Contribution of cytokinesis geometry to epithelial tube organization

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Project description :

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Controlling cytokinesis geometry by regulating asymmetric cleavage furrow ingression has just started to emerge as a key event to couple cell division to specific developmental processes. In the context of an epithelium, controlled cytokinesis geometry is essential to ensure the integrity of proliferative tissues. However, most studies have focused so far on cytokinesis geometry in isolated cells, one cell stage embryos or on *Drosophila* two-dimensional (2D) epithelia . Importantly, very little is known on the contribution of cytokinesis geometry to 3D epithelial tissue architecture. Indeed, how basal-to-apical cytokinesis asymmetry is achieved in 3D epithelia and whether tissue topology impacts on cytokinesis is not yet understood. Moreover, the mechanical impact of cytokinesis geometry on 3D epithelial arrangement has never been directly addressed.

Recent results show that a rigorous control of cytokinesis geometry is required for proper lumen organization in 3D culture of kidney cells. Yet, epithelial tubules which are composed of a curved polarized monolayer of epithelial cells surrounding a central luminal cavity, constitute the functional units of many organs among which the kidney. Maintenance of a proper tubular organization is essential to ensure organ function. Impaired tubule organization and loss of lumen size control are characteristic of renal pathologies including polycystic kidney diseases. Understanding how asymmetric cytokinesis is achieved in tubular structures and whether and how random cytokinesis positioning impacts on tubular epithelia is thus of the utmost importance. However, with more than a million of nephrons, the mammalian kidney poses significant technical challenges to study dynamically the cellular processes contributing to kidney tubule organization. Indeed, live monitoring of cytokinesis events during the formation of tubular epithelia still remains a critical issue.

To overcome the complexity of the mammalian kidney and determine the contribution of cytokinesis geometry to epithelial tubule homeostasis, we propose to take advantage of complementary

approaches: an *in vitro* approach with bioengineered 3D cultures of renal epithelial cell lines using microfabrication techniques, and an *in vivo* approach using zebrafish, a powerful model to study kidney tubule organization. More specifically, combining cell biological and biophysical approaches, our main objectives will be: (1) to study how cytokinesis geometry is controlled in a 3D environment, (2) to assess whether and how local perturbations of cytokinesis geometry affect large scale tissue behavior and (3) to define the involvement of cytokinesis geometry to epithelial tubule structure and lumen size/shape maintenance.

Overall, by linking the cellular to the tissue scale and thanks to the complementarity of the expertises, this project will unravel the molecular and mechanical mechanisms controlling cytokinesis geometry in 3D epithelia, will allow to determine the impact of cytokinesis to large scale tissue organization and will shed light on its impact on kidney tubule organization.

Publications of the team related to the project

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