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Sugar Utilization in the Fungal Pathogen *Candida albicans*

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ABSTRACT

The ability to utilize diverse nutrient sources has made Candida albicans a successful fungal pathogen. As a result of its metabolic plasticity the fungus can colonize multiple host niche. Glucose is the most favorable carbon source forfungi. In the presence of preferred carbon source the catabolic enzymes for other non-preferred carbon sources are repressed at transcriptional level and degraded at protein level via ubiquitin mediated pathway in Saccharomyces. But in case of Candida albicans there are some exceptions, like parallel assimilation of enzymes for the utilization of both preferable and non-preferable carbon sources. Several catabolic regulatory cascades are rewired to provide metabolic flexibility in Candida compared with counter partner Saccharomyces. In this review we discuss about how various signaling elements or sensors are involved in sensing, transport and utilizationof different sugarsin Candida. We also describe about the virulence characteristics acquired by this pathogen due specific sugar utilization.

KEYWORDS Candida albicans, sugar sensing, sugar signaling, sugar transporters, Glucose repression pathway

1.INTRODUCTION

Nowadays fungal infection is on the rise, with nosocomial infections being one of the major contributors. *Candida albicans* causes most frequent fungal infection in human and other mammalian host and also in chicken, oak and turkey (1). Though glucose is the most preferred carbon source, it can also utilize a variety of other sugars as carbon sources (2). In most of the

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fungi the catabolic pathways for non-preferred sugar are not expressed in the presence of preferred sugar, a phenomenon popularly termed as carbon catabolite repression (CCR) (3). In *Candida albicans* the simultaneous assimilation of different sugars is often observed, since its sites of infection are poor in glucose (2). In *Candida albicans* apart from glucose, N-acetyl glucosamine(GlcNAc), galactose, fructose, mannose etc. have different sensing mechanisms and play varied roles in several downstream signaling events like morphogenesis, virulence, oxidative stress resistance, and antifungal drug tolerance etc. (4,5,6,7).

2.GLUCOSE SENSING AND SIGNALING

Most of the fungi use glucose as a main carbon source which helps then to synthesize other biomolecules and harness energy (8). It acts like both ligands and substrate for receptor and transporter respectively (9). In *Candida albicans* 20 hexose transporters(Hxts) are identified (10). All contain 12 conserved transmembrane domains(TMDs) like *S. cerevisae*. These Hxts are divided into two groups: Ca*HXT*, act like transporter (Ca*HGT6*, Ca*HGT7*, Ca*HGT8*, and Ca*HGT11*) and Ca*SNF3*, act like glucose sensor (Ca*HGT4* and Ca*HGT12*). Among them Ca*HGT9*, Ca*HGT10*, Ca*HGT12*, and Ca*HGT17* are high affinity glucose (0.2%) transporter and rest of them express in 2% glucose concentration (10). Unlike glucose sensor, CaHgt12 lacks cytoplasmic tail, an important feature for sensor (11). To see the role of CaHgt4 and CaHgt12, Ca*hgt4Δ* mutant and Ca*hgt12Δ* mutant were plated on different sugar media. Among them Ca*hgt12Δ* mutant grows normally on glucose, mannose and fructose but Ca*hgt4Δ* shows defective growth on fructose, glucose and mannose at < 0.2% (12). The inducible concentration (0.2%) of CaHgt4 reflects glucose level in serum (13). Therefore, we can see the CaHgt4 is an important protein for cell signaling at low concentration of fermentable sugar (12). Upon sensing

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glucose by CaHgt4, CaStd1 at cytoplasmic tail is phosphorylated by CaYck2 followed by the proteasomal degradation of CaStd1 through CaGrr1 mediated ubiquitylation which in turn promotes the transcription of several Ca*HGT*s, and metabolism genes (13). Work by several groups have showed promoters of Ca*HGT*s contains six CaRgt1 binding sites (13), Where Rgt1-Std1 repression complex binds to repress these genes in the absence of glucose (14). The Ca*hgt4Δ* mutant shows repression of Ca*HGT*s and the C*argt1Δ* mutant shows increased expression of these Ca*HGT*s (12). C*argt1Δ* Ca*hgt4Δ* double mutant shows restored expression of these Ca*HGT*s. This study reflects that CaRgt1 works downstream of CaHgt4 (12). N- terminal end of the CaRgt1 has most sequence similarity with ScRgt1 (14). Ca*hgt4Δ* shows defective filamentation other than hyper-filamentation in CaHgt4 due to the inability of utilization of low level of glucose (12). CaHgt4 also plays an important role in virulence by utilizing glucose from the infection site (15).Unlike *S. cerevisiae* glucose is not sensed by G-protein couple receptor system but able to signal PKA pathway by CaCdc25 through CaRas2 proteins like *S. cerevisiae* (16).

3. GLUCOSE REPRESSION PATHWAY

Glucose repression pathway occurs in most of the fungi (17,18). In the presence of glucose, metabolic genesof alternative carbon source utilization are not expressed (19,20). But in *C.albicans* post transcriptional rewiring enables the utilization of other carbon sources in the presence of glucose (2). Interestingly the transcripts of some metabolic genes follow degradation whereas protein levels are maintained to a certain level significance of such maintenance at basal level. (2). Further research showed that unlike *S. cerevisae* the lack of ubiquitin binding site in the glyoxylate and gluconeogenic metabolism genes, prevent degradation but ubiquitination machinery is still present (2). This strategy makes *Candida albicans* a successful pathogen by

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making it flexible towards different carbon sources.CaSnf1 plays an important role in glucose repression pathway (21,22). It is activated by the phosphorylation, mediated by CaSak1 kinase (23). CaSnf1 is an essential gene (21,22). Unlike *S. cerevisiae*, CaMig1 is not phosphorylated by CaSnf1 and has different role in *Candida albicans* (24). CaMig1 represses glucose sensitive promoter by both Tup1 dependent and independent manner in the presence of glucose (24,25). The CaMig1 has repression effect on Ca*GAL1*(24). The KMPPK sequence of CaMig1 helps to translocate in the nucleus (24,26).

4. GALACTOSE SENSING AND SIGNALING

The structural genes of galactose (*GAL1, GAL2, GAL7, GAL10*) are conserved between *C. albicans* and *S. cerevisae*, but not the regulatory genes (*GAL3, GAL4, GAL80*) (13). The binding site of CaGal80 is missing in Ca*GAL4*(27,28). Interestingly CaHgt4 sense the galactose (0.6%) possibly due to the non-specific CaHgt4 and absent of Gal4 pathway (12,29). CaHgt7 transporters the glucose inside the cell and then CaHgt4 sense the galactose and signals Leloir pathway (28,29).

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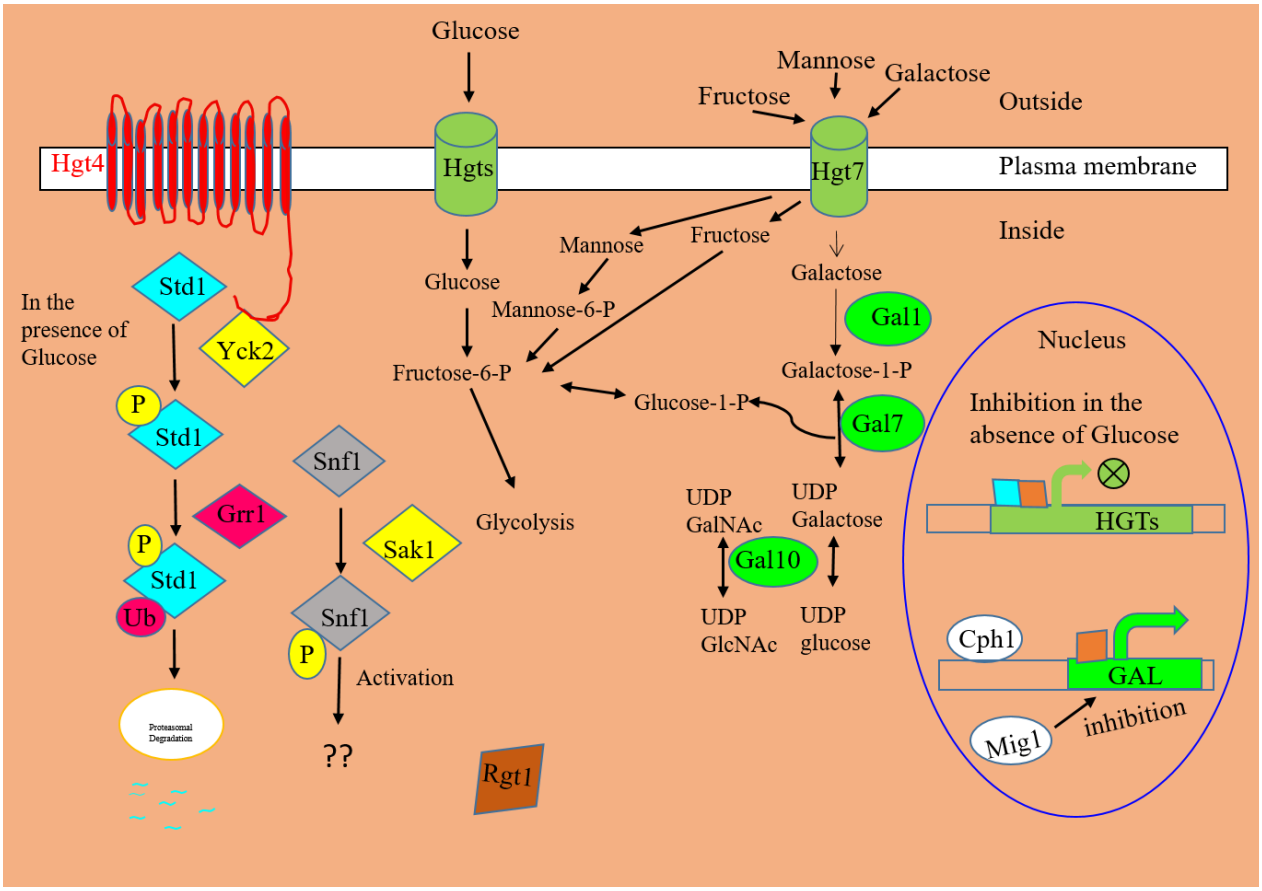

Fig.1. Glucose, Galactose, Fructose and Mannose sensing and signaling pathway in *Candida albicans*. The rhombus shaped proteins indicate glucose metabolism. Oval shaped proteins indicate galactose metabolism.

Approximately 94% genes involved in both glucose and galactose metabolism are induced by both glucose and galactose (29). But CaStd1 isnot affected by galactose (13). Galactose induced genes contain CaRgt1 consensus sequence and coordinately regulated by CaRgt1 and CaCph1(ortholog to ScSte12)(27,28).

5. FRUCTOSE AND MANNOSE SENSING AND SIGNALING:

In *Candida albicans* fructose and mannose are also sensed by CaHgt4 and transported through CaHgt7 and CaHgt12 (12,29,30). CaHgt7 transporter is activated by 0.04% mannose and

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fructose concentration (29). This reflects same signaling pathway as glucose. The fructose transport is more critical than glucose and mannose (12).

6. N-ACETYL GLUCOSAMINE SENSING AND SIGNALING

In *Candida albicans*, GlcNAc activates two pathways- one is cAMP dependent, which triggers morphogenesis and virulence factors (31,32,33) and second is cAMP independent, which triggers GlcNAc catabolic genes (33,34,35). Exogenous GlcNAc taken up by cells can enter the both anabolic and catabolic pathway (36). In anabolic pathway from GlcNAc, UDP-GlcNAc is produced which then produces structural components. In catabolic pathway GlcNAc is converted into glucose-6-phosphate, which undergoes glycolysis to generate energy (36). The exogenous GlcNAc is taken up by the cell through a GlcNAc transporter, Ngt1, the first identified eukaryotic GlcNAc transporter (37). Then endogenous GlcNAc is sensed by a GlcNAc sensor, Ngs1, which has a GlcNAc binding domain, glycoside hydrolase family 3 (GH3) at the N-terminus and a N-Acyltransferase (NAT) domain at the C-terminus and a NLS region in front of NAT domain (37). After GlcNAc binding with Ngs1 an important transcription factor Rep1 recruits Ngs1 to the promoters of the GlcNAc catabolic genes: GlcNAc kinase (Hxk1), GlcNAc-6-phosphate deacetylase (Dac1), and GlcN-6-phosphate deaminase (Nag1); Ngt1, Hex1, hyphal genes, etc. to promotes the transcription which leads to several function within the cell like GlcNAc metabolism, GlcNAc transport, GlcNAc Scavenging, hyphal growth etc. respectively (38).

GlcNAc also plays several important roles in *C. albicans* like- structural support (chitin), GlcNAc Induced Cell death (GICD) (39). GlcNAc also induces *GAL7, GAL1, GAL10* genes irrespective of CaCPH1 disruption (40).

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7. THE RELATION BETWEEN SUGAR UTILIZATION AND VIRULENCE

The supporting characters for pathogenicity in *C. albicans* includes morphogenetic switching, adhesion and invasion, biofilm formation, stress resistance etc. (13).

Ability to utilize multiple carbon sources helps *C. albicans* to be a successful pathogen. Glucose induce the hyphae formationat very low concentration (0.25%) in *C albicans* (13).In *C. albicans*

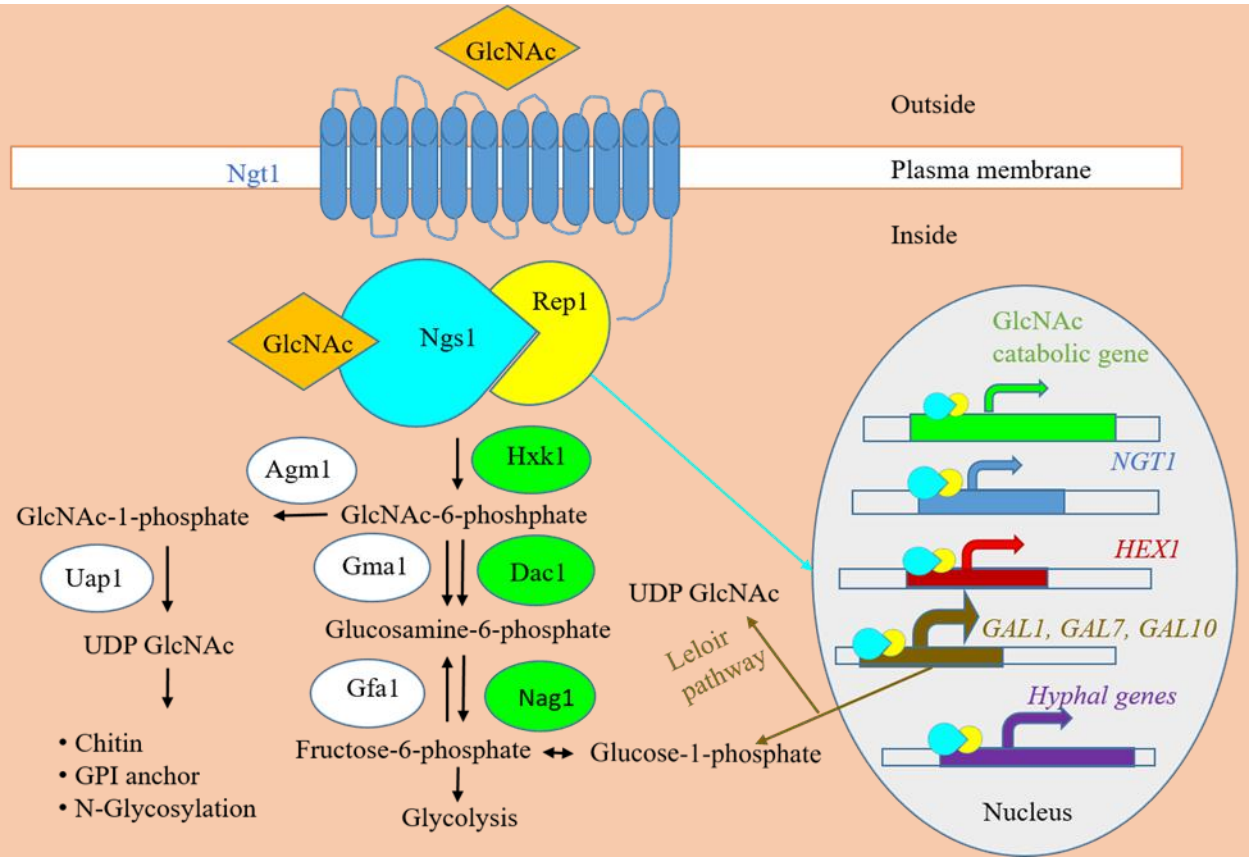

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Fig.2. GlcNAc sensing and signaling in *Candida albicans*. The green colored proteins indicate GlcNAc induced proteins. Leloir path way indicates galactose metabolism. The colored bent arrows in the nucleus indicate transcriptional activation

biofilms contains hyphal cell which provides nutrient, structural support and adherence (41,42). This indicates biofilms is formed at very low concentration (0.25%) of glucose. Therefore, biofilm is a survival strategy in nutrient deficient condition.

Increased glucose concentrations (0.01% –1%) upregulates stress resistant genes including oxidative stress, drug resistance, osmotic stress etc. in *C. albicans*, which is also a survival strategy (7). Upon entrance in bloodstream, suddenly cells are exposed to glucose which leads a fast induction of stress resistant genes (7). This is the survival plan in bloodstream, neutrophils try to kill the pathogens by oxidative stress and nutrient deficiency (7). The systemic infection of *C. albicans* is also induced by glucose (12).

GlcNAc also have some effect in virulence in *C. albicans* like hyphal morphogenesis (37), inhibition of phagocytosis via neutralization of acidic pH in the phagosome. The neutral pH leads to hyphae formation inside the macrophages which disrupt the cell and induce pyroptosis to escape from macrophages (43).

8. CONCLUSION

As Candida infection is increasing and the resistance power towards different antifungal agents is also increasing, findings of some new targets are necessary for proper treatment. Hope this

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review will help to discover some important target for antifungal agents because sugar sensing and signaling pathway is important for pathogenicity in *C. albicans*.

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