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PERSPECTIVES

Restless cell syndrome

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Hong *et al.* (Hong *et al.* 2014), in this issue of *The Journal of Physiology*, present an approach to describe and understand spontaneous elasticity oscillations of vascular smooth muscle cells (VSMCs). Cell elasticity reflects the functional state of the cytoskeleton which is the result of complex regulatory processes. Continually repeating fluctuations of cell elasticity reflect multiple cellular activities rather than specific properties of individual components. Oscillations obviously occur as a consequence of self-organization in complex systems, where many biochemical and mechanical networks interact (Julicher & Prost, 1995). Spontaneous and periodic elasticity changes (elasticity oscillations) have been observed in several cell types, e.g. VSMCs, skeletal and cardiac muscle cells, myofibroblasts and also in endothelial and epithelial cells. These spontaneous oscillations are not strictly sinusoidal but can be modulated by specific substances. As shown by Hong *et al.*, the oscillations observed in VSMCs can be described as high amplitude/low frequency undulations superimposed by low amplitude/high frequency waves, the components of the oscillation pattern after Eigen-decomposition, tuneable by vasoactive agonists.

The fact that cells with completely different functions show this same behaviour may lead to the assumption that mechanical oscillation could be a fundamental biological process. Two major questions arise: (i) what triggers these oscillation, and (ii) what is the physiological relevance behind them.

Cytoskeletal rearrangement and myosin motor protein activity are capable of changing cell elasticity. Both mechanisms are strongly influenced by intracellular concentrations of calcium. Myosin II motors exhibit auto-oscillations when the intracellular level of free Ca^{2+} is 'intermediate', somewhere between the 'high level' during contraction and the 'low level' during relaxation (Ishiwata *et al.* 2007). Both frequency and amplitude of such elasticity oscillations are sensitive to modulations in intracellular free calcium concentration (Schillers *et al.* 2010). Hong *et al.* show in VSMCs that the vasoactive agonist angiotensin II increases oscillation amplitude while adenosine, another vasoactive molecule, does the opposite, matching well with concomitant changes in intracellular calcium. But calcium is not the only candidate. Myosin light chain can also be phosphorylated in a Ca^{2+}-independent way through the RhoA/ROK pathway (Szaszi *et al.* 2005). Generally, the Rho family small GTPases are central regulators of the actin cytoskeleton and associated cytoarchitectures and are most likely involved in elastic oscillations. Possibly, actin polymerization/depolymerization, branching, crosslinking and entanglement of cytoskeletal elements (entropic/enthalpic elasticity) are responsible for the high amplitude/low frequency undulations, whereas myosin activity accounts for the low amplitude/high frequency waves. High amplitude corresponds to a high level of synchronized activities. Probably, a high amplitude/low frequency oscillation dominates when force-generating elements follow a superordinate signal that forms an underlying rhythm. Adding angiotensin II to VSMCs is a signal that increases the level of synchronization and/or intensifies the activity of force-generating elements. In contrast, adenosine reduces synchronization and/or intensity. This is somewhat reminiscent of brain activity (measured by EEG; electroencephalography) in which high amplitude/low frequency waves indicate a high level of synchronized neuronal activity (deep sleep phase, delta waves), whereas low amplitude/high frequency undulations reflect desynchronized neuronal activity (alert, beta waves). It follows that mechanical oscillations may not 'report' on the activity of specific components but rather coordinate the activity of individual force-generating elements.

The physiological relevance of these mechanical oscillations is still unknown. Hong *et al.* (2014) present interesting suggestions which I would like to complement by some further speculations. A cell needs to 'know' its environment to be functional (e.g. dynamical cell–matrix and/or cell–cell interaction). This is achieved not only by 'biochemical' but also by 'mechanical' sensing. Relaxing/contracting VSMCs need to release their contacts to the extracellular matrix and neigbouring cells in order to form new cell–matrix and cell–cell contacts and to allow changes in shape and location within the vascular wall. Mechanical oscillations allow a continuous sampling of the surrounding mechanical environment not only by the passive activation of force sensors but also by detecting static mechanical surroundings actively. Cells may also need to maintain force-sensing elements in an active state by periodic mechanical activity. This could be one of the functions of oscillation, but that does not necessarily need any modulation in oscillation amplitude/frequency. Another interpretation of the Hong *et al.* study is that cells use mechanical oscillations for intercellular communication. The frequency of mechanical oscillations is modulated by a changing environment. This strongly suggests frequency-coded mechanosignalling comparable to neuronal electrosignalling. It would be interesting to know whether cells show a synchronized oscillation in tissue or whether oscillating cells stimulate oscillations with a phase-shift in neighbouring cells generating a 'travelling wave' for long distance communication. This would improve collective mechanical performance and cell-to-cell cooperation. Mechanochemical signal conversion could also be an important effect of mechanical oscillations. The stretching of proteins could expose cryptic binding sites which activate specific intracellular signalling pathways. In this way, mechanical force, acting from outside or generated by the cell itself, is converted into biochemical signals (Vogel & Sheetz, 2006). Huang *et al.* linked mechanical oscillations to cell migration describing a cytoskeletal oscillatory network which is modulated by a signal transduction excitable network. The coupling of these networks leads to a widening protrusion and cell migration (Huang *et al.* 2013). An additional aspect is that mechanical oscillations trigger thixotropic gel–sol transitions of the cytoplasm which possibly influence the viscosity of the cytoplasm and thus may control diffusional transport and organelle movement within the cell. Understanding the nature of mechanical oscillations will open new perspectives

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of cell, tissue and organ physiology, and pathophysiology. The article of Hong *et al.* is an important step in this direction.

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Additional information

Competing interests

None declared.