MECHANOTRANSDUCTION

Forcing nuclei

> isolated nuclei are able to respond to mechanical tension by adjusting their rigidity

The cellular response to mechanical cues involves the transduction of biochemical signals by various subcellular components such as cell-adhesion complexes and the cytoskeleton. Mechanical forces are further transmitted to the nucleus through the linker of nucleoskeleton and cytoskeleton (LINC) complex, but the direct effect of force on the nucleus is not known. Guilluy *et al.* now show that isolated nuclei are able to respond to mechanical tension by adjusting their rigidity, and describe the nuclear mechanotransduction pathway that is involved in this response.

To mimic the transmission of mechanical stress from the cytoskeleton to the nucleus, the authors applied force directly to isolated nuclei of HeLa cells using magnetic tweezers to stimulate the displacement of magnetic beads that were coated with antibodies against the LINC complex component nesprin 1. The application of successive pulses of force triggered an increase in nuclear stiffness within seconds, which resulted in up to 35% reduction in bead displacement. Pharmacological inhibition of factors known to be involved in cell surface mechanotransduction did not prevent nuclear stiffening, which indicates the existence of a separate mechanotransduction pathway that adjusts the rigidity of the nucleus.

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To determine whether the nucleoskeleton mediates nuclear stiffening, Guilluy *et al.* depleted specific nucleoskeletal components using short hairpin RNA (shRNA) and monitored the change in nuclear stiffness. Nuclei that were depleted of lamin A/C exhibited a large decrease in basal nuclear stiffness and failed to stiffen after multiple pulses of force, which suggests that lamin A/C is a major component of the nuclear response to mechanical force. To test this further, the authors isolated LINC complex proteins from nuclei and found that tension induces the recruitment of lamin A/C to the complex. This indicates that applying force on nesprin 1 triggers a reinforcement of the physical connection between the LINC complex and lamin A/C. Other proteins that have been found to be required for nuclear stiffening include SUN1 and SUN2, which interact with nesprins to form the LINC complex and to connect them to lamin A/C, and emerin, a protein of the inner nuclear membrane that binds lamin A/C and was previously shown to affect nuclear mechanics. Interestingly, emerin depletion prevented nuclear adaptation to force but increased basal nuclear rigidity.

Protein phosphorylation is key to mechanotransduction. So, to understand the molecular basis of nuclear adaptation to force, the authors examined global Tyr phosphorylation of proteins from isolated nuclei. They found that force strongly induces the phosphorylation of emerin, and that this is mediated by the SRC family kinases (SFKs). The authors generated shRNA-resistant emerin mutants for residues known to be phosphorylated by SFKs and expressed them in *emerin*-knockdown cells. Nuclei expressing emerin mutant Tyr74 and Tyr95 showed decreased emerin phosphorylation in response to force and abolished lamin A/C recruitment to the LINC complex. Importantly, such nuclei failed to adapt to force.

Taken together, these results indicate that applying force to nesprin 1 activates SFKs, which phosphorylate emerin at Tyr74 and Tyr95, and mediates the mechanical adaptation of isolated nuclei. Thus, the structure of the LINC complex and nucleoskeleton organization are key factors in the transmission of mechanical stress to the nucleus.

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ORIGINAL RESEARCH PAPER Guilluy, C. *et al.* Isolated nuclei adapt to force and reveal a mechanotransduction pathway in the nucleus. *Nature Cell Biol.* http://dx.doi.org/10.1038/ncb2927 (2014)

FURTHER READING

DuFort, C. C. *et al.* Balancing forces: architectural control of mechanotransduction. *Nature Rev. Mol. Cell Biol.* **12**, 308–319 (2011)