The PTP4A3 inhibitor KVX-053 reduces *Severe Acute Respiratory Syndrome Coronavirus* 2 (SARS-CoV-2) virulence, inflammation, and development of acute lung injury in K18-hACE2 mice

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Abstract

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has caused a global health crisis, marked by high transmissibility and virulence. Despite widespread vaccination efforts, effective treatments for COVID-19, particularly for severe cases leading to Acute Respiratory Distress Syndrome (ARDS), remain limited. This study investigates the efficacy of KVX-053, a protein tyrosine phosphatase type IVA (PTP4A3) small molecule inhibitor, in modulating SARS-CoV-2-induced inflammation and lung injury using in vitro cell models and in vivo K18-hACE2 transgenic mice. KVX-053 reduced in vitro pro-inflammatory cytokine expression, including TNFα, CXCL10, and CXCL11, without impacting viral replication or cell viability. K18-hACE2 mice treated with KVX-053 demonstrated marked improvement in clinical scores and reduced histological evidence of lung injury compared to untreated SARS CoV-2-infected controls. KVX-053 mitigated the activation of key inflammatory mediators in the lung, including NLRP3 inflammasomes, IL-6, and phosphorylated STAT3, effectively curbing the "cytokine storm" associated with severe COVID-19. Importantly, treatment preserved lung parenchymal integrity, reduced edema, and minimized macrophage infiltration. Our findings highlight PTP4A3 as a potential critical regulator of the inflammatory response during SARS-CoV-2 infection. KVX-053, a potent and selective PTP4A3 inhibitor, emerges as a promising host-directed therapeutic strategy for mitigating ARDS and inflammation-driven lung injury in SARS-CoV-2 and potentially other respiratory viral infections. Future studies are required to optimize dosing strategies, elucidate precise molecular mechanisms, and validate these findings in clinical settings.

Background

Introduction

The COVID-19 pandemic has placed an unprecedented strain on global healthcare, leading to over 676 million infections and and nearly 7 million deaths worldwide. The epidemics of COVID in 2003, Middle Eastern Respiratory Syndrome in 2017, and SARS-CoV-2 pandemic in 2020 have historically posed significant global threats, making continued research into their pathophysiology and the development of innovative therapeutic approaches necessary.

Host-directed therapies that focus on altering the host-response offer promising potential for addressing underlying disease mechanisms. SARS-CoV-2 infections can range from mild cold-symptoms to severe conditions such as Acute Respiratory Distress Syndrome (ARDS), with associated mortality rates up to 50% in critically ill patients.

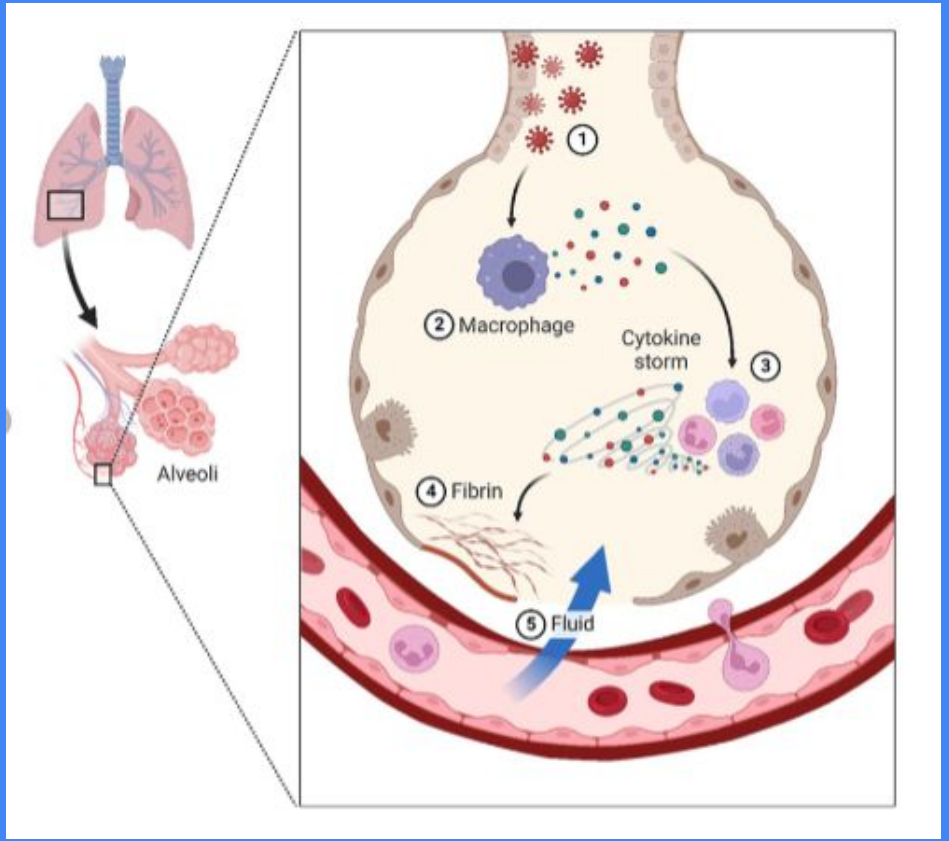
Colunga-Biancatelli et al. employed a human mouse model (K18-hACE2) of live SARS-CoV-2 infection and explored the effectiveness of the PTP4A3 inhibitor, KVX-053, to reduce SARS-CoV-2 -induced lung injury.

What is COVID-19?

- COVID-19 is caused by a virus called **SARS-Cov-2**
- Primarily affects the lungs
- While some people contract mild symptoms, others are vulnerable to developing severe lung injury
- This is dangerous because the virus can cause severe inflammation, fluid buildup in the lungs, difficulty breathing
- **In serious cases, this leads to Acute Respiratory Distress Syndrome (ARDS), which can be life-threatening**

The Body's Immune Response

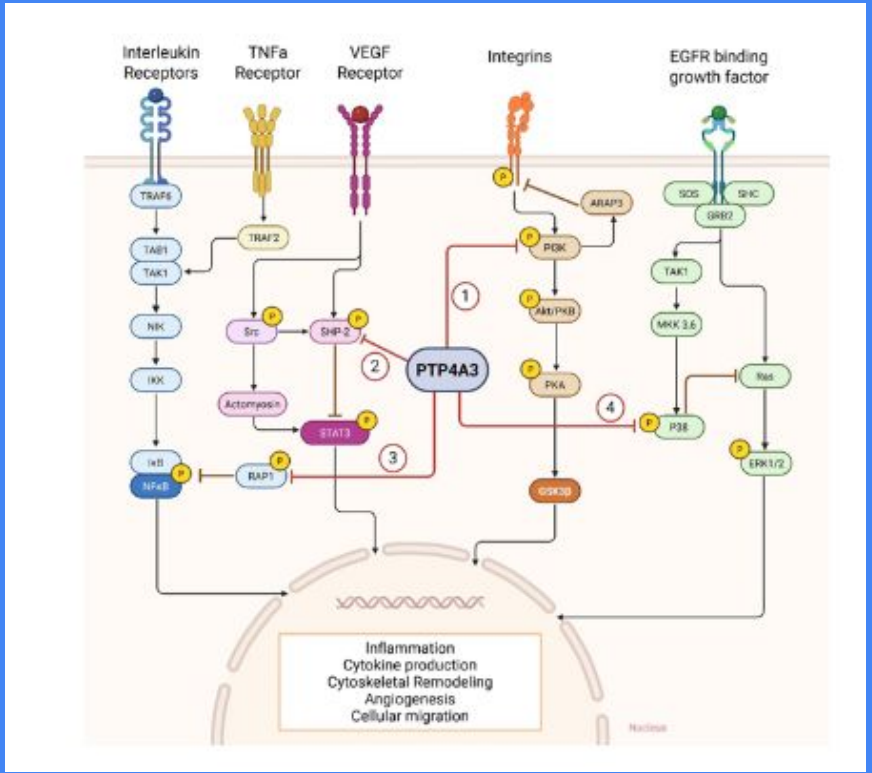
- An overreaction of our immune system is called a "cytokine storm"
- **Cytokines** are signaling proteins that help control inflammation in your body
- Too much inflammation can damage healthy lung tissue



PTP4A3 & KVX-053

- PTP4A3 is a protein inside cells that helps control inflammation, cell movement, and immune signaling
- In severe COVID-19, it's overactive

- KVX-053 is a drug that blocks PTP4A3
- Scientists wanted to see if blocking PTP4A3 would reduce inflammation and whether it would protect the lungs



Objective

Colunga-Biancatelli et al. asked:

- Can we reduce lung inflammation without stopping the body from fighting the virus?
- Is there a way to prevent lung damage in severe cases of COVID-19?

Methodology

Colunga-Biancatelli et al. performed two experiments through in-vitro cell models and in vivo K18-hACE2 transgenic mice. **In-vitro** cell models are biological testing platforms where living cells are grown and studied in a controlled, artificial laboratory environment. **In vivo** research represents the monitoring of a cell inside of an organism (transgenic mice). **K18-hACE2 transgenic mice** were used because standard mice are unable to be affected with SARS-CoV-2 and, when infected, they develop respiratory tract infections that mirror the lung inflammation and distress seen in severe human COVID-19 cases.

The use of both experiments allowed Colunga-Biancatelli et al. to differentiate between what happened in cells and in living organisms.

Clinical Scoring System

One day before infection with SARS-CoV-2 and during the entire experimental period, mice were monitored for changes in their clinical status. Colunga-Biancatelli et al. employed a scoring system using different criteria to address a mouse's health. For each criterion, a value between 0 (best) and 3 (worst) was given and summed to the others.

Table 1 Clinical scoring system

Appearance	Mobility	Attitude	Body Condition	Total Score
0 Smooth coat, bright eyes	0 Active, exploring	0 Alert	0 Obese or normal	0–5 Normal 1x/daily monitoring
1 Slightly scruffy and/or slightly hunched	1 Walking, less active	1 Mildly lethargic	1 Underconditioned	6–10 2x/daily monitoring
2 Scruffy and/or hunched at rest	2 Slow movement	2 Lethargic	2 Emaciated	≥11 Euthanize
3 Very scruffy and/or hunched, mild eye crust	3 No movement	3 Unaware		

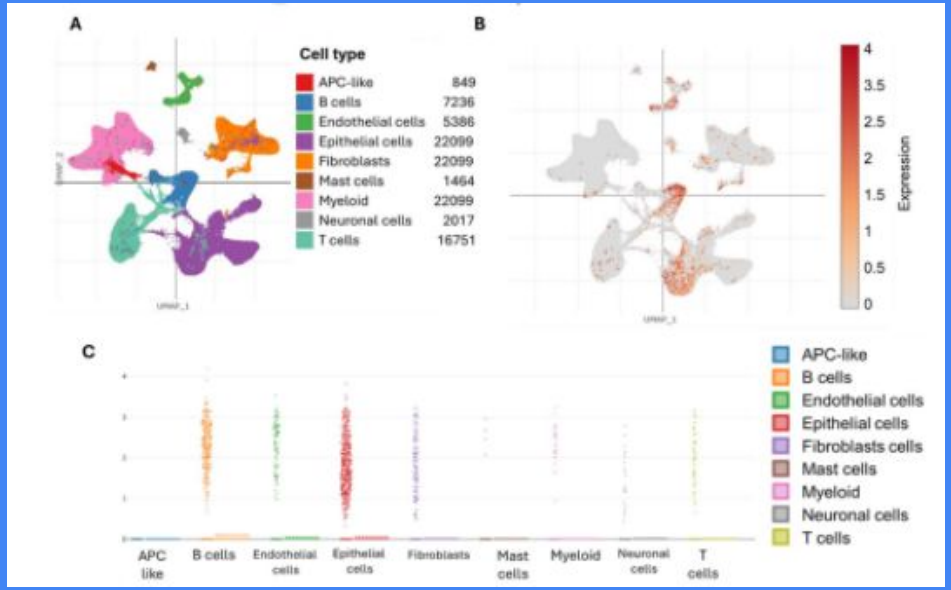
Any animal scoring the highest in any criteria will be euthanized

Results

In-vitro Lung Cells

When the in-vitro human lung cells were treated with KVX-053, inflammation chemicals decreased, the virus continued to replicate normally, and the cells stayed healthy.

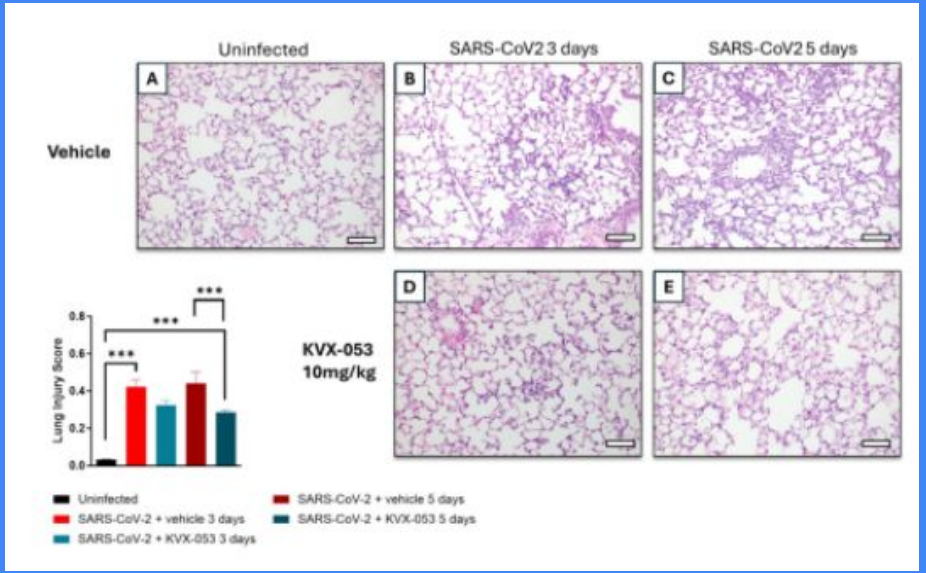
KVX-053 reduced inflammation without killing cells.



In vivo Transgenic Mice

When K18-hACE2 transgenic mice were given KVX-053, the results included less lung damage, **better overall health scores**, reduced inflammation in lung tissue.

- Infected mice had damaged, inflamed lungs
- Treated mice had less swelling and injury



Analysis

The drug did not significantly reduce virus levels; instead, it reduced harmful inflammation. This is called host-directed therapy and it helps the body respond better.

This is important because current treatments mostly target the virus or use general anti-inflammatory drugs. The KVX-053 drug targets a specific inflammation pathway, has the potential to reduce severe lung injury, and could be helpful in future viral outbreaks.

More studies are needed in humans and researchers must test safety, correct dosage, and long-term effects. However, this study displays a promising new direction capable of becoming a future treatment option.

Discussion

- *Why can too much inflammation be harmful?*
  - Excessive inflammation can be harmful because it causes the immune system to attack healthy tissues instead of just foreign invaders.

- *Why might it be helpful to target the body's response instead of the virus?*
  - Targeting the body's immune response instead of a virus directly can be helpful because it leverages the body's natural defense mechanisms. Additionally, it promotes healing by supporting the immune system's processes (inflammation) and can provide long-lasting immunity by generating specialized cells that recognize the virus in the future.

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