MAX-PLANCK-ZENTRUM
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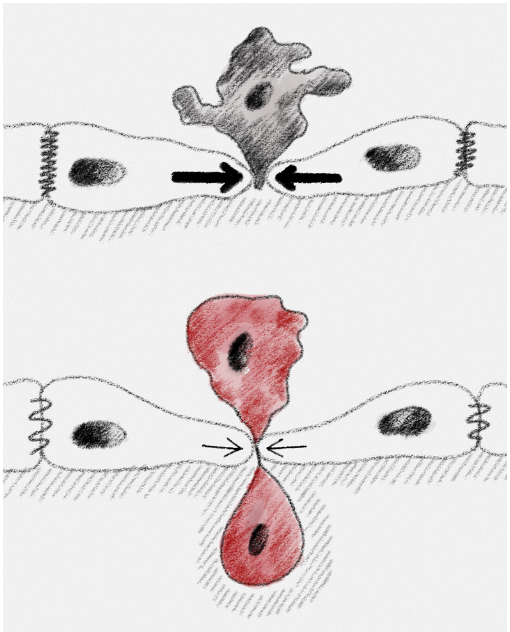
Ein gemeinsames Forschungszentrum mit der FAU und dem Universitätsklinikum Erlangen


ERLANGEN, 09 JANUARY 2025

# Physical signals as fate deciders: how mechanical forces extrude cells from tissues


**Epithelial tissues are in constant interaction with their environment. Maintaining their functionality requires dynamic balance (homeostasis) and that their cell numbers are tightly regulated. This is achieved by cell extrusion programs, a checkpoint mechanism eliminating unwanted or harmful cells. Researchers at the Max-Planck-Zentrum für Physik und Medizin (MPZPM), Institut Jacques Monod (CNRS, UP Cité, France) and Niels Bohr Institute (Denmark) have now demonstrated how physical signals can have an impact on the fate of extruding cells governing their death or survival. The results recently published in ›Nature Physics‹ may establish novel paths for understanding tissue properties in both normal and pathological conditions.**



Intercellular forces generate distinct patterns of extrusion: high compressive forces (top panel) drive apoptotic cell extrusion toward the upper side, while lower compressive forces (bottom panel) can induce live cell extrusion in either the upper or lower direction.

Epithelia are dynamic and must constantly deal with cell renewal. Therefore, the removal of cells from a tissue, called apoptotic extrusion, occurs regularly. Its balance is key for epithelia homeostasis. In addition to this role in tissue homeostasis, cell extrusion is a major cause of tissue shape changes and tumor progression. Thereby, extrusion mechanisms determine cell fates as squeezing out cells either dead or live can lead to fundamentally different biological consequences. This is both particularly important for developmental processes during tissue or organ formation, and plays a significant role in the development of diseases such as cancer. Despite the importance of cell extrusion in development and aging, as well as its pathological importance in cancer progression, the cues which determine the fate of an extruded cell were previously poorly understood.

## Mechanical intercellular forces determine the fate of extruding cells

Cells within epithelial monolayers exert forces on their neighbors, which can trigger cell detachment and subsequent elimination. While the extrusion of dead cells is essential to removing unfit or unwanted cells, the extrusion of live cells both plays a key role in developmental processes and is often linked to pathological responses. The team of Prof. Benoît Ladoux, principal investigator of ›Tissue Mechanobiology‹ at MPZPM, in collaboration with Prof. Amin Doostmohammadi at Niels Bohr Institute and Dr. René-Marc Mège from Institut Jacques Monod, hypothesizes that the physical forces within epithelial cells influence how they are extruded and determine their ultimate fate.

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The scientists were able to demonstrate that the intensity and duration of the force applied determines whether dead or living cells are extruded. These physical signals are determined by the strength of intercellular contacts, the E-cadherin junctions. Moreover, they showed that cells are extruded either apically or basally into the tissue, again depending on mechanical intercellular forces. The researchers also reported that, similarly to cell invasion, cells eliminated while alive could be associated significantly more often with extrusion toward the basal part.

Ladoux's, Mege's and Doostmohammadi's teams combined the physical modelling of three-dimensional cell assemblies with experiments involving cells expressing varying levels of specific proteins. These proteins connect cells and serve as mechano-sensors (E-cadherin-based) regulating cell-cell interactions. Their joint efforts in collaboration with Dr. Philippe Chavrier's team (Curie Institute) were thereby able to show that altered transmission of force via cell-cell junctions (Adherens Junctions) alters apoptotic cell death during extrusion. The scientists also demonstrated that the altered force transmission promotes a shift in the extrusion mode from the apical to the basal side, influencing the fate of the extruded cells.

"Our work demonstrates that different modes of cell extrusion processes are attributed to alterations in the generation, exertion, and transmission of mechanical forces within the tissue leading to genetic and protein level changes," says Ladoux. "Thus, intercellular force transmission regulated by cell-cell communication is crucial in cell extrusion mechanisms with potential implications during morphogenesis and invasion of cancer cells."

"Our work also shows the importance of force transmission to be regulated by the ability of epithelial tissues to interact with each other through adherens junctions with potential in understanding the role of adherens junctions in different types of cancer tissues," add Dr. Lakshmi Balasubramaniam and Dr. Siavash Monfared, co-first authors of the paper.



**Original publication in Nature Physics**
Balasubramaniam, L., Monfared, S., Ardaševa, A. et al.
Dynamic forces shape the survival fate of eliminated cells.
*Nat. Phys.* (2025).

**DOI:** https://doi.org/10.1038/s41567-024-02716-5

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*The **Max-Planck-Zentrum für Physik und Medizin** is conceived as a joint effort between the Max Planck Institute for the Science of Light (MPL), the Friedrich Alexander University (FAU) and the FAU University Hospital in Erlangen. The new scientific center aims to apply advanced methods from experimental physics and mathematics to basic biomedical research with an emphasis on the intercellular microenvironment. Learn more at mpzpm.mpg.de.*



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