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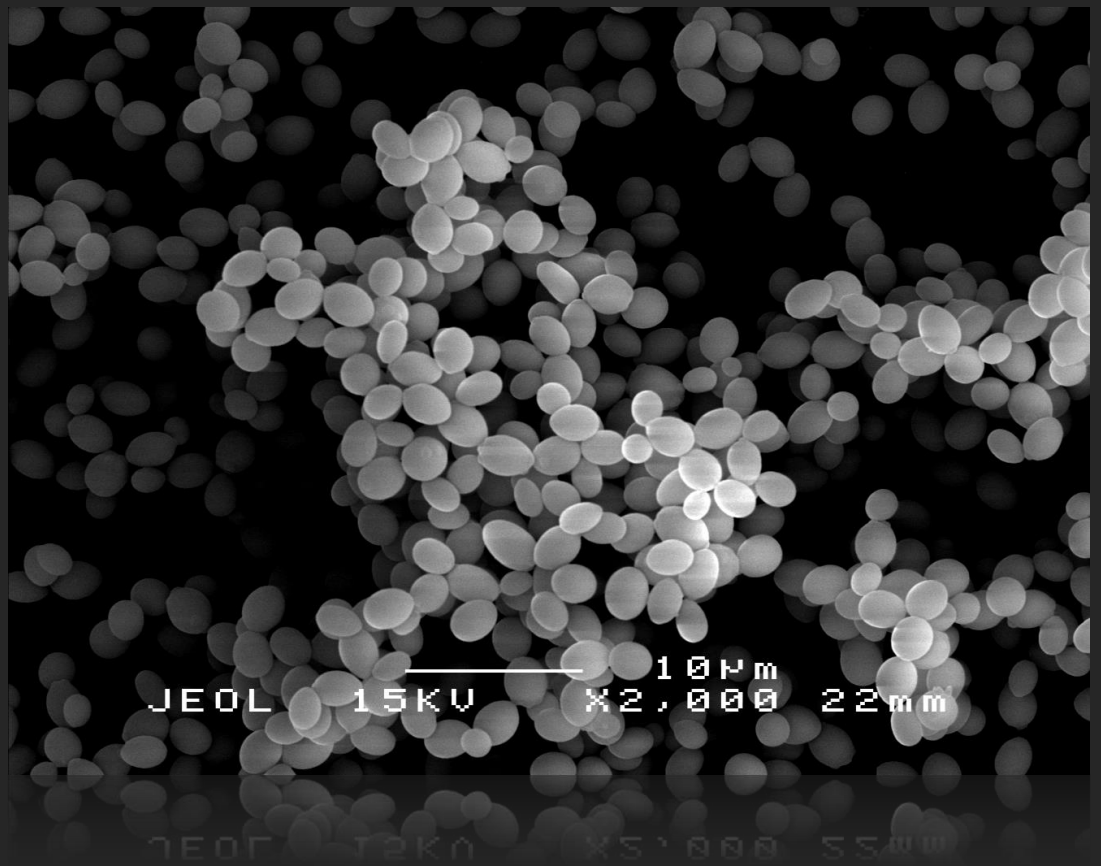
SNF3 as high affinity glucose sensor and its role in supporting *Candida glabrata* viability within the macrophages.

Candida glabrata



- Haploid
- Acquired antifungal resistance
- Second most prevalent *Candida* species (Pfaller et al., 2011)
- Higher mortality rate (Fidel *et al*., 1999).

Candida glabrata

TABLE 1. Species distribution of *Candida* bloodstream infection isolates across geographic regions: SENTRY Surveillance Program, 2008 to 2009

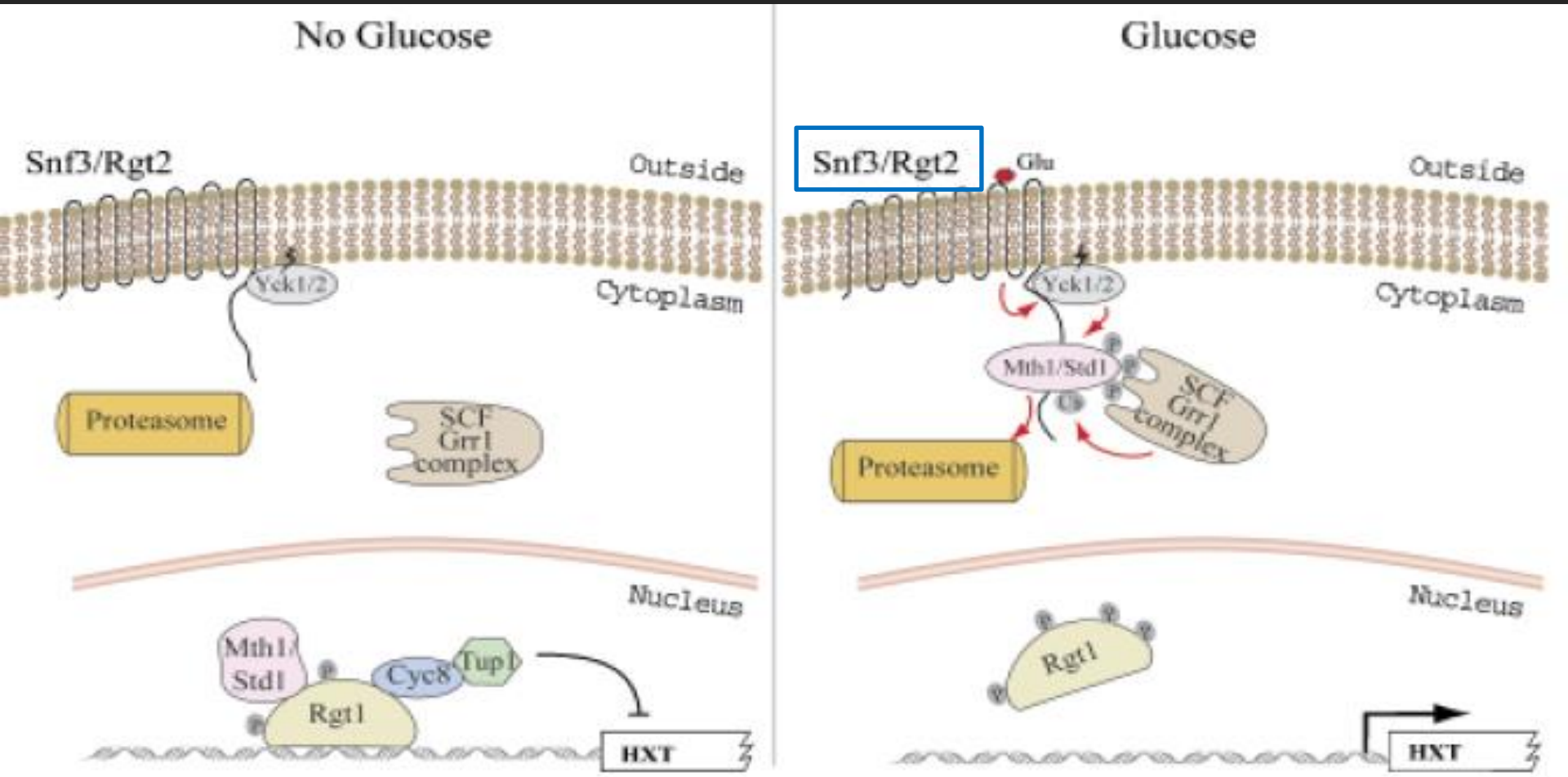
Species	% of isolates by species and geographic region (n^b)				
	Asia-Pacific (51)	Latin America (348)	Europe (750)	North America (936)	Total (2,085)
C. albicans	56.9	43.6	55.2	43.4	48.41
C. glabrata	13.7	5.2	15.7	23.5	18.0
C. parapsilosis	13.7	25.6	13.7	17.1	17.2
C. tropicalis	11.7	17.0	7.3	10.5	10.5
C. krusei	2.0	1.4	2.5	1.6	1.9
C. lusitaniae	0.0	0.9	1.2	2.2	1.6
C. dubliniensis	0.0	0.3	0.8	1.0	0.8
C. guilliermondii	0.0	1.7	0.1	0.1	0.4
Misc.[a]	2.0	1.6	1.7	0.6	1.2

Adapted from Pfaller et al. (2011) Report from the SENTRY Antimicrobial Surveillance Program (2008 to 2009) Journal of Clinical Microbiology

Glucose

- Important carbon and energy source.
- Availability varies in different sites of human niches e.g. 0.05-0.1% (vaginal secretion) and ~0.1% (blood) (Ehrtröm *et al*., 2006).
- Promotes stress resistance in *C. albicans* (Rodaki et al., 2009). → Fitness of *C. albicans*

Sugar receptor-repressor (SRR) pathway



Sugar receptor-repressor (SRR) pathway in yeast

Adapted from Gancedo (2008) The early steps of glucose signalling in yeast. *FEMS Microbiology Review*.

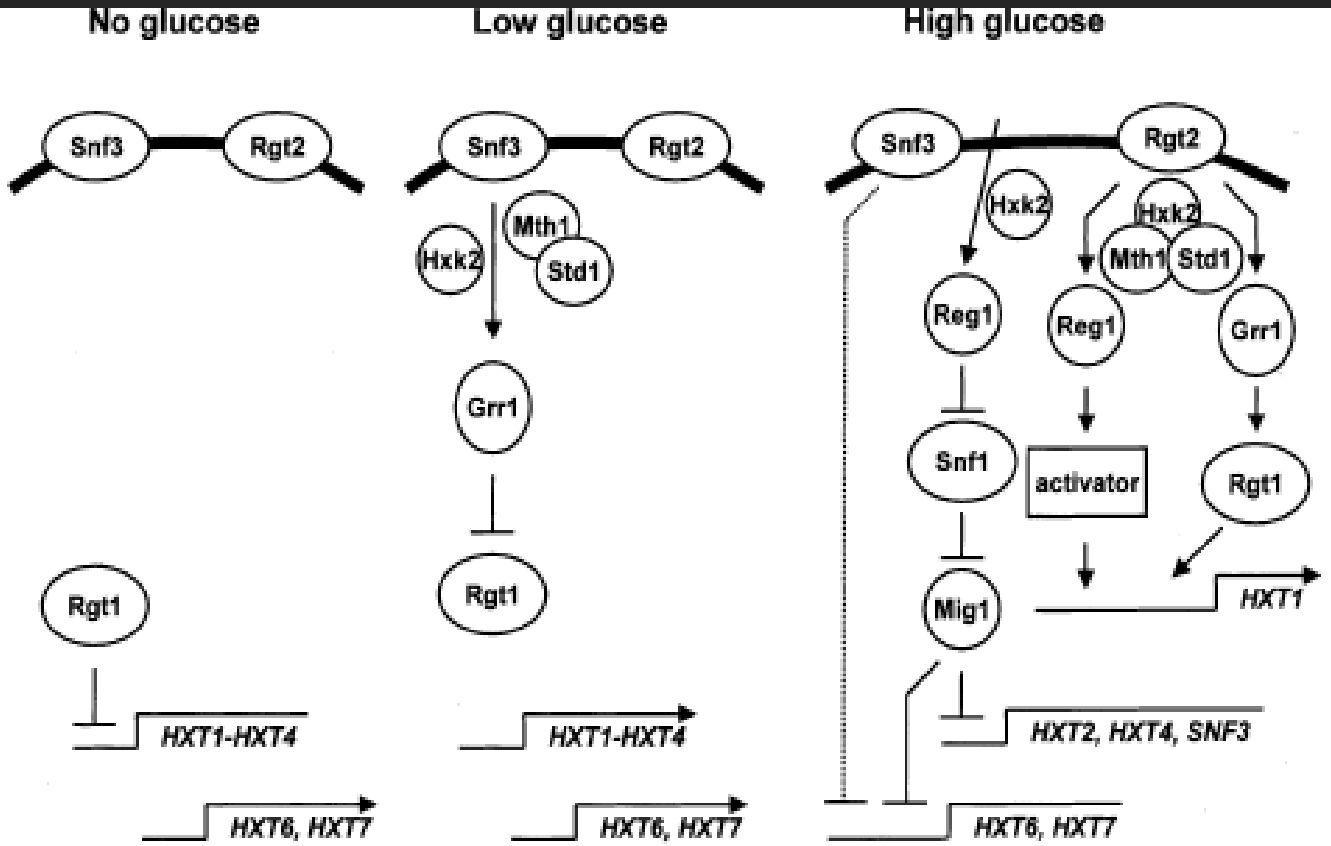


Fig. 2. Regulation of *HXT* transporter gene expression in response to glucose. In the absence of glucose, Rgt1-represses transcription of *HXT1-4*. Low amounts of glucose inhibit the Rgt1-repressing activity, a process triggered by Snf3 via Grr1-mediated ubiquitination. At high concentrations of glucose, Rgt2 triggers *HXT1* expression. This involves Grr1-dependent conversion of Rgt1 into a transcriptional activator and another mechanism in which several components of the main glucose-repression pathway are involved. The Snf3- and Rgt2-mediated derepression of the *HXT* genes also involves sequestering at the plasma membrane of the transcriptional repressors Mth1 and Std1. At high glucose concentrations *HXT2*, *HXT4*, *HXT6* and *SNF3* are repressed by Mig1 via the main glucose-repression pathway. In addition, Snf3 is involved in a second pathway leading to the high-glucose-induced

Rolland et al. (2002). Glucose-sensing and –signaling mechanism. FEMS Yeast Research.

Sucrose Non Fermenting 3, *SNF3*

Hgt4, a high affinity glucose sensor in *C. albicans*,
Removal → failure to grow in low glucose and fermentation-preferred environment (Brown et al., 2006).

Hxs1, a high affinity glucose sensor-like protein in *C. neoformans*,
Removal → delay in lethal infections on mice model (Liu et al., 2013).

Problem statement

- The wide range of *C. glabrata* caused-candidiasis suggests the ability of this yeast to adapt and survive in various host niches.

- Glucose sensing is crucial in contributing to the development and also the physiological fitness of *C. glabrata*, particularly in low glucose environment.

Objective

- To characterize the role of *SNF3* (Sucrose Non Fermenting 3) as glucose sensor and its possible role in coordinating the growth and survivability of *C. glabrata* in local microenvironment.

Methodology

- Derived from BG14 (from Brendan Cormack)

- Different glucose concentration: (0.01%, 0.1%, 0.2%, 1% and 2%)
- CgSNF3Δ vs Cg BG2 (wild type) from Paul Fidel.

- CgSNF3Δ vs Cg BG2 (wild type)

Results

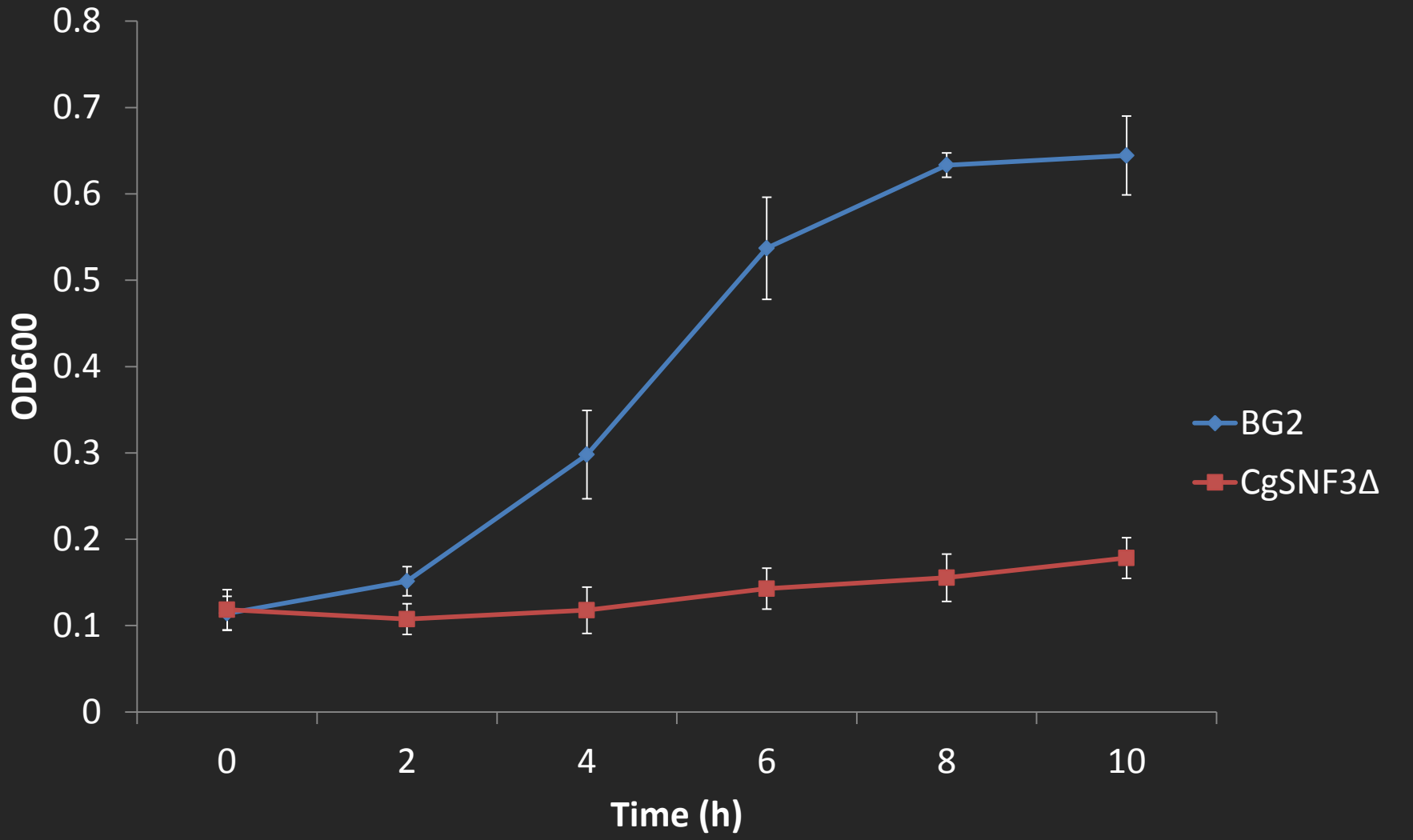


Fig. 1 SNF3Δ mutant displays a growth reduction by 72.3% in 0.01% glucose.

Results

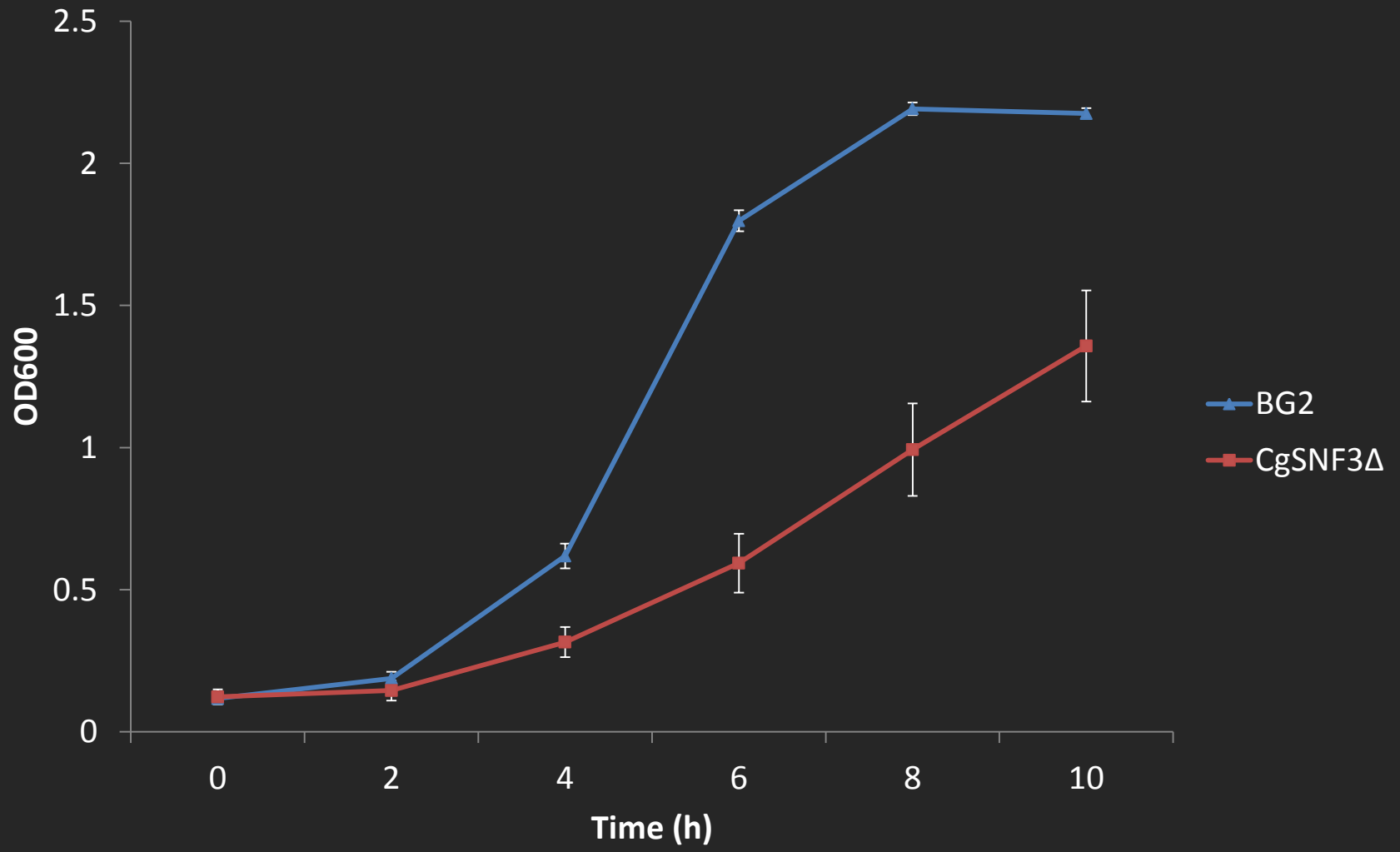
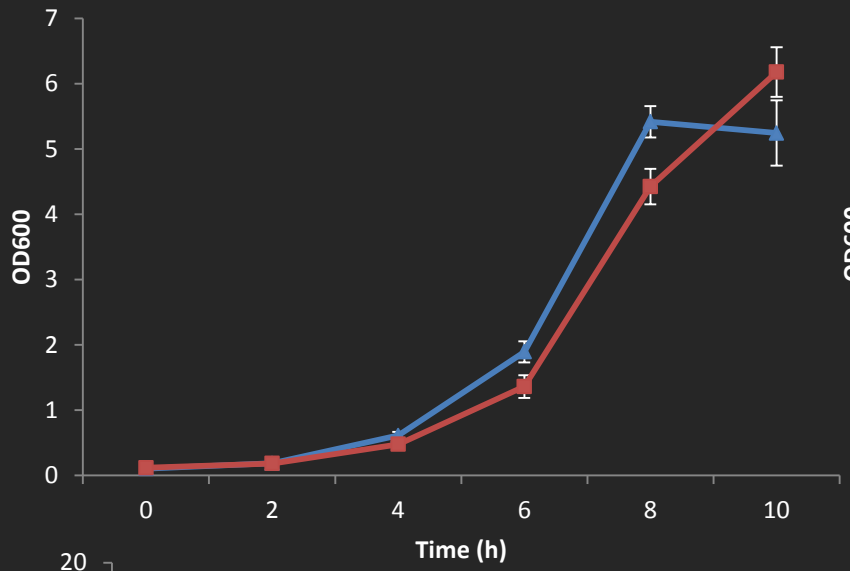
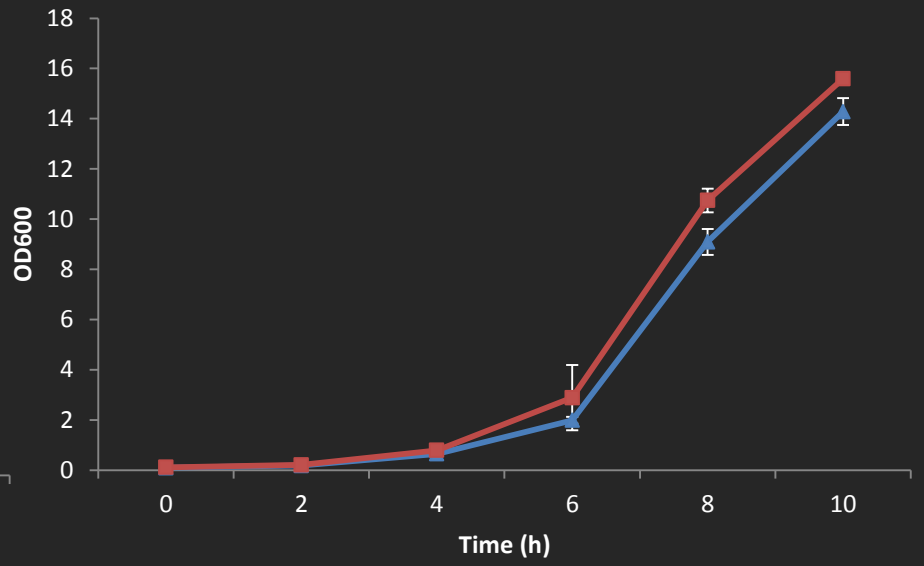


Fig. 2 SNF3Δ mutant displays a growth reduction by 37.5% in 0.1% glucose.

Results





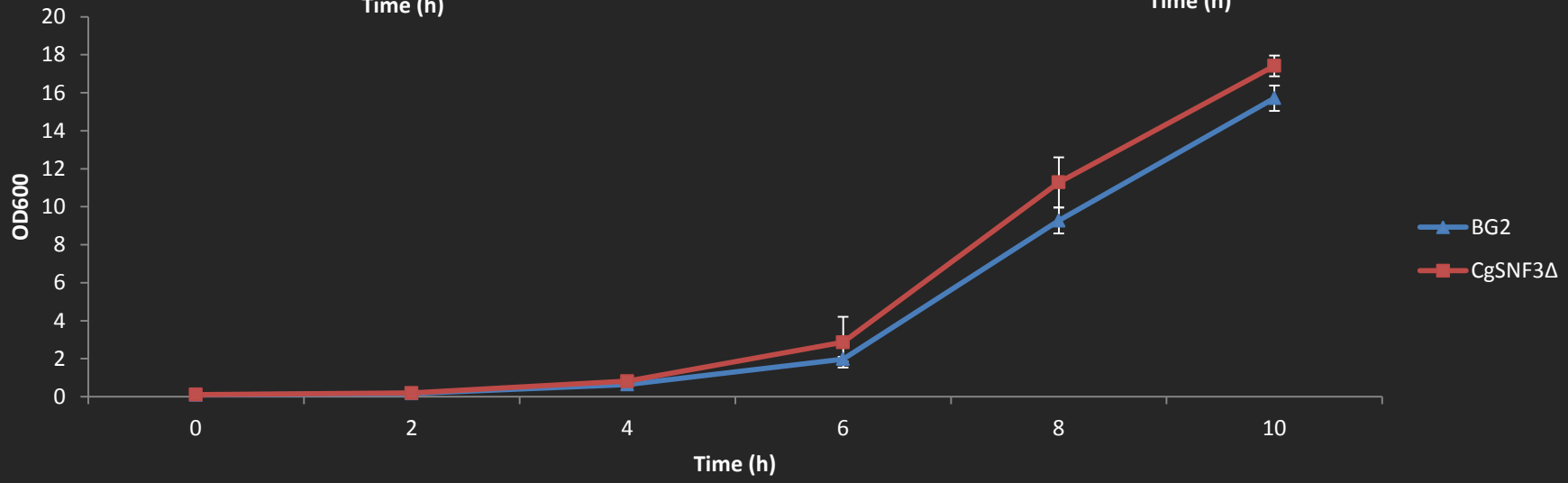


Fig. 3 SNF3Δ mutant displays no significant difference in terms of growth in 0.2%, 1% and 2% glucose.

Results

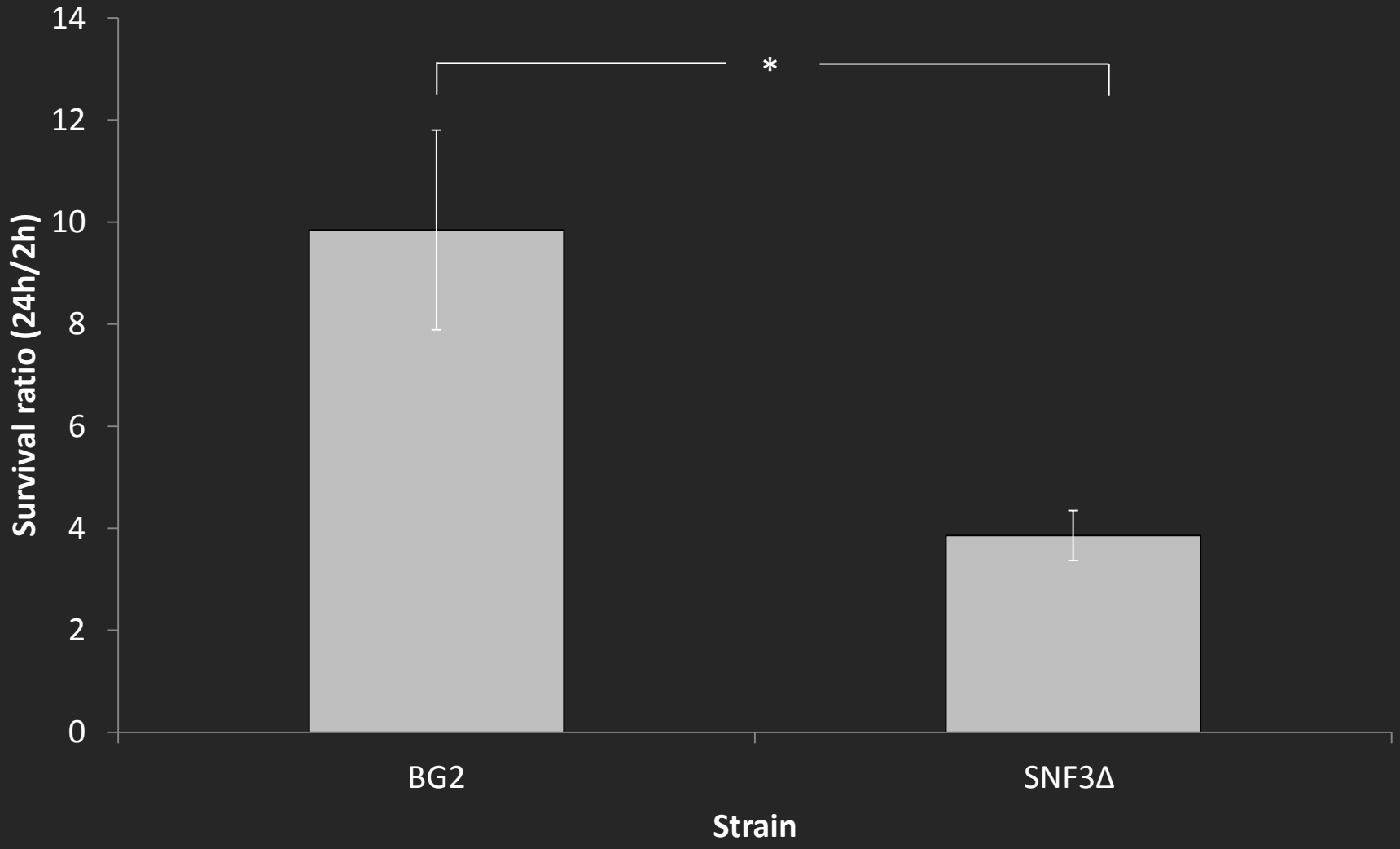


Fig. 3 SNF3Δ mutant displays weaker survivability upon engulfment by macrophage ($p < 0.05$).

Discussion

- *SNF3* serves as a high affinity glucose sensor in yeast and regulates the intake of glucose through SRR (Sugar Receptor Repressor) pathway.
- During phagocytosis, *C. glabrata* is trapped in a microenvironment with limited access to nutrients.
- Deletion of *SNF3* results in the shutdown of *C. glabrata* ability to sense the limited surrounding glucose; thus disrupts its competency to transport and perform the uptake of this critical nutrient.

Conclusion and future work

- These observations have demonstrated the role of *SNF3* as a high affinity glucose sensor and its role in aiding the survivability of *C. glabrata*, particularly in glucose limited environment.
- Further elucidation of glucose sensing and intake pathway may assist in yielding valuable information on the glucose metabolism of *C. glabrata* and be potentially be useful in identifying novel potential anti-fungal drug target site.

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Thank you@Terima kasih

"With knowledge, we serve"