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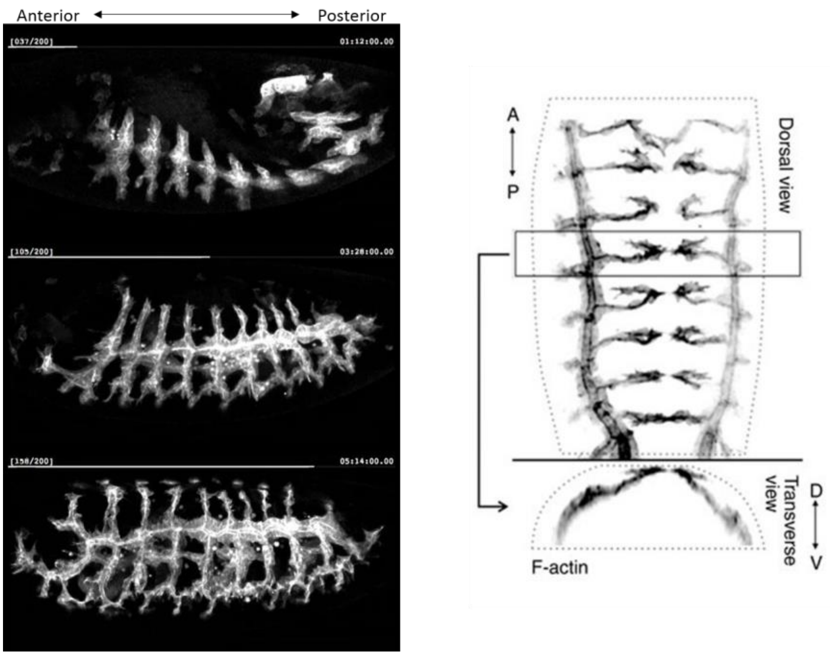
How cells can turn into donuts

May 2, 2016– From a topological perspective, a ball and a fork are considered equivalent forms as one can be deformed into other by stretching or shrinking the form of the outer surface. They are inequivalent to a donut (torus), as neither forms can be continuously deformed into a torus. In the natural world, however, where cells making up the animal body are found in diverse shapes, there appears to be way to turn a sphere-like cell into a torus. This extreme example is seen in tip cells of the developing *Drosophila* tracheal system. Tracheal primordia arise in each segment of *Drosophila* embryo to form an epithelial tube unit, and tubular branches of each unit must connect to those in neighboring segments to form a continuous network circulating the body. Tip cells are located at the tips of migrating tubules and lead the branches to pair and connect with a neighboring branch. As tip cell pairs begin adhering to one another, they also undergo dramatic shape changes to facilitate luminal fusion, but how this shape change occurs was not well understood.

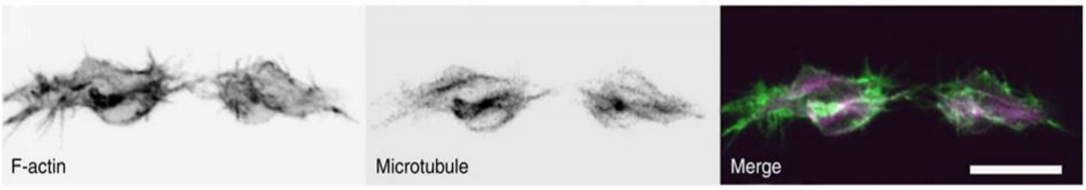
Now, in a paper published in *Nature Communications*, research scientists Kagayaki Kato (now at National Institutes of Natural Sciences, Okazaki, Japan) and Bo Dong (now at Ocean University, China) of the Laboratory for Morphogenetic Signaling (Shigeo Hayashi, Team Leader) reveal a mechanism underlying topological changes of the tip cells observed in the developing branches of the *Drosophila* tracheal system. Their study demonstrates that microtubules within the tip cells play an important role in bringing about the dramatic shape changes.



Tubular arrangement of epithelial tissues in the fly tracheal system. The tracheal network extending to all regions of the body is generated by connections formed between tracheal branches (left, lateral view; right, dorsal view). Bottom left and right panels were taken at stage 14 of development.

To change the cell topology from sphere-like into a torus requires opposing sides of the cell to compress inwards, followed by fusion of the cell membrane. The team employed live imaging technology to track the behavior of tip cells destined to pair and fuse, from migration, to cell-cell contact, and finally fusion to connect the tracheal branches. During migration, the leading edge of tip cells extended a radial array of filopodia, with microtubules actively elongating in direction of the target cell and punctate distribution of the cell adhesion molecule E-cadherin. When tip cells came into contact with their partner, they saw E-cadherin accumulating near the tip cell interface and forming new cell adhesion sites. Furthermore, dense central bundles of actomyosin and microtubules were found to span across the pairing tip cells. Morphological changes in tip cells were compromised when myosin activity was blocked, indicating that intrinsic actomyosin forces were driving the contraction of tip cells.

The team also investigated the effects of disrupting microtubule organization by treating the tip cells with different microtubule severing factors. They found that contraction of interfacing tip cells showed a range of problems, from an imbalance of contractile forces between tip cell leading to asynchronous contraction, to delays in or prolonged contraction phase, or even failed tip cell fusion. Thus, these observations suggested that a microtubule mechanism underlies the synchronization of cell fusion of the cells.



Microtubules (middle and magenta in right panel) formed bundles in the contact area of the paired tip cells. In this area, the actin filaments (left and green in right panel) overlapped with microtubules and formed dense bundles used for cell contraction.

Microtubules also serve as transport routes to shuttle molecular cargo within the cell, and the lab previously reported that in fly tracheal formation, the chitin deacetylase Serpentine (Serp) is shuttled by vesicular transport to be secreted in the tracheal lumen to promote luminal formation (*Science news: November 25, 2014; February 1, 2013). When microtubules were disrupted in the tip cells, the Serp transport machinery was also disrupted and tracheal branch fusion was arrested before luminal fusion was complete.

“A cell changing its topology to assume a torus-shape is an extremely rare occurrence, but our current study shows that even these radical morphological changes can be realized by skillful manipulation of cellular components found in any cell. Studying these extreme examples may shed light on the universal principles guiding morphological changes in cells,” explains Hayashi. “It is still unclear how microtubules can sense and balance the contractile and tensile forces. We would like to understand the mechanism linking the sensing of these forces by microtubules to cell morphogenesis.”

*Science news: November 25, 2014
http://www.cdb.riken.jp/en/news/2014/researches/1125_5309.html

*Science news: February 1, 2013
http://www.cdb.riken.jp/eng/04_news/articles/13/130201_rab9retromer.html