



Decoding Intercellular Communication in COPD: Linking Lung Aging to Regenerative Failure

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is an age-associated lung disease characterized by persistent inflammation, impaired epithelial repair, and progressive tissue remodeling. Aging promotes cellular senescence and altered intercellular communication, potentially contributing to regenerative failure in COPD.

To investigate these mechanisms, we combined human patient samples, murine aging models, epithelial organoids, air-liquid interface (ALI) cultures, and precision-cut lung slices (PCLS). Lifespan-resolved transcriptomic profiling revealed a shift from regenerative programs in early life toward inflammatory states in aged epithelial progenitors. Aged organoids exhibited impaired regeneration and increased sensitivity to inflammatory stimuli, while activation of developmental signaling pathways partially restored regenerative capacity. Single-cell RNA sequencing of patient-derived ALI cultures further revealed disease-associated alterations in epithelial cell states and inflammatory responses, highlighting disrupted epithelial communication in COPD.

We investigated extracellular vesicles (EVs) as mediators of age-associated intercellular communication. Aging altered EV abundance and proteomic composition in bronchoalveolar lavage fluid, while cellular senescence increased EV secretion and modified EV cargo. EVs derived from senescent fibroblasts and aged lungs impaired epithelial regeneration, suggesting that EV-mediated signaling contributes to a dysfunctional regenerative microenvironment.

Together, these findings highlight how epithelial aging and altered intercellular communication converge to impair lung regeneration, identifying potential therapeutic targets for COPD.

BIOSKETCH

Mareike Lehmann is a Professor of Translational Inflammation Research at Philipps University Marburg and leads the Lung Inflammaging research group at Helmholtz Munich. Her research focuses on understanding how aging and chronic inflammation impair lung regeneration and contribute to chronic lung diseases, particularly COPD and pulmonary fibrosis. Her group combines advanced human lung models, including organoids and precision-cut lung slices, with single-cell and spatial technologies to investigate cellular senescence, epithelial-immune interactions, and extracellular vesicle-mediated communication. A major goal of her research is to translate mechanisms of lung aging into novel regenerative and precision therapeutic strategies.