Feasting, fasting and fermenting: glucose sensing in yeast and other cells

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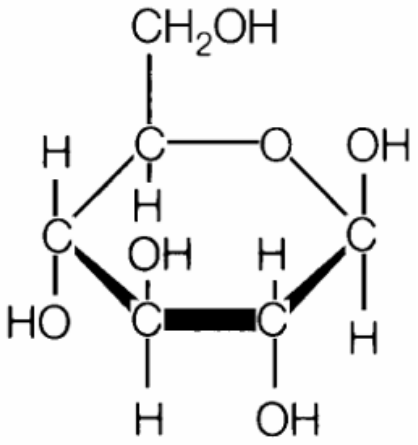
Article Overview

- Glucose is a primary fuel for most cells
- Ability to sense level of glucose in the environment is important for survival and proper functioning of cells
- Major effect of glucose on the cells is altering the gene expression

- Study of model organism-*Saccharomyces cerevisiae*- to understand glucose related pathways in humans and other organisms

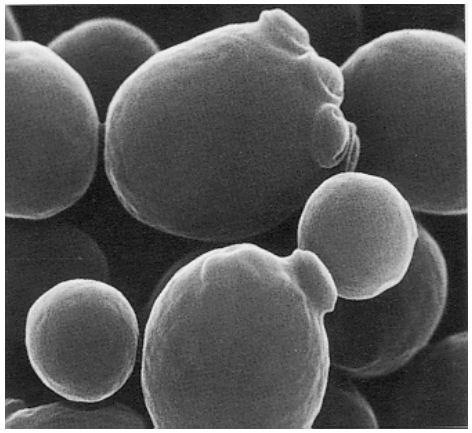
Background

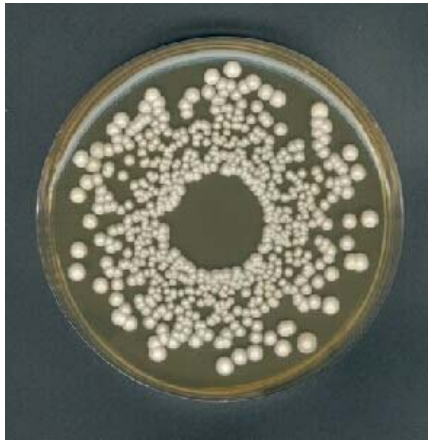
- **Glucose** is the ultimate end product of our meals
  - primary fuel for microorganisms and most abundant monosaccharide in nature
  - Preferred food choice of yeast but not the only one
    - Galactose, sucrose, maltose,
- It is present in our blood at constant levels
- Imbalances and changes in the blood glucose levels lead to *diabetes*
  - Mechanism for glucose transport (disposal) is indirect in humans, controlled by hormone insulin
- Major effect of glucose on both mammalian and yeast cells is the increase the number of glucose transporters in the cell membrane



Subject of Study

- Yeast *Saccharomyces cerevisiae*
  - Regulation of glucose sensing is important for fermentation (metabolism) of this organism
- Commonly used as bakers' yeast, brewers' yeast, research purposes and others…





Gene expression and glucose

- In ***S. cerevisiae***
  - two major effects of **glucose** on gene expression

1. Represses expression of genes required for respiratory pathway, and enzymes for utilization of alternative carbon sources
   - Mig1 transcriptional repressor
   - Snf1 protein kinase
2. Induces expression of genes required for utilization of glucose such as glycolytic enzymes and glucose transporters
   - Rgt1 transcriptional repressor
   - SCF^{Grr1} protein complex

Glucose repression mechanism

- Components
  - Mig1, Snf1protein kinase, glc7 protein phosphatase, Reg1

- **Mig1**
  - Gene repressor whose location is regulated by glucose
    - Nucleus in HG, Cytoplasm in LG
- **Snf1 protein kinase**
  - Mediates phosphorylation of Mig1
    - Phosphorylated Mig1 leaves nucleus
  - Functions fully only in LG

Glucose repression Signal

- **Snf1 protein kinase**
  - Its activation leads to increased ATP production
  - Controls use of alternative carbon sources
  - Snf1 PK regulation
    - Could be controlled by AMP:ATP but there is no evidence of direct activation AMP (homology to human AMPK)
    - Phosphorylation
    - Interaction with its subunits
    - Possible existence of Snf1 kinase kinase
  - More research needed

Glucose-Mediated Regulation of Snf1

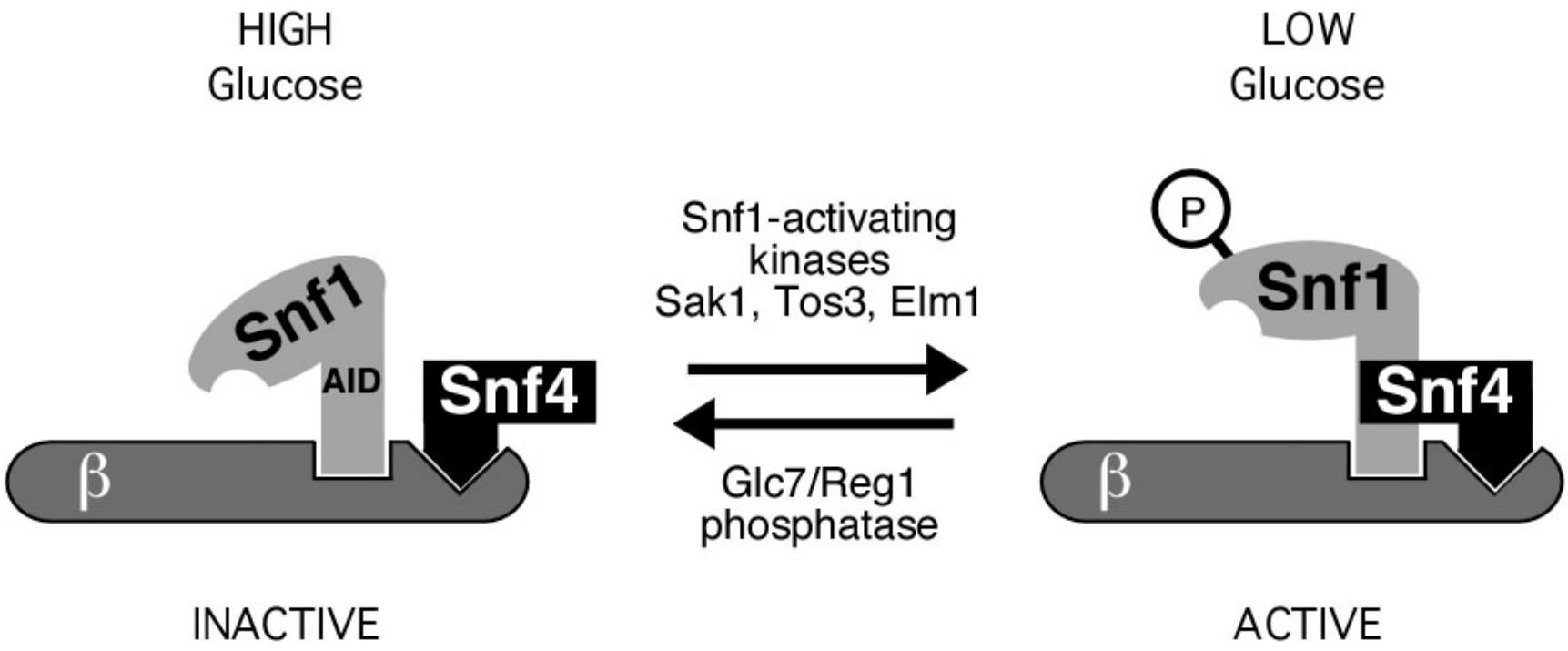
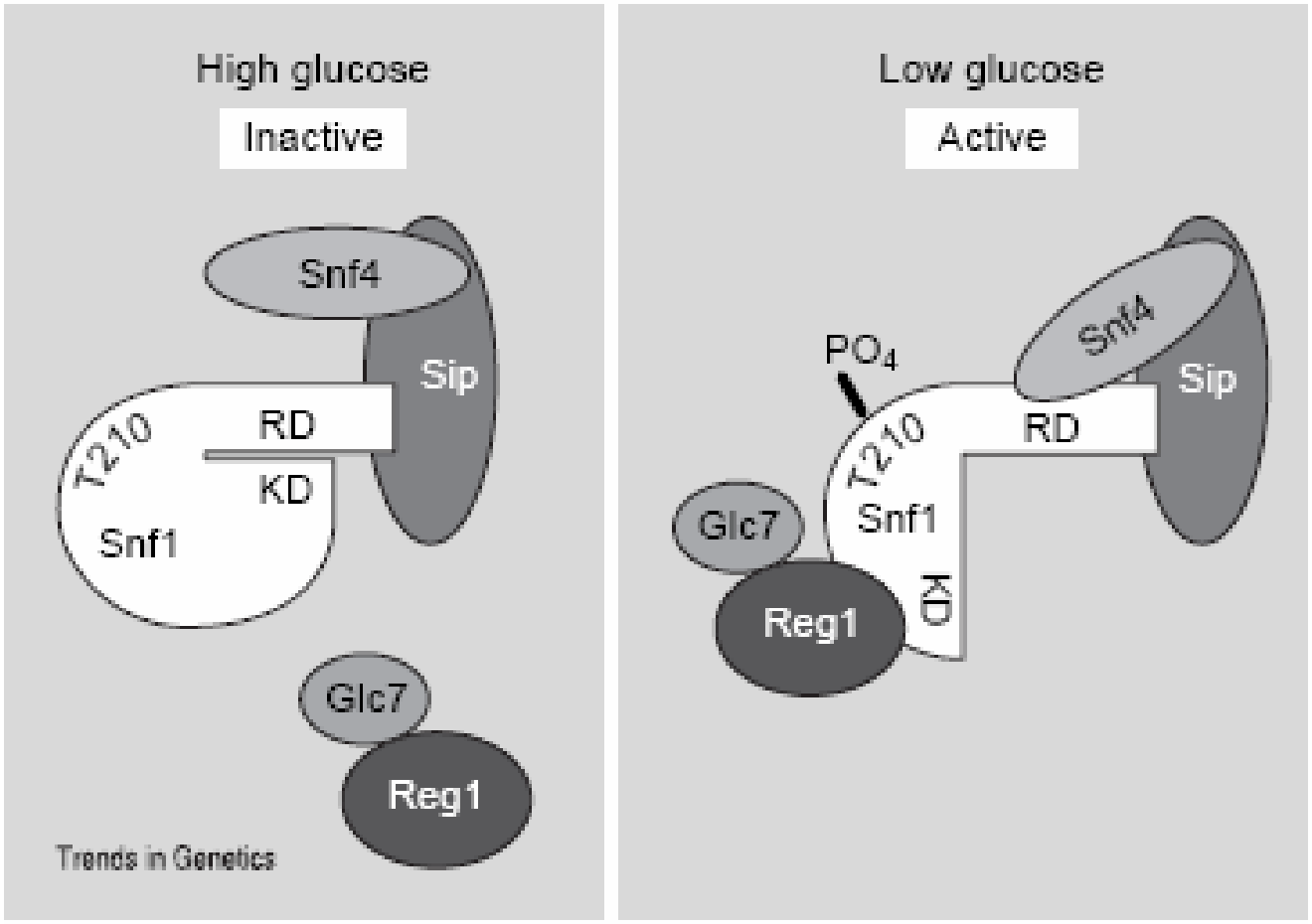


FIGURE 2. Regulation of Snf1



Proposed mechanism of regulation of Snf1 kinase function (after Fig. 1 of Ref. 20; see text for details). Abbreviations: KD, Snf1 kinase domain, responsible for catalytic function of the enzyme; RD, Snf1 regulatory domain that interacts with the kinase domain, and with Snf4; T210, threonine residue conserved in many kinases that must be phosphorylated for the Snf1 kinase to be active.

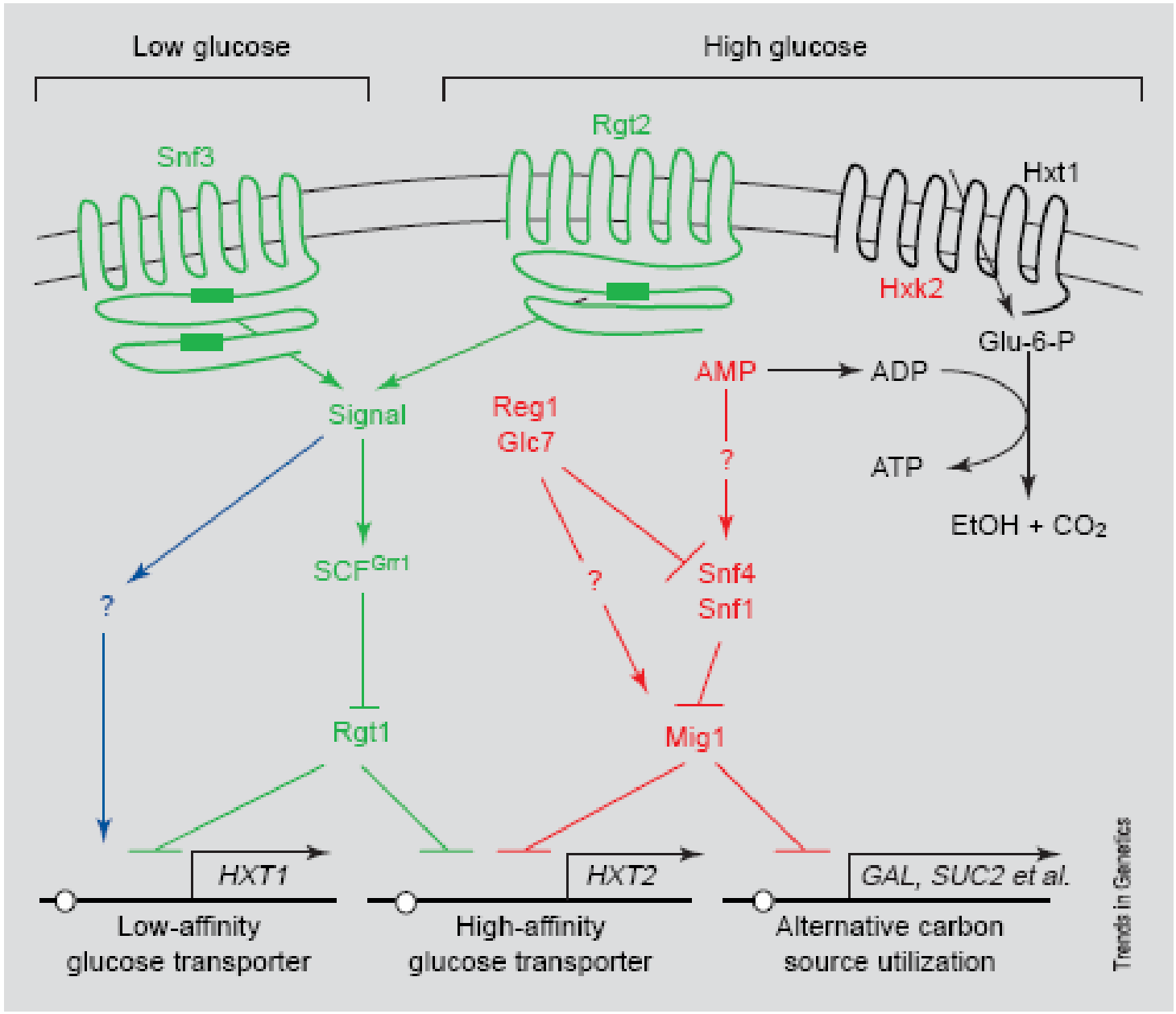
Glucose Induction Mechanism

- Mechanism that ensures that yeast can live well on glucose
  - Fermentation generates only few ATP
  - Large amounts of glucose needed for its production
  - Glucose induces expression of glycolysis genes as well as HXT glucose transporters genes
  - High and Low affinity transporters
- Enables yeas to detect presence and amount of glucose in the environment
  - Appropriate gene expression
  - Rgt1 transcriptional repressor
  - SCFGrr1 multi-protein complex, inhibits repressor function
  - Snf3 and Rgt2

Glucose Induction Signal

- Glucose signal is generated by Snf3 and Rgt2 glucose sensors residing in the cell membrane
  - Glucose receptors present
- Glucose signal and its nature
  - Glucose binds and induces conformational change in receptors which in turn alter the events inside of the cell
  - Long C-terminal tails facilitate these changes
- No glucose metabolism needed for the generataion of the signal
- Signal eventually induces expression of HXT transport genes

FIGURE 1. Glucose repression and induction



Summary

- Glucose is an important signaling molecule in mammals and other microorganisms
- Yeast *S. cerevisiae* has a novel system for regulating glucose sensing
  - Signal proteins Snf3 and Rgt2 can sense presence and amount of glucose in the environment
  - Transport proteins activity depends on the glucose levels outside
  - Mig1 and Snf1 protein kinase are important glucose sensing regulatory mechanisms
  - Glucose sensing effect the gene expression

Thank you!

Questions?