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Letter to the editor

Mechano-molecular transduction: Putting the pieces together

ABSTRACT

When subjected to extracellular mechanical loads, cells express a variety of responses ranging from differentiation to apoptosis. The transducing mechanism between the physical stimulus and the molecular response is known as mechanotransduction. In this study, a mechano-molecular model is established that facilitates the integration of cellular mechanics with molecular signaling. It reveals a unique coupling mechanism between the physical stimuli, the extracellular mechanical properties, and the Rho signaling pathway. Myosin activation is shown to be correlated with the rate of intracellular activity and found to vary extremely for different extracellular rigidities. These findings can explain and interpret the fundamental observations of mechanotransduction.

Extracellular mechanical signals are known to affect and modulate the structural and functional properties of cells [1]. The mechanism by which cells sense and transduce these signals is known as mechanotransduction. Previously, insights being deepened into the complexities of many transduction pathways, the extracellular microenvironment was suggested to play a key role in activating cellular pathways [1, 2]. The microenvironments have been investigated using miscellaneous substrates which mimic different tissue elasticities, resulting in the appealing phenomenon that cells can initiate *in-vitro* neurogenic, myogenic and osteogenic phenotypes by directly altering cellular contractility [3–5]. Additionally, recent studies reveal that extracellular mechanical perturbations can alter specific cellular functions associated with morphogenesis [6, 7]. These observations suggest that the transduction of external forces involve a coupling mechanism which allows cells to gradually modulate the activation of mechano-sensitive intracellular pathways [1]. In spite of these evidences, questions are still raised concerning the way mechanical signals are intracellularly transduced to biochemical and genetic expressions. Moreover, the mechanism through which cells compensate for mechanical perturbation is not fully understood. Several studies have been conducted to study the relation between cellular appearances and extracellular perturbations [8–14]. These focus mainly on phonotypical aspects such as morphological variety, stress-fibers aliment, and the formation of adhesion complexes. However, till date, the generic coupling between the physical stimulus and the intramolecular response has not been specifically studied. This can shade a light on understanding the mechanism by which cells can sense and adapt to their environments. To address this challenge, a conceptual scheme for mechano-molecular transduction is proposed. This theoretical framework implements a self-regulating, mechanical to molecular coupling, within which extracellular loads induce the activity of intracellular signaling pathways to allow cells to compensate for external perturbation. The model is derived based on a generic description of adhering cells in which Myosin actuators play a central role in regulating cellular forces. The activation of Myosin leads to the generation of cytoskeletal contractile forces which allow cells to mechanically compensate for external perturbations.

The model is based on an analog description of the cell by which feedback elements are used to simulate its intracellular response. The self-regulatory mechanism is represented by a series of "tuning constants" which reflect the relative activation of Myosin actuators for a given perturbation. This mechanism is inspected through engineering perspectives and benefits from the simplicity of treating molecular complexity as grouped modules [15, 16]. Spring-damper compositions are utilized to simulate the viscoelastic properties of the cellular components as described in Fig. 1a. It includes the extracellular matrix (ECM), phospholipids membrane, cytoplasm, and the actin filaments. Since the viscosity of the membrane is much smaller in comparison to its deforming modulus; its damping effect can be neglected. The cellular mass is represented by an effective mass element in parallel to the ECM and membrane components. The extracellular perturbations are represented by a displacement generator X_s which exerts force through ECM and disseminate throughout the cytoplasm and actin filaments. The intracellular force F_m is generated by the Myosin actuators located within the actin filament bundles. In order to ease the treatment of the mechanical system, the scheme is transformed into an equivalent electrical system as shown in Fig. 1b and c. Mechanical-electrical analogies are the representation of mechanical systems as electrical networks. Using the impedance analogy method (See supplementary material appendix S1 for complete details), the mechanical circuit is represented by analogous electrical circuits when the inducers, resistors and capacitors stand respectively for spring, damper and mass elements. The displacement and force generators are equivalently represented by the voltage V_i and current I_i sources respectively.

A block diagram describing the mechano-cellular response for external perturbations is given in Fig. 2a. The two transfer functions H and T stand for the membrane force response based on the circuits given by Fig. 1b & c respectively. The functions represents the relation between the intracellular force generated by myosin actuators (F_m), the ECM displacement (X_s) and the net membrane force (F_{mem}). The surface displacement convolutes the H block and generates force on the cell membrane. A feedback loop between the membrane output and the block T represent the intracellular response in which the cell tends to counterbalance for external load (See supplementary material appendix S2 for the complete derivation). The tuning constant k describes the "intracellular compensation" which is required to lower the net membrane force below a given threshold of 0.1 pN. From physiological point of view, the given diagram closely simulates the native mechano-cellular response. Once the membrane is agitated, the cell quenches the

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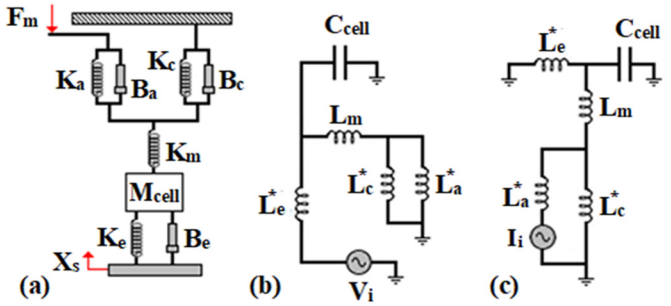

Fig. 1. (a) Mechanical analog model describing the different cellular components based on their viscoelastic properties. (b) Equivalent electrical model stands for the ECM excitation. (c) Equivalent electrical model stands for the Myosin excitation. The sub notations e, m, a, and c, are referred to the ECM, membrane, actin, and cytoplasm components respectively (See supplemental material for Table S1.2 for values used during simulations). The L* notation is referred to a parallel inducer-resistor configuration.

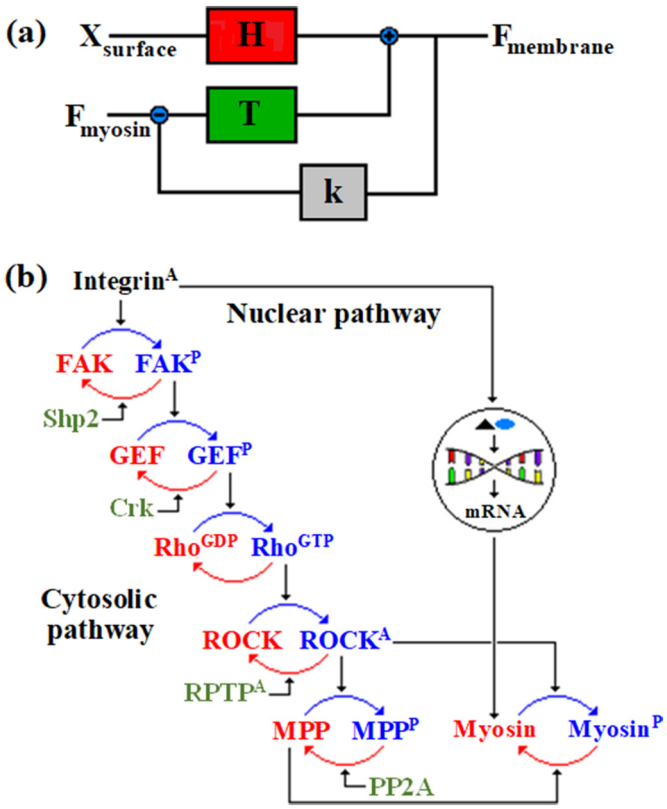

Fig. 2. (a) Block diagram simulates the mechano-cellular response. (b) Main interaction steps of the Rho signaling pathway.

oscillations until below a certain threshold of sensitivity. The actin filaments bundles are contracted by Myosin actuators in order to suppress the membrane agitation below the threshold value. The degree of cellular response is represented by the tuning constant k, which can be treated as an equivalent analog to the activity required to balance the external membrane force. Fig. 3a demonstrates the system activity in suppressing a sinusoidal force signal. For a k greater than 10^3, the membrane force is reduced below a threshold of 0.1 pN, hence, the extremal force is balanced by the endogenous tensional force.

The activation of Myosin actuators allows cells to maintain their structure and to avoid cellular rupture. From molecular point of view, the Myosin actuators are activated by Rho signaling network through membrane Integrin mechanoreceptors that attached to the ECM Fibronectin fibers [17]. The Integrin-Fibronectin bonds used as mechanical clutches for cellular spreading and known to respond to mechanical loads [18, 19]. This allows to increase bond strength and to gradually initiate intercellular signals to control homeostasis. Fig. 2b illustrates the main interaction steps of the Rho pathway [20]. Once the mechanoreceptors become active, they stimulate two parallel pathways which operate at different timescales: “fast pathway” which activates the signaling network and a “slow pathway” which promotes the activation of the nucleus to induce and alter specific gene activities. From biophysical point of view, this separation of timescales allows to study the intracellular dynamics using steady-state approximation for the fast timescale interactions [16, 21]. The dynamics of the network is simplified by describing only the basic biochemical interactions between the signaling molecules [16]. It includes information regarding the active or inactive states of the molecules and the formation and degradation rates of each interaction.

The initiation of the Rho signaling pathway is triggered by the active Integrin mechanoreceptors throughout the membrane. The activation of the bounded (by Fibronectin) Integrin mechanoreceptors is enhanced by mechanical loads and is mainly attributed to the membrane tensional force. Biophysically, the interaction between the tensile