Uncoordinated regulation of focal adhesions and cytoskeletal tension due to the loss of a-type lamins.

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Abstract
The nuclear lamina mechanically integrates the nucleus with the cytoskeleton and extracellular environment and regulates gene expression. These functions are exerted through direct and indirect interactions with the lamina’s major constituent proteins, the A-type lamins, which are encoded by the LMNA gene. Using quantitative stable isotope labeling-based shotgun proteomics we have analyzed the proteome of human dermal fibroblasts in which we have depleted A-type lamins by means of a sustained siRNA-mediated LMNA knockdown. Gene ontology analysis revealed that the largest fraction of differentially produced proteins was involved in actin cytoskeleton organization, in particular proteins involved in focal adhesion dynamics, such as actin-related protein 2 and 3 (ACTR2/3), subunits of the ARP2/3 complex, and fascin actin-bundling protein 1 (FSCN1). Functional validation using quantitative immunofluorescence showed a significant reduction in the size of focal adhesion points in A-type lamin depleted cells, which correlated with a reduction in early cell adhesion capacity and an increased cell motility. At the same time, loss of A-type lamins led to more pronounced stress fibers and higher traction forces in cells undergoing enzymatic detachment. This phenotype could not be mimicked or reversed by experimental modulation of the STAT3-IL6 pathway, but it was partly recapitulated by chemical inhibition of the ARP2/3 complex. Thus, our data suggest that the loss of A-type lamins perturbs the balance between focal adhesions and cytoskeletal tension. This imbalance may contribute to mechanosensing defects observed in certain laminopathies.
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KEYWORDS: LMNA; SILAC; cytoskeleton; focal adhesion; nuclear lamina; proteomics; stress fibers; wound healing

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