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# Cross talk between the cytoplasm and nucleus during development and disease

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Mechanotransduction is a process whereby mechanical stimuli outside the cell are sensed by components of the plasma membrane and transmitted as signals through the cytoplasm that terminate in the nucleus. The nucleus responds to these signals by altering gene expression. During mechanotransduction, complex networks of proteins are responsible for cross talk between the cytoplasm and the nucleus. These proteins include cell membrane receptors, cytoplasmic filaments, LINC complex members that bridge the nucleus and cytoplasm, and nuclear envelope proteins that connect to the chromatin. Mechanotransduction also plays a critical role in development. Furthermore, it is possible that disrupted mechanotransduction leads to changes in gene expression that underlie the pathogenic mechanisms of disease.

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## Introduction

The nucleus is typically the largest and stiffest organelle within a cell, yet it can respond to changes in the extracellular environment through mechanotransduction [1]. This process relies on a series of interconnected cellular components that bridge the outside of the cell to the nucleus. Mechanical stimulation can initiate at the extracellular matrix (ECM) and affect proteins in the plasma membrane such as integrins [2] (Figure 1). Integrins and classical cadherins connect to cytoplasmic actin, whereas constituent desmosome and hemidesmosome proteins interact with microtubules and intermediate filaments (IFs) such as keratins and desmin [3••]. The three types of major cytoskeletal filament proteins (actin, microtubules and intermediate filaments) bind the LINC (linker of the nucleoskeleton and cytoskeleton) complex (Figure 1) [2,4,5]. This complex contains the outer nuclear membrane KASH (Klarsicht/ANC-1/Syne Homology) domain proteins that connect to these cytoplasmic filaments (Figure 1). Within the perinuclear space, KASH domain proteins interact with SUN (Sad1p, UNC-84) domain proteins that are embedded within the inner membrane of the nuclear envelope. SUN domain proteins bind lamins, intermediate filaments that form distinct networks on the inner side of the nuclear envelope, as revealed by super resolution microscopy and computational analysis [6]. Lamin phosphorylation regulates the assembly of the networks and potentially impacts associations between lamins and other nuclear envelope proteins [7•].

Lamins bind a diverse group of nuclear envelope transmembrane proteins (NETs) [8], several of which possess a LAP2-Emerin-MAN1 (LEM) domain [9] that associate with Barrier-to-autoantigen (BAF) (Figure 1) [10]. BAF, lamins and lamin-associated polypeptide 2alpha bind chromatin and tether regions of the genome to the nuclear envelope, thereby regulating gene expression [10–12]. While lamins are globally expressed, NETs are often tissue-restricted, providing an explanation for tissue-specific phenotypes and changes in gene expression observed for nuclear envelope protein diseases [8].

## Mechanocoupling between the cytoplasm and the nucleus

External forces on cells can result in altered expression of mechanosensitive genes. This process occurs in epidermal and muscle cells in response to exercise and mechanical load and in blood vessels exposed to fluid sheer stress [13]. Mechanosensors, proteins that translate mechanical inputs into distinct outputs, are typically localized at the plasma membrane. Prominent mechanosensors include integrins, cell adhesion molecules, growth factor receptors, cadherins, and stretch-activatable ion channels [14–17]. Stimulation of mechanosensors by physical forces results in changes in their localization and/or conformation, in some cases unmasking cryptic binding sites for cytoplasmic adapter proteins. Cytoskeletal complexes such as actomyosin mediate mechanical force from the mechanosensors to LINC complex members [18•], which experience mechanical force [18•] that results in changes in gene expression.

### Nuclear positioning

Mechanocoupling between cytoskeletal components and the nucleus is used to actively position nuclei within cells

**Figure 1**

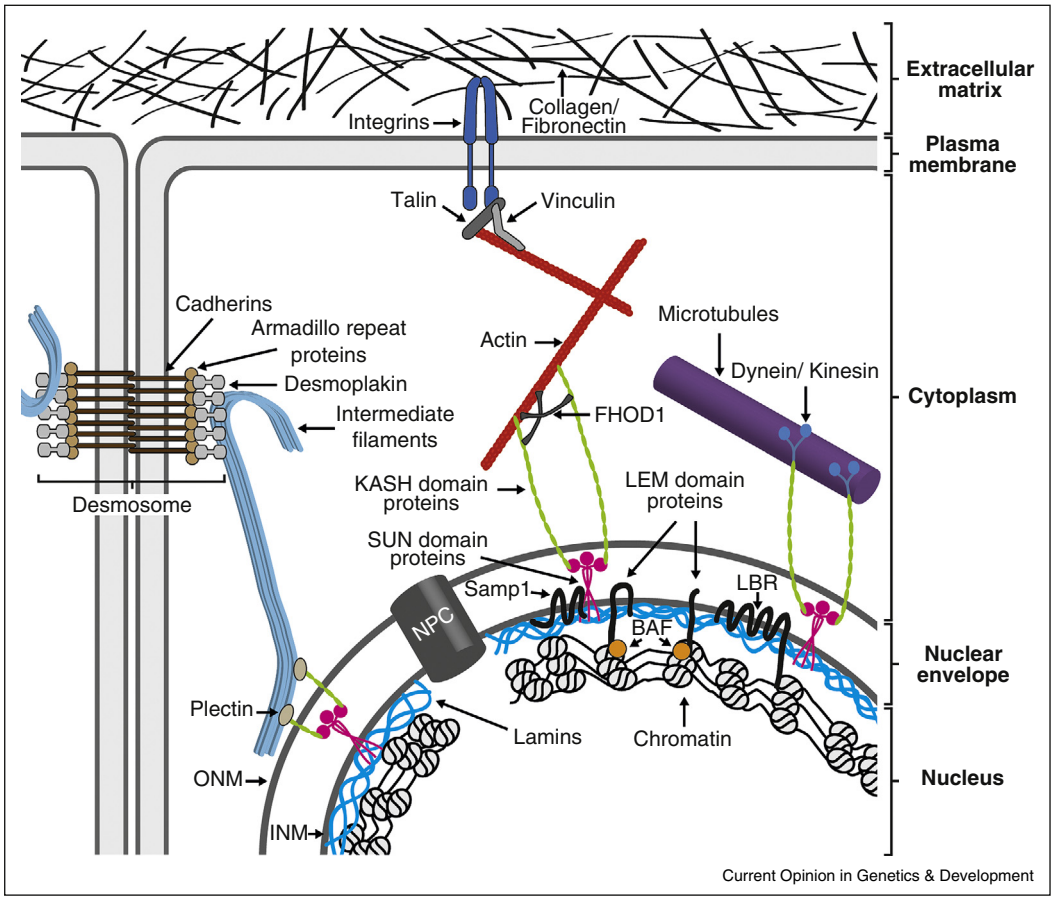


**Diagram of the cellular components that play a role in mechanocoupling**. Mechanical stimulation from the extracellular matrix is received by mechanosensors such as integrins within the plasma membrane. Force transmission alters the organization of cytoskeletal networks of actin, microtubules and intermediate filaments. These factors either directly or indirectly (through proteins such as plectin) connect to nesprins, components of the LINC complex that spans the nuclear envelope. Nesprins (KASH domain proteins) associate with SUN domain proteins within the lumen between the inner and outer nuclear membranes. SUN domain proteins interact with lamins, a major component of the nuclear lamina that lines the inner side of the nuclear envelope. The lamina also contains LEM domain proteins, including emerin, LAP2beta, and LBR. LEM domain proteins interact with the chromatin binding protein BAF to organize the genome. Thus, mechanical stimulation is transmitted through a cell by a complex network of proteins that terminate in the nucleus and alter gene expression, allowing the cell to respond to its environment.

[19]. Nuclear positioning occurs during developmental processes such as cellular polarization, migration and differentiation. Nuclei often assume specific positions based on the particular cell type; their position can dictate cell shape, cell polarity, cell cycle stage, and provide protection from external forces. For example, in muscle, nuclei migrate to peripheral positions where they are thought to be protected them from the contractile action of the cytoskeletal network [20]. Nuclear migration and anchoring needed to achieve positioning is an active process that requires coordination between the cytoplasm and nucleus.

Cytoskeletal components exert force on the nucleus in various ways to generate movement and position of nuclei. For example, in polarizing fibroblasts actin filaments make up a peri-nuclear cap and terminate at focal adhesions [21]. Loss of the LINC complex causes disappearance of the actin cap and failure to properly position the nuclei [22,23]. Within the perinuclear cap, a subset of actin bundles form transmembrane actin-associated (TAN) lines containing nesprin-2G and SUN2 that attach to retrograde moving dorsal actin cables [23,24]. The actin binding protein Formin homology domain-containing protein 1 (FHOD1) is also a component of TAN lines. FHOD1 interacts with the KASH-domain protein nesprin-2G [25] on the cytoplasmic side of the LINC [26•]. Nesprin-2G directly attaches to actin cables by its calponin homology domains; FHOD1 attaches to actin via a unique actin binding site in its N-terminus, which reinforces the actin-LINC connection [24]. These interactions foster nuclear movement and coordinate centrosome orientation during cellular