Post-COVID lung disease shares origins with other scarring lung disorders

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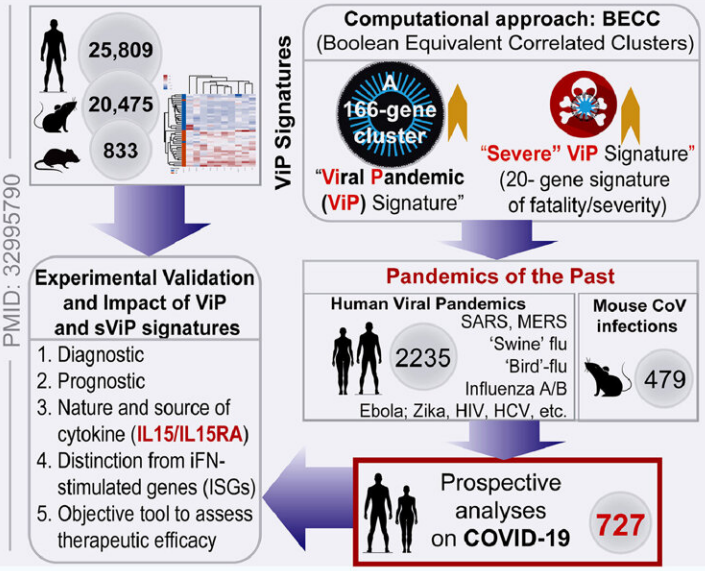
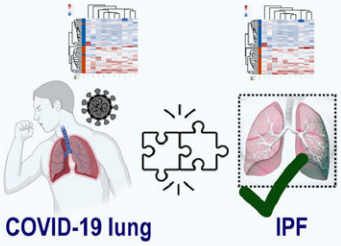
Step 0- DISCOVERY AND VALIDATION OF A SET OF SIGNATURES THAT CAPTURE THE INVARIANT HOST IMMUNE RESPONSE IN COVID-19

Artificial Intelligence- guided Discovery of Viral Pandemic (ViP) and severe ViP (sViP) Signatures.
PMID: 34127431

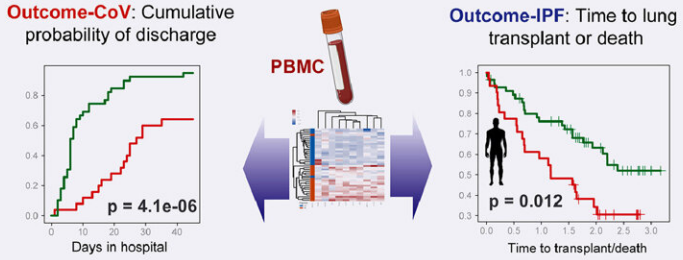


Step 1- COVID-19 LUNG DISEASE RESEMBLES IDIOPATHIC PULMONARY FIBROSIS

AI-enabled screening of numerous infectious, immune, granulomatous interstitial and neoplastic lung conditions against COVID-19 lungs.

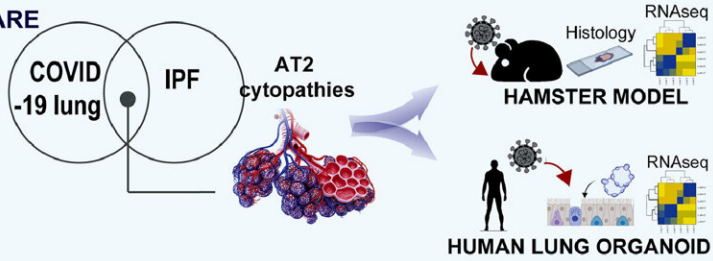


Step 2- PBMC-DERIVED SIGNATURES (sViP and IPF) PROGNOSTICATE OUTCOMES AND SHOW CROSS-OVER UTILITY IN BOTH COVID-19 and IPF



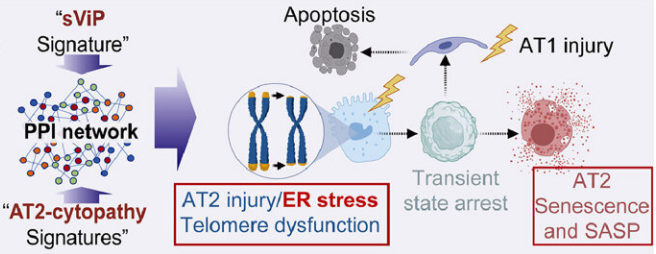
Step 3- BOTH COVID-19 lung and IPF SHARE DYSFUNCTIONAL CYTOPATHIC CHANGES IN ALVEOLAR TYPE II (AT2) PNEUMOCYTES

AT2 senescence
AT2 telomere dysfunction
Damage-associated transient progenitors (DATP)



Step 4- ALVEOLAR ER STRESS IS SUFFICIENT TO INDUCE VIP AND IPF SIGNATURES AND RECAPITULATE ALL AT2 CYTOPATHIES OBSERVED IN PCLD.

Mice with Tam-inducible *GRP78-/-* in AT2 cells.



Study design: Artificial Intelligence-guided navigation of COVID-19 lung disease. (From top to bottom) Step 0: Over 45,000 human, mouse, and rat gene expression databases were mined using machine learning tools called Boolean Equivalent Correlated Clusters (BECC133) to identify invariant host response to viral pandemics (ViP). In the absence of a sufficiently large number of COVID-19 datasets at the onset of the COVID-19 pandemic, these ViP signatures were trained on only two datasets from the pandemics of the past (Influenza and avian flu; GSE47963, n = 438; GSE113211, n = 118) and used without further training to prospectively analyze the samples from the current pandemic (i.e., COVID-19; n = 727 samples from diverse datasets). A subset of 20-genes classified disease severity called severe-ViP (sViP) signature. The ViP signatures appeared to capture the 'invariant' host response, i.e., the shared fundamental nature of the host immune response induced by all viral pandemics, including COVID-19. Step1: The set of ViP/sViP signatures and a CoV-lung specific13 gene signature was analyzed on diverse transcriptomic datasets representing a plethora of lung diseases; these efforts identified COVID-19 lung disease to be the closest to Idiopathic pulmonary fibrosis (IPF); both conditions induced a common array of gene signatures. Step 2: Clinically useful whole-blood and PBMC-derived prognostic signatures previously validated in IPF27 showed crossover efficacy in COVID-19, and vice versa. Step 3: Gene signatures of alveolar type II (AT2) cytopathic changes that are known to fuel IPF were analyzed in COVID-19 lung, and predicted shared features were validated in human and hamster lungs and lung-organoid derived models. Step 4: Protein-protein interaction (PPI) network built using sViP and AT2 cytopathy-related signatures was analyzed to pinpoint ER stress as a major shared feature in COVID-19 lung disease and IPF, which was subsequently validated in human and hamster lungs. Credit: *eBioMedicine* (2022). DOI: 10.1016/j.ebiom.2022.104185

While most people recover from COVID-19 within a week or two, up to one-third of survivors experience persistent or new symptoms weeks and months after initial infection.

One form of "long COVID" is interstitial lung disease (ILD), a group of chronic pulmonary disorders characterized by inflammation and scarring (fibrosis) that make it hard for the lungs to get enough oxygen. Little is currently known about ILD, from diagnosis to prognosis to management. In its most severe form, the disease is fatal without a lung transplant.

In a new study, published in the July 20, 2022 online issue of *eBioMedicine*, researchers at University of California San Diego provide the first insights into the fundamental cellular pathologies that drive ILD.

"Using an artificial intelligence (AI) approach, we found that lung fibrosis caused by COVID-19 resembles idiopathic pulmonary fibrosis (IPF), the most common and the deadliest form of ILD," said co-senior study author Pradipta Ghosh, MD, professor in the departments of Medicine and Cellular and Molecular Medicine at UC San Diego School of Medicine. "At a fundamental level, both conditions display similar gene expression patterns in the lungs and blood, and dysfunctional processes within alveolar type II (AT2) cells."

AT2 cells play several critical roles in pulmonary function, including the production of lung surfactant that keeps lung cells from collapsing after exhalation and regeneration of lung cells after injury.

"The findings are insightful because AT2 cells are known to contain an elegant quality control network that responds to stress, internal or external," said Ghosh. "Failure of quality control leads to broader organ dysfunction and, in this case, fibrotic remodeling of the lung."

To conduct their study, Ghosh collaborated with co-senior author Debashis Sahoo, Ph.D., associate professor in the departments of Computer Science, Engineering and Pediatrics at UC San Diego to access transdisciplinary approaches, such as AI-assisted "big data"

analysis.

Ghosh and Sahoo said the approach would help them stay unbiased in navigating the unknowns of an emerging, post-pandemic disease. They analyzed more than 1,000 human lung transcriptomic datasets associated with various lung conditions, specifically looking for gene expression patterns, inflammation signaling and cellular changes. The disease with the closest match: IPF.

The authors were able to successfully induce these tell-tale elements in human lung organoids, in a hamster model of COVID-19, and could confirm their presence in the lungs of deceased individuals with COVID-19. Key elements were also reversed in the hamsters using anti-SARS-COV-2 therapeutics. A deeper analysis pinpointed endoplasmic reticulum stress as the shared early trigger of both post-COVID lung disease and ILD.

Ghosh said the use of computational models to identify shared gene expression and cellular processes between COVID-19 and IPF suggests utility of our findings beyond the current pandemic.

"The insights, biomarkers, tools, mechanisms and promising therapeutic avenues identified here are likely to spur the development of therapies for patients with IPF and other fibrotic interstitial lung diseases, all of whom have limited or no treatment options."

IPF affects approximately 100,000 persons in the United States, with 30,000 to 40,000 new cases annually. The condition has a poor prognosis, with an estimated mean survival of 2 to 5 years from time of diagnosis.

More information: Saptarshi Sinha et al, COVID-19 lung disease shares driver AT2 cytopathic features with Idiopathic pulmonary

fibrosis, *eBioMedicine* (2022). DOI: 10.1016/j.ebiom.2022.104185