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Current Biology

Hidden Complexity of Yeast Adaptation under Simple Evolutionary Conditions

Highlights

- Fitness benefits from different phases of a growth dilution cycle were quantified
- Benefits were "accrued" in respiration but largely "realized" as a shortened lag phase
- Analysis of high-throughput data reveals different adaptive strategies
- Trade-offs exist between accrued respiration benefits and stationary survival

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In Brief

Quantitative details of how adaptive genotypes gain fitness have rarely been studied. By quantifying fitness benefits of thousands of yeast clones in different parts of the growth-saturation cycle, Li et al. identify distinct adaptive strategies, with some strategies showing clear trade-offs between growth and survival.

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Hidden Complexity of Yeast Adaptation under Simple Evolutionary Conditions

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SUMMARY

Few studies have "quantitatively" probed how adaptive mutations result in increased fitness. Even in simple microbial evolution experiments, with full knowledge of the underlying mutations and specific growth conditions, it is challenging to determine where within a growth-saturation cycle those fitness gains occur. A common implicit assumption is that most benefits derive from an increased exponential growth rate. Here, we instead show that, in batch serial transfer experiments, adaptive mutants' fitness gains can be dominated by benefits that are accrued in one growth cycle, but not realized until the next growth cycle. For thousands of evolved clones (most with only a single mutation), we systematically varied the lengths of fermentation, respiration, and stationary phases to assess how their fitness, as measured by barcode sequencing, depends on these phases of the growth-saturation-dilution cycles. These data revealed that, whereas all adaptive lineages gained similar and modest benefits from fermentation, most of the benefits for the highest fitness mutants came instead from the time spent in respiration. From monoculture and high-resolution pairwise fitness competition experiments for a dozen of these clones, we determined that the benefits "accrued" during respiration are only largely "realized" later as a shorter duration of lag phase in the following growth cycle. These results reveal hidden complexities of the adaptive process even under ostensibly simple evolutionary conditions, in which fitness gains can accrue during time spent in a growth phase with little cell division, and reveal that the memory of those gains can be realized in the subsequent growth cycle.

INTRODUCTION

Experimental microbial evolution combined with genomics has succeeded in delineating the molecular basis and population dynamics of adaptation for multiple species and under diverse conditions [1–14]. However, this stands in sharp contrast to the difficulty of "quantitatively" understanding how these genetic events lead to fitness benefits [15, 16]. Whereas the beneficial effects of some mutations are obvious, e.g., amplification of a gene encoding a transporter of the limiting nutrient, there are many cases where it is far from clear. Furthermore, beneficial mutations may have multiple phenotypic effects at the organismic level. Whether the net effect of these will be beneficial, and if so by how much, likely depends on the subtleties of the specific environmental conditions. Whereas some detailed analyses of observed fitness gains in experimentally evolved microbes have been carried out [17, 18], these approaches were low throughput and required detailed knowledge of the fitness-related phenotypic changes.

For serial batch culture experiments with distinct physiological growth phases, one possible approach is to study where within the growth cycle adaptive clones acquire their fitness benefits. A challenge of this approach is that the growth cycle phase where fitness gains might accrue may be distinct from the phase where reproduction occurs, even in a "simple" system, such as asexually growing single cells. An example from metazoans provides a useful analogy: in some animal species, such as Richardson's ground squirrels (*Spermophilus richardsonii*), females that gain more body mass outside of the reproductive season have a higher fecundity the following spring when they do reproduce [19]. Thus, understanding fitness by focusing on the parts of the growth cycle that are associated with a faster rate of cell division might miss the importance of the part of the growth cycle where the physiological gains actually accrue.

We previously isolated yeast clones containing single adaptive mutations from a glucose-limited serial transfer evolution [6, 12]; in the evolutionary condition, the clones experienced lag, fermentation, and respiration phases. Here, we have quantitatively investigated where in the growth cycle these clones accrue and realize their fitness benefits. We first studied realized fitness by generating detailed cell number measurements throughout

