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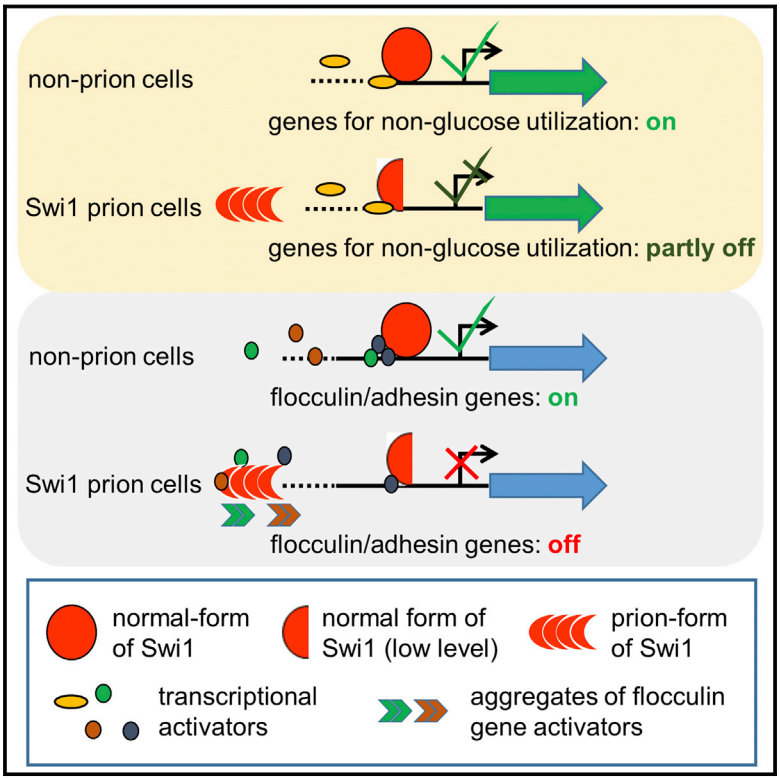
The Yeast Prion [*SWI*$^+$] Abolishes Multicellular Growth by Triggering Conformational Changes of Multiple Regulators Required for Flocculin Gene Expression

Graphical Abstract



Highlights

- The yeast prion [*SWI*$^+$] abolishes flocculin (*FLO*) expression and multicellularity
- Insufficient Swi1 function is not the only cause of the defects in multicellularity
- Multiple *FLO* gene upregulators undergo conformational changes in [*SWI*$^+$] cells
- Some *FLO* gene upregulators can exist as prion-like aggregates in [*SWI*$^+$] cells

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In Brief

Du et al. report that the yeast prion [*SWI*$^+$] eliminates *FLO* gene expression and multicellularity. They demonstrate that multiple *FLO* gene upregulators undergo conformational changes in the presence of [*SWI*$^+$], changes that are responsible for the observed defects in multicellularity.

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The Yeast Prion [*SWI*$^+$] Abolishes Multicellular Growth by Triggering Conformational Changes of Multiple Regulators Required for Flocculin Gene Expression

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SUMMARY

Although transcription factors are prevalent among yeast prion proteins, the role of prion-mediated transcriptional regulation remains elusive. Here, we show that the yeast prion [*SWI*$^+$] abolishes flocculin (*FLO*) gene expression and results in a complete loss of multicellularity. Further investigation demonstrates that besides Swi1, multiple other proteins essential for *FLO* expression, including Mss11, Sap30, and Msn1 also undergo conformational changes and become inactivated in [*SWI*$^+$] cells. Moreover, the asparagine-rich region of Mss11 can exist as prion-like aggregates specifically in [*SWI*$^+$] cells, which are SDS resistant, heritable, and curable, but become metastable after separation from [*SWI*$^+$]. Our findings thus reveal a prion-mediated mechanism through which multiple regulators in a biological pathway can be inactivated. In combination with the partial loss-of-function phenotypes of [*SWI*$^+$] cells on non-glucose sugar utilization, our data therefore demonstrate that a prion can influence distinct traits differently through multi-level regulations, providing insights into the biological roles of prions.

INTRODUCTION

Prions are self-perpetuating protein conformations that are often associated with protein misfolding, aggregation, and amyloidogenesis (Prusiner, 1998). Although the term prion was originally used to describe PrP^{Sc}, a causative agent of the infectious neurodegenerative disease known as transmissible spongiform encephalopathy or prion disease, it has now been extended to include a large group of proteins in fungi and mammals that can also be transmitted as altered and self-propagating conformations (Cascarina and Ross, 2014; Crow and Li, 2011; Prusiner, 2012; Soto, 2012). In the budding yeast *Saccharomyces cerevisiae*, at least nine prion proteins have been identified (Crow and Li, 2011; Garcia and Jarosz, 2014; Suzuki et al., 2012). Yeast prions can be manifested as epigenetic modifiers of important cellular processes, including translation and transcription, resulting in distinct and heritable phenotypic changes (Crow and Li, 2011; Sugiyama and Tanaka, 2014; Tuite, 2015).

There are at least six transcription factors among the identified yeast prions (Crow and Li, 2011). This prevalence of transcription factors suggests that the prion-based conformational switch may play a role in transcriptional regulation. Although a number of studies have shed light on how prions modify transcription of yeast (Holmes et al., 2013; True et al., 2004), the impact on transcriptional regulation by prion remains to be fully understood. Comparing to gene mutations, prion-mediated regulation has the advantage of being not only heritable but also reversible, as well as responsive to extreme environmental changes (Halfmann and Lindquist, 2010; Tuite, 2013). In particular, prion conformational switch of a global transcriptional regulator like Swi1 or Cyc8 may robustly alter the yeast transcriptome by turning on or off the expression of many target genes simultaneously (Du et al., 2008; Patel et al., 2009). However, we are just at the beginning of this line of research, and definitive evidence, particularly the mechanisms through which yeast prions impose their impacts on transcription, remains to be elucidated.

S. cerevisiae can undergo a reversible change from a single-cell form to multiple distinct multicellular forms, and it is believed that such a dimorphic switch is important for yeast to survive extreme environmental conditions (Gimeno et al., 1992). Yeast multicellular features include flocculation, biofilm formation, invasive growth of haploid cells, and pseudohyphal development of diploid cells. Flocculins or adhesins, a group of lectin-like cell wall proteins, are known to be important for yeast to exhibit the described multicellular growth features (De Las Peñas et al., 2003; Dranginis et al., 2007). In *S. cerevisiae*, flocculins are encoded by the *FLO* gene family, which includes the genes of *FLO1*, *FLO5*, *FLO9*, *FLO10*, and *FLO11* (Guo et al., 2000; Hahn et al., 2005). These genes may have been evolved via gene duplication, and they often undergo genomic silencing, noncoding RNA insertion, and rearrangement, thus their expression and