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MECHANOTRANSDUCTION

Enforcing protein import

Mechanotransduction — the process of converting mechanical forces into biochemical signals — often terminates in the nucleus, leading to changes in gene expression. These changes in gene expression can be achieved by mechanosensitive transcription factors, such as the effector of Hippo signalling pathway Yes-associated protein (YAP), which translocates to the nucleus in a manner that is regulated by extracellular mechanical signals. The exact mechanisms that govern the import of proteins into the nucleus in response to mechanical stimuli remain poorly understood. Roca-Cusachs and colleagues now show that the key event regulating this shuttling is the application of force to the nucleus, which promotes nuclear import by reducing the permeability barrier of nuclear pores.

YAP is mostly cytoplasmic when cells are grown on soft substrates, whereas it accumulates in the nucleus when cells are grown on stiff matrices. This translocation requires various cellular components, including cell adhesion complexes (cell–cell or cell–extracellular matrix (ECM) adhesions), the actin cytoskeleton and the nuclear envelope, all of which are mechanically coupled. Growing cells on stiff substrates increased coupling between the nucleus and cytoskeleton, whereas depletion of talin — a mechanosensitive intracellular component of cell–ECM adhesions — abolished this coupling. Loss of mechanical coupling between cell–ECM adhesions and the nucleus impaired the translocation of YAP from the cytoplasm to the nucleus on stiff substrates, which indicated that transmission of force to the nucleus is important for nuclear accumulation of YAP. Interestingly, direct application of force to the nucleus using atomic force microscopy (AFM) was sufficient to induce nuclear import of YAP on soft substrates, which suggested that nuclear import is promoted by force acting directly on the nucleus.

> “nuclear import is promoted by force acting directly on the nucleus”

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The authors observed that nuclei of cells grown on stiff substrates as well as after force application with AFM were consistently flatter than nuclei of cells grown on soft matrices. Nuclear flattening increases membrane curvature and consequently could promote stretching and opening of nuclear pores towards the cytoplasm. Indeed, using electron microscopy, they observed that nuclear pores were wider in cells grown on stiffer substrates. Moreover, inducing nuclear flattening by hyper-osmotic shock promoted YAP nuclear accumulation on soft substrates, whereas preventing nuclear flattening by hypo-osmotic shock interfered with nuclear translocation of YAP on stiff substrates. Thus, nuclear accumulation of YAP is driven by nuclear flattening.

Probing mechanical properties of YAP with AFM revealed that it is a mechanically labile molecule, prone to unfolding. Interestingly, when YAP was attached to a mechanically stable protein, nuclear translocation occurred only on highly stiff substrates. Similarly, stiff substrates promoted nuclear accumulation of proteins other than YAP, and the stiffness threshold at which nuclear accumulation was observed was higher for more mechanically stable proteins. Finally, high substrate stiffness was required to promote nuclear translocation of a recombinant YAP when its molecular mass was increased by attaching two copies of a fluorescent tag as opposed to a single copy. This suggested that nuclear protein translocation in response to force largely depends on physical properties of proteins including mechanical stability and molecular mass.

This study demonstrated that application of force to the nucleus — either directly or as a result of intracellular transmission of forces (as occurs *in vivo*) — leads to nuclear flattening, which increases permeability of nuclear pores to mechanically labile and/or low molecular mass proteins. Overall, this mechanism links external forces, intracellular mechanical coupling and mechanical properties of the nucleus to nuclear transport, thereby providing a new framework to understand the pathology of diseases associated with aberrant mechanotransduction, such as cancer.

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FURTHER READING Panciera, T., Luca Azzolin, L., Cordenonsi, M. & Piccolo, S. Mechanobiology of YAP and TAZ in physiology and disease. *Nat. Rev. Mol. Cell Biol.* http://dx.doi.org/ 10.1038/nrm.2017.87 (2017) | Uhler, C. & Shivashankar, G. V. Regulation of genome organization and gene expression by nuclear mechanotransduction. *Nat. Rev. Mol. Cell Biol.* http://dx.doi.org/ 10.1038/nrm.2017.101 (2017)