STEM CELLS
More than just a pool

An intricate stem cell niche boundary formed by finger-like extensions generates asymmetry in stem cell divisions.

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Related research article

Gordon KL, Zussman JW, Li X, Miller C, Sherwood DR. 2020. Stem cell niche exit in C. elegans via orientation and segregation of daughter cells by a cryptic cell outside the niche. eLife 9:e56383. doi: 10.7554/eLife.56383

Stem cells have the ability to divide and self-renew or specialize into many different types of cells that replenish tissues and organs. Historically, and based largely on blood stem cells, divisions have been thought to be asymmetric, resulting in two daughter cells with different fates: an identical, slow-cycling stem cell and a faster-cycling progenitor cell committed to differentiation. However, self-renewal of many tissues, such as the intestine, is ensured by cells that do not display strong division asymmetry and are instead organized as pools of progenitor cells. Daughter cells of these progenitors frequently do not appear to differ in their likelihood to self-renew or specialize (Post and Clevers, 2019).

Establishing the design principles underlying such progenitor pools is key to understanding how continuous self-renewal is maintained. Now, in eLife, Kacy Gordon and colleagues from the University of North Carolina and Duke University report new insights about stem cell division in the nematode Caenorhabditis elegans (Gordon et al., 2020).

In C. elegans, germ stem cells – which ensure the production of oocytes and sperm – reside at one end of tube-shaped gonads in what is known as the progenitor zone. The progenitor zone is capped by a large cell called the distal tip cell. The distal tip cell controls the proliferation of germ stem cells, and its finger-like extensions are thought to communicate with these cells (Fitzgerald and Greenwald, 1995; Byrd et al., 2014). Proximal sheath cells (Sh1 cells) surround the gonads and wrap the differentiating germ stem cells exiting the progenitor zone.

Germ stem cells within the progenitor zone show some variation in specialization (the cells closest to the proximal end of the gonads start expressing genes associated with the differentiation of reproductive cells). But the orientation of progenitor division was reported to be largely random, compatible with the idea that the progenitor zone, or at least a distal portion thereof, forms a ‘bag’ of mostly equivalent proliferating cells – with the most proximal being randomly pushed out and differentiating. The speed of the cell cycle is largely similar among progenitors, apparently furthering the notion that the differentiation process is not controlled by division asymmetry (Maciejowski et al., 2006; Crittenden et al., 2006; Jaramillo-Lambert et al., 2007; Chiang et al., 2015; Rosu and Cohen-Fix, 2017).

To investigate how the cell fate of germ stem cells is regulated, Gordon et al. used fluorescent labeling of both the distal tip cell and the Sh1 cells and tracked the dividing germ stem cells. This revealed that both the distal tip cell and Sh1 cells intercalate long protrusions that contact the germ stem cells (Figure 1a). Unexpectedly, most cell divisions happened at the distal tip cell-Sh1 interface. Most strikingly, these divisions were often asymmetrical, with one daughter cell staying in contact with the distal tip cell and the other one with Sh1 cells – turning the
idea on its head that the progenitor zone is a pool of randomly proliferating cells. Manipulation of the cytoskeleton-related gene expression further suggested that a tightly knit interface between the distal tip cell and Sh1 cells may be necessary for robust proliferation. However, this does not rule out that this interface could also respond to signals from dividing germ stem cells. This interface may also play a role in positioning gene expression patterns within the progenitor zone.

The work of Gordon et al. illustrates that a niche is more than just a region that accommodates a given number of stem cells or that serves as a punctual source of a self-renewal signals (Schofield, 1978). Rather, these experiments have unearthed hidden layers of control and thus provide a stepping stone to future research unraveling unknown mechanisms underlying cell fate determination. For example, what is the purpose of asymmetric cell division in this specific area? Could the intricate shape of the niche enlarge the surface area and so increase the number of asymmetric divisions in this progenitor zone? This asymmetry, even if it does not anchor stem cells, could still shape clonal dynamics in a way that helps minimize mutations and prevent premature senescence of germline stem cells (Cairns, 2006; Chiang et al., 2015; Cinquin et al., 2016).

In the future, it will be important to study germ stem cells below the gonad surface, which
may have different behaviors; and to assay the impact of asymmetric division on the dynamics of stem cell clones. It remains to be seen if protrusions similar to those of the distal tip cell and those of other cell types such as embryonic stem cells (Ramírez-Weber and Kornberg, 1999; Inaba et al., 2015; Junyent et al., 2020), are a prevalent feature of stem cell niches. Such structures could have remained hidden because of imaging difficulties, and may represent a hub for asymmetric cell divisions in tissues currently viewed as lacking those features.

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References

Byrd DT, Knobel K, Affeldt K, Crittenden SL, Kimble J. 2014. A DTC niche plexus surrounds the germline stem cell pool in Caenorhabditis elegans. PLOS ONE 9:e88372. DOI: https://doi.org/10.1371/journal.pone.0088372, PMID: 24586318

Cairns J. 2006. Cancer and the immortal strand hypothesis. Genetics 174:1069–1072. DOI: https://doi.org/10.1534/genetics.104.66886, PMID: 17121966

Chiang M, Cinquin A, Paz A, Meeds E, Price CA, Welling M, Cinquin O. 2015. Control of Caenorhabditis elegans germ-line stem-cell cycling speed meets requirements of design to minimize mutation accumulation. BMC Biology 13:51. DOI: https://doi.org/10.1186/s12915-015-0148-y, PMID: 26187634

Cinquin A, Chiang M, Paz A, Hallman S, Yuan O, Vysniauskaitė J, Fowlkes CC, Cinquin O. 2016. Intermittent stem cell cycling balances self-renewal and senescence of the C. elegans germ line. PLOS Genetics 12:e1005985. DOI: https://doi.org/10.1371/journal.pgen.1005985, PMID: 27077385

Crittenden SL, Leonhard KA, Byrd DT, Kimble J. 2006. Cellular analyses of the mitotic region in the Caenorhabditis elegans adult germ line. Molecular Biology of the Cell 17:3051–3061. DOI: https://doi.org/10.1091/mbc.e06-03-0170, PMID: 16672375

Fitzgerald K, Greenwald I. 1995. Interchangeability of Caenorhabditis elegans DSL proteins and intrinsic signalling activity of their extracellular domains in vivo. Development 121:4275–4282. PMID: 8575327

Gordon KL, Zussman JW, Li X, Miller C, Sherwood DR. 2020. Stem cell niche exit in C. elegans via orientation and segregation of daughter cells by a cryptic cell outside the niche. eLife 9:e56383. DOI: https://doi.org/10.7554/eLife.56383, PMID: 32692313

Inaba M, Buszczak M, Yamashita YM. 2015. Nanotubes mediate niche-stem-cell signalling in the Drosophila testis. Nature 523:329–332. DOI: https://doi.org/10.1038/nature14602, PMID: 26131929

Jaramillo-Lambert A, Ellefson M, Villeneuve AM, Engebrect J. 2007. Differential timing of S phases, X chromosome replication, and meiotic prophase in the C. elegans germ line. Developmental Biology 308:206–221. DOI: https://doi.org/10.1016/j.ydbio.2007.05.019, PMID: 17599823

Junyent S, Garicn CL, Szczerekowski JLA, Trieu TJ, Reeves J, Habib SJ. 2020. Specialized cytonemes induce self-organization of stem cells. PNAS 117:7236–7244. DOI: https://doi.org/10.1073/pnas.1920837117, PMID: 32184326

Maciejowski J, Ugel N, Mishra B, Isopi M, Hubbard EJ. 2006. Quantitative analysis of germline mitosis in adult C. elegans. Developmental Biology 292:142–151. DOI: https://doi.org/10.1016/j.ydbio.2005.12.046, PMID: 16480707

Post Y, Clevers H. 2019. Defining adult stem cell function at its simplest: the ability to replace lost cells through mitosis. Cell Stem Cell 25:174–183. DOI: https://doi.org/10.1016/j.stem.2019.07.002, PMID: 31374197

Ramírez-Weber FA, Kornberg TB. 1999. Cytonemes: cellular processes that project to the principal signaling center in Drosophila imaginal discs. Cell 97:599–607. DOI: https://doi.org/10.1016/s0092-8674(00)80771-0, PMID: 10367889

Rosu S, Cohen-Fix O. 2017. Live-imaging analysis of germ cell proliferation in the C. elegans adult supports a stochastic model for stem cell proliferation. Developmental Biology 423:93–100. DOI: https://doi.org/10.1016/j.ydbio.2017.02.008, PMID: 28215939

Schofield R. 1978. The relationship between the spleen colony-forming cell and the haemopoietic stem cell. Blood Cells 4:7–25. PMID: 747780