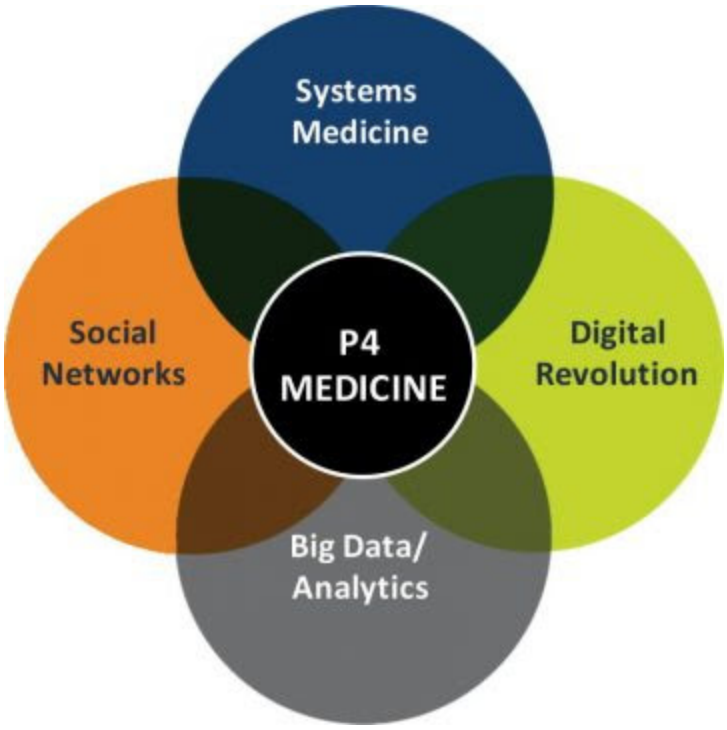
Cannabinoids as anti-inflammatory agents and respiratory function

The information and understanding of COVID-19 continues to change rapidly. We encourage you to make integrative recommendations carefully and with consideration of the underlying mechanisms of both the COVID-19 infection and the intended intervention. It is also important to reiterate that to date there are no clinically evidence-based integrative prevention or treatment strategies for COVID-19 infection.

Chapter 21 - The Patient-Centered Decision System as per the 4Ps of Precision Medicine

IlariaBaiardini EnricoHeffler



Prediction	• detect the risk for disease development • identify the presence of prodromal signs • determine the disease progression • recognize the individual likelihood of responding to treatments

Prevention	• reduce the likelihood of disease and disability by introducing individualized tailored preventive measures • move from disease treatment to wellness maintenance
Personalization	• use genetic, biomedical, environmental and lifestyle data to better target the delivery of healthcare and treatments to individuals • tailor each decision and intervention to the individual patient
Participation	• involve the individual in strategy aimed to predict, prevent and personalize the process of care • increase the individual's confidence to shift from a passive receiver of care to and active, responsible and aware driver of his/her wellness

A ssociation of cannabis potency with mental ill health and addiction: a systematic review.

Read this Review

Cochrane Review:

- ❏ Cannabis and cannabis oil for the treatment of ulcerative colitis

  The effects of cannabis and cannabis oil on ulcerative colitis are uncertain, thus no firm conclusions regarding the effectiveness and safety of cannabis or cannabis oil in adults with active ulcerative colitis can be drawn. There is no evidence for cannabis or cannabis oil use for maintenance of remission in ulcerative colitis. Further studies with a larger number of participants are required to assess the effects of cannabis in people with active and inactive ulcerative colitis. Different doses of cannabis and routes of administration should be investigated. Lastly, follow-up is needed to assess the long term safety outcomes of frequent cannabis use.

- ❏ Oral Janus kinase inhibitors (tofacitinib) for maintenance of remission in ulcerative colitis

- ❏ Cannabis and cannabis oil for the treatment of Crohn's disease

- ❏ This summary of a Cochrane review presents what we know from research about the effect of Anakrina on rheumatoid arthritis (RA).

- ❏ Steroids -- But Not Anti-TNF -- Tied to Severe COVID-Infectious Disease News: COVID-1919 in IBD Patients
  — Large registry study supports recommendations to taper steroids when possible
  by Diana Swift, Contributing Writer May 18, 2020

COVID 19 and the Cytokine Storm

A cytokine is a short-lived signaling molecule that the body can release to activate inflammation in an attempt to contain and eradicate a virus. In a cytokine storm, the immune system floods the body with these molecules, essentially sounding a fire alarm that continues even after the firefighters and ambulances have arrived.

Of the millions of individuals who are infected with the Coronavirus the group that pose the greatest urgency are those who experience respiratory failure. Although we are still early in our understanding of pathophysiology and the mechanisms of action in the lungs, a preliminary picture is emerging. Although the specific underlying pathology on the cellular level has not clearly elucidated yet, clinicians have seen that many of those who become critically ill from SARS-CoV2 (Covid 19) are experiencing a so-called cytokine storm, which happens when the immune system overreacts and attacks the body's organs. Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might have a cytokine storm syndrome. We recommend identification and treatment of hyperinflammation using existing, approved therapies with proven safety profiles to address the immediate need to reduce the rising mortality. The pathogenesis of highly pathogenic human coronavirus is still not completely understood. Cytokine storm and viral evasion of cellular immune responses are thought to play important roles in disease severity.[9]

Cytokine storm syndrome

The symptoms of cytokine storm syndrome can include high fever, enlarged spleen, excessive bleeding, low counts of all types of blood cells (red, white, and platelets), and, potentially, multiple organ failures.

In a recent article in The Atlantic, James Hamblin described Why Some People Get Sicker Than Others when infected by the SARS-CoV-2 virus as follows,

"When the coronavirus attaches to cells, it hooks on and breaks through, then starts to replicate. It does so especially well in the cells of the nasopharynx and down into the lungs, but is also known to act on the cells of the liver, bowels, and heart. The virus spreads around the body for days or weeks in a sort of stealth mode, taking over host cells while evading the immune response. It can take a week or two for the body to fully recognize the extent to which it has

been overwhelmed. At this point, its reaction is often not calm and measured. The immune system goes into a hyperreactive state, pulling all available alarms to mobilize the body's defense mechanisms. This is when people suddenly crash….
Such a quick decline—especially in the later stages of an infectious disease—seems to result from the immune response suddenly kicking into overdrive".

Targeting the catecholamine-cytokine axis to prevent SARS-CoV-2 cytokine storm syndrome
April 2020

To investigate a potential role for α1-AR antagonists in preventing poor outcomes in ARDS, we conducted a retrospective analysis of hospitalized patients diagnosed with ARDS. Using data from the Truven Health MarketScan Research Database (2010-2017), we identified 12,673 men (age 45-64) with ARDS, of whom 1,189 patients (9.4%) were prescribed α1-AR antagonists in the previous year. Applying logistic regression models, we found that patients with prior use of α1-AR antagonists had lower odds of the composite of need for invasive mechanical ventilation and mortality compared to non-users (AOR 0.80, 95% CI 0.69-0.94, p=0.008). Mirroring findings from pre-clinical models, these data support a clinical rationale to study α1-AR antagonists in the prophylaxis of ARDS and states of local and systemic immune dysregulation. Prospective, randomized clinical trials of alpha-1 receptor antagonists (e.g. prazosin) administered prior to the onset of severe symptoms are needed to assess their efficacy in preventing CSS and reducing mortality in COVID-19.

- How Covid Sends Some Bodies to War With Themselves
  Many Covid-19 patients may be dying from their immune response to the virus, not from the virus itself. Can science figure out how to save them?

- What We Don't Know About the Coronavirus By Clifford Marks and Trevor Pour
  April 29, 2020
  Within hours of a viral invasion, the body's immune system
  swings into action. The "innate" immune system, which recognizes protein structures common to many pathogens, reacts first, by releasing a family of chemical distress signals called cytokines. They spread from the site of the infection, instructing the body to raise its temperature and divert blood flow to the affected area; they also activate other immune-system cells, which begin developing antibodies specifically targeting the invaders. Without cytokines, the immune system would slumber while infections wreak havoc. But the cytokine system has a weakness. Some pathogens can provoke it in a perverse way, so that it goads the immune system as a whole into overdrive. In what's known as a cytokine storm, fever and inflammation spike out of control. It's unclear why some patients might experience this phenomenon while others do not.

  Faced with a cytokine storm in a patient, a doctor can try to modulate the immune system's response. The problem is striking the right balance. While some patients may benefit from a degree of medically induced immunosuppression, there are others for

whom such an intervention could cause great harm. Some hospitals have begun cautiously administering steroids or drugs that inhibit the cytokine IL-6. But high-quality clinical-trial data about such treatments won't be ready for a long time. Moreover, even if early results are encouraging, we will still have to distinguish between those patients who will benefit from immunosuppression and those who won't. In the past, physicians have interpreted elevated blood levels of the protein ferritin as a sign that a cytokine storm is in progress. Some are now using that analysis in the treatment of covid-19. Only time will tell if they're right.

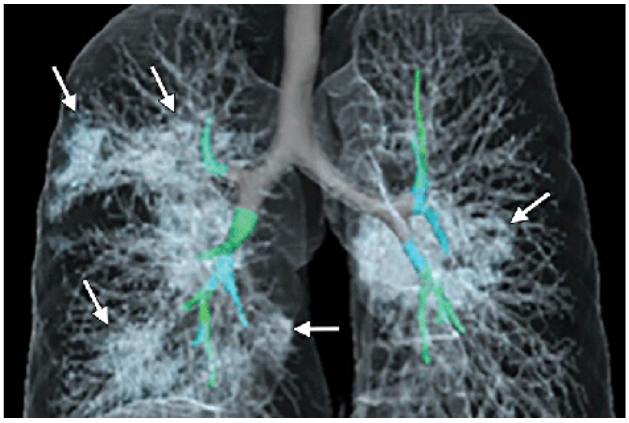
- ❏ Cytokine storm syndrome - how to stop it
  During a cytokine storm, the immune system isn't just going berserk but is also generally off its game, attacking at will without hitting the right targets. When this happens, people become more susceptible to infectious bacteria. The storms can also affect other organs besides the lungs, especially if people already have chronic diseases. This might explain why some COVID-19 patients end up with complications such as heart problems and secondary infections.

- ❏ One Emergency Physician's Cheat Sheet to COVID-19
  The Clinical course is predictable.
  2 to 11 days after exposure (day 5 on average), flu-like symptoms start. Common are fever, headache, dry cough, myalgias (often back pain), nausea without vomiting, abdominal discomfort with some diarrhea, loss of smell, anorexia, fatigue.
  Day 5 of symptoms- increased shortness of breath, and bilateral viral pneumonia from direct viral damage to lung parenchyma.
  Day 10 - Cytokine storm leading to acute ARDS and multiorgan failure. You can literally watch it happen in a matter of hours.
  81% mild symptoms, 14% severe symptoms requiring hospitalization, 5% critical.

Unexpected Results in New COVID-19 'Cytokine Storm' Data

Medscape Medical News

A review of Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China noted that the risk for developing ARDS included factors consistent with immune activation; older age was associated with both ARDS development and death, likely owing to less robust immune responses.



The virus's destructive impact can be demonstrated with radiologic studies.
Images in a 41-year-old woman who presented with fever and positive polymerase chain reaction assay for the 2019 novel coronavirus (2019-nCoV). Three representative axial thin-section chest CT images show multifocal ground glass opacities without consolidation. Three-dimensional volume-rendered reconstruction shows the distribution of the ground-glass opacities (arrows). See also the three-dimensional movie.

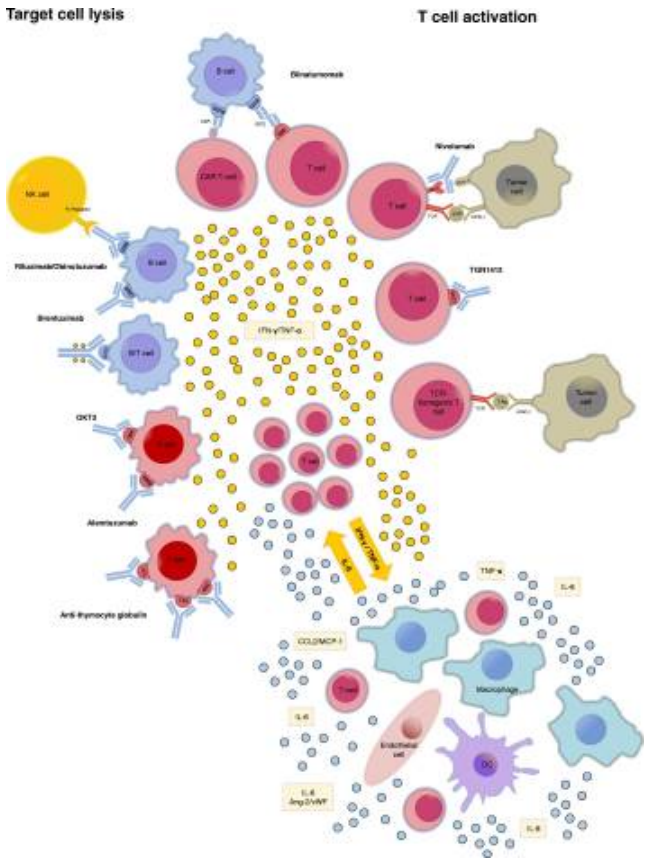
Acute respiratory distress syndrome (ARDS)

Neutrophilia was found in both the peripheral blood[10] and lung[11] of patients with SARS-CoV. The severity of lung damage correlated with extensive pulmonary infiltration of neutrophils and macrophages and higher numbers of these cells in the peripheral blood in patients with Middle East respiratory syndrome.[12-14] Neutrophils are the main source of chemokines and cytokines. The generation of cytokine storm can lead to ARDS, which is a leading cause of death in patients with severe acute respiratory syndrome [15] and Middle East respiratory syndrome.[14] In this study, patients with COVID-19 pneumonia who had developed ARDS had significantly higher neutrophil counts than did those without ARDS, perhaps leading to the activation of neutrophils to execute an immune response against the virus, but also contributing to cytokine storm. This may partly explain the positive association of high fever and ARDS found at the early stages of COVID-19. In addition, considering that older age is associated with declined immune competence,[16] the results of the present study showed that older age was associated with both ARDS and death. Therefore, older age related to death may be due to less robust immune responses.

About the Human coronaviruses (hCoVs)
Human coronaviruses (hCoVs) can be divided into low pathogenic and highly pathogenic coronaviruses. The low pathogenic CoVs infect the upper respiratory tract and cause mild, cold-like respiratory illness. In contrast, highly pathogenic hCoVs such as severe acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV) predominantly infect lower airways and cause fatal pneumonia. Severe

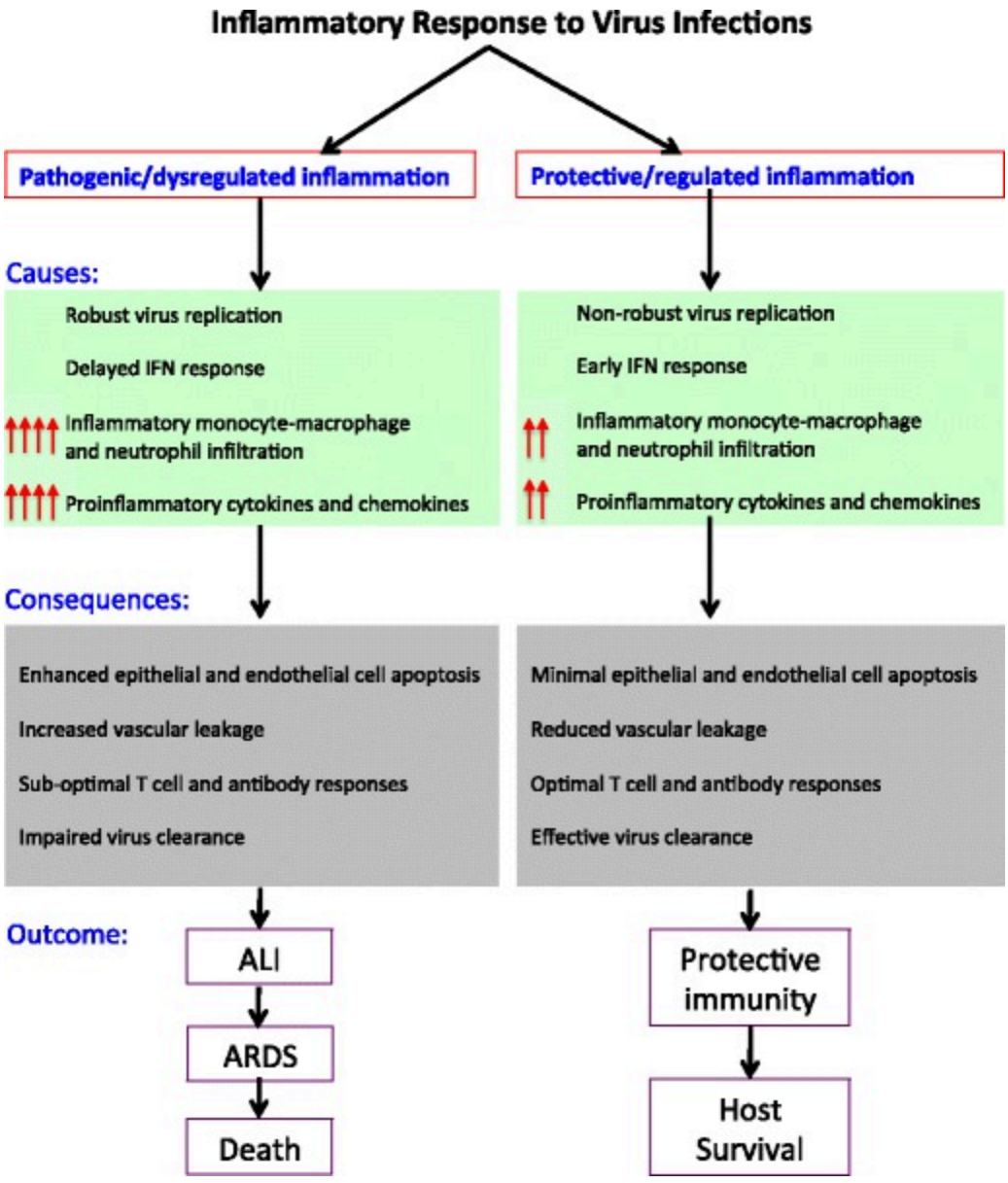
pneumonia caused by pathogenic hCoVs is often associated with rapid virus replication, massive inflammatory cell infiltration and elevated pro-inflammatory cytokine/chemokine responses resulting in acute lung injury (ALI), and acute respiratory distress syndrome (ARDS). Recent studies in experimentally infected animals strongly suggest a crucial role for virus-induced immunopathological events in causing fatal pneumonia after hCoV infections. Here we review the current understanding of how a dysregulated immune response may cause lung immunopathology leading to deleterious clinical manifestations after pathogenic hCoV infections.

Cytokine release syndrome Alexander Shimabukuro-Vornhagen, Philipp Gödel, Marion Subklewe, Hans Joachim Stemmler, Hans Anton Schlößer, Max Schlaak, Matthias Kochanek, Boris Böll, and Michael S. von Bergwelt-Baildon, J Immunother Cancer. 2018; 6: 56.



Reported inducers of CRS. CRS can be induced by direct target cell lysis with consecutive release of cytokines like interferon gamma (IFN-γ) or tumor necrosis factor alpha (TNF-α) or by activation of T cells due to therapeutic stimuli with subsequent cytokine release. These cytokines trigger a chain reaction due to the activation of innate immune cells like

macrophages and endothelial cells with further cytokine release. Abbreviations: Ang-2: Angiopoetin 2; CAR: chimeric antigen receptor; DC: dendritic cell; IFN-γ: interferon gamma; MHC-I: major histocompatibility complex I;NK cell: natural killer cell; PD-(L)1: programmed cell death protein (ligand) 1; TCR: T cell receptor.; TNF-α: tumor necrosis factor alpha; vWF: von Willebrand factor



Risk factors:
Age:

But why do some people with COVID-19 get incredibly sick, while others escape with mild or nonexistent symptoms? Age is a factor. Elderly people are at risk of more severe infections possibly because their immune system can't mount an effective initial defense, while children are less affected because their immune system is less likely to progress to a cytokine storm. But other factors—a person's genes, the vagaries of their immune system, the amount of virus they're exposed to, the other microbes in their bodies—might play a role too. In general, "it's a mystery why some people have mild disease, even within the same age group," Iwasaki says.

Genetic factors:

Alternative Treatments

Elderberry

There's no scientific evidence that elderberry or any other herbal remedy is effective for COVID-19 prevention/tx[1]

Cytokine storm media debate. Some suggest OK for prevention, but should d/c @ COVID-19 sx onset, due to possible immune inflammatory up-regulation;[2] theory based on in vitro S nigra (Sambucol) study on ↑inflammatory cytokine production in human monocytes[3]

3 Barak V, et al. The Effect of Sambucol, a Black Elderberry-based, Natural Product, on the Production of Human cytokines: I. Inflammatory cytokines. Eur Cytokine Netw. 2001. Apr-Jun;12(2):290-6. Accessed 3/28/20

Echinacea

Cytokine storm media debate. Some suggest OK for prevention, but should d/c @ COVID-19 sx onset, due to possible immune inflammatory up-regulation; 2 theory based on in vitro E purpurea study on ↑inflammatory cytokine production in human macrophages 3 and other limited data4

3 Burger RA, et al. Echinacea-Induced Cytokine Production by Human Macrophages. Int J Immunopharmacol. 1997 Jul;19(7):371-9. Accessed 4/2/20

MedRxiv 2020

Vitamin D

The Role of Vitamin D in Suppressing Cytokine Storm in COVID-19 Patients and Associated Mortality

Reported medical characteristics of 793 COVID-19 patients were used to evaluate the intensity of cytokine storm in severe COVID-19 using C-reactive protein (CRP) levels.

Interferon-a2b

Interferon-a2b treatment for COVID-19

Qiong Zhou, Xiao-Shan Wei, Xuan Xiang, Xu Wang, Zi-Hao Wang, Virginia Chen, Casey P Shannon, Scott J Tebbutt, Tobias R Kollmann, Eleanor N Fish

doi: https://doi.org/10.1101/2020.04.06.20042580

Targeting the catecholamine-cytokine axis to prevent SARS-CoV-2 cytokine storm syndrome
Maximilian F Konig, Mike Powell, Verena Staedtke, Ren-Yuan Bai, David L Thomas, Nicole Fischer, Sakibul Huq, Adham M Khalafallah, Allison Koenecke, Nickolas Papadopoulos, Kenneth W Kinzler, Bert Vogelstein, Joshua T Vogelstein, Susan Athey, Shibin Zhou, Chetan Bettegowda
doi: https://doi.org/10.1101/2020.04.02.20051565

Unprepared for a Pandemic By Michael T. Osterholm Foerign Affairs March/April 2007

Save this article to read later

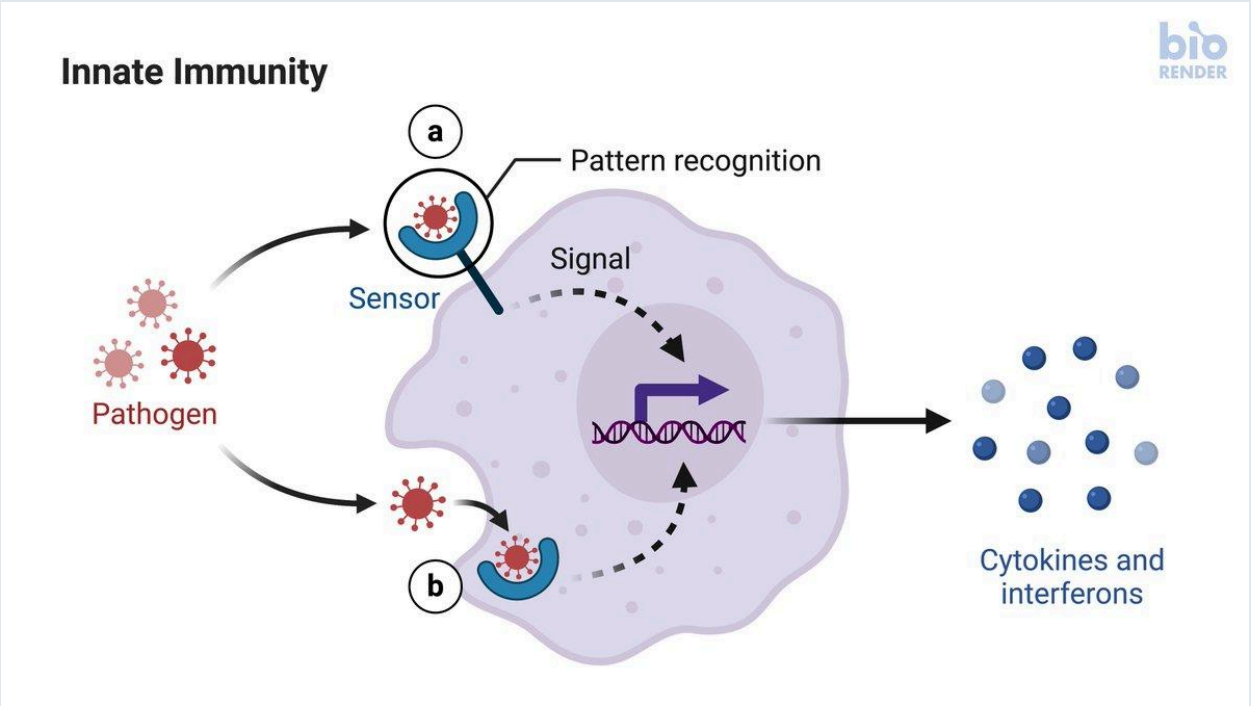
Prof. Akiko Iwasaki

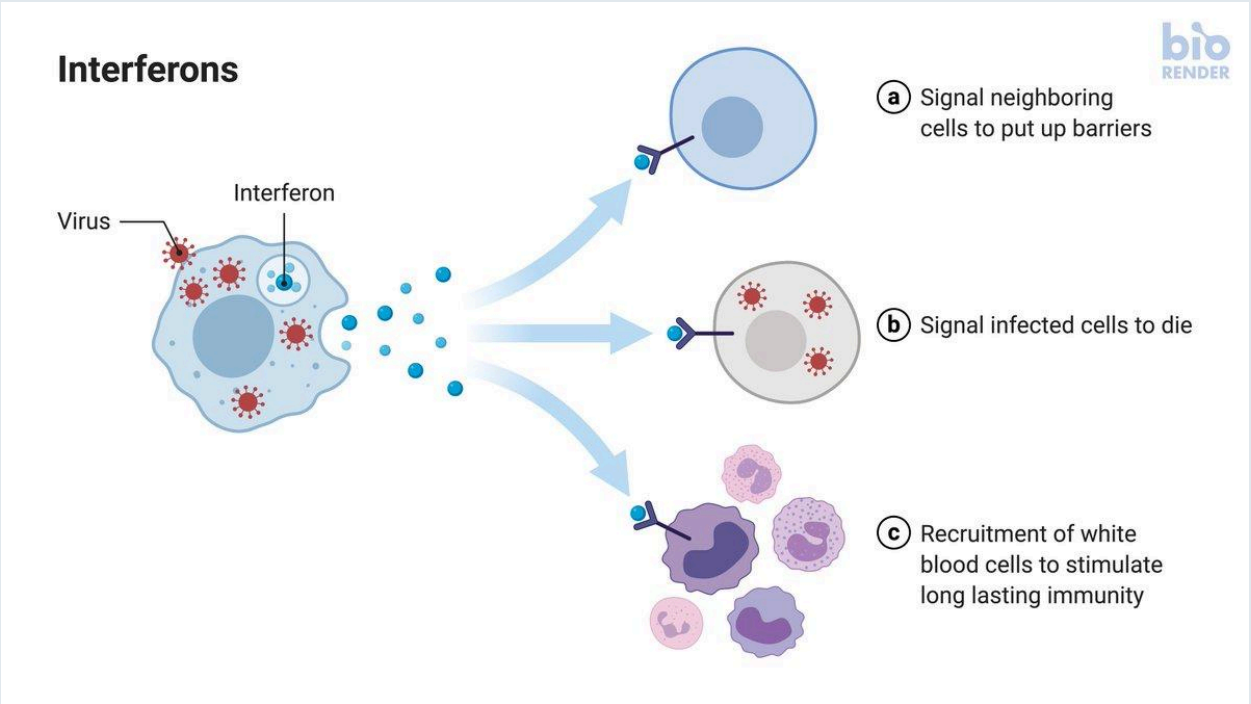
Jul 22nd 2020, 13 tweets, 7 min read
How does the immune system work? Will there be #COVID19 vaccines? @BioRender & I put together 'immunology 101 tweetorial for non-immunologists'. @jerryguartist, @shizaoki, @JungHeeSciViz also made this accompanying video. Please share widely! (1/n)
https://threadreaderapp.com/thread/1285944893085491204.html

110 views

Eric Topol

1. The early use of inhaled interferons is emerging as a promising strategy to prevent severe #COVID19: lines of support include mechanism, rare genomic variants, a multicenter retrospective report, and a small randomized trial
2. On mechanism, our innate immune response, first line of defense relies, at least in part, on the interferon response.
2 figures from @VirusesImmunity's terrific thread, and the link to it
Unroll available on Thread Reader



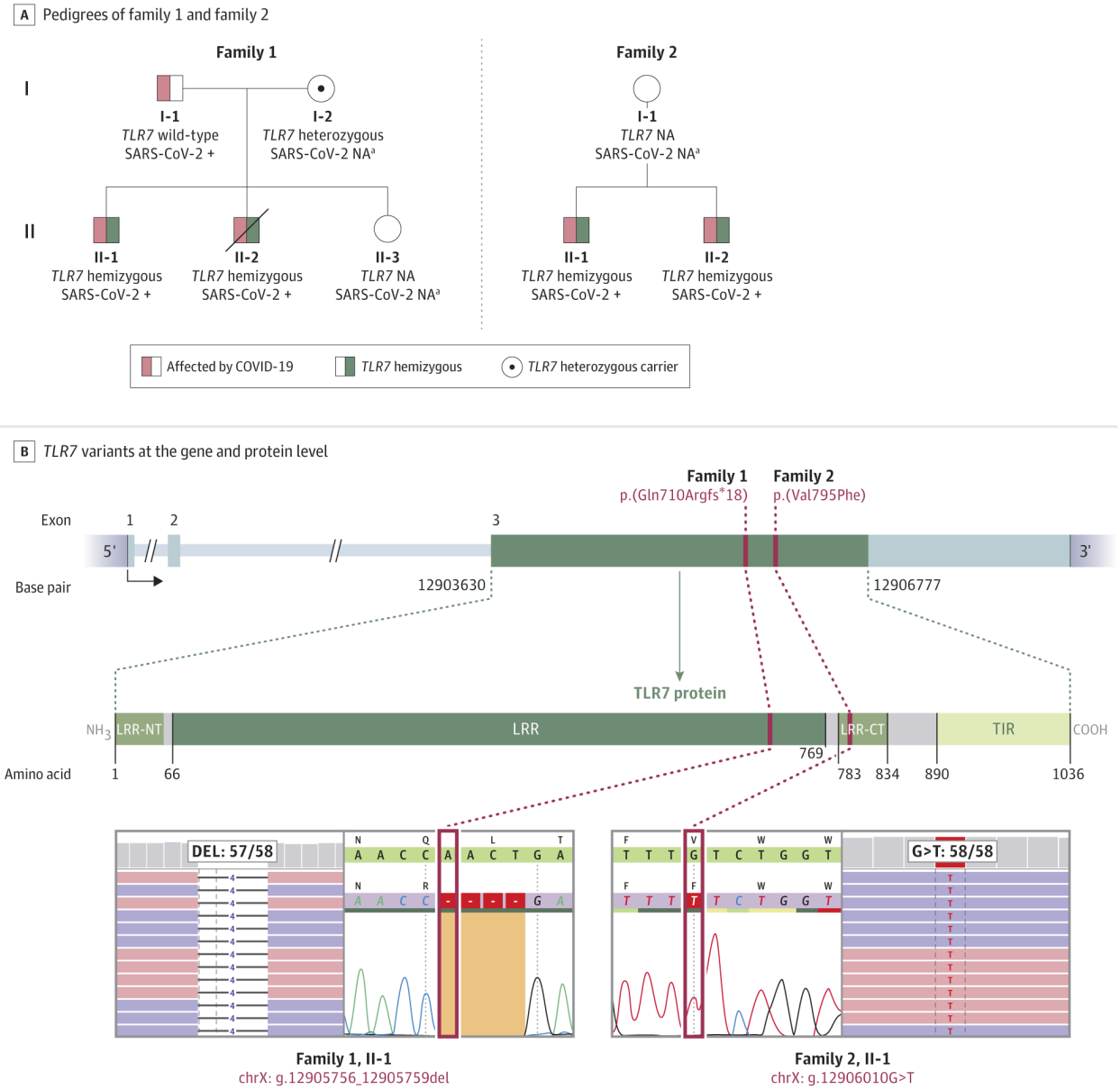


3. Yesterday's @JAMA_current report of loss-of-function TRL7 rare variants in 4 young men from 2 independent families w/ severe #COVID19 connects with their impaired interferon response
Editorial @rplenge

Molecular Underpinnings of Severe Coronavirus Disease 2019

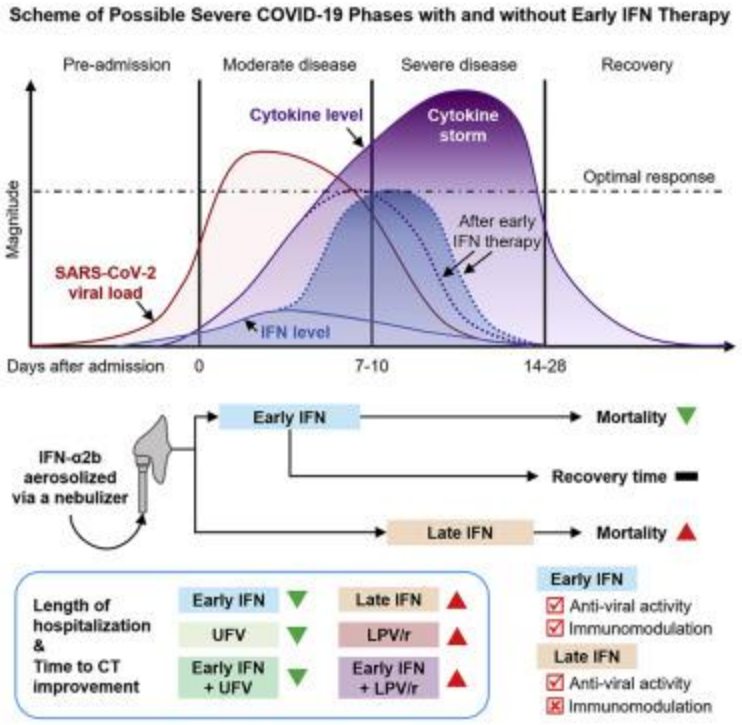
[The molecular underpinnings of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the disease it causes, coronavirus disease 2019 (COVID-19), are poorly understood. Inherited …
https://jamanetwork.com/journals/jama/fullarticle/2768925](https://jamanetwork.com/journals/jama/fullarticle/2768925)

Paper by @ahoischen et al



[Presence of Genetic Variants Among Young Men With Severe COVID-19
This case series describes rare putative X-chromosomal loss-of-function variants associated with impaired peripheral mononuclear blood cell interferon signaling in 4 young male patients hospitalized …
https://jamanetwork.com/journals/jama/fullarticle/2768926](https://jamanetwork.com/journals/jama/fullarticle/2768926)

4. Multicenter report of inhaled interferon-alpha2b (Type1) showed benefit if given early, harm if late (opposite of pattern with dexamethasone)

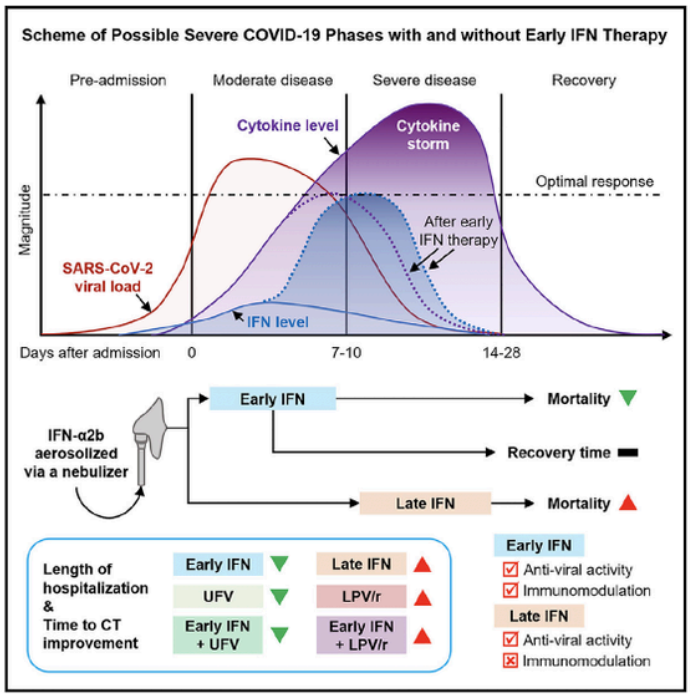


Retrospective Multicenter Cohort Study Shows Early Interferon Therapy Is Associated with Favorable Clinical Responses in COVID-19 Patients
In a retrospective cohort study of 446 COVID-19 patients, Wang et al. determine that early administration of interferon-α2b was associated with reduced in-hospital mortality. In contrast, late interf…
https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(20)30401-7
@cellhostmicrobe

Clinical and Translational Report
Cell Host & Microbe

Retrospective Multicenter Cohort Study Shows Early Interferon Therapy Is Associated with Favorable Clinical Responses in COVID-19 Patients

Graphical Abstract



Highlights

- 242 of 446 analyzed COVID-19 patients received IFN-α2b, a type I IFN
- Early initiation of IFN therapy was associated with reduced mortality
- IFN therapy was not associated with recovery time for COVID-19
- IFN-α2b was associated with better responses than were lopinavir/ritonavir

Authors

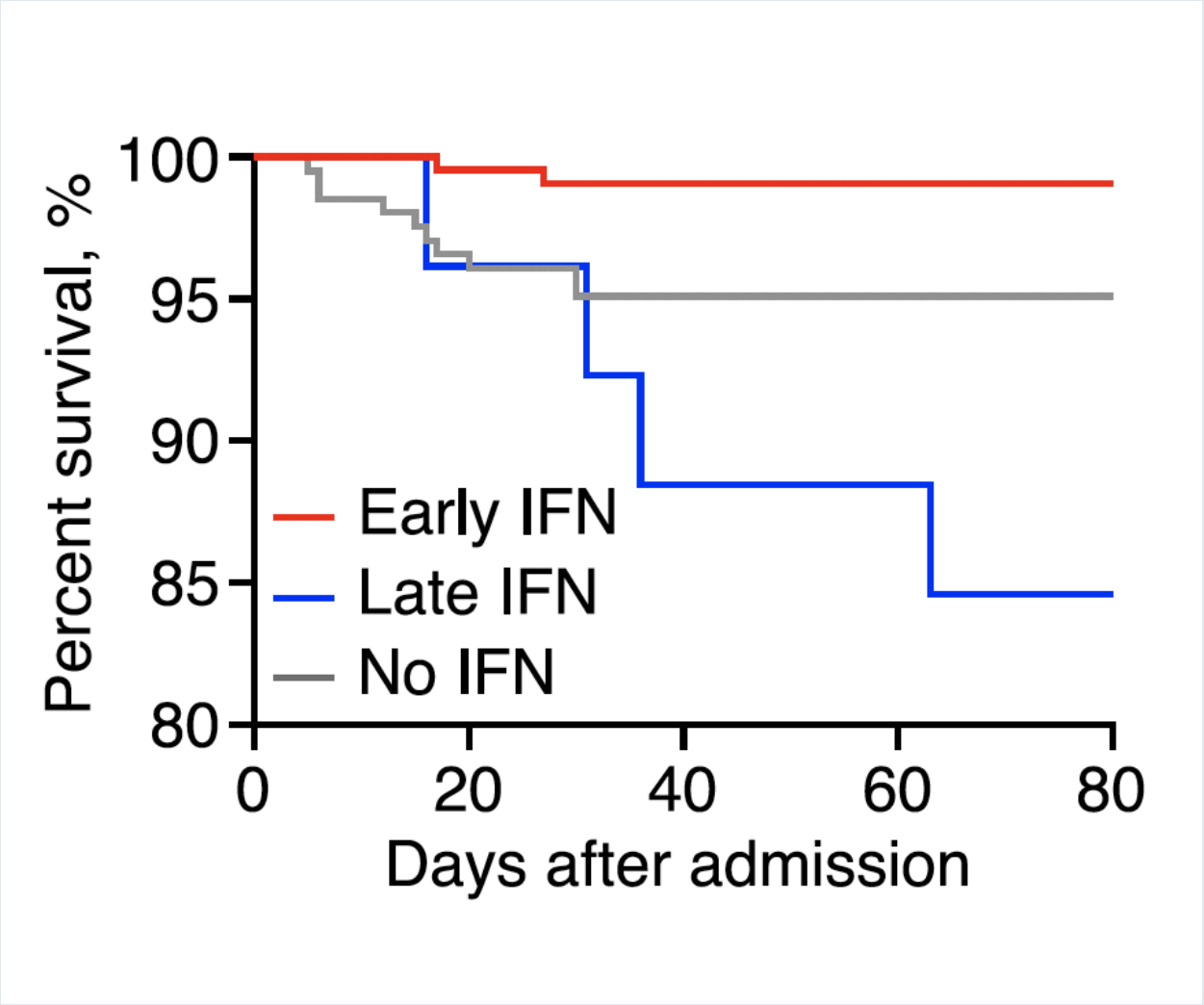
Nan Wang, Yan Zhan, Linyu Zhu, ..., Zhihua Zheng, Yingying Lu, Peng Hong

Correspondence

peng.hong@downstate.edu

In Brief

In a retrospective cohort study of 446 COVID-19 patients, Wang et al. determine that early administration of interferon-α2b was associated with reduced in-hospital mortality. In contrast, late interferon therapy increased mortality and delayed recovery, suggesting the timing of interferon therapy is crucial for favorable responses in COVID-19 patients.



5. A small randomized trial of inhaled beta interferon in 100 patients, only available via press release so far, but very encouraging results synairgen.com/wp-content/upl…
and important caveats here, by @benjmueller

New Treatment for Covid-19 Shows Promise, but Scientists Urge Caution
A small study of an inhaled form of a commonly available drug, interferon beta, suggests it could reduce the odds of patients becoming severely ill.
https://www.nytimes.com/2020/07/20/world/covid-19-treatment-synairgen-interferon-beta.html

Key findings:

The odds of developing severe disease (e.g. requiring ventilation or resulting in death) during the treatment period (day 1 to day 16) were significantly reduced by 79% for patients receiving SNG001 compared to patients who received placebo (OR 0.21 [95% CI 0.04-0.97]; p=0.046).

Patients who received SNG001 were more than twice as likely to recover (defined as 'no limitation of activities' or 'no clinical or virological evidence of infection') over the course of the treatment period compared to those receiving placebo (HR 2.19 [95% CI 1.03-4.69]; p=0.043).

Over the treatment period, the measure of breathlessness was markedly reduced in patients who received SNG001 compared to those receiving placebo (p=0.007).

Three subjects (6%) died after being randomised to placebo. There were no deaths among subjects treated with SNG001.

6. There are dozens of ongoing trials, an overview by @meredithwadman @ScienceMagazine

[Can interferons stop COVID-19 before it takes hold?
> Science's COVID-19 coverage is supported by the Pulitzer Center. On 30 April, Valerie McCarthy's test result confirmed that her grinding fatigue and pummeling headaches were caused by the new cor…
https://science.sciencemag.org/content/369/6500/125]

but if this holds up it will be the first class of drugs that can be given early in the course of an infection, fulfilling a major unmet need

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@threadreaderapp unroll
You can practice here first or read more on our help page!

Related hashtags

#COVID19

More from @EricTopolsee all

Eric Topol
@EricTopol
Jul 21st 2020
Very sad to note that today is the first day since May 29th (>6 weeks ago) there were more than 1,000 American #COVID19 deaths @COVID19Tracking

> 8 weeks (not 6, my mistake) We haven't seen this level of US #COVID19 hospitalizations since the April 15th peak

While attention has focused on Texas, Arizona, and Florida, many news states have hit new hospitalization and death numbers recently or today. Including South Carolina, Mississippi, Georgia, Tennessee and Idaho

Read 4 tweets

Eric Topol
@EricTopol
Jul 20th 2020
On the 4 published Phase 1/2 #SARSCoV2 vaccine programs (@moderna_tx @UniofOxford @Pfizer CanSino) 1. None have shown prevention of infections or disease; they show an antibody response, some T cell response, and preliminary safety. Can't be emphasized enough. 2. We have no idea about durability. The virus is only ~8 months old! 3. Only 2 of these programs presented specific T-cell response data (perhaps a proxy for longer-lasting protection): Pfizer/BioNTech program CD4+ in 34/36 patients, CD8+ 29/36 patients Moderna mostly only CD4+
References for T cell data Pfizer/BioNTech medrxiv.org/content/10.110… Moderna nejm.org/doi/suppl/10.1…

Read 4 tweets

Eric Topol
@EricTopol
Jul 18th 2020
On #diabetes, glucose control, #COVID19, #SARSCoV2 A new @Cell_Metabolism paper on the mechanism for uncontrolled glucose and severe covid19 cell.com/action/showPdf… A new @TheLancetEndo review goes deep on why there are worse outcomes thelancet.com/journals/landi…

The one thing I was surprised about in the review was lack of mention of the affinity of #SARSCoV2 to pancreatic islet β cells. This is thought to be another mechanism for new onset #T1D; there have been many cases reported and an ongoing registry

Summary of #SARSCoV2 affinity to ACE2, direct pancreas hit and COVIdiab registry

nejm.org/doi/full/10.10...

Editorial June 30, 2020
Is a "Cytokine Storm" Relevant to COVID-19?
Pratik Sinha, MB, ChB, PhD[1,2]; Michael A. Matthay, MD[1,2,3]; Carolyn S. Calfee, MD, MAS[1,2,3]
Author Affiliations Article Information
JAMA Intern Med. Published online June 30, 2020. doi:10.1001/jamainternmed.2020.3313
In its most severe form, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), leads to a life-threatening pneumonia and acute respiratory distress syndrome (ARDS). The mortality rate from COVID-19 ARDS can approach 40% to 50%.[1,2] Although the mechanisms of COVID-19–induced lung injury are still being elucidated, the term cytokine storm has become synonymous with its pathophysiology, both in scientific publications and the media. Absent convincing data of their effectiveness in COVID-19, drugs such as tocilizumab and sarilumab, which are monoclonal antibodies targeting interleukin (IL)-6 activity, are being used to treat patients; trials of these agents typically cite the cytokine storm as their rationale (NCT04306705, NCT04322773). A critical evaluation of the term cytokine storm and its relevance to COVID-19 is warranted.

Startup Spotlight: Going after immune regulators when they cause disease instead of prevent it
By ELIZABETH COONEY @cooney_lizMAY 27, 2020

It appears that after infection, the virus replicates itself inside a patient, leading to a disease phase where the immune system mounts an inflammatory response against the invader, says Charles Dela Cruz, a pulmonologist at Yale School of Medicine who is researching COVID-19. Then, in those patients who progress to severe disease, "potentially this inflammatory response is too much and hyper-inflames, causing a lot of side effects in terms of tissue damage and organ failure and things like that," he says.

CLINICAL PRACTICE Severe Covid-19 David A. Berlin, M.D., Roy M. Gulick, M.D., M.P.H., and Fernando J. Martinez, M.D.

The delayed onset of critical illness in patients with Covid-19 suggests a maladaptive host response to infection.10 Therefore, there is intense interest in the effects of immunomodulating therapies. Glucocorticoids have been used widely for cytokine storm and respiratory failure in patients with Covid-19; however, there is concern that they may prolong viral shedding and lead to secondary infections.58-60 Current guidelines offer conflicting advice on the use of glucocorticoids. The Surviving Sepsis Campaign suggests a short course of glucocorticoids for moderate-to-severe ARDS related to Covid-19,18 whereas the Infectious Diseases Society of America recommends their use only in the context of a clinical trial.62 For reversal of vasopressor-dependent shock in patients with Covid-19, the Surviving Sepsis Campaign recommends low-dose glucocorticoids (hydrocortisone at a dose of 200 mg daily by means of infusion or with intermittent dosing).18
Other immunomodulating agents currently being evaluated for severe Covid-19 include passive immunotherapy with convalescent plasma,56,57 intravenous immunoglobulin, and interleukin-1 and interleukin-6 pathway inhibition.63 Pending results of randomized trials, the risks and benefits of these approaches are also unknown. Candidate therapies for Covid-19 warrant evaluation separately in patients with established severe disease and in those with milder illness to determine whether they reduce the risk of progression.10

Drugs targeting patients' immune systems, rather than the virus itself, could be key to recovery from severe cases of the disease, some researchers suggest.

Shawna Williams
Apr 21, 2020
, SAKKMESTERKE
Among the many outstanding questions about COVID-19 is how the same virus, SARS-CoV-2, can kill some patients and leave others unaware they were ever exposed. Clinical evidence combined with hints from laboratory research indicate that for at least some patients with severe cases, the primary danger comes from a runaway immune response that irreparably injures tissue, researchers say. Understanding the mechanisms behind that response could be key to finding a treatment for those patients.
It appears that after infection, the virus replicates itself inside a patient, leading to a disease phase where the immune system mounts an inflammatory response against the invader, says Charles Dela Cruz, a pulmonologist at Yale School of Medicine who is researching COVID-19. Then, in those patients who progress to severe disease, "potentially this inflammatory response is too much and hyper-inflames, causing a lot of side effects in terms of tissue damage and organ failure and things like that," he says.

That picture is backed up by early clinical reports that find elevated levels of biomarkers associated with inflammation, such as C-reactive protein. Some studies suggest certain patients with severe disease experience what's known as cytokine release syndrome, or a cytokine storm, meaning their immune cells ramp up the production of inflammation-driving cytokines to dangerously high levels.

In a preprint posted in February, for example, researchers in Guangzhou, China, reported that eight of 11 COVID-19 patients with severe acute respiratory distress syndrome had hallmarks of cytokine release syndrome, including fever, an increase in the numbers of CD4/CD8 T cells, and elevated levels of the cytokine IL-6. Similarly, a study of 150 COVID-19 patients in Wuhan found that those who died had significantly higher IL-6 levels than did those who were later released from the hospital. The authors suggest "cytokine storm syndrome" as a possible cause of death from the disease.

"Cytokine storm syndrome is this kind of an umbrella term for a variety of [physiological phenomena] named by different types of physicians for different types of diseases," explains Randy Cron, a rheumatologist at the University of Alabama at Birmingham whose research focuses on the phenomenon. For example, cytokine storms are known as macrophage activation syndrome when they occur as a result of inflammatory diseases, and cytokine release syndrome when they stem from CAR T cell therapy for leukemia.

In general, the onslaught of cytokines causes blood vessels to leak, allowing immune cells to get into organs, potentially driving organ failure. Cytokine storms can also cause blood clotting. In influenza infections, cytokine storms are also tied to abberrant glucose metabolism, researchers reported recently based on experiments in mice.

Doctors and researchers are scrambling to find therapies to stop the cytokine onslaught.

Cron suspects that the answer to why some patients with COVID-19 develop cytokine storms while others don't may be partly genetic. His own past research has identified genes that cause familial hemophagocytic lymphohistiocytosis, a rare autoimmune disease involving cytokine storms, when a person inherits two mutated copies. In analyses of patients' genes and work with cultured cells, he says, his group has found indications that just one mutated copy could cause macrophage activation syndrome if cells are exposed to a trigger such as an infection. He doesn't know of any current effort to look for such mutations in COVID-19 patients, but expects they will happen eventually. Some studies looking broadly for genetic variants associated with COVID-19 severity are already underway.

In the meantime, doctors and researchers are scrambling to find therapies to stop the cytokine onslaught. One possibility is tocilizumab, an antibody that binds to receptors for IL-6, inhibiting that cytokine's action. A recent case report from France found that two doses of the drug were associated with a marked improvement in symptoms of one COVID-19 patient, and trials of tocilizumab for the disease are happening now in multiple countries.

Another possibility is anakinra, a drug for rheumatoid arthritis and a condition known as neonatal-onset multisystem inflammatory disease that blocks receptors for the cytokine IL-1. Along with other drugs, anakinra is now being trialed as a COVID-19 treatment in separate studies in Greece, Belgium, and Italy. Baricitinib, a drug for rheumatoid arthritis that blocks enzymes that lead to cytokine release, is another drug for which multiple trials are planned.

Dousing the flames of fiery cell death

As clinicians try existing cytokine-blocking drugs against COVID-19, other researchers are looking for potential targets that would head off cytokine storms before they begin, says Dela Cruz. One candidate is a process known as pyroptosis (Greek for “fiery falling”), a form of cell death that often occurs as a result of infection and spurs cytokine production.

Akiko Iwasaki, an immunologist at Yale who sometimes collaborates with Dela Cruz, says the heightened levels of lactate dehydrogenase (LDH) some studies have reported in the blood of COVID-19 patients points toward pyroptosis as core to the disease. LDH is an enzyme common in the body that converts lactate to pyruvate and is released from cells during pyroptosis, or from tissue damage in general. In addition, she says, pyroptosis would explain elevated levels of two cytokines, IL-1β and IL-6, that have been associated with severe cases. “I’m just thinking this kind of smoldering, fiery death that’s happening inside the person is initiating the downstream cascade . . . that leads to [a] cytokine storm,” she says.

Unlike apoptosis, in which cells typically die quietly without inciting an immune response, pyroptosis is distinguished by the activation of protein complexes known as inflammasomes by pathogens, says Kate Fitzgerald, an immunologist at the University of Massachusetts Medical Center who studies inflammasomes. That activation sets off a chain of events that includes processing of IL-1 and other cytokines for release from the cell, and the formation of pores in the cell membrane that let out “danger signals” such as the cytokines and LDH. Eventually, the cell ruptures and dies. “It’s thought that this pyroptotic cell death is particularly important for exposing intracellular niches of bacteria,” she says, allowing those bacteria to be destroyed.

Based on the clinical evidence she’s seen, Fitzgerald says she thinks it may well be the case that pyroptosis gone awry could help explain severe COVID-19 cases, but it’s not yet proven. LDH, she notes, seems to be a nonspecific marker of tissue damage, so may not by itself point to pyroptosis. But inflammasome activation has been found during infections from other RNA viruses, such as influenza, and overall, “I think there’s a really good rationale to think that these pathways could be dysregulated in this disease,” she says.

Another piece of evidence that may point to pyroptosis in severe cases of COVID-19 comes from previous work on SARS-CoV-2’s close relative SARS-CoV, the coronavirus that caused the 2003 SARS outbreak. Two years ago, John Kehrl’s group at the National Institute of Allergy and Infectious Diseases reported that a genetic region called open reading frame 3a is critical for SARS-CoV’s ability to kill mice, and that the protein it codes for triggers the assembly of a type of inflammasome known as NLRP3, indicating that the protein may induce pyroptosis.

Working in shifts, one person to a room, his team is now working to understand SARS-CoV-2’s arsenal, including whether the protein from its open reading frame 3a acts in the same way as SARS-CoV’s does. “We would be surprised if it’s not doing many of the same things [in SARS-CoV-2] that that open reading frame did in the SARS virus,” he says. “But we obviously want to test that.”

There is an existing drug, disulfiram, that’s thought to inhibit the pore formation that occurs during pyroptosis. Although its approved use is to curb alcohol abuse, it’s also shown up in screens for drugs that could inhibit a key SARS-CoV-2 protein, and it’s been proposed for use in COVID-19 clinical trials. In addition, Fitzgerald notes, several companies have been developing inhibitors of the inflammasome NLRP3 with the goal of halting aberrant pyroptosis in other conditions, and she expects such drugs will be tried for COVID-19. “When you have too much

production of inflammatory mediators, that leads to tissue damage, damage to the lung in particular," she says. "And maybe if you can reverse that with patients who were really in these more severe stages of disease, you could improve their outcomes."
Keywords:
cell deathCOVID-19cytokine release syndromecytokine stormscytokinesimmune cellsimmune responseimmunologyinfectious diseaseinflammasomesinflammationinfluenzanecroptosisNewsSARS-CoV-2

NEWS RELEASE 11-JUN-2020
A novel mechanism that triggers a cellular immune response

The Cytokine Storm, target for the treatment of Covid 19 ARDS
While the pathogenicity of COVID-19 is complex, it is important to understand the role of inflammation in this disease. The virulence and pathogenicity (including acute respiratory distress syndrome) associated with SARS coronaviruses develops as the result of viral activation of cytoplasmic NLRP3 inflammasome. This inflammasome within activated (upregulated NFkB) macrophages and Th1 immune cells releases proinflammatory cytokines, namely IL-1B and IL-18, which dictate the pathogenic inflammation responsible for the virulence and symptoms of COVID-19.1

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❏ Highly pathogenic respiratory viruses, such as influenza A virus, have been associated with a cytokine storm that describes an uncontrolled pro-inflammatory cytokine response [38,39]. Cytokine storms also seem to be highly relevant for pathogenic human CoVs [40]. Contemporary investigations on SARS-CoV-2 strongly suggest the involvement of cytokine storm with disease severity [22]. COVID-19 mortality is associated with enhanced **IL-6** levels and consistent cell death, as measured by LDH release22. We showed that ATV and ATV/RTV decreased IL-6 release in SARS-CoV-2- infected human primary monocytes. Moreover, we also included in our analysis TNF-α, another hallmark of inflammation during respiratory virus infections [22,41]. Our results revealed that cellular mortality and cytokine storm-associated mediators were reduced after treatment with the repurposed antiretroviral drugs used in this study.

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- ❏ Hyperinflammatory shock in children during COVID-19 pandemic

The Science Underlying COVID-19: Implications for the Cardiovascular System
Peter P. Liu , Alice Blet, David Smyth, and Hongliang Li
15 Apr 2020

> Corona Virus Disease 2019 (COVID-19) pandemic has impacted health and economy worldwide on an unprecedented scale. Patients have diverse clinical outcomes, but those with pre-existing cardiovascular (CV) disease, hypertension, and related conditions incur disproportionately worse outcomes. The high infectivity of the SARS-CoV-2 virus is in part related to new mutations in the receptor binding domain, and acquisition of a furin cleavage site in the S spike protein. The continued viral shedding in the asymptomatic and pre-symptomatic individuals enhances its community transmission.

The virus uses the ACE2 receptor for internalization, aided by TMPRSS2 protease. The tissue localization of the receptors correlates with COVDI-19 presenting symptoms and organ dysfunction. Virus-induced ACE2 down regulation may attenuate its function, diminish its anti-inflammatory role, and heightened angiotensin II effects in the predisposed patients.

Lymphopenia occurs early and is prognostic, potentially associated with reduction of the **CD4+ and some CD8+ T cells.** This leads to imbalance of the innate/acquired immune response, delayed viral clearance, and hyper stimulated macrophages and neutrophils. Appropriate type I interferon pathway activation is critical for virus attenuation, and balanced immune response. Persistent immune activation in predisposed patients, such as the elderly and those with CV risk, can lead to hemophagocytosis like syndrome, with uncontrolled amplification of cytokine production, leading to multi-organ failure and death.

In addition to the airways and lungs, the cardiovascular system is often involved in COVID-19 early, reflected in the release of highly **sensitive troponin** and **natriuretic peptides**, which are all extremely prognostic, particularly in those showing continued rise, along with **cytokines such as IL-6**. Inflammation in the vascular system can result in diffuse microangiopathy with thrombosis. Inflammation in the myocardium can result in myocarditis, heart failure, cardiac arrhythmias, acute coronary syndrome, rapid deterioration and sudden death.

Aggressive support based on early prognostic indicators with expectant management can potentially improve recovery. Appropriate treatment for heart failure, arrhythmias, acute coronary syndrome and thrombosis remain important. Specific evidence based treatment strategies for COVID-19 will emerge with ongoing global collaboration on multiple approaches being evaluated. To protect the wider population, antibody testing and effective vaccines will be needed to make COVID-19 history.

Proinflammatory Cytokine Responses in Extra-Respiratory Tissues During Severe Influenza.
Short KR, Veeris R, Leijten LM, van den Brand JM, Jong VL, Stittelaar K, Osterhaus ADME, Andeweg A, van Riel D .J Infect Dis. 2017 Oct 17;216(7):829-833.

Severe influenza is often associated with disease manifestations outside the respiratory tract. While proinflammatory cytokines can be detected in the lungs and blood of infected patients, the role of extra-respiratory organs in the production of proinflammatory cytokines is unknown. Here, we show that both 2009 pandemic H1N1 influenza A (H1N1) virus and highly pathogenic avian influenza A (H5N1) virus induce expression of tumor necrosis factor α, interleukin-6, and interleukin-8 in the respiratory tract and central nervous system. In addition, H5N1 virus induced cytokines in the heart, pancreas, spleen, liver, and jejunum. Together, these data suggest that extra-respiratory tissues contribute to systemic cytokine responses, which may increase the severity of influenza.

Immunotherapeutic implications of IL-6 blockade for cytokine storm Tanaka, Toshio ; Narazaki, Masashi ; Kishimoto, Tadamitsu Immunotherapy, 0, 2016, Vol.8(8), p.959

For example Tanaka, Narazaki, and Kishimoto found that,

> **IL-6 contributes** to host defense against infections and tissue injuries. However, exaggerated, excessive synthesis of IL-6 while fighting environmental stress leads to an acute severe systemic inflammatory response known as 'cytokine storm', since high levels of IL-6 can activate the coagulation pathway and vascular endothelial cells but inhibit myocardial function. Remarkable beneficial effects of IL-6 blockade therapy using a humanized anti-IL-6 receptor antibody, tocilizumab were recently observed in patients with cytokine release syndrome complicated by T-cell engaged therapy. In this review we propose the possibility that IL-6 blockade may constitute a novel therapeutic strategy for other types of cytokine storm, such as the systemic inflammatory response syndrome including sepsis, macrophage activation syndrome and hemophagocytic lymphohistiocytosis.[16]

Hyperinflammatory states and cytokine storming, including elevated IL-6, has been reported in severe COVID-19 and were associated with increased mortality in patients in China [36]..

Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Zhou F, Tu T, Du R, et al. *Lancet* 2020; 395:1054–62.

A preprint (nonpeer reviewed) case series of 21 patients treated with **tocilizumab** between February 5 and 14, 2020 in China reported marked success, including rapid resolution of fever and C-reactive protein, decreased oxygen requirements, and resolution of lung opacities on computerized tomography imaging [46]

.

Effective treatment of severe COVID-19 patients with tocilizumab. Xu X, Han M, Li T, et al. *ChinaXiv* 2020;

Tocilizumab[21]

Tocilizumab is a humanized monoclonal antibody that inhibits both membrane-bound and soluble interleukin-6 (IL-6) receptors. Interleukin-6, which is secreted by monocytes and macrophages, is one of the main drivers of immunologic response and symptoms in patients with cytokine-release syndrome (CRS). Although tocilizumab was first approved by the FDA in 2010 for the treatment of rheumatoid arthritis, it has gained traction in recent years for treatment of patients with CRS following chimeric antigen receptor T-cell (CAR T) therapy as a corticosteroid-sparing agent [42]. Indeed, it received FDA approval for severe or life-threatening CAR T-associated CRS in 2017 due to its efficacy and safety profile.

The authors state the patients all had “routine treatment for a week” before tocilizumab, which was described as “standard care according to national treatment guidelines” including lopinavir, methylprednisolone, and other supportive care. All patients had IL-6 analyzed before

tocilizumab administration with a mean value of 132.38 ± 278.54 pg/mL (normal <7 pg/mL). It should be noted that in the United States, IL-6 monitoring is a send-out laboratory for most institutions with a turnaround time of 3–7 days. No adverse events were described in the Chinese cohort; however, long-term assessment was not done.

Test called the Ella ™ Cytokine Storm Panel to determine when someone infected with COVID-19 is entering a critical point in their disease. When patients take a turn for the worse, they are experiencing a burst in their body's immune response, particularly with a group of immune molecules called cytokines. This burst of cytokines, called cytokine release syndrome or a "cytokine storm," contributes to the severity of COVID-19, because the cytokines attack the patient's organs, which can be fatal in some cases.

- ❏ Anti–spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection

  Li Liu,1,2 Qiang Wei,3 Qingqing Lin,1 Jun Fang,1 Haibo Wang,1 Hauyee Kwok,1 Hangying Tang,1 Kenji Nishiura,1 Jie Peng,1 Zhiwu Tan,1 Tongjin Wu,1 Ka-Wai Cheung,1 Kwok-Hung Chan,1 Xavier Alvarez,4 Chuan Qin,3 Andrew Lackner,4 Stanley Perlman,5,6 Kwok-Yung Yuen,1 and Zhiwei Chen1,2 JCI Insight February 21, 2019 - More info

  During acute infection, monocytes/macrophages often display a phenotype of classically activated macrophages. These cells mediate host defenses against viruses and also promote lung injury by producing nitric oxide (NO); ROS; IL-1, IL-6, and IL-8; and TNF. Simultaneously, some macrophages may become alternatively activated, exerting antiinflammatory function and regulating wound healing by producing matrix metalloproteinases (MMPs), growth factors, and antiinflammatory cytokines, particularly TGF-β. When the pathogen or inflammatory stimulus is eliminated, proinflammatory macrophages diminish. The predominant macrophage population assumes a wound-healing phenotype. At the final recovery stage, macrophages show a regulatory/suppressive phenotype, secreting increased levels of IL-10, which facilitates the resolution of wound healing and restores homeostasis. When the wound-healing response is well organized and controlled, the inflammatory response resolves quickly, and normal tissue architecture is restored. Disturbances in wound-healing response can lead to uncontrolled production of inflammatory mediators, contributing to a state of persistent injury (9–11)

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Recent FOIA

US Marijuana Research Policy Violated International Law For Decades, DEA Lawsuit Memo Reveals April 29, 2020

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- ❏ Cannabinoids as novel anti-inflammatory drugs.

Nagarkatti P, Pandey R, Rieder SA, Hegde VL, Nagarkatti M.
Future Med Chem. 2009 Oct;1(7):1333-49. DOI: 10.4155/fmc.09.93. Review.
PMID: 20191092 Free PMC Article Future Med Chem. 2009 Oct;1(7):1333-49. doi: 10.4155/fmc.09.93.
Cannabinoids are a group of compounds that mediate their effects through cannabinoid receptors. The discovery of Δ9-tetrahydrocannabinol (THC) as the major psychoactive principle in marijuana, as well as the identification of cannabinoid receptors and their endogenous ligands, has led to a significant growth in research aimed at understanding the physiological functions of cannabinoids. Cannabinoid receptors include CB1, which is predominantly expressed in the brain, and CB2, which is primarily found on the cells of the immune system. The fact that both CB1 and CB2 receptors have been found on immune cells suggests that cannabinoids play an important role in the regulation of the immune system. Recent studies demonstrated that administration of THC into mice triggered marked apoptosis in T cells and dendritic cells, resulting in immunosuppression. In addition, several studies showed that cannabinoids downregulate cytokine and chemokine production and, in some models, upregulate T-regulatory cells (Tregs) as a mechanism to suppress inflammatory responses. The endocannabinoid system is also involved in immunoregulation. For example, the administration of endocannabinoids or use of inhibitors of enzymes that break down the endocannabinoids, led to immunosuppression and recovery from immune-mediated injury to organs such as the liver. Manipulation of endocannabinoids and/or use of exogenous cannabinoids in vivo can constitute a potent treatment modality against inflammatory disorders. This review will focus on the potential use of cannabinoids as a new class of anti-inflammatory agents against a number of inflammatory and autoimmune diseases that are primarily triggered by activated T cells or other cellular immune components.
PMID: 20191092 PMCID: PMC2828614 DOI: 10.4155/fmc.09.93

- Into the Eye of the Cytokine Storm
  Jennifer R. Tisoncik,a Marcus J. Korth,a Cameron P. Simmons,b Jeremy Farrar,b Thomas R. Martin,c and Michael G. Katze⊠a
  We also address evidence for and against the role of the cytokine storm in the pathology of clinical and infectious disease and discuss why it has been so difficult to use knowledge of the cytokine storm and immunomodulatory therapies to improve the clinical outcomes for patients with severe acute infections. Microbiol Mol Biol Rev. 2012 Mar; 76(1): 16–32. doi: 10.1128/MMBR.05015-11'

- Anti–spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection
  Li Liu,1,2 Qiang Wei,3 Qingqing Lin,1 Jun Fang,1 Haibo Wang,1 Hauyee Kwok,1 Hangying Tang,1 Kenji Nishiura,1 Jie Peng,1 Zhiwu Tan,1 Tongjin Wu,1 Ka-Wai

Cheung,1 Kwok-Hung Chan,1 Xavier Alvarez,4 Chuan Qin,3 Andrew Lackner,4 Stanley Perlman,5,6 Kwok-Yung Yuen,1 and Zhiwei Chen1,2 JCI Insight February 21, 2019 - More info

During acute infection, monocytes/macrophages often display a phenotype of classically activated macrophages. These cells mediate host defenses against viruses and also promote lung injury by producing nitric oxide (NO); ROS; IL-1, IL-6, and IL-8; and TNF. Simultaneously, some macrophages may become alternatively activated, exerting antiinflammatory function and regulating wound healing by producing matrix metalloproteinases (MMPs), growth factors, and antiinflammatory cytokines, particularly TGF-β. When the pathogen or inflammatory stimulus is eliminated, proinflammatory macrophages diminish. The predominant macrophage population assumes a wound-healing phenotype. At the final recovery stage, macrophages show a regulatory/suppressive phenotype, secreting increased levels of IL-10, which facilitates the resolution of wound healing and restores homeostasis. When the wound-healing response is well organized and controlled, the inflammatory response resolves quickly, and normal tissue architecture is restored. Disturbances in wound-healing response can lead to uncontrolled production of inflammatory mediators, contributing to a state of persistent injury (9–11) J Infect Dis. 2017 Oct 17;216(7):829-833. doi: 10.1093/infdis/jix281.

- Proinflammatory Cytokine Responses in Extra-Respiratory Tissues During Severe Influenza.
  Short KR1,2, Veeris R1, Leijten LM1, van den Brand JM1, Jong VL1,3, Stittelaar K4, Osterhaus ADME1,5, Andeweg A1, van Riel D1. Author information
  Abstract
  Severe influenza is often associated with disease manifestations outside the respiratory tract. While proinflammatory cytokines can be detected in the lungs and blood of infected patients, the role of extra-respiratory organs in the production of proinflammatory cytokines is unknown. Here, we show that both 2009 pandemic H1N1 influenza A (H1N1) virus and highly pathogenic avian influenza A (H5N1) virus induce expression of tumor necrosis factor α, interleukin-6, and interleukin-8 in the respiratory tract and central nervous system. In addition, H5N1 virus induced cytokines in the heart, pancreas, spleen, liver, and jejunum. Together, these data suggest that extra-respiratory tissues contribute to systemic cytokine responses, which may increase the severity of influenza.

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Mobile and pervasive computing technologies and the future of Alzheimer's clinical trials

Brad Moore on the impact of artificial intelligence in the medicinal marijuana market

No PhDs needed: how citizen science is transforming research 23 October 2018
Projects that recruit the public are getting more ambitious and diverse, but the field faces some growing pains.

Addressing the challenge of cannabis research: Recommendations to Support and Improve The push to legalize marijuana may overtake research on medical benefits.
By SARAH OWERMOHLE 12/25/2018

The research, policy and political challenges associated with research of cannabis
NIH Staci Gruber

Cannabis bombshell: Pa. throws out all 8 marijuana research applications. What's next?
by Sam Wood, December 5, 2018

Mr. M. is an 80 YO male resident of a retirement community

Opportunity lost
http://nationalacademies.org/hmd/Activities/PublicHealth/MarijuanaHealthEffects/2017-Feb-21/Videos/Welcome-Overview/1-Welcome-Video.aspx

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- Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19)
  A Review James M. Sanders, PhD, PharmD[1,2]; Marguerite L. Monogue, PharmD[1,2]; Tomasz Z. Jodlowski, PharmD[3]; et al April 13, 2020

Anticytokine or Immunomodulatory Agents
Monoclonal antibodies directed against key inflammatory cytokines or other aspects of the innate immune response represent another potential class of adjunctive therapies for COVID-19. The rationale for their use is that the underlying pathophysiology of significant organ damage in the lungs and other organs is caused by an amplified immune response and cytokine release, or "cytokine storm."79 IL-6 appears to be a key driver of this dysregulated inflammation based on early case series from China.80 Thus, monoclonal antibodies against IL-6 could theoretically dampen this process and improve clinical outcomes. Tocilizumab, a monoclonal antibody IL-6 receptor antagonist, is FDA approved to treat RA and cytokine release syndrome following chimeric antigen receptor T-cell therapy. Given this experience, tocilizumab has been

used in small series of severe COVID-19 cases with early reports of success. A report of 21 patients with COVID-19 showed receipt of tocilizumab, 400 mg, was associated with clinical improvement in 91% of patients as measured by improved respiratory function, rapid defervescence, and successful discharge, with most patients only receiving 1 dose.35 The lack of a comparator group limits the interpretation of the drug-specific effect and warrants caution until more rigorous data are available. Several RCTs of tocilizumab, alone or in combination, in patients with COVID-19 with severe pneumonia are underway in China (NCT04310228, ChiCTR200002976), and it is included in the current Chinese national treatment guidelines.12

Sarilumab, another IL-6 receptor antagonist approved for RA, is being studied in a multicenter, double-blind, phase 2/3 trial for hospitalized patients with severe COVID-19 (NCT04315298).81 Other monoclonal antibody or immunomodulatory agents in clinical trials in China or available for expanded access in the US include bevacizumab (anti–vascular endothelial growth factor medication; NCT04275414), fingolimod (immunomodulator approved for multiple sclerosis; NCT04280588), and eculizumab (antibody inhibiting terminal complement; NCT04288713).40

Dysregulation of immune response in patients with COVID-19 in Wuhan, China
The novel coronavirus might mainly act on lymphocytes, especially T lymphocytes. Surveillance of NLR and lymphocyte subsets is helpful in the early screening of critical illness, diagnosis and treatment of COVID-19.

Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients In this retrospective analysis of 11 critically ill pneumonia patients infected with COVID-19, we defined and identified eight patients (72.7%) with cytokine release syndrome-like (CRSL). We found that a large area of lung injury (≥50%) with an decrease of CD4, CD8 (Lower than 50% minimum normal range) and increase of IL-6 in All rights reserved. No reuse allowed without permission. author/funder, who has granted medRxiv a license to display the preprint in perpetuity.The peripheral blood was the highest risk factor of CRSL. IL-6 was a early indicators of CRSL in COVID-19-infected pneumonia. We also found that reduce injury to the lung is a useful method to prevent and improve COVID-19-infected pneumonia-related CRSL in critically ill pneumonia patients.
medRxiv 2020.02.16.20023671; doi: https://doi.org/10.1101/2020.02.16.20023671
cytokine release syndrome-like (CRSL)

The Potential Role of IL-6 in Monitoring Coronavirus Disease 2019

Conclusion: On admission, the baseline level of IL-6, CRP, LDH and ferritin was closely related to the severity of COVID-19, and the high level of IL-6 was significantly related to the clinical manifestation of severe type patients. The decrease of IL-6 was closely related to treatment effectiveness, while the increase of IL-6 indicated disease progression. Collectively, the dynamic change of IL-6 level can be used as a marker for disease monitoring in patients with severe COVID-19.

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) Mervyn Singer, MD, FRCP[1]; Clifford S. Deutschman, MD, MS[2]; Christopher Warren Seymour, MD, MSc[3]; et al February 23, 2016

Proinflammatory Cytokine Responses in Extra-Respiratory Tissues During Severe Influenza. Short KR1,2, Veeris R1, Leijten LM1, van den Brand JM1, Jong VL1,3, Stittelaar K4, Osterhaus ADME1,5, Andeweg A1, van Riel D1.J Infect Dis. 2017 Oct 17;216(7):829-833. doi: 10.1093/infdis/jix281. Severe influenza is often associated with disease manifestations outside the respiratory tract. While proinflammatory cytokines can be detected in the lungs and blood of infected patients, the role of extra-respiratory organs in the production of proinflammatory cytokines is unknown. Here, we show that both 2009 pandemic H1N1 influenza A (H1N1) virus and highly pathogenic avian influenza A (H5N1) virus induce expression of tumor necrosis factor α, interleukin-6, and interleukin-8 in the respiratory tract and central nervous system. In addition, H5N1 virus induced cytokines in the heart, pancreas, spleen, liver, and jejunum. Together, these data suggest that extra-respiratory tissues contribute to systemic cytokine responses, which may increase the severity of influenza.

S.-L. Puhl, Cannabinoid-sensitive receptors in cardiac health and disease, BBA - Molecular Cell Research, https://doi.org/10.1016/j.bbamcr.2019.03.009

The CB2 receptor and its role as a regulator of inflammation Caroline Turcotte, Marie-Renée Blanchet, Michel Laviolette, and Nicolas Flamand Cell Mol Life Sci. 2016; 73(23): 4449–4470

> In light of the evidence that was generated over the past two decades by the scientific community, we can draw a few general conclusions regarding the role of the CB2 receptor. First, it is mainly found in immune tissues and is expressed in most immune cell types. Second, its deletion in animals usually causes an exacerbated inflammatory phenotype in several models, due to an upregulation of immune cell functions. Third, CB2 activation by cannabinoids, either in vitro or in vivo, usually decreases inflammatory cell activation. Finally, the administration of CB2 agonists in animal models of inflammatory disease can slow the progression of some diseases, in addition to reducing inflammation.

Infection and immune response in the elderly Smith, Philip W ; Roccaforte, Jane S ; Daly, Pamela B Annals of Epidemiology, 1992, Vol.2(6), pp.813-822
Immunologic function in the elderly Immune parameter Age-related change References T-lymphocyte function Cell-mediated immunity Serum antibody levels Antibody response to immunization or infection Complement activity White blood cell activity Febrile response to infection Decreased I,2 Decreased 384 Variable 5 Decreased 637 Stable 5 Stable 58 Decreased 9

The Endocannabinoid System as an Emerging Target of Pharmacotherapy

Impact of Cannabis, Canna**binoids, and Endocannabinoids in the Lungs.**
Turcotte C1, Blanchet MR1, Laviolette M1, Flamand N1.
Front Pharmacol. 2016 Sep 15;7:317. eCollection 2016.

Abstract
Since the identification of cannabinoid receptors in the 1990s, a research field has been dedicated to exploring the role of the cannabinoid system in immunity and the inflammatory response in human tissues and animal models. Although the cannabinoid system is present and crucial in many human tissues, studying the impact of cannabinoids on the lungs is particularly relevant because of their contact with exogenous cannabinoids in the context of marijuana consumption. In the past two decades, the scientific community has gathered a large body of evidence supporting that the activation of the cannabinoid system alleviates pain and reduces inflammation. In the context of lung inflammation, exogenous and endogenous cannabinoids have shown therapeutic potential because of their inhibitory effects on immune cell recruitment and functions. On the other hand, cannabinoids were shown to be deleterious to lung function and to impact respiratory pathogen clearance. In this review, we present the existing data on the regulation of lung immunity and inflammation by phytocannabinoids, synthetic cannabinoids and endocannabinoids.

Endocannabinoid System in the Airways. Bozkurt TE. Molecules. 2019 Dec 17;24(24).

> Cannabinoids and the mammalian endocannabinoid system is an important research area of interest and attracted many researchers because of their widespread biological effects. The significant immune-modulatory role of cannabinoids has suggested their therapeutic use in several inflammatory conditions. Airways are prone to environmental irritants and stimulants, and increased inflammation is an important process in most of the respiratory diseases. Therefore, the main strategies for treating airway diseases are suppression of inflammation and producing bronchodilation. The ability of cannabinoids to induce bronchodilation and modify inflammation indicates their importance for airway physiology and pathologies. In this review, the contribution of cannabinoids and the endocannabinoid system in the airways are discussed, and the existing data for their therapeutic use in airway diseases are presented.[16.1]

> Therefore, appropriate cannabinoid receptor ligands may be rational candidates for the treatment of airway diseases because of their anti-inflammatory and bronchodilatory effects.[16.1]

Cell	Normal Response	Cytokine Storm	Cannabinoid Receptors	Cannabinoid action
T-lymphocytes				
B-lymphocyte				
Macrophages				
Natural killer cells				
Tumor necrosis factor–α (TNF-α)				
IL-1α and IL-1β	Proinflammatory cytokines that mediate the host response to infection through both direct and indirect mechanisms (41).			

IL-1β, IL-6, TNF-α, IL-8, and IL-10

Major types and actions of cytokines

Type	Actions
Interferons	Regulation of innate immunity, activation of antiviral properties, antiproliferative effects
Interleukins	Growth and differentiation of leukocytes; many are proinflammatory
Chemokines	Control of chemotaxis, leukocyte recruitment; many are proinflammatory
Colony-stimulating factors	Stimulation of hematopoietic progenitor cell proliferation and differentiation
Tumor necrosis factor	Proinflammatory, activates cytotoxic T lymphocytes

TNF-α is a pleiotropic cytokine, with a wide range of functions: homeostatic, immune, and inflammatory. The beneficial homeostatic functions of TNF-α include defense against pathogens, development of lymphoid organ architecture, resolution of inflammation, tissue regeneration, immune regulation, and inhibition of tumor growth. The pathogenic functions of TNF-α comprise triggering of inflammation, stimulation of vascular endothelium, proliferation of immune cells, and tissue damage [3, 4]. Under physiological conditions, macrophages, lymphocytes (T and B), natural killer cells, dendritic cells, and monocytes produce TNF-α in the periphery [5], while in the CNS TNF-α is produced mainly by migroglia, neurons, and astrocytes [4–7].

Effect of cannabinoids on cytokine and chemokine production[5]

Cannabinoid	Receptor	Cell/tissue/serum	Effect	Ref.

THC	ND	Macrophage cell line (RAW264.7)	Decreases TNF-α	[40]
THC	ND	Peritoneal macrophages	Increases IL-1α and IL-1β	[41]
THC	ND	Human cell lines	Decreases TNF-α, GM-CSF and IFN-γ, IL-10 Increases IL-8	[26]
THC	CB1 and CB2 independent	Rat microglial cells	Decreases TNF-α, IL-1α, IL-1β and IL-6	[28]
In vivo WIN55,212-2 and HU-210	CB1 dependent	Serum	Decreases TNF-α, IL-12 Increases IL-10	[29]
Ajulemic acid	ND	Human synovial monocyte-derived macrophage	Decreases IL-6 and IL-1β	[32]
HU-308	CB2 dependent	Serum and liver homogenates	Decreases TNF-α, MIP-1α and MIP-2	[33]
CP55,940 WIN55,212–2	CB1 and CB2 independent	Rheumatoid fibroblast-like synoviocytes	IL-6 and IL-8	[34]
2-AG	CB2 dependent	Promyelocytic leukemia cell line (HL-60)	Increases IL-8, CXCL8 and CCL2	[37]

AG: Arachidonoylglycerol; CB: Cannabinoid receptor; CCL: CC-chemokine ligand; CXCL8: CXC-chemokine ligand 8; ND: Not determined; THC: Tetrahydrocannabinol.

Dronabinol (marinol) is the principal psychoactive constituent enantiomer form, (−)-trans-Δ⁹-tetrahydrocannabinol, found in cannabis.[5] Dronabinol does not include any other tetrahydrocannabinol (THC) isomers or any cannabidiol.

Delta-9-tetrahydrocannabinol suppresses tumor necrosis factor alpha maturation and secretion but not its transcription in mouse macrophages.
Zheng ZM1, Specter SC. Author information
Abstract
Various in vitro studies have shown that **delta-9-tetrahydrocannabinol (THC), the major psychoactive component of marijuana, has a variety of inhibitory effects on immune functions including effects on macrophages.** The present studies have examined the mechanism of THC's effects on tumor necrosis factor alpha (TNF-alpha), a major macrophage-produced cytokine and an important mediator involved in cytokine networks and in host defense mechanisms. Exposure of macrophages to medium containing THC has resulted in low levels of soluble TNF-alpha protein and reduced TNF-alpha bioactivity in the culture supernatant. However, THC did not inhibit the levels of LPS-induced TNF-alpha mRNA and intracellular TNF-alpha precursor protein, had only a weak effect on expression of membrane-bound TNF-alpha, but suppressed TNF-alpha maturation/secretion by macrophages. The higher the THC concentration in the medium during TNF-alpha induction, the greater the amount of intracellular TNF-alpha precursors that accumulated in the activated macrophages and the less mature TNF-alpha was released from the cells. Data suggest that TNF-alpha production by macrophages was altered greatly by exposure to THC at the levels of TNF-alpha precursor maturation and secretion.

- Published: January 2005

Cannabinoids in Models of Chronic Inflammatory Conditions Raphael Mechoulam, Percy F. Sumariwalla, Marc Feldmann & Ruth Gallily Phytochemistry Reviews
These results suggest that CBD and HU-320 hold promise as potential novel anti-inflammatory agents.
Sir Feldmann, 2014 Canada Gairdner International Awardee, talks about his research on anti-TNF therapy and it's applications for patients with rheumatoid arthritis and other inflammatory diseases.

*Marc Feldmann, marc.feldmann@kennedy.ox.ac.uk Kennedy Institute of Rheumatology, Nuffield Depart
Age and sexual determined immune function

Sexual-dimorphism in human immune system aging Nature 06 February 2020
“Unexpectedly, genomic differences between sexes increase after age 65, with men having higher innate and pro-inflammatory activity and lower adaptive activity. Impact of age and sex on immune phenotypes can be visualized at https://immune-aging.jax.org to provide insights into future studies.”

Tumor necrosis factor alpha - Wikipedia
en.wikipedia.org › wiki › Tumor_necrosis_factor_alpha
Tumor necrosis factor is a cell signaling protein (cytokine) involved in systemic inflammation and is one of the cytokines that make up the acute phase reaction.

THC regulates TNF-alpha

THC upregulates TNF-alpha
Positive_regulation(C: THC, T: TNF-alpha)
Confidence: Very high
It was found that THC suppressed IL-12, IL-15 and IL-6 and increased IL-1 alpha, IL-1 beta, and TNF alpha in all of the stimulated cultures. Described in 1 sentence

THC downregulates TNF-alpha
Negative_regulation(C: THC, T: TNF-alpha)
Confidence: High
WIN 55,212-2 and delta9-THC induced a concentration-dependent decrease in TNF-alpha level in the bronchoalveolar lavage fluid (BALF) (maximum inhibition 52.7% and 36.9% for intranasal doses of 750 nmol x kg(-1) and 2.65 mmol x kg(-1), respectively). Described in 2 sentences

THC regulates TNF-alpha expression
Regulation(C: THC, T: Gene_expression(T: TNF-alpha))
Confidence: Average
To examine the effects of THC on TNF-alpha and IL-1beta gene expression at the transcriptional level, RT-PCR was performed in the LPS-stimulated BV2 microglial cells. Described in 2 sentences

THC downregulates TNF-alpha expression
Negative_regulation(C: THC, T: Gene_expression(T: TNF-alpha))
Confidence: Low
The present study clearly showed that THC suppresses LPS-induced expression of TNF-alpha and IL-1beta and their extracellular release. Described in 4 sentences

THC upregulates TNF-alpha localization
Positive_regulation(C: THC, T: Localization(T: TNF-alpha))
Confidence: Low
With regard to NC function, neither the cytotoxic activity of the cells nor release of tumor necrosis factor was interrupted by THC. Described in 1 sentence

Showing 1 to 5 of 5 entries
FirstPrevious1NextLast

CBD regulates TNF-alpha

CBD downregulates TNF-alpha expression
Negative_regulation(C: CBD, T: Gene_expression(T: TNF-alpha))
Confidence: Low
Our present finding that CBD blocked oxidative and nitrative stress, macrophage infiltration, TNF-alpha production, and prevented retinal neurodegeneration suggest that CBD represents novel therapeutics in the treatment of inflammation-mediated retinal damage. Described in 1 sentence

CBD downregulates TNF-alpha
Negative_regulation(C: CBD, T: TNF-alpha)
Confidence: Very low
Additionally, CBD is able to inhibit tumor necrosis factor-alpha (TNF-alpha) in its own right in a rodent model of rheumatoid arthritis (Malfait et al 2000). Described in 1 sentence

Impact of Cannabis, Canna**binoids, and Endocannabinoids in the Lungs.**
Turcotte C1, Blanchet MR1, Laviolette M1, Flamand N1.
Front Pharmacol. 2016 Sep 15;7:317. eCollection 2016.
Abstract
Since the identification of cannabinoid receptors in the 1990s, a research field has been dedicated to exploring the role of the cannabinoid system in immunity and the inflammatory response in human tissues and animal models. Although the cannabinoid system is present and crucial in many human tissues, studying the impact of cannabinoids on the lungs is particularly relevant because of their contact with exogenous cannabinoids in the context of marijuana consumption. In the past two decades, the scientific community has gathered a large body of evidence supporting that the activation of the cannabinoid system alleviates pain and reduces inflammation. In the context of lung inflammation, exogenous and endogenous cannabinoids have shown therapeutic potential because of their inhibitory effects on immune cell recruitment and functions. On the other hand, cannabinoids were shown to be deleterious to lung function and to impact respiratory pathogen clearance. In this review, we present the existing data on the regulation of lung immunity and inflammation by phytocannabinoids, synthetic cannabinoids and endocannabinoids.

Cannabinoids and the immune system: an overview. Immunobiology. 2010 Aug;215(8):588-97. doi: 10.1016/j.imbio.2009.12.005. Epub 2010 Jan 4.
Tanasescu R1, Constantinescu CS.
Author information
Abstract
Cannabinoids can influence the immune network. Data on the impact of exogenous cannabinoid ligands on immune function serve not only to understand how the endocannabinoid system modulates immune phenomena associated with infection or inflammation, but also to identify therapeutic targets for immune diseases. Cannabinoids can modulate immune reactions in the

periphery but also in the brain, influence T cell subset balance and cytokine expression and play a role in the balance between neuroinflammation and neurodegeneration. Immune cells can synthesize endocannabinoids and also be influenced by cannabinoid analogues. Cannabinoid receptors show different expression on immune cells depending on activation status and stimuli. The complexity of relation between cannabinoid ligands of various classes and cannabinoid receptors brought the need to refine the simple conceptual frame of agonist-antagonists and offered potential implications for understanding interactions in pathological conditions. The immune influence of cannabinoid ligands is not fully elucidated. However, aspects of their immunomodulatory effects provide the basis for a context-dependent targeted therapeutic approach, thus leading to the possibility for the use of cannabinoids in the treatment of inflammatory disease.

PMID: 20153077 DOI: 10.1016/j.imbio.2009.12.005

The endocannabinoid system: a revolving plate in neuro-immune interaction in health and disease. Tanasescu R1, Gran B, Constantinescu CS. Amino Acids. 2013 Jul;45(1):95-112. doi: 10.1007/s00726-012-1252-8. Epub 2012 Feb 26.
Author information
Abstract
Studies of the last 40 years have brought to light an important physiological network, the endocannabinoid system. Endogenous and exogenous cannabinoids mediate their effects through the activation of specific cannabinoid receptors. This modulatory homoeostatic system operates in the regulation of brain function and also in the periphery. The cannabinoid system has been shown to be involved in regulating the immune system. Studies examining the effect of cannabinoid-based drugs on immunity have shown that many cellular and cytokine mechanisms are modulated by these agents, thus raising the hypothesis that these compounds may be of value in the management of chronic inflammatory diseases. The special properties of endocannabinoids as neurotransmitters, their pleiotropic effects and the impact on immune function show that the endocannabinoid system represents a revolving plate of neural and immune interactions. In this paper, we outline current information on immune effects of cannabinoids in health and disease.

.Cannabinoids, endocannabinoids, and related analogs in inflammation.
Burstein SH1, Zurier RB. AAPS J. 2009 Mar;11(1):109-19. doi: 10.1208/s12248-009-9084-5. Epub 2009 Feb 6
Author information
Abstract
This review covers reports published in the last 5 years on the anti-inflammatory activities of all classes of cannabinoids, including phytocannabinoids such as tetrahydrocannabinol and cannabidiol, synthetic analogs such as ajulemic acid and nabilone, the endogenous

cannabinoids anandamide and related compounds, namely, the elmiric acids, and finally, noncannabinoid components of Cannabis that show anti-inflammatory action. It is intended to be an update on the topic of the involvement of cannabinoids in the process of inflammation. A possible mechanism for these actions is suggested involving increased production of eicosanoids that promote the resolution of inflammation. This differentiates these cannabinoids from cyclooxygenase-2 inhibitors that suppress the synthesis of eicosanoids that promote the induction of the inflammatory process.
PMID: 19199042 PMCID: PMC2664885 DOI: 10.1208/s12248-009-9084-5

Immunoactive effects of cannabinoids: considerations for the therapeutic use of cannabinoid receptor agonists and antagonists.
Greineisen WE, Turner H.
Int Immunopharmacol. 2010 May;10(5):547-55. doi: 10.1016/j.intimp.2010.02.012. Epub 2010 Feb 25. Review.
PMID: 20219697 Free PMC Article

Immunoregulatory Role of Cannabinoids during Infectious Disease.
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Effects of marijuana smoking on pulmonary function and respiratory complications: A systematic review. Tetrault, J. M., K. Crothers, B. A. Moore, R. Mehra, J. Concato, and D. A. Fiellin. 2007. Archives of Internal Medicine 167:221–228.

Delta 9-tetrahydrocannabinol treatment suppresses immunity and early IFN-gamma, IL-12, and IL-12 receptor beta 2 responses to Legionella pneumophila infection.
Klein TW1, Newton CA, Nakachi N, Friedman H.
Author information

Abstract
The marijuana cannabinoid, delta 9-tetrahydrocannabinol (THC), suppresses immunity to Legionella pneumophila and development of Th1 activity and cell-mediated immunity. In the current study, THC effects on cytokines regulating the development of Th1 cells were examined. BALB/c mice showed significant increases in serum IL-12 and IFN-gamma within hours of infection; however, the levels of these Th1-promoting cytokines as well as resistance to a challenge infection were suppressed by THC (8 mg/kg) injected 18 h before priming. The Th2-promoting cytokine, IL-4, was increased within hours of a Legionella infection and was further increased by THC treatment. These results suggested that THC injection suppressed the cytokine environment promoting Th1 immunity. In additional experiments, THC pretreatment and infection of IL-4 knockout mice showed that serum IL-12 and IFN-gamma were suppressed equally in both knockout and normal mice. This suggested that the drug-induced increase in IL-4 was not responsible for the decreases in serum IL-12 and IFN-gamma. However, THC treatment was shown to suppress the expression of IL-12 receptor beta 2 mRNA, indicating that, in addition to suppression of IL-12, THC injection suppressed the expression of IL-12 receptors. Finally, the role of cannabinoid receptors in Th1-promoting cytokine suppression was examined, and results with receptor antagonists showed that both cannabinoid receptors 1 and 2 were involved. It is suggested that suppression of Th1 immunity to Legionella is not due to an increase in IL-4 production but to a decrease in IFN-gamma and IL-12. Furthermore, both types of cannabinoid receptors are involved.

Popular Media
The Coronavirus Patients Betrayed by Their Own Immune Systems NYTimes 4/1/2020 By Apoorva Mandavilli
A “cytokine storm” becomes an all-too-frequent phenomenon, particularly among the young. But treatments are being tested.

Modulation of Airway Responses to Influenza A/PR/8/34 by Δ9-Tetrahydrocannabinol in C57BL/6 Mice
John P. Buchweitz, Peer W. F. Karmaus, Jack R. Harkema, Kurt J. Williams and Norbert E. Kaminski

“Likewise, the magnitude of inflammation and virus-induced mucous cell metaplasia, as assessed by histopathology, was reduced in Δ9-THC-treated mice by 10 dpi. Collectively, these results suggest that Δ9-THC treatment increased viral load, as assessed by H1 mRNA levels, through a decrease in recruitment of macrophages and lymphocytes, particularly CD4+ and CD8+ T cells, to the lung.”

Unraveling the complexities of cannabinoid receptor 2 (CB2) immune regulation in health and disease Sreemanti Basu & Bonnie N. Dittel

It has become clear that the endocannabinoid system is a potent regulator of immune responses, with the cannabinoid receptor 2 (CB2) as the key component due to its high expression by all immune subtypes. CB2 has been shown to regulate immunity by a number of mechanisms including development, migration, proliferation, and effector functions. In addition, CB2 has been shown to modulate the function of all immune cell types examined to date. CB2 is a Gi-protein-coupled receptor and thus exhibits a complex pharmacology allowing both stimulatory and inhibitory signaling that depends on receptor expression levels, ligand concentration, and cell lineage specificities. Here, we discuss both in vitro and in vivo experimental evidence that CB2 is a potent regulator of immune responses making it a prime target for the treatment of inflammatory diseases.

Of particular interest is the role played by the endocannabinoid system in response to traumatic brain injury (TBI) and potentially acute cardiac inflammation triggered by preceding ischemia.

ACE2 Is the SARS-CoV-2 Receptor Required for Cell Entry, March 18, 2020
George Sakoulas, MD reviewing Hoffmann M et al. Cell 2020 Mar 5
The angiotensin-converting enzyme 2 is the receptor required for cellular entry of COVID-19, consistent with the epidemiologic risk for severe disease seen in patients with cardiovascular disease and hypertension in China.
The COVID-19 pandemic is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which shares high amino-acid sequence homology with the SARS coronavirus that emerged in 2002. The surface unit (S1) of the spike (S) protein of SARS engages the angiotensin-converting enzyme 2 (ACE2) as the entry receptor and then uses the host serine protease TMPRSS2 for S priming, allowing fusion of viral and cellular membranes and viral entry into the cell. Researchers have now examined how the S protein from SARS-CoV-2 facilitates viral entry into target host cells and compare the process to that used by SARS.
They found that:

- The S proteins of SARS and SARS-2 mediate viral entry into a similar spectrum of cell lines.
- Like SARS, SARS-CoV-2 employs the same host-cell ACE2 as the receptor for cell entry.
- The host cell serine protease TMPRSS2 primes the S protein of SARS-CoV-2 for entry.
- The serine protease inhibitor camostat mesylate, available in Japan to treat chronic pancreatitis and reflux esophagitis, inhibits TMPRSS2 and partially blocks SARS-CoV-2 infection of lung epithelial cells.
- Antibodies against S1 from convalescent sera of SARS patients inhibited SARS-CoV-2 from infecting cultured cells.

COMMENT
Although offering a promising therapeutic and vaccine target against SARS-CoV-2, these new findings remind us that the viral pathogenesis of COVID-19 focuses on blood-pressure homeostasis mediated by the renin-angiotensin system (Future Virology 2010; 5:145). High risk for severe COVID-19 disease has been assumed to be driven largely by waning innate

immunity that comes with advanced age, but younger patients with cardiovascular disease or hypertension may have unappreciated risk (NEJM JW Infect Dis Mar 2020 and Lancet 2020; 395:565). Clinical studies are needed to help translate how the interaction of SARS-CoV-2 with the renin-angiotensin system can be harnessed therapeutically (Lancet Respir Med 2020 Mar 11; [e-pub] and Drug Dev Res 2020; Mar 4 [e-pub]).'

How doctors can significantly reduce the number of deaths from Covid-19

But during a storm, these cytokines are overproduced, which causes severe inflammation, high fever, and organ failure. In other words, it's not just a sluggish response to infections that can harm older adults; the immune system's overreaction to an invader can also kill, Leng said. "The cause of death of this virus is, No. 1, respiratory failure, and then No. 2, probably the cytokine storm." The good news, as two doctors at the University of Alabama Birmingham wrote for Vox, is that we have treatments for cytokine storm syndrome, which could help save a significant number of lives in this outbreak.

How doctors can potentially significantly reduce the number of deaths from Covid-19
Why Covid-19 is so dangerous for older adults

We already have medicines for treating cytokine storm syndrome, the immune response that's killing many who die of Covid-19.
By Randy Cron and W. Winn Chatham Mar 12, 2020, 3:20pm EDT

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UNITED STATES FOOD AND DRUG ADMINISTRATION PATHOGEN REDUCTION TECHNOLOGIES (PRT) FOR BLOOD SAFETY
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Keck Medicine studies anti-Inflammatory drug as COVID-19 treatment
9:10 PM CT on 5/7/2020

Physicians at Keck Medicine of USC are launching a clinical trial to evaluate the efficacy and safety of the anti-inflammatory drug baricitinib in treating COVID-19. It is used to treat rheumatoid arthritis.

Baricitinib has been shown to lower levels of a cytokine known as interleukin-6, as well as other cytokines. Some COVID-19 patients experience a “cytokine storm,” or overproduction of the small proteins in the body that help the immune system battle infection. The excess inflammation caused by that reaction causes tissue damage and organ failure.

Researchers plan to enroll 144 patients from Keck Hospital of USC, USC Verdugo Hills Hospital and Los Angeles County + USC Medical Center. The pharmaceutical company Eli Lilly and Company provided funding for this study.

But Lilly is hoping that a lower **price**-tag can give it an edge. The company is launching the drug with a wholesale acquisition **cost** of **$25,000 per yea**r, 60% below Humira's list **price** of $60,000 per year, said Lilly

Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed

With more than 81000 deaths worldwide from coronavirus disease 2019 (COVID-19) by April 8, 2020,[1] it is incumbent on researchers to accelerate clinical trials of any readily available and potentially acceptably safe therapies that could reduce the rising death toll. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) gains access to host cells via angiotensin-converting enzyme [2], which is expressed in the type II surfactant secreting alveolar cells of the lungs.[2] Severe COVID-19 is associated with a major immune inflammatory response with abundant neutrophils, lymphocytes, macrophages, and immune mediators. Which mediators are most important in driving the immune pathology remains to be elucidated. Deaths from COVID-19 are chiefly due to diffuse alveolar damage with pulmonary oedema, hyaline membrane formation, and interstitial mononuclear inflammatory infiltrate compatible with early-phase adult respiratory distress syndrome (ARDS).[3] Prevention of ARDS and death in patients with COVID-19 is a pressing health emergency. There is evidence of an inflammatory excess in patients with COVID-19. *Lung pathology in COVID-19 is characterised by capillary leakage of fluid and recruitment of immune-inflammatory lymphocytes, neutrophils, and macrophages,[6] implying a role for adhesion molecules, chemokines, and cytokines targeting vascular endothelium. Cytokine upregulation is documented in COVID-19.* ***In patients with COVID-19, there is upregulation of pro-inflammatory cytokines in the blood, including interleukin (IL)-1, IL-6, TNF, and interferon γ,7,8 and patients in intensive care units have increased concentrations of many cytokines.*** Initial reports comprising a trial of 21 severe and critical COVID-19 patients in China (ChiCTR2000029765) and a case study from France[9] of clinical benefit with the anti-IL6 receptor antibody[10] tocilizumab in COVID-19 suggest that cytokines are of importance in the “cytokine storm” and further controlled clinical trials are in progress.
Preliminary data from Salford Royal Hospital and the University of Manchester in the UK document the presence of proliferating excess monocytes expressing TNF by intracellular staining in patients with COVID-19 in intensive care (Hussell T, Grainger J, Menon M, Mann E, University of Manchester, Manchester, UK, personal communication). Available cytokine data on immunology and inflammation in COVID-19 are summarised in the appendix.

Anti-tumour necrosis factor (TNF) antibodies, have been used for more than 20 years in severe cases of autoimmune inflammatory disease such as rheumatoid arthritis, inflammatory bowel disease, or ankylosing spondylitis. (In the US millions of patients utilize state sponsored medical cannabis) There are ten (as reported on Sept 29, 2019) US Food and Drug Administration approved and four off-label indications for anti-TNF therapy,[4] indicating that TNF is a valid target in many inflammatory diseases. TNF is present in blood and disease tissues of patients with COVID-19[5] and TNF is important in nearly all acute inflammatory reactions, acting as an amplifier of inflammation.

We propose that anti-TNF therapy should be evaluated in patients with COVID-19 on hospital admission to prevent progression to needing intensive care support.

Although there are many potential drug candidates for reducing inflammation in COVID-19, only a few drugs such as the anti-TNF antibodies infliximab or adalimumab are potentially effective, widely available, and have a well established safety profile. The potential role of anti-TNF therapy thus warrants consideration. Preclinical studies suggest that the response to severe respiratory syncytial virus (RSV) and influenza in mice is ameliorated by anti-TNF therapy, which reduces weight loss, disease duration, and cell and fluid infiltrate.[11] This research suggests a potential rationale for use of anti-TNF therapy in viral pneumonia, especially given the known mechanism of action of TNF and the reversal of TNF-induced immunopathology by TNF blockade in multiple diseases. It is known TNF is produced in most types of inflammation, especially in the acute phase, and is important in the coordination and development of the inflammatory response. However, too much production of TNF for too long becomes immune suppressive.[12] Blockade of TNF alone is clinically effective in many circumstances and diseases, despite the presence of many other pro-inflammatory cytokines and mediators.

There is evidence of a “TNF dependent cytokine cascade” in rheumatoid arthritis tissue and upon bacterial challenge in baboons.[13,14] Thus, if TNF is blocked, there is a rapid (ie, <12 h) decrease of IL-6 and IL-1 concentrations in patients with active rheumatoid arthritis[15] and, importantly, a reduction of adhesion molecules and vascular endothelial growth factor, which is also known as vascular permeability factor, denoting its importance in capillary leak.[15–19] Furthermore, a reduction in leucocyte trafficking occurs in inflamed tissues of joints due to reduction in adhesion molecules and chemokines[20] with reduction in cell content and exudate. Finally, after anti-TNF infusion tissue TNF is reduced as it passes into the blood bound to the antiTNF antibody. Blood concentrations of immunoreactive, but biologically inactive, TNF increase more than ten times after infusion.[15] For these reasons it is possible that a single infusion of anti-TNF antibody might reduce some of the processes that occur during COVID-19 lung inflammation, reducing TNF and other inflammatory mediators, cellularity, and exudate. What would be the best time for intervention with antiTNF therapy in patients with COVID-19? We postulate that the earlier the better after hospital admission might be the answer because patients will already have initiated anti-viral immunity for several days. There is a balance to be struck between stage of intervention and ensuring patients are at sufficient risk of a poor outcome and can be appropriately monitored. We propose that initial assessment of anti-TNF therapy in clinical trials should be in patients with moderate disease admitted to hospital and who require oxygen support but not intensive care. If this treatment approach proved beneficial with a good safety profile, treatment in the community for people identified as being at high risk of progressing to hospital admission might be considered. The range of available formulations and administration routes of anti-TNF products could facilitate this treatment approach. Is there a trade-off between immunity and virus clearance? The use of powerful anti-inflammatory drugs in acute viral diseases has to be approached with caution because of the risk of increasing viral replication or bacterial infections. For lung viral infections, the higher the infectious dose, the greater the tissue damage from viral replication and the ensuing immune response. In animal models that resemble lung viral infection in humans, the immune response to the virus is so great that even a moderate reduction in inflammation is beneficial—eg, mice with severe pneumonia from RSV or influenza benefit from anti-TNF treatment without compromising viral

clearance[11] because more of the lung architecture is preserved. However, concerns about safety are important when considering new therapy. Would anti-TNF therapy increase the risk of bacterial or fungal super-infections? After respiratory viral infection, superinfections with other organisms occur at the most severe end of the disease spectrum. Many research groups have elucidated the mechanisms responsible[21] and anecdotal evidence suggests that bacteria might have a role in COVID-19,[5,22] although this remains to be confirmed. Bacteria gain a foothold faster in a lung that is damaged. Experimental studies suggest that if the duration of inflammation is limited, with its associated collateral lung damage, then bacterial superinfection is reduced.[23] There is concern that anti-TNF therapy might increase the risk of bacterial infection.24 Yet two randomised studies in critically unwell patients with septic shock[25,26] showed that monoclonal antiTNF therapy had good safety data with no evidence of increased secondary bacterial infections in the anti-TNF treated group. In an observational trial in rheumatoid arthritis patients with serious infections, the risk of sepsis and death was reduced in patients on TNF inhibitors compared with those on synthetic disease-modifying anti-rheumatic drugs (DMARDS).27 46 (11%) of 399 patients on TNF inhibitors developed sepsis after serious infection, of whom 20 (43%) died, compared with 74 (17%) of 444 patients on DMARDS who developed sepsis, of whom 54 (74%) died.[27] Paradoxically, another class of TNF inhibitor, a TNF-R2 Ig-Fc fusion protein, etanercept, was associated with moderately increased mortality in a randomised trial of this treatment for sepsis,[28] possibly due to its faster offrate for TNF potentially resulting in some redistribution and bioavailability of pathogenic TNF rather than its clearance.

There has been interest as to whether the safety of anti-TNF therapy in patients with COVID-19 might be gleaned from analysis of the course of COVID-19 in patients with inflammatory bowel disease (IBD) or rheumatoid arthritis who are already on anti-TNF treatment. As of April 6, 2020, on SECURE-IBD, a coronavirus and IBD reporting database with a register of outcomes of IBD patients with COVID-19, there were 116 patients on anti-TNF therapy alone, 99 of whom recovered without hospitalisation and one patient died. By contrast, about half of 71 patients on sulfasalazine/ mesalamine recovered without hospital admission and six patients died. Thus IBD patients with COVID-19 on anti-TNF therapy do not fare worse than those treated with other drugs, but there are insufficient data to make conclusions about a better outcome. We believe there is sufficient evidence to support clinical trials of anti-TNF therapy in patients with COVID-19. With an average of 2 days between hospital admission and ARDS,[7] we propose anti-TNF therapy should be initiated as early as is practicable. If there is preliminary evidence of benefit and safety of antiTNF therapy in hospitalised patients, we suggest consideration should be given to out of hospital treatment for patients with COVID-19 at high risk, such as older people and those with pre-existing conditions, and who can be monitored appropriately.

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