

Students' Annual Webinar

Spatial heterogeneity of metabolism associated with the stages of epithelial contact inhibition of proliferation

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In the epithelium, cell density and proliferation are closely connected to each other through contact inhibition of proliferation (CIP). Starting from a low-density state, as the cell density increases, CIP proceeds through three distinct stages, namely the free growing stage, pre-epithelial transition stage, and post-epithelial transition stage. Previous studies have elucidated how cell morphology, motion and mechanics vary in these stages. However, it remains unknown whether cellular metabolism also has a density-dependent behaviour. By measuring the mitochondrial membrane potential at different cell densities, we reveal a heterogeneous landscape of metabolism in the epithelium, whose length-scale depends on cell density and appears distinct in three distinct stages of CIP. Subsequently, to understand how metabolic heterogeneity emerges as a function of cell proliferation, we construct a system biological model of the proliferating epithelium. Finally, we show that the collective heterogeneity in metabolic state can be developed even only in presence of active contractile cell mechanics. Taken together, our results reveal a density-dependent collective heterogeneity in the metabolic field of an epithelial monolayer, which should have critical consequences on the spatiotemporal evolution of epithelial form and function.

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