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SUCCESSFUL GENERATION OF THREE-DIMENSIONAL HUMAN PRECISION-CUT LUNG SLICES FOR PULMONARY FIBROSIS MODELING

Laurie Perdigon[1], Manon Barthe[1], Jean-Paul Thénot[1], Franck Chiappini[2], Agnes Choppin[2], Hanan Osman-Ponchet[1]
[1] PKDERM Laboratories, 45 Boulevard Marcel Pagnol, 06130 Grasse – France
[2] OTR3, 4 rue Française, 75001 Paris – France
Corresponding author's e-mail: hanan.osman.ponchet@pkderm.com

Occurrence of diffuse alveolar damage is a real storm in the course of pulmonary diseases leading to an acute and/or chronic inflammatory processes with poorly understood etiologies and cellular mechanisms. To address this gap in knowledge, we developed a model of lung fibrosis using human precision-cut lung slices (hPCLS). hPCLS preserve the native 3D structure of the lung and contain all lung cell types, making them an ideal in vitro model for studying lung diseases and testing potential safety, toxicity, and efficacy of promising therapies.

We generated hPCLS of 8 mm diameter and 300 µm thickness from surgical lung resections from nine patients using a vibrating microtome. We treated hPCLS with a profibrotic cocktail (PFC) for 5 days to induce fibrogenesis, and added nintedanib, an anti-fibrotic drug, to PFC-treated PCLS for 3 days to inhibit fibrogenesis. We used different methods to study the properties of PCLS, including metabolic activity, cell viability, actin staining, and mRNA expression of fibrotic markers.

We obtained hPCLS from 6 of 9 lung resections, with an average of 120 hPCLS per lung (range: 48-190). hPCLS maintained metabolic activity, viability, and actin cytoskeleton for up to 14 days in culture. Treatment with PFC increased mRNA expression of fibrotic markers COL1A1 and FN1 by more than 4-fold, and nintedanib reduced PFC-induced expression of COL1A1 and FN1 by more than 60%, confirming its anti-fibrotic properties.

We successfully generated large numbers and repeatable hPCLS that remained viable and structurally intact for up to 14 days in culture conditions. We also used these hPCLS to model pulmonary fibrosis, creating a model that can be used to evaluate new treatments. Generating hPCLS is a challenging task that requires skill and expertise. Therefore, our results demonstrate that hPCLS are a feasible and promising platform for studying lung diseases and developing new therapies.

References