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Mapping a diversity of genetic interactions in yeast

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Abstract

Genetic interactions occur when the combination of multiple mutations yields an unexpected phenotype, and they may confound our ability to fully understand the genetic mechanisms underlying complex diseases. Genetic interactions are challenging to study because there are millions of possible different variant combinations within a given genome. Consequently, they have primarily been systematically explored in unicellular model organisms, such as yeast, with a focus on pairwise genetic interactions between loss-of-function alleles. However, there are many different types of genetic interactions, such as those occurring between gain-of-function or heterozygous mutations. Here, we review recent advances made in the systematic analysis of such diverse genetic interactions in yeast, and briefly discuss how similar studies could be undertaken in human cells.

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Introduction

In this era of affordable whole-genome sequencing, causal mutations have been identified for many Mendelian or monogenic diseases. However, most common diseases cannot be traced to a single genetic cause and may result from complex combinations of genetic and environmental factors. Genome-wide association studies (GWAS) have linked thousands of variants to complex diseases [1], but these variants generally explain only a small fraction of the observed disease phenotype. Several factors may contribute to this so-called "missing heritability", including failure to detect causal variants, either because they are rare or have very small effects. In addition, the phenotypic effects of observed variants may not combine additively but instead interact in a synergistic manner, causing the variants to be responsible for a larger fraction of the heritability than expected based on their individual effects [2,3]. Detecting genetic interactions in human genotyping datasets is a major challenge because there are so many different possible gene combinations and there are many different types of genetic interactions. However, an understanding of the diversity of the genetic interactions and their general principles as derived from model organism analysis, may provide insights that will help us identify or possibly predict interactions between human variants, which will further our understanding of the complex genetic networks underlying common diseases.

Systematic studies of genetic interactions have mainly used genetically tractable model organisms, which enable rigorous assessment of the effects of combining mutations in an otherwise isogenic background. The budding yeast *Saccharomyces cerevisiae* is an ideal model organism for these studies, due to its well-annotated genome and the availability of genome-wide mutant libraries and reagents [4–6]. We recently completed a survey of genetic interactions between loss-of-function alleles for nearly all possible pairs of yeast genes [6]. The resultant global genetic network provides insight into the functional organization of a yeast cell, revealing how different pathways work together to coordinate cellular functions and connecting uncharacterized genes to known pathways.

Although the global yeast genetic interaction network quantitatively mapped nearly 1 million genetic interactions and reveals the general principles underlying genetic networks, our ability to predict how genetic variants in natural populations contribute to phenotypes remains limited for several reasons. First, genetic interactions have been predominately mapped using partial or complete loss-of-function alleles, whereas naturally occurring variation can encompass a spectrum of genetic lesions, including separation-of-function and gain-of-function alleles. Second, interactions have largely been studied in haploid cells, while most organisms are naturally diploid and the majority of variants

are heterozygous [7]. Finally, in general, systematic studies have focused on interactions between two alleles, but most traits, including gene essentiality [8], are complex and likely modulated by the combined effects of multiple gene variants [3,9]. These complex sets of variants can either combine additively or interact synergistically, either as digenic interactions or more complex combinations, such as trigenic interactions, to lead to profound phenotypes. Here, we review efforts to address these challenges in yeast, and briefly discuss how lessons learned from yeast genetic networks can be used to guide exploration of genetic interactions in more sophisticated biological systems, including human cells.

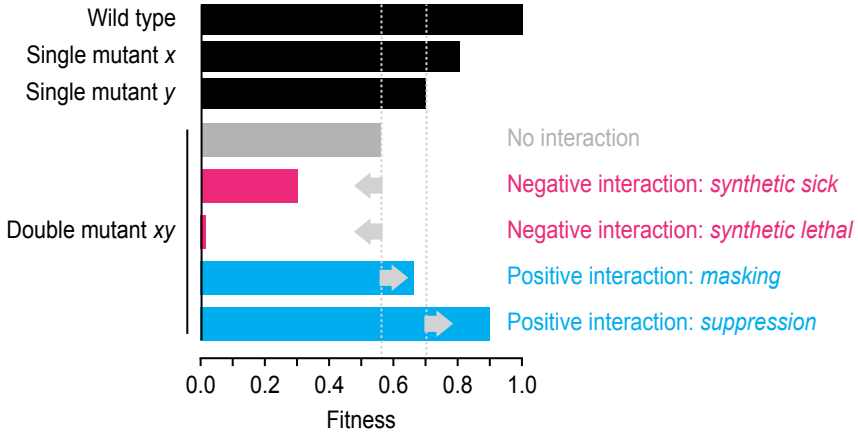
Mapping digenic interactions involving loss-of-function alleles

A digenic genetic interaction occurs when the combination of two mutations yields a phenotype that is unexpected given the effects of mutating each gene on its own. In yeast, fitness measured as either growth rate or colony size is often the phenotype of choice, and a multiplicative model is frequently applied to score genetic interactions (Figure 1) [10]. According to this model, negative digenic interactions occur when the double mutant is less fit than expected based on the multiplicative combination of the single mutant fitness values. The most extreme example of a negative genetic interaction is synthetic lethality, in which the combination of two viable mutations leads to cell death (Figure 1). By contrast, positive digenic interactions occur when the double mutant is more fit than expected (Figure 1). Positive interactions can be further classified by their relative strength, ranging from masking, in which the double mutant fitness is higher than expected but less than or equal to that of the slowest growing single mutant, to suppression, in which the double mutant is healthier than the slowest growing single mutant and possibly has a fitness that is comparable to wild type (Figure 1) [11].

Different types of genetic interactions can reflect distinct mechanistic relationships between genes. Synthetic lethal interactions between nonessential genes often reflect the combined effect of impaired function in two parallel pathways that impinge on the same essential biological function and thus can compensate for or buffer each other (Figure 2A) [12]. Masking positive genetic interactions are frequently observed between members of the same nonessential pathway or complex, such that in the absence of one complex or pathway member, additional loss of another member does not lead to an added fitness effect [13]. Essential genes, on the other hand, for which in general hypomorphic (partial loss-of-function) alleles are used, frequently show negative genetic interactions among genes within the same pathway or complex, as the combination of two partially functional alleles can lead to complete inactivation of the pathway or complex [6]. Finally, suppression interactions can occur between genes that have opposing biochemical roles (Figure 2A) [14].

The systematic analysis of digenic interactions in yeast has shown that genes encoding proteins that function together in the same pathway or complex tend to share a common set of genetic interactions [6,15]. Genetic interaction profile similarity correlates with functional relation, and can be used to form a hierarchical model of

Figure 1



Genetic interaction classes involving two genes. In yeast, genetic interactions are frequently scored using a multiplicative model. When two single mutants (*x* and *y*) have a fitness of 0.8 and 0.7 relative to wild-type cells, the expected double mutant (*xy*) fitness is 0.8 × 0.7 = 0.56. Negative and positive interactions occur when the fitness defect of a double mutant is either more or less severe, respectively, than this expected fitness. A synthetic sick negative genetic interaction occurs when the observed double mutant fitness is lower than expected, but still viable. In a synthetic lethal negative genetic interaction, the combination of two viable single mutants results in an inviable double mutant. A masking positive interaction occurs when the fitness of the double mutant is greater than expected, but lower or equal to that of the slowest growing single mutant. Suppression positive interactions occur when the double mutant fitness is greater than that of the slowest growing single mutant.