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Research Roundup

Passing along polarity

Fly ovarioles spit out oocyte-containing cysts “like a sausage machine,” says Daniel St. Johnston. In the process, the cysts are endowed with a clearly defined anterior-posterior polarity axis based on the posterior positioning of the oocyte. “The [axis] is hardwired into the geometry of the ovary,” says St. Johnston. “What we’re describing is the mechanism that transmits this.”

That mechanism is based on a relay of axis information from older to newer cysts, according to Isabel Torres, Hernán López-Schier and St. Johnston (University of Cambridge, Cambridge, UK). They started with the observation that Delta in the germ-line cyst cells signals to Notch in the surrounding follicle cells, thus inducing the formation of specialized polar cells at each end of the cyst. Earlier work had shown that the oocyte sticks to the posterior follicle cells because both cell types express high levels of the same cadherin. But, says St. Johnston, “there was one thing that was missing. How do the posterior follicle cells know that they are posterior?”

This is where the relay comes in. The Cambridge team now reports that when only a single cyst lacks Delta, it is always fused to the more anterior (younger) cyst. And it is the younger cyst that fails to position its oocyte correctly. Thus the older cyst induces its anterior polar cells to induce the formation of stalk cells between two cysts, and the stalk cells induce the cadherin expression that defines the posterior of the younger cyst.

Somewhere the relay is made unidirectional. St. Johnston believes this comes down to the timing of different events, which is in turn “a consequence of the whole thing being a production line. Because the previous cyst has already signaled, the response is biased to the side that is naive.”

This timing mechanism would overcome the possibly symmetrical nature of the Delta signal. Delta establishes the identity of both anterior and posterior polar cells. But by the time the Delta arrives, a polarization signal has already passed through the precursors of the posterior polar cells, perhaps altering them. And the posterior cells were also born earlier (at the same time as the anterior polar cells of the older cyst). One or both of those differences might ensure that the polarization signal always travels from posterior to anterior, and never in reverse.

Reference: Torres, I.L., et al. 2003. Dev. Cell. 5:547–558.

A kinase that activates by occupancy

A new output mode for a kinase is reported by Feroz Papa, Peter Walter, and colleagues (HHMI and University of California, San Francisco [UCSF], CA). They find that, for Ire1 kinase, the key to activation is not phosphotransfer but rather ligand binding in the kinase’s nucleotide-binding site. Occupancy of that site restores function to a kinase-dead mutant of Ire1.

The new findings just add to the uniqueness of the Ire1 pathway, which responds to unfolded proteins. “This pathway is really a sort of duck-billed platypus,” says Papa. “There have been so many surprises.”

The response starts when unfolded proteins recruit chaperones away from Ire1; this is thought to expose a patch on Ire1 that mediates oligomerization. Transphosphorylation by Ire1 oligomers then somehow activates the RNase activity of Ire1, which excises an inhibitory intron from the HAC1 mRNA. After tRNA ligase joins the mRNA fragments, the active Hac1 transcriptional activator can be produced.

The new activation discovery began with an attempt to create a specific inhibitor of the Ire1 kinase. That inhibitor, 1NM-PP1, binds only mutant versions of Ire1 that have a redesigned nucleotide-binding site. Although 1NM-PP1 inhibited the kinase activity of Ire1, there was a surprise further downstream. “The drug is working exactly as you would expect as a kinase inhibitor,” says Papa, “yet the RNase is still activated.”

This activation by 1NM-PP1 also worked in Ire1 mutants that were dead for kinase activity or lacked transphosphorylation sites. When kinase-dead and constitutive mutations were combined in a single mutant version of Ire1, the 1NM-PP1 could now be used as an instructive chemical that could, by itself, activate the entire pathway.

In wild-type cells, the UCSF team thinks that an occasional molecule of ATP can sneak into the nucleotide-binding site of oligomerized Ire1. This allows transphosphorylation, which further opens the nucleotide-binding site so that nucleotide can bind more easily and activate the RNase activity of Ire1.

A nucleotide signal, in particular the efficient Ire1 activator ADP, may help Ire1 to do its job, because high concentrations of ADP indicate low energy status and thus incipient problems in the energy-intensive process of protein folding. 1NM-PP1 revealed this unusual pathway because the drug’s small size allowed it to sneak into Ire1’s nucleotide-binding site even without Ire1 transphosphorylation, and its particular binding properties may allow it to stay around long enough to effect RNase activation.

Reference: Papa, F.R., et al. 2003. Science. 10.1126/science.1090031.

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