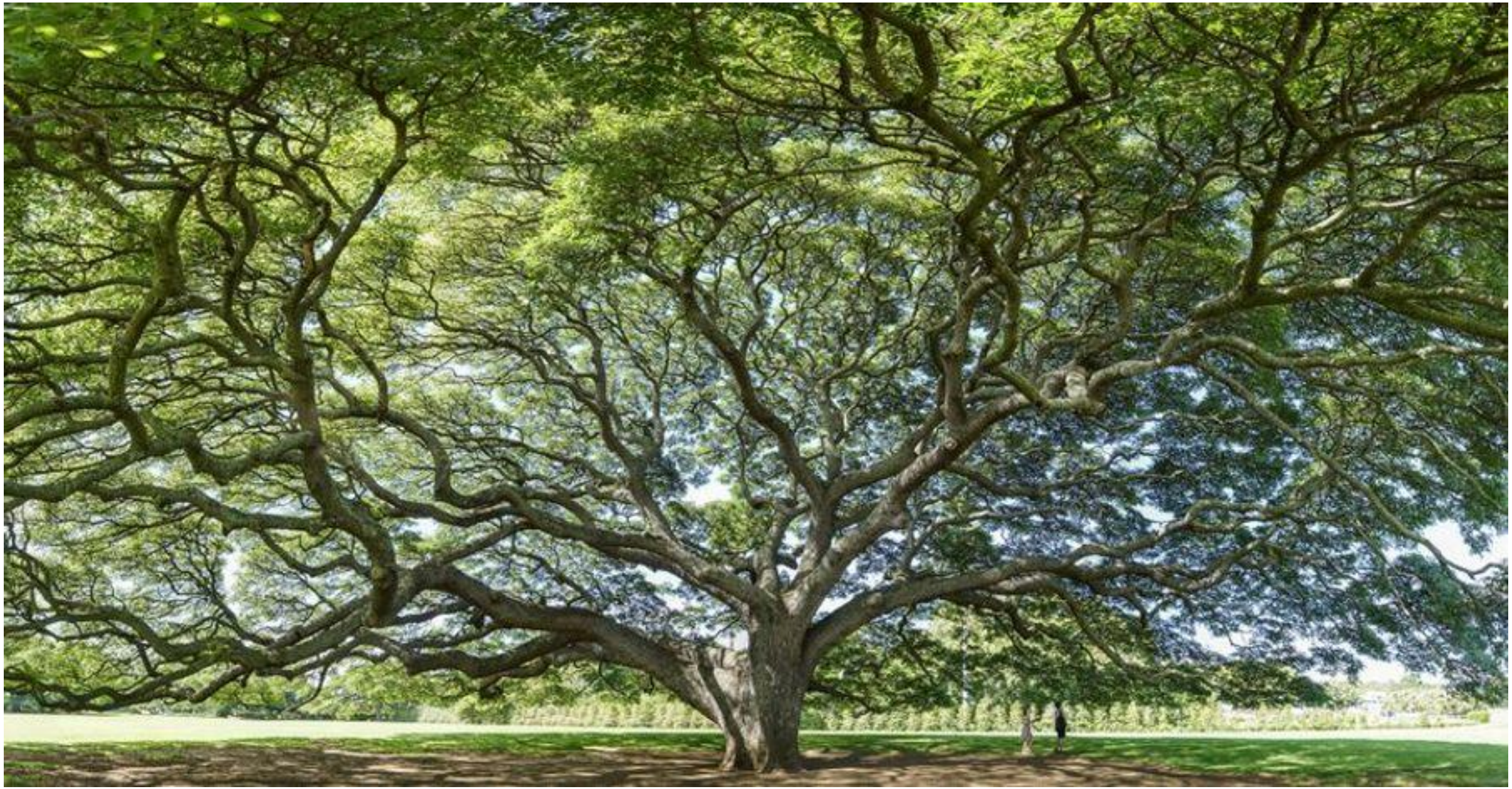
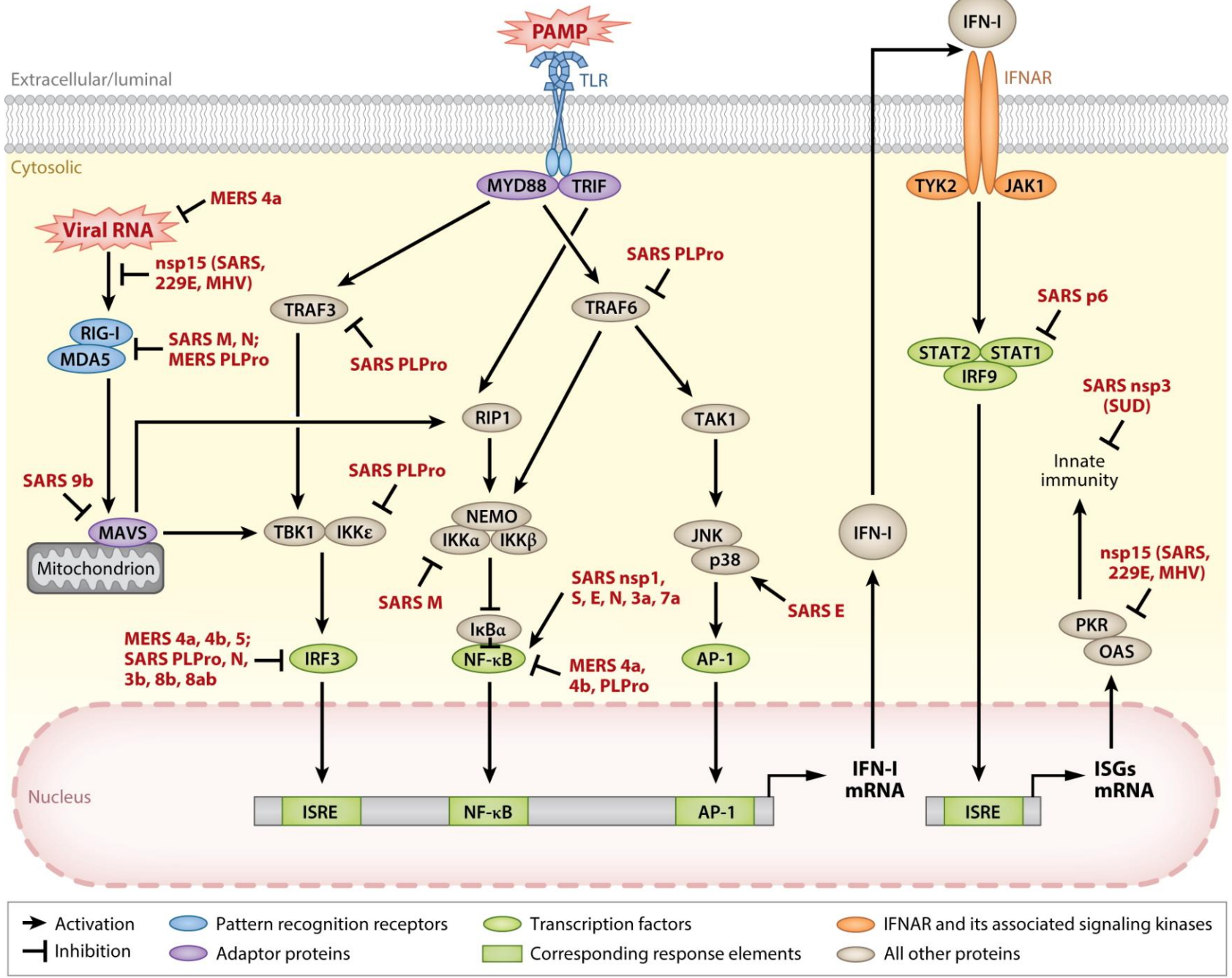
Aux racines de la pathogénie du COVID sévère?

Michel Moutschen

Immunologie, Médecine Interne Générale et Maladies Infectieuses

U Liège/CHU de Liège





Fung TS, Liu DX. 2019.
Annu. Rev. Microbiol. 73:529–57

(Selamed Riyanto/EyeEm/Getty Images)

NATURE

There's Something Special About Bat Immunity That Makes Them Ideal Viral Incubators

PETER DOCKRILL 12 FEBRUARY 2020

Ebola. SARS. Rabies. MERS. Most probably even the flourishing new coronavirus, COVID-19. There's one animal that innocently and unwittingly gifts all these virulent scourges to humanity. Bats.

Contraction of the type I IFN locus and unusual constitutive expression of *IFN-α* in bats

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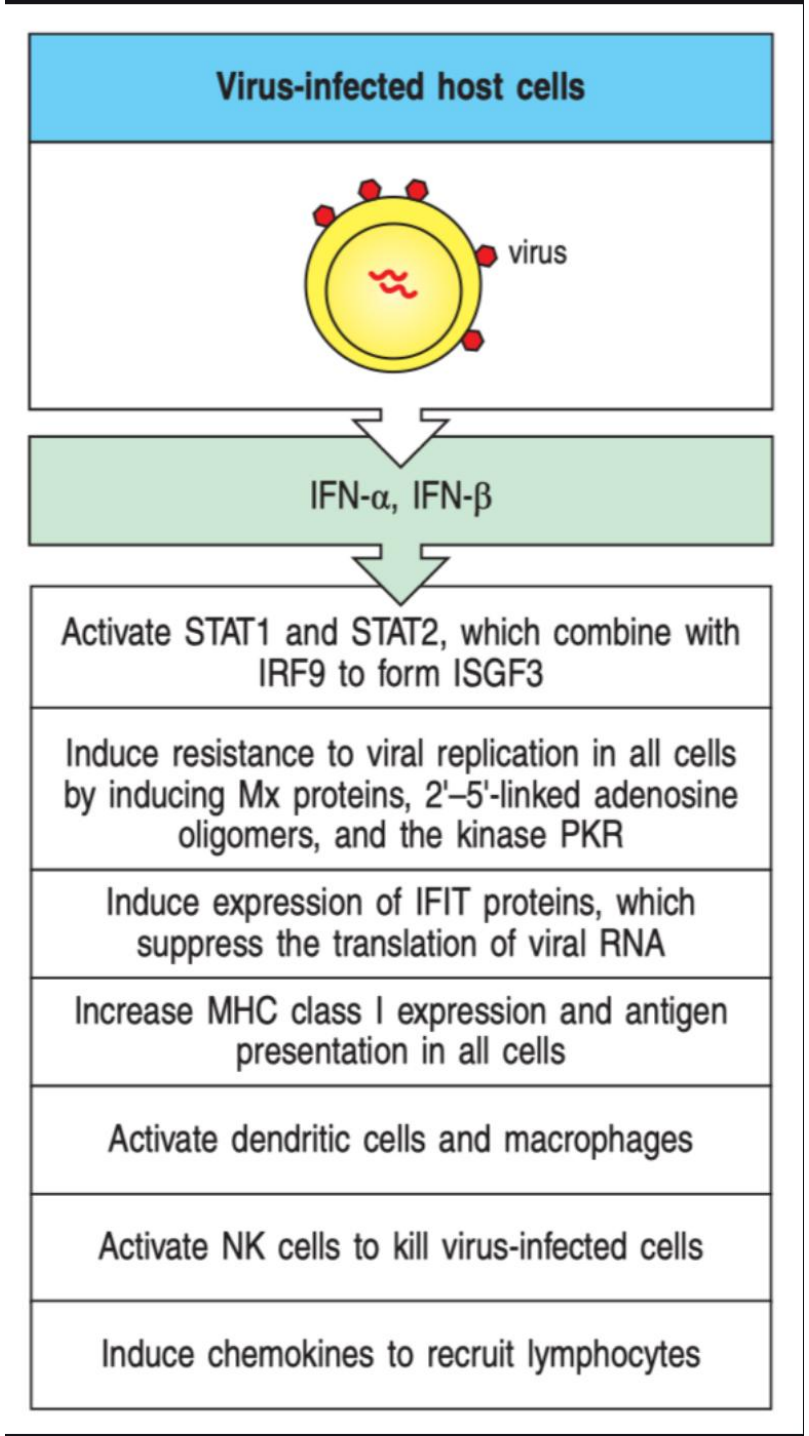
Edited by George R. Stark, Lerner Research Institute, The Cleveland Clinic Foundation, Cleveland, OH, and approved January 26, 2016 (received for review September 22, 2015)

Bats harbor many emerging and reemerging viruses, several of which are highly pathogenic in other mammals but cause no clinical signs of disease in bats. To determine the role of interferons (IFNs) in the ability of bats to coexist with viruses, we sequenced the type I IFN locus of the Australian black flying fox, *Pteropus alecto*, providing what is, to our knowledge, the first gene map of the IFN region of any bat species. Our results reveal a highly contracted type I IFN family consisting of only 10 IFNs, including three functional *IFN-α* loci. Furthermore, the three *IFN-α* genes are constitutively expressed in unstimulated bat tissues and cells and their expression is unaffected by viral infection. Constitutively expressed *IFN-α* results in the induction of a subset of IFN-stimulated genes associated with antiviral activity and resistance to DNA damage, providing evidence for a unique IFN system that may be linked to the ability of bats to coexist with viruses.

"ready to go" by stimulating amplified IFN-α/β production in response to viral infection and enhanced responses to other cytokines (16, 17). In the promoter regions of human *IFN-α* genes, three modules that are responsible for binding to IFN regulatory factors (IRFs) 3 and 7 determine the induction profile of different IFN-αs. For constitutively expressed human *IFN-α1*, it is believed that binding of IRF3 to the unique module II (also called module C) in the promoter region leads to weak endogenous expression. The promoter regions of all other human *IFN-α* genes (except *IFN-α13*) use modules I and III for binding to IRF3 or IRF7, respectively (18, 19).

IFN-α and IFN-β proteins bind to the IFN-αR and trigger the phosphorylation of STAT1 and STAT2, which then forms a ternary complex with IRF9 to form the tripartite transcription factor IFN-stimulated gene (ISG) factor 3 (ISGF3) and drives the expression


Virus-infected host cells
virus
IFN-α, IFN-β
Activate STAT1 and STAT2, which combine with IRF9 to form ISGF3
Induce resistance to viral replication in all cells by inducing Mx proteins, 2'–5'-linked adenosine oligomers, and the kinase PKR
Induce expression of IFIT proteins, which suppress the translation of viral RNA
Increase MHC class I expression and antigen presentation in all cells
Activate dendritic cells and macrophages
Activate NK cells to kill virus-infected cells
Induce chemokines to recruit lymphocytes

Open Access | Published: 13 October 2015

Activation of Vago by interferon regulatory factor (IRF) suggests an interferon system-like antiviral mechanism in shrimp

Chaozheng Li, Haoyang Li, Yixiao Chen, Yonggui Chen, Sheng Wang, Shao-Ping Weng, Xiaopeng Xu & Jianguo He

Scientific Reports **5**, Article number: 15078 (2015) | Cite this article

Figure 7

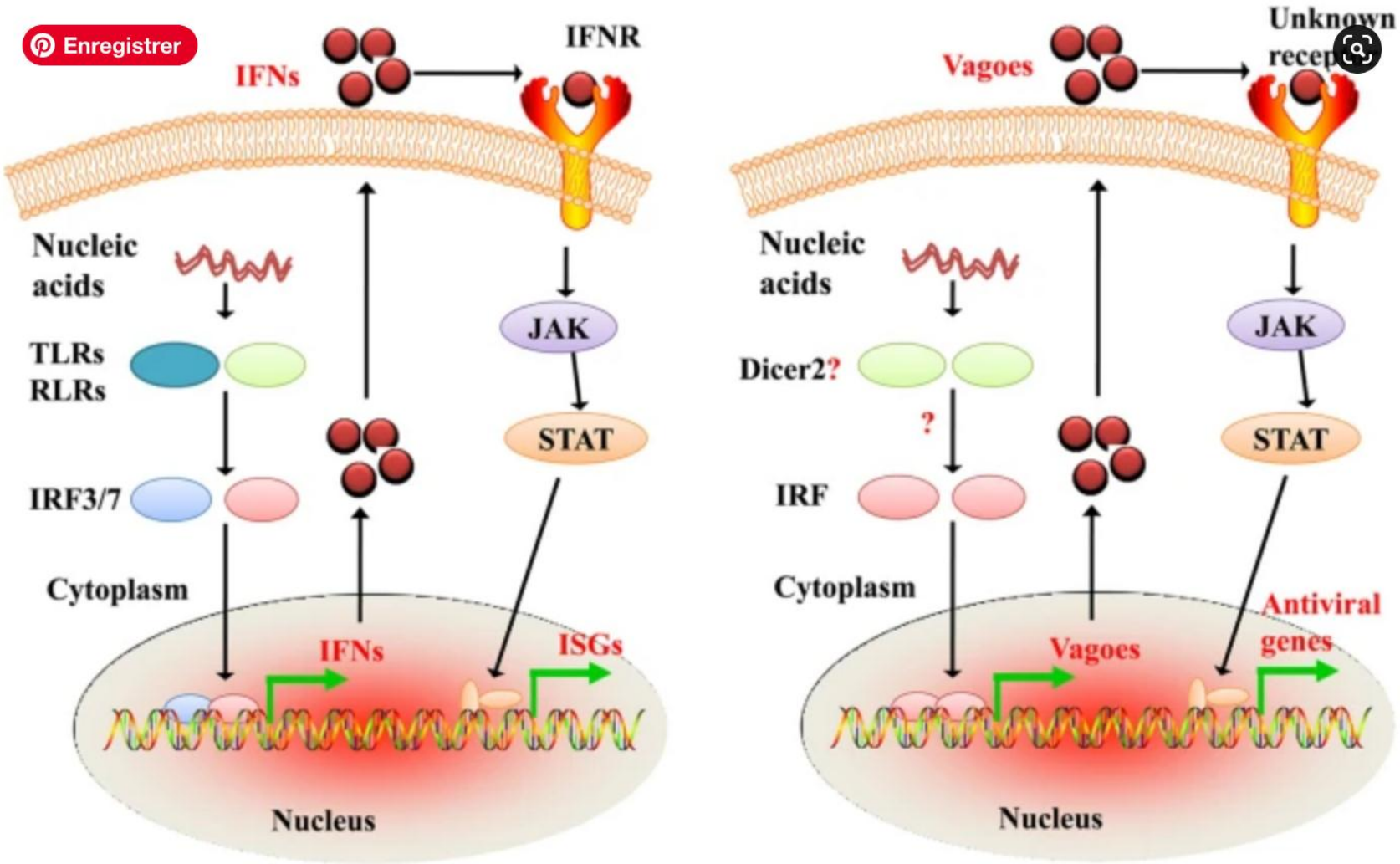
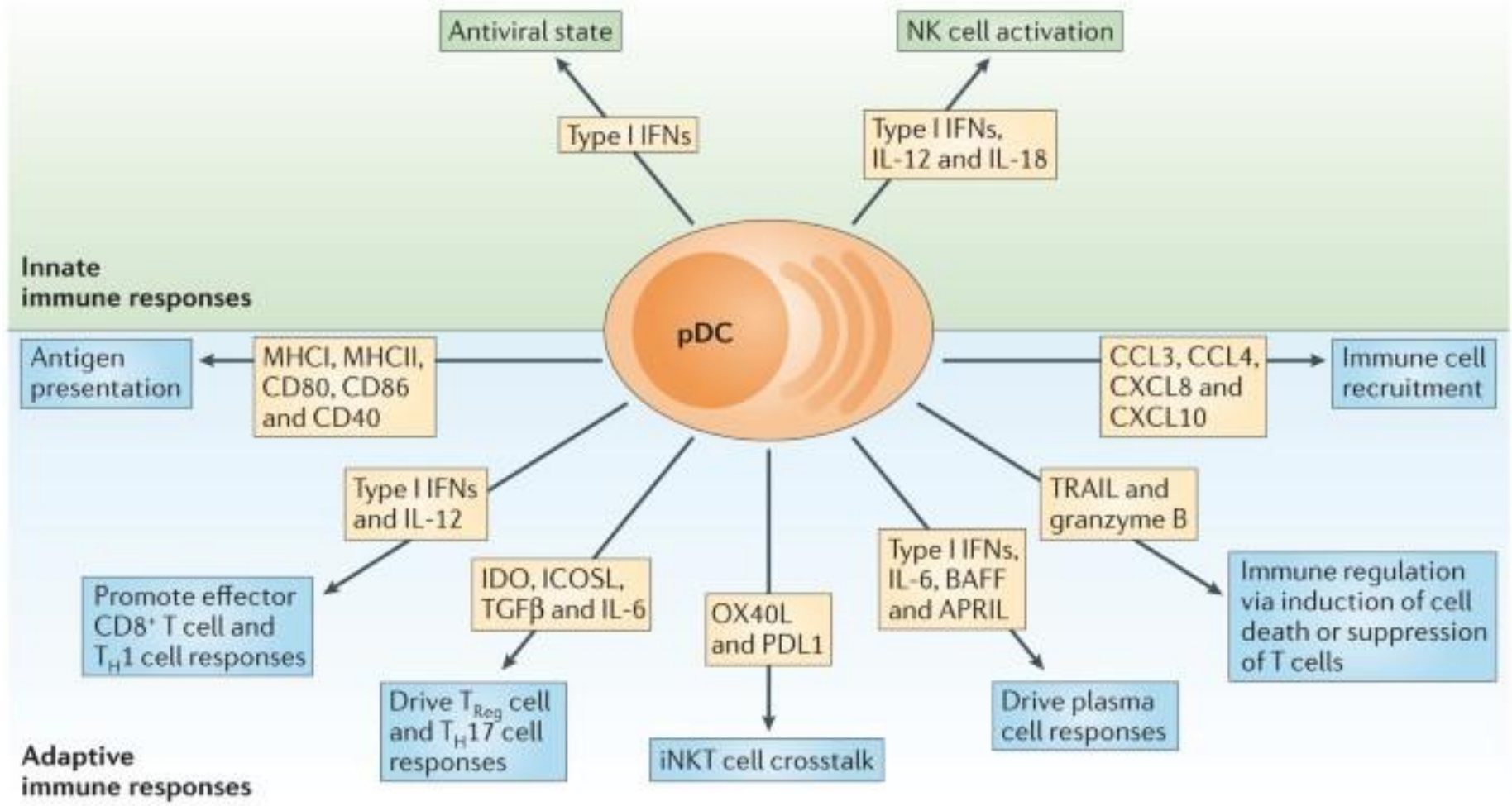


Diagram of activation of the vertebrate IFN system (left panel) and the crustacean Vago system (right panel).

(C.L. drew the figure).



Nature Reviews | Immunology

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10.1126/science.abd4570 (2020).

Inborn errors of type I IFN immunity in patients with life-threatening COVID-19

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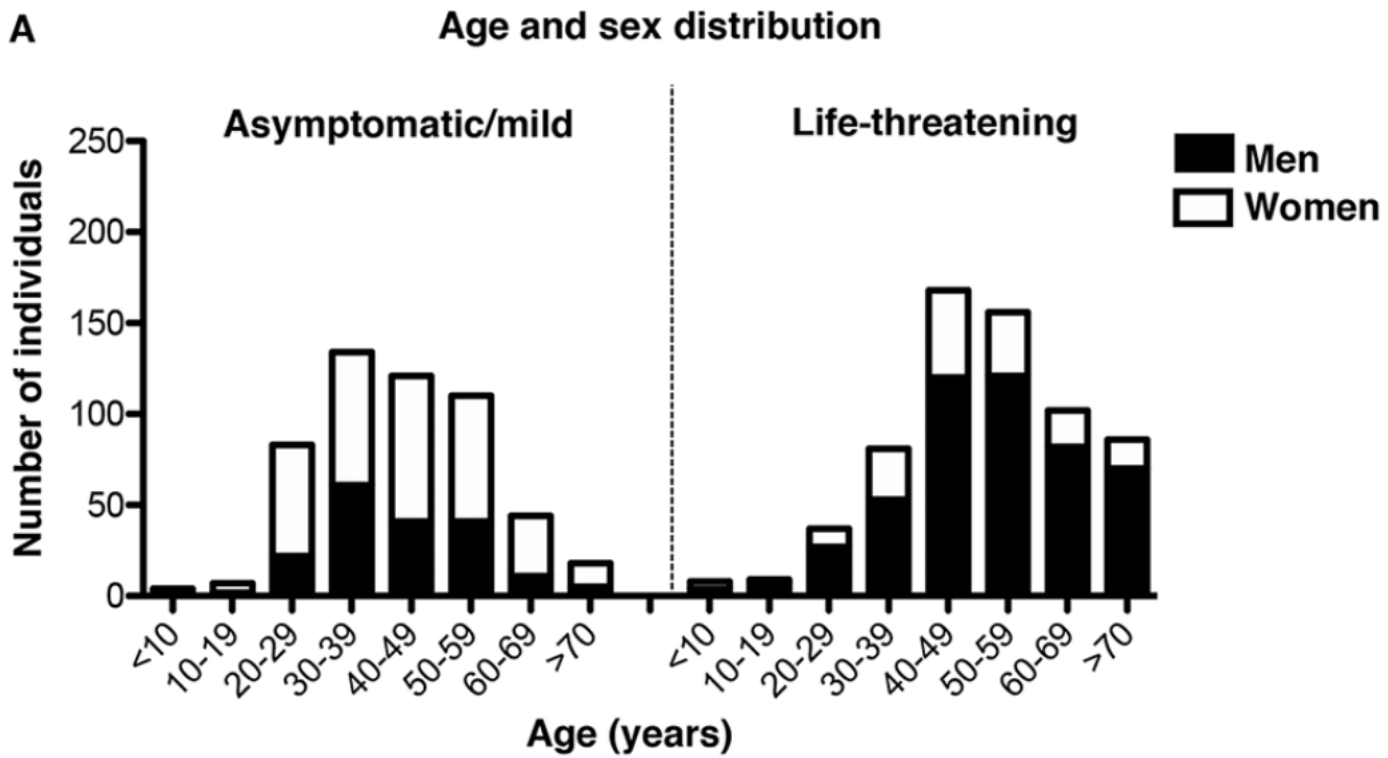

A
Age and sex distribution
Asymptomatic/mild
Life-threatening
Men
Women
Number of individuals
250
200
150
100
50
0
<10
10-19
20-29
30-39
40-49
50-59
60-69
>70
Age (years)

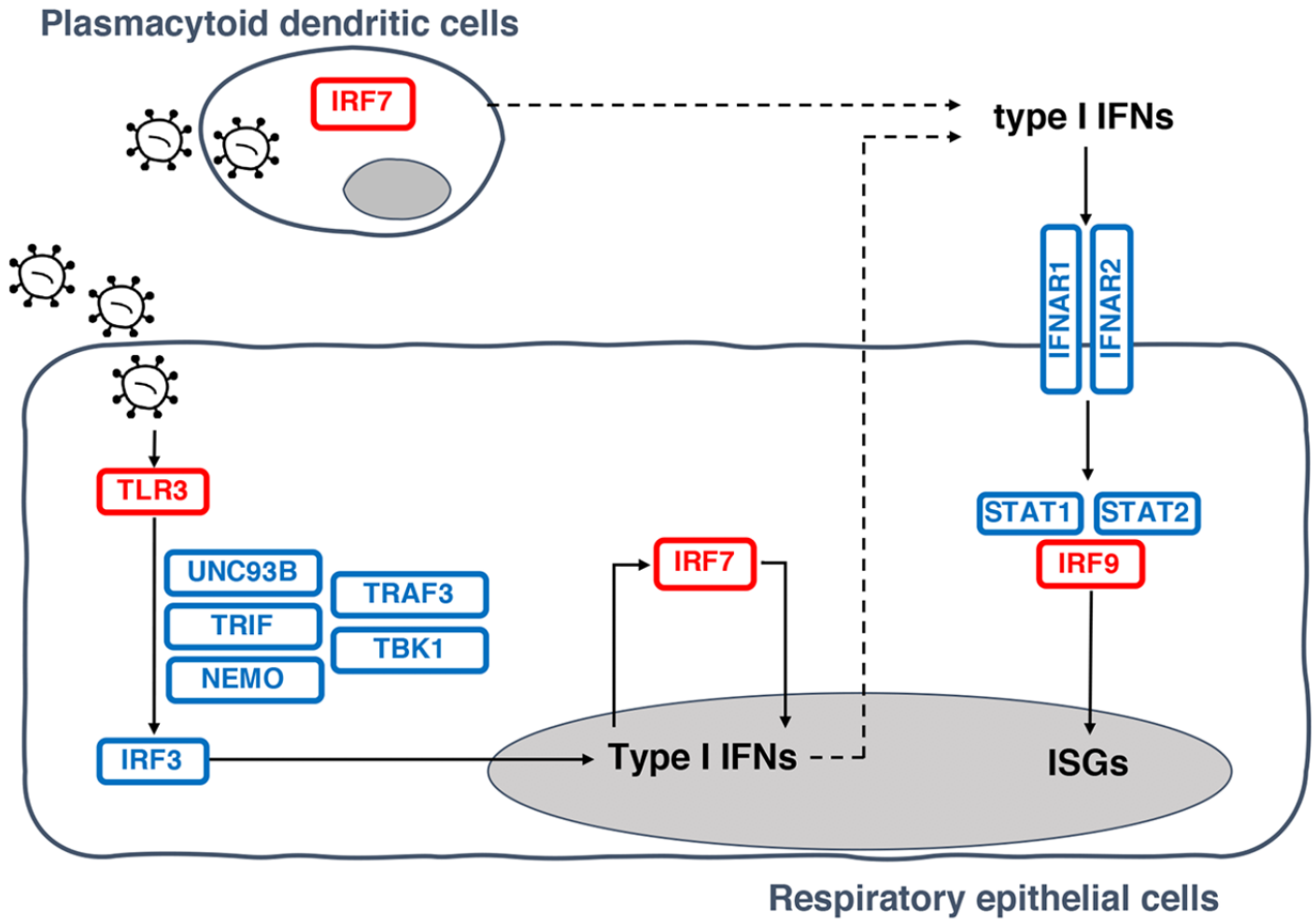


Fig. 2. Illustration of TLR3- and IRF7-dependent type I IFN production and amplification pathway. Molecules in red are encoded by core genes, deleterious variants of which underlie critical influenza pneumonia, with incomplete penetrance, while deleterious variants of genes encoding biochemically related molecules in blue underlie other viral illnesses. ISGs: interferon-stimulated genes.

- We collected both mono- and biallelic non-synonymous variants with a minor al-lele frequency (MAF) < 0.001 at all 13 loci.
- Twelve of the thirteen candidate loci are autosomal, while *NEMO* is X-linked.
- Autoso-mal dominant (AD) inheritance bas not been proven for six of the 12 autosomal loci *(UNC93Bl, IRF7, IFNARl, IFNAR2, STAT2, IRF9),* but we nevertheless considered heterozygous variants, be- cause none of the patients enrolled had been hospitalized for critical viral infections before COVID-19, raising the possibility that any underlying genetic defects they might have display a lower penetrance for influenza and other viral illnesses than for COVID-19, which is triggered by a more virulent virus.

Table S1. Variants of the 12 autosomal loci identified in patients with life-threatening COVID-19.

Gene	Chromosome	Position (GRCh37)	Reference	Altered	Genotype	Zygocity	Predicted LOF	Function	Number of patients
TLR3	4	187003591	C	G	p.Arg251Gly	het		hypermorphic	1
TLR3	4	187005920	A	G	p.Met870Val	het		LOF	1
TLR3	4	187005034	T	C	p.Phe732Leu	het		neutral	1
TLR3	4	187004500	C	T	p.Pro554Ser	het		LOF	1
TLR3	4	186998173	T	C	p.Ser134Pro	het		neutral	1
TLR3	4	187003852	AT	A	p.Ser339fs	het	pLOF	LOF	1
TLR3	4	187005146	G	A	p.Trp769*	het	pLOF	LOF	1
UNC93B1	11	67763289	C	T	p.Ala385Thr	het		neutral	1
UNC93B1	11	67763138	T	C	p.Tyr435Cys	het		neutral	1
UNC93B1	11	67763307	C	T	p.Val379Met	het		neutral	1
UNC93B1	11	67764078	C	T	p.Ala361Thr	het		neutral	1
UNC93B1	11	67770598	C	A	p.Glu96*	het	pLOF	LOE	1
UNC93B1	11	67759034	C	T	p.Gly592Arg	het		neutral	2
UNC93B1	11	67767052	G	A	p.Ser164Leu	het		neutral	1
UNC93B1	11	67763238	C	G	p.Val402Leu	het		neutral	1
UNC93B1	11	67759150	C	T	p.Gly553Asp	het		neutral	1
TICAM1	19	4817486	C	G	p.Val302Leu	het		neutral	1
TICAM1	19	4818059	C	T	p.Ala111Thr	het		neutral	1
TICAM1	19	4818178	C	T	p.Arg71Gln	het		neutral	3
TICAM1	19	4816721	C	T	p.Asp557Asn	het		neutral	1
TICAM1	19	4817216	C	A	p.Gln392Lys	het		LOF	1
TICAM1	19	4816285	T	C	p.Gln702Arg	het		neutral	1
TICAM1	19	4816598	C	A	p.Gly598Trp	het		neutral	1
TICAM1	19	4817233	A	G	p.Leu386Pro	het		neutral	1
TICAM1	19	4816607	T	A	p.Met595Leu	het		neutral	1
TICAM1	19	4816996	C	T	p.Ser465Asn	het		neutral	1
TICAM1	19	4818211	G	C	p.Ser60Cys	het		LOF	1
TICAM1	19	4817920	G	A	p.Thr157Met	het		neutral	1
TICAM1	19	4817260	G	A	p.Thr377Ile	het		neutral	1
TICAM1	19	4818379	G	A	p.Thr4Ile	het		LOF	1
TICAM1	19	4818152	C	T	p.Val80Met	het		neutral	1
TRAF3	14	103342855	C	T	p.Ala188Val	het		neutral	1
TRAF3	14	103371648	G	A	p.Ala412Thr	het		neutral	1
TRAF3	14	103369593	G	A	p.Arg321Gln	het		neutral	1
TRAF3	14	103357733	G	C	p.Trp266Cys	het		neutral	1
TRAF3	14	103355963	G	A	p.Val240Ile	het		neutral	1
TRAF3	14	103369730	G	A	p.Val367Met	het		neutral	1
TBK1	12	64878253	A	G	p.Asn388Ser	het		neutral	1
TBK1	12	64889344	G	A	p.Ala535Thr	het		neutral	1
TBK1	12	64875731	C	T	p.Arg308*	het	pLOF	LOF	1
TBK1	12	64891037	G	C	p.Glu653Gln	het		neutral	1
TBK1	12	64879235	T	C	p.Ile397Thr	het		neutral	2
TBK1	12	64889307	C	G	p.Ile522Met	het		neutral	1
TBK1	12	64889263	C	A	p.Leu508Ile	het		neutral	1
TBK1	12	64849721	T	C	p.Phe24Ser	het		LOF	1
TBK1	12	64891443	C	T	p.Pro659Ser	het		neutral	1
TBK1	12	64860776	G	C	p.Val152Leu	het		neutral	1
TBK1	12	64878241	G	A	p.Arg384Gln	het		neutral	1
IRF3	19	50165507	C	T	p.Arg227Gln	het		neutral	1
IRF3	19	50164059	C	T	p.Gly337Arg	het		hypermorphic	1
IRF3	19	50165845	G	C	p.Asn146Lys	het		HYPO §	1
IRF3	19	50167946	ATCC	A	p.Glu49del	het		HYPO	1
IRF3	19	50162988	G	C	p.Leu401Val	het		neutral	1
IRF7	11	615095	A	C	p.Arg7fs	het	pLOF	LOF	1
IRF7	11	613100	C	T	p.Ala419Thr	het		neutral	1
IRF7	11	614799	C	T	p.Arg131Gln	het		neutral #	4
IRF7	11	613337	C	T	p.Arg369Gln	het		HYPO	1
IRF7	11	613087	C	G	p.Arg423Pro	het		neutral	1
IRF7	11	615170	C	T	p.Arg37His	het		neutral	1
IRF7	11	614842	C	T	p.Asp117Asn	het		HYPO	1
IRF7	11	614300	G	A	p.Gln185*	het	pLOF	LOF	1
IRF7	11	614532	C	G	p.Gly133Arg	het		neutral	1
IRF7	11	614212	C	T	p.Gly214Glu	het		neutral	1
IRF7	11	613978	C	T	p.Gly247Arg	het		neutral #	4
IRF7	11	613332	T	C	p.Met371Val	het		LOF	1
IRF7	11	614907	A	G	p.Phe95Ser	het		LOF	1
IRF7	11	613966	CGGGCTGGGGCCCG	C	p.Pro246fs	het	pLOF	HYPO	1
IRF7	11	613353	G	GC	p.Pro364fs	hom	pLOF	HYPO	1
IRF7	11	613957	T	C	p.Thr254Ala	het		neutral	1
IFNAR1	21	34697431	C	T	p.Ala24Val	het		neutral	2

Table 1. Disease-causing variants identified in patients with life-threatening COVID-19.

Gene	Inheritance	Genetic form	Genotype	Gender	Age (year)	Ancestry/Residence	Outcome
TLR3	AD	Known	p.Ser339fs/WT	M	40	Spain	Survived
TLR3	AD	Known	p.Pro554Ser/WT	M	68	Italy	Survived
TLR3	AD	Known	p.Trp769*/WT	M	77	Italy	Survived
TLR3	AD	Known	p.Met870Val/WT	M	56	Colombian/Spain	Survived
UNC93B1	AD	New	p.Glu96*/WT	M	48	Venezuelan/Spain	Survived
TICAM1	AD	Known	p.Thr4Ile/WT	M	49	Italy	Survived
TICAM1	AD	Known	p.Ser60Cys/WT	F	61	Vietnamese/France	Survived
TICAM1	AD	Known	p.Gln392Lys/WT	F	71	Italy	Deceased
TBK1	AD	Known	p.Phe24Ser/WT	F	46	Venezuelan/Spain	Survived
TBK1	AD	Known	p.Arg308*/WT	M	17	Turkey	Survived
IRF3	AD	Known	p.Glu49del/WT	F	23	Bolivian/Spain	Survived
IRF3	AD	Known	p.Asn146Lys/WT	F	60	Italy	Survived
IRF7	AR	Known	p.Pro364fs/p.Pro364fs	F	49	Italian/Belgium	Survived
IRF7	AR	Known	p.Met371Val/p.Asp117Asn	M	50	Turkey	Survived
IRF7	AD	New	p.Arg7fs/WT	M	60	Italy	Survived
IRF7	AD	New	p.Gln185*/WT	M	44	France	Survived
IRF7	AD	New	p.Pro246fs/WT	M	41	Spain	Survived
IRF7	AD	New	p.Arg369Gln/WT	M	69	Italy	Survived
IRF7	AD	New	p.Phe95Ser/WT	M	37	Turkey	Survived
IFNAR1	AR	Known	p.Trp73Cys/Trp73Cys	M	38	Turkey	Survived
IFNAR1	AR	Known	p.Ser422Arg/Ser422Arg	M	26	Pakistan/Saudi Arabia	Deceased
IFNAR1	AD	New	p.Pro335del/WT	F	23	Chinese/Italy	Survived
IFNAR2	AD	New	p.Glu140fs/WT	F	54	Belgium	Survived

AD: autosomal dominant; AR: autosomal recessive; WT: wild-type.

- In a sample of 534 controls with asymptomatic or mild SARS-CoV-2 infec-tion, we found only one heterozygous pLOF variation with a MAF < 0.001 at the 13 loci (IRF7p.Leu99fs).
- A PCA-adjusted burden test on the 12 autosomal loci revealed significant en- richment in pLOF variants in patients relative to controls *(p*= 0.01, OR = 8.28 [1.04-65.64, 95%CI]) under an AD mode of inheritance.

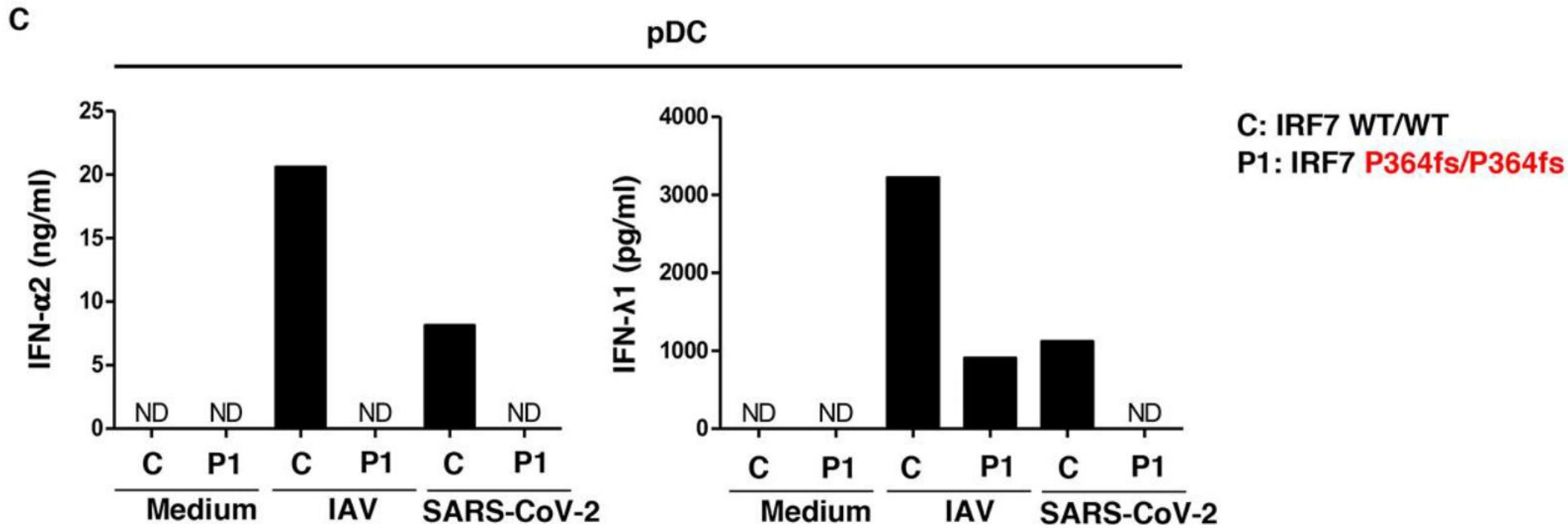
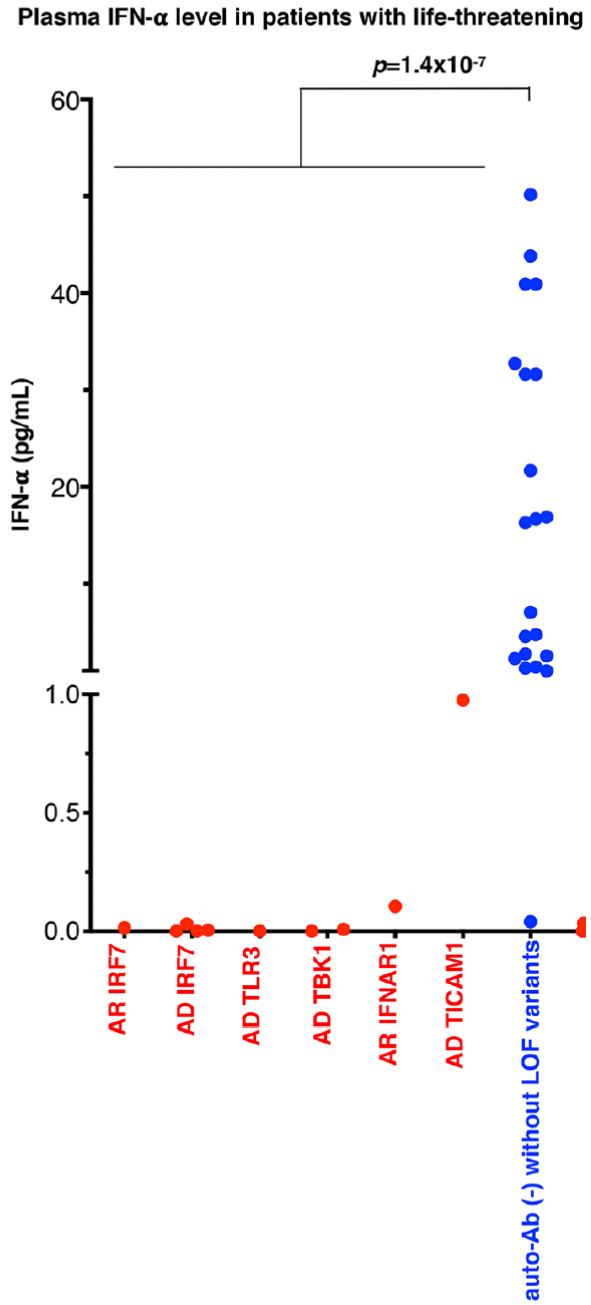


Fig. 4. Type I IFN responses in patient cells defective for IRF7. (A) Levels of IRF7 protein in

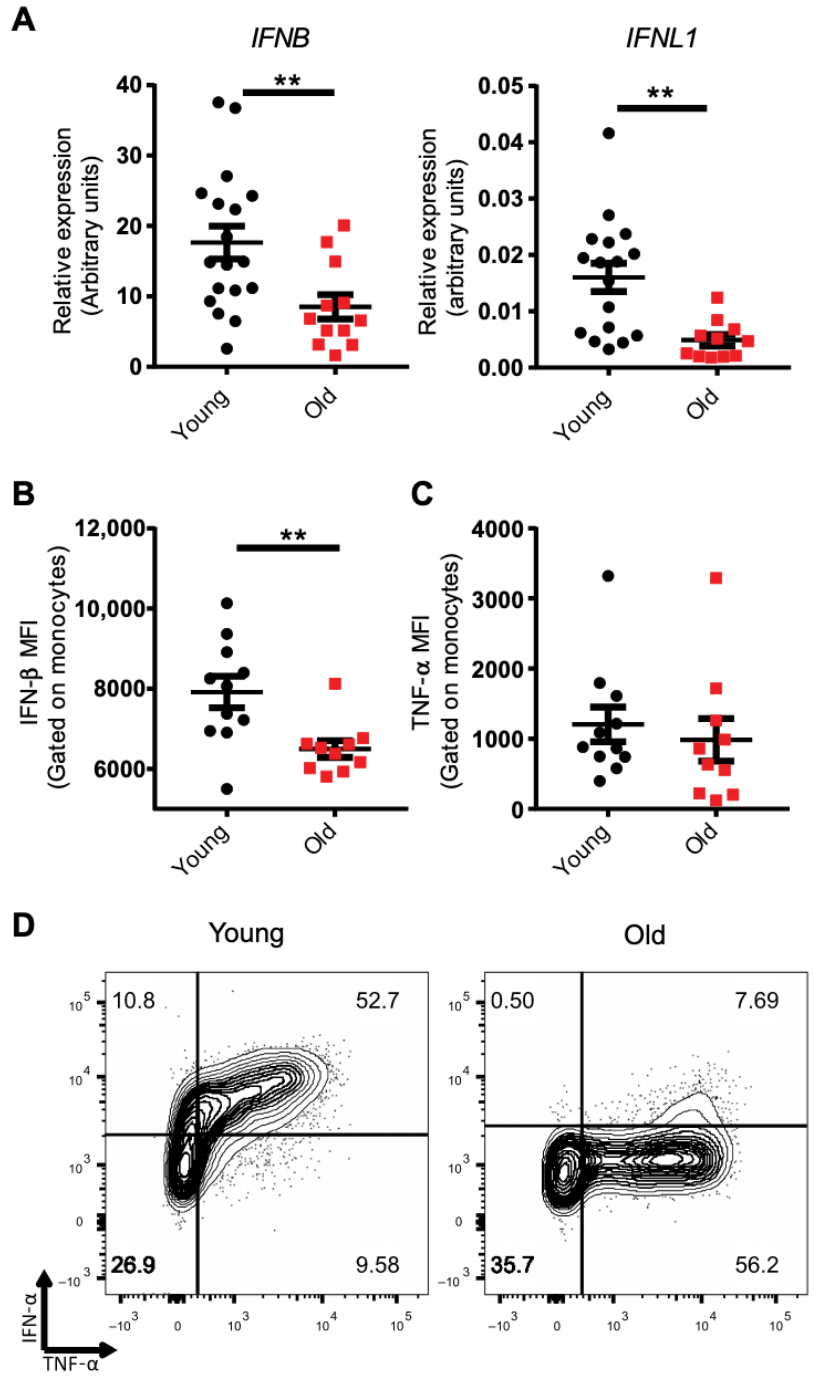

Plasma IFN-α level in patients with life-threatening
p=1.4x10-7
IFN-α (pg/mL)
60
40
20
1.0
0.5
0.0
AR IRF7
AD IRF7
AD TLR3
AD TBK1
AR IFNAR1
AD TICAM1
auto-Ab (-) without LOF variants

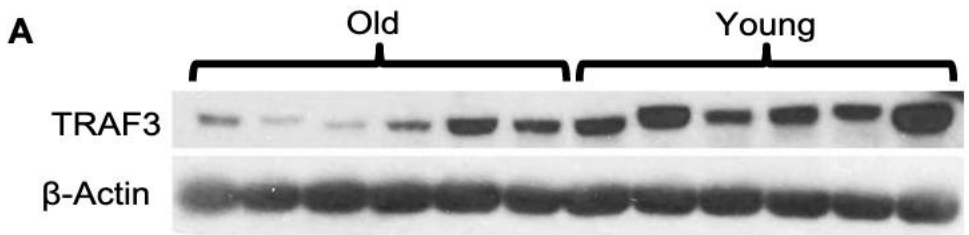
IMMUNOLOGY

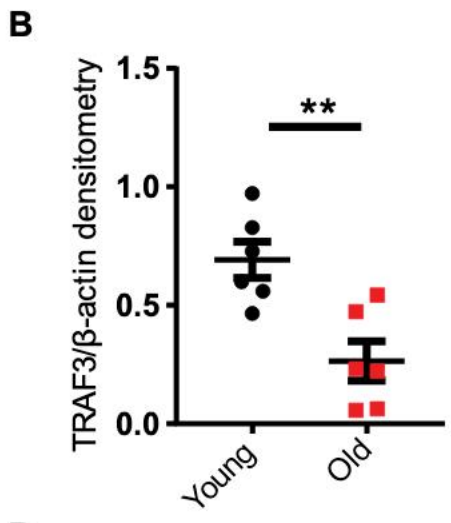
Aging impairs both primary and secondary RIG-I signaling for interferon induction in human monocytes

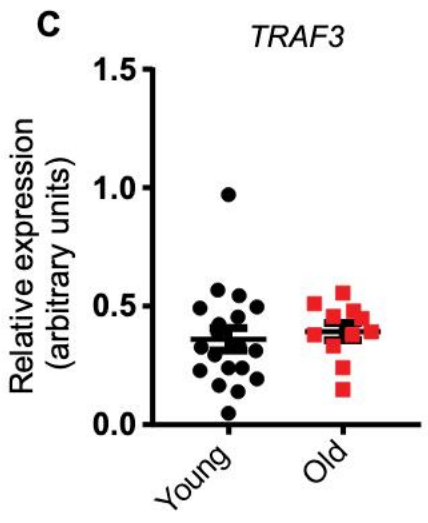
Ryan D. Molony,[1] Jenny T. Nguyen,[1] Yong Kong,[2] Ruth R. Montgomery,[3] Albert C. Shaw,[4] Akiko Iwasaki[1,5]*

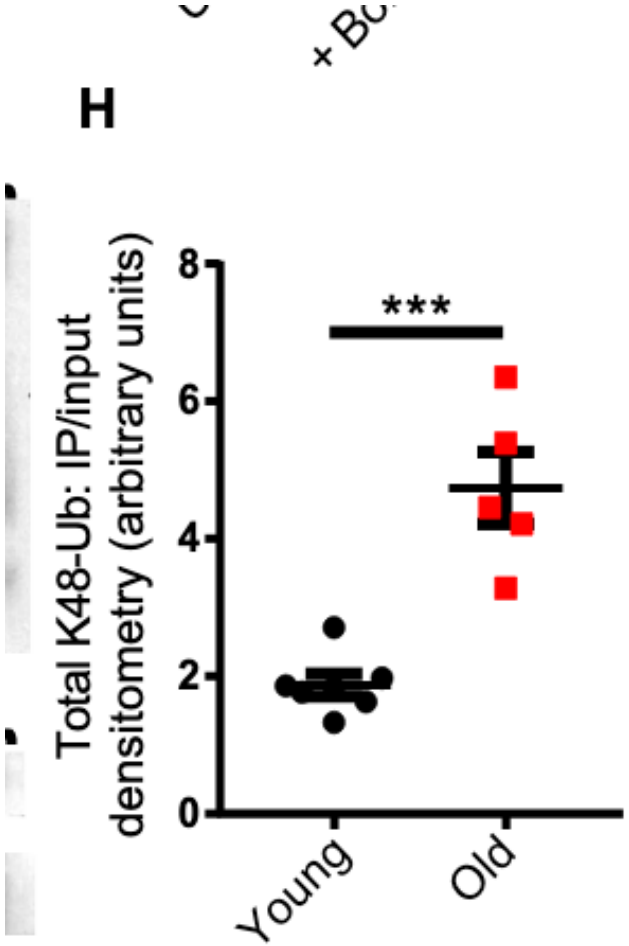
Adults older than 65 account for most of the deaths caused by respiratory influenza A virus (IAV) infections, but the underlying mechanisms for this susceptibility are poorly understood. IAV RNA is detected by the cytosolic sensor retinoic acid–inducible gene I (RIG-I), which induces the production of type I interferons (IFNs) that curtail the spread of the virus and promote the elimination of infected cells. We have previously identified a marked defect in the IAV-inducible secretion of type I IFNs, but not proinflammatory cytokines, in monocytes from older (>65 years) healthy human donors. We found that monocytes from older adults exhibited decreased abundance of the adaptor protein TRAF3 (tumor necrosis factor receptor–associated factor 3) because of its increased proteasomal degradation with age, thereby impairing the primary RIG-I signaling pathway for the induction of type I IFNs. We determined that monocytes from older adults also failed to effectively stimulate the production of the IFN regulatory transcription factor IRF8, which compromised IFN induction through secondary RIG-I signaling. IRF8 played a central role in IFN induction in monocytes, because knocking down IRF8 in monocytes from younger adults was sufficient to replicate the IFN defects observed in monocytes from older adults, whereas restoring IRF8 expression in older adult monocytes was sufficient to restore RIG-I–induced IFN responses. Aging thus compromises both the primary and secondary RIG-I signaling pathways that govern expression of type I IFN genes, thereby impairing antiviral resistance to IAV.


A
IFNB
IFNL1
Relative expression (Arbitrary units)
Relative expression (arbitrary units)
**
**
40
30
20
10
0
0.05
0.04
0.03
0.02
0.01
0.00
Young
Old
B
C
IFN-β MFI (Gated on monocytes)
TNF-α MFI (Gated on monocytes)
12,000
10,000
8000
6000
4000
3000
2000
1000
0
D
Young
Old
10.8
52.7
26.9
9.58
0.50
7.69
35.7
56.2
IFN-α
TNF-α


A
Old
Young
TRAF3
β-Actin


B
TRAF3/β-actin densitometry
1.5
1.0
0.5
0.0
**
Young
Old


C
TRAF3
Relative expression (arbitrary units)
1.5
1.0
0.5
0.0
Young
Old


H
Total K48-Ub: IP/input densitometry (arbitrary units)
8
6
4
2
0
***
Young
Old

Published in final edited form as:
J Immunol. 2015 August 1; 195(3): 865–874. doi:10.4049/jimmunol.1402389.

Age-associated Failure to Adjust Type I Interferon Receptor Signaling Thresholds after T-cell Activation[1]

Guangjin Li[*], **Jihang Ju**[*], **Cornelia M. Weyand**[*], and **Jörg J. Goronzy**[*]

[*]Department of Medicine, Palo Alto Veterans Administration Health Care System, Palo Alto, CA 94304 and from the Department of Medicine, Stanford University School of Medicine, Stanford, CA 94305

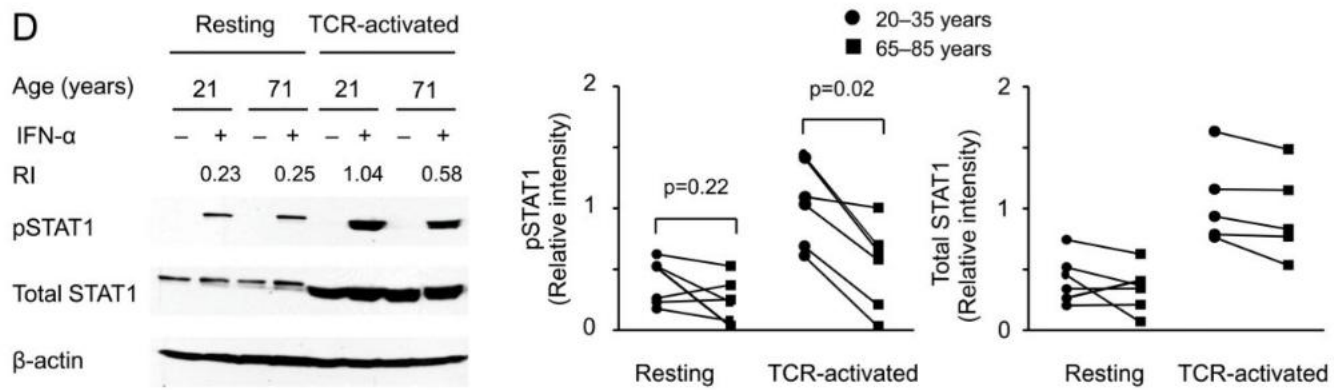


Figure 2. STAT1 phosphorylation after type I IFN stimulation of activated naïve CD4 T cells declines with age

Questions non résolues?

- Quel est le lien entre l'émoussement des réponses IFN de type 1, *l'inflamm aging* et *la trained immunity*?
- Question corolaire : les réponses en IFN de type 1 sont-elles préservées dans le « *healthy aging* »?
- En quoi l'inflamm aging est-il différent de la trained immunity?
  - Quantité – durée?
  - Nature : *garb* aging?

Cytokine and Growth Factor Reviews 53 (2020) 33–37

Contents lists available at ScienceDirect

Cytokine and Growth Factor Reviews

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

Inflamm-aging: Why older men are the most susceptible to SARS-CoV-2 complicated outcomes

Massimiliano Bonafè[a], Francesco Prattichizzo[b,*], Angelica Giuliani[c,**], Gianluca Storci[a], Jacopo Sabbatinelli[c,1], Fabiola Olivieri[c,d,1]

[a] Department of Experimental, Diagnostic and Specialty Medicine, AlmaMater Studiorum, Università di Bologna, Bologna, Italy
[b] IRCCS MultiMedica, Milano, Italy
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frontiers in Immunology

REVIEW
published: 04 September 2020
doi: 10.3389/fimmu.2020.02059

Check for updates

Mitigating Coronavirus Induced Dysfunctional Immunity for At-Risk Populations in COVID-19: Trained Immunity, BCG and "New Old Friends"

Thomas-Oliver Kleen[1], Alicia A. Galdon[2], Andrew S. MacDonald[2] and Angus G. Dalgleish[3]**

[1] Immodulon Therapeutics Limited, Uxbridge, United Kingdom, [2] Lydia Becker Institute of Immunology and Inflammation, Manchester Collaborative Centre for Inflammation Research, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, University of Manchester, Manchester, United Kingdom, [3] Institute for Infection and Immunity, St George's, University of London, London, United Kingdom

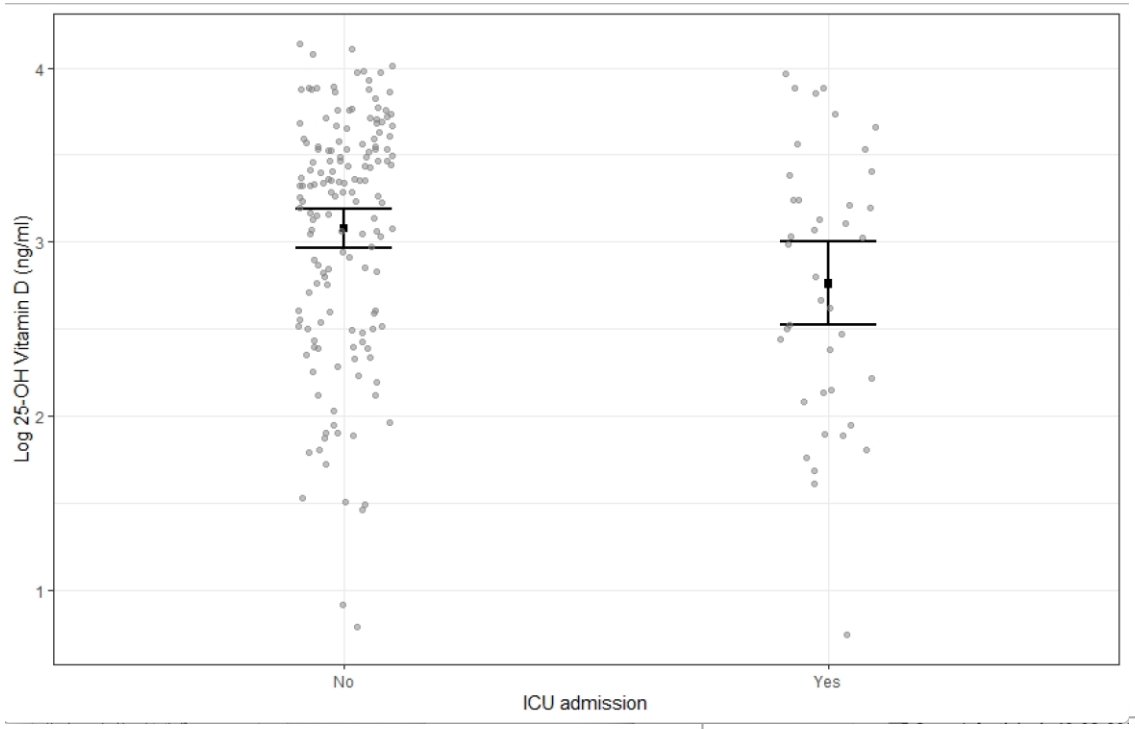
OPEN ACCESS

Questions non résolues?

- Quel est le lien entre l'émoussement des réponses IFN de type 1, *l'inflamm aging* et *la trained immunity*?
- Question corolaire : les réponses en IFN de type 1 sont-elles préservées dans le « *healthy aging* »?
- En quoi l'inflamm aging est-il différent de la trained immunity?
  - Quantité – durée?
  - Nature : *garb* aging?

Implications pratiques

Vitamine D

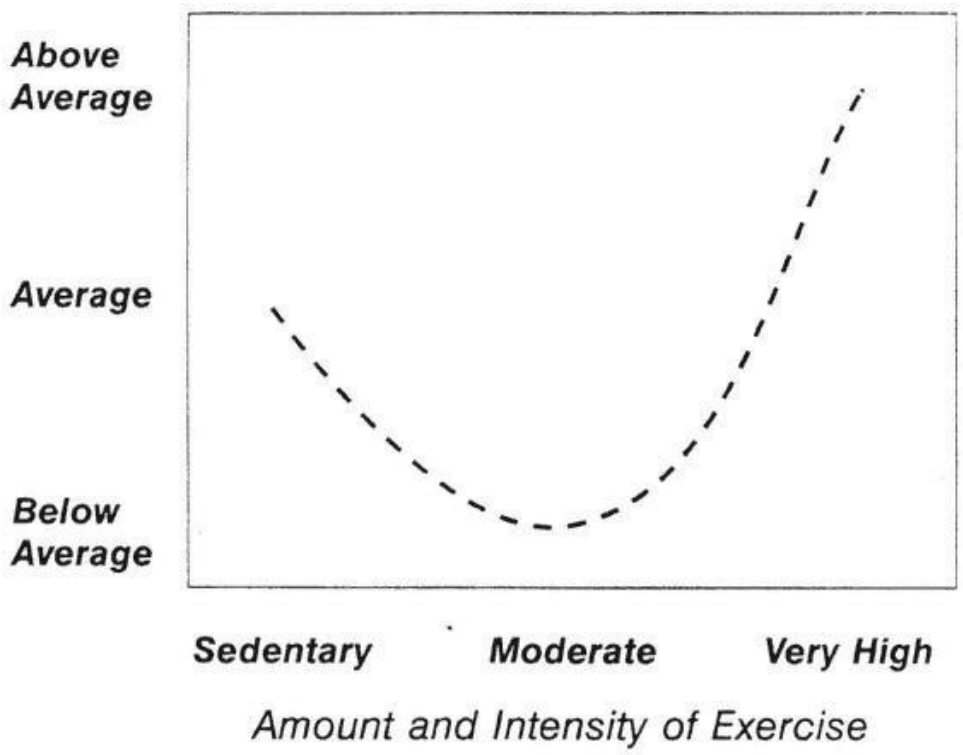


Vitamin D Receptor and Jak–STAT Signaling Crosstalk Results in Calcitriol-Mediated Increase of Hepatocellular Response to IFN-α

Christian M. Lange, Jérôme Gouttenoire, François H. T. Duong, Kenichi Morikawa, Markus H. Heim and Darius Moradpour

J Immunol June 15, 2014, 192 (12) 6037-6044; DOI: https://doi.org/10.4049/jimmunol.1302296

De l’exercice physique



Physiology & Behavior 194 (2018) 191–198

Contents lists available at ScienceDirect

Physiology & Behavior

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

Acute aerobic exercise induces a preferential mobilisation of plasmacytoid dendritic cells into the peripheral blood in man

Frankie F. Brown[a,1], John P. Campbell[a,b,1], Alex J. Wadley[c], James P. Fisher[d], Sarah Aldred[d], James E. Turner[a,*]

[a] Department for Health, University of Bath, Bath, UK
[b] Clinical Immunology, University of Birmingham, Birmingham, UK
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[d] School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, UK

Un « bon » microbiome intestinal?

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-019-11152-6 OPEN

Microbiota-derived acetate protects against respiratory syncytial virus infection through a GPR43-type 1 interferon response

Krist Helen Antunes et al.#

Severe respiratory syncytial virus (RSV) infection is a major cause of morbidity and mortality in infants <2 years-old. Here we describe that high-fiber diet protects mice from RSV infection. This effect was dependent on intestinal microbiota and production of acetate. Oral administration of acetate mediated interferon-β (IFN-β) response by increasing expression of interferon-stimulated genes in the lung. These effects were associated with reduction of viral load and pulmonary inflammation in RSV-infected mice. Type 1 IFN signaling via the IFN-1 receptor (IFNAR) was essential for acetate antiviral activity in pulmonary epithelial cell lines and for the acetate protective effect in RSV-infected mice. Activation of Gpr43 in pulmonary epithelial cells reduced virus-induced cytotoxicity and promoted antiviral effects through IFN-β response. The effect of acetate on RSV infection was abolished in *Gpr43*$^{-/-}$ mice. Our findings reveal antiviral effects of acetate involving IFN-β in lung epithelial cells and engagement of GPR43 and IFNAR.

Pas d'hydroxychloroquine

RHEUMATOLOGY

Rheumatology 2020;59:107–111
doi:10.1093/rheumatology/kez242
Advance Access publication 25 June 2019

Concise report

Hydroxychloroquine treatment downregulates systemic interferon activation in primary Sjögren's syndrome in the JOQUER randomized trial

Iris L. A. Bodewes[1], Jacques-Eric Gottenberg[2], Cornelia G. van Helden-Meeuwsen[1], Xavier Mariette[3] and Marjan A. Versnel[1]

Abstract

Objective. HCQ is frequently used to treat primary SS (pSS), but evidence for its efficacy is limited. HCQ blocks IFN activation, which is present in half of the pSS patients. The effect of HCQ treatment on the expression of IFN-stimulated genes (ISGs) was studied in pSS. Furthermore, HCQ-treated patients were stratified based on IFN activation and differences in disease activity and clinical parameters were studied.

Methods. Expression of ISGs and IFN scores was determined in 77 patients, who were previously enrolled in the placebo-controlled JOQUER trial. Patients were treated for 24 weeks with 400 mg/d HCQ or placebo.

Results. HCQ treatment reduced IFN scores and expression of ISGs compared with the placebo-treated group. HCQ reduced ESR, IgG and IgM levels independently of the patients' IFN activation status. No differences in EULAR SS disease activity index or EULAR SS patient reported index scores were observed after HCQ treatment, even after IFN stratification.

Conclusion. Treatment for 24 weeks with HCQ significantly reduced type I IFN scores and ISG-expression compared with the placebo-treated group. HCQ reduced several laboratory parameters, but failed to improve clinical response. This suggests that in pSS, type I IFN is associated to some laboratory parameters abnormalities, but not related to the clinical response.

Key words: primary Sjögren's syndrome, interferon, hydroxychloroquine

De l’interféron alpha ou beta?

- Oui mais

Cite as: P. Bastard *et al.*, *Science* 10.1126/science.abd4585 (2020).

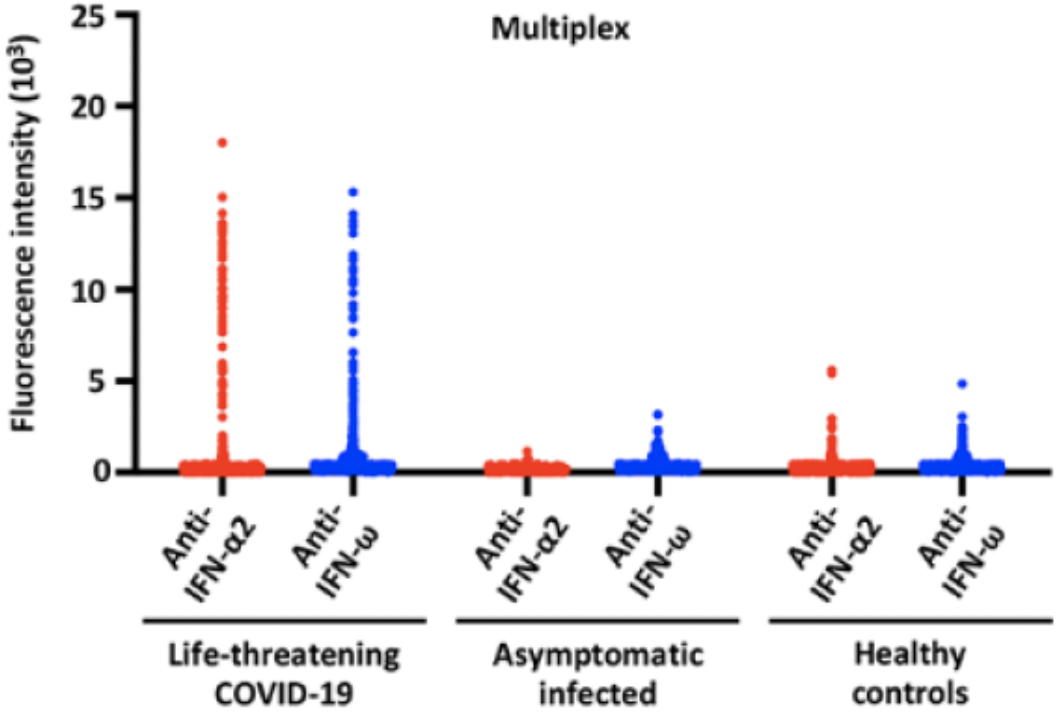
Auto-antibodies against type I IFNs in patients with life-threatening COVID-19

Paul Bastard[1,2,3*†], Lindsey B. Rosen[4†], Qian Zhang[3‡], Eleftherios Michailidis[5‡], Hans-Heinrich Hoffmann[5‡], Yu Zhang[4‡], Karim Dorgham[6‡], Quentin Philippot[1,2‡], Jérémie Rosain[1,2‡], Vivien Béziat[1,2,3‡], Jérémy Manry[1,2], Elana Shaw[4], Liis Haljasmägi[7], Pärt Peterson[7], Lazaro Lorenzo[1,2], Lucy Bizien[1,2], Sophie Trouillet-Assant[8,9], Kerry Dobbs[4], Adriana Almeida de Jesus[4], Alexandre Belot[10,11,12], Anne Kallaste[13], Emilie Catherinot[14], Yacine Tandjaoui-Lambiotte[15], Jeremie Le Pen[5], Gaspard Kerner[1,2], Benedetta Bigio[3], Yoann Seeleuthner[1,2], Rui Yang[3], Alexandre Bolze[16], András N. Spaan[3,17], Ottavia M. Delmonte[4], Michael S. Abers[4], Alessandro Aiuti[18], Giorgio Casari[18], Vito Lampasona[18], Lorenzo Piemonti[18], Fabio Ciceri[18], Kaya Bilguvar[19], Richard P. Lifton[19,20,21], Marc Vasse[22], David M. Smadja[23], Mélanie Migaud[1,2], Jérome Hadjadj[24], Benjamin Terrier[25], Darragh Duffy[26], Lluis Quintana-Murci[27,28], Diederik van de Beek[29], Lucie Roussel[30,31], Donald C. Vinh[30,31], Stuart G. Tangye[32,33], Filomeen Haerynck[34], David Dalmau[35], Javier Martinez-Picado[36,37,38], Petter Brodin[39,40], Michel C. Nussenzweig[41,42], Stéphanie Boisson-Dupuis[1,2,3], Carlos Rodríguez-Gallego[43,44], Guillaume Vogt[45], Trine H. Mogensen[46,47], Andrew J. Oler[48], Jingwen Gu[48], Peter D. Burbelo[49], Jeffrey Cohen[50], Andrea Biondi[51], Laura Rachele Bettini[51], Mariella D'Angio[51], Paolo Bonfanti[52], Patrick Rossignol[53], Julien Mayaux[54], Frédéric Rieux-Laucat[24], Eystein S. Husebye[55,56,57], Francesca Fusco[58], Matilde Valeria Ursini[58], Luisa Imberti[59], Alessandra Sottini[59], Simone Paghera[59], Eugenia Quiros-Roldan[60], Camillo Rossi[61], Riccardo Castagnoli[62], Daniela Montagna[63,64], Amelia Licari[62], Gian Luigi Marseglia[62], Xavier Duval[65,66,67,68,69], Jade Ghosn[68,69], HGID Lab§, NIAID-USUHS Immune Response to COVID Group§, COVID Clinicians§, COVID-STORM Clinicians§, Imagine COVID Group§, French COVID Cohort Study Group§, The Milieu Intérieur Consortium§, CoV-Contact Cohort§, Amsterdam UMC Covid-19 Biobank§, COVID Human Genetic Effort§, John S. Tsang[70,71], Raphaela Goldbach-Mansky[4], Kai Kisand[7], Michail S. Lionakis[4], Anne Puel[1,2,3], Shen-Ying Zhang[1,2,3], Steven M. Holland[4¶], Guy Gorochov[6,72¶], Emmanuelle Jouanguy[1,2,3¶], Charles M. Rice[5¶], Aurélie Cobat[1,2,3¶], Luigi D. Notarangelo[4¶], Laurent Abel[1,2,3¶], Helen C. Su[4#], Jean-Laurent Casanova[1,2,3,42,73*#]

- We searched for auto-Abs against type I IFNs in 987 patients hospitalized for life-threatening COVID-19 pneumonia.
- We also examined 663 individuals infected with SARS-CoV-2 presenting asymptomatic or mild disease, and 1,227 healthy controls whose samples were collected before the COVID-19 pandemic.
- Plasma or serum samples were collected from patients with critical COVID-19 during the acute phase of disease.

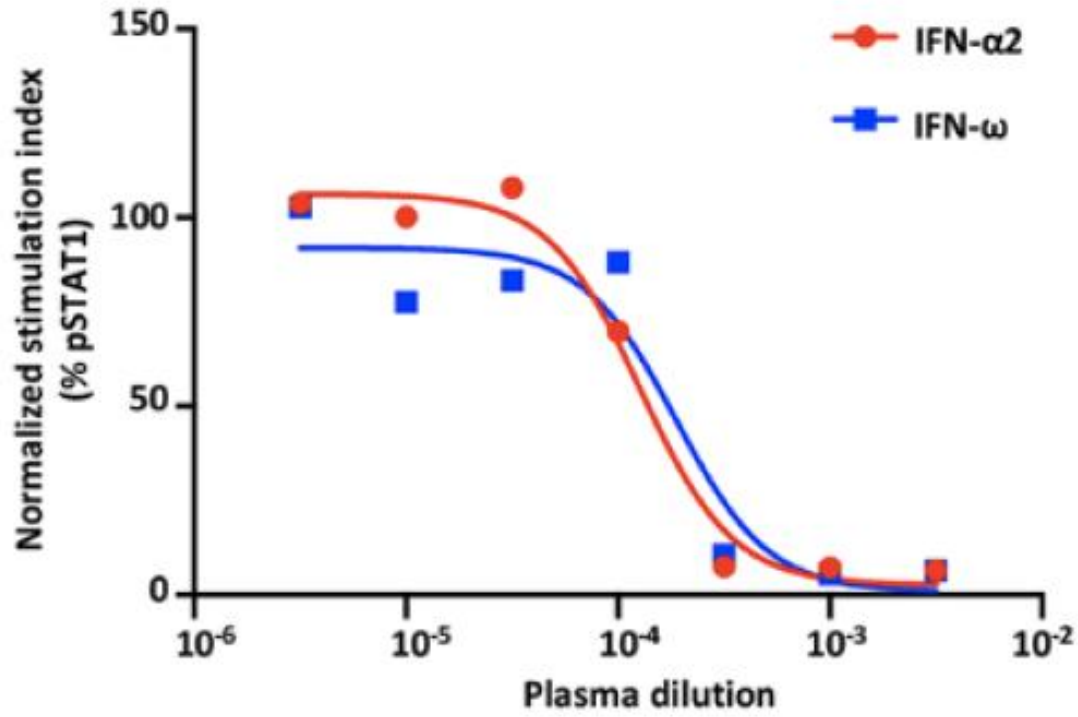
Multiplex particle-based flow cytometry revealed a high fluorescence intensity (FI; >1,500) for IgG auto-Abs against IFN-α2 and/or IFN-ω in 135 patients (13.7%) with life-threatening COVID-19

A



B

E


IFN-α2
IFN-ω
Normalized stimulation index
(% pSTAT1)
150
100
50
0
10-6
10-5
10-4
10-3
10-2
Plasma dilution

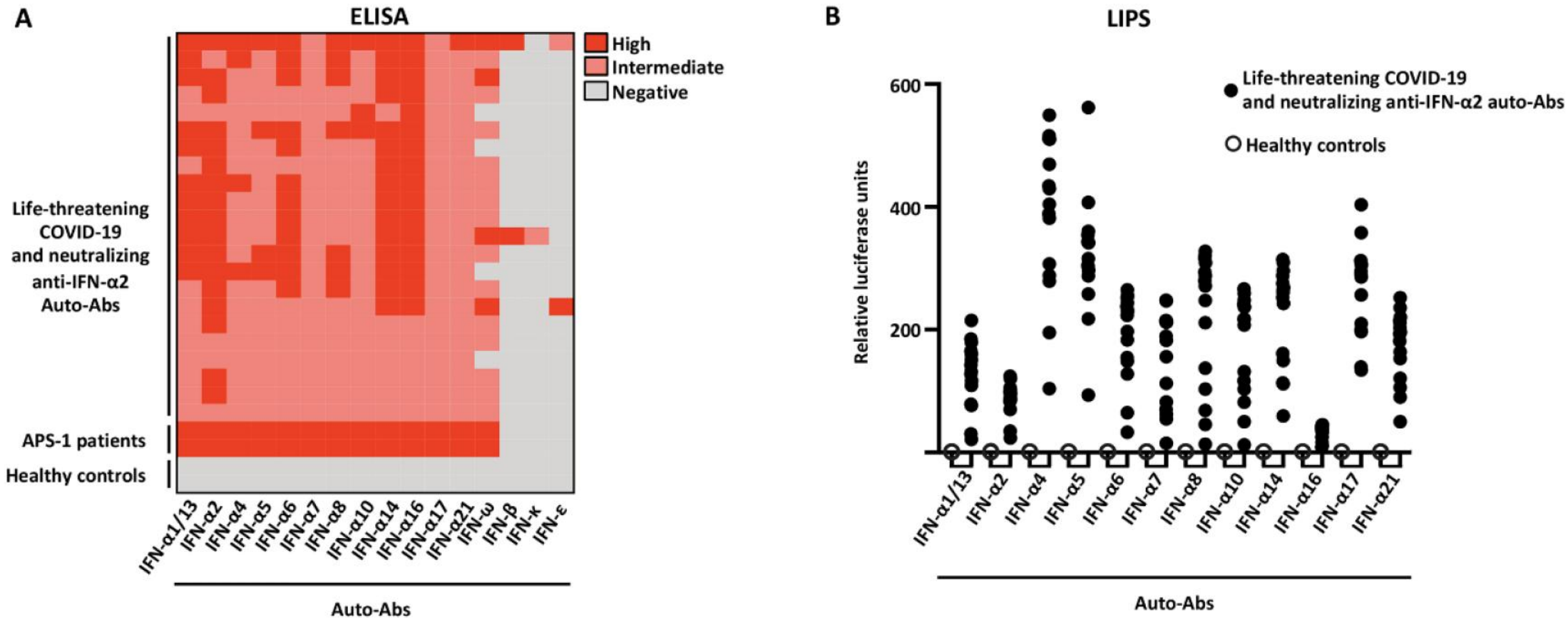

A
ELISA
High
Intermediate
Negative
Life-threatening COVID-19 and neutralizing anti-IFN-α2 Auto-Abs
APS-1 patients
Healthy controls
IFN-α1/13
IFN-α2
IFN-α4
IFN-α5
IFN-α6
IFN-α7
IFN-α8
IFN-α10
IFN-α14
IFN-α16
IFN-α17
IFN-α21
IFN-ω
IFN-β
IFN-κ
IFN-ε
Auto-Abs
B
LIPS
Life-threatening COVID-19 and neutralizing anti-IFN-α2 auto-Abs
Healthy controls
Relative luciferase units
600
400
200
IFN-α1/13
IFN-α2
IFN-α4
IFN-α5
IFN-α6
IFN-α7
IFN-α8
IFN-α10
IFN-α14
IFN-α16
IFN-α17
IFN-α21
Auto-Abs

Table 1. Sex and age distribution of patients with critical COVID-19 with and without autoAbs.
Age and sex of the patients and controls, and information about auto-Abs against IFN-α2 and IFN-ω by age and sex. OR: odds ratio.

Life-threatening COVID-19	N total	N auto-Abs positive (%)	OR [95% CI]	p-value*
		Sex		
Female	226	6 (2.7%)	1	
Male	761	95 (12.5%)	5.22 [2.27-14.80]	$2.5\,10^{-6}$
		Age		
<65 years	602	51 (8.5%)	1	
≥65 years	385	50 (13.0%)	1.61 [1.04 - 2.49]	0.024

*p-value were derived from Fisher's exact test, as implemented in R (https://cran.r-project.org/).

The Journal of Infectious Diseases

SUPPLEMENT ARTICLE

Impact of Type I and III Interferons on Respiratory Superinfections Due to Multidrug-Resistant Pathogens

Dane Parker

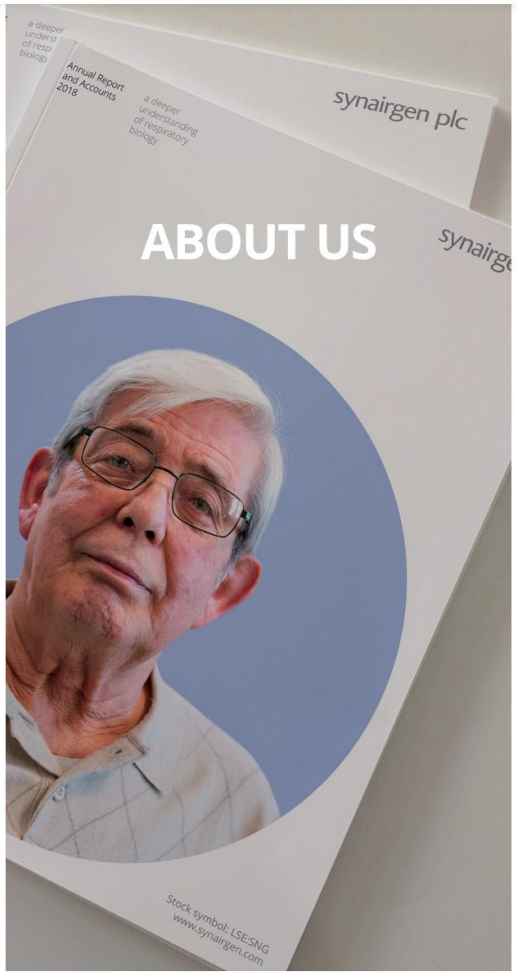
Department of Pediatrics, Columbia University, New York

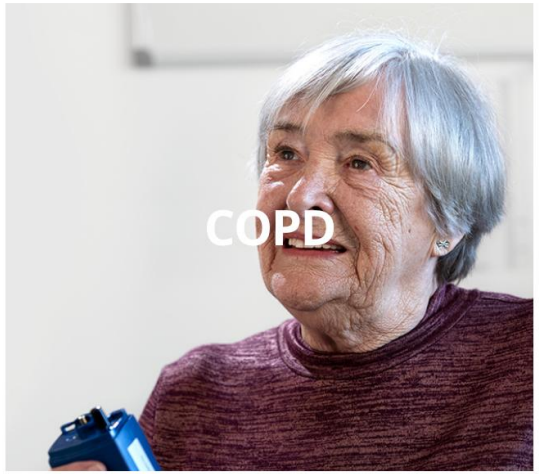
The increased morbidity and mortality associated with bacterial pneumonias that are acquired following influenza infection are well appreciated by clinicians. One of the major components of the immune response to influenza is the induction of the types I and III interferon cascades, which encompasses the activation of over 300 genes. The immunological consequences of IFN activation, while important for viral clearance, modify the host proinflammatory responses through effects on the inflammasome, Th17 signaling and recruitment of phagocytic cells. IFN signaling affects both susceptibility to subsequent *Streptococcus pneumoniae* and *Staphylococcus aureus* infection as well as the intensity of the immune responses associated with pulmonary damage. Appreciation for the effects of IFN activation on anti-bacterial pulmonary defense mechanisms should help to inform therapeutic strategies in an ICU setting.

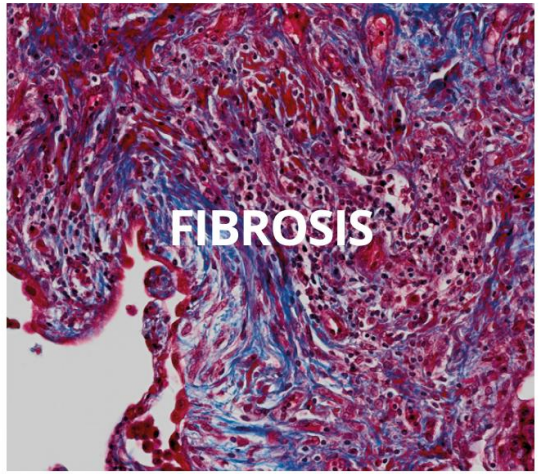
Keywords. influenza; *Staphylococcus aureus*; *Streptococcus pneumoniae*; type I interferon; type III interferon; superinfection; pneumonia.

De l’interféron alpha ou beta?

- Oui mais







LATEST NEWS

15th October 2020
Result of Placing

A ratio above 1 signifies a greater likelihood of (for HR), or odds of (for OR), the effect occurring on SNG001 compared to placebo

	ITT population (n = 98)		PP population (n = 86)	
Analysis	**Ratio (95% CI)**	**p-value**	**Ratio (95% CI)**	**p-value**
Odds of improvement across the OSCI (any improvement at day 15/16 compared to baseline)	OR 2·32 (1·07, 5·04)	0·033	OR 2.80 (1.21, 6.52)	0·017
Time to Recovery[a] (time from first dose to no limitation of activities without subsequent relapse)	HR 2·19 (1·03, 4·69)	0·043	HR 2.29 (1.07, 4.91)	0.033
Odds of Recovery (no limitation of activities recorded at day 15/16 without subsequent relapse)	OR 3·19 (1·24, 8·24)	0·017	OR 3.18 (1.21, 8.39)	0.019
Time to Hospital Discharge[b] (time from first dose to hospital discharge with no subsequent hospital re-admission)	HR 1·37 (0·85, 2·20)	0·196	HR 1.53 (0.96, 2.42)	0.072
Odds of Hospital Discharge (discharged from hospital at day 15/16 without subsequent hospital re-admission)	OR 1·63 (0·61, 4·35)	0·330	OR 2.14 (0.64, 7.12)	0.215

[a] Recovery was defined as a post baseline OSCI score of 0 or 1 which does not rise above 1 at any subsequent visits.
[b] Hospital Discharge was defined as a post baseline OSCI score of 2 or less which does not rise above 2 at any subsequent visits.

A ratio below 1 signifies a lower likelihood of (for HR), or odds of (for OR), the effect occurring on SNG001 compared to placebo

	ITT population (n = 98)		PP population (n = 86)	
Analysis	**Ratio (95% CI)**	**p-value**	**Ratio (95% CI)**	**p-value**
Time to severe disease or death (time from first dose until first incidence of OSCI≥5)	HR 0·50 (0.18, 1.38)	0·179	Not calculated as not part of statistical analysis plan	
Odds of severe disease or death (OSCI≥5 at any time in the first 16 days after first dose)	OR 0·28 (0·07, 1·08)	0·064[a]	OR 0.18 (0.04, 0.93)	0.041[b]
Time to intubation or death (time from first dose until first incidence of OSCI≥6)	HR 0·38 (0·09, 1·65)	0·198	Not calculated as not part of statistical analysis plan	
Odds of intubation or death (OSCI≥6 at any time in the first 16 days after first dose)	OR 0·42 (0·09, 1·83)	0·246[b]	OR 0.31 (0.05, 1.79)	0.189[b]

[a] Using the pre-specified logistic regression analysis, SNG001 reduced the odds of developing severe disease or dying in the ITT population by 79% (OR 0·21; 95% CI: 0·04, 0·97; p=0·046). As quasi-complete separation of data occurred in some model covariates, an additional post-hoc, Firth logistic regression analysis was conducted. This showed there was a trend towards reduced odds of progression to severe disease or death in the ITT population (72% reduction; OR 0·28; 95% CI: 0·07, 1·08; p=0·064) that became significant in the per protocol population (82% reduction; OR 0.18; 95% CI: 0.04, 0.93; p=0.041).

[b] Post hoc analysis using the Firth logistic regression analysis.