Can Metformin Downshift the Gears of Aging to Slow Emphysema Progression?

In this issue of the *Journal*, Polverino and colleagues (pp. 651–666) report beneficial effects of metformin treatment on markers of lung and systemic injury and remodeling induced by prolonged cigarette smoke exposure in mice (Figure 1) and an association of metformin use with decreased emphysema progression in individuals with chronic obstructive pulmonary disease (COPD) enrolled in the COPDGene (Genetic Epidemiology of COPD) cohort (1).

Metformin, a biguanide compound derived from the galegine extract of the plant *Galega officinalis*, has been shown to induce a plethora of biological effects that have been harnessed to improve glucose control in diabetes mellitus (2). After uptake via the organic cation transporter-1, metformin activates multiple signaling pathways ranging from mitochondrial metabolism and mitophagy; lysosomal signaling; endoplasmic reticulum unfolded protein response and stress; and nuclear select transcription factor modulation, although indirect effects may be exerted by changes in gut microbiome and incretin secretion (3, 4). The response of lung cells to metformin has been little explored until now. Polverino and colleagues show in mouse lungs and cultured human bronchial epithelial cells that metformin treatment was associated with significant activation of the AMPK (5′ adenosine monophosphate–activated protein kinase) signaling pathway. This was corroborated by lung proteomics analyses that identified perturbations of cellular energy sensing and mitochondrial bioenergetics in mice. However, it remains unknown which of these pathways are mechanistically responsible for the beneficial effects of metformin on markers of lung, kidney, and skeletal muscle injury caused by chronic smoking. Notably, mice in this study were fed a fat-enriched diet usually associated with impaired glucose tolerance, and the study design did not make it possible to discern whether lung or systemic outcomes of metformin treatment were directly linked to glucose control. In addition, future studies are necessary to elucidate which cell types are responsible for the outcomes improved by metformin therapy.

Numerous studies identified that the therapeutic effect of metformin that is unrelated to the drug's effect on glucose metabolism is linked to antiaging effects, adding metformin to a growing list of senotherapeutics (5). Indeed, this report shows that treatment with metformin mitigated markers of cellular senescence induced by cigarette smoke in all the different tissues studied. This is relevant to emphysema pathogenesis, in which even remote chronic cigarette smoke exposure causes excessive oxidative, inflammatory, and genotoxic stress, as well as mitochondrial dysfunction, impaired autophagy, and progenitor cell exhaustion, all linked to accelerated cellular senescence (6, 7). Furthermore, metformin has shown promising therapeutic effects in both idiopathic pulmonary fibrosis (8) and lung cancer (9), lung diseases that are also more prevalent in smokers and are linked to accelerated cellular senescence.

The authors complement their murine studies with data from the COPDGene cohort and, after correcting for confounders, identify a compelling association between metformin use and a decreased rate of progression of emphysema over 5 years. This is an exciting novel observation that underpins the use of metformin as potential therapy in COPD and emphysema. A therapeutic role for metformin in COPD has been previously suggested by a meta-analysis (10) and by a recent report from COPDGene that found improved patient-reported outcomes and lower rates of total and severe exacerbations, particularly in asthma–COPD overlap syndrome (11). Although the current report does not include data on the effect of metformin on functional outcomes in murine models (lung compliance, muscle strength, exercise endurance, etc.), most published clinical studies support a favorable effect of metformin on functional outcomes in human COPD.

The study design offers limited insight into metformin's side effects or its effect on the likelihood of developing COPD in at-risk individuals, and on COPD mortality. The impact of metformin on mortality in this study is difficult to gauge because these data were not captured in individuals who missed the follow-up visit at 5 years. Intriguingly, individuals with lung cancer who were on metformin at the time or even preceding their diagnosis had better lung cancer–specific survival (9). This suggests a potential prophylactic effect of the drug that may be of interest to study in those at risk for COPD.

Together, the results of the complementary studies in the current report, the mounting evidence of senostatic effects of metformin, and the role of accelerated senescence in emphysema pathogenesis support the therapeutic potential of metformin in emphysema and its comorbidities, a hypothesis that needs to be tested in future clinical trials. ■

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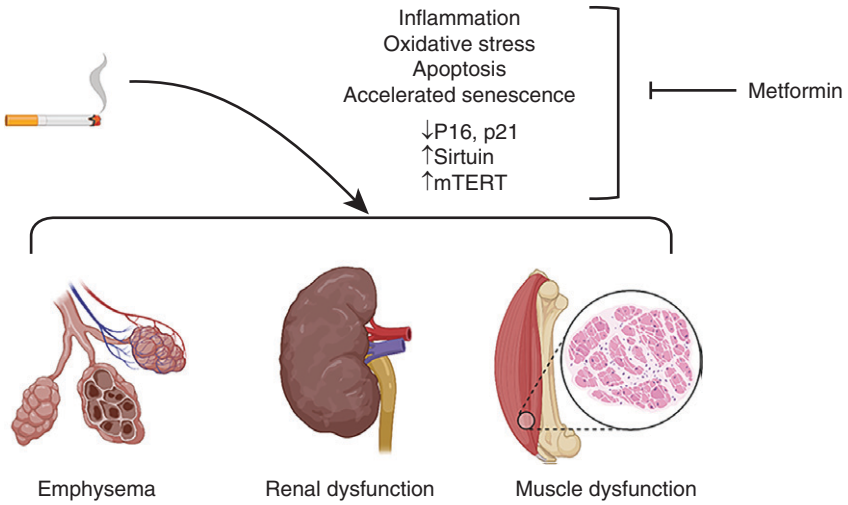

Figure 1. Schematic of effects of metformin in the mouse model of cigarette smoke–induced emphysema. mTERT = mouse telomerase. Created with Biorender.com.

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The Saga of Necroptosis in Chronic Obstructive Pulmonary Disease Continues

Chronic obstructive pulmonary disease (COPD) is a disease state in which chronic inflammation drives irreversible airway remodeling and airspace destruction, leading to chronic bronchitis and emphysema. COPD is predicted to be the third leading cause of death worldwide by the year 2030 and there remains a paucity of therapies (1). Cigarette smoke (CS) exposure is the primary risk factor for the development of COPD, and subsequent imbalances in oxidative stress, inflammation, and growth factor signaling support dysregulation and/or death of the epithelial, endothelial, and immune cellular compartments within the lung (2).

Regulated cell death (RCD) pathways are genetically encoded programs that support the maintenance of tissue homeostasis after cellular stress and/or injury. RCD can also represent aberrant responses in the pathogenesis of tissue injury, leading to deleterious consequences in human diseases (3). Apoptosis is the prototypical form of RCD in which caspase activation is associated with chromatin condensation, cell shrinkage, DNA fragmentation, and

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