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Review

Survival and innovation: The role of mutational robustness in evolution

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ABSTRACT

Biological systems are resistant to perturbations caused by the environment and by the intrinsic noise of the system. Robustness to mutations is a particular aspect of robustness in which the phenotype is resistant to genotypic variation. Mutational robustness has been linked to the ability of the system to generate heritable genetic variation (a property known as evolvability). It is known that greater robustness leads to increased evolvability. Therefore, mechanisms that increase mutational robustness fuel evolvability. Two such mechanisms, molecular chaperones and gene duplication, have been credited with enormous importance in generating functional diversity through the increase of system's robustness to mutational insults. However, the way in which such mechanisms regulate robustness remains largely uncharacterized. In this review, I provide evidence in support of the role of molecular chaperones and gene duplication in innovation. Specifically, I present evidence that these mechanisms regulate robustness allowing unstable systems to survive long periods of time, and thus they provide opportunity for other mutations to compensate the destabilizing effects of functionally innovative mutations. The findings reported in this study set new questions with regards to the synergy between robustness mechanisms and how this synergy can alter the adaptive landscape of proteins. The ideas proposed in this article set the ground for future research in the understanding of the role of robustness in evolution.

1. Introduction

Biological systems are inherently robust (resistant) to perturbations, maintaining the same phenotype in the face of external challenges and noise internal to the system [1,2]. Therefore, phenotypes are said to be robust if they resist perturbations. Robustness was first suggested by Waddington who observed that developmental programs are generally robust to minor perturbations, a property he called canalization [3,4]. Robustness applies to many different levels of biological organization and its effects are visible in the expression patterns of genes, resistance of protein structures to mutations and proteins functional promiscuity. The form of robustness most easily measured is the one resulting from the resistance of phenotypes to environmental challenges, such as variable temperatures, limited nutrients and various kinds of environmental stresses. Perturbations also occur within organisms or cells, however less obvious, in the form of variation in expression levels and mal-adaptive mutations (e.g., changes in the genetic composition of an individual–also known as genotypic variation). What underlying molecular mechanisms and population genetic parameters provide and regulate the resistance of systems to perturbing mutations remains largely unknown.

The recent meeting in "Protein structure, Protein Evolution" organized by the Royal Swedish Academy of Sciences in June 2014 in Stockholm has provided the ideal scientific environment to link the knowledge generated by structural (phenotype) and evolutionary (genotype) biologists to understand many questions directly or indirectly linked to robustness. The link between the main changes at the structural and sequence levels and the emergence of novel functions has also been discussed and, to a lesser extent, so has the *de novo* emergence of protein functions. In particular, it has been of great interest the fact that most talks led to distinguishing between the plasticity of protein structures, their tolerance to destabilizing mutations, and the dynamics of the mechanisms of mutational buffering. In this review, I will discuss on the mechanisms of mutational buffering, including gene or genome duplication and heat-shock proteins, as these mechanisms have enthralled researchers for many decades but remain uncharacterized.

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As said before, robustness against environmental and genetic perturbations is a property inherent to all living systems and is ubiquitous to all biological organization levels [5,6]. This tolerance to perturbations, however uncharacterized, have been observed in the form of phenotypic resistance to hundreds of mutations in proteins [7], the resilience of biological networks to single deletions [8], and the resistance of the cell to changes in the expression levels of genes [9]. Moreover, it has been shown that cells are tremendously tolerant to single gene deletions. For example, 80% of the genes in *Saccharomyces cerevisiae* growing in lenient laboratory conditions have little to no effect on the fitness of this yeast [10]. Likewise, only 42% of all the induced gene deletions are essential for mouse viability [11].

The origin and consequences of robustness remain to be uncovered, although a number of observations link robustness to certain biological traits or to the complexity underlying such traits. For example, complex traits seem to be more robust than simple ones to gene perturbations, likely owing to the lower impact of deleterious mutations on the greater set of genes that encode complex traits [12]. The correlation between the complexity of biological traits and the robustness of their encoding genes to mutations suggests a link between robustness and the ability of systems to generate heritable genetic variation (a property known as evolvability). A number of studies have explored the main consequences of increasing robustness and found that there is a complex but significant relationship between robustness and evolvability. Indeed, in a genotypic network, in which the transition between genotypes is phenotypically silent (also known as neutral genotypic network), increasing robustness makes the system more phenotypically evolvable if each of the genotypes can only access a subset of all possible phenotypes [13]. Under this condition, the wider the network the larger is the set of accessible phenotypes, and thus the greater is the system's evolvability (Fig. 1a). Conversely, when each genotype can access all possible phenotypes of the phenotypic space, then higher robustness decreases evolvability (Fig. 1b). Examples on the relationship between robustness and evolvability using entire organisms or populations are lacking in the literature owing to the complexity that experiments devoted to disentangling robustness from other population genetic or environmental factors involves. Advances in the understanding of the role of robustness in evolvability have nevertheless been conducted using simple molecules, in which evolvability can be linked to the distribution of mutations effects on fitness. As a case in point, Hayden and colleagues addressed the role of robustness in

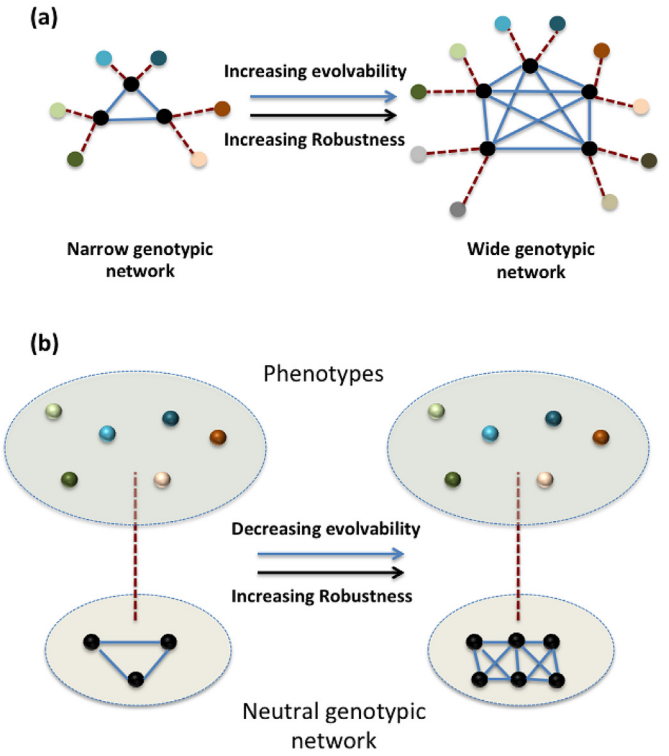

Fig. 1. Increasing robustness leads to larger evolvability and phenotypic plasticity. (a) In this figure I represent two genotypic networks a narrow network and a wide network—a genotypic network is defined as the number of genotypes (black circles) interlinked by a single mutation that are neutral with regards to the phenotype, so that the transition from one genotype to another is phenotypically silent. Increasing the robustness of a biological system increases the genotypic network and the possibility of accessing a larger set of phenotypes (colored circles) through subsequent single mutations. Increasing robustness increases then the evolvability of a system if the set of phenotypes accessible through each genotype by a single mutation is smaller than the entire phenotypic space. In this particular case, the narrow genotypic network in the left of the figure leads to potentially six different accessible phenotypes. Increasing the robustness of the network by two additional genotypes (network in the right of the figure) increases the accessible phenotypic space (evolvability) in four additional phenotypes. (b) This figure represents a case in which each of the genotypes of the same genotypic network can access all of the phenotypes in the phenotypic space. In such a scenario, increasing robustness, that is the number of genotypes in the network, leads to lower evolvability as the number of phenotypes accessible by a single mutation remains constant.

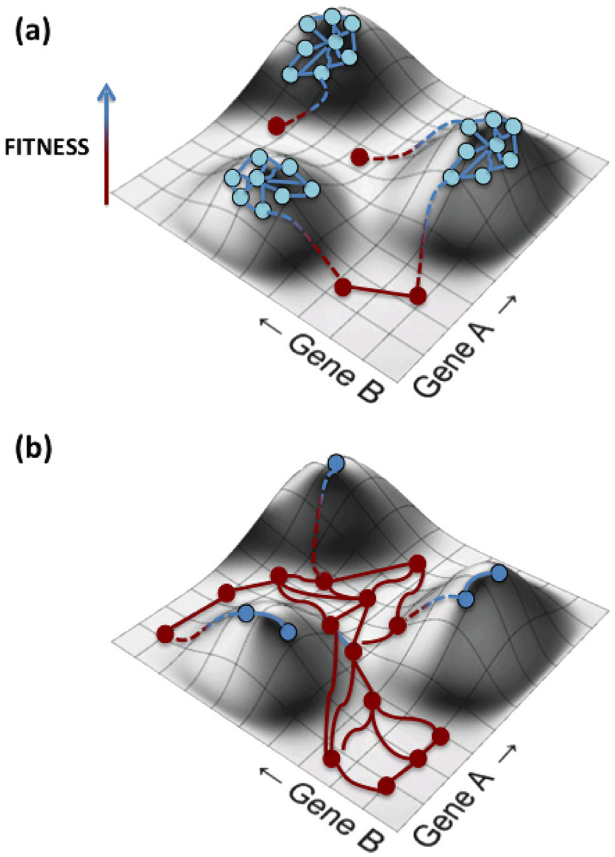

Fig. 2. Distribution of genotypes in a fitness landscape. Circles symbolize genoytpes (red circles are negatively selected genotypes while blue ones are positively selected genotypes) and lines are links between two genotypes, which differ in a single mutation (blue links are allowed transitions by natural selection while red ones are those evolutionary trajectories under strong purifying selection). (a) In a population with high robustness to mutations, most genotypes are part of the same neutral genotypic network and these networks are concentrated on adaptive picks, while genotypes in deleterious valleys are sparsely distributed. (b) Populations with low robustness to mutations present a low number of genotypes populating the adaptive picks with most genotypic transitions being deleterious, and thus leading to genotypes occupying low-fitness valleys in the landscape.

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