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Mechanical Relaxation during Cell Reprogramming

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Abstract: Cell reprograming technologies have broad applications in cell therapy, disease modeling and drug screening. Direct reprogramming of fibroblasts into induced neuronal (iN) cells has been achieved via the forced expression of three transcription factors: Ascl1, Brn2 and Myt1l. Accumulative evidence suggests that biophysical factors in the microenvironment can regulate the epigenetic state and cell reprogramming. However, whether intracellular mechanical properties regulate cell reprogramming remains unknown. Here, we show for the first time, that the mechanical property of cells is modulated during the early phase of reprogramming as determined by atomic force microscopy (AFM) and high-throughput quantitative deformability cytometry (q-DC). We observed that cell stiffness increased (i.e. 2-fold compared to control) by day 1, which was followed by a pronounced decrease on day 3. Immunofluorescence analysis of cytoskeletal structures demonstrated that by day 1 of the reprogramming process, actin assembled into a network with a cage-like structure around the nucleus, but this structure along with the majority of the cytoskeleton gradually disappeared by day 3, thus coinciding with the changes in intracellular mechanical property. Furthermore, we found that the inhibition of actin contractility by using small molecules altered the reprogramming efficiency. These findings suggest actin cytoskeleton and the mechanical property of cells play an important role during iN reprogramming, which provides new insights into the mechanisms of how biophysical cues modulate cell fate.

Keywords: Cell reprogramming; actin cytoskeleton; mechanical property

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