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Comment

Cell adhesion mechanosensitivity, an active biological process Comment on "Cellular mechanosensing of the biophysical microenvironment: A review of the mathematical models of biophysical regulation of cell responses" by Bo Cheng et al.

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The mechanisms that allow cells to sense the mechanical properties or the mechanical stimulations of their extracellular environment are being debated for the last 20 years. Cheng et al. offer a synthetic review of a large panel of theories that have been explored [1]. Scenarios based on cytoskeleton (acto-myosin), ion channels, adhesion or nucleus as initiators of cell mechanosensitivity have been proposed. A striking feature of all these theories is that albeit quite diverse in their assumptions, they succeed in describing one or another feature of cell mechanosensitivity. Several of them even address the description of identical observations, and models with very different assumptions, for instance distinct biochemical partners or distinct locations or range of action, lead to results that are consistent with the experiments. This may suggest that cell mechanosensitivity is driven by several mechanisms that are simultaneously at stake.

This is for instance the case of cell adhesion mechanosensitivity (section 6 in Cheng et al.). Cell adhesion mechanosensitivity is the ability of cells to adapt their anchorages to the rheological properties of their extracellular environment. Experiments show that changes in composition or size of cell anchorages relate to changes in biochemical signaling and influence cell's basic behaviors such as cell cycle, differentiation, protein and DNA synthesis etc. For this reason, understanding whether basic physical mechanisms control cell adhesion mechanosensitivity has motivated several hundreds of studies for the last 20 years. As the distribution of cell anchorages to the extracellular matrix resembles a frozen condensation process, the first modelings of cell adhesion have been inspired by the physics of phase separation [2–4]. These approaches have rapidly shown discrepancies with the observations, but they have emphasized a non-intuitive critical ingredient that is required to account for cell adhesion mechanosensitivity: the formation and the regulation of cell adhesions are out-of-equilibrium processes, that rely on energy input from the cell. And not surprisingly, the panel of theories that Cheng et al. report [1] are all out-of-equilibrium approaches, based either on stochastic physics (molecular clutch model, stochastic elasticity model, adhesion clustering model) or non-conservative thermodynamics (2D molecular mechanical model, linear elastic chain adhesion model, multi-scale stress fibers model).

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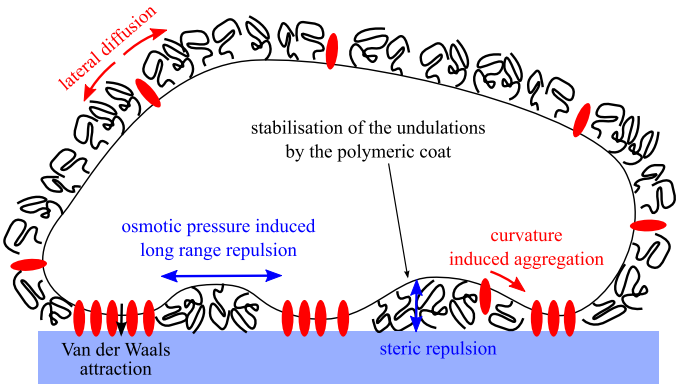

Fig. 1. Ingredients of engineered vesicles needed to mimic cell adhesion. With permission of [5].

The aim of this comment is to point how and why the input of energy from the cell is required to account for cell adhesion mechanosensitivity.

1. Passive modeling of cell adhesion

The first trials to model cell adhesion were assuming that the adhesive domains result from a two-dimensional phase separation of adhesion proteins into condensed domains [2–4]. In these models, cell activity is not considered at all, nor the cellular stresses from the acto-myosin cytoskeleton that pull on the adhesive domains. Although it is now proven that cell activity regulates cell adhesion, these works nevertheless brought valuable information on the contribution of passive components that contribute to cell adhesion: the fluid cell membrane, the polymeric extracellular coat named glycocalix and membrane fluctuations (Fig. 1). Using decorated vesicles as biomimetic models [6], micron sized domains with consistent lifespan could be obtained. Major limitations of these passive models are that the mechanosensitivity of these biomimetic adhesions is not consistent with observations on cells [5]: (i) forces that pull off the vesicle normal to the substrate lead to adhesion reinforcement simultaneously to the reduction of the contact area [7,8], and (ii) shear stresses are predicted to enlarge the adhesion belt, but make the cell roll [9]. Both predictions differ from the observations that the adhesion size decreases in response to normal forces [10], and that shear stresses make cell adhesions grow with no retraction of lamelipodia [11]. Additionally, prediction of the larger size of cell adhesive domains on stiff materials compared to soft ones seems unattainable as the elastic interaction of inclusions in a semi-infinite, deformable substrate is attractive [12,13], and therefore promotes larger domains on soft materials.

2. Activity is required for cell adhesion mechanosensitivity

Thus energy supplies from the cell have entered physical modeling. Many active models have focused on acto-myosin cytoskeleton, that permanently stresses cell adhesive domains. They assume a constitutive law that relates cell stresses to the resistance to the stresses. This law is extrapolated from the experimental measurement by Hill on muscle sarcomers [14] (Fig. 2a). Consequently, while an acto-myosin stress fiber would contract from a certain amount due to motor activity, this zero load tension from the motors may adapt in response to the resistance it is opposed. This occurs when the stress fiber is attached via cellular adhesions to a substrate. If the substrate is more deformable than the internal cellular components, stress fibers or adhesions, tension in stress fibers mainly induces the deformation of the material and not of the cellular components. Then stress fibers are less deformed than on a stiff material. Following Hill's law, the intern tension is reduced. This then limits conformational changes or cryptic sites unveiling in the adhesive domains, and adhesions are therefore expected to be smaller in cells plated on soft materials, as experimentally observed. Models differ by the way they consider protein response to stress and the chemo-mechanical coupling of proteins and actin stress fibers as discussed in details by Cheng et al. But in all these approaches, the driving parameter is the energy input from the cell to set up the tension in the stress fibers. The softer the extracellular environment, the less energy is provided by the cell, and this limits the activation of the growth of the adhesions. Thus, schematically, in these approaches, mechanosensitivity is accounted by minimizing the free energy of the proteins that compose the

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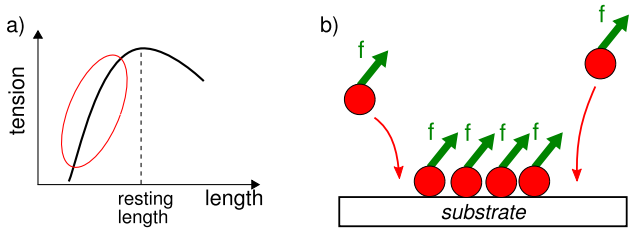

Fig. 2. a) Length–tension relationship in muscle, derived from [15]. Acto-myosin fibers work in the contraction regime, encircled in red: shortening of the fibers from their resting length induces tension. b) Formation of adhesive domains as an active condensation process: elementary units composed of proteins stressed by the acto-myosin fibers condense into an adhesive domain. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

adhesion clusters in the presence of an energy input from the cell that is determined by Hill's law and coupled to the adhesion size.

Another point of view analyzes the dynamics of adhesion clusters as a condensation process, as was originally done using passive thermodynamic models. Tension in the stress fibers is then no more assumed to counteract with resistance to deformation as in Hill's law. For instance, it is assumed to keep constant for simplicity. Adhesions are seen as the association of elementary protein complexes, including stress fibers (Fig. 2b). Growth of adhesions results from the condensation of these stressed elementary units. When the adhesion grows onto a deformable material, anchoring induces the elastic deformation of the material as every elementary unit is subjected to tension from actin stress fibers. This deformation costs elastic energy. The elastic energy that is required to condense stressed elementary unit on a flat semi-infinite elastic medium is [12,16]:

$$\mathcal{H}_{el} = \frac{1}{2}\sum_{i,j}\left(f^{(i)}u(i, f^{(j)}) + f^{(j)}u(j, f^{(i)})\right) \propto \frac{1}{Y} \tag{1}$$

with $f^{(i)}$ the stress on site i, $u(i, f^{(j)})$ the displacement field at site i due to stress on site j and Y the Young's modulus of the deformable material. From cell's point of view, adding a new stressed elementary unit to an adhesive domain requires more energy on a soft material than on a stiff one. On the contrary, the elementary units recover the elastic energy from the material, and therefore gain more energy on a soft material. Experiments show large adhesive domains on stiff materials, smaller ones on soft materials. Then, in order to account for cell adhesion mechanosensitivity, the free energy to consider has to include the energy cost to maintain stresses on growing adhesive domain. So here also, mechanosensitivity is accounted by minimizing the free energy of the proteins that compose the adhesive domains in the presence of an energy input from the cell that is controlled by the size of the adhesion.

3. Conclusion

Both generic approaches aim at describing cell adhesion mechanosensitivity. Although quite different in their assumptions, regulation of the cellular intern tensions or optimization of the energy that is required to stress the adhesive domains, both indeed converge to the same prerequisite: the driving role of the energy input from the cell. Both approaches then offer predictions on the spatial range for rigidity sensing (cell or adhesion scales), actin fluxes, stress distributions inside adhesions (that have to correlate to protein organization), etc, which then have contributed to raise numerous biological investigations for the last decade (see [17] for a representative example). This makes cell adhesion mechanosensitivity an example of a complex biological pathway that can constructively be modeled by out-of equilibrium physical approaches.

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