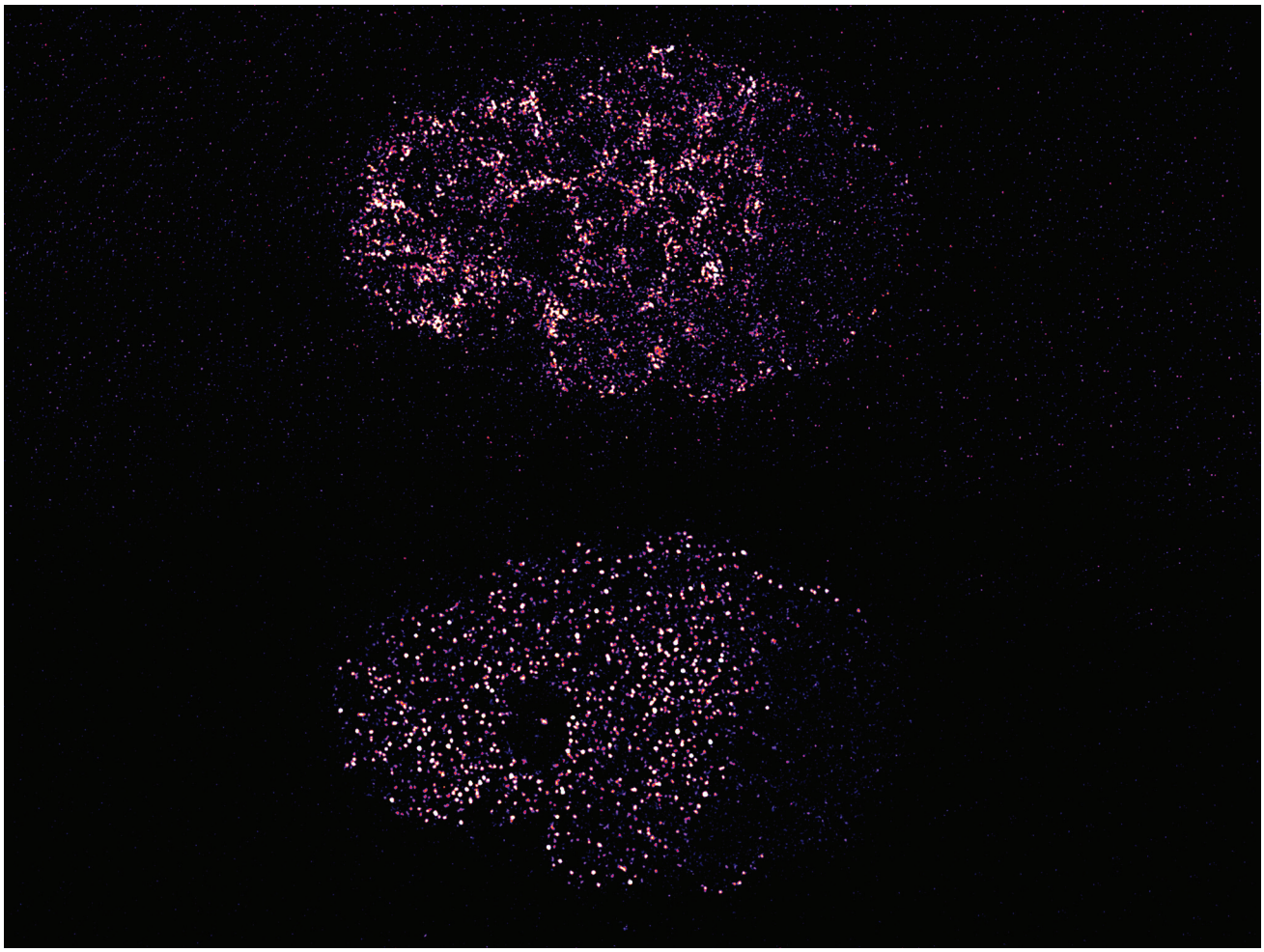

BREAKING CELL SYMMETRY

A force driven mechanism for establishing cell polarity

A team of researchers from the Mechanobiology Institute, National University of Singapore, along with colleagues from Temasek Life-sciences Laboratory and the Institute of Molecular and Cell Biology, A*STAR in Singapore, reveal a novel mechanism for establishing cell polarity that relies on tension force induced clustering of proteins.

Figure: Contraction drives PAR protein clustering to break symmetry in a *C. elegans* embryo. The top image shows the contractile activity of cortical myosin, which leads causes clustering of PAR-3 protein (bottom image). Both myosin and PAR-3 segregate at the left side of the embryo, the anterior pole. This breaks the previous symmetrical distribution of these proteins and polarizes the cell.

Fumio Motegi

Principal Investigator at the Mechanobiology Institute, and Assistant Professor, Department of Biological Sciences, National University of Singapore, and Principal Investigator, Temasek Life Sciences Laboratory. The Motegi lab combines genetics and biochemistry with modern imaging technology to investigate the mechanics underlying the initiation of cell polarization, and spatial patterning of cellular asymmetry.

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Reference

Wang S *et al.*, Cortical forces and CDC-42 control clustering of PAR proteins for *Caenorhabditis elegans* embryonic polarization. Nature Cell Biology, 2017 Aug; 19(8):988-995. doi: 10.1038/ncb3577

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Cortical forces induce protein clustering for cell polarization

By Andrew MS Wong, PhD | 21 Sep 2017

Biological cells are typically visualized as round (or spherical) in shape, with a nucleus centred in the middle, and other cellular components scattered throughout. In reality, each cell type exhibits a distinct shape, size and composition. Depictions of symmetrical spheres is in essence an over simplification that hides the fact that nearly all cells are asymmetric in their composition, and that this asymmetry develops in precise, and well-ordered, steps.

Known as cell polarity, this key characteristic of cells sees the separation of the sub-cellular components into distinct regions of the cell. If cells were symmetrical, processes like the division and movement of cells would not occur correctly, and tissues and organs would be deformed and non-functional. Despite being integral to organism development, scientists have yet to fully define the processes by which cells become polarized.

One way to visualise the asymmetrical nature of cellular composition is to think about the components of a car, and how they are arranged. Some parts of the car have to be located in a balanced layout, for instance the wheels. Other components need to be arranged in a specific orientation to work properly, i.e. the driver's seat has to be located in front of the rear passenger seats. Finally, components such as the engine can be located in the front or back of the car, and importantly this organization imparts different properties to the car's handling. In the same way, the arrangement of cellular components can have drastic effects on cell function.

Many of the existing studies on cell polarity have been carried out in the nematode worm C. elegans. At the one-cell stage, the embryo divides along a front/back axis to generate two differently sized daughter cells, with a larger cell at the front and a smaller cell at the back. This front/back axis is established by the movement and segregation of a group of proteins known as PAR (partition defective) proteins.

These PAR proteins reside in the cell cortex, a dynamic layer of protein filaments that lies just inside the cell membrane. Before polarization, the PAR proteins are distributed throughout the cortex, where they move freely. During polarization, the cortex contracts, and this causes different PAR proteins to separate, and accumulate at either the front or back of the cell, thereby breaking their previously symmetrical organization and establishing polarity along the front/back axis. However, the mechanism by which contractile activity transports and segregates PAR proteins remains unclear.

Tension flow

A team of researchers led by Asst. Prof. Fumio Motegi, Principal Investigator at MBI and Temasek Life Sciences Laboratory sought to answer this question by observing the movement of fluorescently labelled PAR protein complexes under the microscope in live C.elegans embryos as they underwent polarization. Using advanced microscopy techniques, they discovered that certain PAR proteins assembled into clusters at the beginning of polarization, and these clusters grew in size as polarization progressed. Once cortical contraction stopped, the clusters disassembled, with the proteins spreading out as a gradient along the front/back axis.

Despite these findings, the researchers did not observe a direct connection between the contractile fibres and PAR proteins, and this led them to hypothesize that an indirect effect of contraction was responsible for clustering. By disrupting or reinforcing the actomoysin cortex and observing the effect on cluster formation, they discovered that the key force driving PAR clustering was cortical tension, which developed as the cortex contracted.

From this the researchers were able to propose a new model that explained the segregation of PAR proteins. Here, contraction of the actomyosin cortex leads to an increase in cortical tension, causing the PAR proteins to assemble into clusters. As these large clusters move slowly, they become caught up in the overall cortical flow and segregate at one end of the cell, thereby establishing polarity. These segregated clusters of PAR proteins then act as a scaffold that mediates a local accumulation of other proteins needed for the establishment of front/back axes along the body.

The mechanism discovered in this study is a simple yet elegant example of how cells use internal forces to move and organize their protein components in a precise, well-ordered manner. Importantly, the force-driven mechanism described allows the cell to establish polarity without wasting energy by actively transporting proteins or cellular components against a concentration gradient. It is believed that similar mechanisms are used to break symmetry in other organisms, including humans, and it is hoped that this new knowledge will help scientists understand how and why cell polarity fails to be properly established in diseases such as cystic fibrosis and cancer.

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