When feeling the pinch, nuclei instigate cells to escape crowded spaces

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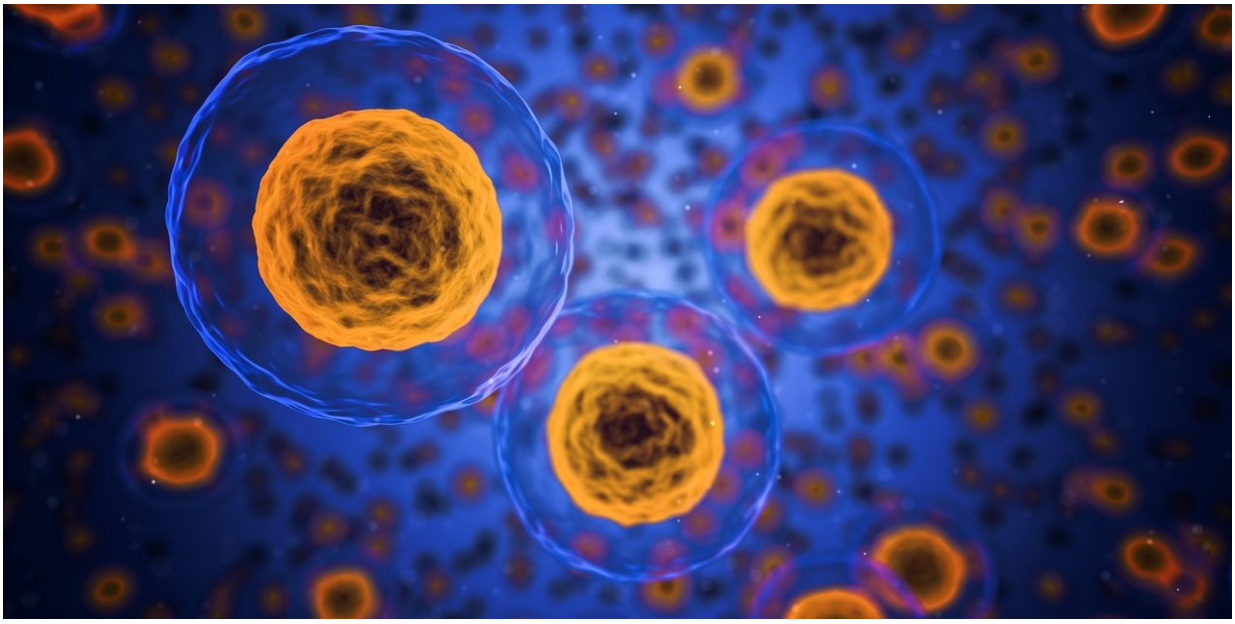

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The threat of serious deformation triggers a rapid escape reflex that enables cells to move away and squeeze out from tight spaces or crowded tissues.

In a new study published today in the journal *Science*, researchers reveal that squeezing a cell to the point where its nucleus starts to stretch triggers the activation of motor proteins which in turn transform the

cell's cytoskeleton so that it can flee a packed environment.

Each cell has a nucleus, and each nucleus has a membrane that separates the chromosomes from the rest of the cell. At a rest state, the nuclear membrane is saggy, akin to a loose shopping bag. Now researchers at the Centre for Genomic Regulation (CRG) and ICFO—The Institute of Photonic Sciences—have found that when the nuclear membrane is squeezed, the wrinkles on its surface iron themselves out, instigating a cascade of events that transform the cytoskeleton and eventually aid the cell in escaping its crowded environment.

"Our work represents a paradigm shift where the nucleus itself is not simply a static-container of genetic material but rather a dynamic sensor that cells can use to make sense of the environment around them," says Valeria Venturini, a Ph.D. student with dual affiliation at ICFO—The Institute of Photonic Sciences—and the CRG. "The intensity of nuclear stretching predicted the intensity of the response, shedding new light on this 'fight or flight' reflex at the single cell level. Understanding this ability to sense deformation, measure it and react accordingly may have important implications in understanding processes like cancer growth and homeostasis."

It is the first time researchers have been able to explain how single cells measure and respond to acute shape deformation, a real threat to their survival.

The reflex is activated in less than a minute, reversing when cells have escaped their packed environment.

"We are all familiar with the traditional senses of sight, hearing, smell, taste and touch, but we also depend on the lesser known 'sixth sense' - proprioception—our ability to perceive changes in our body posture and movement," says Verena Ruprecht, Principal Investigator at the Centre

for Genomic Regulation (CRG) and last author of the study. "It is remarkable that this sense also exists at the single cell level. Here we show for the first time that the nucleus helps cells measure changes to their shape and adjust their behaviour to mechanical challenges in variable tissue niches."

The researchers used primary cells from the zebrafish embryo to study this cellular reflex. An accompanying study published today in the same issue of *Science* by researchers at the Institut Curie Paris (France), ETH Zurich (Switzerland), King's College London (UK), and Children's Cancer Research Institute Vienna (Austria) identified the same reflex in immune and cancer cells, suggesting it is conserved across species and in adulthood.

The human body is composed of trillions of cells which similarly require multiple sensations to fulfill their task in specific tissues. From a single cell's perspective, its environment is a crowded place with many types of physical constraints and mechanical forces.

These conditions induce changes in cell shape that can threaten a tissue's integrity. Cells need to be able to respond to these physical challenges during embryonic development and in adulthood, but how they measure their own shape and adapt their behavior to their surroundings has been an open question.

More information: The nucleus measures shape changes for cellular proprioception to control dynamic cell behavior, *Science* (2020). DOI: 10.1126/science.aba2644

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