Metformin in Idiopathic Pulmonary Fibrosis “Seeking the Holy-Grail through Drug-Repositioning”

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Idiopathic pulmonary fibrosis (IPF) is a debilitating chronic lung disease that is characterized by fibrotic remodeling of lung architecture, ultimately leading to respiratory failure and death within 2.5–3 years of diagnosis [1]. IPF represents a disease paradigm of accelerated aging with many of the hallmarks of aging representing major events of IPF pathogenesis, including telomere attrition, genomic instability, epigenetic alterations, impaired cellular bioenergetics, and metabolic derangements [2]. In particular, metabolic comorbidities including diabetes mellitus and hypothyroidism have been associated with worst clinical outcomes in patients with IPF [3].

In this issue of *Respiration*, Spagnolo et al. [4] perform a post-hoc analysis on the efficacy of metformin in 624 patients with IPF with or without diabetes or insulin glucose tolerance derived from the placebo arms of the 3 randomized controlled trials of pirfenidone. The study rationale was based on: (1) epidemiological data linking diabetes with IPF development and progression (knowledge of disease phenotypes and comorbidities) [5] and (2) pre-clinical evidence showing that metformin may exert anti-fibrotic properties through regulation of

cellular bioenergetics and autophagy via activation of AMP-activated protein kinase in experimental models of lung fibrosis (knowledge of drug and disease mechanisms) [6–8]. Authors report that metformin users were mostly males (85 vs. 73%) and had increased prevalence of metabolic profile as assessed by the coexistence of diabetes, hypercholesterolemia, and hypertension compared to non-metformin users (99 vs. 12%). Importantly, they state that metformin has no significant impact on disease outcomes including disease progression as assessed by FVC decline, as well as IPF-related mortality and all-cause hospitalization. Observations derived from the placebo-arms of the pirfenidone trials were also extended to the intention-to-treat population ($n = 1,247$) derived from the placebo and treatment arms combined. On the contrary, metformin users were more likely to experience disease progression (relative decline of FVC >5%) compared to non-users; yet, statistical significance was borderline and thus may not reflect the clinical significance.

Despite the presence of major caveats that preclude generalizability of the results into a broader IPF popula-

tion including: (1) Post-hoc nature of the analysis, (2) limited number of metformin users (11%) and lack of subsequent power analysis, (3) lack of link between drug mechanisms and disease pathogenesis, (4) absence of stringent definition criteria for both diagnosis and assessment of diabetes control (i.e., use of HbA1c); (5) inability to delineate potential drug-drug interactions between metformin and N-acetylcysteine or other anti-diabetics, the study has some major attributes that should be properly highlighted. These include the following: (1) This is the first study that implicates the regulation of impaired glucose metabolism through anti-diabetic drugs with IPF clinical outcomes in a large and well-defined population, (2) The study also highlights an important aspect of IPF therapeutic pipeline, namely drug-repositioning.

Drug repurposing represents a very attractive path to boost the discovery of disease therapeutics compared to the traditional pharmaceutical drug development as the latter is relatively slow, expensive, and risky even in late-stage development [9]. The challenge with the development of new chemical entities is that many molecules may show *in vitro* activity, but subsequently fail in pre-clinical efficacy models, or later in the more expensive and time-consuming animal safety studies prior to entry into human clinical trials. In addition, systemic side-effects are not observed with new chemical entities until late-stage clinical trials, or post-approval. Considering the above and the fact that the total cost for a new chemical entity to reach the market may exceed 1.1 billion USD, reformulating existing marketed drugs for pulmonary delivery to treat lung conditions should be faster, cheaper, and involve less risk as much of the information regarding the drug and its biological effects are already known [9]. Drug-repositioning accounts for an approximately 30% of the newly FDA-approved compounds. Intriguingly, it has been reported that almost 95% of the recent FDA-approved drugs for lung cancer were initially used for off-label indications and were serendipitously identified [10]. In addition, nintedanib, one of the two FDA-approved anti-fibrotic agents, represents a paradigm of drug-repositioning [11]. In particular, nintedanib was seminally developed as an anti-cancer agent with angiostatic and hypo-proliferating properties and later introduced as a therapeutic compound for lung fibrosis based on pathway similarities between lung cancer and IPF [12]. These included enhanced activation of angiogenesis and fibroblast differentiation originating from an imbalance between tyrosine kinases and phosphatases [13]. Several methods have been developed for drug-re-

positioning including the following: (1) drug-oriented methods such as the traditional blinded phenotypic screening that do not require specific knowledge and the repositioned drugs are serendipitously tested on an off-label basis, (2) disease-oriented methods that apply existing omics data to identify key target molecules and identify unknown drug targets and new disease biomarkers, and (3) treatment-oriented approaches that incorporate more sophisticated methods including systems biology techniques to define similarities between drugs and diseases. Implementation of efficient drug-repositioning pipelines on IPF clinical trials requires further knowledge about disease pathogenesis and treatment mechanisms [9].

On the contrary, the idea that restoring impaired glucose metabolism and cellular bioenergetics may halt the vicious cycle of aging-related alveolar epithelial cell apoptosis and fibroblast activation has recently gained much of attention. Recent pre-clinical studies have shown that glycolytic reprogramming is necessary for fibroblast-to-myofibroblast differentiation [14], and alveolar epithelial cells from aged patients with IPF display damaged and dysfunctional mitochondria, as well as impaired mitophagy and thus are more susceptible to injurious stimuli leading to apoptosis [15]. In the same context, our study group has recently revealed that thyroid hormone resolves experimental lung fibrosis through a mechanism that involves improvement of mitochondrial biogenesis and mitophagy in alveolar epithelial cells. These results open new therapeutic revenues for patients with IPF through repurposing a commonly used hormone for the treatment of hypothyroidism to treat lung fibrosis [16]. On the basis of these findings, mimicking AMP-activated protein kinase activity could hold promise as a therapeutic agent for IPF through restoration of the impaired mitophagy-mediated lung fibrosis. Nevertheless, failure of metformin to show a therapeutic impact on patients with IPF should not discourage similar efforts, as the need to identify novel and more effective therapeutic agents that will enter clinical practice on a fast-track basis is urgent.

To this end, application of mechanism-based repositioning approaches by using elegant computational models which incorporate drug-target information into existing disease-oriented gene signatures are fundamental for personalized medicine approaches. Unfortunately, there is major lack of knowledge on gene signatures predicting treatment responsiveness in patients with IPF, and therefore future studies aiming towards this direction are sorely needed.

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