IPF: Let's Keep the Focus on the A(ge)TII cell

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Chronic lung diseases (CLDs) such as idiopathic pulmonary fibrosis (IPF) are the third leading cause of death worldwide [1], and lung transplantation remains the only curative therapy to date. In the case of IPF, aging has emerged as the single most significant risk factor. With the worldwide aging population, its incidence is expected to rise significantly [2]. On a cellular level, several hallmarks have been identified as drivers of aging [3, 4], and IPF exhibits strong aging hallmarks, leading to severely compromised regeneration of the diseased lung [2]. Among these hallmarks are cellular senescence and metabolic reprogramming, which have been described as significant cellular changes in IPF, especially in ATII cells [2, 5]. Transient development of fibrosis characterizes the bleomycin mouse model of pulmonary fibrosis. However, when bleomycin is instilled into aged animals, the fibrosis is persistent, further highlighting the contribution of lung aging to the development of non-resolving fibrosis [6, 7]. The increase in cellular senescence leads to a senescence-associated secretory phenotype (SASP), culminating in a pro-inflammatory and pro-fibrotic milieu in the aged lung. At the same time, geroprotective factors such as Klotho or SIRT1 are downregulated. The main drivers of cellular aging in ATII cells are incompletely understood and deciphering the upstream regulators will be a significant step in identifying therapeutic targets to reduce or reverse this process.

Here, the authors describe a role of a cardinal nicotinamide adenine dinucleotide (NAD) hydrolase, CD38, in promoting mitochondrial dysfunction and cellular senescence of ATII cells leading to pulmonary fibrosis [8]. The authors use mouse models, cell lines, and primary mouse cells to show that CD38, a NAD consuming enzyme, increases fibrosis. At the same time, in both IPF and experimental fibrosis, there is a decrease in NAD levels in ATII cells. Changes in NAD levels are accompanied by a differential regulation of cellular energetics and mitochondrial function that have been well described in the literature [9]. Similarly, the authors confirm the existence of senescent ATII cells in experimental fibrosis and explanted lungs from IPF patients [10]. It remains unclear what drives CD38 overexpression in aged lungs, and future studies are

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needed to define the mechanisms in the aging human lung. In this paper, the authors demonstrate that overexpression of CD38 in ATII cell lines leads to decreased NAD levels, mitochondrial dysfunction, and increased cellular senescence. Notably, CD38 downregulation or inhibition blunts in vitro, bleomycin-induced cellular senescence, and mitochondrial dysfunction, suggesting CD38 as a promising pharmacological target. By decreasing NAD levels, CD38 overexpression inhibits major NAD consuming enzymes like Sirtuins and PARPs, likely to contribute to the observed mitochondrial and senescence effects.

It has been identified in other models of fibrosis that in vivo CD38 inhibition effectively decreases fibrosis in aged mice, improving mitochondrial function and decreasing the cellular senescence [11]. In the present manuscript, similarly, CD38 knockout mice are protected from the development of pulmonary fibrosis. Even more importantly, bleomycin-induced fibrosis can be reversed with a molecule inhibition of CD38.

This study builds upon a growing body of literature identifying cellular aging hallmarks in ATII cells of IPF patients [2, 9, 10, 12]. Targeting specific hallmarks such as cellular senescence with the help of senolytics showed promising preclinical results, and first in human trials demonstrated initial tolerability in IPF patients [10, 12-14]. This further highlights the applicability of therapies targeting cellular aging mechanisms in IPF. The finding that CD38 inhibition does not only decrease the level of cellular senescence but also reduces oxidative stress and reverts mitochondrial dysfunction is intriguing and argues that CD38 is a master regulator of multiple aging-related mechanisms. This suggests that aging processes are highly interlinked and supports the “Unitary theory of targeting fundamental aging mechanisms,” which suggests that targeting one aging mechanism might positively impact one or all other aging mechanisms [15]. Interestingly, therapies clearing senescent cells can be administered in an intermittent manner suggesting that potential off-target effects will be reduced. It will be of specific interest to

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understand the role of CD38 in other age-related lung diseases that have been linked to ATII senescence, such as COPD.

Although these studies demonstrate that pharmacological inhibition of CD38 has both preventive and therapeutic benefits in relevant mouse models of pulmonary fibrosis, several unknowns need to be considered when moving towards the clinical application of CD38 inhibition as a novel IPF therapy. The authors show an effect of CD38 inhibition one week after Bleomycin administration; it remains unknown if CD38 inhibition might be able to revert established fibrosis, 14 to 21 days after fibrosis, as seen in IPF patients. Furthermore, the study presents limited human data, and a human preclinical model of IPF such as PCLS is needed to confirm suitability for human disease. Again, not only ATII cells express CD38 In the fibrotic lung. Other epithelial cells, such as basal and basaloid cells, show detectable CD38 expression, and future studies are needed to address the relationship between CD38 and premature aging in other cell types. Similarly, other senescent cells, such as fibroblasts, have been implicated in the pathogenesis of IPF [7, 16], do not seem to overexpress CD38, and the effect of CD38 inhibition on these cell populations remains elusive.

This does not diminish enthusiasm for targeting cellular aging in ATII cells of IPF patients but highlights the need to characterize cell-type-specific susceptibility to specific therapeutic strategies further. Additionally, it underlines the potential market and promise of combination therapies affecting different aging hallmarks in multiple cellular compartments.

In summary, this exciting study identifies CD38 as a potential regulator of aging hallmarks in fibrotic ATII cells and suggests CD38 inhibition as a possible novel therapeutic strategy to target age-associated IPF.

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