New and Notable

Systems Perspective on Mechanobiology: Producing the Right Proteins in the Right Place at the Right Time

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Mechanical forces are ubiquitous in biological systems and the field of mechanobiology has emerged with research subjects being investigated from the molecular through the cellular to the tissue level. However, there is a well-defined experimental observation on the cell biological level that can be considered as the defining core of this field, namely the finding that the morphology of adherent cells is strongly determined by the mechanical stiffness of their extracellular environment and that the cells sense this stiffness by self-generated forces (1). The biomedical relevance of this observation became even more obvious when it was discovered that stem cell differentiation can also be guided by substrate stiffness (2). Based on many experimental observations of this type, evidence has been mounting over the last decade that a close relationship exists between cellular function and the mechanics of the microenvironment, with dramatic consequences for health and disease (3).

With the cell biological observations firmly in place, it becomes important to ask for the underlying molecular mechanisms. Although integrin-based focal adhesions and actomyosin force generation have been identified early as key components, it now becomes increasingly clear that in general, the stiffness response of adherent cells relies on a spatially distributed network of many different mechanotransductive modules (4). Several high-throughput screens have been directed toward the stiffness response of cells—for example, a siRNA-screen of kinases regulating adhesion sites (5) and mass spectrometry of proteins involved in the stiffness response (6,7). Given the growing body of high throughput data in mechanobiology, it becomes imperative to ask how they can be integrated into a system-level understanding of the role of forces for cellular decision-making.

In their contribution to this special *Biophysical Journal* issue on quantitative cell biology, Dingal and Discher (8) demonstrate how this challenge can be tackled by kinetic modeling. Their starting point is the recent finding that expression levels of lamin-A, an intermediate filament of the nuclear lamina that not only mechanically protects the nucleus, but also modulates transcription, increases with tissues rigidity via a characteristic power law that is reminiscent of the scaling of the rigidity of polymer gels with concentration (Fig. 1 *A*) (7). This suggests that cells in tissue under higher mechanical stress produce more structural proteins that protect them from the detrimental effect of force and at the same time allow them to regulate their cellular function through mechanics. Such a production on demand is similar to the way bacteria switch their metabolism when encountering different food sources, except that in the tissue case, we deal with a more complicated feedback system inasmuch as many cell types build their own microenvironment.

The first aim of Dingal and Discher (8) is to perform a dynamical systems analysis for the lamin-A case. For this purpose, they turn to a classical model for gene expression that shows with simple kinetic equations that a positive feedback between protein expression and transcription leads to bistability. Thus gene expression is turned either on or off, with an expression level that is determined by the model parameters and independent of the exact initial conditions. Such a mechanism is actually known for lamin-A, which upregulates it own expression through the transcription factor retinoic acid receptor-γ (RARG), as shown in Fig. 1 *B*.

However, it is not clear how forces would enter this classical picture. Often, the effect of force is attributed to changes in association and dissociation rates; for example, for the short-time dynamics of integrin-based focal adhesions (9,10). Dingal and Discher (8), however, aim at the long-time effects of forces on gene expression. Motivated by the recent finding that similar types of proteins show similar degradation times in cells, they focus on the effect of force on protein degradation. Various experimental observations suggest that degradation is diminished for structural proteins such as lamin-A, e.g., by compactifying and thus protecting cleavage sites for attack by proteases.

Extending the gene expression model by a tension-dependent degradation term (compare Fig. 1 *B*), the authors show that their kinetic model can predict the experimentally measured scaling of lamin-A expression level with tissue elasticity as a function of rate constants (Fig. 1 *C*). The quantitative agreement between the simple model and experiments indicates that the authors might have identified the core mechanism for force-dependent lamin-A regulation, and that other mechanobiological modules might function in a similar manner. The authors confirm this view by extending their kinetic approach to two other, more complicated systems, namely, the stabilization of myosin IIA minifilaments in the cytoskeleton and collagen secretion in the developing heart—again in very good quantitative agreement with experimental results.

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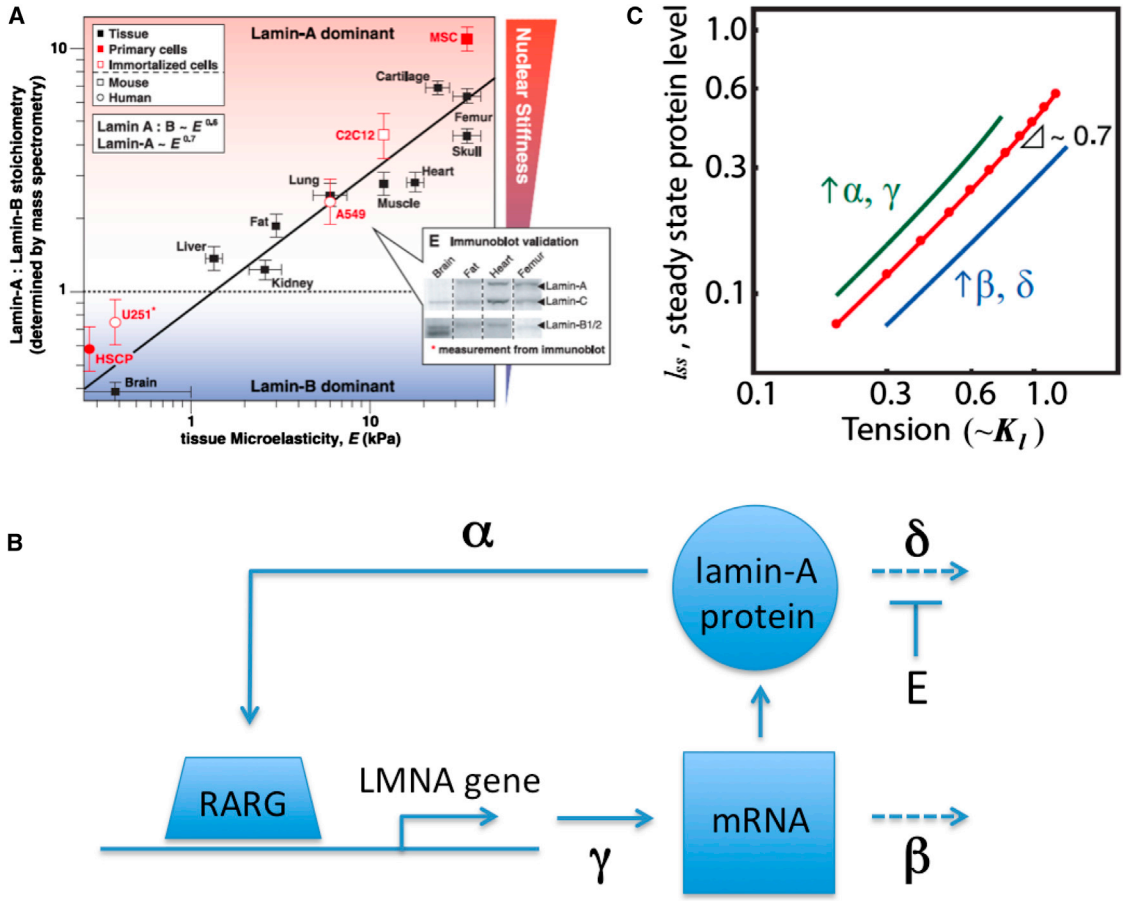

FIGURE 1 A genetic feedback loop can explain the scaling of lamin-A expression with tissue stiffness. (*A*) Using mass spectrometry, it has been shown that lamin-A expression levels scale via a power law with tissue stiffness *E* (lamin-B is used as only a weakly force-dependent reference) (7). (*B*) A positive feedback loop exists between lamin-A transcription and translation. The main effect of stiffness *E* might be to diminish protein degradation. (*C*) Kinetic modeling of this scheme leads to the experimentally observed scaling and predicts the effect of changing the reaction constants (8). To see this figure in color, go online.

In summary, the authors have introduced an appealing concept for force-mediated protein expression that can now serve as a blueprint for a systems-wide approach to high throughput data in mechanobiology. The beauty of this study is the convincing combination of a very clear conceptual scheme with a mathematical framework that can easily be upscaled to large data sets. Such conceptual advances are urgently needed to make sense out of the rapidly growing body of high-throughput data of mRNA and protein levels (including posttranslational modifications) as a function of environmental stiffness and cellular contractility. Although this study can be only a first step given the complexity of cell and tissue regulation, it will certainly inspire more detailed experimental and theoretical work along these lines in the near future.

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