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Pleiotropic Signaling Pathways Orchestrate Yeast Development

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Abstract

Developmental phenotypes in *Saccharomyces cerevisiae* and related yeasts include responses such as filamentous growth, sporulation, and the formation of biofilms and complex colonies. These developmental phenotypes are regulated by evolutionarily conserved, nutrient-responsive signaling networks. The signaling mechanisms that control development in yeast are highly pleiotropic – all of the known pathways contribute to the regulation of multiple developmental outcomes. This degree of pleiotropy implies that perturbations of these signaling pathways, whether genetic, biochemical or environmentally induced, can manifest in multiple (and sometimes unexpected) ways. We summarize the current state of knowledge of developmental pleiotropy in yeast and discuss its implications for understanding functional relationships.

Keywords

pleiotropy; gene networks; tradeoffs; developmental switches

Introduction

In response to stress, the baker's yeast *Saccharomyces cerevisiae* and related fungi undergo a variety of developmental switches. These developmental switches include transitions to filamentous growth [1], changes in interactions between cells that lead to biofilms [2] and architecturally complex colonies [3, 4], or the induction of meiosis and sporulation [5]. These responses are induced by signals that act through a variety of signaling pathways, all of which regulate multiple developmental phenotypes. In this review, we emphasize the pleiotropic nature of developmental pathways in yeast. We consider the implications of pleiotropy for understanding functional relationships among developmental responses and discuss the ecological, industrial, and clinical implications of developmental pleiotropy.

Yeast developmental phenotypes

Filamentous growth

Filamentous growth refers to both diploid pseudohyphal growth and haploid invasive growth, both of which are induced by nutrient limitation. Pseudohyphal growth is primarily induced by nitrogen starvation [6], although several reports demonstrate a secondary role for carbon type and quality in its regulation (Figure 1B) [7, 8, 9]. The pseudohyphal response is

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characterized by a switch from bipolar to unipolar budding, incomplete mother-daughter cell separation, and cell elongation. These characteristics result in branching chains of cells that give the margins of pseudohyphal colonies a characteristic “fuzzy” appearance (Figure 1A). Haploid invasive growth [10] is primarily triggered by glucose limitation [11] and involves a switch from axial to bipolar budding. Substrate invasion is common to both responses. Filamentous growth is of medical interest because these phenotypes contribute to virulence in both *S. cerevisiae* [12] and related fungal pathogens such as *Candida albicans*.

Complex colony morphology and biofilms

Complex colony morphology is another form of mitotic growth that is characterized by intricate, organized, and strain-specific patterns of colony growth and architecture (Figure 1D) [13, 4]. The switch from smooth, simple colonies to the formation of complex colonies is reliably induced by a combination of limited fermentable carbon with rich nitrogen (Figure 1C) [4].

There is mounting evidence that complex colonies are a form of biofilm [3]. Biofilms are emergent microbial communities that provide benefits to their constituents, including cooperative metabolism, and protection from biotic and abiotic stresses [14, 15]. Microbial biofilms are a concern for human health and human infrastructure because of their tendency to form on solid surfaces and their resistance to conventional antimicrobial treatments [16, 17].

Sporulation

Severe limitation of both nitrogen and fermentable carbon sources can induce diploid cells to sporulate (Figure 1E) [18]. In addition to nutrient availability, sporulation is also sensitive to pH [19]. During sporulation, cells exit vegetative growth and undergo meiosis. Spores, the haploid products of meiosis, are encased in thick cell walls and are packaged into a structure called an ascus (Figure 1F) [20]. Spores are highly resistant to a variety of environmental insults, including temperature extremes, desiccation, and the absence of nutrients.

Developmental pathways

Genetic and biochemical studies have identified five major signaling pathways [21] that are involved in nutrient-induced developmental responses in yeast: 1) the cAMP-PKA pathway; 2) the TOR pathway; 3) the SNF1/AMPK pathway; 4) the Rim101 pathway; and 5) the Kss1-MAPK pathway. As we discuss below, all of these pathways have known or predicted pleiotropic effects on at least two (and in some cases all three) developmental phenotypes.

The cAMP-PKA pathway

The cAMP-PKA signaling pathway is a prime regulator of metabolism, cell differentiation, and development in animals, fungi, and amoebae. The basic structure and signaling logic of the pathway is highly conserved [22]. In *S. cerevisiae*, cAMP-PKA activity is correlated with the availability and quality of carbon sources [23, 24]. When glucose is ample, cAMP-PKA signaling promotes cell cycle progression, ribosome biogenesis, and mass accumulation. Simultaneously, cAMP-PKA signaling downregulates stress responses, such as autophagy [25].

cAMP-PKA signaling is required for pseudohyphal growth [26, 27] and complex colony morphology [28, 4], and therefore is positively pleiotropic with respect to these phenotypes. Conversely, increased cAMP-PKA pathway activity inhibits sporulation [5, 29, 30], and thus is antagonistically pleiotropic for sporulation relative to the aforementioned responses.

TOR signaling

TOR (Target of Rapamycin) signaling regulates temporal and spatial aspects of cell growth, primarily in response to nitrogen availability, although carbon likely plays a role [31, 32]. The regulation of growth related activities by TOR runs parallel to cAMP-PKA signaling, and the interactions of these pathways govern cellular growth and proliferation [33, 34, 35]. TOR signaling involves two functionally distinct, yet structurally overlapping complexes: TOR Complex 1 (TORC1) and TOR Complex 2 (TORC2) [31]. The rapamycin-sensitive TORC1 facilitates mass accumulation by upregulating protein synthesis through ribosome biogenesis, translation initiation, and elongation [36, 37]. TORC1 antagonizes stress-induced processes, such as Nitrogen Catabolite Repression (NCR), the mitochondrial retrograde response (RTG) pathway, and autophagy [38, 25, 39]. The rapamycin-insensitive TORC2 contributes to the regulation of cell polarity through actin polymerization [40].

Both treatment with rapamycin and loss-of-function mutations in TOR pathway genes result in decreased pseudohyphal growth [41]. In contrast, cells treated with rapamycin show increased sporulation efficiency [42], possibly via induced changes in the stability and localization of the transcriptional activator Ime1, a key regulator of meiosis and sporulation [43]. Thus, the TOR pathway exhibits antagonistic pleiotropy with respect to pseudohyphal growth and sporulation. A direct role for TOR signaling in *S. cerevisiae* colony morphology has not been demonstrated, although we predict that this pathway contributes positively to the complex colony response based on the phenotype's sensitivity to elevated nitrogen levels [4]. Thus, like the cAMP-PKA pathway, the TOR pathway exhibits both positive and antagonistic pleiotropy on developmental traits.

SNF1/AMPK pathway

In eukaryotes, Snf1/AMPK signaling is a central mediator of carbon metabolism through its effects on gene expression and metabolic enzyme activities [44, 45]. Snf1/AMPK functions as a metabolic switch that represses anabolic reactions and promotes catabolism. Under poor conditions, Snf1/AMPK helps maintain energy balance and cell growth by negatively regulating costly processes such as protein and phospholipid biosynthesis [44]. In parallel, it generates cellular energy by triggering the uptake and metabolism of alternative carbon sources, fatty-acid breakdown, and organelle recycling through autophagy [9].

SNF1 signaling is required for both sporulation [46, 47] and filamentous growth on non-glucose carbon sources [9]. Recent work in our lab (unpublished studies) also implicates SNF1 signaling in the regulation of colony morphology. Thus the effects of the SNF1 pathway on all three phenotypes appear to be largely positively pleiotropic.

Rim101 pathway

Alkaline conditions, which can interfere with nutrient acquisition and homeostasis, induce the activation of the Rim101/PacC pathway [48]. Lamb et al. [49] showed that Rim101 signaling is required for both sporulation and haploid invasive growth. Piccirillo et al. [50] recently reported that structured patterns of differentiation within colonies are also driven by Rim101 signaling. Rim101 represses the transcription factor Nrg1, a negative regulator of glucose-repressed genes. Nrg1's targets include *FLO11* [51], a gene that encodes a key cell surface protein required for invasive and pseudohyphal growth [52]. Lamb and Mitchell [51] also identified Smp1 as a target of Rim101. Smp1 is a transcription factor of unknown function, and *smp1* mutants suppress *rim101* defects in invasive growth and sporulation and restore rough colony morphology. Thus, like the SNF1 pathway, Rim101 signaling is positively pleiotropic with respect to all three developmental responses in *S. cerevisiae*.

Kss1-MAPK pathway

MAPK (Mitogen Activated Protein Kinase) signaling mechanisms regulate cell survival and death under adverse conditions, including nutrient deprivation [53]. In *S. cerevisiae*, nutrient depletion activates the Kss1-MAPK pathway. The Ras2-Cdc42 complex activates Ste20 (MAPKKKK), which in turn triggers a phosphorylation cascade involving Ste11 (MAPKKK) and Ste7 (MAPKK), both of which are shared with the pheromone-responsive Fus3-MAPK module [54]. Ste7, in turn, activates Kss1 (MAPK), whose kinase activity regulates a variety of transcription factors important for developmental responses [55].

The Kss1-MAPK pathway affects both pseudohyphal growth [55] and the formation of complex colonies and biofilms [56, 4], although it has no reported effects on sporulation. Cullen and colleagues [57] recently presented evidence that many of the signaling pathways described above contribute to the regulation of the Kss1-MAPK pathway.

Functional and evolutionary implications of pathway pleiotropy

Combinatorial patterns of pathway activity regulate yeast development

If almost every one of the key signaling pathways regulates multiple developmental phenotypes, often in the same direction, how then do yeast mount appropriate responses in the face of particular nutrient challenges? The answer almost surely lies in combinatorial pathway interactions. The joint effects of multiple signaling pathways and their relative activities are key features of the cellular decision making that leads to different developmental fates in yeast [58]. Recent studies have used both experimental and computational methods to understand the roles of different pathways in transducing the nutrient signals that control developmental outputs [59, 60, 61].

Correlations between developmental traits are the default expectation

Given the predominance of pleiotropy in key signaling networks, correlated phenotypic responses are the default expectation for genetic or chemical manipulations of pathway function. For example, mutations and drugs that decrease cAMP-PKA signaling activity are known to enhance sporulation while simultaneously repressing pseudohyphal growth (a negative correlation) [27]. Similarly, mutations that upregulate Rim101 signaling are expected to positively affect sporulation, haploid invasive growth, and the formation of complex colonies (positive correlations) [51]. Simultaneously assaying multiple phenotypes to probe the state of several signaling pathways has the potential to provide a very sensitive readout of pathway interactions. We suggest that violations of expected pleiotropic relationships (e.g. [62]) may be useful for identifying parts of networks where feedback, conditional interactions, and complex epistasis are particularly important.

Pleiotropic interactions and phenotypic variability

With the ubiquity of pleiotropic effects, one question of interest is how these pleiotropic interactions impact standing patterns of phenotypic variation among *S. cerevisiae* lineages. For example, our lab recently demonstrated a tradeoff between sporulation efficiency and pseudohyphal growth in *S. cerevisiae* [63]. The mechanistic basis of this tradeoff is likely attributable to naturally segregating variation that affects one or more of the pleiotropic pathways discussed above. Similarly, Sicard and colleagues have documented a life history tradeoff in *S. cerevisiae* related to resource utilization [64, 65]. We predict that variation in nutrient responsive signaling pathways may underlie this tradeoff as well.

Pleiotropy and aging

Antagonistic pleiotropy involving tradeoffs between reproduction and senescence is one of the predominant hypotheses explaining why organisms age [66]. Caloric restriction and general nutrient stress extend lifespan in both microbes and multicellular eukaryotes [67, 68]. Because yeast developmental responses involve nutrient limitation, an intriguing question is the extent to which lifespan (either chronological or replicative) is correlated with one or more of the developmental processes under consideration. Complex morphology is of particular interest because low dextrose media, the most reliable inducer of complex morphology, is calorie restricted and has been shown to extend lifespan in *S. cerevisiae*. Furthermore, key pathways like TOR and SNF1 are implicated in both lifespan and induction of colony morphology.

Industrial and clinical considerations

Signaling pathways that control fungal morphogenesis have been proposed to be good targets for antifungal drugs [1, 69]. For example, drugs that inhibit cAMP-PKA or TOR signaling should lead to decreased pseudohyphal and invasive growth. However, because of pleiotropic pathway effects, such drugs might also lead to greater stress resistance or induce sporulation, potentially allowing virulent cells to persist. This suggests that effective treatments might require a combination of therapies that target multiple pathways simultaneously in order to minimize “escape” due to pleiotropy. Similar considerations should be made in genetic engineering or artificial selection experiments for industrial applications. For example, selection for phenotypes such as velum formation, a biofilm-like response of interest in wine production [70, 71], is likely to also select for mutations that favor pseudohyphal and invasive growth thereby creating a greater risk for opportunistic pathogenicity.

Summary

Yeast, like most microbes, make developmental decisions in response to nutrient cues. Most investigations aimed at understanding the mechanisms that regulate developmental switches in *S. cerevisiae* have focused on single developmental outcomes, without considering the potential for parallel responses in other phenotypes. As we have outlined above, the gene networks that regulate development in yeast are highly pleiotropic, and thus correlated changes in developmental responses are likely to be common when such networks are perturbed by genetic or biochemical means. Future studies should employ multi-trait approaches and consider development switches not as a set of individual outcomes but rather as a spectrum of related responses. Such work will lead to new insights regarding the structure, function, and evolution of developmental signaling networks in yeast.

Highlights

- > Nutrient stress induces developmental switches in *Saccharomyces cerevisiae* (baker's yeast) and related fungi.
- > The signaling pathways that control development are highly pleiotropic.
- > Because of signaling pathway pleiotropy, developmental phenotypes can be strongly correlated.
- > Pleiotropy can be exploited in functional studies to discover or understand interactions within and between signaling pathways.
- > Understanding the causes and consequences of pleiotropy is important in ecological, clinical, and agricultural contexts.

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Figure 1.

Developmental pathways in *Saccharomyces cerevisiae*. Yeast cells detect and transduce information on nutrients and pH through the combined action of the cAMP-PKA, SNF1/AMPK, TOR, Kss1-MAPK, and Rim101 pathways. The networks on the left (A,C,E) depict the effects of the inducing signals on each pathway and the effects of each pathway on three developmental phenotypes: pseudohyphal growth (B), complex colony morphology (D), and sporulation (F). Arrows indicate enhancing/activating effects; bars indicate repressive effects. The dashed lines indicate pathway activity in the face of repressive signals.