Année de publication : 2018

Bipul R Acharya, Alexander Nestor-Bergmann, Xuan Liang, Shafali Gupta, Kinga Duszyc, Estelle Gauquelin, Guillermo A Gomez, Srikanth Budnar, Philippe Marcq, Oliver E Jensen, Zev Bryant, Alpha S Yap (2018 Oct 16)

A Mechanosensitive RhoA Pathway that Protects Epithelia against Acute Tensile Stress.

Developmental cell : DOI : S1534-5807(18)30776-7

Résumé

Adherens junctions are tensile structures that couple epithelial cells together. Junctional tension can arise from cell-intrinsic application of contractility or from the cell-extrinsic forces of tissue movement. Here, we report a mechanosensitive signaling pathway that activates RhoA at adherens junctions to preserve epithelial integrity in response to acute tensile stress. We identify Myosin VI as the force sensor, whose association with E-cadherin is enhanced when junctional tension is increased by mechanical monolayer stress. Myosin VI promotes recruitment of the heterotrimeric Gα12 protein to E-cadherin, where it signals for p114 RhoGEF to activate RhoA. Despite its potential to stimulate junctional actomyosin and further increase contractility, tension-activated RhoA signaling is necessary to preserve epithelial integrity. This is explained by an increase in tensile strength, especially at the multicellular vertices of junctions, that is due to mDia1-mediated actin assembly.

Vincent Nier, Grégoire Peyret, Joseph d'Alessandro, Shuji Ishihara, Benoit Ladoux, Philippe Marcq (2018 Oct 11)

Kalman Inversion Stress Microscopy.

Biophysical journal : DOI : S0006-3495(18)31065-8

Résumé

Although mechanical cues are crucial to tissue morphogenesis and development, the tissue mechanical stress field remains poorly characterized. Given traction force time-lapse movies, as obtained by traction force microscopy of in vitro cellular sheets, we show that the tissue stress field can be estimated by Kalman filtering. After validation using numerical data, we apply Kalman inversion stress microscopy to experimental data. We combine the inferred stress field with velocity and cell-shape measurements to quantify the rheology of epithelial cell monolayers in physiological conditions, found to be close to that of an elastic and active material.

Duclos G., Blanch-Mercader C., Yashunsky V., Salbreux G., Joanny J.-F., Prost J., Silberzan P. (2018 Oct 3)

Spontaneous shear flow in confined cellular nematics

Nature Physics : DOI : 10.1038/s41567-018-0099-7

Résumé

In embryonic development or tumour evolution, cells often migrate collectively within confining tracks defined by their microenvironment[1,2]. In some of these situations, the displacements within a cell strand are antiparallel[3], giving rise to shear flows. However, the mechanisms underlying these spontaneous flows remain poorly understood. Here, we show that an ensemble of spindle-shaped cells plated in a well-defined stripe spontaneously develops a shear flow whose characteristics depend on the width of the stripe. On wide stripes, the cells self-organize in a nematic phase with a director at a well-defined angle with the stripe's direction, and develop a shear flow close to the stripe's edges. However, on stripes narrower than a critical width, the cells perfectly align with the stripe's direction and the net flow vanishes. A hydrodynamic active gel theory provides an understanding of these observations and identifies the transition between the non-flowing phase oriented along the stripe and the tilted phase exhibiting shear flow as a Fréedericksz transition driven by the activity of the cells. This physical theory is grounded in the active nature of the cells and based on symmetries and conservation laws, providing a generic mechanism to interpret in vivo antiparallel cell displacements.

Année de publication : 2017

Francesco Gianoli, Thomas Risler, Andrei S. Kozlov (2017 Dec 19)

Lipid bilayer mediates ion-channel cooperativity in a model of hair-cell mechanotransduction

Proceedings of the National Academy of Sciences of the United States of America : 114 : E11010-E11019 : DOI : 10.1073/pnas.1713135114

Résumé

Mechanoelectrical transduction in the inner ear is a biophysical process underlying the senses of hearing and balance. The key players involved in this process are mechanosensitive ion channels. They are located in the stereocilia of hair cells and opened by the tension in specialized molecular springs, the tip links, connecting adjacent stereocilia. When channels open, the tip links relax, reducing the hair-bundle stiffness. This gating compliance makes hair cells especially sensitive to small stimuli. The classical explanation for the gating compliance is that the conformational rearrangement of a single channel directly shortens the tip link. However, to reconcile theoretical models based on this mechanism with experimental data, an unrealistically large structural change of the channel is required. Experimental evidence indicates that each tip link is a dimeric molecule, associated on average with two channels at its lower end. It also indicates that the lipid bilayer modulates channel gating, although it is not clear how. Here, we design and analyze a model of mechanotransduction where each tip link attaches to two channels, mobile within the membrane. Their states and positions are coupled by membrane-mediated elastic forces arising from the interaction between the channels' hydrophobic cores and that of the lipid bilayer. This coupling induces cooperative opening and closing of the channels. The model reproduces the main properties of hair-cell mechanotransduction using only realistic parameters constrained by experimental evidence. This work provides an insight into the

fundamental role that membrane-mediated ion-channel cooperativity can play in sensory physiology.

Shunsuke Yabunaka, Philippe Marcq (2017 Sep 28)
Cell growth, division, and death in cohesive tissues: A thermodynamic approach.
Physical review. E : 022406 : DOI : 10.1103/PhysRevE.96.022406

Résumé

Cell growth, division, and death are defining features of biological tissues that contribute to morphogenesis. In hydrodynamic descriptions of cohesive tissues, their occurrence implies a nonzero rate of variation of cell density. We show how linear nonequilibrium thermodynamics allows us to express this rate as a combination of relevant thermodynamic forces: chemical potential, velocity divergence, and activity. We illustrate the resulting effects of the nonconservation of cell density on simple examples inspired by recent experiments on cell monolayers, considering first the velocity of a spreading front, and second an instability leading to mechanical waves.

Shuji Ishihara, Philippe Marcq, Kaoru Sugimura (2017 Sep 28)
From cells to tissue: A continuum model of epithelial mechanics.
Physical review. E : 022418 : DOI : 10.1103/PhysRevE.96.022418

Résumé

A two-dimensional continuum model of epithelial tissue mechanics was formulated using cellular-level mechanical ingredients and cell morphogenetic processes, including cellular shape changes and cellular rearrangements. This model incorporates stress and deformation tensors, which can be compared with experimental data. Focusing on the interplay between cell shape changes and cell rearrangements, we elucidated dynamical behavior underlying passive relaxation, active contraction-elongation, and tissue shear flow, including a mechanism for contraction-elongation, whereby tissue flows perpendicularly to the axis of cell elongation. This study provides an integrated scheme for the understanding of the orchestration of morphogenetic processes in individual cells to achieve epithelial tissue morphogenesis.

Shunsuke Yabunaka, Philippe Marcq (2017 Aug 30)
Emergence of epithelial cell density waves.
Soft matter : DOI : 10.1039/c7sm01172e

Résumé

Epithelial cell monolayers exhibit traveling mechanical waves. We rationalize this

observation thanks to a hydrodynamic description of the monolayer as a compressible, active and polar material. We show that propagating waves of the cell density, polarity, velocity and stress fields may be due to a Hopf bifurcation occurring above threshold values of active coupling coefficients.

Thuan Beng Saw, Amin Doostmohammadi, Vincent Nier, Leyla Kocgozlu, Sumesh Thampi, Yusuke Toyama, Philippe Marcq, Chwee Teck Lim, Julia M Yeomans, Benoit Ladoux (2017 Apr 14)
Topological defects in epithelia govern cell death and extrusion.
Nature : 212-216 : DOI : 10.1038/nature21718

Résumé

Epithelial tissues (epithelia) remove excess cells through extrusion, preventing the accumulation of unnecessary or pathological cells. The extrusion process can be triggered by apoptotic signalling, oncogenic transformation and overcrowding of cells. Despite the important linkage of cell extrusion to developmental, homeostatic and pathological processes such as cancer metastasis, its underlying mechanism and connections to the intrinsic mechanics of the epithelium are largely unexplored. We approach this problem by modelling the epithelium as an active nematic liquid crystal (that has a long range directional order), and comparing numerical simulations to strain rate and stress measurements within monolayers of MDCK (Madin Darby canine kidney) cells. Here we show that apoptotic cell extrusion is provoked by singularities in cell alignments in the form of comet-shaped topological defects. We find a universal correlation between extrusion sites and positions of nematic defects in the cell orientation field in different epithelium types. The results confirm the active nematic nature of epithelia, and demonstrate that defect-induced isotropic stresses are the primary precursors of mechanotransductive responses in cells, including YAP (Yes-associated protein) transcription factor activity, caspase-3-mediated cell death, and extrusions. Importantly, the defect-driven extrusion mechanism depends on intercellular junctions, because the weakening of cell-cell interactions in an α-catenin knockdown monolayer reduces the defect size and increases both the number of defects and extrusion rates, as is also predicted by our model. We further demonstrate the ability to control extrusion hotspots by geometrically inducing defects through microcontact printing of patterned monolayers. On the basis of these results, we propose a mechanism for apoptotic cell extrusion: spontaneously formed topological defects in epithelia govern cell fate. This will be important in predicting extrusion hotspots and dynamics in vivo, with potential applications to tissue regeneration and the suppression of metastasis. Moreover, we anticipate that the analogy between the epithelium and active nematic liquid crystals will trigger further investigations of the link between cellular processes and the material properties of epithelia.

M E Dolega, M Delarue, F Ingremeau, J Prost, A Delon, G Cappello (2017 Jan 28)
Cell-like pressure sensors reveal increase of mechanical stress towards the core of multicellular spheroids under compression.
Nature communications : 14056 : DOI : 10.1038/ncomms14056

Résumé

The surrounding microenvironment limits tumour expansion, imposing a compressive stress on the tumour, but little is known how pressure propagates inside the tumour. Here we present non-destructive cell-like microsensors to locally quantify mechanical stress distribution in three-dimensional tissue. Our sensors are polyacrylamide microbeads of well-defined elasticity, size and surface coating to enable internalization within the cellular environment. By isotropically compressing multicellular spheroids (MCS), which are spherical aggregates of cells mimicking a tumour, we show that the pressure is transmitted in a non-trivial manner inside the MCS, with a pressure rise towards the core. This observed pressure profile is explained by the anisotropic arrangement of cells and our results suggest that such anisotropy alone is sufficient to explain the pressure rise inside MCS composed of a single cell type. Furthermore, such pressure distribution suggests a direct link between increased mechanical stress and previously observed lack of proliferation within the spheroids core.

Année de publication : 2016

Valentino F, Sens P, Lemière J, Allard A, Betz T, Campillo C, Sykes C (2016 Nov 28)
Fluctuations of a membrane nanotube revealed by high-resolution force measurements
Soft Matter : 12 : 9429-9435 : DOI : 10.1039/c6sm02117d

Résumé

Pulling membrane nanotubes from liposomes presents a powerful method to gain access to membrane mechanics. Here we extend classical optical tweezers studies to infer membrane nanotube dynamics with high spatial and temporal resolution. We first validate our force measurement setup by accurately measuring the bending modulus of EPC membrane in tube pulling experiments. Then we record the position signal of a trapped bead when it is connected, or not, to a tube. We derive the fluctuation spectrum of these signals and find that the presence of a membrane nanotube induces higher fluctuations, especially at low frequencies (10-1000 Hz). We analyse these spectra by taking into account the peristaltic modes of nanotube fluctuations. This analysis provides a new experimental framework for a quantitative study of the fluctuations of nanotubular membrane structures that are present in living cells, and now classically used for in vitro biomimetic approaches.

Laura Devis, Cristian P Moiola, Nuria Masia, Elena Martinez-Garcia, Maria Santacana, Tomita Vasilica Stirbat, Françoise Brochard-Wyart, Ángel García, Francesc Alameda, Silvia Cabrera, Jose Palacios, Gema Moreno-Bueno, Miguel Abal, William Thomas, Sylvie Dufour, Xavier Matias-Guiu, Anna Santamaria, Jaume Reventos, Antonio Gil-Moreno, Eva Colas (2016 Nov 23)
Activated leukocyte cell adhesion molecule (ALCAM) is a marker of recurrence and promotes cell migration, invasion and metastasis in early stage endometrioid endometrial cancer.

The Journal of pathology : DOI : 10.1002/path.4851

Résumé

Endometrial cancer is the most common gynaecological cancer in western countries, being the most common subtype of endometrioid tumours. Most patients are diagnosed at an early stage and present an excellent prognosis. However, a number of those continue to suffer recurrence, without means of identification by risk classification systems. Thus, finding a reliable marker to predict recurrence becomes an important unmet clinical issue. ALCAM is a cell-cell adhesion molecule and member of the Immunoglobulin superfamily that has been associated with genesis of many cancers. Here, we first determined the value of ALCAM as marker of recurrence in endometrioid endometrial cancer by conducting a retrospective multicentre study of 174 primary tumours. In early stage patients (N = 134), recurrence-free survival was poorer in patients with ALCAM-positive compared to ALCAM-negative tumours (HR 4.237; 95%CI 1.01-17.76). This difference was more significant in patients with early stage moderately-poorly differentiated tumours (HR 9.259; 95%CI 2.12-53.47). In multivariate analysis, ALCAM-positivity was an independent prognostic factor in early stage disease (HR 6.027, 95% CI 1.41-25.74). Then, we demonstrated in vitro a role for ALCAM in cell migration and invasion by using a loss-of-function model in two endometrial cancer cell lines. ALCAM depletion resulted in a reduced primary tumour size and reduced metastatic local spread in an orthotopic murine model. Gene expression analysis of ALCAM-depleted cell lines supported that motility, invasiveness, cellular assembly and organization were the most deregulated functions. Finally, we assessed some of the downstream effector genes that are involved in ALCAM mediated cell migration; specifically FLNB, TXNRD1 and LAMC2 were validated at the mRNA and protein level. In conclusion, our results highlight the potential of ALCAM as a recurrent biomarker in early stage endometrioid endometrial cancer and point to ALCAM as an important molecule in endometrial cancer dissemination by regulating cell migration, invasion and metastasis.

Benjamin Brunel, Grégory Beaune, Usharani Nagarajan, Sylvie Dufour, Françoise Brochard-Wyart, Françoise M Winnik (2016 Oct 8)
Nanostickers for cells: a model study using cell-nanoparticle hybrid aggregates.
Soft matter : 7902-7907

Résumé

We present direct evidence that nanoparticles (NPs) can stick together cells that are inherently non-adhesive. Using cadherin-depleted S180 murine cells lines, which exhibit very low cell-cell adhesion, we show that NPs can assemble dispersed single cells into large cohesive aggregates. The dynamics of aggregation, which is controlled by diffusion and collision, can be described as a second-order kinetic law characterized by a rate of collision that depends on the size, concentration, and surface chemistry of the NPs. We model the cell-cell adhesion induced by the « nanostickers » using a three-state dynamical model, where the NPs are free, adsorbed on the cell membrane or internalized by the cells. We define a « sticking efficiency parameter » to compare NPs and look for the most efficient type of NP. We find that 20 nm carboxylated polystyrene NPs are more efficient nanostickers

than 20 nm silica NPs which were reported to induce fast wound healing and to glue soft tissues. Nanostickers, by increasing the cohesion of tissues and tumors, may have important applications for tissue engineering and cancer treatment.

Année de publication : 2017

Duclos G., Erlenkämper C., Joanny J.-F., Silberzan P. (2016 Sep 12)
Topological defects in confined populations of spindle-shaped cells
Nature Physics : 13 : 58-62 : DOI : 10.1038/nphys3876

Résumé

Most spindle-shaped cells (including smooth muscles and sarcomas) organize in vivo into well-aligned 'nematic' domains, creating intrinsic topological defects that may be used to probe the behaviour of these active nematic systems. Active non-cellular nematics have been shown to be dominated by activity, yielding complex chaotic flows. However, the regime in which live spindle-shaped cells operate, and the importance of cell–substrate friction in particular, remains largely unexplored. Using in vitro experiments, we show that these active cellular nematics operate in a regime in which activity is effectively damped by friction, and that the interaction between defects is controlled by the system's elastic nematic energy. Due to the activity of the cells, these defects behave as self-propelled particles and pairwise annihilate until all displacements freeze as cell crowding increases. When confined in mesoscopic circular domains, the system evolves towards two identical +1/2 disclinations facing each other. The most likely reduced positions of these defects are independent of the size of the disk,the cells' activity or even the cell type, but are well described by equilibrium liquid crystal theory. These cell-based systems thus operate in a regime more stable than other active nematics, which may be necessary for their biological function.

Année de publication : 2016

Jean-Francois Rupprecht, Jacques Prost (2016 Apr 30)
PHYSICAL BIOLOGY. A fresh eye on nonequilibrium systems.
Science (New York, N.Y.) : 514-5 : DOI : 10.1126/science.aaf4611

Résumé

Alexander Y Grosberg, Jean-François Joanny, Watee Srinin, Yitzhak Rabin (2016 Apr 28)
Scale-Dependent Viscosity in Polymer Fluids.
The journal of physical chemistry. B

Résumé

In this communication, we use simple physical arguments to construct a « phase diagram » of various frequency and wave vector-dependent regimes of effective viscosity for polymer fluids, including nonentangled and entangled melts, semidilute solutions without and with hydrodynamic interactions, as well as the more exotic case of a melt of unconcatenated ring polymers.