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COMMENTARY

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Peroxisomes countering long-COVID: The anti-inflammatory organelles of alveolar macrophages halt chronic viral diseases

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In a recent study published in *Science*,[1] Wei X. et al. unveiled that severe viral infections, including COVID-19, cause significant damage to peroxisomes, the key organelles in macrophages. Macrophage peroxisome depletion may impede lung injury repair, whereas treatment with 4-phenylbutyric acid (4-PBA), an FDA-approved compound, can restore peroxisome function and enhance the ability of immune system to repair lung damage (Figure 1).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection leads to both acute illness and ultimately long-term complications, collectively known as post-acute sequelae of COVID-19 (PASC) or Long COVID. Similar persistent symptoms have been observed in the chronic period of other respiratory viral infections, such as influenza. Following alveolar injury, type 2 alveolar epithelial (AT2) cells renew themselves and differentiate into type 1 alveolar epithelial (AT1) cells through a transitional progenitor state characterized by enhanced expression of cytokeratin 8 ($KRT8^{high}$).[2] Notably, the accumulation and prolonged existence of $KRT8^{high}$ transitional cells have been identified as a major driver of lung fibrosis[3] and key characteristics of chronic tissue sequelae post-acute COVID-19.[4]

The team noticed that pulmonary macrophages in COVID-19 patients exhibited a significant reduction in peroxisome quantity, accompanied by enlarged morphology and abnormal aggregation, which were determined by integrated assessments, including scRNA-Seq from bronchoalveolar lavage fluid, protein expression profiling, and immunofluorescence of healthy donors and COVID-19 patients. These observations were consistent with the findings from their mouse models of SARS-CoV-2 and influenza A virus (IAV) respiratory infections. Thus, the authors propose that viral infections may induce alterations in peroxisome biogenesis and compartment remodeling within pulmonary macrophages, ultimately leading to functional impairment. They used IFNα or IFNγ to treat mice, which led to a reduction in peroxisome quantity and an increase in peroxisomal aggregates, with IFNγ inducing more pronounced changes than IFNα. Furthermore, in SARS-CoV-2-infected mice, blocking IFNα and IFNγ signaling using neutralizing antibodies resulted in elevated PMP70 levels, reduced peroxisome aggregates in alveolar macrophages (AMs), and triggered selective autophagy of peroxisomes. These findings indicate that IFNγ drives peroxisome remodeling by suppressing peroxisome biogenesis and promoting peroxisome degradation.

To investigate the functional consequences of the peroxisome loss, the team used $Pex5^{\Delta Cd11c}$ (CD11c-Cre peroxisome knockout in macrophages) mice and $Pex5^{\Delta Lyz2}$ (lysozyme-Cre peroxisome knockout in myeloid cells) mice, infected with SARS-CoV-2 MA30 or H1N1 influenza virus vs. control $Pex5^{fl/fl}$ mice. The $Pex5^{\Delta Cd11c}$ mice exhibited higher post-infection mortality, delayed weight recovery, and unchanged viral loads, indicating that peroxisome function is independent of antiviral immunity. Collectively, peroxisome dysfunction does not affect the host's antiviral immunity or acute inflammatory response but impedes the resolution of pulmonary inflammation and tissue damage repair following viral clearance.

scRNA-Seq revealed enrichment of inflammation-related genes and downregulation of repair-related pathways (cell junction assembly) in SARS-CoV-2-infected $Pex5^{\Delta Cd11c}$ mice. Additionally, $Pex5^{\Delta Cd11c}$ mice possessed fewer AT2 cells with reduced proliferative capacity, suggesting that peroxisome dysfunction impairs alveolar epithelial repair. In vitro wound-healing and 3D organoid assays further support that macrophages from the $Pex5^{\Delta Cd11c}$ mice failed to support alveolar epithelial cell migration and proliferation, reinforcing the importance of peroxisomes in lung regeneration. Poly(I:C) treatment of AMs isolated from the PEX5-KO mice revealed that peroxisomes may be involved in lipid metabolism, facilitating ether lipid synthesis and the breakdown of very-long-chain fatty acids (VLCFAs). Lipidomic profiling unveiled aberrant VLCFA accumulation and reduced ether lipid production in peroxisome-deficient AMs. Peroxisome deficiency also led to suppressed mitochondrial pathways in AMs, reduced oxidative respiration, and diminished extracellular acidification rates (ECAR). These findings together highlight the role of macrophage peroxisomes in maintaining mitochondrial health and promoting tissue repair.

Using PEX5-KO AMs co-cultured with primary AT2 cells dissected IL-1β's roles in the regulation of KRT8, α-SMA and collagen I. The study delineated a mechanistic pathway linking peroxisome dysfunction to fibrosis through mitochondrial ROS accumulation, NLRP3 inflammasome activation, Caspase-1-mediated GSDMD cleavage and ultimately IL-1β release. Consequently, IL-1β inhibits AT2-to-AT1 differentiation, resulting in $KRT8^{high}$ transitional cell retention, TGF-β secretion, collagen deposition, myofibroblast activation, and ultimately pulmonary fibrosis.

This study uncovers a previously unrecognized role of peroxisomes in orchestrating macrophage-mediated alveolar epithelial repair, while demonstrating their pathological inactivation in post-viral pulmonary fibrosis. By establishing a mechanistic link between peroxisomal dysfunction, inflammasome hyperactivation, and KRT8+ progenitor cell dysplasia, this work advances our understanding of the molecular pathogenesis underlying Long COVID (PASC) and related fibrotic sequelae. Strikingly, pharmacological induction of peroxisome biogenesis via 4-phenylbutyric acid (4-PBA)-an FDA-approved drug for urea cycle disorders-mediated PEX5/PMP70 upregulation was shown to reverse IFNγ-induced peroxisomal degradation, restore macrophage metabolic reprogramming, and break the vicious cycle of unresolved inflammation-fibrosis. Thus, peroxisomal pathways may be druggable targets for precision medicine approaches, offering a therapeutic paradigm to prevent chronic lung remodeling after many types of serious viral infections.

The global pandemic of COVID-19 has shown that the initial infection can lead to acute lung injury (ALI). In some patients, particularly those with underlying medical conditions, persistent or progressive respiratory symptoms may continue post-COVID-19. Computed tomography (CT) often reveals interstitial lung abnormalities, while histopathology analysis demonstrates chronic inflammation and/or fibrotic tissue proliferation, leading to post-acute COVID-19 interstitial lung disease (PC-ILD). In severe cases, pre-existing interstitial lung fibrosis may worsen, posing a life-threatening risk.

Data show that up to 17.5% of COVID-19 patients have pulmonary fibrosis changes in CT images. The incidence of pulmonary fibrosis in patients with severe or critical COVID-19 pneumonia is significantly higher than that in patients with moderate COVID-19.[5] Autopsy reports of patients who died from COVID-19 pneumonia reveal diffuse alveolar damage characterized by intra-alveolar fibroblast proliferation and fibrin deposition in the basement membrane, resulting in a pulmonary consolidation. Survivors may suffer from progressive pulmonary fibrosis, which could become a significant cause of mortality. Unlike broad-acting antifibrotics, 4-PBA's targeted peroxisome restoration may mitigate systemic adverse effects while addressing disease-specific pathophysiology. Current FDA-approved therapies Pirfenidone and Nintedanib exhibit limitations in efficacy, significant adverse effects, and prohibitive costs. In pulmonology practice, post-COVID patients commonly present with progressive fibrotic lung changes and viral infection accelerates interstitial fibrosis progression in susceptible individuals.

The study provides the first comprehensive elucidation of macrophage peroxisomal involvement in post-COVID-19 chronic pulmonary pathology, specifically delineating their essential regulatory role in alveolar tissue regeneration and inflammatory cascade resolution, which fundamentally advances our understanding of their pathogenetic significance in progressive lung disorders. The integrated application of multidisciplinary research approaches comprehensively evaluated the impact of peroxisomal dysfunction on pulmonary pathological alterations. This multidisciplinary strategy

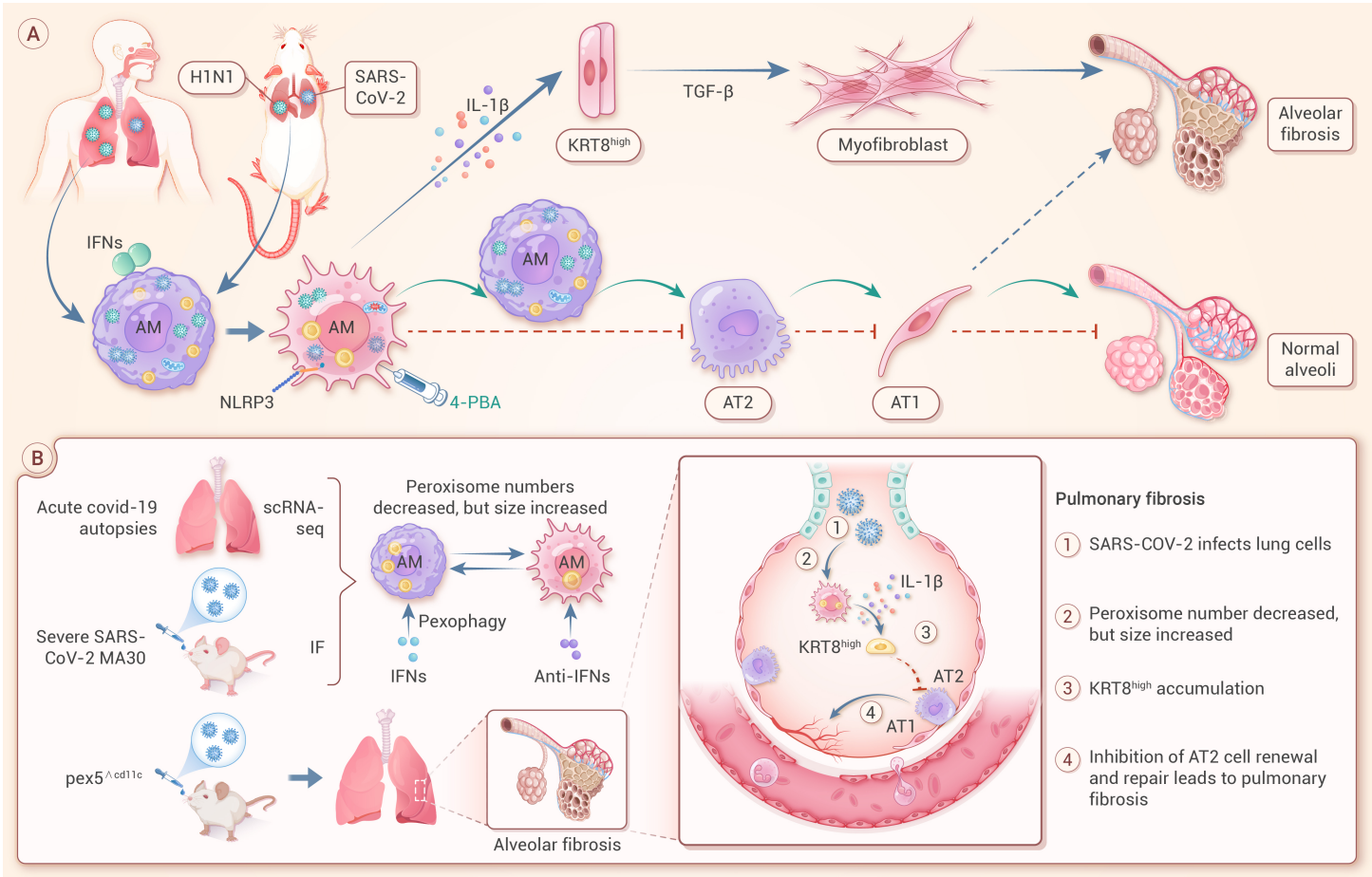

Figure 1. (A) Model of peroxisome function in macrophage-mediated alveolar regeneration after viral injury. Peroxisome activity in alveolar macrophages (AM) is essential for AT2 self-renewal and alveolar repair following viral infection. Dysfunction of macrophage peroxisomes causes excessive inflammasome activation and KRT8^{high} accumulation, resulting in a chronic tissue sequelae post acute infection. Critically, 4-PBA treatment facilitates peroxisome biogenesis in macrophages and enhancing alveolar regeneration after respiratory viral infection. (B) Analysis of lung tissues from COVID-19 patients and in mice of severe infection models revealed reduced peroxisome numbers and structural abnormalities in macrophages. In Pex5$^{\Delta cd11c}$ mice (with AM specific deficiency), impaired alveolar regeneration, accumulation of KRT8^{high}, and fibrosis occur.

provides novel insights for addressing complex biomedical challenges. The study reveals how macrophage peroxisomes regulate lung repair and inflammation resolution after COVID-19, offering important insights into PASC development. With its existing safety data, 4-PBA could become a new treatment for long-term complications in COVID-19 and similar viral diseases. The link between peroxisome dysfunction and chronic lung diseases in this study may have implications for battling with other chronic lung diseases, such as chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis.

In summary, this study elucidates the critical role of peroxisomes in regulating alveolar regeneration and suppressing progressive pulmonary fibrosis following viral infection. These findings enhance our understanding of post-viral sequelae, including post-acute sequelae of SARS-CoV-2 infection (PASC), and propose novel therapeutic strategies targeting peroxisomal pathways. Notably, FDA-approved drugs 4-PBA, currently indicated for hyperammonemia, shows promise for repurposing in the management of long COVID and may accelerate the recovery of pulmonary function. However, translational studies are required prior to clinical application in this context. Furthermore, the involvement of peroxisomes in modulating inflammatory responses and facilitating alveolar repair suggests broader relevance in addressing persistent complications following influenza and other respiratory viral infections. This mechanistic insight may also inform research on aging, neurodegenerative disorders, and metabolic diseases. Future efforts should focus on precise modulation of peroxisomal activity, optimized therapeutic interventions for lung injury, and the development of targeted peroxisome-based therapies, ultimately aiming to restore respiratory function and improve quality of life.

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AUTHOR CONTRIBUTIONS

P.J., J.C., and K.W. have prepared the initial draft. P.J. and K.W. were responsible for the illustration. P.J., K.W., and M.W. discussed the core concepts of the manuscript and also contributed to its revision. All authors have reviewed and given their approval for the final version of the article.

DECLARATION OF INTERESTS

The authors declare no competing interests.