Title – "Glucose Regulation of the Paralogous Glucose Sensing Receptors Rgt2 and Snf3 of the Yeast *Saccharomyces Cerevisiae"*

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Glucose is an essential source of energy that fuels both aerobic and anaerobic cellular respiration. Not only a nutrient, glucose serves as a signaling molecule that controls cell growth and development. A variety of devasting metabolic disorders such as obesity, diabetes, and cancer arise from defects in glucose metabolism. The yeast *Saccharomyces cerevisiae* senses extracellular glucose levels through the two paralogous glucose sensing receptors Rgt2 and Snf3, which appear to sense high and low levels of glucose, respectively. Rgt2 and Snf3 are expressed at different levels in response to different glucose concentrations. Snf3 expression is repressed by high glucose, whereas Rgt2 is turned over in response to glucose starvation. As a result, Rgt2 is predominant in cells grown on high glucose, whereas Snf3 is more abundant of the two paralogs in cells grown on low glucose. When expressed from a constitutive promoter, however, Snf3 behaves like Rgt2, being able to transduce the high glucose signal that induces *HXT1* expression. Of note, constitutively active Rgt2 does not undergo glucose starvation-induced endocytic downregulation, whereas signaling defective Rgt2 is constitutively targeted for vacuolar degradation. These results suggest that glucose protects Rgt2 from endocytic degradation and reveal a previously unknown function of glucose as a signaling molecule that

regulates the stability of its receptor. Expression of Rgt2 and Snf3 is regulated by different mechanisms: Rgt2 expression is highly regulated at the level of protein stability; Snf3 expression is mainly regulated at the level of transcription. The difference in the roles of Rgt2 and Snf3 in glucose sensing is a consequence of their cell surface abundance rather than a result of the two paralogous proteins having different functions.