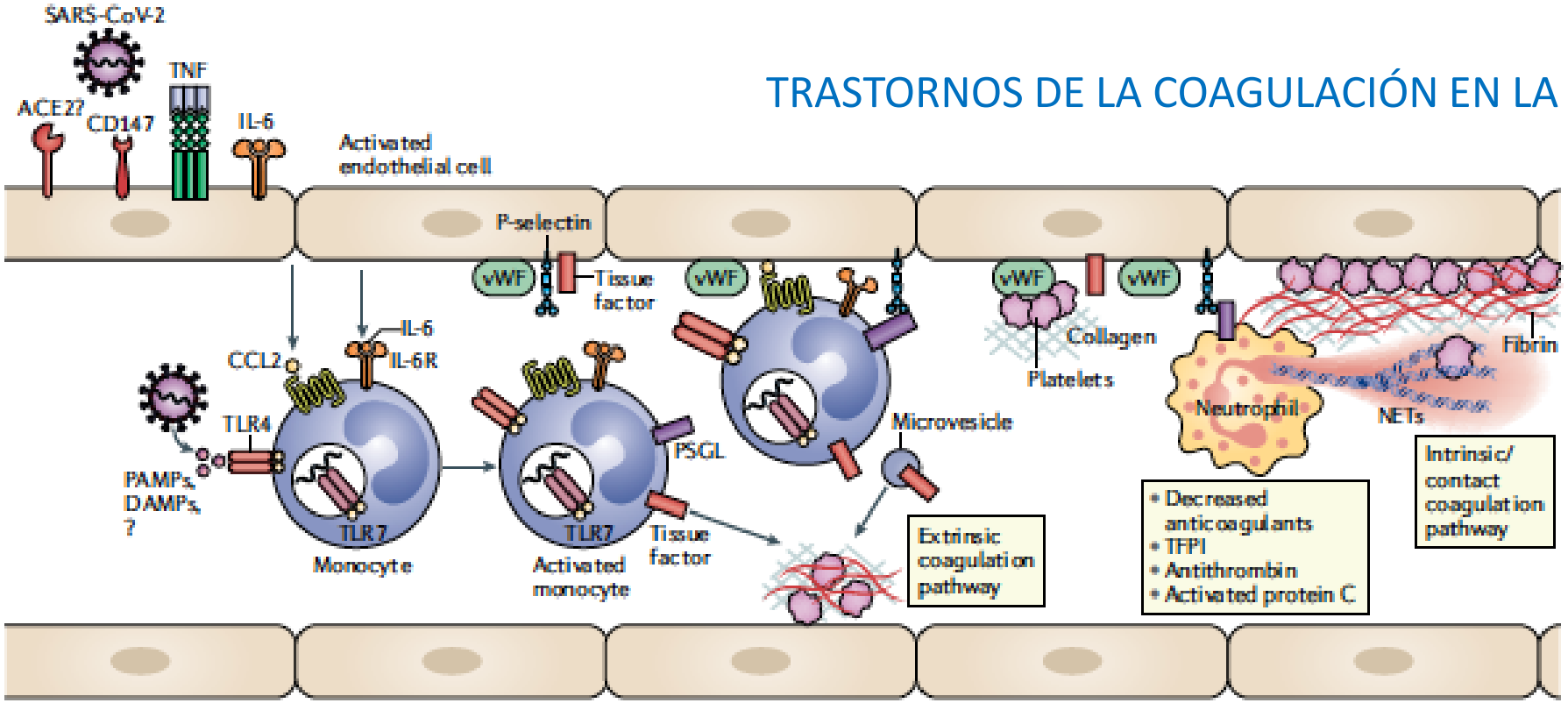

Fig. 2 | **Possible contribution of hyperactivated monocytes to coagulation in COVID-19.** Circulating pro-inflammatory stimuli, such as viral pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs) and cytokines trigger activation of blood monocytes, which respond by inducing tissue factor membrane expression. Endothelial cells are activated by cytokines and viral particles and produce monocyte chemo-attractants and adhesion molecules. Endothelial damage induced by the virus can also expose tissue factor on endothelial cells. Activated monocytes are recruited to endothelial cells. Tissue factor expressed by activated monocytes, monocyte-derived microvesicles and endothelial cells activates the extrinsic coagulation pathway, leading to fibrin deposition and blood clotting. Neutrophils are recruited by activated endothelial cells and release neutrophil extracellular traps (NETs), which activate the coagulation contact pathway and bind and activate platelets to amplify blood clotting. Major endogenous anticoagulant pathways, which include tissue factor pathway inhibitor (TFPI), antithrombin and protein C, are reduced further, supporting coagulation activation. CCL2, CC-chemokine ligand 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TLR, Toll-like receptor; TNF, tumour necrosis factor; vWF, von Willebrand factor.

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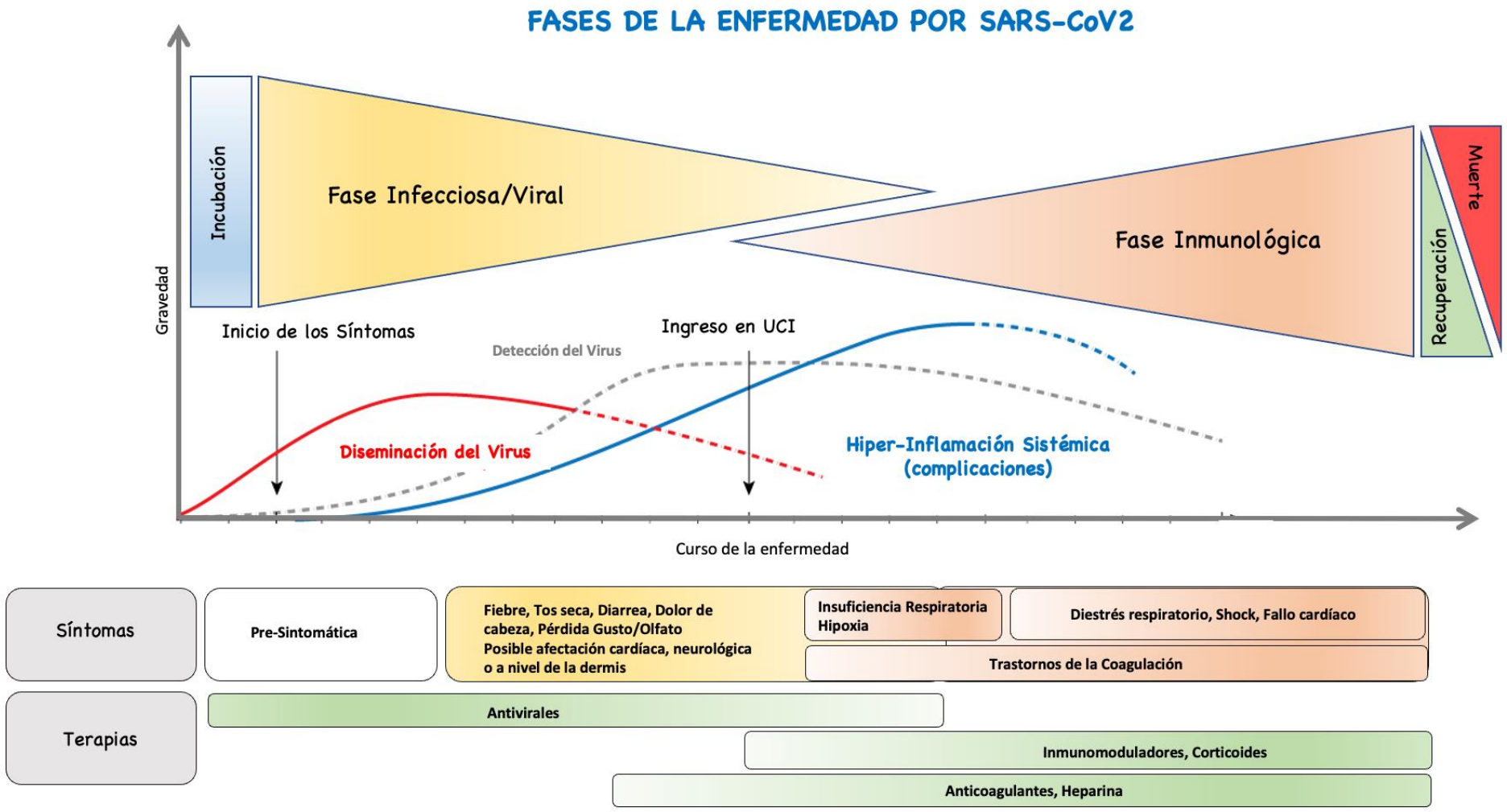
COVID-19: ENFERMEDAD EN DOS FASES



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Cell

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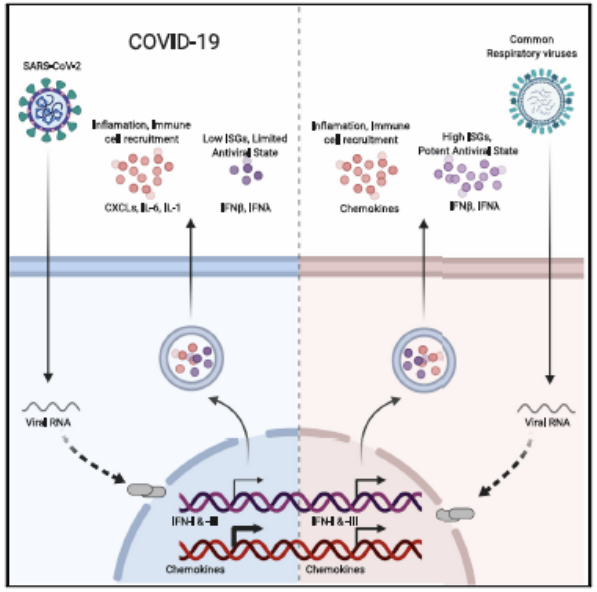
Article

Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19

Graphical Abstract



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In Brief

In comparison to other respiratory viruses, SARS-CoV-2 infection drives a lower antiviral transcriptional response that is marked by low IFN-I and IFN-III levels and elevated chemokine expression, which could explain the pro-inflammatory disease state associated with COVID-19.

Highlights

- SARS-CoV-2 infection induces low IFN-I and -III levels with a moderate ISG response
- Strong chemokine expression is consistent across *in vitro*, *ex vivo*, and *in vivo* models
- Low innate antiviral defenses and high pro-inflammatory cues contribute to COVID-19

En comparación con otros virus respiratorios, la infección por SARS-Cov2 induce una respuesta antiviral muy pobre con niveles bajos de IFN-I y –III y con una elevada expresión de citocinas inflamatorias, responsables de la enfermedad grave

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NATURE IMMUNOLOGY | VOL 22 | JANUARY 2021 | 32–40 | www.nature.com/natureimmunology

LETTERS

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nature immunology

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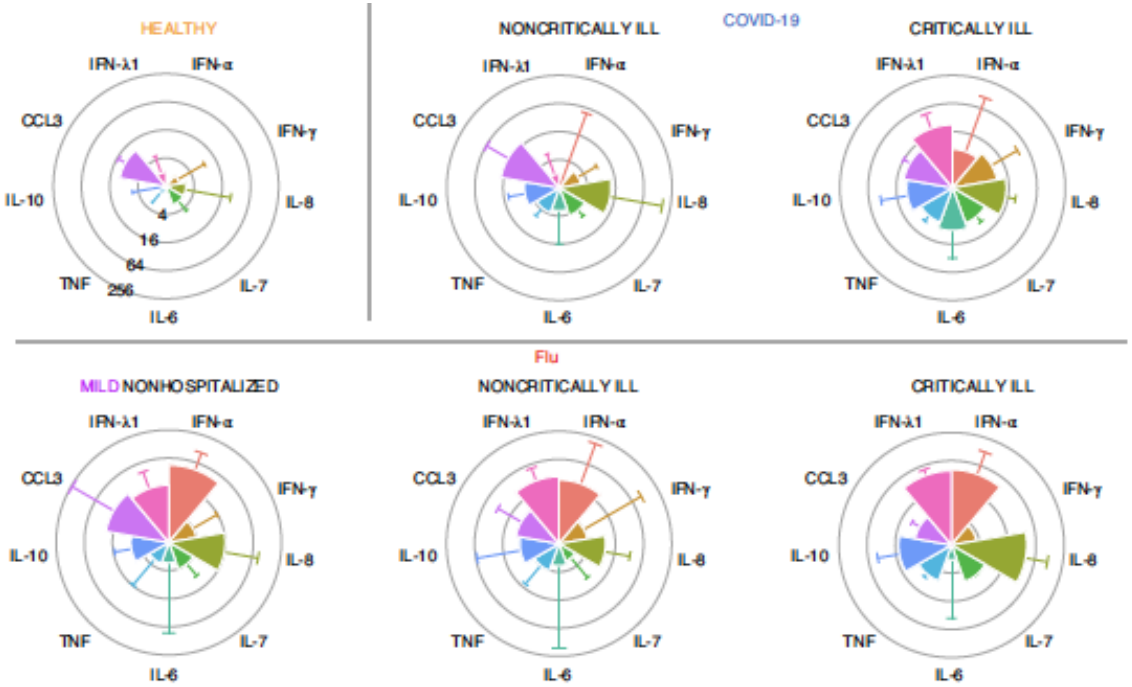
Untuned antiviral immunity in COVID-19 revealed by temporal type I/III interferon patterns and flu comparison

Ioanna-Evdokia Galani[1,8], Nikoletta Rovina[2,8], Vicky Lampropoulou[1], Vasiliki Triantafyllia[1], Maria Manioudaki[1], Eleftherios Pavlos[1], Evangelia Koukaki[3], Paraskevi C. Fragkou[4], Vasiliki Panou[3], Vasiliki Rapti[4], Ourania Koltsida[5], Andreas Mentis[6], Nikolaos Koulouris[3], Sotirios Tsiodras[4], Antonia Koutsoukou[2] and Evangelos Andreakos[1,7]



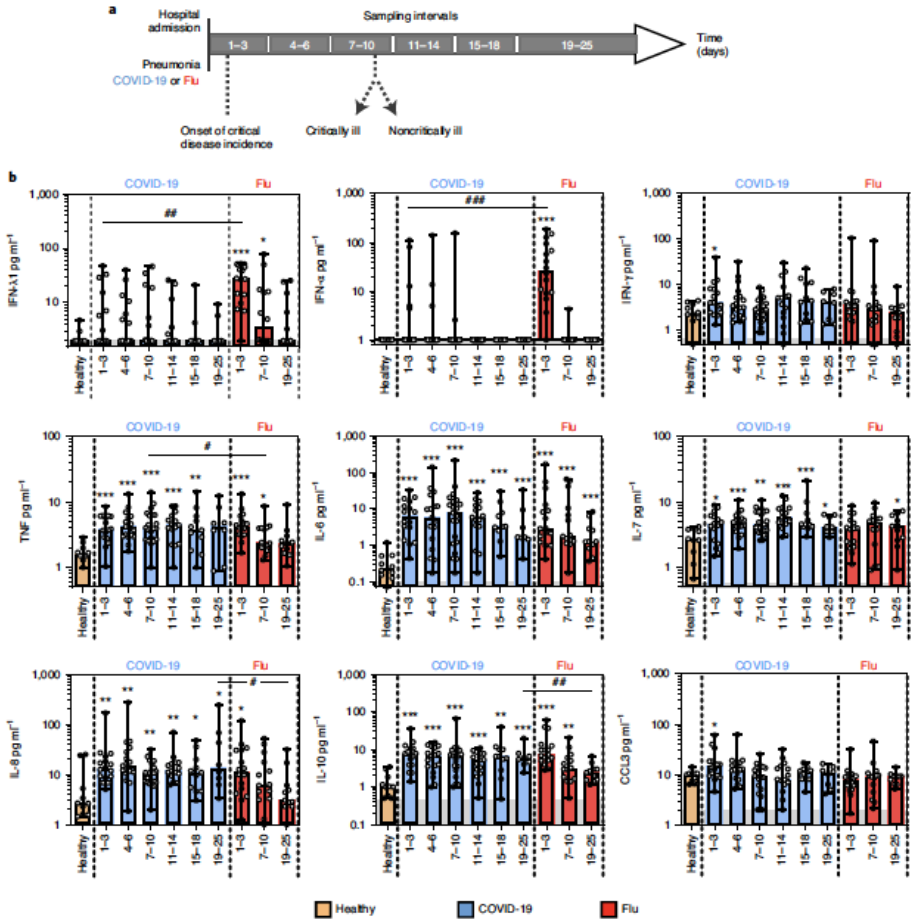


Fig. 1 | Temporal IFN and inflammatory cytokine patterns of patients with COVID-19 and flu in relation to hospital admission. a, Schematic showing the experimental design with sampling at specific time intervals after hospital admission of 32 patients with COVID-19 and 16 patients with flu with pneumonia followed longitudinally. Dashed lines indicate the time of the first and last onset of critical disease, respectively. **b**, Serum levels of IFN-λ1, IFN-α, IFN-γ, TNF, IL-6, IL-7, IL-8, IL-10 and CCL3 at various time intervals after hospital admission. Data are presented as scatter plots with dots showing individual patient measurements, columns median values and error bars the range. For COVID-19, $n=16$, 17, 21, 15, 11 and 8 for each of the six consecutive time intervals. For flu, $n=16$, 14 and 11, respectively. For healthy, $n=10$. Gray shading marks the limit of quantification of the assay. *P* values were determined by a two-tailed Mann–Whitney *U*-test for nonparametric comparisons. $^{*}P<0.05$, $^{**}P<0.01$ and $^{***}P<0.001$ show significance over healthy controls. $^{\#}P<0.05$, $^{\#\#}P<0.01$ and $^{\#\#\#}P<0.001$ show significance between COVID-19 and flu groups.

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RESEARCH

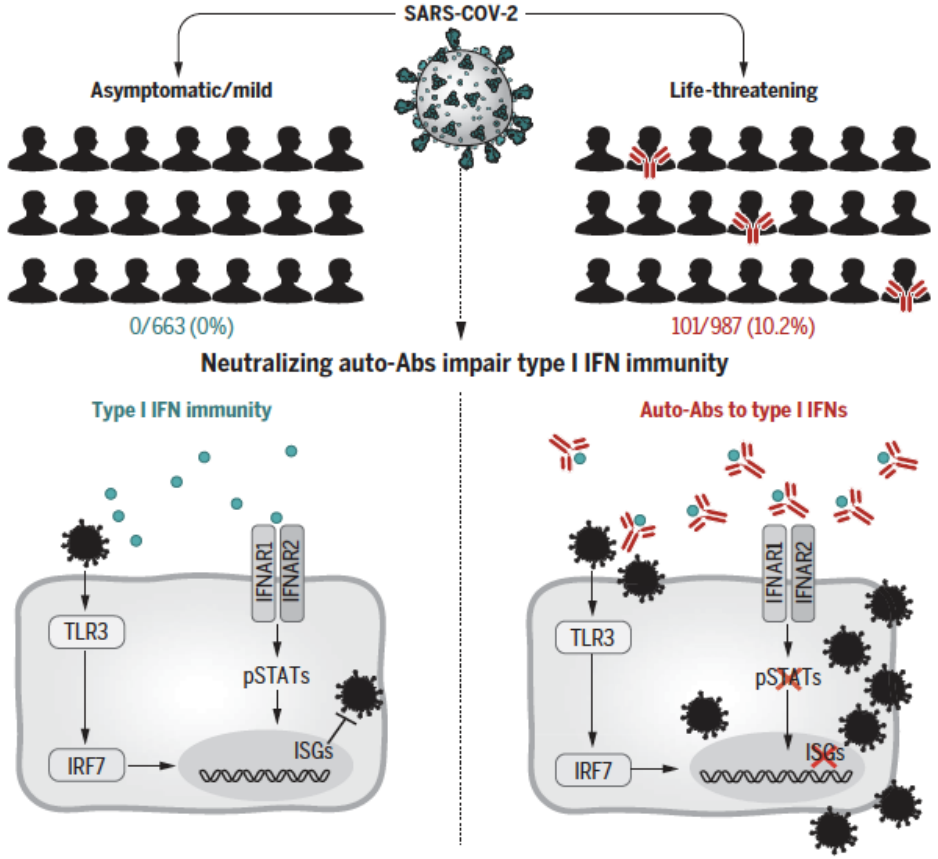
RESEARCH ARTICLE SUMMARY

CORONAVIRUS

Autoantibodies against type I IFNs in patients with life-threatening COVID-19

Paul Bastard*† and Lindsey B. Rosen† *et al.*

Interindividual clinical variability in the course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is vast. We report that at least 101 of 987 patients with life-threatening coronavirus disease 2019 (COVID-19) pneumonia had neutralizing immunoglobulin G (IgG) autoantibodies (auto-Abs) against interferon-ω (IFN-ω) (13 patients), against the 13 types of IFN-α (36), or against both (52) at the onset of critical disease; a few also had auto-Abs against the other three type I IFNs. The auto-Abs neutralize the ability of the corresponding type I IFNs to block SARS-CoV-2 infection in vitro. These auto-Abs were not found in 663 individuals with asymptomatic or mild SARS-CoV-2 infection and were present in only 4 of 1227 healthy individuals. Patients with auto-Abs were aged 25 to 87 years and 95 of the 101 were men. A B cell autoimmune phenocopy of inborn errors of type I IFN immunity accounts for life-threatening COVID-19 pneumonia in at least 2.6% of women and 12.5% of men.



Neutralizing auto-Abs to type I IFNs underlie life-threatening COVID-19 pneumonia. We tested the hypothesis that neutralizing auto-Abs against type I IFNs may underlie critical COVID-19 by impairing the binding of type I IFNs to their receptor and the activation of the downstream responsive pathway. Neutralizing auto-Abs are represented in red, and type I IFNs are represented in blue. In these patients, adaptive autoimmunity impairs innate and intrinsic antiviral immunity. ISGs, IFN-stimulated genes; TLR, Toll-like receptor; IFNAR, IFN-α/β receptor; pSTAT, phosphorylated signal transducers and activators of transcription; IRF, interferon regulatory factor.

<u>Auto-Ac frente al IFN-I</u> en Covid-19 grave (2,6% mujeres / 12,5% hombres)

@gomez_rial5

JCI The Journal of Clinical Investigation

The intersection of COVID-19 and autoimmunity

Jason S. Knight, … , Julia Y. Wang, William J. McCune

J Clin Invest. 2021;131(24):e154886. https://doi.org/10.1172/JCI154886.

Acute COVID-19, caused by SARS-CoV-2, is characterized by diverse clinical presentations, ranging from asymptomatic infection to fatal respiratory failure, and often associated with varied longer-term sequelae. Over the past 18 months, it has become apparent that inappropriate immune responses contribute to the pathogenesis of severe COVID-19. Researchers working at the intersection of COVID-19 and autoimmunity recently gathered at an American Autoimmune Related Diseases Association Noel R. Rose Colloquium to address the current state of knowledge regarding two important questions: Does established autoimmunity predispose to severe COVID-19? And, at the same time, can SARS-CoV-2 infection trigger de novo autoimmunity? Indeed, work to date has demonstrated that 10% to 15% of patients with critical COVID-19 pneumonia exhibit autoantibodies against type I interferons, suggesting that preexisting autoimmunity underlies severe disease in some patients. Other studies have identified functional autoantibodies following infection with SARS-CoV-2, such as those that promote thrombosis or antagonize cytokine signaling. These autoantibodies may arise from a predominantly extrafollicular B cell response that is more prone to generating autoantibody-secreting B cells. This Review highlights the current understanding, evolving concepts, and unanswered questions provided by this unique opportunity to determine mechanisms by which a viral infection can be exacerbated by, and even trigger, autoimmunity. The potential role of autoimmunity in post-acute sequelae of COVID-19 is also discussed.

Table 1. SARS-CoV-2 shares some characteristic features with other viruses that trigger autoimmunity

Features of other viruses	Evidence for SARS-CoV-2
Precedes autoimmunity	Case reports of patients developing classifiable autoimmune diseases following SARS-CoV-2 infection (56–64)
Induces type I IFNs	SARS-CoV-2 induces robust type I IFN responses in a subset of patients (23–26)
Breaks tolerance	SARS-CoV-2 induces autoantibody production in patients with severe COVID-19 (42, 77)
Superantigen activity	SARS-CoV-2 spike protein contains a superantigen motif and patients with severe COVID-19 exhibit TCR skewing consistent with superantigen activation (109)
Inhibits apoptosis of infected cells	No evidence to date
Interferes with its own destruction	No evidence to date

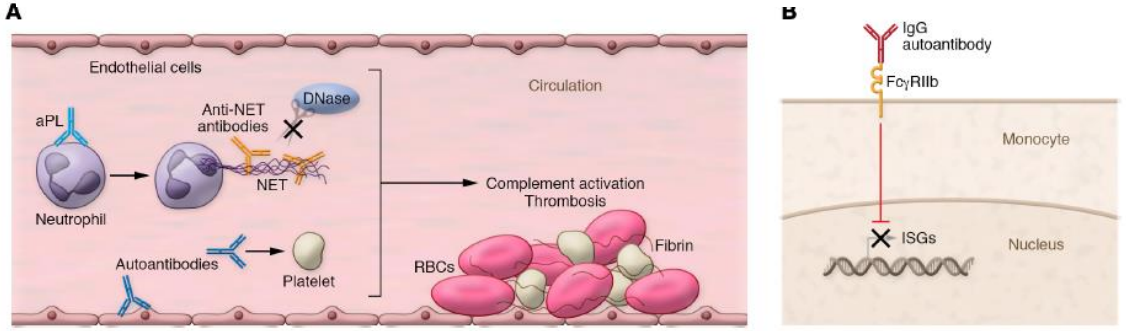


Figure 2. Potential downstream mechanisms of autoantibodies identified in patients with severe COVID-19. (**A**) A subset of patients with severe COVID-19 have anti-phospholipid antibodies (aPLs) and/or anti–neutrophil extracellular trap (anti-NET) autoantibodies. aPLs may activate endothelial cells and platelets and stimulate neutrophils to release NETs. Anti-NET antibodies bind to NETs, impairing NET degradation by DNase. Together, these autoantibodies may activate complement and promote thrombosis. (**B**) In some patients with severe COVID-19, antibodies can prevent the expression of ISGs by antagonizing signaling through the type I IFN receptor in an FcγRIIb-dependent fashion, impairing antiviral immunity.

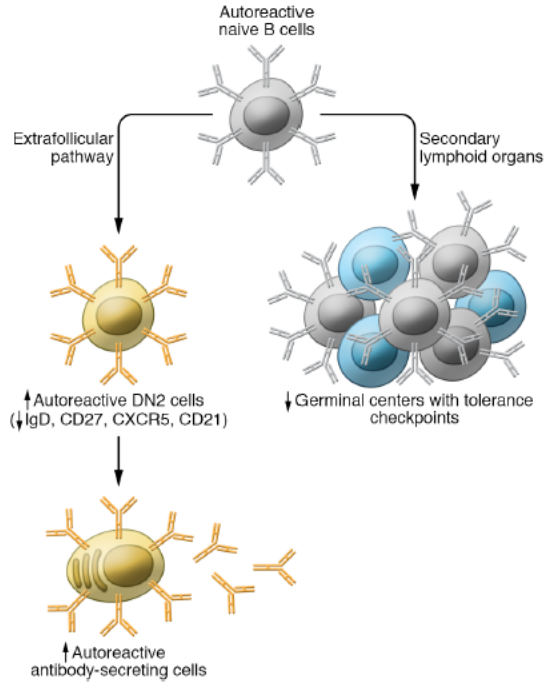


Figure 3. Potential mechanisms of de novo autoimmunity in COVID-19. Naive B cells can be activated via both the germinal center and the extrafollicular pathway. The extrafollicular pathway lacks some tolerance checkpoints that prevent the activation and maturation of autoreactive B cells and is, therefore, more prone to generating autoantibodies. Patients with severe COVID-19 exhibit higher levels of extrafollicular B cells lacking IgD, CD27, CXCR5, and CD21 (known as double-negative [DN2] cells) and plasma cells. They may also lack germinal centers. Red arrows indicate increased or reduced levels in patients with severe COVID-19 compared with patients with mild COVID-19.

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COVID-19

Overlapping B cell pathways in severe COVID-19 and lupus

An exaggerated extrafollicular B cell response characteristic of active systemic lupus erythematosus also characterizes the B cell response to SARS-CoV-2 in those with severe COVID-19.

A. Darise Farris and Joel M. Guthridge

NATURE IMMUNOLOGY | VOL 21 | DECEMBER 2020 | 1477–1485 | www.nature.com/natureimmunology

La enfermedad de Covid-19 grave y el Lupus comparten vías patogénicas donde están implicadas las células B

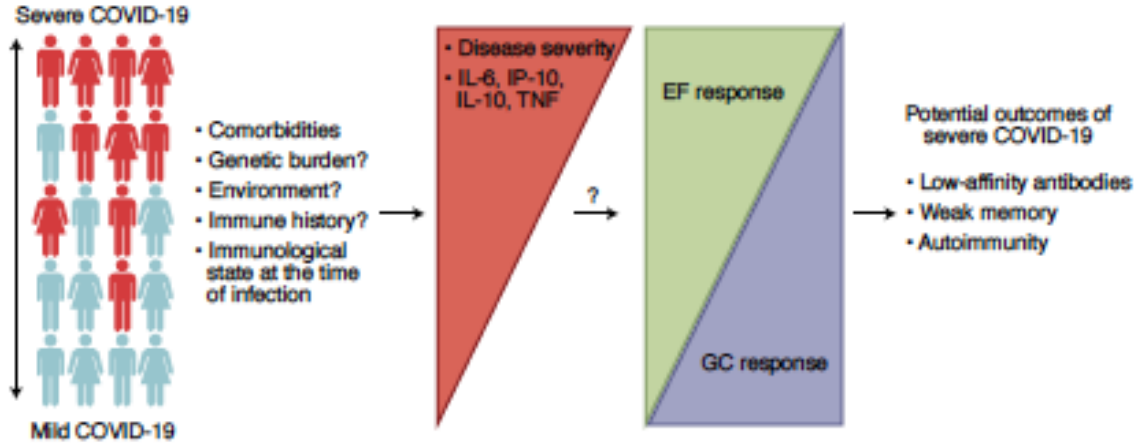

Fig. 1 | Does intrinsic immune bias predispose to severe COVID-19? In a largely AA cohort, Woodruff et al. show that subjects with severe COVID-19 make exaggerated extrafollicular (EF) B cell responses, which are also observed in AAs with active SLE. This raises the question of whether an increased propensity for inflammation contributes to the risk for severe COVID-19. Among the elevated soluble mediators in severe COVID-19 are IL-6, IP-10, IL-10 and TNF, which may promote EF and suppress GC responses. Other studies showing reduced or absent GC responses and EF-response-associated autoantibodies in severe SARS-CoV-2 infection support an EF bias in the adaptive immune response in people with a severe disease course. Potential deleterious outcomes of an EF-biased response range from inadequate immunologic memory to possible autoimmune sequelae. Understanding the precise cellular mechanisms leading to innate bias in the adaptive immune response to severe COVID-19 could lead to therapeutic approaches that restore the balance between EF and GC responses.

Article

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Diverse functional autoantibodies in patients with COVID-19

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Check for updates

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COVID-19 manifests with a wide spectrum of clinical phenotypes that are characterized by exaggerated and misdirected host immune responses[1–6]. Although pathological innate immune activation is well-documented in severe disease[1], the effect of autoantibodies on disease progression is less well-defined. Here we use a high-throughput autoantibody discovery technique known as rapid extracellular antigen profiling[7] to screen a cohort of 194 individuals infected with SARS-CoV-2, comprising 172 patients with COVID-19 and 22 healthcare workers with mild disease or asymptomatic infection, for autoantibodies against 2,770 extracellular and secreted proteins (members of the exoproteome). We found that patients with COVID-19 exhibit marked increases in autoantibody reactivities as compared to uninfected individuals, and show a high prevalence of autoantibodies against immunomodulatory proteins (including cytokines, chemokines, complement components and cell-surface proteins). We established that these autoantibodies perturb immune function and impair virological control by inhibiting immunoreceptor signalling and by altering peripheral immune cell composition, and found that mouse surrogates of these autoantibodies increase disease severity in a mouse model of SARS-CoV-2 infection. Our analysis of autoantibodies against tissue-associated antigens revealed associations with specific clinical characteristics. Our findings suggest a pathological role for exoproteome-directed autoantibodies in COVID-19, with diverse effects on immune functionality and associations with clinical outcomes.

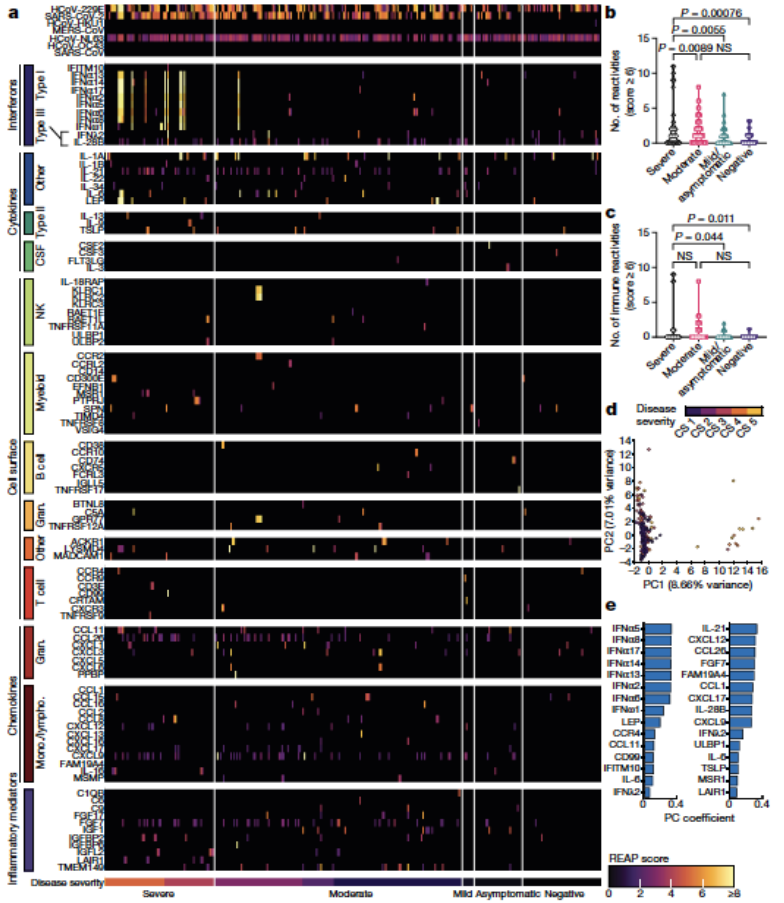

Fig. 1 | Immune-targeting autoantibodies are increased in patients with COVID-19. a, Heat map of REAP scores for immune-related proteins and RBDs

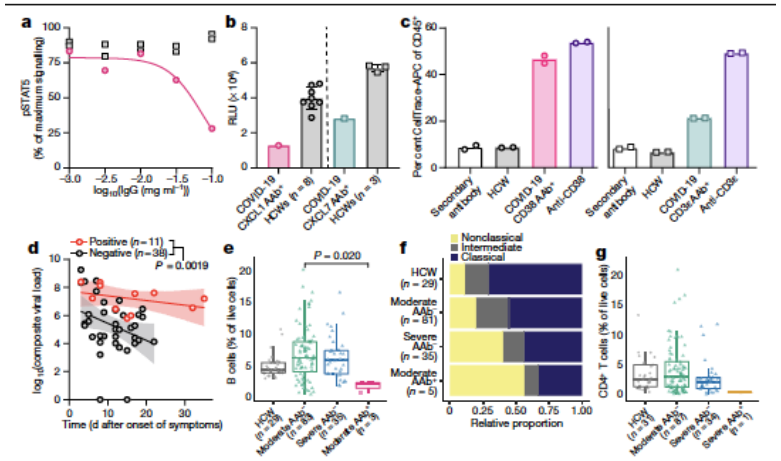

Fig. 2 | Immune-targeting autoantibodies in patients with COVID-19 have functional effects. a, GM-CSF signalling assay performed with IgG from a

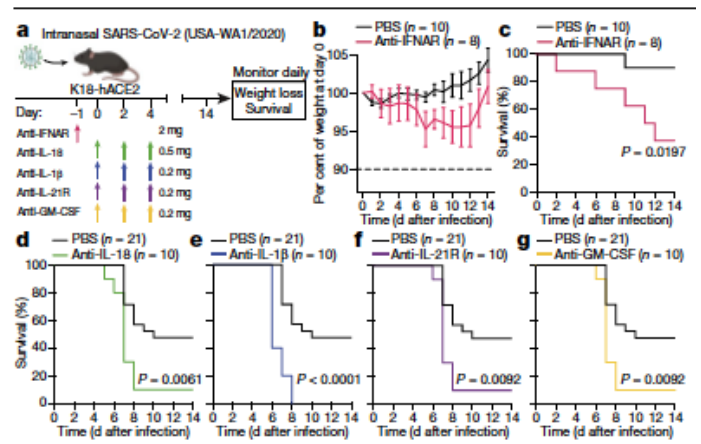

Fig. 3 | Immune-targeting autoantibodies increase disease severity in a mouse model of COVID-19. a–g, K18-hACE2 mice were intranasally infected

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ARTICLE

https://doi.org/10.1038/s41467-021-25509-3 OPEN

New-onset IgG autoantibodies in hospitalized patients with COVID-19

Sarah Esther Chang[1,2,26], Allan Feng[1,2,26], Wenzhao Meng[3,26], Sokratis A. Apostolidis[4,5,26], Elisabeth Mack[6], Maja Artandi[7,8], Linda Barman[7], Kate Bennett[9], Saborni Chakraborty[10], Iris Chang[2,11], Peggie Cheung[1,2], Sharon Chinthrajah[2,11], Shaurya Dhingra[1,2], Evan Do[2,11], Amanda Finck[12], Andrew Gaano[3], Reinhard Geßner[13], Heather M. Giannini[14], Joyce Gonzalez[3], Sarah Greib[13], Margrit Gündisch[13], Alex Ren Hsu[1,2], Alex Kuo[1,2], Monali Manohar[2,10], Rong Mao[1,2], Indira Neeli[14], Andreas Neubauer[6], Oluwatosin Oniyide[15], Abigail E. Powell[16,17], Rajan Puri[7], Harald Renz[13,18], Jeffrey Schapiro[19], Payton A. Weidenbacher[16,17], Richard Wittman[7], Neera Ahuja[20], Ho-Ryun Chung[21], Prasanna Jagannathan[2,10,22], Judith A. James[23], Peter S. Kim[14,16,24], Nuala J. Meyer[5,15], Kari C. Nadeau[2,11], Marko Radic[14], William H. Robinson[1,2,25], Upinder Singh[2,10,22], Taia T. Wang[10,22,24], E. John Wherry[5,12], Chrysanthi Skevaki[13,18✉], Eline T. Luning Prak[3,5✉] & Paul J. Utz[1,2✉]

COVID-19 is associated with a wide range of clinical manifestations, including autoimmune features and autoantibody production. Here we develop three protein arrays to measure IgG autoantibodies associated with connective tissue diseases, anti-cytokine antibodies, and anti-viral antibody responses in serum from 147 hospitalized COVID-19 patients. Autoantibodies are identified in approximately 50% of patients but in less than 15% of healthy controls. When present, autoantibodies largely target autoantigens associated with rare disorders such as myositis, systemic sclerosis and overlap syndromes. A subset of autoantibodies targeting traditional autoantigens or cytokines develop de novo following SARS-CoV-2 infection. Autoantibodies track with longitudinal development of IgG antibodies recognizing SARS-CoV-2 structural proteins and a subset of non-structural proteins, but not proteins from influenza, seasonal coronaviruses or other pathogenic viruses. We conclude that SARS-CoV-2 causes development of new-onset IgG autoantibodies in a significant proportion of hospitalized COVID-19 patients and are positively correlated with immune responses to SARS-CoV-2 proteins.

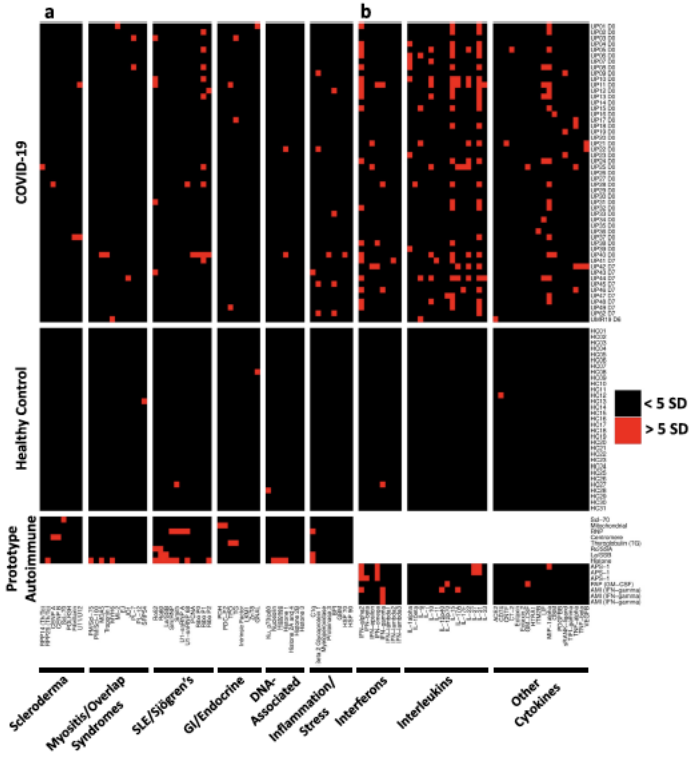

Fig. 1 High prevalence of autoantibodies in hospitalized COVID-19 patients. a Heatmap depicting serum IgG antibodies discovered using a 53-p

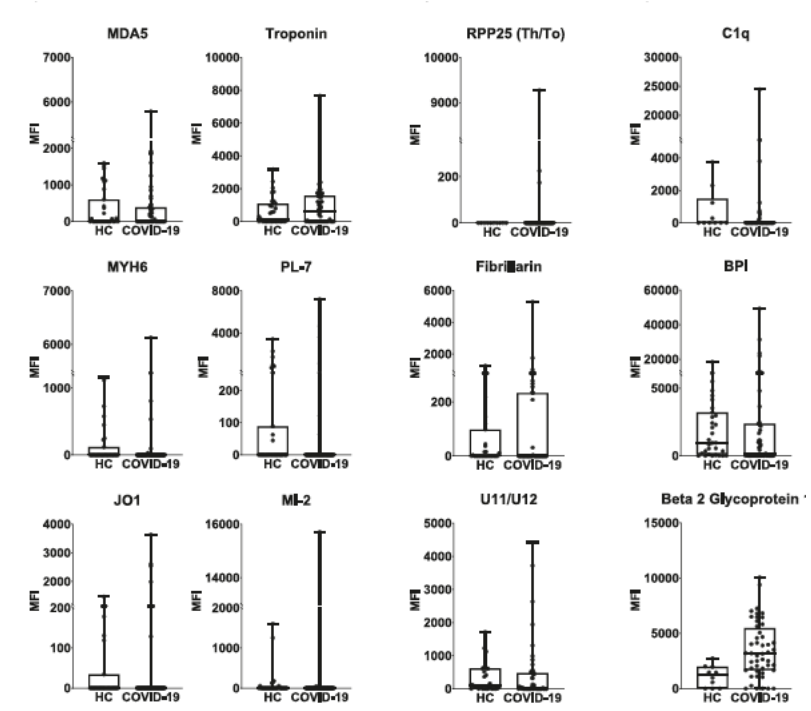

Fig. 2 Serum autoantibodies in COVID-19 patients recognize antigens targeted in rare connective tissue diseases, and antigens associated wit pathogenicity. Boxplots of twelve antigens corresponding to Fig. 1. **a** Antigens associated with autoimmune myositis and myocarditis (MDA5, tropo

Se identifican autoAc en 50% pacientes Covid-19 hospitalizados

Dianas: autoAg tradicionales, citocinas, prots regulación inmune

Correlación con gravedad

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ARTICLE

https://doi.org/10.1038/s41467-021-25509-3 OPEN

New-onset IgG autoantibodies in hospitalized patients with COVID-19

Sarah Esther Chang[1,2,26], Allan Feng[1,2,26], Wenzhao Meng[3,26], Sokratis A. Apostolidis[4,5,26], Elisabeth Mack[6], Maja Artandi[7,8], Linda Barman[7], Kate Bennett[9], Saborni Chakraborty[10], Iris Chang[2,11], Peggie Cheung[1,2], Sharon Chinthrajah[2,11], Shaurya Dhingra[1,2], Evan Do[2,11], Amanda Finck[12], Andrew Gaano[3], Reinhard Geßner[13], Heather M. Giannini[14], Joyce Gonzalez[3], Sarah Greib[13], Margrit Gündisch[13], Alex Ren Hsu[1,2], Alex Kuo[1,2], Monali Manohar[2,10], Rong Mao[1,2], Indira Neeli[14], Andreas Neubauer[6], Oluwatosin Oniyide[15], Abigail E. Powell[16,17], Rajan Puri[7], Harald Renz[13,18], Jeffrey Schapiro[19], Payton A. Weidenbacher[16,17], Richard Wittman[7], Neera Ahuja[20], Ho-Ryun Chung[21], Prasanna Jagannathan[2,10,22], Judith A. James[23], Peter S. Kim[14,16,24], Nuala J. Meyer[5,15], Kari C. Nadeau[2,11], Marko Radic[14], William H. Robinson[1,2,25], Upinder Singh[2,10,22], Taia T. Wang[10,22,24], E. John Wherry[5,12], Chrysanthi Skevaki[13,18]✉, Eline T. Luning Prak[3,5]✉ & Paul J. Utz[1,2]✉

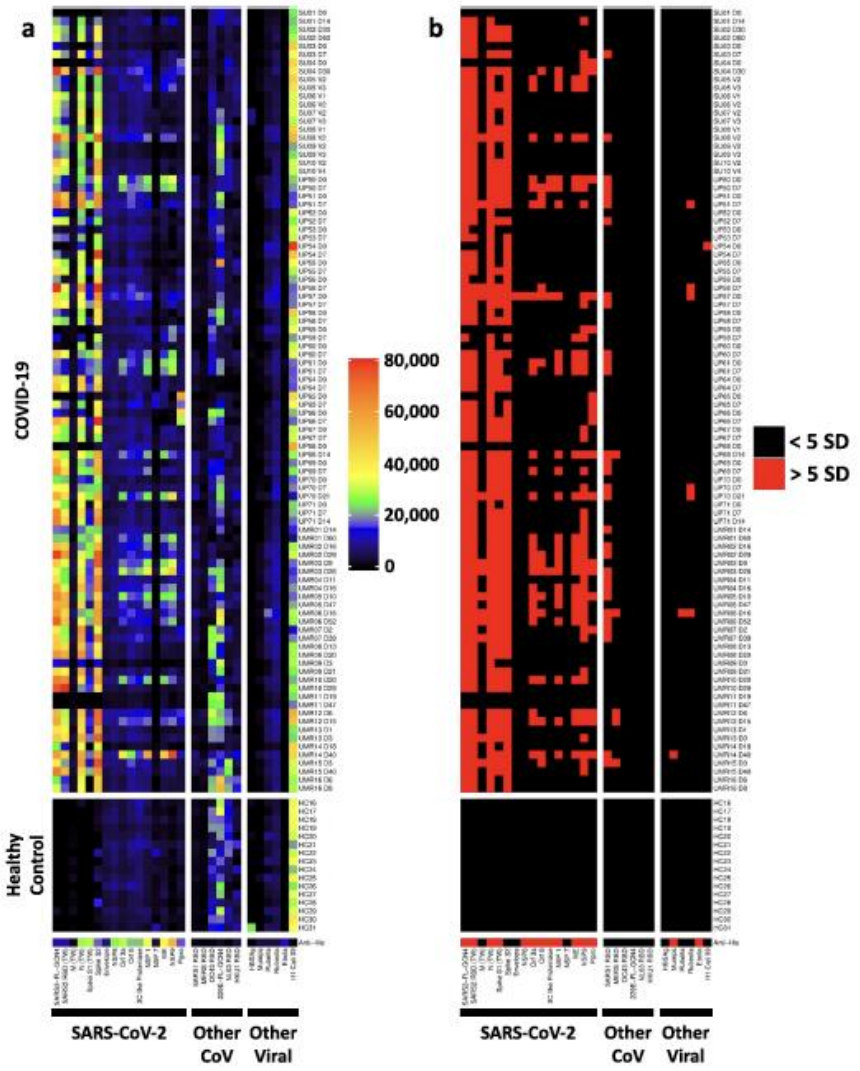

Fig. 4 Measurement of anti-viral IgG responses using a COVID-19 viral array. a Heatmap depicting IgG antibodies using a 28-plex bead-based protein array. Viral protein antigens are grouped based on sixteen proteins from SARS-CoV-2 (left panel), other coronaviruses (middle panel), and other viruses (right panel), labeled on the x-axis. Most recombinant viral proteins were engineered to include a 6X-His-tag, which was used to validate conjugation to beads using an anti-epitope monoclonal antibody (bottom of the panel). The same COVID-19 patients from Fig. 3 (see Supplementary Figures 9 and 10) were analyzed (top panel, $n = 94$ longitudinal COVID-19 samples, including paired samples from 44 subjects and 2 subjects who had 3 available time points each, subjects UP70 and UP71). HC ($n = 16$, middle panel). Two patient sample pairs (UP63 and UMR20) were excluded from analysis due to technical failure on the viral array assay. Colors correspond to the MFI values shown at right. **b** Heatmap depicting statistically significant anti-viral IgG responses. Colors indicate IgG antibodies whose MFI measurements are >5 SD (red) or <5 SD (black) above the average MFI for HC samples collected prior to the COVID-19 pandemic. Source data are provided as a Source Data file.

AutoAcs reconocen proteínas del SARS-Cov2 pero no de otros coronavirus estacionales u otras infecciones virales

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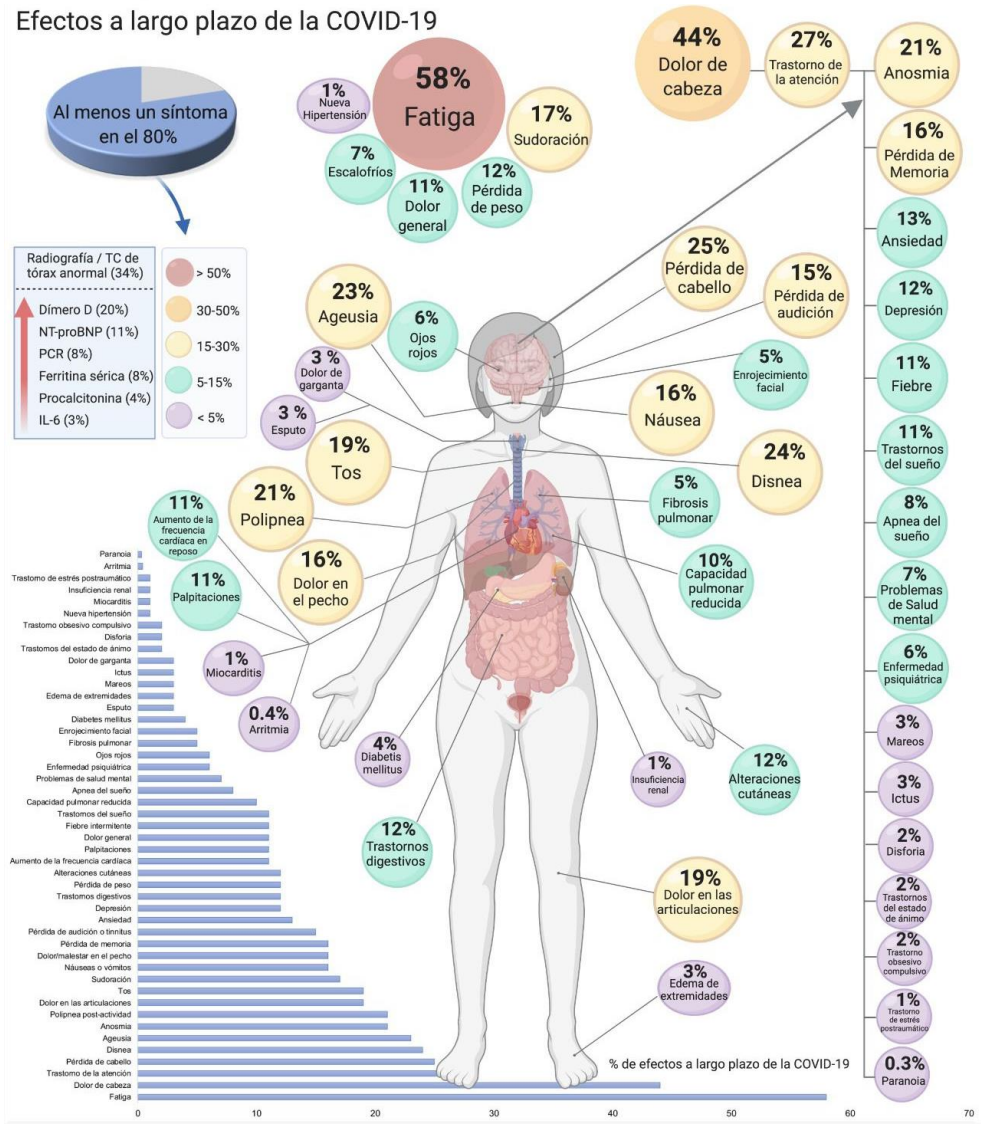


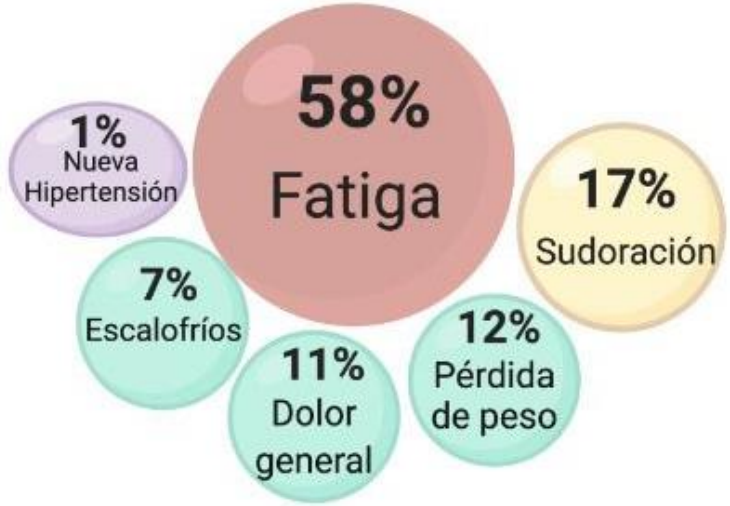
scientific reports

Sandra Lopez-Leon, Talia Wegman-Ostrosky, Carol Perelman, Rosalinda Sepulveda, Paulina A. Rebolledo, Angelica Cuapio & Sonia Villapol

More than 50 long-term effects of COVID-19: a systematic review and meta-analysis.

Sci Rep 11, 16144 (2021). https://doi.org/10.1038/s41598-021-95565-8

COVID-PERSISTENTE: problema de Salud Pública en los próximos años



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NATURE IMMUNOLOGY | VOL 23 | FEBRUARY 2022 | 194–202 | www.nature.com/natureimmunology

Pathological sequelae of long-haul COVID

Saurabh Mehandru[1,2] ✉ and Miriam Merad[1,3] ✉

The world continues to contend with successive waves of coronavirus disease 2019 (COVID-19), fueled by the emergence of viral variants. At the same time, persistent, prolonged and often debilitating sequelae are increasingly recognized in convalescent individuals, named 'post-COVID-19 syndrome' or 'long-haul COVID'. Clinical symptomatology includes fatigue, malaise, dyspnea, defects in memory and concentration and a variety of neuropsychiatric syndromes as the major manifestations, and several organ systems can be involved. The underlying pathophysiological mechanisms are poorly understood at present. This Review details organ-specific sequelae of post-COVID-19 syndromes and examines the underlying pathophysiological mechanisms available so far, elaborating on persistent inflammation, induced autoimmunity and putative viral reservoirs. Finally, we propose diagnostic strategies to better understand this heterogeneous disorder that continues to afflict millions of people worldwide.

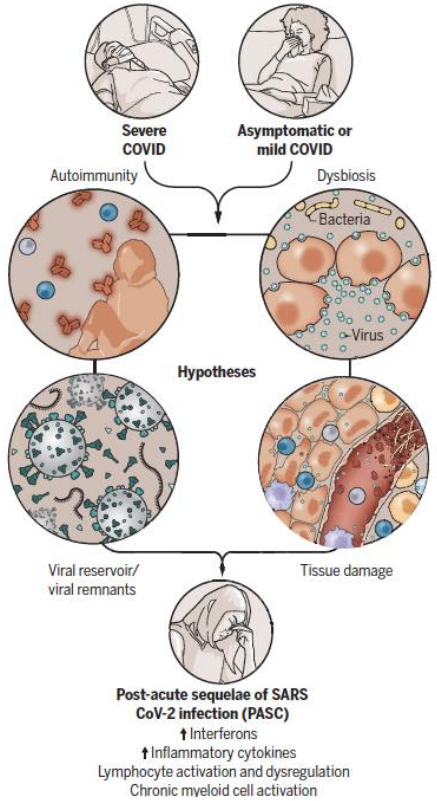

Fig. 2. Immunology of PASC. A fraction of COVID-19 patients with either severe or mild COVID-19 develop a variety of new, recurring, or ongoing symptoms and clinical findings 4 or more weeks after infection. Analyses of immune responses in people with PASC reveal key inflammatory cytokines and cellular activation phenotypes that are significantly elevated over nonPASC convalescent controls. Further studies are needed to identify the drivers of PASC pathophysiology.

Merad *et al.*, *Science* **375**, 1122–1127 (2022) 11 March 2022

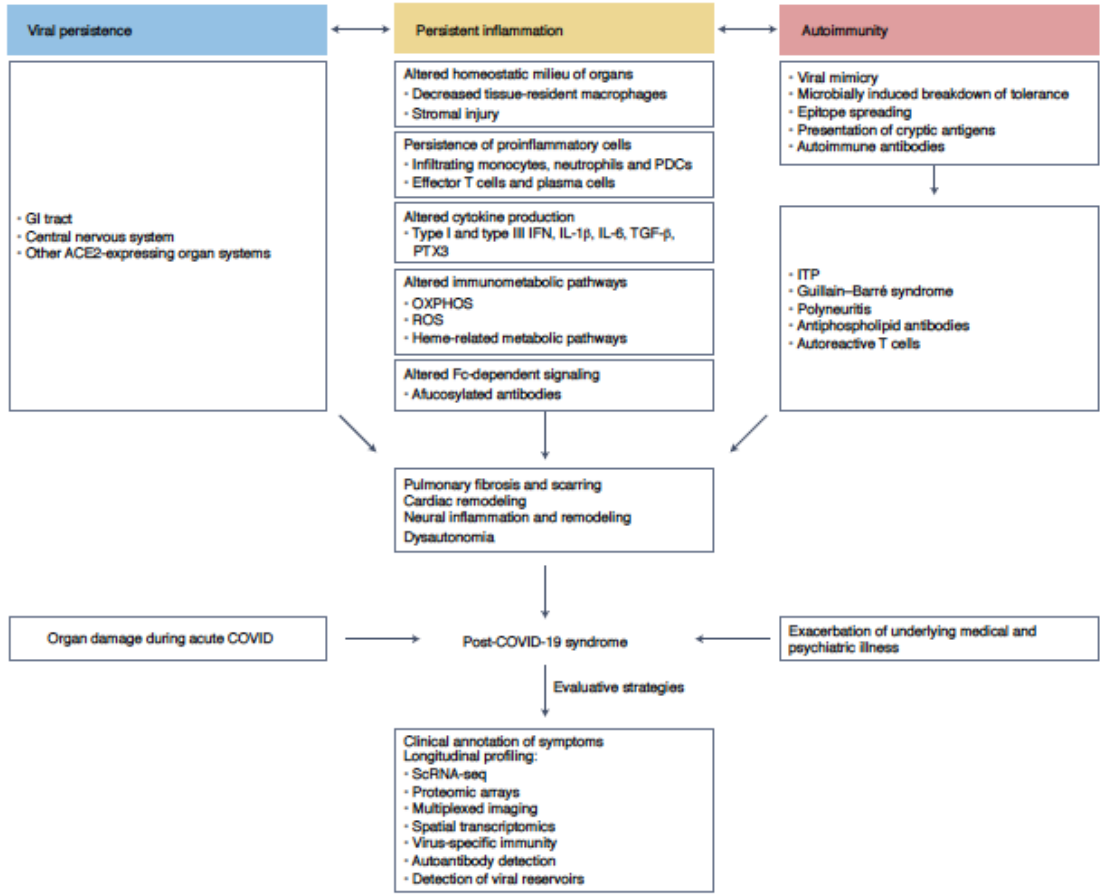

Fig. 1 | Putative mechanisms and diagnostic strategies for patients with post-COVID-19 syndromes. Delayed resolution of inflammation, autoimmunity and viral persistence represents overlapping mechanisms that may contribute to the pathogenesis of post-COVID-19 syndromes. Strategies to better characterize patients with post-COVID-19 syndromes are indicated. ITP, idiopathic thrombocytopenic purpura; OXPHOS, oxidative phosphorylation; PDCs, plasmacytoid dendritic cells; ROS, reactive oxygen species; TGF-β, transforming growth factor-β.

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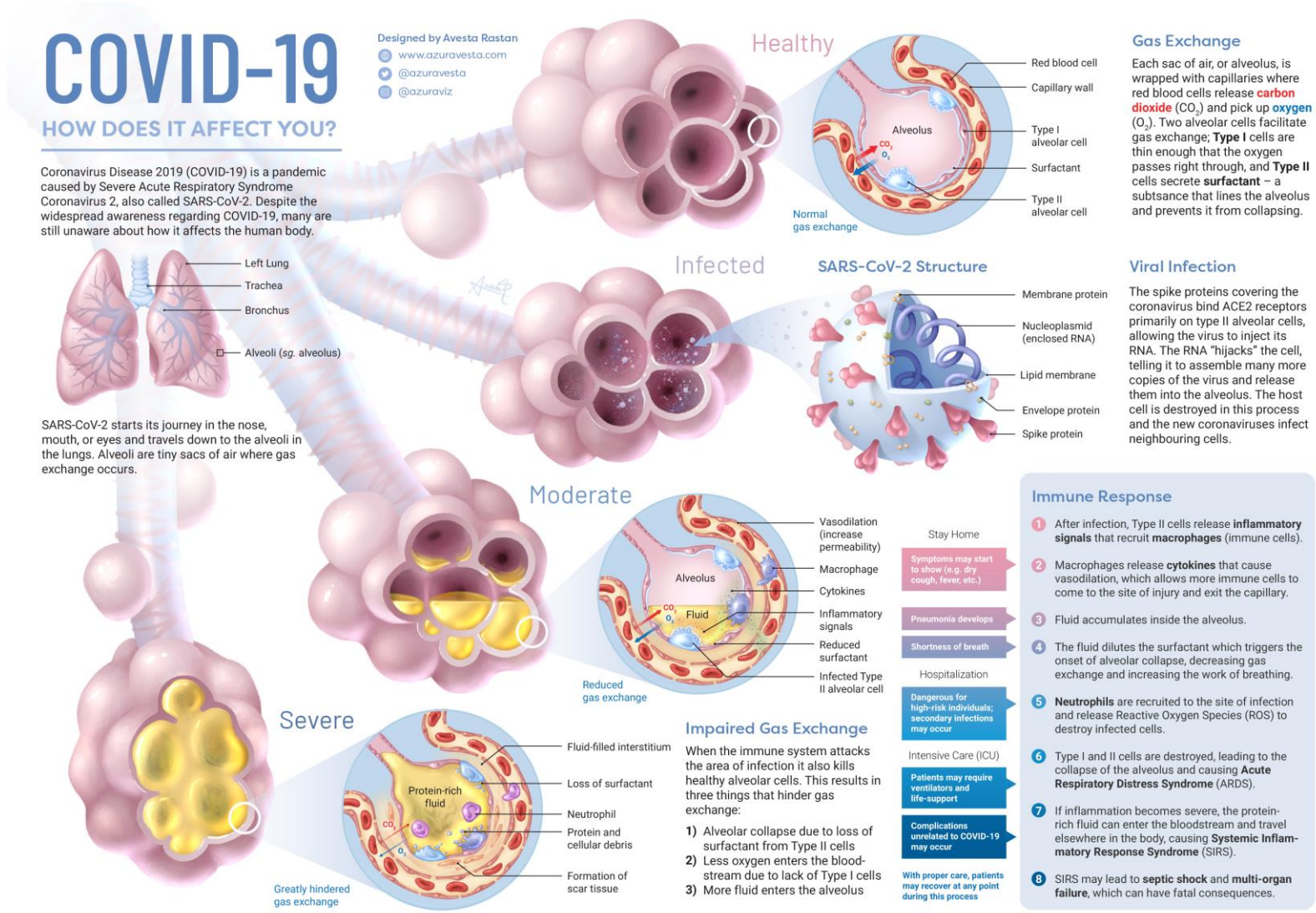
COVID-19
HOW DOES IT AFFECT YOU?
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Coronavirus Disease 2019 (COVID-19) is a pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2, also called SARS-CoV-2. Despite the widespread awareness regarding COVID-19, many are still unaware about how it affects the human body.
Left Lung
Trachea
Bronchus
Alveoli (sg. alveolus)
SARS-CoV-2 starts its journey in the nose, mouth, or eyes and travels down to the alveoli in the lungs. Alveoli are tiny sacs of air where gas exchange occurs.
Healthy
Red blood cell
Capillary wall
Alveolus
Type I alveolar cell
Surfactant
Type II alveolar cell
Normal gas exchange
Gas Exchange
Each sac of air, or alveolus, is wrapped with capillaries where red blood cells release carbon dioxide (CO_2) and pick up oxygen (O_2). Two alveolar cells facilitate gas exchange; Type I cells are thin enough that the oxygen passes right through, and Type II cells secrete surfactant – a subtsance that lines the alveolus and prevents it from collapsing.
Infected
SARS-CoV-2 Structure
Membrane protein
Nucleoplasmid (enclosed RNA)
Lipid membrane
Envelope protein
Spike protein
Viral Infection
The spike proteins covering the coronavirus bind ACE2 receptors primarily on type II alveolar cells, allowing the virus to inject its RNA. The RNA "hijacks" the cell, telling it to assemble many more copies of the virus and release them into the alveolus. The host cell is destroyed in this process and the new coronaviruses infect neighbouring cells.
Moderate
Vasodilation (increase permeability)
Macrophage
Cytokines
Alveolus
Fluid
Inflammatory signals
Reduced surfactant
Infected Type II alveolar cell
Reduced gas exchange
Stay Home
Symptoms may start to show (e.g. dry cough, fever, etc.)
Pneumonia develops
Shortness of breath
Hospitalization
Dangerous for high-risk individuals; secondary infections may occur
Intensive Care (ICU)
Patients may require ventilators and life-support
Complications unrelated to COVID-19 may occur
With proper care, patients may recover at any point during this process
Immune Response
1 After infection, Type II cells release inflammatory signals that recruit macrophages (immune cells).
2 Macrophages release cytokines that cause vasodilation, which allows more immune cells to come to the site of injury and exit the capillary.
3 Fluid accumulates inside the alveolus.
4 The fluid dilutes the surfactant which triggers the onset of alveolar collapse, decreasing gas exchange and increasing the work of breathing.
5 Neutrophils are recruited to the site of infection and release Reactive Oxygen Species (ROS) to destroy infected cells.
6 Type I and II cells are destroyed, leading to the collapse of the alveolus and causing Acute Respiratory Distress Syndrome (ARDS).
7 If inflammation becomes severe, the protein-rich fluid can enter the bloodstream and travel elsewhere in the body, causing Systemic Inflammatory Response Syndrome (SIRS).
8 SIRS may lead to septic shock and multi-organ failure, which can have fatal consequences.
Severe
Fluid-filled interstitium
Loss of surfactant
Protein-rich fluid
Neutrophil
Protein and cellular debris
Formation of scar tissue
Greatly hindered gas exchange
Impaired Gas Exchange
When the immune system attacks the area of infection it also kills healthy alveolar cells. This results in three things that hinder gas exchange:
1) Alveolar collapse due to loss of surfactant from Type II cells
2) Less oxygen enters the blood-stream due to lack of Type I cells
3) More fluid enters the alveolus

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COVID19: ¿ENFERMEDAD INFECCIOSA O INMUNITARIA?

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