Facultative sex regulated by a prion-like switch

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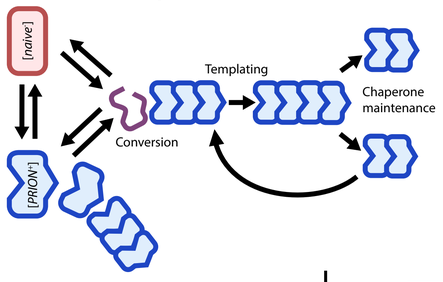
Abstract

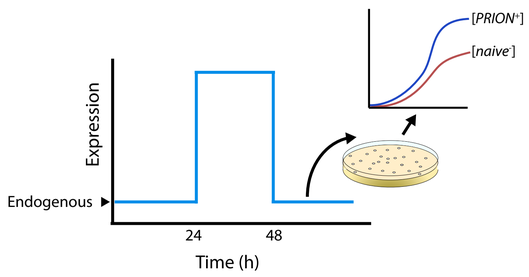
Prions are proteins that can adopt multiple conformations, at least one of which is self-templating. Ensuing changes in protein activity and subsequent adaptive traits are heritable over long biological timescales. In budding yeast, transient overexpression of different ORFs can induce prion-like states associated with fitness benefits in various conditions. The induction of these prions influences cellular decisions to optimize growth, often in a manner sensitive to the environment through shifts in proteostasis. For budding yeast, mating is an important, well-characterized decision. Protein-based systems rooted in mechanisms of self-templating aggregation, in the case of Whi3, and cytosolic titration, in the case of Far1, inform this decision with memories of pheromone exposure. However, Whi3 aggregation is not transmitted trans-generationally, and the Far1 titration system does not benefit from the meso-scale stability afforded by self-templating. Overexpression of *SLI15*, a component of the chromosome passenger complex (CPC) regulator of mitosis, results in a prion-like state with an insensitivity to mating pheromone, referred to as *Ste*$^+$. Acquisition of *Ste*$^+$ modulates histone patterning and global transcriptomic repression, downregulating the mating pathway. This novel behavior associated with a CPC component represents a molecular relationship between the decisions to reproduce sexually and asexually, delineated by a prion-like memory.

Yeast prions: Protein-based inheritance



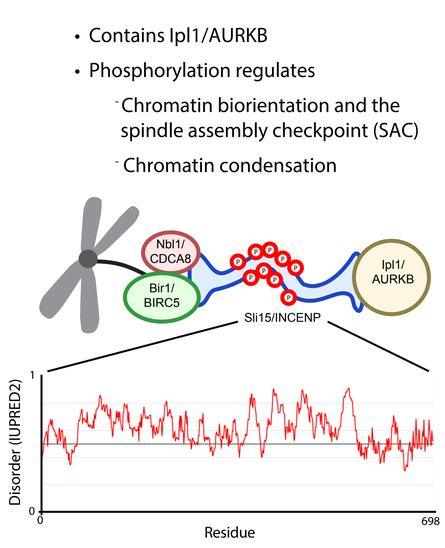
- Cytoplasmic inheritance
- Chaperone dependent

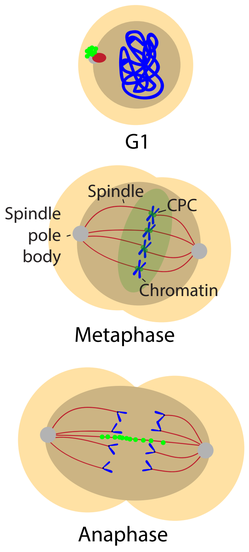
- Environmentally sensitive
- Inducable through stress response and overexpression

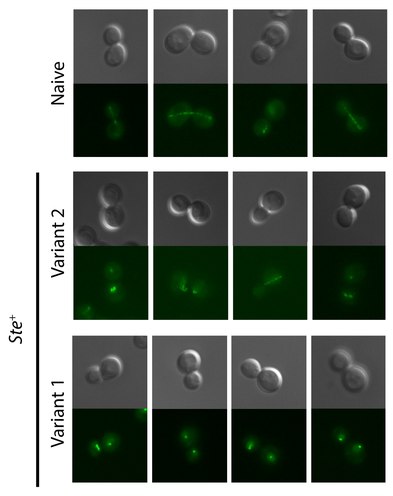


Overexpression of *SLI15* induces a heritable change in Sli15 distribution

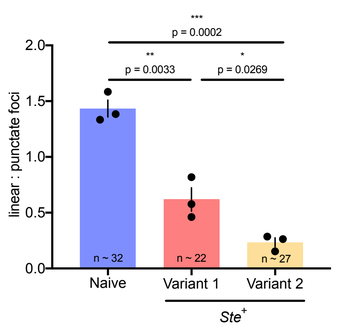
- Contains Ipl1/AURKB
- Phosphorylation regulates
  - Chromatin biorientation and the spindle assembly checkpoint (SAC)
  - Chromatin condensation



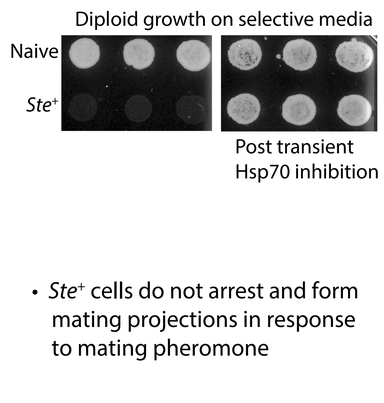




- Transient overexpression of *SLI15* results in isolates with altered Sli15-GFP distribution
- These isolates are unable to mate, and referred to as *Ste*$^+$

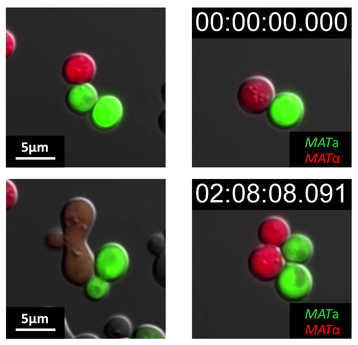


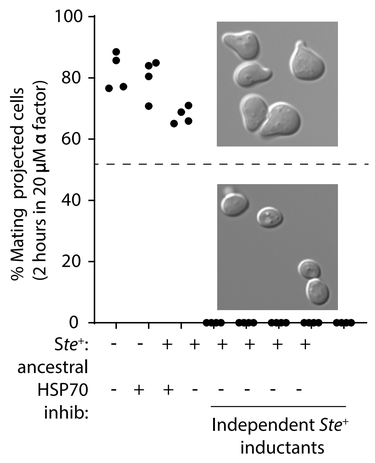
Overexpression of *SLI15* induces a novel state characterized by heritable sterility: *Ste*$^+$

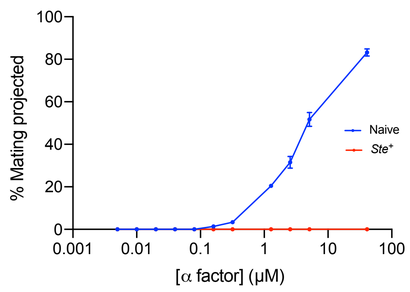


- *Ste*$^+$ cells do not form diploid progeny
- *Ste*$^+$ sterility is chaperone (Ssa1) dependent

- *Ste*$^+$ cells do not arrest and form mating projections in response to mating pheromone







Ste$^+$ cells maintain checkpoint related CPC activity

SAC metaphase arrest

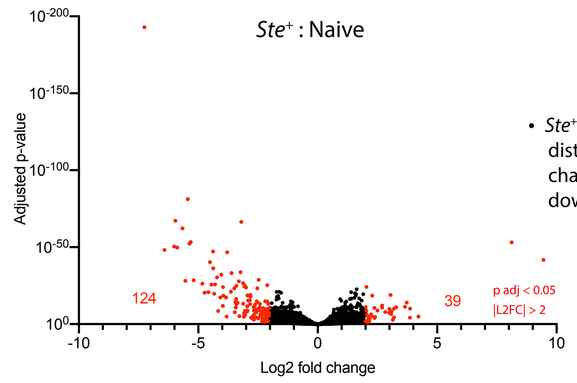
- *Ste*$^+$ cells do not exhibit compromised SAC metaphase arrest in response to nocodazole treatment

- *Ste*$^+$ cells maintain phosphorylation of kinetochore component NDC80 at Ipl1-specific S37

Summary

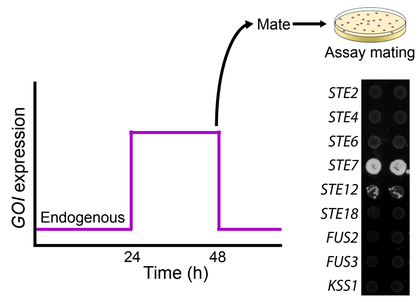
- Transient overexpression of *SLI15* can induce the heritable, prion-like state: *Ste*$^+$
- *Ste*$^+$ encompasses altered Sli15 distribution, histone modification, transcription, and mating dynamics
- Working hypothesis: Altered CPC activity in *Ste*$^+$ cells results in a distinct chromatin state via rewiring of chromatin condensation pathways. This chromatin state enforces a transcriptional profile underlying the observed fitness and mating phenotypes.

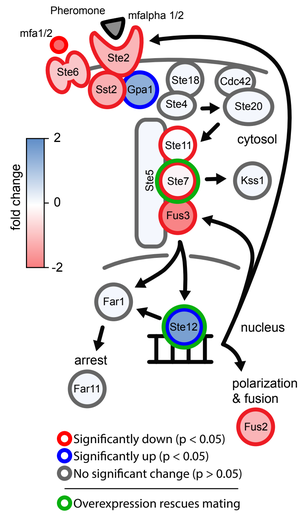
Ste$^+$ cells harbor a distinct transcriptome and mating pathway rewiring



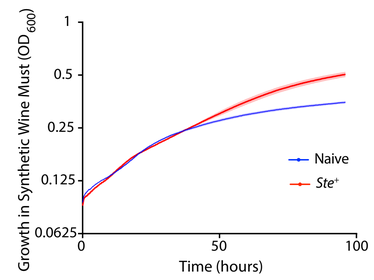
- *Ste*$^+$ cells harbor a distinct transcriptome characterized by downregulation

- *Ste*$^+$ cells display subtle downregulation of several mating pathway components
- Among mating pathway components, overexpresion of either *STE7* or *STE12* is sufficient to transiently rescue mating



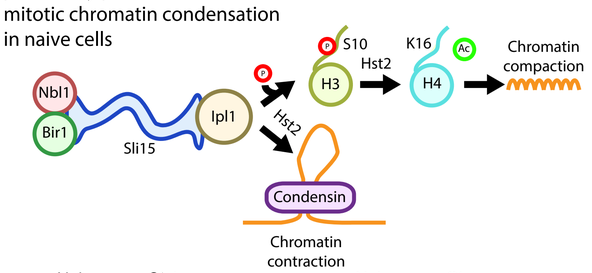


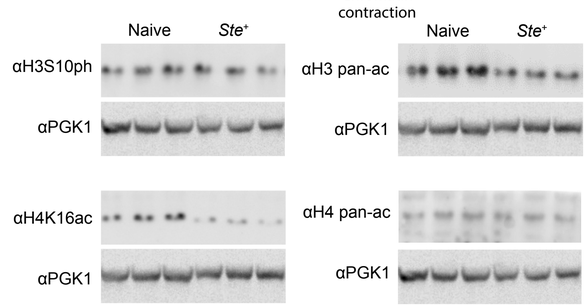
- *Ste*$^+$ cells have increased fitness in conditions predicted by transcriptomic analysis
- The transcriptional and phenotypic characteristics of the *Ste*$^+$ state extend beyond mating



Ste$^+$ cells demonstrate altered histone patterning

- Ipl1 activity promotes mitotic chromatin condensation in naive cells





- *Ste*$^+$ cells maintain naive H3S10ph levels
- *Ste*$^+$ cells display decreased H4K16ac

Acknowledgements

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