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Research Article

THE ROLE OF SWI/SNF CHROMATIN REMODELING COMPLEX IN THE METABOLISM OF TREHALOSE

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ABSTRACT

Trehalose is required for stress tolerance and regulation of glucose uptake. Trehalose-6-phosphate synthase enzyme, encoded by *TPS1*, is the first enzyme in trehalose biosynthetic pathway. The neutral trehalase enzyme, encoded by *NTH1* gene, is responsible from the hydrolysis of stress accumulated trehalose in *Saccharomyces cerevisiae*. It is known that promoter regions of transcriptionally active genes are cleared by chromatin modifying complexes to provide access to transcription initiation complex. In this study, we have analyzed if the chromatin modifying complexes involves in the transcription of *NTH1* and *TPS1* genes under normal and stress inducing growth conditions. We tested the effect of Snf2p, catalytic subunit of SWI/SNF complex, on the transcriptional regulation of *NTH1* and *TPS1*. We have found that *NTH1* gene expressions in *Δsnf2* mutants were 3-fold higher than wild type yeast strain, but *TPS1* gene expression in *Δsnf2* mutants didn't differ from wild type yeast strain. The nitrogen starvation triggered only *NTH1* gene expression in wild type yeast cells but no change was observed in *Δsnf2* mutants and *TPS1* gene expression. Our results indicated that SWI/SNF chromatin remodeling complex is essential for the transcriptional repression of *NTH1* gene, but not *TPS1* gene.

INTRODUCTION

Trehalose is a non-reducing disaccharide, formed by two glucose units linked in an α,α-1,1-glycosidic linkage. It is present in many organisms from bacteria to plants. About 50 years ago, trehalose was regarded as 'storage carbohydrate' only, but later scientists stated that trehalose is also a stress protector and could protect cellular membranes and proteins from denaturation and inactivation of various stresses (Elbein *et al*., 2003; Rubio-Texeira *et al*., 2016). Moreover, in recent years, scientists have emphasized that trehalose-6-phosphate synthase (Tps1p) is the essential determinant of stress resistance in yeast (Petitjean *et al*., 2015).

In *S. cerevisiae*, starvation or stress may result in changes in the trehalose content of the cell. Trehalose accumulation is initiated by cells throughout the diauxic phase and during the stationary phase. Furthermore, the accumulation of trehalose is also initiated by cells during the exponential phase of cells growing in stressed environments. Trehalose must be rapidly degraded when the stress is over or the nutrients in the medium are refreshed. Because, the energy needed for stress recovery is derived from trehalose hydrolysis. Moreover, the presence of high levels of trehalose is hazardous since it is responsible for the reactivation of denatured proteins (Eleutherio *et al*., 2015). Thus, synthesis and degredation of trehalose are strictly regulated (Eleutherio *et al*., 2015; Gibney *et al*., 2015).

In *S. cerevisiae*, trehalose is synthesized by a complex called TPS, comprising Tps1p (Trehalose-6 phosphate synthase) and Tps2p (Trehalose-6 phosphate phosphatase) enzymes, which catalyze the reactions of the synthase, and Tps3p and Tsllp regulatory proteins. Tps3p is a target of phosphorylation mediated by protein kinase A (PKA) and Tsllp plays structural role on TPS enzyme complex (Eleutherio *et al.,* 2015). Strains with *TPS1* gene deletion cannot synthesize trehalose and exhibit various pleiotropic disorders, including inability to grow on glucose or fructose, inability to grow at 39°C, deregulation of glycolysis and the loss of glucose signaling phenomena (Jules *et al.,* 2008; Conrad *et al.,* 2014; Gibney *et al.,* 2015; Eleutherio *et al.*, 2015).

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The cleavage of trehalose is dependent on the enzyme called trehalase. Intracellular trehalose hydrolysis is mainly fulfilled by neutral trehalase, encoded by *NTH1*(Kopp *et al.,* 1993; Zähringer *et al.,* 2000; Eleutherio *et al*., 2015).Strains with *NTH1* gene deletion are unable to hydrolyze trehalose, which results in excessive trehalose accumulation (Zähringer *et al.,* 2000; Eleutherio *et al.,* 2015).

The activity of both Tps1p and the Nth1p enzymes in *S. cerevisiae* increases in the presence of environmental stress conditions and nutrient depletion, like nitrogen starvation. This is because both *NTH1* and *TPS1* promoters contain the STRE elements (STress Responsive Elements) (consensus sequence CCCCT/AGGGG). STRE elements are the regions to which the Msn2p and Msn4p transcriptional activator proteins bind to regulate expression of stress responsive genes. Nth1p must be phosphorylated by PKA in order to be active (Zähringer *et al*., 2000; Eleutherio *et al.,* 2015).

Although the chromatin structure is responsible for the packaging and integrity of the genetic material, it prevents some cellular processes, such as replication and transcription, because it acts as a barrier to DNA mediated transactions. Generally cells have developed different ways in order to achieve these important cellular processes. One of these ways is ATP-dependent chromatin remodeling complexes (Awad and Hassan, 2008; Xia *et al.,* 2016).

The SWI/SNF family (mating type SWItching (SWI)/ Sucrose Non Fermenting (SNF)) of ATP-dependent chromatin remodeling complexes was originally discovered in yeast and evolutionarily conserved from yeast to humans (Zhang *et al*., 2013; Sen *et al.,* 2017). The yeast SWI/SNF is a 1.15MDa complex. It utilizes the energy of ATP hydrolysis to remodel the structure of chromatin by eviction or sliding of nucleosomes, leading to changes in the expression of a subset of the yeast gene (Vignali *et al*., 2000; Awad and Hassan, 2008). It consists of 12 subunits and the catalytic subunit of SWI/SNF complex is Snf2p (or Swi2p) (Trotter and Archer, 2008; Awad and Hassan, 2008).

Previous studies have shown that the SWI/SNF complex is involved in the transcription of many stress response genes and the level of Snf2p changes depending on the nutrient conditions (Dutta *et al*., 2014; Awad *et al*., 2017). The transcriptional regulation of the *NTH1* and *TPS1* genes, which are activated under different stress conditions, and the transcription factors and other proteins involved in this regulatory process are not fully known. Furthermore, no information is available in the literature on the role of nucleosomes in the transcriptional regulation of these genes. Therefore, under normal and nitrogen starvation conditions, the role of SWI/SNF complex in the transcriptional regulation of the *NTH1* gene and *TPS1* gene has been determined in this study. It was found that the SWI/SNF complex has a role in the repression of *NTH1* gene.

MATERIALS AND METHODS

Yeast Strains and Plasmids

The genotypes of *S. cerevisiae* strains used in this study are: BY4741 (MATa; ura3Δ0; leu2Δ0; his3Δ1; met15Δ0 (Wild Type)) and its mutant derivative *Δsnf2* Y01586 (MATa; ura3Δ0; leu2Δ0; his3Δ1; met15Δ0; YOR290c::kanMX4). Both strains were obtained from EUROSCARF (European *Saccharomyces cerevisiae* Archive for Functional Analysis, Frankfurt, GERMANY). BY4741 strain of *S. cerevisiae,* which is a standard haploid strain, has not any known mutation regarding to trehalose metabolism and *Δsnf2* yeast strain is isogenic with BY4741 strain.

In this study, plasmids containing *NTH1*-LacZ and *TPS1*-LacZ gene fusions were used to measure the *NTH1* and *TPS1* promoter activity, respectively, induces by nitrogen deficiency (Parrou *et al.,* 1997). Likewise, the plasmid containing the *SUC2*-LacZ gene fusion was used as control because *SUC2* gene regulated with carbon source not nitrogen (Türkel*et al*., 2003).

Growth Conditions

S. cerevisiae strains were grown in a rich medium YPD Medium containing 1% (w/v) Yeast Extract, 2% (w/v) Bacto-peptone and 2% (w/v) Dextrose. Yeast transformations were performed as described previously using lithium acetate polyethylene glycol (LiOAc + PEG) method (Rose *et al.,* 1990). The transformant yeasts were selected on YNBD-HLM (Yeast Nitrogen Base without amino acid and ammonium sulfate + 0.5% Ammonium sulfate + 2% Agar + 2% Dextrose + 0.2% Histidine + 0.3% Leucine + 0.2% Methionine).

The wild-type and mutant transformants were grown in YNBD-HLM culture at 30°C incubator shaker (150 rpm/min) overnight to obtain saturated yeast culture. Using these saturated yeast precultures, yeast transformants were inoculated 10 mL of fresh YNBD-HLM medium to get initial cell densities of OD_{600} value was about 0.1 then grown to log stage (OD_{600} value was about 0.8-1.0) at incubator shaker. Once the yeast cultures reach to log stage, the yeast cultures were divided into two parts and one part was harvested and used for enzyme assays. The second part of culture was washed and transferred to YN-D-HLM culture supplemented with 0.1% proline instead of ammonium sulfate. At the end of 4 h incubation, yeast cultures were harvested and used for determining enzyme activities. Yeast transformants were grown as triplicate for determination of β-galactosidase activity and intracellular accumulation of trehalose, that all repeated twice.

β-galactosidase Assay

For the β-galactosidase assay, harvested cells were resuspended in 200 µL of breaking buffer (100 mM Tris HCl pH8.0, 1 mM DL-Dithiothreitol, 20% (V/V) Glycerol, 4mM Phenylmethane sulfonyl fluoride) then stored at -80°C until use. Cells were permeabilized with 20 µL of 0.1% SDS and 20 µL of chloroform in Z-Buffer (60 mM Na_2HPO_4, 40 mM NaH_2PO_4, 10 mM KCl, 1 mM $MgSO_4$, 50 mM 2-mercaptoethanol, pH 7.0). β-Galactosidase assays using *o*-nitrophenyl-β-d-galactose (ONPG) as substratewere carried out in triplicate as described previously (Guarente, 1983). β-Galactosidase activities were given as nmol *o*-Nitrophenyl β-D-Galactopyranoside (ONPG) cleaved per minute per mg of protein. Protein concentration was determined using the Lowry assay described previously (Lowry *et al.,* 1951).

Trehalose Assay

Trehalose assay of the transformant yeast cells were determined as described previously (Parrou and François, 1997). The wet weights of yeast transformants were determined and cells resuspended in 250 µL

of 0.25 M Na_2CO_3 and boiled for 2 h. Then 150 µL of 1 M acetic acid, 600 µL of 0.2 M ($C_2H_3NaO_2$)pH5.2 was added to cell lysates and incubated at 37°C for 18 h after adding 3 mU trehalase enzyme (Sigma-Aldrich T8778). The amount of glucose released into the endogenous cleavage of trehalose was determined using the Glucose Oxidase-Peroxidase method as described by manufacturer (Goldstein and Lampen, 1975). The results were calculated as microgram glucose (µg glucose /mg yeast weight) accumulated in milligram of wet weights of yeast cells.

RESULTSAND DISCUSSION

In this report, we have analyzed that the role of SWI/SNF complex on transcriptional regulation of *NTH1* and *TPS1* gene. The SWI/SNF complex utilizes ATP hydrolysis by Snf2p, to slide or eviction of nucleosomes (Awad *et al*., 2017). Even a single amino acid change that occurs in Snf2p ATPase domain causes the loss of ATPase activity. This leads to the loss of chromatin remodeling activity of the SWI/SNF complex (Dror and Winston, 2004; Richmond and Peterson, 1996). Consequently, Snf2p activity promotes to transcriptional regulation of targeted promoters of relevant genes. But, SWI/SNF complex is not necessary for viability. However, mutations of SWI/SNF complex subunits affect transcription of a broad variety of diversely regulated genes. This shows that SWI/SNF complex plays a universal role in transcriptional control (Carlson and Laurent, 1994). For this purpose, we determine the effect of SWI/SNF complex on the expression of *NTH1* and *TPS1* gene under normal growth conditions and nitrogen starvation conditions, both in *Δsnf2* and the wild-type strain.

As shown in Table 1, the expression of *NTH1*-LacZ fusion gene was approximately 3-fold higher in *Δsnf2* mutants (489.4±8.9 Unit) than in wild-type yeast strains (141.16±53.47 Unit) at the exponential phase, where good nitrogen source present in non-stress conditions. The fact that the *NTH1* gene expression in the *Δsnf2* yeast strain is increased 3-fold compared with the wild-type in non-stress conditions indicates that Snf2p can act as a transcriptional repressor on the *NTH1* gene expression. It is known that SWI/SNF complex does not have ATPase activity in the absence of Snf2p. Hence, it can be suggested that SWI/SNF complex is involved in the transcriptional repression of the *NTH1* gene at normal growth conditions.

Table 1 Transcriptional level of *NTH1* in BY4741 and *Δsnf2* yeast strain

β-Galactosidase Activity*		
***NTH1*-LacZ**	**Non-Stressed**	**Proline**
BY4741	141.16±53.47	550.43±76.08
Δsnf2	489.4±8.9	487.56±2.82

*β-Galactosidase activities were determined as nanomoles of ONPG hydrolyzed per minute per milligram of protein and were the average (± standard deviation) of three independent experiments assayed in duplicate

As shown in Table 2, *TPS1* gene expression was 1272.05±15.00 Unit in *Δsnf 2* yeast strain and 1010.61±59.73 Unit in wild-type yeast strain. As shown, there was no change in the expression of *TPS1* gene in *Δsnf2* yeast strain than wild-type yeast strain in non-stress condition. The results of *TPS1* gene expression in *Δsnf 2* yeast strain compared with the wild-type yeast strain in non-stress conditions indicate that Snf2p is not necessary for activation of *TPS1* gene in log phase.

Table 2 Transcriptional level of *TPS1* in BY4741 and *Δsnf2* yeast strain

β-Galactosidase Activity*		
***TPS1*-LacZ**	**Non-Stressed**	**Proline**
BY4741	1010.61±59.73	1578.93±113.33
Δsnf2	1272.05±15.00	1332.65±27.22

*β-Galactosidase activities were determined as nanomoles of ONPG hydrolyzed per minute per milligram of protein and were the average (± standard deviation) of three independent experiments assayed in duplicate

In *S. cerevisiae*, both the *TPS1* and the *NTH1* genes activities significantly increase in response to environmental stress and nutrient starvation. The reason for this is that they contain STRE regions in their promoters. There are a variable number of STRE elements on the promoter of the *TPS1* gene, while there are three STRE regions in the *NTH1* gene promoter (Winderickz *et al.,* 1996; Zähringer *et al*., 2000; Eleutherio *et al.,* 2015). Besides, Nth1p requires post-translational modifications to become an active enzyme. This activation of the inactive form of Nth1p is mediated by a mechanism involving phosphorylation mediated by cAMP-dependent PKA (Eleutherio *et al*., 2015).

Cells growing on poor nitrogen sources, such as proline or urea, activate the transcription of a set of genes. Tor1 kinase is inactivated in poor nitrogen source and TOR-repressed Msn2/Msn4 proteins pass through the nucleus to activate the transcription of STRE-dependent genes, such as *NTH1* and *TPS1* gene (Schreve *et al.,* 1998; Zähringer *et al*., 2000; De Wever *et al*., 2005; Conrad *et al.,* 2017). As shown in Table 1, under nitrogen starvation, *NTH1* expression increased 4-fold in the wild-type yeast strain (550.43±76.08 Unit), but no change was observed in the *Δsnf2* mutants (487.56±2.82 Unit). Furthermore, as shown in Table 2, *TPS1* gene expression increased approximately 1.5-fold in wild-type yeast strain (1578.93±113.33 Unit) but no change was observed in *Δsnf2* mutants (1332.65±27.22 Unit) under nitrogen starvation.

In our study, to specify the effect of SWI/SNF complex in intracellular trehalose accumulation, the wild-type and *Δsnf2* yeast cells were cultivated in YNBD-HLM growth medium to logarithmic phase. The amount of intracellular trehalose was determined by taking samples before and 4 h after transfection of the cells into proline-containing culture medium. The OD_{546} values, determined using the GOD method, were calculated based on the absorbance value given by the glucose standard. The amount of glucose contained in cellular lysates was determined as milligrams of accumulated microgram glucose (µg glucose / mg wet weight) per milligram cell, normalized over the yeast wet weight according to the amount of glucose contained in the glucose standard solution.

As shown in Table 3, in wild-type yeast cells, the amount of intracellular trehalose was determined as 120.3±65.9 µg glucose/mg wet weight and *Δsnf2* yeast cells 2688.2±429.4 µg glucose/mg wet weight in non-stress conditions. There was 22-fold increase in trehalose accumulation in the *Δsnf2* mutants compared to the wild-type in non-stress conditions. Despite the repressive effect of the SWI/SNF complex on the expression of the *NTH1* gene and the absence of any effect on the expression

of the *TPS1* gene, this high amount of trehalose accumulation is interesting. This suggests that the effect of the SWI/SNF complex on Tps1p, rather than the expression of the *TPS1* gene. Indeed, recent studies have shown that the SWI/SNF chromatin remodeling complex is not only a chromatin remodeling complex, but it also has a role on non-chromatin substrates (Kapoor *et al*., 2015; Kapoor and Shen, 2015). In a recent study shows that SWI/SNF complex is capable of the regulating checkpoint kinase Mec1 activity, which is a main master regulator of genomic integrity (Kapoor *et al.,* 2015). This study, which relates to SWI/SNF mediated Mec1 activation, provides the first evidence of non-chromatin substrates for ATP-dependent chromatin remodeling complexes. Our results presented in this study can be evaluated as another important set of data supporting the presence of protein substrates for SWI/SNF complex in yeast.

Table 3 Trehalose accumulation in BY4741 and *Δsnf2* yeast strain

Trehalose Content		
Yeast Strains	**Non-Stressed**	**Proline**
BY4741	120.3±65.9	936.3±195.8
Δsnf2	2688.2±429.4	2531.2±579.7

* Trehalose content is µg glucose/mg wet weight

As shown in Table 3, under nitrogen starvation, the amount of intracellular trehalose in wild-type yeast cells were determined as 936.3±195.8 µg glucose/mg wet weight and *Δsnf2* yeast cells 2531.2 ± 579.7 µg glucose / mg wet weight. Under nitrogen starvation, trehalose accumulationwas 8-fold higher in the wild-type yeast strain, but no change was observed in the *Δsnf2* mutants.

Under nitrogen starvation *NTH1* gene expression and trehalose accumulation in creased in the wild-type yeast strain, while *TPS1* gene expression did not show any increase. This may be explained by the entity of STRE elements in *TPS1* gene promoter is not adequate under different stress conditions (Bonini *et al.,* 2004). Similar to our study, in previous studies, it was shown that ethanol and pH did not activate the *TPS1* gene while showing activation of some stress responsive genes, such as *HSP12, DDR2* and *CTT1* (Parrou *et al.,* 1999).

In our study, we found that *TPS1* gene expression was incompatible with Tps1p activity and trehalose accumulation.In one study, changes in *TPS1* gene expression, Tps1p activity, and trehalose content of psychrotolerant yeast *Guehomyces pullulans* 17-1 cultivated at different temperatures were examined and contrary to our results, the expression of the *TPS1* gene was shown to be consistent with changes in Tps1p activity and trehalose content (Zhang *et al.,* 2013). However, in another study that is consistent with our study, it was found that the increase in the amount of Tre6P synthase was not accompanied by transcriptional activation of *TPS1*. Therefore, it has been suggested that transcriptional activation of *TPS1* is not strictly related to trehalose accumulation and there is no sole and common mechanism for trehalose accumulation in yeasts (Alexandre *et al*., 1998).

Under nitrogen starvation, no differences were observed in *NTH1* and *TPS1* gene expression and trehalose accumulation in *Δsnf2* mutants. The absence of any change in the expression of *NTH1* and *TPS1* genes and trehalose accumulation in the *Δsnf2* mutants suggest that the SWI/SNF complex in the *Δsnf2* mutants cannot cluster and that the cells produce stress signals under non-stress conditions. Under nitrogen starvation, since the cells are already stressed, no other effect is observed compared to the non-stress condition. In brief, these results show us that the SWI/SNF chromatin remodelling complex does not play a role on transcriptional regulation on *NTH1* and *TPS1* gene under nitrogen starvation condition.

For control purposes, we also examined the role of SWI/SNF complex in transcriptional regulation of *SUC2*,a gene necessary for growth of yeasts as sucrose and raffinose as a carbon source,by using LacZ reporter gene fused plasmidin this study (Sudarsanam and Winston, 2000). The *SUC2* gene is controlled by glucose repression: *SUC2* is transcriptionally repressed in the presence of high glucose; in low glucose *SUC2* is derepressed and transcriptionally active (Hirschhorn *et al.,* 1992; Wu and Winston, 1997).

In our study, *SUC2* gene expression was 0.491±0.007 Unit in wild-type yeast strain and 10.2±0.145 Unit in*Δsnf2* yeast strain. As it turns out, there was no expression of *SUC2* gene in wild-type yeast strain and *Δsnf2* yeast strain, in non-stress condition. Under nitrogen starvation, *SUC2* gene expression was 0.598±0,005 Unit and 4.9 ± 0.120 Unit in wild-type yeast strain and *Δsnf2* yeast strain, respectively. We have found that *SUC2* promoter was not activated under normal and nitrogen starvation conditions in the wild-type yeast strain. But in *Δsnf2* yeast strain, nitrogen starvation caused to 2-fold decrease in *SUC2* promoter activity.

Studies have shown that the SWI/SNF chromatin remodeling complex is required *in vivo* to achieve a transcriptionally active chromatin structure in the promoter of the *SUC2* gene (Matallana *et al*., 1992; Hirschhorn *et al.,* 1992; Wu and Winston, 1997; Sudarsanam and Winston, 2000).

Previous studies have shown that the SWI/SNF chromatin remodelling complex is considered as a transcriptional activator, while subsequent studies have shown that this complex can also serve as transcriptional repression (Mao *et al.,* 2008; Martens and Winston, 2002). Studies with mutations of Swi1p, Snf2p and Swi3p, subunits of the SWI/SNF complex, have shown that this complex is involved in the induction of transcription of some genes such as *HO*, *INO1*, *ADH1*, *ADH2*, *GAL1* and *GAL10* in *S. cerevisiae* (Peterson and Herskowitz, 1992; Biggar and Crabtree, 1999; Sudarsanam *et al*., 1999; Zhang *et al*., 2013).

In recent studies, it is emphasized that the SWI/SNF complex also represses the transcription. SWI/SNF complex represses transcription directly of the *SER3* gene, encoding an enzyme necessary for serine biosynthesis. But, on the contrary of the transcriptional activation by SWI/SNF complex, which requires most SWI/SNF complex subunits, the transcriptional repression of *SER3* by SWI/SNF complex is dependent predominately only one SWI/SNF component, Snf2p. These results demonstrate that the different subunits of SWI/SNF complex play a role in transcriptional repression and activation. Therefore, it is thought that there is a main difference between the mechanisms that the SWI/SNF complex exhibits both in repression and activation (Martens and Winston, 2002).

There are suggesting that a SWI/SNF involves in the transcription of many genes in *S. cerevisiae*, both as an

activator and repressor complex. Our study also supports these studies by showing that the SWI/SNF complex is responsible for the repression of the *NTH1* gene at normal growth conditions.

In conclusion, this is the first study to examine the effect of the SWI/SNF complex, one of the ATP-dependent chromatin remodeling complexes, on the *NTH1* and *TPS1* gene. As a result, it was determined that the SWI/SNF complex was involved in the repression of the *NTH1* gene, but there is no effect on the *TPS1* gene. It has also been found that the *NTH1* gene is active under nitrogen starvation but not the *TPS1* gene.

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