10-1-2023

Reclaiming the Balance: Blocking Glutamine Uptake to Restrain Pulmonary Fibrosis

Gang Liu

Ross Summer
Thomas Jefferson University

Reclaiming the Balance: Blocking Glutamine Uptake to Restrain Pulmonary Fibrosis

Idiopathic pulmonary fibrosis and other chronic progressive fibrosing conditions represent a group of disorders that cause substantial morbidity and mortality by gradually replacing the lung with dense, fibrotic scar tissue (1). Central to the pathogenesis of these conditions are myofibroblasts, specialized cells that play a crucial role in lung injury and repair processes (1, 2). Once activated, these cells acquire contractile proteins that exert mechanical forces on neighboring lung tissue and produce large quantities of extracellular matrix that contribute to the formation of fibrotic scars (3). Furthermore, myofibroblasts secrete a multitude of profibrotic and proinflammatory molecules that participate in amplifying organ disrepair and inflammation. Altogether, these actions help explain why existing antifibrotic therapies target these cells and why many interventions being developed follow a similar approach (4).

Glutamine addiction refers to the dependence of cells on high concentrations of glutamine for their survival, proliferation, and/or function (5). Although this term is most commonly used in the context of cancer cells, it has been used to describe other noncancerous cells when consumption of glutamine is pathologically increased. In pulmonary fibrosis, several studies have demonstrated that myofibroblasts depend on glutamine for important biosynthetic reactions, including the production of collagen and other extracellular matrix proteins (6). In animal models, this dependency has been exploited by pharmacologically inhibiting glutaminase, the first step in the conversion of glutamine to glutamate upon entering cells (7). However, unfavorable side-effect profiles and metabolic adaptations observed in patients with cancer treated with glutaminase inhibitors suggest that alternative approaches to targeting glutamine will be needed for patients with pulmonary fibrosis (8).

In this issue of the *Journal*, Choudhury and colleagues (pp. 441–455) present a novel glutamine-directed therapy for pulmonary fibrosis (9). Through a series of meticulously designed and executed studies, these investigators identified and validated the use of a specific neutral amino acid transporter by myofibroblasts for glutamine uptake. This transporter, known as SLC1A5 (solute carrier family 1 member 5), exhibits significant upregulation in idiopathic pulmonary fibrosis lung fibroblasts and human fibroblasts in response to TGF-β (transforming growth factor-β). Exploiting this knowledge, Choudhury and colleagues demonstrate that silencing SLC1A5 not only limits the growth and proliferation of lung myofibroblasts but also inhibits key signaling pathways and impedes the production of essential extracellular matrix proteins. Consistent with these multifaceted effects, *in vivo* targeting of SLC1A5 using V-9302, a small-molecule inhibitor, dramatically reduced the severity of pulmonary fibrosis in response to bleomycin in mice (Figure 1). This was demonstrated by both biochemical and histological measures. Importantly, toxicity studies indicated that V-9302 mediates its therapeutic effects without causing appreciable harm to other organs, including highly proliferative tissues such as the bone marrow and liver.

Although the findings of Choudhury and colleagues (9) hold considerable significance, the potential translation of this therapy to human disease remains uncertain. For instance, previous preclinical studies have shown promise using the single bleomycin model; however, the results have been far less impressive when repeated in other clinically relevant models, such as aged mice, or the long-term bleomycin model. In addition, although toxicity studies showed encouraging results, the short duration of therapy (13 d) may have been insufficient to cause significant organ injury. Furthermore, it should be acknowledged that other cells, including alveolar epithelial cells, rely on SLC1A5 in times of stress, and it is also possible that these cells depend on SLC1A5 for glutamine import (10, 11). If true, this suggests that cell-specific targeting may be needed for the treatment of pulmonary fibrosis with SLC1A5 inhibitors. Nevertheless, these concerns are generally considered minor and should not delay the progress of moving this novel approach closer to the clinic.

In conclusion, there is a pressing need for new treatments for patients with progressive forms of pulmonary fibrosis, and this study offers a novel approach involving blocking the entry of glutamine into cells. Although it is premature to celebrate, these findings offer reason to be optimistic about future treatments for patients with these life-threatening diseases. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Gang Liu, Ph.D.
School of Life Sciences
University of Technology Sydney
Ultimo, New South Wales, Australia
and
Centre for Inflammation
Centenary Institute and University of Technology Sydney
Camperdown, New South Wales, Australia

Ross Summer, M.D.
Sidney Kimmel Medical College
Thomas Jefferson University
Philadelphia, Pennsylvania

ORCID IDs: 0000-0002-0489-2638 (G.L.); 0000-0003-4615-4956 (R.S.).

Supported by the Lung Foundation Australia CREATE Hope Scientific Fellowship (G.L.).

Originally Published in Press as DOI: 10.1165/rcmb.2023-0189ED on July 18, 2023

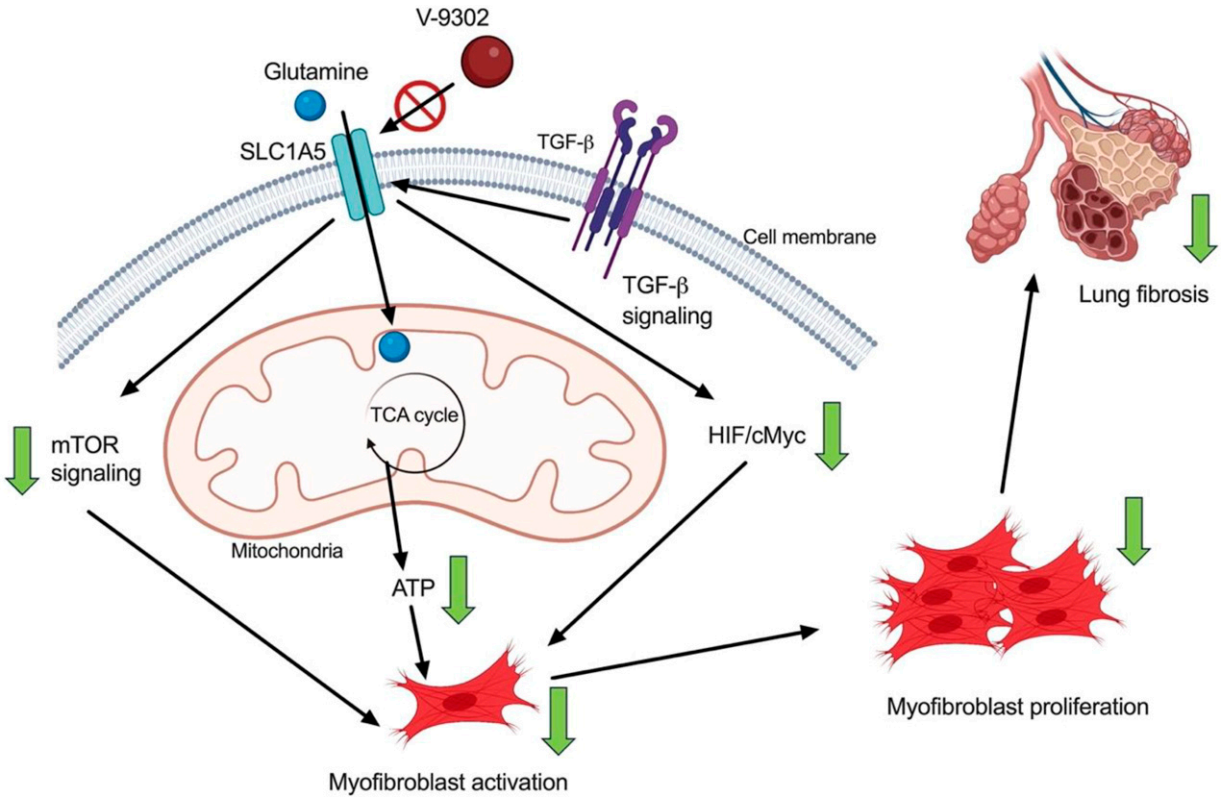

Figure 1. Targeting the glutamine transporter SLC1A5 with V-9302 ameliorates pulmonary fibrosis in mice by reducing myofibroblast growth and proliferation and blocking key signaling molecules and the production of extracellular matrix molecules. c-Myc = cellular myelocytomatosis; HIF = hypoxia-inducible factor; IPF = idiopathic pulmonary fibrosis; SLC1A5 = solute carrier family 1 member 5; TCA = tricarboxylic acid; TGF = transforming growth factor.

References

1. Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. *N Engl J Med* 2018;379:797–798.
2. Pardo A, Selman M. Lung fibroblasts, aging, and idiopathic pulmonary fibrosis. *Ann Am Thorac Soc* 2016;13:S417–S421.
3. Liu G, Cooley MA, Jarnicki AG, Borghuis T, Nair PM, Tjin G, *et al.* Fibulin-1c regulates transforming growth factor-β activation in pulmonary tissue fibrosis. *JCI Insight* 2019;5:4.
4. Liu G, Philp AM, Corte T, Travis MA, Schilter H, Hansbro NG, *et al.* Therapeutic targets in lung tissue remodelling and fibrosis. *Pharmacol Ther* 2021;225:107839.
5. Wise DR, Thompson CB. Glutamine addiction: a new therapeutic target in cancer. *Trends Biochem Sci* 2010;35:427–433.
6. Hamanaka RB, O'Leary EM, Witt LJ, Tian Y, Gökalp GA, Meliton AY, *et al.* Glutamine metabolism is required for collagen protein synthesis in lung fibroblasts. *Am J Respir Cell Mol Biol* 2019;61:597–606.
7. Cui H, Xie N, Jiang D, Banerjee S, Ge J, Sanders YY, *et al.* Inhibition of glutaminase 1 attenuates experimental pulmonary fibrosis. *Am J Respir Cell Mol Biol* 2019;61:492–500.
8. Yang W-H, Qiu Y, Stamatatos O, Janowitz T, Lukey MJ. Enhancing the efficacy of glutamine metabolism inhibitors in cancer therapy. *Trends Cancer* 2021;7:790–804.
9. Choudhury M, Schaefbauer KJ, Kottom TJ, Yi ES, Tschumperlin DJ, Limper AH. Targeting pulmonary fibrosis by SLC1A5-dependent glutamine transport blockade. *Am J Respir Cell Mol Biol* 2023;69: 441–455.
10. Wang S, Li X, Ma Q, Wang Q, Wu J, Yu H, *et al.* Glutamine metabolism is required for alveolar regeneration during lung injury. *Biomolecules* 2022;12:728.
11. Shaghaghi H, Para R, Tran C, Roman J, Ojeda-Lassalle Y, Sun J, *et al.* Glutamine restores mitochondrial respiration in bleomycin-injured epithelial cells. *Free Radic Biol Med* 2021;176: 335–344.