Roles of *Candida albicans* Gat2, a GATA-Type Zinc Finger Transcription Factor, in Biofilm Formation, Filamentous Growth and Virulence

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**Introduction**

*Candida albicans* is the most common human fungal pathogen, causing not only superficial infections, but also life-threatening systemic disease. *C. albicans* can grow in several morphological forms including unicellular yeast-form, elongated hyphae and pseudohyphae. In certain natural environments, *C. albicans* also exists as biofilms, which are structured and surface-attached microbial communities. Transcription factors play a critical role in morphogenesis and biofilm development. In this study, we identified four adhesion-promoting transcription factors (Tec1, Cph1, Ume6 and Gat2) by screening a transcription factor overexpression library. Sequence analysis indicates that Gat2 is a GATA-type zinc finger transcription factor. Here we showed that the gat2/gat2 mutant failed to form biofilms on the plastic and silicone surfaces. Overexpression of *GAT2* gene promoted filamentous and invasive growth on agar containing Lee’s medium, while deletion of this gene had an opposite effect. However, inactivation of Gat2 had no obvious effect on N-acetyl-glucosamine (GlcNAc) induced hyphal development. In a mouse model of systemic infection, the *gat2/gat2* mutant showed strongly attenuated virulence. Our results suggest that Gat2 plays a critical role in *C. albicans* biofilm formation, filamentous growth and virulence.

**Abstract**

*Candida albicans* is the most common human fungal pathogen, causing not only superficial infections, but also life-threatening systemic disease. *C. albicans* can grow in several morphological forms including unicellular yeast-form, elongated hyphae and pseudohyphae. In certain natural environments, *C. albicans* also exists as biofilms, which are structured and surface-attached microbial communities. Transcription factors play a critical role in morphogenesis and biofilm development. In this study, we identified four adhesion-promoting transcription factors (Tec1, Cph1, Ume6 and Gat2) by screening a transcription factor overexpression library. Sequence analysis indicates that Gat2 is a GATA-type zinc finger transcription factor. Here we showed that the gat2/gat2 mutant failed to form biofilms on the plastic and silicone surfaces. Overexpression of *GAT2* gene promoted filamentous and invasive growth on agar containing Lee’s medium, while deletion of this gene had an opposite effect. However, inactivation of Gat2 had no obvious effect on N-acetyl-glucosamine (GlcNAc) induced hyphal development. In a mouse model of systemic infection, the *gat2/gat2* mutant showed strongly attenuated virulence. Our results suggest that Gat2 plays a critical role in *C. albicans* biofilm formation, filamentous growth and virulence.

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incubation time to 48 hours. In this study, we identified three 
more adhesion-promoting transcription factors (Cph1, Ume6 and 
Gat2) in addition to Tec1 which has also been discovered in 
the previous study [15]. Since the roles of Cph1, Ume6 and Tec1 in 
morphogenesis and biofilm formation have been intensively 
investigated, in this study we focused on the biological roles of 
Gat2, a GATA-type zinc finger transcription factor.

Results

Screen for the adhesion-promoting transcription factors

C. albicans biofilm development includes a series of sequential 
steps: adherence → initiation → maturation → dispersal [10]. A lot of 
transcriptional regulators have been reported to control specific 
steps of the developmental process. By screening an overexpression 
library under the control of a doxycycline-inducible promoter 
[16], Sahni et al. have identified one adhesion-promoting 
transcription factor, that is, Tec1. Tec1 has been proved to be 
required for pheromone induced response in C. albicans white cells 
[15]. Given the complexity of biofilm development, we hypothe-
sized that there would be more transcription factors or a 
transcription circuitry involved in the process. To prove this, we 
did another screen by using the same overexpression library 
constructed by the Soll lab [15]. We did the screen in 96-well 
plates at 30°C rather than at 25°C published in the previous study 
[15]. More importantly, we extended culture time to 48 hours 
since the culture time was critical for full biofilm development. 
These changes allowed mature biofilm development and lowered 
the threshold of screening the adhesion-promoting genes. Besides 
Tec1 identified in the early publication [15], we found 3 more 
adhension-promoting transcription factors, including Cph1, Ume6 
and Gat2 Figure 1. Cph1 is a homolog of S. cerevisiae Stc12, which is required for mating and filamentous growth in the yeast. Deletion of CPH1 results in hyphal growth defect on solid Spider medium [8] and blocks mating in C. albicans [17], but does not affect biofilm formation [5,13,15]. Ume6 has been shown to be 
required for hyphal extension, adherence to plastic and virulence 
[12]. Gat2 is a GATA-type zinc finger transcription factor, which 
has been shown to regulate filamentous growth on Spider medium 
in a high-throughput screen [18]. However, the molecular 
mechanism of filamentous growth regulation of Gat2 and its roles 
in invasive growth, biofilm formation and virulence remain 
unclear.

Overexpression of adhesion-promoting genes (GAT2, 
TEC1, CPH1 and UME6) induces filamentous growth

Filamentous growth ability directly relates to adhesion and 
biofilm formation in C. albicans. To further confirm the 
transcription factors we screened, we investigated the roles of the 
four transcription factors in promoting filamentous growth. Since 
the WT strain forms normal filamentous colonies at 37°C, the 
experiment was performed at 30°C, a temperature not favoring 
filamentous growth for C. albicans. As shown in Figure S1, 
overexpression of the transcription factors GAT2, TEC1, CPH1 and 
UME6 in a WT strain promoted filamentous growth dramatically. 
The strain WT+ vector served as a negative control.

Role of Gat2 in biofilm formation

To validate the adhesion-promoting activity of Gat2, we first 
tested the ability of adherence to the plastic 96-well plate bottoms 
in the GAT2-overexpression strain (WT+TETp-GAT2), gat2/gat2 
mutant (gat2/gat2+) and the GAT2-reconstituted strain (gat2/ 
gat2+TETp-GAT2). The wild type strain (WT+ v) carrying an 
empty vector served as control. At 30°C, all the strains were 
unable to adhere to the plastic bottom in the absence of 
doxycyline, while WT+TETp-GAT2 and gat2/gat2+TETp- 
GAT2 showed enhanced adhesion in the presence of 100 µg/ml 
doxycyline. The WT+ v and gat2/gat2+ v strains failed to adhere 
to the plastic bottom even in the presence of 100 µg/ml 
doxycyline. The cells adhered to the bottoms were released and 
quantitated by counting (Figure 2A).

At 37°C, in contrast to the WT+ v and WT+TETp-GAT2 
strains, the gat2/gat2+ v mutant was unable to form biofilms on 
the plastic bottom either in the presence or in the absence of 100 µg/ 
ml doxycyline. However, the reconstituted strain gat2/gat2+ 
TETp-GAT2 adhered to the bottom almost as strongly as the 
WT+TETp-GAT2 strain did in the presence of 100 µg/ml 
doxycyline (Figure 2B).
We also tested for the ability of biofilm development on a silicone cob in the strains as indicated in Figure 2C and D. The gat2/gat2v+ mutant failed to form biofilm on the silicone surface at both 30°C and 37°C either in the presence or in the absence of doxycycline. The gat2/gat2v+TETp-GAT2 strain formed normal biofilm as the reference strain did in the medium containing 100 μg/ml doxycycline at both temperatures (Figure 2C, D). At 30°C, the WT+ v formed normal biofilms on the silicone surface, although the ratio of hyphal cells to yeast cells was much lower than that at 37°C (data not shown). The cells adhered to the surface were quantified (Figure 2C, D). Visualization of scanning electron microscopy (SEM) confirmed the inability of biofilm development of the gat2/gat2 mutant on silicone material surface (Figure 3). The gat2/gat2+TETp-GAT2 and WT+ TETp-GAT2 strains underwent robust filamentous growth and formed thick biofilms under inducing condition (Figure 3), while their phenotypes were similar to the gat2/gat2 mutant and WT strains, respectively, under non-inducing condition (data not shown). The biofilm ultrastructure indicated that the biofilm formed by the wild type reference strain was a mixture of yeast cells and filamentous cells both at 30°C and at 37°C. However, the percentage of filamentous cells was much higher at 37°C than that at 30°C. The gat2/gat2 mutant failed to undergo filamentous growth at 30°C and formed a few elongated cells at 37°C. Notably, the SEM images showed that the gat2/gat2 mutant remained the basal level ability of adhering to the surface, although the number of adhered cells was much less than that of the WT.

Deletion of gat2/gat2 results in filamentous growth defect on Lee’s medium plates

Given the importance of hyphal development in biofilm formation, we hypothesized that Gat2 could play critical roles in filamentous growth. To test this, we first examined the hyphal growth ability of the strains WT+ v, gat2/gat2v+, WT+TETp-GAT2 and gat2/gat2v+TETp-GAT2 on agar containing Lee’s medium. In contrast to WT+ v, the mutant gat2/gat2v+ was unable to form filamentous colonies at 37°C (Figure 4A). In the presence of 50 μg/ml doxycycline, the overexpression strain WT+TETp-GAT2 showed slightly stronger ability of filamentation than the WT+ v and gat2/gat2v+TETp-GAT2 strains did (Figure 4A). At the cellular level, under inducing condition the WT+TETp-GAT2 was composed of over 90% of filamentous cells, while the WT+ v and gat2/gat2v+TETp-GAT2 were composed of ~80% and 95% of filamentous cells, respectively. We also did similar experiments at 25°C, a temperature unfavorable for C. albicans filamentous growth. We observed that only the overexpression strain was able to form star-like filamentous colonies under inducing condition at this temperature (Figure 4B). The gat2/gat2v+TETp-GAT2 strain showed weak filamentous growth. The cellular images were also presented in...
Figure 4B. The additive effect of the endogenous and the ectopic expression of \textit{GAT2} gene could result from the increased gene copies.

Gat2 is not required for serum and GlcNAc induced filamentous growth

Different environmental cues induce filamentous growth through distinct pathways. Serum is thought to be the most potent hyphal inducer. We therefore tested whether Gat2 was also required for serum induced hyphal development. As shown in Figure 5, deletion of \textit{GAT2} obviously attenuated filamentous growth ability but did not block the effect of serum induction both on agar and in liquid medium at 37°C. Compared to the reference strain, the \textit{gat2/gat2} mutant formed small and less branched hyphal colonies on agar+serum plates. Consistently, the \textit{gat2/gat2}

**Figure 4.** \textit{Gat2} is required for filamentous growth on Lee's medium. The strains indicated were incubated under non-inducing (0 µg/ml doxycycline) or inducing (50 µg/ml doxycycline) conditions. Colony and cellular pictures were shown. A. Filamentous growth at 37°C. B. Filamentous growth at 25°C. doi:10.1371/journal.pone.0029707.g004
mutant formed shorter hyphal cells in liquid YPD+10% serum medium.

GlcNAc is a powerful filamentous growth inducer in *C. albicans* [19]. Recently, we have reported that GlcNAc also regulates white-to-opaque transition via Ras1-cAMP/PKA pathway in this organism [20]. To investigate whether Gat2 was essential for GlcNAc induced yeast-to-hyphal transition, we incubated the reference and the mutant strains on SD-GlcNAc plates at 37°C. We found that the *gat2/gat2* null mutant formed obviously wrinkled hyphal colonies, although they were not highly wrinkled as those formed by the reference strain (*Figure 5*). These results indicate that Gat2 is not required for serum or GlcNAc induced filamentous growth.

**Gat2 is required for invasive growth**

The ability of *C. albicans* to undergo invasive growth is tightly linked to infection. To test the role of Gat2 in invasive growth, we performed the experiments at both 25 and 37°C. At 25°C, all the strains indicated in the figure were unable to undergo invasive growth under non-inducing condition, while the WT+TETp-GAT2 and *gat2/gat2+TETp-GAT2* strains showed invasive growth under inducing condition (*Figure 6*). And the WT+TETp-GAT2 showed stronger invasive growth ability than the *gat2/gat2+TETp-GAT2* strain did. At 37°C, under non-inducing condition the *gat2/gat2+TETp* and *gat2/gat2+TETp-GAT2* failed to undergo invasive growth as the WT+ v and WT+TETp-GAT2 strains did. Under inducing condition, in contrast to the *gat2/gat2+TETp* strain, the *gat2/gat2+TETp-GAT2* also underwent invasive growth as the WT+ v and WT+TETp-GAT2 strains did (*Figure 6*).

**Deletion of GAT2 attenuates *C. albicans* virulence in a mouse model of systemic infection**

Filamentous morphogenesis is important for *C. albicans* virulence. Therefore, we tested the virulence of *gat2/gat2* mutant in a mouse model of systemic candidiasis. All of the mice injected with the WT reference strain died within 6 days, whereas the mice

![Image](https://example.com/image.png)

*Figure 5. Deletion of GAT2 impaired, but did not block filamentous growth induced by serum or GlcNAc.* On solid agar, the strains were cultured for 5 days at 37°C and then imaged. In liquid YPD+serum medium, the strains were cultured for 4 hours at 37°C with shaking.

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injected with *gat2/gat2* mutant died after a longer time period. Three mice (37.5%) were still alive at 20 days post-infection (Figure 7). To confirm the decrease of virulence was due to the deletion of *GAT2*, we constructed a complemented strain by inserting a fragment containing *GAT2* ORF and ~400 bp promoter on the original *GAT2* locus. The filamentous growth ability of the complemented strains was restored (Figure 7A), although it was weaker than the WT. Notably, all the mice injected with the complemented strain were died within 8 days, suggesting that it was almost as virulent as the reference strain (Figure 7B). These results indicate that *gat2/gat2* mutant plays a role in virulence at least in a systemic infection model of mice.

**Discussion**

Recently, Sahni et al. have identified *C. albicans* Tec1 as a key regulator of pheromone induced biofilm development through screening a transcription factor overexpression library [15]. To get more extensive insights into the molecular mechanism of biofilm and hyphal development, we did another screen using the same library with modified protocols in this study. We identified three more adhesion-promoting transcription factors (Cph1, Ume6 and Gat2) besides Tec1 that was also described in the previous report [15]. The roles of Tec1, Cph1 and Ume6 have been intensively investigated by us and others [8,12,15,21]. Tec1 plays a critical role in both biofilm formation and filamentous growth [14,15,21]. The transcription of *TEC1* gene is regulated by Cph2, a Myc-bHLH family transcriptional activator of filamentous growth [22], while Tec1 controls the expression of biofilm regulator Bcr1 [14]. Cph1 regulates mating and filamentous growth in *C. albicans* [8,17]. Ume6 has been proved to be required for hyphal extension, adhesion and virulence [12]. The GATA-type transcription factor Gat2 has been reported to be required for filamentous growth on Spider medium, a nutrient-poor medium for morphological analysis [18]. Consistent with previous study, we found that all the four transcription factors (Tec1, Cph1, Ume6 and Gat2) promote filamentous growth on solid Lee’s medium. Additional experiments indicate that Gat2 plays important roles in biofilm formation, filamentous and invasive growth, and also virulence.

Biofilm development is controlled by a number of transcription factors including Tec1, Bcr1, Ume6, Efg1 and Zap1 [12,14,15,23,24]. Here, we added Gat2 to the list of biofilm regulators. Overexpression of *GAT2* in a wild type strain promotes adhesion and biofilm formation, while deletion of *GAT2* results in biofilm development defect.

Filamentous growth ability is thought to be important for biofilm development. Hyphae provide the structure integrity and multilayered architecture feature of mature biofilms [9]. Although Gat2 is not essential for serum- and GlcNAc-induced hyphal growth, deletion of *GAT2* notably attenuated the ability of hyphal growth stimulated by these two inducers, especially by serum. Remarkably, deletion of *GAT2* completely blocked filamentous growth in Lee’s medium. These data suggest that different environmental cues activate filamentous growth via different pathways. Gat2 plays critical roles in Lee’s medium induced morphogenesis and is at least partially involved in regulation of serum- and GlcNAc-induced yeast-to-hyphal transition. Consistently, we found that Gat2 is also not required for GlcNAc induced white-to-opaque switching in an *MTLa/a* strain (data not shown).

Given the importance of filamentous growth ability in biofilm
development, Gat2 possibly regulates biofilm development through filamentous growth control. Gat2 could be involved in regulation of the biofilm “initiation” and “maturation” steps, in which filamentous cells play critical roles [10].

In S. cerevisiae, ScTec1 binds to the promoter of ScGAT2 [25]. By sequence analysis, we found two putative Tec1 binding sites on the promoter region of GAT2 gene (TCATTCT and ACATTCT) [26]. Interestingly, tec1/tec1 mutant showed similar phenotypes on SD-glucose and SD-GlcNAc media as gat2/gat2 mutant did. Both Tec1 and Gat2 were not required for filamentous growth induced by GlcNAc, but were essential for full hyphal development on SD-glucose medium (data not shown). Similar roles of Gat2 and Tec1 in adhesion and GlcNAc induced filamentous growth suggest that Gat2 possibly functions downstream of Tec1 in regulation of morphogenesis and biofilm development.

Our findings reveal that Gat2 is involved in regulation of biofilm development, morphogenesis and virulence. On Lee’s medium plates which are characterized by neutral pH and poor nutrient, deletion of GAT2 gene completely blocked filamentous and invasive growth. However, Gat2 is not essential for filamentous growth induced by some environmental cues, such as serum and GlcNAc. We propose that Gat2 specifically regulates morphogenesis in some host niches.

**Materials and Methods**

**Strains and growth conditions**

The transcription factor overexpression library was constructed by the Soll lab [15]. The gat2/gat2 mutant and the reference strain were requested from the Johnson’s lab [18]. While the strains used in **Figure 1** and **Supplemental figure S1** were homozygous at MTL locus (a/a), all the others were MTL heterozygous (a/α). Solid YPD medium (20 g/L Difco peptone, 10 g/L Yeast extract, 20 g/L glucose, 20 g/L Agar) and Lee’s medium supplemented with 5 μg/ml phloxin B were used for routine growth. Lee’s medium, SD-glucose, SD-GlcNAc and agar+serum plates were used for filamentous development [27]. In the SD-GlcNAc medium, 2% GlcNAc replaced glucose as carbon source. K2HPO4 (2.5 g/L) was added to the SD-glucose and SD-GlcNAc media for pH maintenance. The pH of Lee’s and SD media was adjusted to 6.8 with 10% HCl.

To construct the complemented strain gat2/gat2+GAT2p-GAT2, we first generated a plasmid pGAT2res for transformation of the gat2/gat2 mutant. A fragment of the 3-UTR of GAT2 and a fragment containing the GAT2 ORF and 400 bp of the promoter region were subsequently inserted into the plasmid pNIM1, and yielded pGAT2res. The complemented strain was generated by transforming the gat2/gat2 mutant with SalI digested pGAT2res fragments. The oligonucleotides used for PCR were listed below:

- GAT2-3F-xho: 5-aatcaaCTCGAGcgctgtaaattatatcctga-3;
- GAT2-3R-Bglsal: 5-aatcaaAGATCTatGTCGACatatctcagtg-3acaggagaa-3;
- GAT2-5F-Sal: 5-aatcaaGTCGACaacccgtttaacatttgcagc-3;
- GAT2-5R-Bgl: 5-aatcaaAGATCTaattagatgtgtacattaatttctatg-3.

**Biofilm assay**

Biofilm experiments were performed as described previously with slight modifications [15]. For adhesion to the plastic bottoms, cells

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**Figure 7.** The gat2/gat2 mutant is attenuated for virulence in a mouse systemic infection model. A. Filamentous growth of the reference strain, gat2/gat2 mutant and the complemented strain gat2/gat2+GAT2p-GAT2. 3000 cells of each strain in 3 μL of ddH2O were dropped onto solid Lee’s medium plates and incubated at 37°C for 3 days. Two independently isolated strains were shown. B. Survival curves for the reference strain, gat2/gat2 mutant and the complemented strain gat2/gat2+GAT2p-GAT2. For each strain, 8 mice were used for infection. doi:10.1371/journal.pone.0029707.g007
were cultured in Costar 96-well Cell Culture Plates at temperatures indicated in the main text. After 40 hours of incubation with shaking, the wells were gently washed with 1× PBS (phosphate-buffered saline). The bottoms were imaged. Biofilm growth on silicone material was performed as reported with slight modification [14]. Briefly, cells were incubated in a well of a 24-well cell culture plate containing a round silicone block with a diameter of 1 cm. Silicone blocks were cut from Cardiovascular Instrument silicone sheets. After 48 hours of culture, the silicone blocks were carefully washed and taken out for imaging. After gently washing, the cells adhered to the bottoms of 96-well plates or silicone material were treated with trypsin and collected for quantitation.

Scanning electron microscopy (SEM)

For SEM, we developed C. albicans biofilms on silicone blocks. The SEM assay was performed as previously reported [11]. Briefly, the samples were gently washed with 1× PBS and fixed with 2.5% glutaraldehyde. Then, the samples were washed three times with 0.1 M Na2PO4 buffer (pH 7.2), dehydrated in increasing concentrations of ethanol (30% - 50% - 70% - 85% - 95% - 100%) and coated with gold. The surface of the biofilm was imaged with a scanning electron microscope (FEI QUANTA 200).

Invasive and filamentous growth assays

Lee’s medium plates with or without doxycycline as indicated were used for invasive growth. 3 μl of liquid medium containing 2×10^4 cells was dropped onto the agar for 2 days (at 37°C) or 5 days (at 25°C) of incubation. The plates were imaged before and after washing with H2O. Agar containing serum, Lee’s medium, SD-glucose or SD-GlcNAc medium was used for filamentous growth analysis. The colonies were imaged after 5 days’ culture at temperatures indicated.

Virulence experiments

The virulence of C. albicans strains was performed as reported by Chen et al. [28]. ICR male mice (18-22 g) were used for the systemic infection experiments. 100 μl of 1× PBS containing 2×10^6 cells was injected into each mouse. All animal experiments were performed according to the guidelines approved by the Animal Care and Use Committee of the Institute of Microbiology, Chinese Academy of Sciences (permit number: IMCAS2011002). The present study was approved by the Committee.

Supporting Information

Figure S1 Ectopic expression of adhesion-promoting genes (GAT2, TEC1, CPH1 and UME6) induces filamentous growth in C. albicans. The strains were cultured at 30°C for 5 days and imaged. (TIF)

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Author Contributions

Conceived and designed the experiments: HD LZ GH. Performed the experiments: HD GG JX YS YT GH. Analyzed the data: HD GH. Contributed reagents/materials/analysis tools: HD GG JX YS YT GH. Wrote the paper: HD GH.

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