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Credit: Stephan Geist/EyeEm

Morphological transitions of tissues enable organ development and are central to tissue regeneration, but also play an important role in the pathology of diseases, such as cancer. Cells generate forces and dynamically interact with their microenvironment to modify tissue shape, size and stiffness. Now, writing in *Nature Physics*, Xavier Trepat and colleagues apply an active polar fluid model to describe the morphological changes of tissues as an active wetting transition, revealing a critical tissue size for tissue spreading that depends on substrate stiffness, cell adhesion and tissue geometry.

The fluidic behaviour of tissues on substrates can be described as a wetting problem — the spreading of tissue on a 2D surface as wetting and 3D cell aggregation as dewetting. Trepat and co-workers cultured epithelial cell layers of different sizes on substrates with different stiffnesses to quantitatively measure these wetting and dewetting processes and to correlate tissue spreading with tissue mechanics.

The researchers employed traction force microscopy and monolayer stress microscopy to assess traction forces on the substrates and tension within and between epithelial cells. Transfection of the cells with an inducible vector expressing E-cadherin further allowed the scientists to control cell–cell adhesion. E-cadherin affects both intercellular and traction forces and thus determines the mechanical behaviour of the cell monolayer. Using this approach, Trepat and colleagues revealed that the dewetting of an epithelial monolayer into 3D structures is triggered by an increase in tissue tension, which causes the failure of cell–substrate adhesions.

By describing the cell monolayer as a 2D active polar fluid, the researchers could define a critical tissue radius above which the tissue spreads owing to traction forces and below which the tissue retracts driven by cell contractility. "Our experiments and theory show that, instead of relying on a balance of local interfacial energies as in passive wetting, the tissue wetting transition results from a competition between active cell–cell and cell–substrate interactions that involve the entire tissue. Therefore, tissue spreading only occurs above a critical tissue size — a striking feature that has no counterpart in classical wetting," explains Trepat.

The timescale of dewetting also depends on the size of the tissue; small monolayers are dewetting faster than larger ones. Moreover, the stiffness of the underlying substrate impacts the wetting transition. Stiff substrates with a densely coated collagen surface, which causes strong cellular adhesion, lead to a slower dewetting process compared with softer, less densely coated substrates.

In contrast to dewetting of passive fluids, for example, of a water drop, the evolution of tissue morphology is further characterized by a symmetry breaking owing to an increase of active fluctuations in tissue shape, eventually resulting in a defined 3D architecture. "Our work connects morphological transitions in tissues to the physics of wetting in active matter systems, thus establishing a new bridge between the fields of tissue biology and active matter physics," says Trepat.

Using the theoretical framework of active matter physics, the connection between size, physical forces and spreading of tissues, such as tumours, can be potentially explained. "Our prediction of a critical radius for tissue wetting suggests that the transition towards tumour spreading might occur once the tumour reaches a critical size," comments Trepat. "We also believe that active wetting is a general phenomenon that can be extrapolated to many different biological systems beyond the cell type used in our work."

The researchers are now exploring their theory for the description of tissue migration in 3D environments, including parameters such as matrix pore size, microstructure and degradability, and they want to employ stiffness gradients to predict the conditions under which a tissue exhibits directed migration towards increasing stiffness.

Christine-Maria Horejs

> "Our work connects morphological transitions in tissues to the physics of wetting in active matter systems"

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