GENOMICS

Uncovering hidden relationships

Two new studies tackle the complexities of synthetic genetic interaction—identifying relationships between gene products that interact functionally rather than physically.

The word 'interaction' typically brings to mind methods like immunoprecipitation and the two-hybrid screen, tools for measuring direct physical association. But a group of laboratories at the University of Toronto is interested in exploring a different interaction concept—that of synthetic genetic interaction. Extensive genetic studies in yeast have revealed genes that are 'essential' or 'nonessential' for survival, with nonessential genes understood to be at least partially redundant, to the extent that other genes in the same pathway can partially cover for their loss. By identifying secondary mutations that induce lethality, one can find synthetic interactions—funct ionally related genes whose products work cooperatively, though they might not interact physically.

This is the foundation of the yeast synthetic genetic array (SGA), in which a set of query mutants is crossed against a larger array of mutants, identifying pairs that are only lethal in combination. Such studies obviously become problematic with essential genes, which can't simply be shut off. Fortunately, two investigators on the team, Charlie Boone and Timothy Hughes, had previously developed mutant yeast strains in which essential gene expression can be modulated by temperature- or drug-induced repression. Using these strains, the Toronto group set up a large-scale SGA experiment, using a mixed query set of 16 essential and 14 nonessential gene mutants, crossed against a panel of 575 essential gene mutants (Davierwala *et al.*, 2005). The experiments proved bountiful—surprisingly so, according to Hughes, with the number of interactions exceeding initial predictions by more than fivefold. Their interaction web also showed a striking pattern, in which essential query genes form key interaction 'nodes', with many more connections than the queried nonessential genes.

Following up on this work, authors Charlie Boone and Brenda Andrews collaborayed with Phil Hieter's lab at the University of British Columbia to do a second, more focused SGA study, using synthetic interaction analysis to specifically identify genes involved in chromosome segregation during cell division (Measday *et al.*, 2005). They now, however, complemented their synthetic-lethal screen with a 'synthetic dosage lethal' (SDL) screen, identifying double mutations where overexpression of the query protein induces lethality. Both sets of screens yielded useful data and were surprisingly nonredundant. "We were obviously hoping that the [overlapping] data set would be particularly rich, and in fact it was… but it was relatively small," says Andrews. "So what that tells us is that these methods really do probe different things, and that was sort of a surprise."

Andrews indicates that they also hope to apply SDL screens to the rest of the essential gene population—and Hughes points out that a lot of work remains, with their first round of SGA queries only covering 1% of yeast essential genes. But by applying both techniques on a larger scale, the researchers believe they will uncover valuable and informative principles of functional genomics, many of which may also hold for higher eukaryotes. Furthermore, data on the detrimental interaction of relatively 'silent' essential gene mutations with secondary mutations could prove relevant to understanding how subtle allelic variations in gene dosage can affect larger genetic networks, even in complex multicellular organisms. "That's really one of the big questions in genetic interactions in general," says Hughes, "how well these principles apply to animals—essentials versus nonessentials. And I think we could probably approach that—not cheaply or easily…[but] to me, that would be the best demonstration of long-term impact."

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RESEARCH PAPERS

Davierwala, A.P. *et al.* The synthetic genetic interaction spectrum of essential genes. *Nat. Genet.* **37**, 1147–1152 (2005).

Measday, V. *et al.* Systematic yeast synthetic lethal and synthetic dosage lethal screens identify genes required for chromosome segregation. *Proc. Natl. Acad. Sci. USA* **102**, 13956–13961 (2005).