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GENE NETWORKS

Meaningful connections

The magnitude and direction of epistasis and the functional consequences of these gene–gene interactions are fundamental to relating genotype to phenotype and thus for informing fields from human disease to speciation. The detailed analysis of global metabolic and genetic interactions in *Escherichia coli* and *Saccharomyces cerevisiae* highlights the potential of such surveys for functionally annotating the genome, and also overturns some widely held assumptions.

Zhang and colleagues used the high-quality metabolic network of *E. coli* as the starting point for studying the epistatic relationships between biochemical reactions. By flux balance analysis (FBA) they found that 270 of the 931 reactions analysed affected organismal fitness when absent. Single and double genetic perturbations were used to test for pairwise epistasis and, if present, its direction: epistasis is 'positive' or 'negative' when the fitness of the double mutant is higher or lower, respectively, than the product of the fitnesses of the single mutants.

The results were clear-cut but unexpected. Negative epistasis was rare, comprising <0.1% of reaction pairs, and generally involved non-essential biochemical reactions with overlapping functions (removal of one reaction would be compensated by the function of the other). By contrast, >97% of reaction pairs showed positive epitasis; most of these pairs involved essential reactions and had no functional overlap. These findings run counter to the prevailing view that the detection of positively interacting gene pairs provides insights into their functional associations and therefore into common genetic pathways. The authors found a similar trend in *S. cerevisiae*, in which results from the computational FBA approach were also validated experimentally by single-allele knockout or knockdown of 61 gene pairs.

In a second study, Costanzo, Baryshnikova and colleagues reported the construction of an unbiased, genome-scale genetic interaction network in yeast and interpreted it with respect to various cellular processes and the functional relationships between genes. The connectivity map (see figure) was built by examining 5.4 million mutant gene pairs for positive or negative epistatic interactions, leading to a network comprising ~75% of yeast genes. Interactions between alleles were assayed using a sensitive measure of colony size to assess the degree of epistasis.

The network topology, although complex, shows the functional distribution of genes across the cell and can highlight genes with a common function (those within a cluster) and those with interacting functions (clusters that are linked by an edge). Furthermore, it can be used to infer the functional and interaction properties of uncharacterized genes. Here too, negative epistasis involved genes of similar function, and the network revealed that positive interactions — which are half as prevalent as negative interactions — are not restricted to genes belonging to the same pathway or protein complex, but rather frequently connect functionally diverse genes. The sensitivity of the genetic network to a drug was used to predict the cellular target of chemical compounds, therefore aiding an early step in drug discovery.

As global gene networks become increasingly feasible in more complex cells, it will be possible to discover which of these patterns are conserved.

Tanita Casci

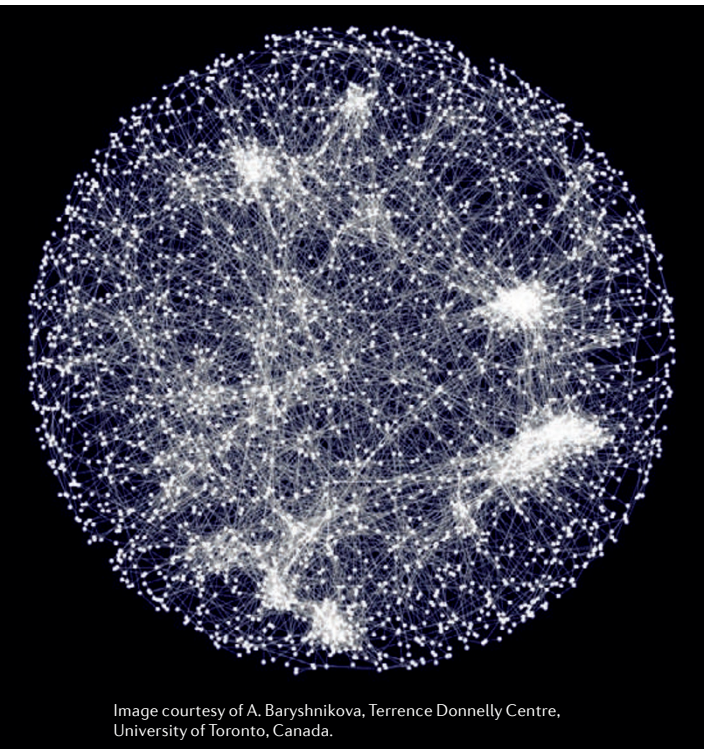

Image courtesy of A. Baryshnikova, Terrence Donnelly Centre, University of Toronto, Canada.

ORIGINAL RESEARCH PAPERS He, X., Qian, W., Wang, Z., Li, Y. & Zhang, J. Prevalent positive epistasis in *Escherichia coli* and *Saccharomyces cerevisiae* metabolic networks. *Nature Genet.* 24 Jan 2010 (doi:10.1038/ng.524) | Costanzo, M., Baryshnikova, A. *et al.* The genetic landscape of a cell. *Science* **327**, 425–431 (2010)
FURTHER READING Cordell, H. J. Detecting gene–gene interactions that underlie human diseases. *Nature Rev. Genet.* **10**, 392–404 (2009)