Dissecting dispensability

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Like most organisms, yeast has relatively few genes that are necessary for viability. The presence of a duplicate gene elsewhere in the genome underpins many cases of dispensability. A new study suggests that the backup mechanism is more complex than previously assumed and requires feedback loops that ensure transcriptional upregulation of the duplicate.

Four-fifths of yeast's genes are not essential for viability[1]. This preponderance of dispensable genes is observed in eukaryotes[2,3] and prokaryotes[4,5], with only one known exception to date (the intracellular parasite *Mycoplasma genitalium*)[6]. Many examples of apparent dispensability may depend on the specific conditions under which some genes are required (conditions not normally seen in the laboratory)[7], but this explanation cannot account for all cases. What mechanisms, then, underlie real dispensability? Recent work[7,8] suggests that the presence of a duplicate elsewhere in the genome (a paralog) increases the chance that a given gene will be dispensable. A report on page 295 by Kafri and colleagues[9] shows that the ability of a paralog to be transcriptionally reprogrammed upon deletion or mutation of its partner gene is central to compensation.

The paradox of the paralogs

How might paralogs provide backup? At first, the mechanistic basis for this seems obvious and little different from metabolic explanations for dominance of the wild type in diploids. These explanations suppose that the relationship between enzyme concentration and flux through a metabolic pathway follow the law of diminishing returns[10]: for each extra dose of enzyme, the increase in flux gets smaller. Hence, reducing the concentration of an enzyme by half (a knockout heterozygote) does not greatly reduce fitness, as the flux through the metabolic pathway is reduced by less than half. One might similarly imagine that, in a haploid, if two proteins with similar functions were expressed at the same time, then removing one would leave the other to do the same job.

This simple model cannot, however, represent the whole truth. In paralogous pairs of yeast genes with some degree of coexpression, there is no relationship between the degree of coexpression and the likelihood that a gene will be dispensible[11]. Kafri *et al.* show that, in yeast, most duplicate-associated backup involves genes that, on average, are not strongly coexpressed, do not share many similar 5′ motifs (that bind particular transcription factors) and diverged from each other a long time ago. How can such genes be redundant but not coexpressed?

Kafri *et al.* argue that it is not important whether two genes are usually coexpressed under normal conditions, but rather whether the remaining paralog is expressed at a sufficient level when one of the two genes is knocked out. By analyzing expression profiles in single-gene knockouts, Kafri *et al.* show that dispensability is not passive but is associated with upregulation of the remaining paralog, even if it is normally silent under the given growth conditions (**Fig. 1**).

The idea that the process involves active reprogramming of transcription might lead some to suggest that the process might be the product of selection for dispensability. But this would be too hasty a conclusion. Isozymes are not maintained for key reactions in the metabolic network, suggesting that their retention is not due to selection[7].

Feedback loops and upregulation

What might be the mechanism of upregulation after deletion? Examining the correlation between RNA levels of paralogs in 40 time series under different growth conditions, Kafri *et al.* report that although the mean correlation of expression is low for dispensable paralogs, the variance in the correlation of expression is high. They interpret this as evidence that dispensable paralogs have highly correlated expression in a few conditions but not in most conditions. As expected, then, the dispensable

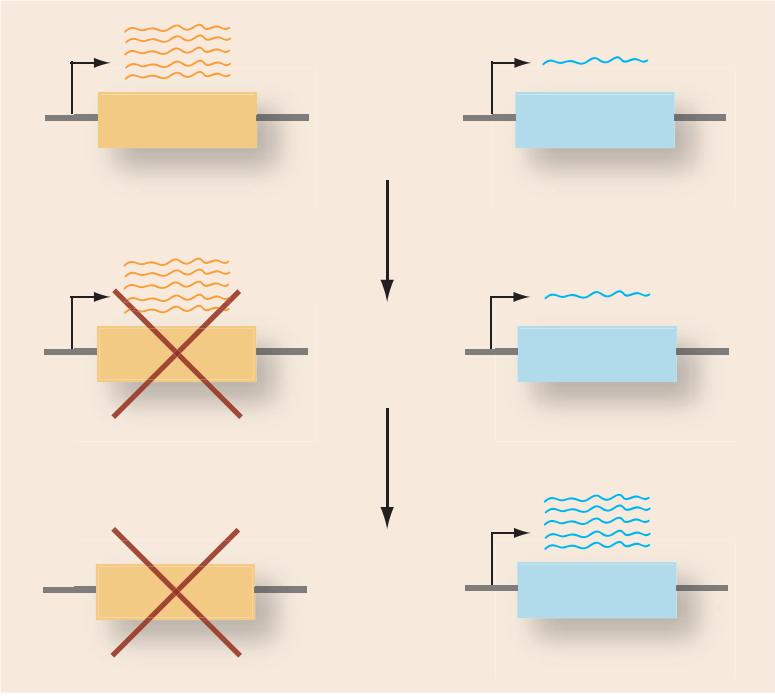

Figure 1 Transcriptional reprogramming of paralogous genes functions as a backup mechanism following gene loss.

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genes have some 5′ motifs in common. They suggest that this underpins the capacity for transcriptional reprogramming of one of the genes after deletion of the other.

Inspired by a few well-described examples (*e.g.*, ref. 12), the authors suggest a simple model involving a pair of isozymes, both of which can convert a given substrate into the same product. The genes share certain *cis*-regulatory motifs that allow regulation by a particular transcription factor, the concentration of which is regulated by the substrate. Removal of one of the isozymes leads to higher levels of the substrate, which leads to increased levels of the transcription factor and, hence, upregulation of the remaining isozyme.

Not straightforwardly consistent with this model is the finding that those paralogs with relatively high motif similarity are less likely to be redundant than those with intermediate overlap. But this finding may reflect the fact that many such highly correlated genes are mutually binding members of protein complexes[9].

Nonetheless, the model is worth further consideration, particularly for insights into the molecular basis of both dominance and pleiotropy. For example, the model predicts that in a diploid knockout heterozygote, the wild-type allele of the knocked-out gene should be upregulated (although possibly only to a small extent), potentially contributing to dominance of the wild-type allele. There is no *a priori* reason to suppose that the upregulation need be specific to the isozyme in question, as the model predicts upregulation of all those genes under the control of the transcription factor regulated by the substrate of the deleted gene. This sort of model is consistent with the odd finding that only 7% of genes upregulated under normal growth conditions are required for optimal growth[1]. Perhaps the mechanism suggested by Kafri *et al.* could also explain compensation of a knockout by genes that are unrelated by sequence but share similar metabolic functions. A systematic catalog of the effects of double gene deletions would be an excellent way to begin to examine this idea.

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Dynamin in disease

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Dynamins are dynamic scaffolding proteins that function in membrane trafficking. A new study shows that mutations in the gene encoding dynamin 2 underlie a distinct form of peripheral neuropathy, establishing the first link between dynamins and human disease.

Hereditary motor and sensory neuropathies are prevalent neuromuscular disorders affecting more than 1 in 3,000 people in the general population. Originally described by Charcot and Marie in 1886, Charcot-Marie-Tooth disease (CMT) includes various progressive distal sensory maladies such as numbing of the extremities, deafness, skeletal deformities (particularly in the feet and hands) and muscle weakness[1,2]. Histological and electrophysiological studies identified at least four different types of CMT, two of which predominate and include demyelination (CMT type 1) and axonal degeneration (CMT type 2). In addition, genetic studies have classified more than one dozen distinct loci associated with CMT, half of which are transmitted recessively. On page 289 of this issue, Stephan Züchner and colleagues[3] identify mutations in the gene encoding dynamin 2 as the cause of a dominant intermediate form of CMT, establishing the first link between dynamins and human disease.

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A contractile scaffold

Dynamins are members of a superfamily of large GTP-binding proteins (80–97 kDa) that participate in a variety of membrane trafficking–based processes[4], including formation of various endocytic and secretory vesicle types, mitochondrial and peroxisomal fission, and actin-based cytoskeletal dynamics in the lamellipod[5]. Dynamins are thought to act as mechanochemical scaffolding that can hydrolyze GTP to constrict and deform biological membranes and recruit many different signaling, cytoskeletal and membrane coat proteins[6]. This unique combination of contractile and scaffolding properties may endow dynamins with signaling functions that initiate or terminate specific membrane-trafficking processes[7,8].

Conventional dynamins are highly conserved and most similar in the N-terminal half that includes the tripartite GTPase domain (**Fig. 1**). Within the central region lies a pleckstrin homology domain that mediates interactions with specific phospholipids and is the site of the various mutations identified by Züchner *et al.*[3] The C terminus contains a GED domain believed to activate the GTPase domain and a proline-arginine-rich tail that mediates interactions with scores of effector proteins, including the actin cytoskeleton.

There are three conventional dynamins in mammals (DNM1, DNM2 and DNM3). DNM1 is neuron-specific, DNM2 is expressed in all tissues, and DNM3 exhibits tissue-selective expression as it is found in brain, testis, lung, heart and possibly cells of hematopoietic origin. In addition to this diversity, the gene encoding each dynamin undergoes substantial alternative splicing that could result in several dozen conventional dynamin protein isoforms in the brain alone[9]. Extensive splicing of a single dynamin gene has also been observed in *Drosophila melanogaster*. Temperature-sensitive mutations in the GTP-binding site of the fly dynamin gene (shibire) can induce profound effects at the restrictive temperature, the most notable being rapid paralysis, presumably resulting from an endocytic defect and subsequent synaptic vesicle depletion at the neuromuscular junction[10,11]. Thus,