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# Soft extracellular matrix drives an endoplasmic reticulum stress-dependent S quiescence underlying molecular traits of pulmonary basal cells

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## Abstract

Soft microenvironment, either in 2D and 3D, preserves the characteristics of progenitors. However, the mechanism by which the mechanical microenvironment determines progenitor phenotype, and its relevance to human biology, remains poorly described. To address this point, we designed multi-well hydrogel plates with a high degree of physico-chemical uniformity to reliably address the molecular mechanism underlying cell state modification driven by physiological stiffness. Cell cycle, differentiation and metabolic activity could be studied in parallel assays, showing that the soft environment promotes an atypical S-phase quiescence and prevents cell drift, while preserving the differentiation capacities of human bronchoepithelial cells. These softness-sensitive responses are driven by defects in proteostasis and enhanced basal endoplasmic reticulum stress. The analysis of available single cell data of the human lung also showed that this non-conventional state coming from the soft extracellular environment is indeed consistent with molecular features of pulmonary basal cells. Overall, this study demonstrates that mechanical mimicry in 2D culture supports allows to maintain progenitor cells in a state of high physiological relevance for characterizing novel translational molecular events that govern progenitor biology in human tissues.

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