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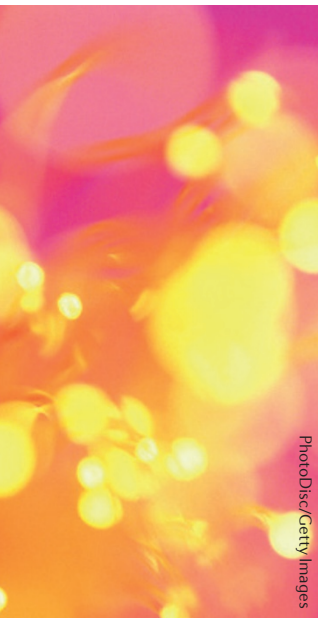

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EVOLUTION

Redefining gene essentiality

Our current definition of essential genes is based on whether or not gene knockout cells survive. Rancati and colleagues now reveal a new class of essential genes — called 'evolvable essential genes' — that can overcome loss of function with time by evolving alternative, usually unrelated, cellular processes driven by aneuploidy.

To identify evolvable essential genes, the authors used a stringent, three-level screen based on the survival of the progeny of *Saccharomyces cerevisiae* cells each with a gene deletion of one of ~1,000 genes that are considered to be essential for viability. At every stage, cells were cultured for at least 10 days to allow time for the adaptive evolution to occur, and mutant strains that yielded either no progeny (inactivation of a non-evolvable essential gene) or too many progeny (inactivation of a non-essential gene) were eliminated. The first screen identified heterozygous diploid strains, of which mutant offspring survived. The second and the third screen involved tetrad analysis, in which the four haploid spores are separated and cultured individually, of the identified mutants in two genetic backgrounds. This strategy yielded 104 putative evolvable essential genes, 16 of which were disregarded after further validation by micromanipulation-based pedigree analysis showed maximum viability of the offspring. Thus, 88 bona fide essential genes (~9%) could be deleted without resulting in stereotypical cell lethality, and are thus classified as evolvable-essential genes.

Adaptive evolution probably involves whole-chromosome and segmental aneuploidy, rather than point mutations. Interestingly, specific karyotypic changes seem to recur when functionally similar genes are deleted. For example, several strains that were deleted in genes associated with the nucleoporin (NUP) complex acquired an extra copy of chromosome VIII. Just introducing an extra copy of this chromosome increased the survival of NUP-associated mutants, indicating that this particular aneuploidy is sufficient to rescue the gene deletion. Further functional analysis found that just one gene — *BRL1* — mitigates the effect of chromosome VIII aneuploidy, not simply by restoring the disrupted function but by altering membrane fluidity. Adaptive evolution thus co-opts seemingly unrelated pathways.

Evolvable genes were enriched for components of subcellular compartments found only in eukaryotes (nucleus, endoplasmic reticulum and Golgi apparatus) but not for proteins involved in universal key processes such as DNA, RNA and protein synthesis. This finding indicates that evolutionary 'younger' essential genes might have retained some degree of adaptability.

Thus, a quantitative redefinition of gene essentiality that incorporates both viability and evolvability is required. Distinguishing non-evolvable from evolvable essential genes should be considered when ranking potential drug targets to minimize drug resistance, if these findings can be validated in pathogenic fungi or in other disease-causing cells such as cancer cells.

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> “a quantitative redefinition of gene essentiality that incorporates both viability and evolvability is required”

ORIGINAL ARTICLE Liu, G. *et al.* Gene essentiality is a quantitative property linked to cellular evolvability. *Cell* http://dx.doi.org/10.1016/j.cell.2015.10.069 (2015)