Control of energy metabolism under salt stress in the yeast *Saccharomyces cerevisiae*

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Abstract

NaCl is present in almost all natural environments. Salinity stress has therefore become a major challenge for biologists and agriculturalists due to the impact on crop yield and food production throughout the world. The understanding of how living organisms respond and adapt to and eventually tolerate salt stress still remains mysterious to a large extent. The budding yeast *Saccharomyces cerevisiae* has been proven to be a fruitful organism to study salt stress. The fundamental cellular processes and the molecules involved are conserved from yeast to plants and human. A better understanding of the mechanism by which yeast cells respond to salt stress and adjust ion homeostasis can therefore be applied to higher eukaryotes, such as plants and animals. It has been suggested that yeast cells acquire salt tolerance by regulating the gene expression of *ENA1*, which encodes the Na^+ extrusion pump. Mutants lacking Ena1 confer hypersensitivity to NaCl. Therefore, Ena1 has been considered to be the key component for yeast sodium tolerance.

In this thesis, I present a novel component, Gis4, which is involved in acquisition of salt tolerance. Our data shows a decreased expression of *ENA1* in a *gis4Δ* mutant. Genetic evidence indicates that Gis4 exerts its function in salt tolerance together with the Snf1 protein kinase. Yeast Snf1 (homologous to plant and mammalian AMPK) is highly conserved and is one of the major components involved in regulating glucose metabolism. Snf1 is inactive in the presence of glucose and becomes activated primarily by phosphorylation at threonine 210 within its activation loop when glucose is deprived. Its activation results in the phosphorylation and inactivation of its well known downstream target Mig1, a transcriptional repressor bound to the promoter of many glucose repressed genes. Phosphorylated Mig1 translocates from the nucleus to cytoplasm and is no longer able to repress. In this study we found that Snf1 was also crucial for salt tolerance. A *snf1Δ* mutant displays a diminished expression of *ENA1* and becomes sensitive to salt. It is also shown that salt stress induces Snf1 phosphorylation at T210. Interestingly, the activation of Snf1 under salt stress does not lead to phosphorylation of Mig1 but appears to control other targets such as Nrg1, a transcriptional repressor for stress responses. However, regardless of the type of stress, activation of Snf1 is dependent on any of the three upstream kinases Sak1, Elm1 or Tos3. Among them, Sak1 appears to be the major kinase for the phosphorylation of Snf1 under salt stress. Intriguingly, Elm1 not only phosphorylates Snf1 but also plays a distinct role in the response to salt stress. These results suggest that the Snf1 protein kinase plays roles in response to a variety of stress conditions through different downstream targets to mediate transcription of different sets of genes. The underlying mechanisms will be subject of futur