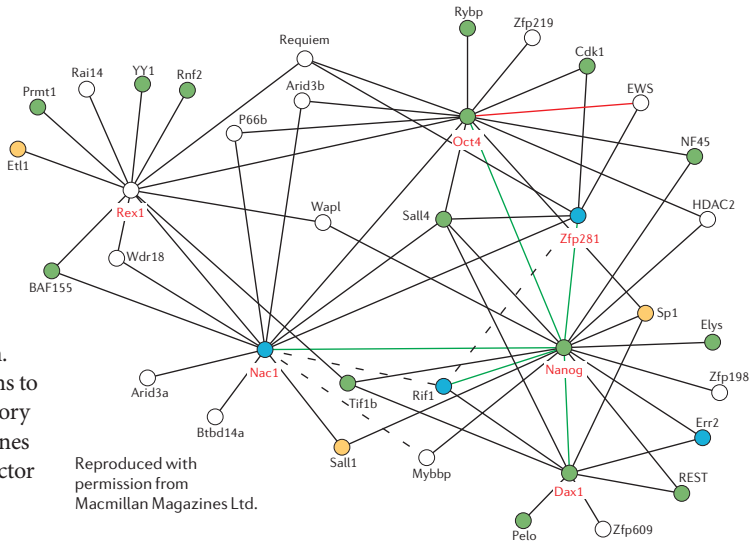
STEM CELLS

The potential of networking



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Embryonic stem (ES) cells are singled out by their pluripotent potential, a property that is fostered by the homeodomain protein Nanog. Reporting in *Nature*, Stuart Orkin and colleagues now reveal the complex network of proteins that work together with Nanog to maintain the developmental options of ES cells.

The authors performed a rigorous and extensive proteomics analysis in mouse ES cells to identify proteins that interact with Nanog and the partners of these Nanog-binding proteins. By combining these approaches with functional studies, they constructed a map of the ES-cell interactome, a network dedicated to establishing and maintaining pluripotency.

The interactome consists of many proteins that are required for the survival or differentiation of the inner cell mass. In addition, the network includes several proteins involved in the early stages of embryonic development. Most of the genes encoding these proteins are co-regulated or downregulated during ES-cell differentiation, which provides further evidence for a common ES-directed cellular function. Importantly, the ES-cell state seems to be reinforced by a positive regulatory circuit — more than half of the genes that encode upstream Nanog-effector proteins are also putative Nanog targets.

It makes sense that a cellular network devoted to maintaining pluripotency would have systems in place to block other developmental options and, indeed, the network is linked to several transcriptional co-repressor complexes, including the histone deacetylase NuRD, polycomb-group proteins and SWI/SNF remodelling complexes.

With all these back-up systems in place to preserve pluripotency, how do ES cells 'escape the net' and differentiate along different lineage pathways? The multitude of interactions in the ES-cell network indicate that the relative concentrations of cellular proteins are crucial for maintaining pluripotency; so, subtle changes in the stoichiometry of protein complexes might allow ES cells to embark along different developmental pathways.

> "It makes sense that a cellular network devoted to maintaining pluripotency would have systems in place to block other developmental options..."

Last, although the function of many interactome components as both Nanog effectors and Nanog targets reinforces pluripotency, this interdependency might represent the ES cell's Achilles' heel — the down-regulation of one component could weaken the interactome at multiple points and lead to the rapid loss of pluripotency.

Shannon Amoils

ORIGINAL RESEARCH PAPER Wang, J. *et al.* A protein interaction network for pluripotency of embryonic stem cells. *Nature* 8 Nov 2006 (doi:10.1038/nature05284)

MEMBRANE TRAFFICKING

GEF a move on!

Central to controlling the flow of membrane traffic through cells are Rab GTPases, which oscillate between active GTP-bound and inactive GDP-bound conformations. Their active state is regulated, in part, by guanine-exchange factors (GEFs) that catalyse the exchange of GDP for GTP. In *Nature Cell Biology*, Morozova *et al.* now report how one GEF complex, TRAPP, might sequentially regulate two very different Rab GTPases.

TRAPP is a multisubunit complex that regulates the yeast Rab protein Ypt1 — which regulates the entry of cargo vesicles into the Golgi apparatus — as well as Ypt31 and Ypt32, which both control the subsequent exit of the cargo from the Golgi. TRAPP comes in two forms, TRAPPI and TRAPPII, which have different cellular localizations.

> "...one GEF complex, TRAPP, might sequentially regulate two very different Rab GTPases."

Both share a core of seven subunits, although the larger TRAPPII complex contains an additional three subunits.

Morozova *et al.* showed that the mutation of the TRAPPII-specific subunit Trs130 abolished the capability of isolated TRAPP complexes to activate Ypt31. By contrast, mutant TRAPP complexes showed a significantly increased activation of Ypt1. By isolating the two TRAPP complexes from wild-type yeast on the basis of their different sizes, TRAPPI and TRAPPII were shown to have opposite specificities for the Ypt GTPases.

The authors showed a physical interaction between Trs130 and Ypt31, which is physiologically important: the overexpression of Trs130 rescued the growth of yeast cells that expressed mutant Ypt31. This effect was specific for Ypt31 mutants over Ypt1 mutants, which confirmed that TRAPPII functions as a GEF for Ypt31, whereas TRAPPI activates Ypt1.

Morozova *et al.* proposed that rather than two discrete TRAPP complexes being expressed at different points in the Golgi, TRAPPI complexes mature into TRAPPII complexes. After the Ypt1- and TRAPPI-dependent entry of cargo into the Golgi, a subcomplex that includes Trs130 associates with TRAPPI, thereby converting it to a TRAPPII complex. TRAPPII, through activating Ypt31, then polices the exit of cargo from the Golgi. This proposal is supported by the fact that the Golgi itself was recently shown to form by the gradual maturation of cisternae, rather than having stable compartments between which cargoes are shuttled.

James Pickett

ORIGINAL RESEARCH PAPER Morozova, N. *et al.* TRAPPII subunits are required for the specificity switch of a Ypt–Rab GEF. *Nature Cell Biol.* **8**, 1263–1269 (2006)
FURTHER READING Smallridge, R. Maturing is part of life. *Nature Rev. Mol. Cell Biol.* **7**, 465 (2006)
WEB SITE
Nava Segev's laboratory: http://www.uic.edu/depts/bios/faculty/segev-n.htm