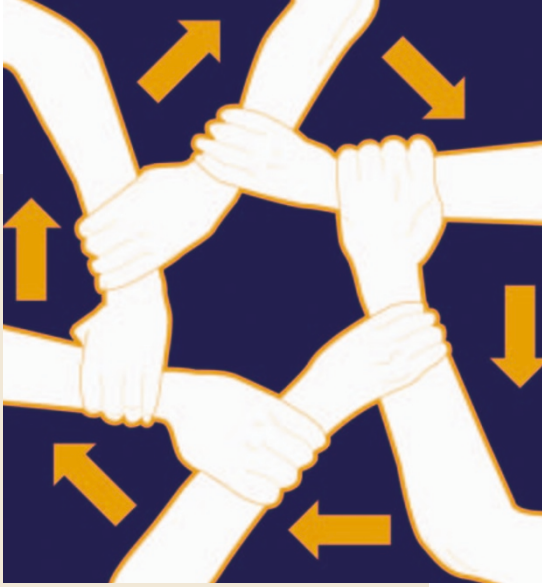

GENE NETWORKS

Grasping the essentials

Understanding how essential genes function in networks presents a challenge — because knocking them out causes lethality, their function must instead be carefully manipulated to probe their interactions. Rising to this challenge, one group has now studied an extensive set of interactions for essential genes in *Saccharomyces cerevisiae*, indicating an unforeseen complexity of genetic networks.

Davierwala and colleagues made conditional expression alleles or conditional temperature-sensitive alleles for over half the essential genes in *S. cerevisiae*. Expression of both types of allele can be controlled so that levels of the gene products are decreased, but not abolished. These strains were crossed to a panel of 30 others, carrying similarly derived mutant alleles of either essential or non-essential genes. The fitness of the double mutants was scored relative to the parent strains, as quantified by colony growth, which revealed a network of 567 interactions among 286 essential genes. Only two of these interactions were already documented, highlighting the power of this approach to identify new relationships.

The most remarkable aspect of the network was the number of interactions it contained. On average, essential genes take part in about five times as many interactions as their non-essential counterparts — significantly more than previously estimated. This indicates that the overall network in budding yeast might be twice as dense as previously thought.

Notably, many of the conditional alleles of essential genes had little or no phenotype as single mutants, but combined with interacting alleles they produced more severe effects. If other gene networks are organized in a similar way, such interactions might underlie variation in many complex traits — including non-Mendelian disease in humans.

Louisa Flintoft

References and links

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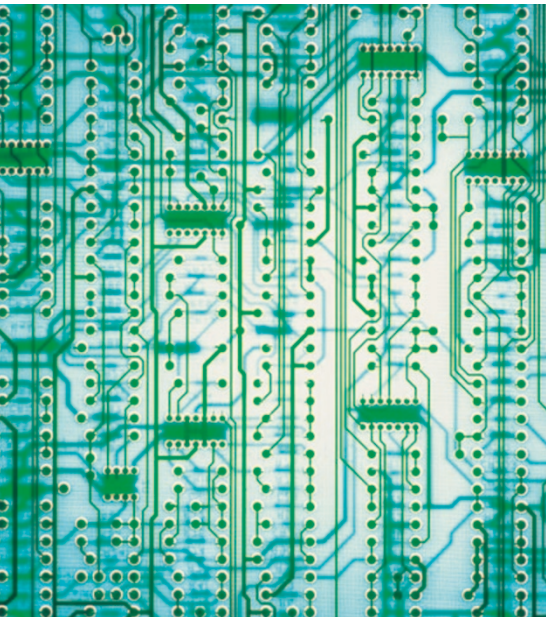
FURTHER READING Barabási, A.-L. & Oltvai, Z. N. Network biology: understanding the cell's functional organization. *Nature Rev. Genet*. **5**, 101–113 (2004)

STEM CELLS

Everything is possible if we work together

Three transcription factors — OCT4, SOX2 and NANOG — are essential for maintaining the pluripotency of human embryonic stem (ES) cells. Young and colleagues have now identified the target genes of these three proteins, and have uncovered several regulatory circuits through which they fulfil their function.



Using a combination of chromatin immunoprecipitation and DNA microarrays, the authors assayed the regions near the promoters of 17,917 annotated human genes. They found that OCT4, SOX2 and NANOG bound near the promoters of 623, 1,271 and 1,687 genes, in that order. What was particularly surprising was that at least 353 of those genes were bound by all three transcription factors, which implies a significant co-ordination of function.

About half these coordinately regulated genes are activated by OCT4, SOX2 and NANOG, and half are repressed. The activated genes include components of the TGFB and WNT signalling pathways, both of which have a role in maintaining pluripotency; the repressed genes include many transcription factors that are important for differentiation.

The authors confirmed the presence of two types of regulatory circuit in human ES cells, using algorithms that had previously been devised in yeast. First, they found feed-forward loops, in which a first regulator regulates a second regulator and both then regulate the target genes. If both regulatory steps are positive this gives stability against transient changes in input; if one step is negative a rapid switch in response to changed conditions is enabled.

The second type of circuitry that they describe is the autoregulatory loop, in which OCT4, SOX2 and NANOG regulate their own expression. This also offers stability of gene expression and rapid responses to environmental stimuli.

These approaches will allow researchers to elucidate the circuits that are controlled by other transcription factors, and also by chromatin regulators. Testing these circuits will be aided by advances in the culture and genetic manipulation of ES cells. A full understanding of the regulatory circuitry of ES cells will help researchers to promote stem cells to differentiate into a range of cell types, and possibly to reprogramme differentiated cells back into pluripotent ones.

Patrick Goymer

References and links

ORIGINAL RESEARCH PAPER Boyer, L. A. *et al.* Core transcriptional regulatory circuitry in human embryonic stem cells. *Cell* **122**, 1–10 (2005)
WEB SITE
Richard A. Young's laboratory: http://web.wi.mit.edu/young