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Current Biology
Dispatches

Stem Cells: Muscle Cells Enwrap Escaped Germline Stem Cells in *C. elegans*

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https://doi.org/10.1016/j.cub.2019.01.035

Interactions between the distal tip cell and germline stem cells maintain a proliferative pool of mitotic cells in the *Caenorhabditis elegans* gonad. A new study shows that escaped germline stem cells induce nearby muscle cells to reach out and wrap around them, forming an ectopic niche similar to the native gonadal germ cell niche.

Stem cells reside within a microenvironment known as a stem cell niche, in which surrounding cells provide mechanical and biochemical cues that promote stem cell survival and homeostasis. During development, or in response to wounding, dynamic interactions within this niche allow for proliferation or differentiation of the stem cell pool. Communication between cells in the niche occurs via secreted factors like Notch, which help to specify differentiation, apoptosis, or proliferation [1–3], and via direct cell–cell signaling, mediated by gap junctions and adherens junctions [4]. Mechanical cues provided by the extracellular matrix are also critical for proper stem cell proliferation and differentiation [4,5]. Organismal homeostasis and health depend upon the maintenance of stem cell niches. For example, the decline in regenerative capacity observed during aging has been attributed in part to changes in niche function [6,7]. Despite considerable interest in stem cells and stem cell niche formation, significant questions remain regarding how niches are established and maintained. In this issue of *Current Biology*, a new study by Gordon *et al.* [8] advances our understanding of how stem cells and support cells can come together to generate stem cell niches.

The cellular interactions that drive the formation of niches during development are difficult to study in most organisms because these structures are difficult to access *in vivo*. Since the nematode *Caenorhabditis elegans* is transparent, interactions between stem cells (e.g. the germline stem cells) and their niche cells (e.g. the support cells of the somatic gonad) are easier to observe *in vivo*. In the hermaphrodite *C. elegans*, the reproductive system is a simple tubular structure composed of two U-shaped gonad arms, which maintain the germ cell pool and support oocyte development, two spermathecae, which store sperm and serve as the site of fertilization, and one common uterus, which retains eggs for a short time before they are laid [9] (Figure 1). The distal gonad arm is a syncytium of germ cell nuclei, which are partially enclosed by cell membranes, but open to a common center, or rachis. The distal end of each gonad arm is capped by a specialized somatic cell, the distal tip cell (DTC) (Figure 1) [3,9]. The DTC reaches out long processes, which enclose the mitotic germ cells and form the germ cell niche. The DTC expresses the ligand LAG-2/Delta, which contacts the receptor GLP-1/Notch on the germline stem cells [2]. Active Notch signaling is required to maintain germ cells in their undifferentiated, proliferative state [2,10]. As the cells move proximally, out of the zone of influence of the DTC, they enter meiosis and undergo oocyte maturation [9]. Although much is known about how the DTC maintains the mitotic germ cell pool, proteins mediating adhesion between the DTC and germ cells have not been identified.

Normally, only the DTC surrounds the germline stem cells; however, ectopic germ cells (i.e. germ cells that have escaped the somatic gonad) are occasionally found to be surrounded by other tissues [11–15], suggesting that neighboring tissues could provide a niche-like environment for the germ cells. In order to address the question of how escaped germ cells form these ectopic associations, Gordon *et al.* [8] ruptured the basement membrane surrounding the gonad to allow for germ cell release. Using time-lapse microscopy of fluorescently labeled germ and muscle cells, the authors showed that muscle cells, and occasionally the hypodermis, reached out and wrapped around the escaped germ cells, but did not fuse with or internalize them (i.e. no phagocytosis occurred) [8]. This result is consistent with a previous observation that CED-1/Draper, which is required for phagocytosis of apoptotic cells, is not required for muscle enwrapment of germ cells [16].

It may seem odd to the non-worm aficionado that muscle cells would reach out and grab escaped germ cells. However, in *C. elegans*, muscle cells produce actin-rich extensions known as 'muscle arms' to contact axons during development of the neuromuscular junction [17]. Surprisingly, Gordon *et al.* [8] showed that the Netrin receptor UNC-40/DCC, which is required for muscle arm extension, was not required for enwrapment of the ectopic germline stem cells; the authors posit that muscle cells might be 'primed' with the correct cytoskeletal machinery for forming muscle arm-like structures that enwrap the germline stem cells. Because neither apoptotic cell engulfment nor muscle arm formation seemed to be involved, the authors turned to a genetic screen to identify the mechanism by which muscle cells enwrap germline cells.

A candidate RNAi screen revealed that the cell–cell adhesion proteins HMR-1/E-cadherin, HMP-1/α-catenin, HMP-2b/β-catenin, and SAX-7/L1CAM drive the interaction between muscle cells and ectopic germline cells. The authors found

that all of these factors were enriched at the contact sites between muscle cells and ectopic germ cells, and that HMR-1/E-cadherin was required for muscle cells to enwrap the germline stem cells [8]. These observations led to the hypothesis that ectopic germline stem cells use cell–cell adhesion proteins to induce muscle cell enwrapment. Because the muscle cells do not enwrap other cell types found in the body cavity, such as coelomocytes, a test of this hypothesis would be to determine whether expression of HMR-1 and the other adhesion proteins in other cell types could induce enwrapment by muscle cells.

In what ways are the interactions between ectopic germline stem cells and muscle cells similar to those in the real niche formed between the DTC and the germline stem cells? Gordon *et al.* [8] found that HMR-1/E-cadherin, HMP-1/α-catenin, and HMP-2b/β-catenin were all similarly enriched at germ–germ and DTC–germ contact sites in the real stem cell niche. HMR-1/E-cadherin and SAX-7/L1CAM were required for the long DTC protrusions to intercalate with germline stem cells [8]. It is worth noting that cadherin-based interactions between cells are also important in other stem cell niches. For instance, E-cadherin is associated with niche–stem cell adhesion in the *Drosophila melanogaster* testis, in which E-cadherin is required to polarize germ stem cells toward their niche cells [5,18].

Despite these similarities between the real and ectopic niche, Gordon *et al.* [8] showed that germline stem cells did not proliferate when enwrapped by muscle cells. The few ectopic germline stem cells that did undergo mitosis in the body cavity were found to have been in contact with nearby DTC protrusions. In fact, laser ablation of the DTC led to a loss of germ cell proliferation [8]. These results suggest that the DTC provides proliferative cue(s) to the germ cells that muscle cells are not able to provide. One likely mediator is the Notch ligand, LAG-2, which is required in the DTC–germ cell niche to maintain a proliferative pool of mitotic cells [2,3], but which is not expressed in the muscle [8]. In addition, the DTC could be providing soluble signals, secreting extracellular matrix molecules, or otherwise supporting the proper biochemical and mechanical environment needed for germline stem cell proliferation. Further studies in this system could identify these missing factors, supporting the goal of engineering stem cell niches *in vitro*.

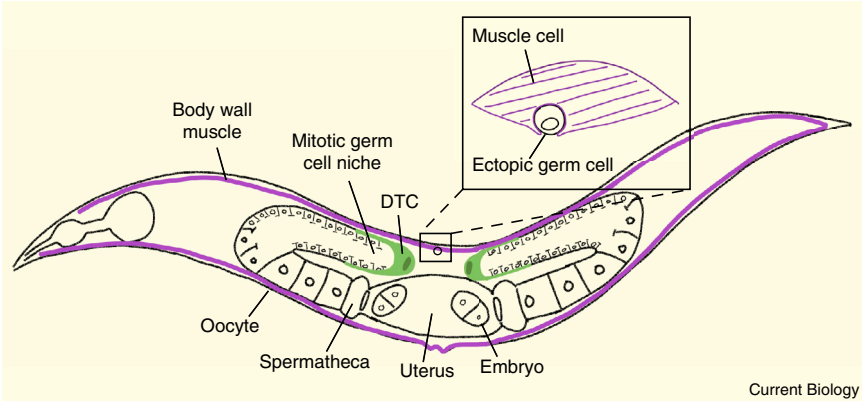

Figure 1. Anatomy of the *C. elegans* gonad and germ cell enwrapment by muscle cells.
Diagram of *C. elegans* anatomy with the distal tip cells (DTC) indicated in green and the body wall muscle cells indicated in purple. The inset shows a muscle cell enwrapping an ectopic germline stem cell.

The results of this study — mainly that ectopic stem cells use cell–cell adhesion to drive close interactions with muscle cells — are relevant not only to the formation of stem cell niches, but also to normal tissue homeostasis and the formation of new cell–cell associations in developmental and pathogenic circumstances. For example, cancer stem cells maintain close associations with other cell types that support proliferation and regulate metastatic behavior [5]. Cell–cell associations are mediated in part by adherens junctions. These cadherin-based interactions maintain tissue integrity and are important for the prevention of the epithelial-to-mesenchymal transition in cancer [19]. Mammary myoepithelial cells use P-cadherin to prevent the escape of luminal mammary epithelial cells by reaching out and grabbing them [20] in a manner reminiscent of the muscle cell capture of germ cells in *C. elegans* described by Gordon *et al.* [8]. When cancer cells do metastasize, they establish secondary metastases in tissues with similar molecular characteristics [19], and cell surface adhesion proteins may play a role in the selection of secondary metastasis sites. In summary, studies like this one in *C. elegans* can help us identify new mechanisms that underlie the formation and maintenance of cell–cell contacts in niches and other contexts relevant to human development and disease.

REFERENCES

1. Artavanis-Tsakona, S., Rand, M.D., and Lake, R.J. (1999). Notch signaling: cell fate control and signal transduction in development. Science *284*, 770–776.
2. Henderson, S.T., Gao, D., Lambie, E.J., and Kimble, J. (1994). *lag-2* may encode a signaling ligand for the GLP-1 and LIN-12 receptors of *C. elegans*. Development *120*, 2913–2924.
3. Kimble, J.E., and White, J.G. (1981). On the control of germ cell development in *Caenorhabditis elegans*. Dev. Biol. *81*, 208–219.
4. Chen, S., Lewallen, M., and Xie, T. (2013). Adhesion in the stem cell niche: biological roles and regulation. Development *140*, 255–265.
5. Jones, D.L., and Wagers, A.J. (2008). No place like home: anatomy and function of the stem cell niche. Nat. Rev. Mol. Cell Biol. *9*, 11–21.
6. Boyle, M., Wong, C., Rocha, M., and Jones, D.L. (2007). Decline in self-renewal factors contributes to aging of the stem cell niche in the *Drosophila* testis. Cell Stem Cell *1*, 470–478.
7. Pan, L., Chen, S., Weng, C., Call, G., Zhu, D., Tang, H., Zhang, N., and Ting, X. (2007). Stem cell aging is controlled both intrinsically and extrinsically in the *Drosophila* ovary. Cell Stem Cell *1*, 458–469.
8. Gordon, K.L., Payne, S.G., Linden-High, L.M., Pani, A.M., Goldstein, B., Hubbard, J.A., and Sherwood, D. (2019). Ectopic germ cells can induce niche-like enwrapment by neighboring body wall muscle. Curr. Biol. *29*, 823–833.
9. Hirsh, D., Oppenheim, D., and Klass, M. (1976). Development of the Reproductive System of *Caenorhabditis elegans*. Dev. Biol. *49*, 200–219.

10. Austin, J., and Kimble, J. (1987). *glp-1* is required in the germ line for regulation of the decision between mitosis and meiosis in *C. elegans*. Cell *51*, 589–599.

11. Huang, C., Hall, D.H., Hedgecock, E.M., Kao, G., Karantza, V., Vogel, B.E., Hutter, H., Chisholm, A.D., Yurchenco, P.D., and Wadsworth, W.G. (2003). Laminin α subunits and their role in *C. elegans* development. Development *130*, 3343–3358.

12. Johnson, R.P., Kang, S.H., and Kramer, J.M. (2006). *C. elegans* dystroglycan DGN-1 functions in epithelia and neurons, but not muscle, and independently of dystrophin. Development *133*, 1911–1921.

13. Trzebiatowska, A., Topf, U., Sauder, U., Drabikowski, K., and Chiquet-Ehrismann, R. (2008). *Caenorhabditis elegans* teneurin, *ten-1*, is required for gonadal and pharyngeal basement membrane integrity and acts redundantly with integrin *ina-1* and dystroglycan *dgn-1*. Mol. Biol. Cell *19*, 3898–3908.

14. Kadyk, L.C., and Kimble, J. (1998). Genetic regulation of entry into meiosis in *Caenorhabditis elegans*. Development *125*, 1803–1813.

15. Qi, W., Huang, X., Neumann-Haefelin, E., Schulze, E., and Baumeister, R. (2012). Cell-nonautonomous signaling of FOXO/DAF-16 to the stem cells of *Caenorhabditis elegans*. PLoS Genet. *8*, e1002836.

16. Zhou, Z., Hartwieg, E., and Horvitz, H.R. (2001). CED-1 is a transmembrane receptor that mediates cell corpse engulfment in *C. elegans*. Cell *104*, 43–56.

17. Alexander, M., Chan, K.K.M., Byrne, A.B., Selman, G., Lee, T., Ono, J., Wong, E., Puckrin, R., Dixon, S.J., and Roy, P.J. (2009). An UNC-40 pathway directs postsynaptic membrane extension in *Caenorhabditis elegans*. Development *136*, 911–922.

18. Inaba, M., Yuan, H., Salzmann, V., Fuller, M.T., and Yamashita, Y.M. (2010). E-Cadherin is required for centrosome and spindle orientation in *Drosophila* male germline stem cells. PLoS One *5*, e12473.

19. Kalluri, R., and Weinberg, R.A. (2009). The basics of epithelial-mesenchymal transition. J. Clin. Invest. *119*, 1420–1428.

20. Sirka, O.K., Shamir, E.R., and Ewald, A.J. (2018). Myoepithelial cells are a dynamic barrier to epithelial dissemination. J. Cell Biol. *217*, 3368–3381.

Evolution: Arrow Worms Find Their Place on the Tree of Life

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https://doi.org/10.1016/j.cub.2018.12.029

A new phylogenomic study places the erstwhile enigmatic chaetognaths, also known as 'arrow worms', within a subgroup of lophotrochozoans, the gnathiferans.

Chaetognaths, also known as 'arrow worms', have been important predators in the world's oceans since the Cambrian. While only around 130 chaetognath species are known, they are nevertheless hugely abundant, showing the success of their life style. Most chaetognaths are pelagic predators ranging in size from a few millimeters to a few centimeters and feed on fish fry, copepods and other plankton, making them a key a link in the ocean's food web. The chaetognath body plan has been tinkered with remarkably little over the past half a billion years. The living taxa are physically all very similar: with a streamlined, tripartite, arrow-like body with fins and a horizontal tail at one end and a head with very obvious grasping spines at the other (hence the name chaetognaths, meaning 'spiny jaws'; Figure 1). The very same morphological characters are immediately recognisable in fossil chaetognaths from the early [1] and mid-Cambrian [2], and the widespread existence of protoconodonts (fossilised chaetognath teeth) betrays their success in Cambrian oceans [3]. Despite their abundance and ecological importance, where exactly arrow worms sit in the animal tree of life has remained enigmatic. A recent phylogenomic study in *Current Biology* by Ferdinand Marlétaz, Daniel Rokhsar and colleagues [4] resolves this puzzle, and in this issue, a new study by Jakob Vinther and Luke Parry [5] on the fossil chaetognath *Amiskwia* provides additional support for the new placement.

There aren't many animal phyla left without a home, but the chaetognaths were one [6]. Chaetognaths have generally been considered close relatives of the deuterostomes, a long-established major animal group that includes chordates, such as humans, and echinoderms, such as sea urchins. The idea of a close relationship between chaetognaths and deuterostomes is based principally on a set of embryological characters: radial cleavage of the early embryonic blastomeres, deriving the mesoderm from out-pocketing of the embryonic gut (enterocoely) and the derivation of the anus, rather than the mouth, from the blastopore of the gastrula (deuterostomy). These traits had been thought to be defining characteristics of the deuterostomes and to differentiate them from the other big animal subdivision, the protostomes. The enigma of the evolutionary affinities of the chaetognaths has been the focus of multiple molecular phylogenetic studies over the years. The first of these concluded that the link with deuterostomes was incorrect [7], and over the years it has become clear that the arrow worms are protostomes [8–10]. This, however, is where the consensus ended.