Published in final edited form as:

Nat Cell Biol. 2016 November 29; 18(12): 1267–1268. doi:10.1038/ncb3449.

Remodelling germ cells by intercellular cannibalism

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Abstract

Work from the early 1980s reported strange lobes protruding from *Caenorhabditis elegans* germ cell precursors. However, the fate and potential significance of these lobes remained unexplored for decades. Now, neighbouring endodermal cells are shown to sever and digest these lobes, in an unexpected process of ‘intercellular cannibalism’, which could play an important part in regulating primordial germ cells.

Germ cell precursors have special roles. Unlike other cells, germ cells are immortal: they alone carry the heritable materials on to the next generation and all future generations. Germ cells must form in a way that guarantees their immortality, a process that is only partially understood. In this issue, Abdu et al. show that in *C. elegans*, special lobes actively push out from germ cells, deforming neighbouring endodermal cells¹. These neighbouring cells then assemble structures that accomplish something unexpected: they sever, internalize and degrade the lobes, thereby actively changing the size and content of the germ cells. The results raise interesting questions about a previously unknown form of cell remodelling, and more generally about how immortal germ cells are shaped.

The discovery by Abdu et al. began with a decades-old observation. In a classic 1983 article on the embryonic cell lineage of *C. elegans*, Sulston and colleagues noted that about halfway through embryogenesis, the germ cells were seen in electron micrographs to have large lobes embedded into neighbouring cells, the endodermal precursor cells². Later, by the time embryos hatched as larvae, the lobes were gone. It remained unclear whether the lobes disappeared by being reabsorbed by the body of the germ cell or by other means. The researchers speculated that the lobes might be important for endodermal cells to help maintain the germ cells.

Abdu et al. followed up on the questions that Sulston and colleagues left unanswered: what is the fate and possible function of these germ cell lobes? The authors live-imaged the germ cells throughout development, with fluorescent membrane tags labelling the germ cells in one colour and their endodermal neighbours in a second colour. Imaging confirmed that the germ cell lobes formed approximately halfway through embryogenesis, and by the time the embryos hatched as larvae, the lobes had disappeared. But in the hatched larvae, the germ cells were approximately half their original size, suggesting that the lobes were somehow lost, rather than being reabsorbed by the germ cells. The authors also observed germ cell debris inside the neighbouring endodermal cells. The debris was encapsulated by lysosomal and endosomal markers, suggesting that germ cell materials were being degraded in the

neighbouring cells. The lobes were degraded with a consistent timing across multiple embryos, suggesting that this process might be developmentally regulated.

These observations prompted the question of whether endodermal cells were capturing lobes that the germ cells had jettisoned, or whether endodermal cells had a more direct role in forming or removing the lobes. Lobes formed in cultured germ cells that had been completely isolated from embryos. And in mutant embryos that lacked endodermal cells, the lobes persisted throughout embryogenesis, remaining attached to the germ cells. These results demonstrated that lobes can form autonomously, and that the endodermal cells subsequently remove the lobes from the germ cells and then degrade the lobes. The authors characterized this direct remodelling of one cell by its neighbour as ‘cell cannibalism’, reflecting the active role they defined for one cell in removing a large part of its neighbour.

Abdu et al. sought to identify the molecular mechanisms underlying cell cannibalism. They first postulated that mechanisms involved in the engulfment of apoptotic cell corpses might contribute to lobe removal. In apoptotic engulfment, a Rac1 small GTPase (termed CED-10 in *C. elegans*) contributes to forming a cup-shaped enrichment of actin in engulfing cells, surrounding the dying cell³. Abdu et al. showed that CED-10/Rac1 was indeed required for actin enrichment in endodermal cells, although in a narrow ring (Fig. 1) around the lobe neck rather than in a broader cup shape, and CED-10/Rac1 was required for lobe scission. But among several other proteins that act with CED-10/Rac1 in engulfment, none were found to be essential for lobe cannibalism.

In the absence of further clear molecular parallels with apoptotic engulfment, the authors pursued the molecular mechanism by taking advantage of *C. elegans* as a system for forward genetics, screening for mutants in which the lobes of fluorescently tagged germ cells failed to be degraded. They identified the gene *lst-4*, which encodes a homologue of a sorting nexin family member known to contribute to vesicle scission along with dynamin⁴. Abdu and colleagues confirmed that both *LST-4* and dynamin accumulated in endodermal cells at lobe necks, and both were required in the endodermal cells for lobe scission. Based on their roles in other cell types, it seems likely that *LST-4*, dynamin, CED-10/Rac1 and actin work together to pinch membranes in around lobe necks, and then to sever the lobes from the germ cell bodies, in a mechanism similar to vesicle scission — but with a giant endocytic-like vesicle surrounding about half of another cell.

Why do germ cells produce these lobes in the first place, and why is there an intricate mechanism in place to ensure their separation and destruction? Answering these questions will without doubt be challenging, given that the molecular players identified in lobe removal so far have other essential cellular functions. But the authors made headway in uncovering some possible clues. Using fluorescent markers, Abdu et al. showed that germ cell mitochondria produce higher levels of potentially damaging oxidants than the mitochondria in other cells. They also found that most germ cell mitochondria were segregated into the lobes and then degraded. Germ granules were enriched in an opposite pattern, with most of them remaining in the body of the germ cell and few being sent to the lobes. These patterns of mitochondria and germ granule segregation establish that intercellular cannibalism has an effect of significantly altering germ cell contents.

It is interesting to imagine how lobe cannibalism might make important contributions to germ cell functions. Lobe removal could play a supporting role in the unique developmental programme of the germ cells within a single generation. For example, germ cell transcriptional quiescence during early development might permit the accumulation of damaged proteins or organelles that need to be cleared. Other possibilities include that lobe removal might set an ideal germ cell size, or an ideal cytoplasmic concentration of germ granules, or somehow prepare the germ cell precursors to proliferate more than any other cell in the animal to populate the germ line of the organism.

It is also possible that lobe removal plays a transgenerational role, rejuvenating germ cells to ensure their immortality in each generation^{5, 6}. Intercellular cannibalism might contribute to a biological ‘fountain of youth’ for germ cells by eliminating damaged mitochondria. Age-related decline in mitochondrial function has long been postulated to contribute to cellular ageing, and in cultured cells and yeast, mitochondria have been shown to segregate asymmetrically, with stem cells and mother cells retaining an older population of mitochondria than daughter cells^{7, 8, 9}. Although to our knowledge there is no apparent asymmetric segregation of mitochondria in *C. elegans*, the oxidant-rich mitochondria identified in germ cells might pose a risk for germ cells and therefore might need to be reduced in number. Lobe removal might also serve a function not in the germ cells but in the endodermal cells that remove the lobes.

Whether cellular cannibalism occurs in other organisms and in other contexts is not yet known, although similar cellular remodelling events — in which engulfing cells play an active role in eliminating a large part of a neighbouring cell — have been at least postulated. Two observations of cells taking up parts of their neighbours have been made in developing nervous systems, where remodelling cell protrusions and connections is frequent^{10, 11}. In the developing mouse brain, engulfment of axon presynaptic terminals by microglia is thought to play a role in synaptic pruning¹⁰. And in the *Drosophila* nervous system, degenerating dendrites are taken up by neighbouring epithelial cells both during development and after injury¹¹. Interestingly, these epithelial cells also require dynamin, although to scavenge degenerating dendrites rather than to actively sever parts of living cells.

The cell biological mechanisms for lobe production and removal, beyond what was reported by Abdu et al., are unknown. The mechanisms by which lobes apparently induce the formation of scission complexes in neighbouring cells also remain to be elucidated. Identifying molecular components that contribute to these processes might provide footholds to answer these outstanding questions, and could contribute routes to decipher the biological functions of lobe production and removal.

References

1. Abdu Y, Maniscalco C, Heddlestone JM, Chew TL, Nance J. *Nat Cell Biol.* 2016; 18:1302–1310. [PubMed: 27842058]
2. Sulston JE, Schierenberg E, White JG, Thomson J. *N Dev Biol.* 1983; 100:64–119.
3. Reddien PW, Horvitz HR. *Annu Rev Cell Dev Biol.* 2004; 20:193–221. [PubMed: 15473839]
4. Lundmark R, Carlsson SRJ. *Cell Sci.* 2009; 122:5–11.
5. Smelick C, Ahmed S. *Ageing Res Rev.* 2005; 4:67–82. [PubMed: 15619471]

6. Ünal E, Amon A. Cold Spring Harb Symp Quant Biol. 2011; 76:73–80. [PubMed: 21890640]
7. McFaline-Figueroa JR, et al. Aging Cell. 2011; 10:885–895. [PubMed: 21726403]
8. Katajisto P, et al. Science. 2015; 348:340–343. [PubMed: 25837514]
9. Sun N, Youle RJ, Finkel T. Mol Cell. 2016; 61:654–666. [PubMed: 26942670]
10. Schafer DP, et al. Neuron. 2012; 74:691–705. [PubMed: 22632727]
11. Han C, et al. Neuron. 2014; 81:544–560. [PubMed: 24412417]

Fig. 1.