STEM CELLS

Making more of yourself

Reporting in Science, Wang and Lin tackle one of the most fundamental problems in stem-cell biology: how does a stem cell decide that, when dividing, it should make at least one more of itself — rather than generating two more-specialized cell types? The authors find that a key to such 'self-renewal' is, at least for one type of stem cell, a translational repressor known as Nanos.

Recent years have seen much progress in understanding the extrinsic signals that regulate stem-cell self-renewal. But the intrinsic cues have, for most stem cells, been more of a mystery. Wang and Lin approached the problem by looking at fruitfly ovaries, and specifically germline stem cells (GSCs), which have certain benefits as a model system — including their distinctive morphology. GSCs are formed from primordial germ cells at the larval/pupal transition. In adult females, GSCs can both self-renew and generate differentiating cell types, namely cystoblasts, which go on to produce egg chambers.

It was already known that Nanos contributes to the production of eggs, but exactly what it does was less clear. To start to find out, Wang and Lin constructed a *nanos* transgene that is switched on by heat shock. They used this transgene to restore functional Nanos to female embryos with *nanos* mutations. Then, after the adults emerged from the pupa, they switched the transgene off. The result was that the number of GSCs dropped sharply in comparison with wild-type flies — as did the number of egg chambers (presumably because there were fewer GSCs to generate them). So, Nanos is required continuously for GSCs to self-renew.

In this experiment, Nanos was switched on and off in the whole fly. It cannot be seen from this, however, whether the Nanos signal is intrinsic or extrinsic to GSCs. To find out, the authors removed the protein only from GSCs. They concluded that Nanos is an intrinsic regulator of GSC self-renewal — and that it works by preventing these cells from differentiating. Moreover, it probably functions by forming complexes with the RNA-binding protein Pumilio.

Nanos–Pumilio complexes are known to bind to Nanos-response elements in target mRNAs, repressing their translation. So one future avenue of research will be to identify the mRNAs that are repressed by Nanos–Pumilio in GSCs. It will also be interesting to see how the activities of this intrinsic regulator are integrated with extrinsic signals — and whether it behaves similarly in other stem cells, and other species.

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References and links

ORIGINAL RESEARCH PAPER Wang, Z. & Lin, H. *Nanos* maintains germline stem cell self-renewal by preventing differentiation. *Science* 19 Feb 2004 (doi:10.1126/science.1093983)

FURTHER READING Lin, H. The stem-cell niche theory: lessons from flies. *Nature Rev. Genet.* **3**, 931–940 (2002)

WEB SITE

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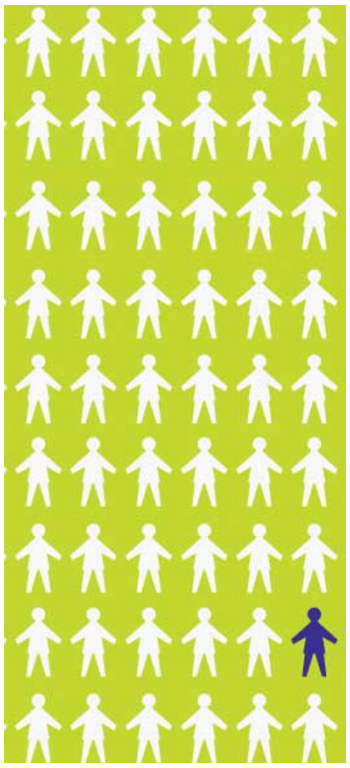

STRUCTURE WATCH

Ironing out the interaction

Because of its potential insolubility and toxicity, ferric iron (Fe^{3+}) is transported around the vertebrate body bound to transferrin, and two iron-bound transferrins can bind the dimeric transferrin receptor (TFR) to deliver iron to cells. Although the endocytic pathway that is involved in this process is well understood, little is known regarding the molecular details of the TFR–transferrin complex. Now, in *Cell*, Walz and colleagues describe the use of cryo-electron microscopy and single-particle-averaging techniques to obtain a density map of the human TFR–transferrin complex at sub-nanometre resolution, which is "…an unusually high resolution for single-particle analysis".

The authors fitted crystal structures of the TFR ectodomain and the N- and C-lobes of transferrin into this map to produce an atomic model of the complex. This model indicates that diferric transferrin and TFR interact in a manner that is different to that proposed by a previous model. Rather than binding to membrane-distal surfaces, the C-lobe interacts with the side of the receptor dimer and the N-lobe extends towards the membrane, binding in the gap between the TFR ectodomain and the membrane surface. In addition, the authors noted that, compared with free diferric transferrin, the N- and C-lobes of bound diferric transferrin have shifted by ~9 Å with respect to each other, and they believe that this is an effect of receptor binding. This work has therefore improved our structural understanding both of the TFR–transferrin complex and of the different iron-binding properties of free and receptor-bound transferrin.

REFERENCE Cheng, Y. *et al.* Structure of the human transferrin receptor–transferrin complex. *Cell* **116**, 565–576 (2004)

A depolymerizing motor

Kinesin superfamily proteins (KIFs) generally move along microtubules using the energy of ATP hydrolysis, but middle-motor-domain-type KIFs (KIF-Ms) depolymerize microtubules from their ends. How this depolymerization occurs has been unclear, but Hirokawa and co-workers now report new insights in *Cell*.

The authors determined the crystal structure of the minimal functional domain of a murine KIF-M (Kif2c) in an ADP-bound form and an ATP-analogue-bound form. They compared these structures to those of other KIFs to identify features that are important for KIF-M function, and identified three main class-specific features. First, the amino-terminal neck forms a long, rigid helical structure that extends out into the interprotofilament groove. This structure targets Kif2c to microtubule ends by preventing tight binding to microtubule side walls and aiding its one-dimensional diffusion. It also destabilizes lateral protofilament interactions. Second, the L2 loop — a long, rigid finger-like structure — can reach the next tubulin subunit when Kif2c is at the curved end of the microtubule and stabilize 'peeling' of the protofilament. Finally, the L8 loop, which can contact microtubules at their curved ends, might trigger ATP hydrolysis. This structural model fits with all the data on KIF-Ms to date, but the authors note that a KIF-M–tubulin-complex structure and single-molecule assays will be needed for confirmation.

REFERENCE Ogawa, T. *et al.* A common mechanism for microtubule destabilizers — M type kinesins stabilize curling of the protofilament using the class-specific neck and loops. *Cell* **116**, 591–602 (2004)