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EDITORS' CHOICE

Cell Biology

Local Caspase for Fertility, Not Death

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During the maturation process, spermatids must eliminate most of their cytoplasm to become small, highly motile sperm with their characteristic small DNA-packed "head" and "tail" for swimming. In fruit flies, caspases contribute to the elimination of the cytoplasm in a process called individualization, which begins in the head and ends with the elimination of the cytoplasmic contents into a "waste bag" from the tail end. Kaplan *et al*. identified Scotti (abbreviated soti), in a yeast two-hybrid screen for partners of the adaptor Klhl10, which is part of the E3 ligase complex required for individualization, and confirmed this interaction by coimmunoprecipitation from transfected S2 cells. Spermatids from *soti*-null mutant flies failed to mature, and immunostaining for active caspase showed that the abundance of activated caspase was abnormally high and that the developing spermatids failed to generate waste bags. In flies double homozygous for *soti* and *cullin3* (*cul3*) or *klhl10*, caspase activation and sperm individualization failed to occur, suggesting that Soti acts upstream of the E3 ligase. Experiments with *soti*-null and *cul3* hypomorphic flies suggested that Soti may inhibit the E3 ligase, a hypothesis confirmed by introducing various combinations of a *soti* transgene, a *klhl10* transgene, and a *cul3* transgene into fly eyes and examining ommatidial disorganization: Cul3 enhanced the disruption caused by Klhl10, whereas Soti suppressed it. Immunostaining revealed that active caspases were most abundant in spermatids in the later stages of individualization and showed a gradient, with highest amounts in the spermatid head region and lowest in the tail region. In contrast, the distribution of Soti was opposite (highest in the tail and lowest in the head), and its abundance was higher at an earlier stage. This temporal difference in the abundance of Soti and active caspases led the authors to investigate whether Soti affected the abundance and distribution of Bruce, an inhibitor of apoptosis protein (IAP), lack of which causes male sterility in genetically deficient flies. Cotransfection of Klhl10 destabilized Bruce peptides in transfected S2 cells, an effect reversed by Soti. Coimmunoprecipitation experiments suggested that Soti and Bruce may compete for binding to Klhl10. Immunostaining in developing spermatids showed that Bruce accumulated in the tail regions and extended in a gradient toward the head at the time when Soti abundance was declining and individualization was commencing. Bruce abundance was reduced in flies with *klhl10* or *cul3* deficiency and was increased and concentrated in the tail regions of *soti*-deficient flies. The authors propose that the decrease in the abundance of the gradient-distributed Soti allows Cul3-mediated Bruce ubiquitylation, which redirects its distribution rather than stimulates its degradation, and thus limits caspase activation to promote maturation instead of apoptosis.

Y. Kaplan, L. Gibbs-Bar, Y. Kalifa, Y. Feinstein-Rotkopf, E. Arama, Gradients of a ubiquitin E3 ligase inhibitor and a caspase inhibitor determine differentiation or death in spermatids. *Dev. Cell* **19**, 160–173 (2010). [PubMed]

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