in vitro, and dramatically extends survival and limits infiltration in vivo. This is the first direct evidence that manipulation of mechanotransductive signaling can alter the tumor-initiating capacity of brain TICs, supporting further exploration of these signals as potential therapeutic targets.

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Spatiotemporal Tension Distribution of Individual Stress Fibers at the Cell-Matrix Interface

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Actomyosin stress fibers (SFs) enable cells to exert traction on planar extracellular matrices (ECMs) by tensing focal adhesions (FAs) at the cell-ECM interface. While it is widely appreciated that the spatiotemporal distribution of these tensile forces play key roles in polarity, motility, fate choice, and other defining cell behaviors, virtually nothing is known about how an individual SF quantitatively contributes to tensile loads borne by specific molecules within associated FAs. We address this key open question by using femtosecond laser ablation to sever single SFs in cells while tracking tension across vinculin using a fluorescence resonance energy transfer (FRET) -based molecular optical sensor. We show that disruption of a single SF reduces tension across vinculin in FAs located throughout the cell, with enriched vinculin tension reduction in FAs oriented parallel to the targeted SF. Remarkably, however, some subpopulations of FAs exhibit enhanced vinculin tension upon SF irradiation and undergo dramatic, unexpected transitions between tension-enhanced and tension-reduced states. These changes depend strongly on the location of the severed SF, consistent with our earlier finding that different SF pools are regulated by distinct myosin activators. To unify these findings, we present a structural model in which central SFs are more interconnected and mutually reinforced than peripheral SFs due in part to the presence of transverse actomyosin structures that link central SFs into a cohesive network. Tension released upon compromise of a central SF is thus broadly redistributed to other stress fibers and focal adhesions, resulting in cell shape stabilization. These studies represent the most direct and high-resolution intracellular measurements of SF contributions to tension on specific FA proteins to date and offer a new paradigm for investigating regulation of adhesive complexes by cytoskeletal force. (Chang and Kumar, J Cell Sci 2013)

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Vascular Smooth Muscle Cell Stiffness: A Novel Mechanism for the Increased Aortic Stiffness in Hypertension and Aging

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Hypertension and aging are both recognized to increase aortic stiffness, but the underlying mechanisms are not completely understood. Most prior studies have attributed increased aortic stiffness to mechanical changes within the extracellular matrix proteins of the aortic wall. Alternatively, we hypothesize that a significant component of increased vascular stiffness in hypertension is also due to changes in the mechanical properties of vascular smooth muscle cells (VSMCs), and that the contribution of this mechanism is augmented during hypertensive aging. Accordingly, we studied aortic stiffness in young (16wks) and old (64wks) spontaneously hypertensive rats (SHR) and Wistar-Kyoto (WKY) wild-type controls. Systolic aortic pressure, measured by Millar micromanometer catheter, was significantly increased in the old compared to young SHR (191 ± 8 mmHg vs 157 ± 6 mmHg, $p < 0.01$), but not in WKY (old, 109 ± 6 mmHg vs young, 102 ± 6 mmHg). Excised aortic ring segments were subjected to physiological levels of mechanical stretch ex vivo, and the wall stress within these ring segments, as well as their tangential elastic moduli, were greater in SHR vs WKY ($p < 0.05$). VSMCs were isolated from the thoracic aorta, and the elastic stiffness of individual VSMCs was measured by an atomic force microscopy nano-indentation technique. Hypertension increased VSMC stiffness more, $p < 0.05$, in young SHR (26 ± 4 kPa) compared to young WKY (14 ± 2 kPa). Aging also increased VSMC stiffness, $p < 0.05$, in old versus young SHR. Importantly, the increase in VSMC stiffness in young SHR versus young WKY ($92 \pm 15\%$) was less, $p < 0.05$, than that observed between old SHR versus old WKY ($131 \pm 2\%$). Our findings that the mechanical properties of VSMCs are sensitive to hypertension, and also to aging, suggests this as a novel mechanism for increased aortic stiffness that occurs with hypertension and aging. (NIH 5R01HL102472-SFV and NIH PO1-HL-095486-GAM)

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The Contribution of the Structural Elements of a Single Plant Cell to its Mechanics: How the Plant Cell becomes Animal-Like

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Changing shape is changing structure. Deciphering the mechanical contribution of the structural elements of the cells in shape changes is thus crucial to link the mechanical control of growth with development. Many measurements on plant and animal cells rather stress the differences in mechanical properties between both kingdoms. However, this conclusion relies on independent measurements, with very different set-ups and tissues, thus impairing any quantitative comparison. Here we took advantage of a previously described micro-rheometer to compare animal and plant single cell rheology with the same set-up. Using this method, we were able to quantitatively assess the dominant elastic behavior of plant cells in different conditions, and compare it with the viscoelastic behavior of animal cells. Surprisingly, we found that wall-less plant cells exhibit the same rheology as animal cells. This suggests that, despite the main structural differences between animal and plant cells, they also share a common mechanical core. Further investigations revealed that microtubules were the main responsible for the rheological behavior of wall-less plant cells whereas the mechanical properties of animal cells were mainly dependent on the actin network. Thus, wall-less plant cells and animal cells may have developed different strategies to converge to the same mechanical behavior.

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Muscle-Like Behaviour of Non-Muscle Cells and Real-Time Single Cell Response to Stiffness

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As part of their physiological functions, most cells need to respond to mechanical stimuli such as deformations, forces, and stiffness of the extracellular matrix. In particular, cells cultured on elastic substrates with a rigidity gradient align their shape, their cytoskeletal structures and their traction forces along the direction of highest stiffness.

In order to identify the role of actomyosin-based contractility in rigidity sensing, we developed a single cell technique allowing us to measure the traction force as well as the speed of shortening of isolated cells deflecting microplates (i.e. springs) of variable stiffness. We will show that the mechanical power (energy per unit time) invested by the cell to bend the microplates was adapted to stiffness, and reflected the force-dependent kinetics of myosin binding to actin (Hill law of muscle contraction)[1]. We will also present a unique force-measurement protocol allowing us to change the effective stiffness felt by a single cell in real time (~0.1 second). This technique revealed that cell contractility was instantaneously adapted to the change in stiffness[2].

Such an instantaneous response could hardly be explained by chemical transduction pathways. It would rather suggest that early cell response to stiffness could be purely mechanical in nature. This mechanical adaptation may translate anisotropy in substrate rigidity into anisotropy in cytoskeletal tension, and could thus coordinate local activity of adhesion complexes and guide cell migration along rigidity gradients.

[1] Mitrosslis et al., ''Single-cell response to stiffness exhibits muscle-like behavior'', *PNAS*, 106, 43, 2009.
[2] Mitrosslis et al., ''Real-time single-cell response to stiffness'', *PNAS*, 107, 38, 2010.

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Desmin, Mechanics and Myofibrillar Myopathies

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The cytoskeleton plays a central role in transmitting and generating mechanical forces through the cell. It is composed of three interconnected networks, actin, microtubules and intermediate filaments (IF). Desmin belongs to the type III IF, specifically expressed in muscles. Desmin is essential to maintain the integrity and functioning of muscles. More than fifty mutations have been