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Review

Karyotypic changes as drivers and catalyzers of cellular evolvability: A perspective from non-pathogenic yeasts

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ABSTRACT

In spite of the existence of multiple cellular mechanisms that ensure genome stability, thanks to the advent of quantitative genomic assays in the last decade, an unforeseen level of plasticity in cellular genomes has begun to emerge in many different fields of cell biology. Eukaryotic cells not only have a remarkable ability to change their karyotypes in response to various perturbations, but also these karyotypic changes impact cellular fitness and in some circumstances enable evolutionary adaptation. In this review, we focus on recent findings in non-pathogenic yeasts indicating that karyotypic changes generate selectable phenotypic variation and alter genomic instability. Based on these findings, we propose that in highly stressful and thus strongly selective environments karyotypic changes could act both as a driver and as a catalyzer of cellular adaptation, i.e. karyotypic changes drive large phenotypic leaps and at the same time catalyze the accumulation of even more genotypic and karyotypic changes.

Contents

1. Introduction

Karyotypic changes refer here to a wide range of mitotically acquired changes in the chromosomal composition and stoichiometry of the nuclear genome. This review specifically focuses on numerical karyotypic changes, i.e. changes in chromosome copy numbers, as opposed to structural changes such as translocations or segmental deletions or amplifications. Karyotypic changes that lead to copy number increase or decrease of entire chromosomal sets are referred to as polyploidization or ploidy reduction, respectively. Gain or loss of a single chromosome or a subset of chromosomes through missegregation events is referred to aneuploidization.

The introduction of accessible and sometimes high-throughput genome analysis methods in the last decade has uncovered a previously unanticipated widespread occurrence of karyotypic changes in many different types of eukaryotic cells [1–6]. In spite of these observations, we are only now starting to appreciate how these karyotypic changes could affect cellular adaptation under a variety of adverse conditions. We will focus this perspective on recent findings in non-pathogenic yeasts, as other articles in this issue

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will cover a variety of other organisms and cell types. Karyotypic changes in yeast have been observed in natural environments, industrial settings and the laboratory. In the course of natural history, a whole-genome duplication (WGD) event is thought to have occurred after the divergence of the *Saccharomyces* from *Kluyveromyces* genus, which has had important consequences on the evolution of the yeast genome [7]. In addition, sampling natural isolates of budding yeasts in modern-day Mount Caramel in Israel has revealed a high degree of variation not only in DNA sequence but also in ploidy [8], although the adaptive value of such karyotypic differences remains to be evaluated. In industrial settings, it is well known that many brewing, wine or baking strains of yeast are aneuploid or polyploid [9–12], suggesting that aneuploidy could underlie adaptation to man-made environments. For instance, some sherry-type wine yeasts carry extra copies of chromosome XIII, a finding that has been linked to the presence of two alcohol dehydrogenase genes on this chromosome [13]. Furthermore, a novel engineering strategy has been recently introduced to generate and select for aneuploid strains displaying higher ethanol production and tolerance to osmotic and thermal stress in very high gravity fermentation processes [14]. In the laboratory, WGD and ploidy reduction events occur both in the presence and in the absence of selection [15] and aneuploidy of various chromosomes arises spontaneously in mutation accumulation experiments in *S. cerevisiae* [16]. Moreover, whole-chromosome or segmental aneuploidy has been shown to correlate with adaptation to various environmental perturbations during experimental evolution under nutrient limitation or salt stress [17–19]. Interestingly, it has been recently shown that while adaptation to abrupt and extremely stressful conditions is underlain by aneuploidization of specific chromosomes, adaptation to gradual increase of stress does not involve chromosome copy number changes. Moreover, after ~2000 generations in presence of stress, the aneuploid chromosomes are lost and alternative adaptation mechanisms are found [20]. This suggests that aneuploidy could be a transient solution for eukaryotic cells to face abrupt and extremely challenging situations. Once the cell has escaped death by changing its karyotype, it could start "looking" for more refined and fine-tuned adaptive solutions [21].

Aneuploidy not only underlies adaptation to environmental or chemical perturbations but also to genetic insults. For instance, aneuploidy of specific sets of chromosomes was shown to be required and sufficient for genetic adaptation to the deletion of an essential gene required for cytokinesis [22] and of genes involved in telomere maintenance [23,24]. Many yeast strains deleted of non-essential genes accumulate extra copies of specific chromosomes, some of which encode paralogs of the deleted genes [1]. Taken together, these observations suggest that some karyotypic changes could be beneficial to yeast cells struggling for survival under strong environmental, chemical or genetic perturbations. In support of this view, it has been recently shown that stress-induced chromosome missegregation increases adaptation of budding yeast to unrelated stress factors [25]. In this review, we provide a theory on how karyotypic changes can underlie evolutionary adaptation of cells to highly adverse conditions.

Evolutionary adaptation to perturbations requires phenotypic variation, i.e. the existence of a pool of variants within the population, each displaying a unique set of phenotypic traits, on which selection acts by favoring the propagation of the variants holding a fitness advantage. In this regard, cell populations characterized by a larger phenotypic variation should theoretically be intrinsically more evolvable than highly clonal populations [26]. Below we first discuss how karyotypic changes can lead to phenotypic leaps, thus "driving" efficient exploration of a large phenotypic space. We then discuss how some aneuploid karyotypes also increase the rate of genotypic and karyotypic changes, thus "catalyzing" the accumulation of further phenotypic diversity.

2. Karyotypic changes as drivers of phenotypic variation

In order to understand how karyotypic changes result in phenotypic changes, in this section we introduce the concept of karyotype–phenotype (KP) map. Since this concept is borrowed and extended from the widely used concept of the genotype–phenotype (GP) map, we begin by briefly reviewing some key aspects of the GP map that will be important to the discussion of KP map.

2.1. Existence of vast genotype networks in the genotype–phenotype map

It is widely accepted that many point mutations have little or no significant effect on phenotype [27]. This is primarily due to the fact that many single-nucleotide substitutions do not change amino acid sequence because of the degeneracy of the genetic code. Even when point mutations do result in polypeptide changes they often do not significantly affect protein folding or function, because codons that differ by a single nucleotide often encode amino acids with similar physical–chemical properties [28]. It has been proposed, and in some cases demonstrated across various model organisms, that even synonymous substitutions may lead to some measurable fitness effects because of suboptimal codon usage or mRNA folding stability [29–31]. Recent experimental evidence in *S. cerevisiae*, however, indicates most of such fitness effects to be very small or nearly neutral during selection [32]. Another argument could be made that DNA sequence mutations outside protein-coding regions could potentially affect gene expression and thus have significant phenotypic impact even without directly affecting protein function [33]. However, cis-regulatory elements are typically short and a large amount of degeneracy exists in the motifs of transcription factor-binding sites [34]. Taken together, we can conclude that many random point mutations do not result in selectable phenotypic change, a key realization at the basis of the neutral theory of evolution [35].

Based on the above consideration, the GP map is more complex than a simple one-to-one relationship between genotype and phenotype. In fact, the many-to-few relationship that exists between genotypes and phenotypes allows for the existence of so-called genotype networks [36]. A genotype network is defined as a cluster of genotypes, directly linked to one another via single point mutations, that can all be mapped to the same phenotype [37]. The existence of these large genotype networks in the GP map is thought to play an important role in molecular evolution, in particular by providing both robustness and evolvability to living systems [26]. For the purpose of this review, however, we would like to emphasize the important corollary that the existence of large genotype networks in the GP map inevitably leads to a high disproportion between the size of the genotype space and the size of the corresponding phenotype space. Specifically, any phenotype space is always significantly smaller than the genotype space that it originates from (Fig. 1A). Above considerations stand in sharp contrast with observations of the KP map (see below).

2.2. Phenotypic changes produced by polyploidization

Across several eukaryotes and especially in fungi, polyploidy caused by WGD inevitably leads to important changes in cell size and distortions in subcellular scaling: nuclear volume generally scales with genome content and, because the cytoplasmic-to-nuclear volume is kept constant, cell volume also generally scales with ploidy (reviewed in [38], also see review by Mayfield et al. in this issue). The cell surface however does not scale linearly