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Current Opinion in Cell Biology

Structural components of nuclear integrity with gene regulatory potential

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The nucleus is a mechanosensitive and load-bearing structure. Structural components of the nucleus interact to maintain nuclear integrity and have become subjects of exciting research that is relevant to cell and developmental biology. Here we outline the boundaries of what is known about key architectural elements within the nucleus and highlight their potential structural and transcriptional regulatory functions.

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Current Opinion in Cell Biology 2017, **48**:63–71

This review comes from a themed issue on **Cell Dynamics**

Edited by **Eugenia Piddini** and **Helen McNeill**

For a complete overview see the Issue and the Editorial

Available online 19th June 2017

http://dx.doi.org/10.1016/j.ceb.2017.06.001

Introduction

It is now well established that the nucleus, cytoskeleton, and extracellular matrix (ECM) exist as interconnected, rather than isolated, structures that can transduce mechanical signals between one another through tensile and compressive interplay that is often termed tensegrity [1,2]. Our understanding of these interconnections is rapidly growing and recent reviews outline ECM–cytoskeleton–nucleus interconnectivity [3–5], although thorough characterisation of the complex interplay between components of the nucleus remains a future goal.

Mechanotransduction represents a uniquely efficient tool for transmitting subcellular signals because mechanical signals are much more rapid than translocation or diffusion of subcellular signals [6]. The cytoskeleton is physically attached to the nuclear envelope through outer nuclear membrane (ONM) Nesprin proteins that are anchored to the inner nuclear membrane (INM) by SUN proteins [7]. In various cell types, it has been demonstrated that dynamic, global changes in subnuclear organisation occur in response to cellular tension in a magnitude and time-dependent manner [8], implying that extracellular shear is transmitted to the nuclear interior. The interconnected nature of the nucleus and cytoskeleton is multifaceted and complex. This relationship is increasingly appreciated as important for the translation of mechanical cues into transcriptional modulation and stem cell differentiation [9,10] and is also critical for nuclear movement and position within the cytoplasm [11,12]. A recent review draws a clear connection from ECM stiffness and shear stress on cells to nuclear import of transcription factors [13••] which we do not cover here.

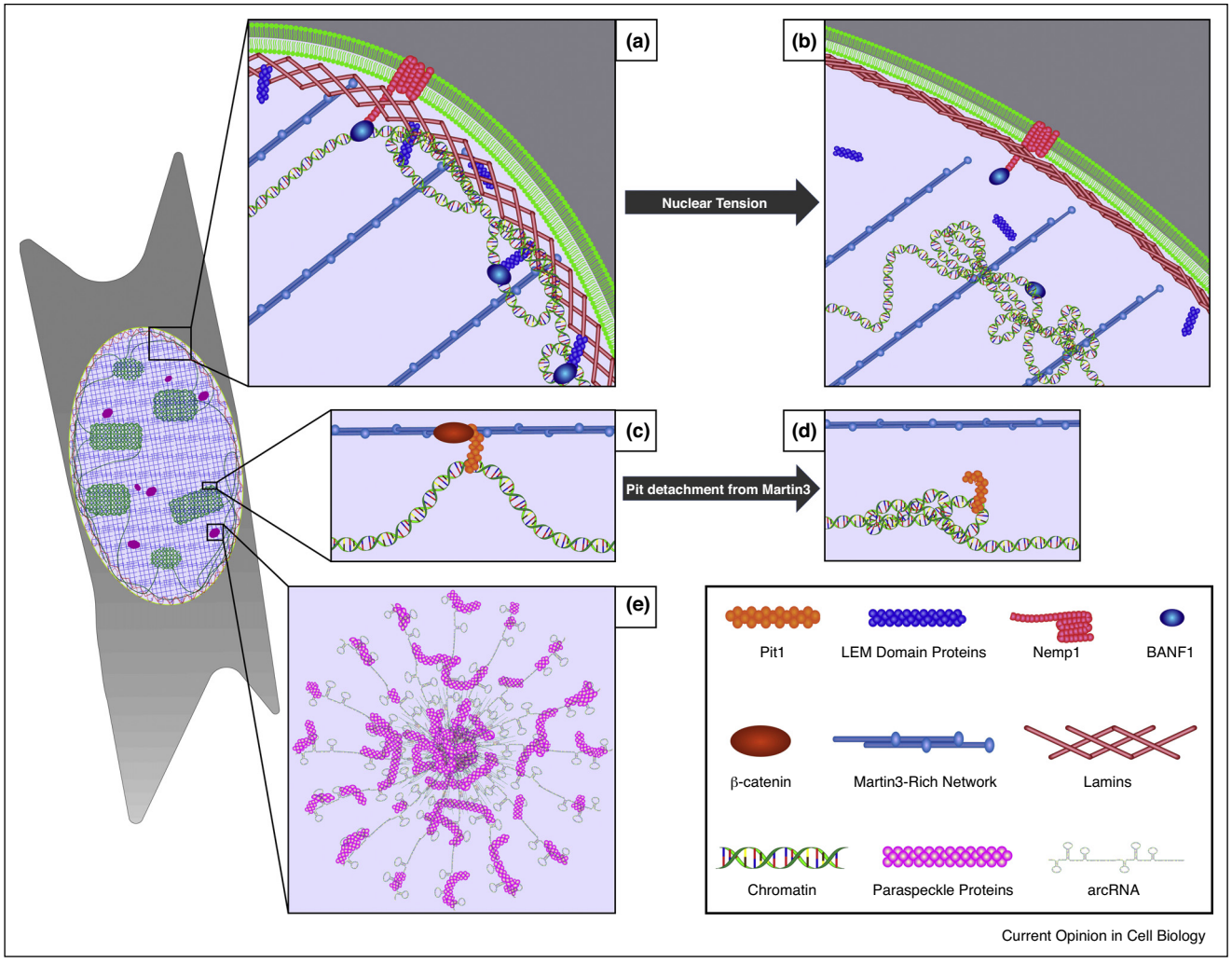
The effects of external mechanical influences on the nucleus have received a great deal of attention in recent years and the downstream consequences of those influences are the focus of recent publications. Cues that are mechanically transduced to the nuclear interior are undoubtedly modulated by the structural components of the nucleus that absorb and transmit forces within the nucleoplasm. Here we review key subnuclear structural components, including exciting players new and old, and attempt to parse structural and gene regulatory functions of each.

The nuclear lamina

Structural aspects

The subnuclear periphery consists of the lamins, a meshwork of interconnected intermediate filaments and the proteins that associate with them, which together are called the nuclear lamina (Figure 1a). In mammals, there are two types of lamins, A-type lamins and B-type lamins, that are encoded by three different genes. *LMNA* encodes LaminA/C, the A-type lamins, while *LMNB1* and *LMNB2* encode Lamin-B1 and Lamin-B2, respectively. Mutations in *LMNA* cause several human diseases, termed laminopathies, including Hutchinson-Gilford progeria syndrome, Emery-Dreifuss muscular dystrophy, dilated cardiomyopathy, and familial partial lipodystrophy [14•]. LaminA/C knockout mice die eight weeks after birth with muscular and lipo-dystrophic progeroid phenotypes, while LaminB1 knockout mice die at birth with lung, brain, and bone shape defects [15,16]. *LMNA* heterozygous null mutations in human cells cause the nuclear envelope to be fragile and susceptible to rupture [17,18] while *Lmnb1* mutant mouse cells exhibit extremely misshapen nuclei, a high rate of polyploidy, and impaired

Figure 1



Scaffolding components within the nucleus.
Top panels: Matrin3-rich nuclear matrix and chromatin are anchored to the nuclear lamina, **(a)** Mechanical strain causes detachment of chromatin from the lamina and, somewhat unexpectedly, can be associated with polycomb-dependent gene silencing, **(b)** Middle panels: Pit1 anchors target genomic domains to the nuclear matrix, **(c, d).** This physical tether is required for proper transcriptional activity of Pit1 targets. Bottom Panel: Architectural RNAs physically link components of many nuclear bodies, as in paraspeckles, **(e)**.

differentiation [16]. Microaspiration experiments have shown that LaminA/C and LaminB contribute to nuclear viscosity and elasticity, respectively [19]. Stiffness of the nucleus scales with the stiffness of the local ECM and the LaminA:LaminB ratio. Interestingly, cells with softer (*i.e.* lower LaminA:LaminB) nuclei preferentially differentiate into softer cell types (*e.g.* adipocytes) whereas higher LaminA proportion directs differentiation towards stiffer cell types (*e.g.* osteocytes) [19]. Additionally, LaminA/C expression coincides with marked changes in the physical properties of the nucleus that are associated with transition of human and mouse embryonic stem cell (ESC) to more differentiated cell states [20,21]. Therefore, Lamins play a fascinating role in development because they link physical properties with cell fate.

Regulatory function

LaminA/C-mediated nuclear stiffness requires the dephosphorylation of LaminA [19], and stiff ECM dephosphorylates four sites on LaminA [22]. One model suggests that rope-like tension might induce conformational tightening of coiled-coil dimers of LaminA fibers as an explanation for their dephosphorylation under high tension or stiff ECM conditions [13••] (Figure 1a, b). This means that the nuclear lamina may act, not only as a structural scaffold for the nucleus, but also as a shear stress sensor and mechanical signal transducer.

The nuclear lamina interacts with many proteins at the nuclear periphery [14•], and Lamin A/C is particularly important for maintaining the peripheral location of