UDC 547.458.223.3:577.124:663.14
ISSN 1330-9862

review

(FTB-1317)

Regulation of Maltose Transport and Metabolism in *Saccharomyces cerevisiae*

Srđan Novak, Vesna Zechner-Krpan and Vladimir Marić*

Faculty of Food Technology and Biotechnology, University of Zagreb, Pierottijeva 6, HR-10 000 Zagreb, Croatia

Received: March 22, 2004
Accepted: July 6, 2004

Summary

Maltose metabolism in the yeast *Saccharomyces cerevisiae* is of great importance both for academic and industrial researchers. It requires the presence of at least one of five independent *MAL* loci: *MAL1*, *MAL2*, *MAL3*, *MAL4* and *MAL6*. Each active locus is made of three genes: two structural genes that encode intracellular enzyme maltase and transport protein for maltose, and the third gene that encodes positive regulatory protein. Maltose is transported unchanged into the cell with the help of specific transmembrane transporter, and then it is hydrolysed by the intracellular maltase into two glucose units which are then channeled through the glycolytic pathway. The maltose metabolism in *S. cerevisiae* is under the control of three general regulation mechanisms: induction, glucose repression and glucose inactivation. Powerful tools of molecular biology have brought many important discoveries in transport, metabolism and regulation of the uptake of maltose in yeast cells at the molecular level. Although the knowledge on these phenomena is far from being complete, it helps us understand the sugar preference in industrial fermentations on complex substrates but also how glucose effects gene expression and entire metabolic activity in other organisms.

Key words: maltose, *Saccharomyces cerevisiae*, transport, metabolism, regulation

Introduction

Yeast *Saccharomyces cerevisiae* has been well known for its use in households and industrial production of fermented beverages and baker's yeast. Being a unicellular eukaryote it has been intensively studied as a model organism for scientific researh in biochemistry and genetics. Maltose metabolism in yeast *S. cerevisiae* is of great importance both for academic and industrial researchers. Maltose is a product of the starch hydrolysis of the action of amylases and it can be found wherever degradation of starch takes place. It makes about 55 % of fermentable sugars in traditional malt worts of brewing and distilling industry (*1*). Although it seems that glucose and galactose metabolisms (*2*,*3*) have been more intensively studied than that of maltose, a large body of research done in recent years has filled that gap substantially. Powerful tools of molecular biology have brought many important discoveries on transport, metabolism and regulation of maltose uptake in yeast cells at molecular level. The increased amount of knowledge could bring many improvements in the industrial practice as well.

Maltose Metabolism and Genes – An Overview

Maltose 4-O-(α-D-glucopyranosyl)-α-D-glucopyranose is transported into the cell unchanged with the help of

* Corresponding author; E-mail: vzkrpan@pbf.hr

specific transmembrane transporter, and then it is hydrolysed by the intracellular enzyme maltase (α-glucosydase or α-D-glucopyranosyl-glucohydrolase E.C. 3.2.1.20.) in two units of glucose, which are then channeled through the glycolytic pathway (*4,5*).

The maltose metabolism in *S. cerevisiae* is under the control of three general regulation mechanisms: induction, glucose repression and glucose inactivation. The presence of maltose in the cell environment is necessary for the induction of synthesis of maltase enzyme and maltose transporters. The carbon source on which yeast was precultivated does not influence the induction rate (*6*). With the addition of glucose into the maltose medium, total inactivation of maltose transport system occurs in 90 min (*7,8*). During that period maltase activity remains almost unchanged. When the cells are shifted back into the pure maltose medium, fast regeneration of maltose transport system is observed (in approximately 1 h). The regeneration requires protein synthesis *de novo* (*7,9*). Fructose has similar effects on maltose metabolism as glucose (*10*). Those observations point out that glucose represses both structural genes for maltose metabolism and inactivates the maltose transporters, but not the maltase activity.

Maltose metabolism requires the presence of at least one of five independent *MAL* loci that had been identified in *S. cerevisiae*: *MAL1*, *MAL2*, *MAL3*, *MAL4* and *MAL6*. These loci are located near the telomeres (*11*): *MAL1* on the chromosome VII, *MAL2* on the chromosome III, *MAL3* on the chromosome II, *MAL4* on the chromosome XI and *MAL6* on the chromosome VIII (*12,13*). The analysis of complementation (*14–17*) and Southern blot analysis (*18,19*) pointed at high level of homology between those loci in the DNA fragment that is about 9.0 kb long. Each active locus is made of three genes: one encodes maltase (MALS), other is a transport protein for maltose (MALT) and the third is positive regulatory protein with *trans* activity (MALR) (*14–16,20–24*). In one of the alternative systems of nomenclature, a number is added to the name of the gene locus: *e.g. MAL61*, *MAL62* and *MAL63* correspond to *MALT*, *MALS* and *MALR*, respectively, of the *MAL6* locus.

Many *Saccharomyces* strains carry »cryptic« *MAL* loci that carry functional copies of some, but not all, of these genes (*19,25,26*).

The gene structure on *MAL6* locus is *MAL63-MAL61-MAL62* (*15,17,23,27,28*). All three genes are necessary for maltose metabolism. The *MAL61* and *MAL62* genes transcribe divergently from the chromosome region around 700 bp, which contains promoters for both genes. The transcription of both genes is strongly induced with maltose, and repressed with glucose (*15,23*).

Mal61 and Maltose Transport

Early studies of maltose transport into the cells of brewer´s and baker´s yeast have revealed the presence of one transport system with the K_m of 4 mM (*7*). Seaston *et al.* (*29*) were the first to notice that transport of maltose and most amino acids in the yeast cell occurs with the absorption of protons from the medium, and Serrano (*30*) postulated that maltose transport occurs as proton-symport. One proton is transported with each molecule of maltose, and K_m for maltose is 4 mM. Busturia and Lagunas (*9*) reported the discovery of the second transport system for maltose that had much lower affinity (K_m=70 mM). The V_{max} of that low-affinity system was 4 times higher than in the high-affinity (low K_m) system. The doubt of the relevance and real existence of the low-affinity system was argued later by the same group (*31*). Other groups brought more evidence for the low-affinity maltose transport system (*1,32)* indicating the existence of strain-specific qualitative and quantitative variations in maltose transporters (both in K_m and V_{max}), particularly when laboratory and production strains are compared. A new body of evidence that low-affinity maltose transport is an experimental artifact has recently been reported (*33*).

The isolation of *mal61* mutant (*28*) enabled the cloning and sequencing of the gene *MAL61* (*34*). The nucleotide sequence showed that the gene *MAL61* encodes an integral membrane protein with high degree of homology with other sugar transporters in eukaryotes. The research on transport kinetics of maltose in mutants which have just one transporter gene (*MAL61* or *MAL11)* showed that those genes encoded high-affinity (low K_m) transport system, which is maltose induced and subject to glucose-induced inactivation (*35*).

Studies on electrochemical proton gradient-driven amino acid transporters in *S. cerevisiae* indicated that these systems are virtually unidirectional (*36,37*) and it was explained that the accumulation of solutes inhibits further uptake (so called *trans*-inhibition). As the intracellular substrate concentration increases, the *trans*-inhibition will lead to the decrease in transport activity, as was reported for bacterial transport systems involved in osmoregulation (*38*).

For some other transport systems it seems that the opposing directions of translocation are kinetically different. Van der Rest *et al.* (*39*) studied hybrid membranes with overexpressed Mal61 and concluded that maltose transport is reversible, because influx as well as eflux transport can be observed. However, the orientation of the maltose transporters in hybrid membranes is mostly random, which could explain the observed phenomenon. Studies with the mutant that lacks the maltase enzyme have shown that Mal61 facilitated bidirectional transport that was not inhibited by the presence of intracellular maltose (*40*).

Mal63 and Maltose Induction

Protein Mal63 is the product of *MAL63* gene. It is a regulatory protein necessary to induce the transcription of two structural genes *MAL61* and *MAL62*. It encodes a predicted 470-residue protein (*41,42*). Mutation in gene *MAL63* unables the induction of expression of genes *MAL61* and *MAL62* and these mutants cannot use maltose as the only carbon source. In deletion mutants, inducible transcripts of genes *MAL61* and *MAL62* could not be found. Suppressors of mutant *mal63* carry constitutive expression of *MAL61* and *MAL62* genes, but are still sensitive to glucose repression (*17*). Very similar structure, function and activity of gene regulation were reported for the *MAL1* locus (*24*).

The regulator protein Mal63 belongs to the same family of C_6 zinc cluster proteins as Gal4 (*27,41*). A cysteine-rich DNA-binding domain similar to the Gal4 DNA--binding domain is found in the N-terminal 100 residues (*43*), and is capable of sequence-specific binding to the UAS_{MAL}. In contrast to Gal4, it is a dimer, found even in the absence of DNA. It lacks acidic or glutamine-rich regions, which appear to be associated with the capacity to activate transcription in other systems. It also activates *MAL61* and *MAL62* by binding to three sequences in the divergent *MAL61–62* promoter region with the parallel recognition motif (*44*). The DNA recognition motif for Mal63 has not been clearly established. It was first suggested that the sequence GAAA(A/T)TTTCGC could be important (*45*) and was found twice in 68 bp region. This region is situated between the *MAL61* and *MAL62* genes and is necessary for their maltose-induced expression. A footprint assay revealed three protected sites in the *MAL61-MAL62* promoter, but neither corresponded to this sequence (*44*). One has the sequence $CGGN_6CGG$ (*46*), the other has the sequence $CGCN_6CGC$ and the third one looks like a half-site sequence. A similar motif, $CGGN_6CGC$, has a sequence in the promoter of *MAL63* itself, which binds Mal63. And finally, in all these sequences, the N_6 region is very AT rich.

There is still no clear information about the mechanism by which Mal63 is activated in the presence of maltose, although it has been speculated that maltose may bind to Mal63, yielding a conformation with functional activity (*47*). Constitutive alleles of *MAL63* or the wild type allele of *MAL43* (an equivalent gene in the *MAL4* locus) have multiple amino acid substitutions in the C-terminal region and may adopt the active conformation, even in the absence of maltose (*47*).

The intracellular maltose in *Saccharomyces cerevisiae* is sufficient to induce *MAL* gene expression (*48*), but there is a great possibility that the true inducer is a maltose metabolite and not maltose. There is a low level of intracellular maltose required to initiate induction and to maintain the induced state. Strains expressing defective maltose permeases exhibit a significant reduction in their maximal induced levels of maltase activity, and the induction correlates well with the reduced rate of maltose transport capacity of these strains. Moreover, very low levels of maltose transport cause a delay in maltase induction when extracellular maltose concentration is limited. Both findings suggest that the accumulation of intracellular maltose to a threshold level is needed to initiate the induction and that the threshold level is rather low (*43*). Maltose permease does not appear to function as a maltose sensor (*48*), but intracellular maltose could be sufficient to stimulate *MAL* gene induction. The *Saccharomyces* maltose permease could also have a sensor-like role in the induction. The constitutive high--level expression of Mal61 maltose permease suppresses the defective *mal13*-encoded *MAL*-activator suggesting a possible role in the induction for maltose permease. One possible mechanism by which constitutive Mal61 permease expression could suppress the defective *mal13* gene is the specific binding of the activator. Mal63 and other *MAL*-activators contain several regions important in negative regulation (*49,50*). Under uninduced growth conditions, the permease might sequester the *MAL*-activator at the plasma membrane and thereby prevent the *MAL*--activator from entering the nucleus and activating *MAL* gene transcription. Conformational changes in maltose permease induced by maltose transport might destabilise the putative interaction between maltose permease and the *MAL*-activator, resulting in *MAL*-activator release, its nuclear entry and *MAL* gene activation. Careful studies of Wang *et al.* (*48*) indicated that maltose permease serves solely as a maltose transporter. It accumulates intracellular concentration of maltose to levels sufficient for both the induction of *MAL* gene expression and the provision of an energy source for growth. In the cells grown under uninduced conditions, the basal low level of maltose permease expression is sufficient to transport enough maltose into the cell when cells are transferred into maltose medium. This will allow the accumulation of intracellular maltose to levels that are adequate to promote the activation of *MAL*-activator and induce further structural gene expression. One likely possibility is that the *MAL*-activator itself binds to maltose directly. The Hsp90 molecular chaperon complex regulates maltose induction and stability of the *Saccharomyces MAL* gene transcription activator Mal63 (*51*). Those results identify the inducible *MAL*-activator as a target protein of the Hsp90 molecular chaperon complex and point to a critical role of chaperon function in alternate carbon source utilisation in *S. cerevisiae*. The genetic studies of the *MAL*-activator indicated that the stability and protein folding are important factors in *MAL*-activator regulation (*43,49,50,52).*

To date, constitutive mutations have been isolated at all of the *MAL* loci (*17,20,47,53–55*) and they all contain alterations in the *MAL*-activator (*13,47,52*). These results indicate that the *MAL*-activator could be regulated by very specific and complex intramolecular protein--protein interactions (*49,50*).

Glucose Repression and Glucose Inactivation

In the yeast *S. cerevisiae* the expression of a large number of genes is under the control and regulation of glucose (*56–58*). Thorough studies of the repression of glucose on galactose metabolism have shown that the phenomenon involves several elements such as glucose signalling, intermediary regulatory factors and proteins that act as specific transcriptional repressors and activators (*57*). The presence of glucose in the cell environment is detected with several membrane proteins like Rgt2, Snf3 and Hxt class of proteins (*59–61*). The glucose signal is then transferred through protein phosphorylation cascade that involves Hxk2 (hexokinase PII) and Reg1-Glc7 (protein phosphatase type-1). General glucose repression pathway ends up with Snf1 protein kinase that acts on Mig1 protein, a DNA-binding transcriptional repressor of the *SUC2*, *GAL* and *MAL* genes (*62–64*). The complex interaction between Mig1 complex and *MAL*-activator proteins like Mal63 seems to be the major step in specific glucose repression of maltose metabolism. The presence of glucose affects *MAL63* transcription and the formation of active conformation of Mal63 (*46,65*). The *MAL63* transcription is mediated largely by Mig1. The disruption of *MIG1* or the removal of a Mig1 binding site in the *MAL63* promoter increases the *MAL63*

expression (*64*). Glucose repression of the *MAL* genes decreases strongly in strains carrying constitutive alleles of the regulatory proteins Mal63 or Mal43 (*47*,*64*).

It is well known that glucose does not act on transcriptional level only, but also increases degradation rates of proteins and mRNA. It was observed that the presence of glucose comprises higher rates of *MAL62* mRNA (and probably *MAL61* mRNA) degradation (*66*).

However, regulation on protein level has been more thoroughly studied. It is well known that glucose, when added to yeast culture, rapidly inactivates many transporters and enzymes, *e.g.* maltose and galactose transporters, fructose-1,6-bisphosphatase and malate dehydrogenase. Such process is called catabolite inactivation (*67*). Catabolite inactivation of the maltose transporter Mal61 involves a rapid inactivation of the protein (*68–70*), which occurs in the vacuole after internalisation by endocytosis and does not require the proteasome function (*70*,*71*). By using mutants deficient in performing protein ubiquitination, it has been proven that ubiquitin pathway is involved in degradation of maltose transporter (*72*,*73*).

The catabolite inactivation of Mal61 requires two glucose-signaling pathways: the first one, independent from glucose transport, requires the presence of low-affinity glucose sensor Rgt2 (*74*,*75*) and the second involves high-affinity glucose transporters for glucose transport (*76*). The actual signal that triggers catabolite inactivation of the maltose transporter is still unknown. Hexoses, transported via the Hxt transporters, galactose and even maltose itself may elicit catabolite inactivation of the maltose transporter (*77*,*78*). Catabolite inactivation of the maltose transporter cannot be triggered by maltose itself, but maltose enhances the catabolite inactivation inflicted by galactose (*78*). Reg1/Glc7 phosphatase complex is involved in the regulation of Snf1 kinase complex that acts as a main regulator of glucose repression pathway. It has recently been found that Reg1/Glc7 complex is also involved in the transduction of the glucose signal in the catabolite inactivation process. The mechanism involves Bmh1 and Bmh2, the members of the 14-3-3 protein family that participates in the regulation of many physiological processes (*79*).

It is still obscure which is the signalling molecule for glucose repression and inactivation, although there is more evidence that a metabolite derived from maltose triggers the catabolite inactivation of the maltose transporter. The accumulation of intracellular glucose cannot be a trigger for catabolite inactivation because 6-deoxyglucose was unable to trigger catabolite inactivation of Mal61. Another glucose analogue, 2-deoxyglucose, can be phosphorylated but cannot be metabolised further in the glycolytic pathway (*32*,*80–82*). In the presence of 2-deoxyglucose Mal61 is inactivated, indicating that metabolism of glucose beyond glucose-6P is not required to trigger catabolite inactivation. However, 2-deoxyglucose is not only a trigger for catabolite inactivation of the maltose transporter, but it is also an elicitor of catabolite repression. This suggests a role for early glycolytic intermediates in catabolite inactivation of the Mal61 protein. Randez-Gil *et al.* (*83*) suggested the accumulation of hexose phosphates as molecules that signal for catabolite repression and inactivation.

However, recent studies have shown that there is no correlation between intracellular glucose-6-phosphate or ATP levels and the rate of catabolite inactivation of Mal61 protein (*40*).

Industrial Strains

Efficient maltose utilisation is crucial for many industrial applications of yeast such as brewing and baking. Regulation of maltose uptake and metabolism has been extensively studied for that reason, but mainly in laboratory haploid and diploid strains. On the other hand, industrial strains are mostly polyploid with more obscure genetic background (*1*). Some strains show an undesirable decrease in CO_2 gassing rate in the second hour after the inoculation in plain (unsugared) dough. These strains are termed lagging strains (*84*,*85*). Recent studies on lagging and nonlagging phenotype in industrial strains have shown that nonlagging strains have high level of maltase and maltose permease activity in noninduced conditions (*e.g.* when grown on galactose or ethanol) indicating the existence of noninduced/nonrepressed mode of regulation of maltose metabolism. Careful genetic studies have proven that nonlagging phenotype can be produced by mutation in MALx3 gene that codes a positive transcriptional regulator of maltose metabolism (*84*,*85*), giving thus new possibilities for improvement of industrial strains by genetic engineering techniques (*86*).

Conclusions

Intensive studies on regulation of maltose metabolism in yeast *S. cerevisiae* have shown a lot of similarities with other sugar degradation pathways where a significant number of regulatory proteins are involved. It seems likely that the analysis of these pathways can help us also to understand how glucose regulates gene expression and entire metabolic activity in other organisms.

References

1. R. M. Crumplen, J. C. Slaughter, G. G. Stewart, *Lett. Appl. Microbiol. 23* (1996) 448–452.
2. S. Novak, V. Marić, *Kem. Ind. 44* (1995) 341–353.
3. S. Novak, V. Zechner-Krpan, P. Raspor, V. Marić, *Kem. Ind. 49* (2000) 433–441.
4. J. A. Barnett, *Adv. Carbohydr. Chem. Biochem. 32* (1976) 125–233.
5. D. G. Fraenkel, Carbohydrate Metabolism. In: *The Molecular Biology of the Yeast Saccharomyces: The Metabolism and Gene Expression*, J. N. Strathern, E. W. Jones, J. R. Broach (Eds.), Cold Spring Harbor Laboratory, Cold Spring Harbor, New York (1982) pp. 1–37.
6. N. R. Eaton, N. A. Khan, F. K. Zimmerman, *Yeast, 20* (1971) 47–48.
7. C. P. M. Gorts, *Biochim. Biophys. Acta, 184* (1969) 299–305.
8. R. A. de Kroon, V. V. Koningsberger, *Biochim. Biophys. Acta, 204* (1970) 590–609.
9. A. Busturia, R. Lagunas, *Biochim. Biophys. Acta, 820* (1985) 324–326.
10. M.-R. Siro, T. Lovgren, *Bakers Digest, 53* (1979) 24–28.

11. M. Carlson, *UCLA Symp. Mol. Cell. Biol. New Ser. 33* (1986) 241–250.

12. R. K. Mortimer, D. Schild: Genetic Map of *Saccharomyces cerevisiae*. In: *The Molecular Biology of the Yeast Saccharomyces: Life Cycle and Inheritance*, J. N. Strathern, E. W. Jones, J. R. Broach (Eds.), Cold Spring Harbor Laboratory, Cold Spring Harbor, New York (1982) pp. 641–651.

13. M. J. Charron, C. A. Michels, *Genetics, 116* (1987) 23–31.

14. G. I. Naumov, *Genetika, 12* (1976) 87–100.

15. R. B. Needleman, D. B. Kaback, R. A. Dubin, E. L. Perkins, N. G. Rosenberg, K. A. Sutherland, D. B. Forrest, C. A. Michels, *Proc. Natl. Acad. Sci. USA, 81* (1984) 2811–2815.

16. J. D. Cohen, M. J. Goldenthal, T. Chow, B. Buchferer, J. Marmur, *Mol. Gen. Genet. 200* (1985) 1–8.

17. R. A. Dubin, E. L. Perkins, R. B. Needleman, C. A. Michels, *Mol. Cell. Biol. 6* (1986) 2757–2765.

18. C. A. Michels, R. B. Needleman, *Mol. Gen. Genet. 191* (1983) 225–230.

19. R. B. Needleman, C. A. Michels, *Mol. Cell. Biol. 3* (1983) 796–802.

20. A. M. A. ten Berge, G. Zoutewelle, K. W. van de Poll, *Mol. Gen. Genet. 123* (1973) 233–246.

21. M. J. Goldenthal, J. D. Cohen, J. Marmur, *Curr. Genet. 7* (1983) 195–199.

22. J. D. Cohen, M. J. Goldenthal, B. Buchferer, J. Marmur, *Mol. Gen. Genet. 196* (1984) 208–216.

23. R. A. Dubin, R. B. Needleman, D. Gossett, C. A. Michels, *J. Bacteriol. 164* (1985) 605–610.

24. M. J. Charron, R. A. Dubin, C. A. Michels, *Mol. Cell. Biol. 6* (1986) 3891–3899.

25. T. Chow, M. J. Goldenthal, J. D. Cohen, M. Hegde, J. Marmur, *Mol. Gen. Genet. 154* (1983) 366–371.

26. C. A. Michels, R. B. Needleman, *J. Bacteriol. 157* (1984) 949–952.

27. Y. S. Chang, R. A. Dubin, E. L. Perkins, D. Forrest, C. A. Michels, R. Needleman, *Curr. Genet. 14* (1988) 201–206.

28. Y. S. Chang, R. A. Dubin, E. Perkins, C. A. Michels, R. B. Needleman, *J. Bacteriol. 171* (1989) 6148–6154.

29. A. Seaston, C. Inkson, A. A. Eddy, *Biochem. J. 134* (1973) 1031–1043.

30. R. Serrano, *Eur. J. Biochem. 80* (1977) 97–102.

31. B. Benito, R. Lagunas, *J. Bacteriol. 174* (1992) 3065–3069.

32. S. Novak, T. D'Amore, I. Russell, G. G. Stewart, *J. Ind. Microbiol. 6* (1990) 149–155.

33. R. E. Day, P. J. Rogers, I. W. Dawes, V. J. Higgins, *Appl. Environ. Microbiol. 68* (2002) 5326–5335.

34. Q. Cheng, C. A. Michels, *Genetics, 123* (1989) 477–484.

35. Q. Cheng, C. A. Michels, *J. Bacteriol. 173* (1991) 1817–1820.

36. A. A. Eddy, *Adv. Microb. Physiol. 23* (1982) 1–78.

37. J. Horak, *Biochim. Biophys. Acta, 864* (1986) 223–256.

38. B. Poolman, E. Glaasker, *Mol. Microbiol. 29* (1998) 397–407.

39. M. E. van der Rest, A. H. Kamminga, A. Nakano, Y. Anraku, B. Poolman, W. N. Konings, *Microbiol. Rev. 59* (1995) 304–322.

40. T. Harma, C. Brondijk, W. N. Konings, B. Poolman, *Arch. Microbiol. 176* (2001) 96–105.

41. J. Kim, C. A. Michels, *Curr. Genet. 14* (1988) 319–323.

42. P. Sollitti, J. Marmur, *Mol. Gen. Genet. 213* (1988) 56–62.

43. Z. Hu, A. W. Gibson, J. H. Kim, L. A. Wojciechowicz, B. Zhang, C. A. Michels, *Curr. Genet. 36* (1999) 1–12.

44. O. I. Sirenko, B. Ni, R. B. Needleman, *Curr. Genet. 25* (1995) 509–516.

45. J. Levine, L. Tanouye, C. A. Michels, *Curr. Genet. 22* (1992) 181–189.

46. L. Zhang, L. Guarente, *Genes Dev. 8* (1994) 2110–2119.

47. J. Wang, R. B. Needelman, *Genetics, 142* (1996) 51–63.

48. X. Wang, M. Bali, I. Medintz, C. A. Michels, *Eukaryot. Cell, 1* (2002) 696–703.

49. S. E. Danzi, B. Zhang, C. A. Michels, *Curr. Genet. 38* (2000) 233–240.

50. S. E. Danzi, M. Bali, C. A. Michels, *Curr. Genet. 44* (2003) 173–183.

51. M. Bali, B. Zhang, K. A. Morano, C. A. Michels, *J. Biol. Chem. 278* (2003) 47441–47448.

52. A. W. Gibson, L. A. Wojciechowicz, S. E. Danzi, B. Zhang, J. H. Kim, Z. Hu, C. A. Michels, *Genetics, 146* (1997) 1287–1298.

53. N. A. Kahn, N. R. Eaton, *Mol. Gen. Genet. 112* (1971) 317–322.

54. F. K. Zimmerman, N. R. Eaton, *Mol. Gen. Genet. 134* (1974) 261–272.

55. R. Rodicio, *Curr. Genet. 11* (1986) 235–241.

56. S. Novak, V. Marić, *Food Technol. Biotechnol. 31* (1993) 35–42.

57. J. M. Gancedo, *Microbiol. Mol. Biol. Rev. 62* (1998) 334–361.

58. M. Johnston, *Trends Genet. 15* (1999) 29–33.

59. S. Ozcan, F. Schulte, K. Freidel, A. Weber, M. Ciriacy, *Eur. J. Biochem. 224* (1994) 605–611.

60. L. G. Vallier, D. Coons, L. F. Bisson, M. Carlson, *Genetics, 136* (1994) 1279–1285.

61. S. Ozcan, M. Johnston, *Mol. Cell. Biol. 15* (1995) 1564–1572.

62. J. O. Nehlin, H. Ronne, *EMBO J. 9* (1990) 2891–2898.

63. J. O. Nehlin, M. Carlberg, H. Ronne, *EMBO J. 10* (1991) 3373–3377.

64. Z. Hu, J. O. Nehlin, H. Ronne, C. A. Michels, *Curr. Genet. 28* (1995) 258–266.

65. J. Houruchi, N. Silverman, B. Pina, G. A. Marcus, L. Guarente, *Mol. Cell. Biol. 17* (1997) 3220–3228.

66. C. J. L. Klein, L. Olsson, B. Ronnow, J. D. Mikkelsen, J. Nielsen, *Food Technol. Biotechnol. 35* (1997) 287–292.

67. H. Holzer, *Trends Biochem. Sci. 1* (1976) 178–181.

68. T. H. Brondijk, M. E. Van der Rest, D. Pluim, K. Stingl, B. Poolman, W. Konings, *J. Biol. Chem. 273* (1998) 15352– 15357.

69. I. Medintz, H. Jiang, E. K. Han, W. Cui, C. A. Michels, *J. Bacteriol. 178* (1996) 2245–2254.

70. E. Ribbalo, M. Herweijer, D. H. Wolf, R. Lagunas, *J. Bacteriol. 17* (1995) 5622–5627.

71. P. Lucero, M. Herweijer, R. Lagunas, *FEBS Lett. 333* (1993) 165–169.

72. P. Lucero, R. Lagunas, *FEMS Microbiol. Lett. 166* (1997) 273–277.

73. I. Medintz, H. Jiang, C. A. Michels, *J. Biol. Chem. 273* (1998) 34454–34462.

74. S. Ozcan, J. Dover, A. G. Rosenwald, S. Woelfl, M. Johnston, *Proc. Natl. Acad. Sci. USA, 93* (1996) 12428–12432.

75. S. Ozcan, J. Dover, M. Johnston, *EMBO J. 17* (1998) 2566–2573.

76. H. Jiang, I. Medintz, C. A. Michels, *Mol. Biol. Cell, 8* (1997) 1293–1304.

77. E. Penalver, P. Lucero, E. Moreno, R. Lagunas, *FEMS Microbiol. Lett. 166* (1998) 317–324.

78. K. S. Robinson, K. Lai, T. A. Cannon, P. McGraw, *Mol. Biol. Cell, 7* (1996) 81–89.

79. I. Mayordomo, J. Regelmann, J. Horak, P. Sanz, *FEBS Lett. 544* (2003) 160–164.

80. S. Novak, T. D'Amore, G. G. Stewart, *FEBS Lett. 269* (1990) 202–204.

81. S. Novak, T. D'Amore, I. Russell, G. G. Stewart, *J. Ind. Microbiol. 7* (1991) 35–40.

82. M. Matošić, S. Novak, V. Marić, *Food Technol. Biotechnol. 34* (1996) 97–100.

83. F. Randez-Gil, A. Blasco, J. A. Prieto, P. Sanz, *Yeast*, *11* (1995) 1233–1240.

84. V. J. Higgins, M. Braidwood, P. Bissinger, I. W. Dawes, P. V. Attfield, *Curr. Genet. 35* (1999) 491–498.

85. V. J. Higgins, M. Braidwood, P. Bell, P. Bissinger, I. W. Dawes, P. V. Attfield, *Appl. Environ. Microbiol. 65* (1999) 680–685.

86. P. J. L. Bell, V. J. Higgins, P. V. Attfield, *Lett. Appl. Microbiol. 32* (2001) 224–229.

Regulacija transporta i metabolizma maltoze u kvascu *Saccharomyces cerevisiae*

Sažetak

Metabolizam maltoze u kvascu *Saccharomyces cerevisiae* ima veliko značenje za istraživače u akademskoj sredini i industriji. Za metabolizam maltoze potreban je barem jedan od pet neovisnih *MAL* lokusa: *MAL1*, *MAL2*, *MAL3*, *MAL4* i *MAL6*. Svaki aktivni lokus se sastoji od tri gena: dva strukturna koji kodiraju unutarstanični enzim maltazu te transportni protein za maltozu, dok treći gen kodira pozitivni regulacijski protein. Maltoza se transportira u stanicu nepromijenjena pomoću specifičnih transmembranskih prijenosnika. Nakon toga se hidrolizira uz pomoć unutarstanične maltaze u dvije jedinice glukoze, koje se dalje usmjeravaju u metabolični put glikolize. Metabolizam maltoze u *S. cerevisiae* kontroliraju tri osnovna regulacijska mehanizma: indukcija, represija i inaktivacija glukozom. Nove spoznaje iz molekularne biologije pridonijele su važnim otkrićima o transportu, metabolizmu i regulaciji maltoze u kvaščevim stanicama na molekularnoj razini. Iako je znanje o tim pojavama još uvijek nepotpuno, ono omogućava razumijevanje pri odabiru vrste šećera u kompleksnim supstratima korištenim u industrijskim fermentacijama. Nova otkrića pomažu razumijevanju mehanizama kojim glukoza utječe na ekspresiju gena i metaboličnu aktivnost u drugim organizmima.