Extracellular Vesicles: Bidirectional Accelerators of Cellular Senescence in Fibrosis?

Aging is major risk factor for idiopathic pulmonary fibrosis (IPF) (1). Among the many hallmarks of aging biology, cellular senescence has emerged as a key driver of this fibrotic lung disease, and targeted therapies are in clinical development (2, 3). Myofibroblasts are the known effector cells of IPF; these cells are transiently activated to function in normal tissue repair and wound healing but become senescent and apoptosis resistant in progressive fibrotic diseases such as IPF (4).

Alveolar epithelial type II cells (AT2) serve essential regenerative functions in the alveolus to maintain lung homeostasis. A number of factors may contribute to AT2 death and dysfunction, including both environmental and intrinsic properties, such as aging (5). AT2 cell senescence has been linked to mitochondrial dysfunction (6). A deficiency in SIRT3 (mitochondrial sirtuin) has been implicated in the promotion of lung fibrosis by inducing AT2 apoptosis (7) or inducing myofibroblast differentiation (8). However, the impact of cross-talk between AT2 cells and myofibroblasts in the perpetuation of senescence among these cell compartments has not been well defined.

In this issue of the *Journal*, Kadota and colleagues (pp. 623–636) identified a novel mode of extracellular vesicle (EV) cargo-mediated fibroblast-to-epithelial cross-talk in lungs that accelerates epithelial cell senescence in IPF (9). Though EVs are known paracrine mediators of cell–cell signaling, this study demonstrates that IPF-lung fibroblast-derived EV can transfer miR-23b-3p and miR-494–3p to lung epithelial cells; these microRNAs (miRNAs) repress SIRT3 and induce production of mitochondrial reactive oxygen species, accumulation of dysfunctional mitochondria,

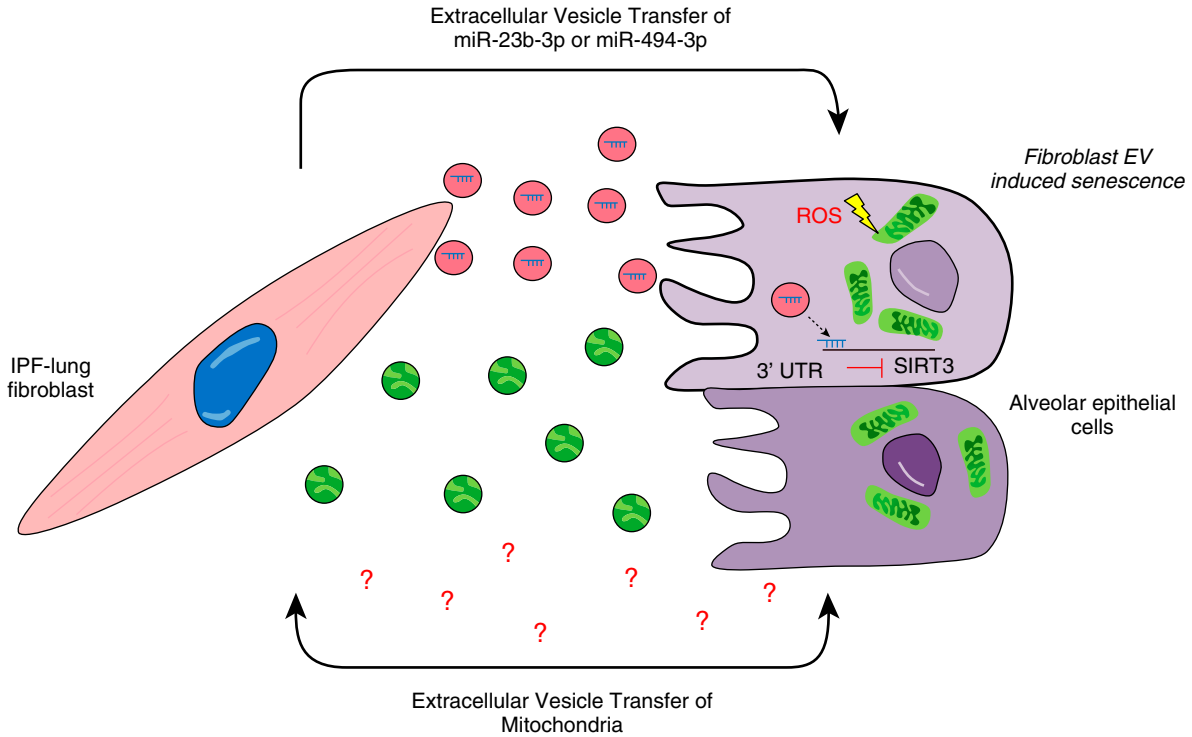

Figure 1. Extracellular vesicle (EV)-mediated induction of alveolar epithelial senescence. Idiopathic pulmonary fibrosis lung fibroblast–derived EVs containing miR-23b-3p or miR-494–3p can induce alveolar epithelial cell senescence via suppression of SIRT3 (mitochondrial sirtuin), as reported by Kadota and colleagues. Bidirectional signaling by EVs may also facilitate transfer of bioactive cargo, including functionally active mitochondria. IPF = idiopathic pulmonary fibrosis; miR = microRNA; ROS = reactive oxygen species; UTR = untranslated region.

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and DNA damage response and enhance cellular senescence, as depicted in Figure 1. Furthermore, Kadota and colleagues establish a causal link between SIRT3, a member of the sirtuin family of nicotinamide adenine dinucleotide (NAD)-dependent deacetylases, localized in the mitochondrial inner membrane and matrix, and EV-induced cellular senescence. They demonstrate that the SIRT3 3′ untranslated region (UTR) has binding sites for these miRNAs, thus facilitating suppression of SIRT3 expression and promoting cellular senescence by direct targeting of SIRT3. IPF lung tissues showed reduced expression of SIRT3 in fibrotic lesions and higher expression of miR-23b-3p and miR-494–3p compared with non-IPF controls. Furthermore, the expression levels of the miRNAs in lung fibroblast-derived EVs correlated with lung function of the donor, suggesting a pathogenic role for these miRNAs and epithelial senescence in the development and/or progression of IPF.

Paracrine mediators of pulmonary fibrosis, including reactive oxygen species, TGF-β, and WNT family ligands, may be produced by both epithelial cells and fibroblasts. Several of these signaling molecules facilitate cross-talk by bidirectional epithelial cell–fibroblast interactions in pulmonary fibrosis (10). EVs have long been recognized as efficient facilitators of cell–cell signaling and cellular reprogramming by transfer of bioactive cargo, including miRNA, mRNA, and lipids (11). Recent studies have highlighted the paracrine and autocrine roles of EV-associated extracellular matrix in lung fibroblast invasion, a critical event in the pathogenesis of fibrotic diseases such as IPF (12). Though the fibrotic program is conventionally thought to be triggered by the injured epithelium, studies reported here by Kadota and colleagues support EV signaling from fibroblasts to AT2 cells. Interestingly, there is strong evidence for functional components of mitochondria in EVs, suggesting a role in redox signaling (13–15). Although intercellular transfer of mitochondria has been suggested to be a mechanism for repair of stressed, bioenergetically deprived cells, such transfer may also function to promote cellular senescence in IPF, as postulated in Figure 1. Understanding how EV-mediated transfer of miRNA as well as mitochondria concurrently propagate IPF pathology may be helpful in the development of novel therapeutic strategies. Furthermore, the upstream mechanisms that initiate this EV-mediated cell–cell cross-talk is currently unknown; elucidating how this process is instigated may lead to viable therapeutic strategies. Additionally, unanswered questions surrounding the role of immune cells in the propagation and clearance of senescent cells and the feedback loop between myofibroblasts and senescent alveolar epithelial cells remain. ■

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