Year of publication 2019

Eric Victor van Leen, Florencia di Pietro, Yohanns Bellaïche (2019 Sep 12)
Oriented cell divisions in epithelia: from force generation to force anisotropy by tension, shape and vertices.

**Summary**

Mitotic spindle orientation has been linked to asymmetric cell divisions, tissue morphogenesis and homeostasis. The canonical pathway to orient the mitotic spindle is composed of the cortical recruitment factor NuMA and the molecular motor dynein, which exerts pulling forces on astral microtubules to orient the spindle. Recent work has defined a novel role for NuMA as a direct contributor to force generation. In addition, the exploration of geometrical and physical cues combined with the study of classical polarity pathways has led to deeper insights into the upstream regulation of spindle orientation. Here, we focus on how cell shape, junctions and mechanical tension act to orient spindle pulling forces in epithelia, and discuss different roles for spindle orientation in epithelia.

Gohta Goshima, Yohanns Bellaïche (2019 Jul 30)
Editorial overview: Cell division - from molecules to tissues.
*Current opinion in cell biology* : iii-v : DOI : S0955-0674(19)30063-8

**Summary**


Year of publication 2018

Diana Pinheiro, Yohanns Bellaïche (2018 Oct 10)
Mechanical Force-Driven Adherens Junction Remodeling and Epithelial Dynamics.
*Developmental cell* : 3-19 : DOI : S1534-5807(18)30743-3

**Summary**

During epithelial tissue development, repair, and homeostasis, adherens junctions (AJs) ensure intercellular adhesion and tissue integrity while allowing for cell and tissue dynamics. Mechanical forces play critical roles in AJs’ composition and dynamics. Recent findings highlight that beyond a well-established role in reinforcing cell-cell adhesion, AJ mechanosensitivity promotes junctional remodeling and polarization, thereby regulating critical processes such as cell intercalation, division, and collective migration. Here, we provide an integrated view of mechanosensing mechanisms that regulate cell-cell contact composition, geometry, and integrity under tension and highlight pivotal roles for mechanosensitive AJ remodeling in preserving epithelial integrity and sustaining tissue dynamics.
Florence di Pietro, Yohanns Bellaïche (2018 Jun 6)
**Actin Network Discussion during Mitotic Pseudo-Furrowing.**
*Developmental cell* : 539-541 : [DOI : S1534-5807(18)30411-8](https://doi.org/S1534-5807(18)30411-8)

**Summary**

Two types of cortical actin networks act during mitotic pseudocleavage furrowing in the Drosophila syncytium, but how they interact has remained elusive. In this issue of Developmental Cell, Zhang et al. (2018) show how these networks shape each other and propose that furrowing is driven by actin polymerization-derived pushing forces.

Floris Bosveld, Zhimin Wang, Yohanns Bellaïche (2018 May 30)
**Tricellular junctions: a hot corner of epithelial biology.**
*Current opinion in cell biology* : 80-88 : [DOI : S0955-0674(18)30025-5](https://doi.org/S0955-0674(18)30025-5)

**Summary**

As the result of an intricate interplay between mechanical and biochemical cues, coordinated cell dynamics are at the basis of tissue development, homeostasis and repair. Numerous studies have addressed the interplay between these two inputs and their impact on cellular dynamics. These studies largely focus on bicellular junctions (BCJs). Recent works have illuminated that tricellular junctions (TCJs), the junctions where three cells contact, play important roles in epithelial tissues beyond their well-known structural function in preserving epithelial barrier integrity. Indeed, TCJs have recently been implicated in the regulation of collective cell migration, division orientation, cell proliferation and cell mechanical properties. More generally, the TCJ distribution aligns with the cell shape and mechanical stress orientation within the tissue, while their number encapsulates the packing topology. Importantly, known regulators of growth signalling and of cell mechanical properties are also localized at TCJs. Therefore, TCJs emerge as spatial sites to sense and integrate biochemical and mechanical inputs to guide epithelial tissue dynamics.

Zhimin Wang, Floris Bosveld, Yohanns Bellaïche (2018 May 10)
**Tricellular junction proteins promote disentanglement of daughter and neighbour cells during epithelial cytokinesis.**
*Journal of cell science* : [DOI : jcs215764](https://doi.org/jcs215764)

**Summary**

In epithelial tissue, new cell-cell junctions are formed upon cytokinesis. To understand junction formation during cytokinesis, we explored formation of tricellular septate junctions (TCJs) in epithelium. We found that upon midbody formation, the membranes of the two daughter cells and of the neighbouring cells located below the adherens junction (AJ) remain entangled in a 4-cell structure apposed to the midbody. The septate junction protein Discs-Large and components of the TCJ, Gliotactin and Anakonda accumulate in this 4-cell...
structure. Subsequently, a basal movement of the midbody parallels the detachment of the neighbouring cell membranes from the midbody, the disengagement of the daughter cells from their neighbours and the reorganisation of TCJs between the two daughter cells and their neighbouring cells. While the movement of midbody is independent of the Alix and Shrub abscission regulators, the loss of Gliotactin or Anakonda function impedes both the resolution of the connection between the daughter-neighbour cells and midbody movement. TCJ proteins therefore control an additional step of cytokinesis necessary for the disentanglement of the daughter cells from their neighbours during cytokinesis.

Year of 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

**Summary**

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.**  

**Summary**

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.


Summary

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.


Summary

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.


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

*Nature cell biology* : 155-163 : DOI : [10.1038/ncb3472](https://doi.org/10.1038/ncb3472)

**Summary**

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.**


**Summary**

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.

Year of 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]

**Summary**

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.

**Godzilla-dependent transcytosis promotes Wingless signalling in Drosophila wing imaginal discs.**
*Nature cell biology*: 451-7 : [DOI: 10.1038/ncb3325]

**Summary**

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](https://doi.org/10.1038/nature16970)

**Summary**

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.