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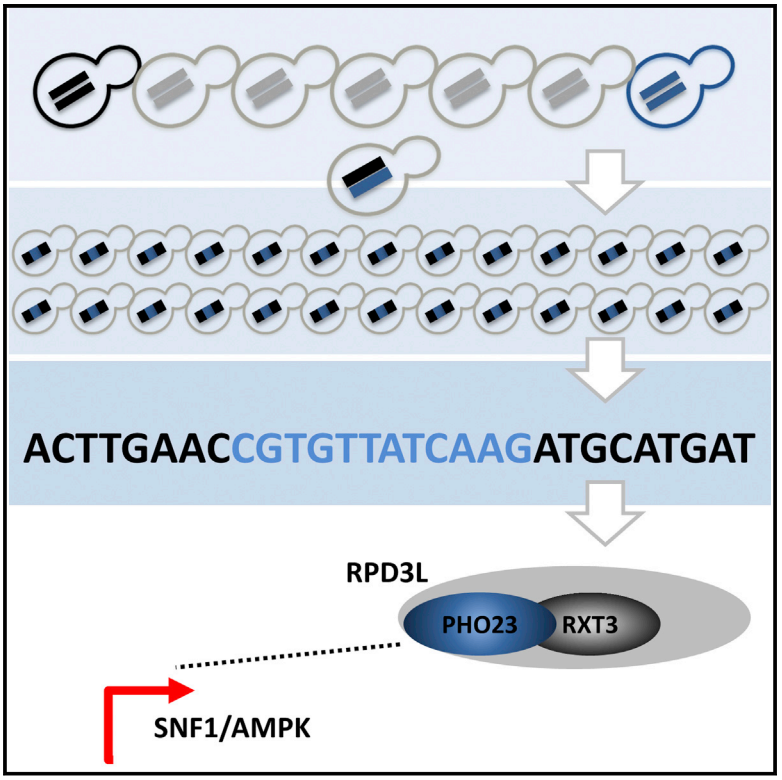
Natural Diversity in Pentose Fermentation Is Explained by Variations in Histone Deacetylases

Graphical Abstract



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In Brief

Tamari and Barkai performed a quantitative trait loci study on ethanol production from the pentose sugar xylulose in budding yeast. Variations in components of the large Rpd3 histone deacetylation complex are causal to increased ethanol production. These variants modulate expression of SNF1/AMPK-dependent respiratory genes.

Highlights

- Natural strains of budding yeast show variable xylulose fermentation
- Causal alleles are mapped to components of RPD3L histone deacetylase complex
- Alleles of this complex differentially modulate respiratory genes' expression

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Natural Diversity in Pentose Fermentation Is Explained by Variations in Histone Deacetylases

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SUMMARY

The extent to which carbon flux is directed toward fermentation versus respiration differs between cell types and environmental conditions. Understanding the basic cellular processes governing carbon flux is challenged by the complexity of the metabolic and regulatory networks. To reveal the genetic basis for natural diversity in channeling carbon flux, we applied quantitative trait loci analysis by phenotyping and genotyping hundreds of individual F2 segregants of budding yeast that differ in their capacity to ferment the pentose sugar xylulose. Causal alleles were mapped to the RXT3 and PHO23 genes, two components of the large Rpd3 histone deacetylation complex. We show that these allelic variants modulate the expression of SNF1/AMPK-dependent respiratory genes. Our results suggest that over close evolutionary distances, diversification of carbon flow is driven by changes in global regulators, rather than adaptation of specific metabolic nodes. Such regulators may improve the ability to direct metabolic fluxes for biotechnological applications.

INTRODUCTION

The budding yeast *Saccharomyces cerevisiae* is unique in its exceptional capacity to ferment sugar even in the presence of oxygen, a phenomenon known as the Crabtree effect. This effect is most pronounced during growth on glucose, although high levels of ethanol production also are observed during growth on other related carbon sources, such as fructose and galactose. However, in the presence of sub-optimal carbon sources, the distribution of carbon flux among ethanol, biomass accumulation, and complete oxidation to CO_2 can vary considerably (Gancedo, 1998; Polakis and Bartley, 1965). Accordingly, a complex network of signaling pathways that orchestrates the channeling of carbon flux in response to changes in environmental conditions was characterized (Johnston and Marian, 1992).

Production of ethanol by fermentation of lignocellulose, the most abundant organic matter on Earth, is an attractive alternative to petroleum-based fuels (Service, 2014). While lignocellulose is comprised of both hexose (primarily glucose) and pentose (primarily xylose) sugars, budding yeast can naturally ferment only the hexose portion. There is, therefore, a great interest in understanding how to rewire central carbon metabolism to allow for increasing (and sometimes decreasing) ethanol production when growing on any given carbon source. While this is typically explored by a genetic engineering approach, natural diversity between related strains can be informative on how such rewiring is achieved during the course of evolution. We recently reported that natural strains of *S. cerevisiae* differ greatly in their ability to ferment xylulose, the only pentose yeast that can naturally metabolize (Tamari et al., 2014). We therefore used this system as a model to identify the genetic variants that contribute to this natural diversity in pentose fermentation.

RESULTS AND DISCUSSION

Among a collection of 12 wild-type *S. cerevisiae* isolates originating from diverse geographical origins and natural habitats (Table S1), T73 and Y12 produced the most ethanol, while CLIB215 produced the least amounts of ethanol, although growing at comparative rates (Figures 1A and 1B). T73 showed increased ethanol production rate and, therefore, was selected, together with CLIB215, for further analysis. In contrast to phenotypic diversity observed in xylulose fermentation, all strains produced approximately the same ethanol levels when grown on glucose (Tamari et al., 2014).

We used quantitative trait locus (QTL) analysis to define genetic variants associated with this difference in xylulose fermentation. T73 and CLIB215 were crossed, sporulated, and over a thousand F2 segregants were phenotyped for ethanol production and growth on xylulose (n = 1,061) (Figure 1C). Significant diversity was observed among segregants, including a 1% transgressive segregation rate (Figure 1D). No correlation was observed between the amount of ethanol produced and optical density reached at saturation, suggesting that differences in ethanol production resulted from differential carbon distribution between fermentation and respiration, rather than differences in biomass production.

We selected the 150 segregants producing the highest amounts of ethanol and the 150 segregants producing the lowest amounts of ethanol and genotyped them individually using restriction site-associated DNA sequencing (Baird et al., 2008;