SYSTEMS BIOLOGY

From genetic interactions to pathway architecture

DOI:

10.1038/nrg2052

URLs

MPH1

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gen&cmd=Retrieve&dopt=full_report&list_uids=854818
SGS1

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gen&cmd=Retrieve&dopt=full_report&list_uids=855228

Genome-wide screens for genetic interactions are an important tool for system-level analysis of cellular processes. Using fitness profiling of *Saccharomyces cerevisiae* deletion strains, St. Onge and colleagues have constructed a genetic interaction network that reveals novel insights into functional relationships and pathway architecture.

Theory predicts that deleterious effects of two alleles are multiplicative in a double mutant if the loci in question function independently. A departure from this expectation therefore identifies loci with products that interact functionally. St. Onge *et al.* used this test as the basis for identifying functional interactions among non-essential genes that are involved in resistance to chemically induced DNA damage.

The authors treated pools of homozygous deletion strains with a DNA-damaging agent, methyl methanesulfonate (MMS). They identified 26 deletion strains using chemogenomic fitness profiling. These were used to create all 650 pairwise combinations, and screens

were carried out to identify deviations from the multiplicative model for fitness. The ‘direction’ of the deviation allowed the authors to differentiate between aggravating and alleviating interactions.

Focusing on a subset of gene pairs that they classified as alleviating in the presence of MMS, the authors subclassified these pairs to further define their relationships. There were cases of masking or partial masking epistasis, in which the effects of one deletion masked those of the other; complete and partial suppression, in which the effects of one deletion were reduced in the presence of the other; and ‘co-equality’, in which the effects of double and single deletions were statistically indistinguishable. Interactions that are similar to co-equality have been previously described as complementary epistasis or asynthetic relationships. As might be predicted, many co-equal partners encode physically interacting proteins. In these cases, deleting either gene product is sufficient to disrupt the function of the complex.

Importantly, asymmetrical alleviating interactions can indicate the order of biochemical events in a pathway — if a double mutant $x\Delta y\Delta$ is more similar to $x\Delta$ than $y\Delta$, x probably lies upstream of y . On a single gene level, this probably isn’t news to a geneticist, but on a genome-wide level, such analysis provides important novel insights, as demonstrated by the authors in the case of genetic regulation of DNA-damage responses. For example, similarities in the spectrum of genetic interactions of *SGS1*, a DNA helicase that has been implicated in homologous recombination, and *MPH1*, which also has helicase activity, led the authors to discover a new role of MPH1 in homologous recombination.

The authors provide important insights into functional interactions on a system level. Although their work provides immediate specific insights into DNA-damage responses, its principles can be applied to other systems. The authors point out that most double mutants show a multiplicative relationship, revealing a level of robustness that will complicate functional system-level studies. “[A]dditional perturbations, either genetic or chemical, will be necessary to fully reveal the architecture of cellular pathways.”

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ORIGINAL RESEARCH PAPER

St. Onge, R. P. *et al.* Systematic pathway analysis using high-resolution fitness profiling of combinatorial gene deletion. *Nature Genet.* 7 January 2007 (doi: 10.1038/ng48)

FURTHER READING Barabási, A. L. & Oltvai, Z. N. Network biology: understanding the cell's functional organization. *Nature Rev. Genet.* 5, 101–113 (2004) | Kitano, H. Biological robustness. *Nature Rev. Genet.* 5, 826–837 (2004)