Année de publication : 2017

Floris Bosveld, Anna Ainslie, Yohanns Bellaïche (2017 Sep 3)

Sequential activities of Dynein, Mud and Asp in centrosome-spindle coupling maintain centrosome number upon mitosis.

Journal of cell science : DOI : jcs.201350

Résumé

Centrosomes nucleate microtubules and are tightly coupled to the bipolar spindle to ensure genome integrity, cell division orientation and centrosome segregation. While the mechanisms of centrosome-dependent microtubule nucleation and bipolar spindle assembly have been the focus of numerous works, less is known on the mechanisms ensuring the centrosome-spindle coupling. The conserved NuMA protein (Mud in Drosophila) is best known for its role in spindle orientation. Here we analyzed the role of Mud and two of its interactors, Asp and Dynein, in the regulation of centrosome numbers in Drosophila epithelial cells. We found that Dynein and Mud mainly initiate centrosome-spindle coupling prior to nuclear envelope breakdown (NEB) by promoting correct centrosome positioning or separation, while Asp acts largely independently of Dynein and Mud to maintain centrosome-spindle coupling. Failure in the centrosome-spindle coupling leads to mis-segregation of the two centrosomes into one daughter cell resulting in cells with supernumerary centrosomes during subsequent divisions. Together, we propose that Dynein, Mud and Asp sequentially operate during the cell cycle to ensure efficient centrosome-spindle coupling in mitosis preventing centrosome mis-segregation to maintain centrosome number.

Boris Guirao, Yohanns Bellaïche (2017 Jul 22)

Biomechanics of cell rearrangements in Drosophila.

Current opinion in cell biology : 113-124 : DOI : S0955-0674(17)30049-2

Résumé

To acquire their adequate size and shape, living tissues grow and substantially deform as they develop. To do so, the cells making up the tissue can grow and deform as well, but they can also divide, intercalate and die. Among those cell behaviors, cell intercalation, also named cell rearrangement, is a major contributor to the morphogenesis of many cohesive tissues since it enables tissues to drastically deform as they develop while keeping their cohesiveness and avoiding extreme deformation of their cells. Here we review the mechanical principles and biological regulations at play during cell rearrangements in Drosophila tissues by first describing them in other cellular materials and by categorizing them. We then briefly discuss their quantifications and their interplay with other cell processes.

Nicolas Tissot, Jean-Antoine Lepesant, Fred Bernard, Kevin Legent, Floris Bosveld, Charlotte Martin, Orestis Faklaris, Yohanns Bellaïche, Maïté Coppey, Antoine Guichet (2017 Apr 28)

Distinct molecular cues ensure a robust microtubule-dependent nuclear positioning in the Drosophila oocyte.
Nature communications : 15168 : DOI : 10.1038/ncomms15168

Résumé

Controlling nucleus localization is crucial for a variety of cellular functions. In the Drosophila oocyte, nuclear asymmetric positioning is essential for the reorganization of the microtubule (MT) network that controls the polarized transport of axis determinants. A combination of quantitative three-dimensional live imaging and laser ablation-mediated force analysis reveal that nuclear positioning is ensured with an unexpected level of robustness. We show that the nucleus is pushed to the oocyte antero-dorsal cortex by MTs and that its migration can proceed through distinct tracks. Centrosome-associated MTs favour one migratory route. In addition, the MT-associated protein Mud/NuMA that is asymmetrically localized in an Asp-dependent manner at the nuclear envelope hemisphere where MT nucleation is higher promotes a separate route. Our results demonstrate that centrosomes do not provide an obligatory driving force for nuclear movement, but together with Mud, contribute to the mechanisms that ensure the robustness of asymmetric nuclear positioning.

Diana Pinheiro, Edouard Hannezo, Sophie Herszterg, Floris Bosveld, Isabelle Gaugue, Maria Balakireva, Zhimin Wang, Inês Cristo, Stéphane U Rigaud, Olga Markova, Yohanns Bellaïche (2017 Mar 16)
Transmission of cytokinesis forces via E-cadherin dilution and actomyosin flows.
Nature : DOI : 10.1038/nature22041

Résumé

During epithelial cytokinesis, the remodelling of adhesive cell-cell contacts between the dividing cell and its neighbours has profound roles in the integrity, arrangement and morphogenesis of proliferative tissues. In both vertebrates and invertebrates, this remodelling requires the activity of non-muscle myosin II (MyoII) in the interphasic cells neighbouring the dividing cell. However, the mechanisms coordinating cytokinesis and MyoII activity in the neighbours are unknown. Here we find that in the Drosophila notum epithelium, each cell division is associated with a mechano-sensing and transmission event controlling MyoII dynamics in the neighbours. We established that the ring pulling forces promote local junction elongation, resulting in local E-cadherin (E-Cad) dilution at the ingressing adherens junction (AJ). In turn, the reduction of E-Cad concentration and the contractility of the neighbouring cells promote self-organized actomyosin flows, ultimately leading to MyoII accumulation at the base of the ingressing AJ. While force transduction has been extensively studied in the context of AJ reinforcement to stabilize adhesive cell-cell contacts, we propose an alternative mechano-sensing mechanism able to coordinate actomyosin dynamics between epithelial cells and to sustain AJ remodelling in response to mechanical forces.

Sangbum Park, David G Gonzalez, Boris Guirao, Jonathan D Boucher, Katie Cockburn, Edward D Marsh, Kailin R Mesa, Samara Brown, Panteleimon Rompolas, Ann M Haberman, Yohanns Bellaïche, Valentina Greco (2017 Mar 2)

Tissue-scale coordination of cellular behaviour promotes epidermal wound repair in live mice.

Nature cell biology : 155-163 : DOI : 10.1038/ncb3472

Résumé

Tissue repair is fundamental to our survival as tissues are challenged by recurrent damage. During mammalian skin repair, cells respond by migrating and proliferating to close the wound. However, the coordination of cellular repair behaviours and their effects on homeostatic functions in a live mammal remains unclear. Here we capture the spatiotemporal dynamics of individual epithelial behaviours by imaging wound re-epithelialization in live mice. Differentiated cells migrate while the rate of differentiation changes depending on local rate of migration and tissue architecture. Cells depart from a highly proliferative zone by directionally dividing towards the wound while collectively migrating. This regional coexistence of proliferation and migration leads to local expansion and elongation of the repairing epithelium. Finally, proliferation functions to pattern and restrict the recruitment of undamaged cells. This study elucidates the interplay of cellular repair behaviours and consequent changes in homeostatic behaviours that support tissue-scale organization of wound re-epithelialization.

Diana Pinheiro, Yohanns Bellaïche (2017 Jan 10)

Studying cytokinesis in Drosophila epithelial tissues.

Methods in cell biology : 73-84 : DOI : S0091-679X(16)30047-4

Résumé

Epithelial tissue cohesiveness is ensured through cell-cell junctions that maintain both adhesion and mechanical coupling between neighboring cells. During development, epithelial tissues undergo intensive cell proliferation. Cell division, and particularly cytokinesis, is coupled to the formation of new adhesive contacts, thereby preserving tissue integrity and propagating cell polarity. Remarkably, the geometry of the new interfaces is determined by the combined action of the dividing cell and its neighbors. To further understand the interplay between the dividing cell and its neighbors, as well as the role of cell division for tissue morphogenesis, it is important to analyze cytokinesis in vivo. Here we present methods to perform live imaging of cell division in Drosophila epithelial tissues and discuss some aspects of image processing and analysis.

Année de publication : 2016

Yohanns Bellaïche (2016 Sep 28)

Cell Division in the Light of Modeling.
Developmental cell : 584-6 : DOI : 10.1016/j.devcel.2016.09.008

Résumé

Theoretical modeling is central to elucidating underlying principles of emergent properties of complex systems. In cell and developmental biology, the last 15 years have witnessed a convergence of empirical and modeling approaches for fresh perspectives. The role of cell division in coordinating size, shape, and fate in particular illustrates the ever-growing impact of modeling.

Yasuo Yamazaki, Lucy Palmer, Cyrille Alexandre, Satoshi Kakugawa, Karen Beckett, Isabelle Gaugue, Ruth H Palmer, Jean-Paul Vincent (2016 Mar 15)
Godzilla-dependent transcytosis promotes Wingless signalling in Drosophila wing imaginal discs.
Nature cell biology : 451-7 : DOI : 10.1038/ncb3325

Résumé

The apical and basolateral membranes of epithelia are insulated from each other, preventing the transfer of extracellular proteins from one side to the other. Thus, a signalling protein produced apically is not expected to reach basolateral receptors. Evidence suggests that Wingless, the main Drosophila Wnt, is secreted apically in the embryonic epidermis. However, in the wing imaginal disc epithelium, Wingless is mostly seen on the basolateral membrane where it spreads from secreting to receiving cells. Here we examine the apico-basal movement of Wingless in Wingless-producing cells of wing imaginal discs. We find that it is presented first on the apical surface before making its way to the basolateral surface, where it is released and allowed to interact with signalling receptors. We show that Wingless transcytosis involves dynamin-dependent endocytosis from the apical surface. Subsequent trafficking from early apical endosomes to the basolateral surface requires Godzilla, a member of the RNF family of membrane-anchored E3 ubiquitin ligases. Without such transport, Wingless signalling is strongly reduced in this tissue.

Floris Bosveld, Olga Markova, Boris Guirao, Charlotte Martin, Zhimin Wang, Anaëlle Pierre, Maria Balakireva, Isabelle Gaugue, Anna Ainslie, Nicolas Christophorou, David K Lubensky, Nicolas Minc, Yohanns Bellaïche (2016 Feb 18)
Epithelial tricellular junctions act as interphase cell shape sensors to orient mitosis.
Nature : 495-8 : DOI : 10.1038/nature16970

Résumé

The orientation of cell division along the long axis of the interphase cell–the century-old

Hertwig's rule–has profound roles in tissue proliferation, morphogenesis, architecture and mechanics. In epithelial tissues, the shape of the interphase cell is influenced by cell adhesion, mechanical stress, neighbour topology, and planar polarity pathways. At mitosis, epithelial cells usually adopt a rounded shape to ensure faithful chromosome segregation and to promote morphogenesis. The mechanisms underlying interphase cell shape sensing in tissues are therefore unknown. Here we show that in Drosophila epithelia, tricellular junctions (TCJs) localize force generators, pulling on astral microtubules and orienting cell division via the Dynein-associated protein Mud independently of the classical Pins/Gαi pathway. Moreover, as cells round up during mitosis, TCJs serve as spatial landmarks, encoding information about interphase cell shape anisotropy to orient division in the rounded mitotic cell. Finally, experimental and simulation data show that shape and mechanical strain sensing by the TCJs emerge from a general geometric property of TCJ distributions in epithelial tissues. Thus, in addition to their function as epithelial barrier structures, TCJs serve as polarity cues promoting geometry and mechanical sensing in epithelial tissues.

Année de publication : 2015

Boris Guirao, Stéphane U Rigaud, Floris Bosveld, Anaïs Bailles, Jesús López-Gay, Shuji Ishihara, Kaoru Sugimura, François Graner, Yohanns Bellaïche (2015 Dec 15)

Unified quantitative characterization of epithelial tissue development.

eLife : DOI : 10.7554/eLife.08519

Résumé

Understanding the mechanisms regulating development requires a quantitative characterization of cell divisions, rearrangements, cell size and shape changes, and apoptoses. We developed a multiscale formalism that relates the characterizations of each cell process to tissue growth and morphogenesis. Having validated the formalism on computer simulations, we quantified separately all morphogenetic events in the Drosophila dorsal thorax and wing pupal epithelia to obtain comprehensive statistical maps linking cell and tissue scale dynamics. While globally cell shape changes, rearrangements and divisions all significantly participate in tissue morphogenesis, locally, their relative participations display major variations in space and time. By blocking division we analyzed the impact of division on rearrangements, cell shape changes and tissue morphogenesis. Finally, by combining the formalism with mechanical stress measurement, we evidenced unexpected interplays between patterns of tissue elongation, cell division and stress. Our formalism provides a novel and rigorous approach to uncover mechanisms governing tissue development.

Floris Bosveld, Boris Guirao, Zhimin Wang, Mathieu Rivière, Isabelle Bonnet, François Graner, Yohanns Bellaïche (2015 Jul 5)

Modulation of junction tension by tumor suppressors and proto-oncogenes regulates cell-cell contacts.

Development (Cambridge, England) : 623-34 : DOI : 10.1242/dev.127993

Résumé

Tumor suppressors and proto-oncogenes play crucial roles in tissue proliferation. Furthermore, de-regulation of their functions is deleterious to tissue architecture and can result in the sorting of somatic rounded clones minimizing their contact with surrounding wild-type (wt) cells. Defects in the shape of somatic clones correlate with defects in proliferation, cell affinity, cell-cell adhesion, oriented cell division and cortical contractility. Combining genetics, live-imaging, laser ablation and computer simulations, we aim to analyze whether distinct or similar mechanisms can account for the common role of tumor suppressors and proto-oncogenes in cell-cell contact regulation. In Drosophila epithelia, the tumor suppressors Fat (Ft) and Dachsous (Ds) regulate cell proliferation, tissue morphogenesis, planar cell polarity and junction tension. By analyzing the evolution over time of ft mutant cells and clones, we show that ft clones reduce their cell-cell contacts with the surrounding wt tissue in the absence of concomitant cell divisions and over-proliferation. This contact reduction depends on opposed changes of junction tensions in the clone bulk and its boundary with neighboring wt tissue. More generally, either clone bulk or boundary junction tension is modulated by the activation of Yorkie, Myc and Ras, yielding similar contact reductions with wt cells. Together, our data highlight mechanical roles for proto-oncogene and tumor suppressor pathways in cell-cell interactions.

Maria-Dolores Martín-Bermudo, Pierre-Luc Bardet, Yohanns Bellaïche, Marianne Malartre (2015 Mar 28)

The vav oncogene antagonises EGFR signalling and regulates adherens junction dynamics during Drosophila eye development.

Development (Cambridge, England) : 1492-501 : DOI : 10.1242/dev.110585

Résumé

Organ shaping and patterning depends on the coordinated regulation of multiple processes. The Drosophila compound eye provides an excellent model to study the coordination of cell fate and cell positioning during morphogenesis. Here, we find that loss of vav oncogene function during eye development is associated with a disorganised retina characterised by the presence of additional cells of all types. We demonstrate that these defects result from two distinct roles of Vav. First, and in contrast to its well-established role as a positive effector of the EGF receptor (EGFR), we show that readouts of the EGFR pathway are upregulated in vav mutant larval eye disc and pupal retina, indicating that Vav antagonises EGFR signalling during eye development. Accordingly, decreasing EGFR signalling in vav mutant eyes restores retinal organisation and rescues most vav mutant phenotypes. Second, using live imaging in the pupal retina, we observe that vav mutant cells do not form stable adherens junctions, causing various defects, such as recruitment of extra primary pigment cells. In agreement with this role in junction dynamics, we observe that these phenotypes can be exacerbated by lowering DE-Cadherin or Cindr levels. Taken together, our findings establish that Vav acts at multiple times during eye development to prevent excessive cell recruitment by limiting EGFR signalling and by regulating junction dynamics to ensure the correct patterning and morphogenesis of the Drosophila eye.

Marisa M Merino, Christa Rhiner, Jesus M Lopez-Gay, David Buechel, Barbara Hauert, Eduardo Moreno (2015 Jan 21)

Elimination of unfit cells maintains tissue health and prolongs lifespan.

Cell : 461-76 : DOI : 10.1016/j.cell.2014.12.017

Résumé

Viable yet damaged cells can accumulate during development and aging. Although eliminating those cells may benefit organ function, identification of this less fit cell population remains challenging. Previously, we identified a molecular mechanism, based on « fitness fingerprints » displayed on cell membranes, which allows direct fitness comparison among cells in Drosophila. Here, we study the physiological consequences of efficient cell selection for the whole organism. We find that fitness-based cell culling is naturally used to maintain tissue health, delay aging, and extend lifespan in Drosophila. We identify a gene, azot, which ensures the elimination of less fit cells. Lack of azot increases morphological malformations and susceptibility to random mutations and accelerates tissue degeneration. On the contrary, improving the efficiency of cell selection is beneficial for tissue health and extends lifespan.

Année de publication : 2014

Anaïs Bouissou, Christel Vérollet, Hélène de Forges, Laurence Haren, Yohanns Bellaïche, Franck Perez, Andreas Merdes, Brigitte Raynaud-Messina (2014 Jan 15)

γ-Tubulin Ring Complexes and EB1 play antagonistic roles in microtubule dynamics and spindle positioning.

The EMBO journal : 114-28 : DOI : 10.1002/embj.201385967

Résumé

γ-Tubulin is critical for microtubule (MT) assembly and organization. In metazoa, this protein acts in multiprotein complexes called γ-Tubulin Ring Complexes (γ-TuRCs). While the subunits that constitute γ-Tubulin Small Complexes (γ-TuSCs), the core of the MT nucleation machinery, are essential, mutation of γ-TuRC-specific proteins in Drosophila causes sterility and morphological abnormalities via hitherto unidentified mechanisms. Here, we demonstrate a role of γ-TuRCs in controlling spindle orientation independent of MT nucleation activity, both in cultured cells and in vivo, and examine a potential function for γ-TuRCs on astral MTs. γ-TuRCs locate along the length of astral MTs, and depletion of γ-TuRC-specific proteins increases MT dynamics and causes the plus-end tracking protein EB1 to redistribute along MTs. Moreover, suppression of MT dynamics through drug treatment or EB1 down-regulation rescues spindle orientation defects induced by γ-TuRC depletion. Therefore, we propose a role for γ-TuRCs in regulating spindle positioning by controlling the stability of astral MTs.

Sophie Herszterg, Diana Pinheiro, Yohanns Bellaïche (2014 Jan 2)

A multicellular view of cytokinesis in epithelial tissue.
Trends in cell biology : 285-93 : DOI : 10.1016/j.tcb.2013.11.009

Résumé

The study of cytokinesis in single-cell systems provided a wealth of knowledge on the molecular and biophysical mechanisms controlling daughter cell separation. In this review, we outline recent advances in the understanding of cytokinesis in epithelial tissues. These findings provide evidence for how the cytokinetic machinery adapts to a multicellular context and how the cytokinetic machinery is itself exploited by the tissue for the preservation of tissue function and architecture during proliferation. We propose that cytokinesis in epithelia should be viewed as a multicellular process, whereby the biochemical and mechanical interactions between the dividing cell and its neighbors are essential for successful daughter cell separation while defining epithelial tissue organization and preserving tissue integrity.