Cell removal as the result of a mechanical instability

June 22 2020

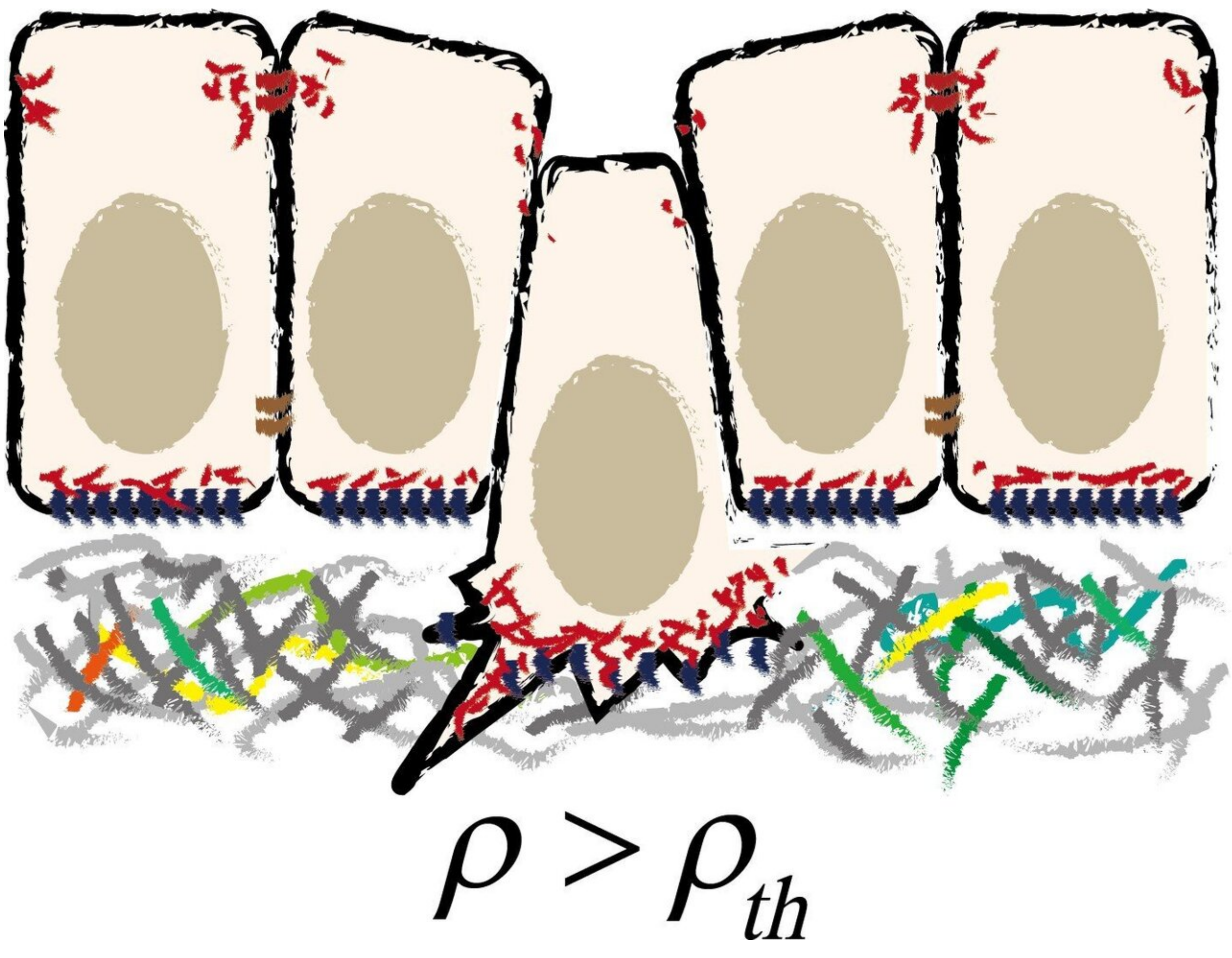

Figure 1. Schematic illustration of cell extrusion from epithelial tissue. Credit: Kanazawa University

Researchers at Kanazawa University report in the *Biophysical Journal* that the process of cell removal from an epithelial layer follows from an inherent mechanical instability. Moreover, the forces generated by an extruding cell can drive the extrusion of other cells in a particular direction.

The outer or inner boundaries of organs in the human body are lined with so-called epithelial sheets. These are layers of epithelial cells that can individually change their 3-D shape—which is what happens during biological processes like organ development (morphogenesis), physiological equilibrium (homeostatis) or cancer formation (carcinogenesis). Of particular interest is the process of cell extrusion, where a single cell loses its "top" or "bottom" surface and is subsequently pushed out of the layer. A thorough understanding of this phenomenon from a mechanical point of view has been lacking, but now, Satoru Okuda and Koichi Fujimoto from Kanazawa University have discovered that there is a purely mechanical cause for cell extrusion.

Mechanically speaking, a simple (single-layer) epithelial sheet is analogous to a foam, and can be represented as a layer of interconnected polyhedra. Okuda and Fujimoto used such a foam model to describe a monolayer of epithelial cells, with each cell a polyhedron with average volume V. Every cell is further characterized by the number of neighboring cells n, the area of the apical ("top") and the area of the basal ('bottom') surface. The model, taking into account mechanical forces between neighboring cells, leads to a formula for the total mechanical energy of an epithelial sheet as a function of only a few parameters, including V and n, as well as the in-plane density and a quantity called sharpness, which can distinguish between situations where basal and/or apical surfaces are present or not. (A vanished apical surface implies basal extrusion and vice versa.) By studying how the energy changes by varying these few parameters, the researchers were able to obtain valuable insights into the mechanics of an epithelial sheet.

The key finding of Okuda and Fujimoto is that the system exhibits an inherent mechanical instability: small changes in cell topology or cell density can cause cell extrusion without additional forces being applied. Furthermore, it turns out that a cell undergoing extrusion generates forces within the layer, which can direct the extrusion of other cells to either side of the layer.

The scientists also found many agreements between the outcomes of their model and observations in living systems, such as the occurrence of different epithelial geometries (e.g. "rosette" or pseudostratified structures).

The model admittedly has limitations, for example the assumptions that the whole sheet and the individual cell surfaces are not curved but flat. However, quoting the researchers, "despite its limitations, [the] model provides a guide to understanding the wide range of epithelial physiology that occurs in morphogenesis, homeostasis, and carcinogenesis."

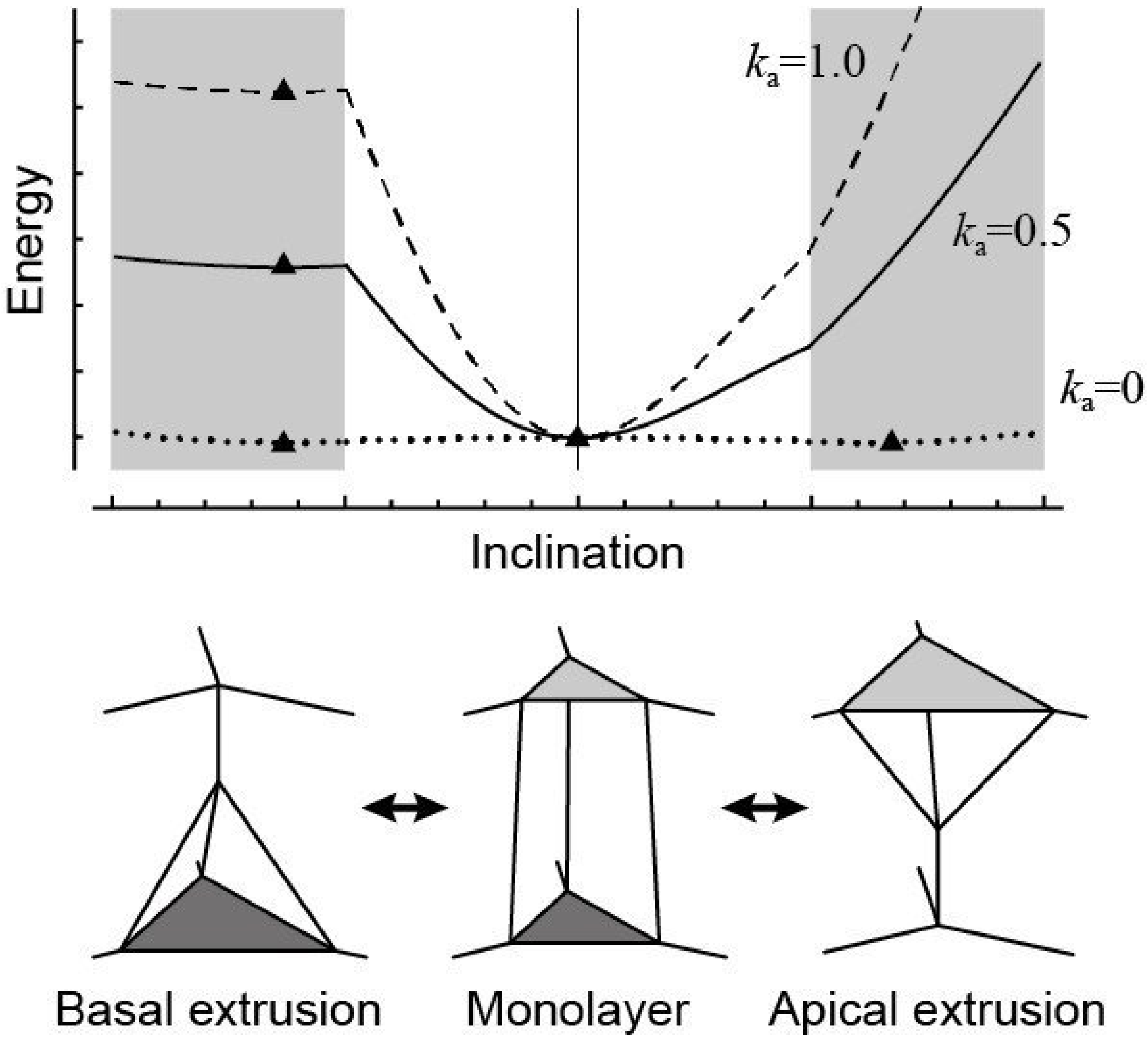

Figure 2. Energy landscape of cell state. A mechanical instability inherent in epithelial tissues appears to cause cell extrusions due to the changes in cellular physical parameters regulated by gene expressions. Credit: Kanazawa University

Epithelial cells

Epithelial tissue, one of four kinds of human (or animal) tissue, is located on the outer surfaces of organs and blood vessels in the human body, and on the inner surfaces of "hollow spaces" in various internal organs. A typical example is the outer layer of the skin, called the epidermis. Epithelial tissue consists of epithelial cells; it can be just one layer of epithelial cells (simple epithelium), or two or more (layered or stratified epithelium). Satoru Okuda and Koichi Fujimoto from Kanazawa University have now modeled a simple epithelium as an arrangement of polyhedra in order to study its mechanical properties and specifically the process of epithelial cell extrusion.

Cell extrusion

In epithelial tissue, cell extrusions happen—the processes whereby epithelial cells are "pushed out" of the epithelium. Cell extrusion is an important biological process, regulating for example the removal of apoptotic (dead) cells, tissue growth and the response to cancer. Okuda and Fujimoto looked at a simple epithelium from a mechanical point of view. Modeling the epithelium as a layer of interconnected polyhedra, they found that cell extrusion—whereby the top or bottom surface of a polyhedron shrinks to a point and then vanishes—can be considered a purely mechanical property. An inherent instability, present in homogeneous sheets, can lead to cells being extruded due to small changes in density or topology.

More information: Satoru Okuda et al. A Mechanical Instability in Planar Epithelial Monolayers Leads to Cell Extrusion, *Biophysical Journal* (2020). DOI: 10.1016/j.bpj.2020.03.028

Provided by Kanazawa University