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Extracellular matrix stiffness modulates nuclear lamina organisation and sets nuclear conditions for PRC2 repression

Capability of cells to respond to tissue-level elasticity has important physiological and pathological implications. Stiffening of the extracellular matrix (ECM) promotes invasive behaviour of cancer cells, supports the transformation of fibroblasts into cancer-associated fibroblasts and primes stem cell differentiation programs. Here, we investigated how ECM stiffness modulates the Nuclear Lamina (NL) and its impact on gene expression programs, epigenetic marking and 3D genome organisation. By combining hydrogel cell culturing of primary fibroblasts, genomics and super-resolution microscopy, we found that ECM stiffness modifies composition of the NL, modulates long range chromatin interactions, induces changes in chromatin motion and regulates thousands of genes. We identified a specific set of genes coding proteins involved in pathways related to mechanical adaptation such as adhesion and signalling. These genes harbour an apparent bivalent chromatin signature and are expressed under soft condition while repressed in stiff condition through Polycomb Repressive Complex 2 (PRC2). We found that this stiffness-specific repression is tempered by mechano-transduction and the NL. This work uncovers mechano-dependent NL composition, changes in 3D genome organisation and in chromatin motion which underlie adaptative gene expression programs controlled through PRC2.

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