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

By: Mark Johnston
Presented by: Pavol Genzor
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, Snf1 protein 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

HIGH Glucose

Snf1

Snf4

β

INACTIVE

Sak1, Tos3, Elm1

Glc7/Reg1 phosphatase

LOW Glucose

Snf1

Snf4

β

ACTIVE

P
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 generation of the signal
- Signal eventually induces expression of HXT transport genes
FIGURE 1. Glucose repression and induction

Low glucose

- SNF3
- Signal (Reg1, Glc7)
- SCF^Grr1
- RGT1

High glucose

- RGT2
- AMP
- ADP
- Glu-6-P
- ATP
- EtOH + CO2

- HXT1
  - Low-affinity glucose transporter

- HXT2
  - High-affinity glucose transporter

- GAL, SUC2 et al.
  - Alternative carbon source utilization
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?