FORUM Developmental biology

Nanotubes in the niche

In fruit flies, protrusions can extend from stem cells in the testes to cells in a regulatory hub, mediating intercellular signalling and stem-cell maintenance. The implications of this finding are presented here from two angles. SEE LETTER P.329

THE PAPER IN BRIEF

- In the testes of fruit flies, germline stem cells, which give rise to sperm, divide asymmetrically.
- One daughter cell retains its stem-cell identity and remains attached to an adjacent cluster of cells called a hub, whereas the other daughter is displaced and differentiates.
- The hub secretes Dpp, a member of the BMP family of proteins, which signals to and regulates maintenance of germline stem cells. But how this signalling is prevented from acting in differentiating daughters is unclear.
- On page 329 of this issue, Inaba *et al.*[1] demonstrate that germline stem cells form protrusions dubbed microtubule-based nanotubes, which extend to the hub and mediate signalling between Dpp in the hub and its receptor proteins in germline stem cells (Fig. 1).

Close encounters

THOMAS B. KORNBERG

Development is not a democracy. As cells arrange themselves into complex patterns and structures, some act as directors and some as their clients. This principle was first uncovered more than 100 years ago in a study of regeneration in the freshwater animal *Hydra*[2], and was crafted into a general theory by work on amphibian development[3]. These early studies showed that not only can some cells (directors) remember their origins when transplanted to abnormal sites in the embryo, but they can also persuade neighbouring host cells (clients) to join them and make structures from that origin. This led to the idea that cell–cell signalling over short distances has a key role in development. How such paracrine signals are relayed has long been a subject of study — one that is addressed by Inaba *et al.* in the germline stem cells (GSCs) of the testes of fruit flies.

The GSC niche is an excellent environment for studying how paracrine signals move from directors to clients and how signals selectively act only on intended targets, because selective Dpp signalling to GSCs is imperative to ensure that some cells self-renew and some become sperm. Inaba and colleagues show that GSCs make microtubule-based nanotubes (MT-nanotubes) that extend into the hub, with which they seem to pick up Dpp. There is no Dpp signalling or self-renewal in GSCs with defective MT-nanotubes, indicating that these cells need to pick up Dpp directly. Therefore, MT-nanotube-mediated protein exchange ensures that Dpp signals selectively to GSCs.

Such direct transfer of signalling proteins between cells is not restricted to GSCs — in fact, it might be a universal method of paracrine signalling. Research from several groups has indicated[4–8] that paracrine signals can be transmitted through cellular protrusions called cytonemes. These structures, which are primarily composed of a structural protein called actin, are a specialized form of the group of cytoplasmic projections called filopodia. Cytonemes have been shown to transport a range of paracrine signalling proteins: Dpp, Hedgehog, fibroblast growth factor and Wingless proteins in fruit flies[4–6]; Sonic hedgehog in the developing chick limb[7]; and Wnt protein in developing zebrafish embryos[8]. These processes of transport and exchange by cytonemes are similar to that reported in the current study.

Signal-mediating protrusions can be short or long, composed of actin filaments or microtubules, and might extend from director to client or from client to director. But in all contexts studied, exchange of signalling proteins occurs between the protrusion and its target cell. It seems that biology has created a varied set of structures to move signals between cells by this basic mechanism. The coming years promise to reveal how these structures select their targets and make functional contacts with them, and how they transport, release and take up signals.

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Reach for self-renewal

LILACH GILBOA

To maintain tissue integrity, stem cells must strike a balance between two fates: self-renewal and differentiation. In the testes of fruit flies, this balance is determined by proximity to the hub — a source of the self-renewing factor Dpp[9]. Many have questioned how the spread of Dpp from the hub is limited, to create the sharp concentration gradient that distinguishes self-renewal from differentiation across one cell diameter. Inaba and colleagues' work suggests that the fate of GSC daughters is determined not by the extracellular spread of Dpp, as had been posited, but by the ability of these cells to directly access Dpp at its source. This change of view requires a general reconsideration of how niche components affect stem-cell self-renewal.

Inaba *et al.* report that Dpp receptors concentrate in puncta (clusters) on MT-nanotubes, which extend from GSCs into the hub. Crucially, increasing the thickness of MT-nanotubes increases both the number of Dpp-receptor puncta and the responsiveness of GSCs to Dpp. This result points to an unexpected property of the GSC self-renewal system — the amount of ligand available is not the limiting factor. Furthermore, GSCs can use more Dpp than normal only if they have MT-nanotubes of increased thickness. Conversely, when the authors shortened MT-nanotubes, Dpp pathway activity decreased in GSCs. The Dpp ligand, which presumably was no longer being sequestered by GSCs, was still unable to elicit Dpp signalling in daughters removed from the niche. These data are incompatible with a simple model in which cell fate is determined by a diffusible ligand, and instead suggest that MT-nanotubes constitute the main way in which Dpp is accessed.

Previous studies[10–12] found a role for proteins

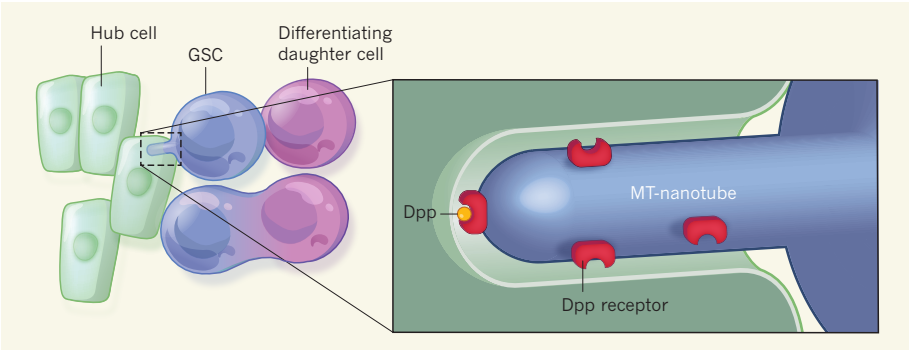

Figure 1 | Maintenance of germline stem cells. In the testes of fruit flies, germline stem cells (GSCs) reside in close proximity to a cellular hub, which produces the signalling protein Dpp. On cell division, the daughter closest to the hub retains its stem-cell identity owing to Dpp signalling. However, Dpp signalling is not activated in the other daughter, which subsequently differentiates to produce sperm. Inaba and colleagues[1] report that this selectivity is mediated by microtubule-based (MT) nanotubes that protrude from GSCs to pick up Dpp from cells of the hub. These protrusions contain clusters of Dpp receptor proteins, which transduce Dpp signalling in GSCs and so induce self-renewal. The right-hand box is a cartoon based on Figure 5e of Inaba and colleagues' paper; the details of the depicted process, including the topology of the nanotubes and localization of receptors, are not yet known.

in the extracellular matrix in maintaining GSCs, presumably by presenting the cells with maintenance factors. How should we view these findings in light of the current study? One explanation could be that components of the extracellular matrix stabilize MT-nanotubes, or promote Dpp–receptor interactions in some other way. Alternatively, extracellular-matrix components might affect other proteins secreted by the niche, such as Unpaired, which supports GSC maintenance by promoting the cells' adhesion to the hub[13]. Future studies will determine whether this adhesion is a prerequisite for MT-nanotube formation, or whether the two pathways act independently.

MT-nanotubes, or similar structures, might well promote stem-cell maintenance in other organs and organisms. If this is the case, there must be a fundamental change in our efforts to understand stem-cell maintenance, moving away from attempts to discover how extracellular ligand spread is limited to stem cells, and towards how stem cells access the ligands that are needed for self-renewal. As our understanding of the connection between the stem cell and its niche continues to increase, one thing is clear — the study of GSCs in fruit flies will continue to provide important insights. ■

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EARTH SCIENCE

Big geochemistry

A compilation of more than 300,000 rock compositions provides crucial input into a 100-year-old debate on how the continental crust formed, and provides new constraints for theories of continental-crust development. SEE ARTICLE P.301

CHRISTY TILL

Earth is the only planet in our Solar System known to have a buoyant continental crust. The origin of this crust has been long debated because its compositional heterogeneity precludes the straightforward testing of formation models. On page 301 of this issue, Keller *et al.*[1] present perhaps the most convincing data so far on this issue. They demonstrate that most of the continental crust's igneous rocks — those formed by the solidification of lava or magma — are formed through progressive crystallization of melted material extracted from Earth's interior, followed by the return of the most dense crystals to the mantle.

Two competing hypotheses that arose in the pioneering experimental geochemistry laboratories of the early 1900s have influenced nearly all models for the formation of the continental crust. In 1915, Norman L. Bowen proposed that the continental crust formed through the progressive crystallization and distillation of magmas generated in Earth's mantle[2] (Fig. 1a). In this theory, the first minerals to crystallize are those with the highest abundance of iron and magnesium (mafic minerals), leaving the remaining melt enriched in silica (SiO_2). Mantle-derived magma that originally contains 50% silica can thus evolve through continuous crystallization to form a composition that matches that of the bulk continental crust (approximately 61% silica). In 1933, Bowen's mentor, Reginald A. Daly, proposed that assimilation was at least as important in forming the modern continental crust — ascending mantle-derived magmas drive the melting of the pre-existing continental crust, and mixing of the two, to produce the observed silica content of the bulk continental crust[3] (Fig. 1b).

As the problems and costs of geochemical analyses and computational time decrease, geoscientists can use ever-larger data sets to answer fundamental questions about our planet. Keller and colleagues[1] report one of the most compelling examples of this so far. They compiled more than 300,000 existing geochemical analyses of igneous rocks from around the world to calculate the average composition of magmas in areas where continental plates converge or are pulled apart (rifted).

By comparing the chemical compositions of plutonic rocks (which formed from magmas that slowly cooled within the Earth) with those of volcanic rocks (formed when magmas erupted on Earth's surface), the researchers assessed the dominant processes that contributed to the rocks' formation. If Daly's assimilation theory is correct, there should be a linear relationship between the concentration of oxides, such as magnesium oxide, and silica. However, Keller and co-workers observe a nonlinear relationship, which confirms the dominance of Bowen's crystallization hypothesis.

One long-standing issue with Bowen's hypothesis is that mafic crystal residues should have accumulated in the lower crust over time, forming cumulate rock. Several lines of