SM Online
Scientific Resources

SM Journal of Infectious Diseases

Research Article

Suppression of *Candida albicans* Growth and Filamentation by Oral *Staphylococcus aureus*

Peng Zhou[1]*, Priyanka Kainthla[2], Xiaoli Li[1] and Fengxia Qi[1]

[1]*Department of Microbiology and Immunology, The University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA*

[2]*Department of Pediatric Dentistry, Baylor College of Dentistry, Texas A&M University Health Science Center, Dallas, TX 75246, USA*

Article Information

Received date: May 24, 2017
Accepted date: Jul 24, 2017
Published date: Jul 28, 2017

***Corresponding author**

Peng Zhou, University of Oklahoma Health Sciences Center, 975 NE 10th Street, Oklahoma City, OK 73104, USA, Tel: 405-271-3668; Fax: 405-271-3603; Email: zhoup1228@gmail.com

Keywords *Staphylococcus aureus; Candida albicans;* Hyphae; Growth suppression

Abstract

Background: *Candida albicans* is the most prevalent yeast isolated from the human body and a natural part of the commensal microbiota; however, under the right conditions, *C. albicans* can cause candidiasis (oral thrush). The oral cavity is colonized by hundreds of bacterial species, and the relationship between these oral bacteria and *C. albicans* has been a topic of interest in understanding the development of candidiasis. Several studies have attempted to explain the bacteria-fungal relationship in the oral environment, but few have focused on single bacterial species inhibiting growth and morphogenesis of *C. albicans*. The aim of this study was to identify specific bacterial species, isolated from the healthy human oral cavity, can suppress *C. albicans*.

Materials and methods: Bacterial and yeast species were isolated and purified from the saliva samples of 12 healthy individuals. PCR was performed by using 16SrDNA and 18S rDNA as templates to identify bacterial and yeast species for all isolates, respectively. Real time qPCR and microscopic examination were carried out to determine the inhibitory effect of *S. aureus* on *C. albicans*.

Result: This study demonstrated that numerous bacterial isolates from the oral cavity of healthy humans could inhibit the growth of *C. albicans* oral isolates, including the model strain CS5314. Among these bacteria, one *Staphylococcus aureus* strain displayed the strongest inhibitory effect on the growth of yeasts. By qPCR assay, all isolated *C. albicans* strains were inhibited on the growth by *S. aureus* in various degrees. Mixed culture experiments also demonstrated suppression of *C. albicans* pseudo hyphae or hyphae formation by *S. aureus* but not by other bacterial species tested.

Conclusion: it is well known that *C. albicans* and *S. aureus* exist in a cooperative relationship and form substantial polymicrobial biofilm, thus, this is a first report about one clinical isolated *S. aureus* strain suppressing the growth and pseudohyphae/hyphae formation of *C. albicans*, indicating the complexity of interspecies interaction in human oral cavity.

Introduction

The human oral cavity is a diverse microbial ecosystem comprised of bacteria, fungi, protozoa, and viruses [1]. Over 700 species of bacteria are known to reside within the human oral cavity, and more than 100 species are found in the mouth of a healthy individual at one time [2].Normally, the different species maintain an ecological homeostasis; however, due to constant competition for limited space and nutrients, any disturbance of the biofilm by environmental factors or interspecies interactions can favor the growth of certain species, leading to diseases [3].

One such disease is oral candidiasis (oral thrush), which is caused by *Candida albicans*, the most prevalent yeast isolated from the human body and a natural part of the commensal microbiota [4]. Studies showed that *C. albicans* can be found in 50-60% of clinically healthy mouths and are often associated with bacterial species in polymicrobial biofilms [5,6]. Under certain conditions, resident *C. albicans* strains can become invasive, causing recurrent mucosal or life-threatening infections [7]. Nevertheless, despite a considerable portion of the population carrying the yeast, very few of these people suffer from oral Candidiasis, suggesting the presence of factors suppressing the pathogenic attributes of *C. albicans* [4].

Researchers have attempted to explore the bacteria-fungal relationship in the oral environment. Co-culture studies utilizing various oral commensal bacterial species showed that higher concentrations of certain bacteria, like *Actinomyces israelii*, *Porphyromonas gingivalis*, and *Prevotella nigrescens*, result in a reduction of Candida in biofilms [5]. The mechanism of this reduction could be explained as a result of nutritional competition as suggested by Cannon et al. [8]. In addition, oral *Streptococcus salivarius* was reported to suppress yeast growth by interfering with its ability to adhere to the oral mucosal surfaces [9]. However, this finding was later challenged by de Miranda et al., who could not reproduce the suppressive effect of *S. salivarius* upon *C. albicans in vivo* and *in vitro* [10].

The mitis group streptococci (principally represented by *Streptococcus mitis*, *Streptococcus oralis* and *Streptococcus gordonii*) are considered 'initial colonizers', comprising greater than 80% of the early biofilm population on a professionally cleaned or newly emerged tooth surface [2,11,12]. *S. gordonii* has been shown to co-aggregate with *C. albicans* and form biofilms, and the interactions between the two species may result in pathogenic synergy, allowing *C. albicans* to integrate into the oral biofilms [13,14]. In the presence of *S. gordonii*, *C. albicans* hyphal morphogenesis was also found to be enhanced [15]. Like *S. gordonii*, *Staphylococcus aureus*, a pathogen that can cause opportunistic infections, has been shown to be able to form substantial polymicrobial biofilm when *C. albicans* presented [16]. Furthermore, co-infection of *S. aureus-C. albicans* results in synergistic effect and increased morbidity and mortality *in vivo* [17,18].

In this study, we isolated bacteria and yeast from the healthy human oral cavity and identified specific bacterial species that can suppress *C. albicans* growth or hyphae formation. Interestingly, among all isolated and identified bacteria, one clinical *S. aureus* strain showed significant suppression of growth and inhibition of pseudohyphae or hyphae formation for all clinically isolated *C. albicans* strains. To our knowledge, this is the first report of the inhibitive effect of *S. aureus* on *C. albicans*.

Materials and Methods

Bacteria and yeast isolation. Saliva from 12 healthy individuals was collected upon IRB approval (#1471). Bacterial species were isolated on brain heart infusion (BHI) agar (1.5% agar) plates under both aerobic and anaerobic conditions. Purified colonies were grown in BHI medium and visualized microscopically (Olympus Microscope 60X/1.40 Oil Ph3). Species were identified by 16S rDNA sequencing (the primers in Table 1) [19], and stored in BHI containing 15% glycerol at -80°C. Yeast strains were isolated on BHI plates grown aerobically, and species were identified by 18S rDNA sequencing (Table 1) (20).*Candida albicans* strain ATCC CS5314 was purchased from ATCC and routinely grown in YEP (1% yeast extract, 2% peptone supplemented with 2% glucose).

Identification of bacterial and yeast strains. The chromosomal DNA was isolated for bacteria or yeast using Wizard® Genomic DNA Purification Kit (Promega, USA) or E.Z.N.A® Yeast DNA Kit (OMEGA, USA) according to the protocols, respectively. The 16S rDNA or 18s rDNA were PCR amplified using universal primers (Table 1). PCR was performed with the following parameters: 1 cycle of 98°C for30 sec; 30 cycles of 98°C for 10 sec; 54°C for 30 sec; 72°C for 45 sec; 1 cycle of 72°C for 7 min. The PCR products were purified and sequenced. The 16S rDNA and 18S rDNA sequence results were then analyzed using the NCBI BLAST tool (http://blast.ncbi.nlm.nih.gov) to identify the bacterial or yeast species.

Bacteria-yeast mixed culture. Single-species overnight cultures of bacteria or yeast were centrifuged, and the cell pellet was washed twice using semi-CDM (Chemical Defined Medium) medium [21] supplemented with 0.1% peptone and 0.1% glucose. The cultures were then re-suspended to OD600of ~1.0 in the same medium prior to mixing. To make the mixed culture, a 20-fold dilution was made for the yeast culture in the semi-CDM medium, and 1 mL was added to each well of a 24-well plate (Falcon Multiwell Culture Plate, USA). Fifty micro liters of the re-suspended bacterial culture were then added to each well of the yeast culture plate leaving one well for yeast only and one well for bacteria only as mono-species controls. The culture plate was incubated for 18 h at 37°C aerobically before sample analysis.

qPCR quantification of *C. albicans* in co-culture.After18 h incubation at 37°C, the mixed cultures described above were collected and total chromosomal DNA was isolated using E.Z.N.A® Yeast DNA Kit (OMEGA, USA) according to the manufacturer's protocol. The abundance of *C. albicans* was analyzed by qPCR using *C. albicans*-specific primers (Table 1). The fold change was expressed as 2-[Ct (co-culture)-Ct (single culture)]. All experiments were repeated at least 3 times.

Statistical Analysis.The Student's test was used for statistical analyses and the significance was accepted ATP < 0.05,0.01<p < 0.05*; 0.005 <p < 0.01**; 0.001 <p < 0.005***; 0.0005 <p < 0.001****; 0.0001< P< 0.0005*****.

Results

Inhibition of *C. albicans* strain CS5314 growth by oral bacteria. To determine the effect of oral bacteria on yeast growth, model *C. albicans* strain CS5314was used in mixed cultures with 8 isolated oral bacterial strains, respectively. After 18h incubation, biofilm formation was visible at the bottom of all wells. Microscopic evaluation revealed a vast array of yeast-bacteria interactions, including bacterial attachment to yeast cells/hyphae, bacterial clumping and/or isolation away from yeast, and bacterial indifference to yeast (Figure 1). The presence of yeast cells, pseudohyphae, and hyphae also varied among yeast mixed with different bacterial strains. In addition, some bacteria appeared to be more effective than others in inhibiting the growth of *C. albicans* (data not shown).

Bacterial strains identification

The four most effective and four least effective bacterial strains in inhibiting yeast growth were chosen. 16S rDNA sequence analysis revealed *S. aureus* (Figure 1B), *S. salivarius* (Figure 1C), and

Table 1: Primers used in this study.

Primer	Sequence (5' to 3')	Purpose
Bac-16S-F	AGAGTTTGATCCTGGCTCAG	Sequence of bacterial 16S rDNA
Bac-16S-R	TACGGTTACCTTGTTACGACTT	Sequence of bacterial 16S rDNA
Yeast-18S-F	ATCTGGTTGATCCTGCCAGT	Sequence of yeast 18S rDNA
Yeast-18S-R	GATCCTTCCGCAGGTTCACC	Sequence of yeast 18S rDNA
Ca-18S-qPCR-F	GACTCAACACGGGGAAACT	qPCR for *C. albicans*
Ca-18S-qPCR-R	ATTCCTCGTTGAAGAGCA	qPCR for *C. albicans*

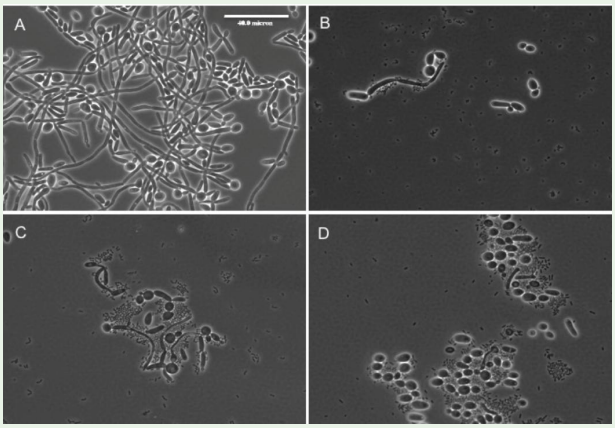

Figure 1: Yeast growth in nutrient media supplemented with individual bacterial species isolated from the oral cavity. Microscope images show growth following 18 h incubation. (A) Control- yeast growth in the absence of bacteria; (B) Yeast growth in the presence of *S. aureus*; (C) Yeast growth in the presence of *S. salivarius*; (D) Yeast growth in the presence of *E. aerogenes*. All experiments were repeated at 3 times. Bar = 40 µm.

Enterobacter aerogenes (Figure 1D) were the species identified as being able to inhibit yeast growth the most; whereas the four strains that were least effective were *Neisseria subflava*, an unidentifiable Neisseria species, *Neisseria meningitides* and *Neisseria flavescens* (data not shown).Among all eight bacterial species, *S. aureus* showed the highest capability of impairing the growth of *C. albicans* CS5314strain.

Inhibition of growth of clinically isolated yeast strains by *S. aureus*. To study the inhibitive effect of clinically isolated *S. aureus* strain on oral yeasts, 7 yeast strains were isolated and purified from the saliva of different healthy human subjects. The18s rDNA sequencing showed that they all belong to *C. albicans*. Mixed culture experiments were carried out in semi-CDM [21]. After an 18 h co-incubation at 37°C, all cultures were harvested, and total genomic DNA was isolated, and qPCR was utilized for measuring the abundance of *C. albicans* by using *C. albicans*-specific primers [22]. This primer pair did not generate any PCR product when using *S. aureus* or S. gordonii chromosomal DNA as template (date not shown). As shown in Figure 2, compared to the single culture control, the growth of *C. albicans* 9# and 20# were reduced by 6.33-fold and 8.50-foldin the presence of *S. aureus*, respectively (0.0001< P< 0.0005), and the other 5 strains displayed 2-3 times reduction as well. This difference of *S. aureus* inhibitory effects might be due to various characteristics of the 7 clinically isolated strains of *C. albicans*, thus, further investigation is required to determine the exact mechanism.

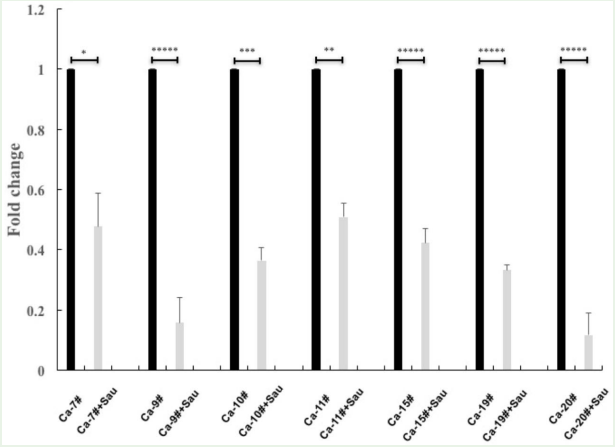

Figure 2: Clinically isolated *C. albicans* strains were inhibited in mixed cultures with *S. aureus* by using qPCR assay. All tests were carried out in semi-CDM media. *C. albicans* single culture and co-cultures with *S. aureus* were grown 18 h at 37°C, after incubation, total DNA was extracted from biofilms, analyzed by qPCR using *C. albicans*-specific primers. The fold change was expressed as $2^{-[Ct\ (co\text{-}culture)-Ct\ (single\ culture)]}$. Ca: *C. albicans*; Sau: *S. aureus*. All experiments were repeated at least 3 times and shown as mean ± SD. The Student's test was used for statistical analyses and the significance was accepted ATP < 0.05, 0.01<p <0.05*; 0.005 <p < 0.01**; 0.001 <p < 0.005***; 0.0005 <p < 0.001****; 0.0001< P< 0.0005*****.

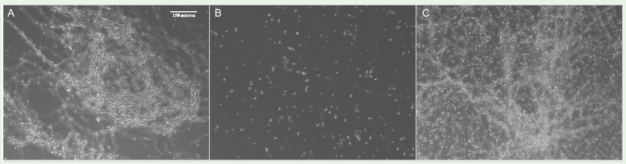

Figure 3: Hyphae generating strain *C. albicans* 7# co-cultured with *S. aureus* or *S. gordonii* in semi-CDM media. Microscope images show growth following 18 h incubation. (A) single culture of *C. albicans* 7# strains as growth control; (B) the growth of *C. albicans* 7# in the presence of *S. aureus*; (C) the growth of *C. albicans* 7#in the presence of *S. gordonii*. All experiments were repeated at 3 times. Bar = 150 µm.

Inhibition of pseudohyphae or hyphae formation of clinically isolated yeast strains by *S. aureus*. It has been demonstrated that S. gordonii can enhance *C. albicans* hyphal morphogenesis [15], due to the inhibitive effect of this *S. aureus* strain on the growth of *C. albicans*; we hypothesized that it might be able to affect hyphal formation of latter. To study this, mixed culture experiments were implemented and showed that *S. aureus* suppressed the formation of pseudohyphae or hyphae of all seven clinical *C. albicans* strains in spite of the discrepant capability of generating pseudohyphae or hyphae (data not shown). *C. albicans* 7#, generating the most luxurious hyphae, was chosen to be representative in this study, and *S. gordonii* was used as control because of its ability to promote *C. albicans* hyphae formation [15,23]. As shown in Figure 3, single culture of *C. albicans* 7# strain formed robust hyphae (Figure 3A), but in the presence of *S. aureus*, the formation of hyphae was nearly suppressed (Figure 3B). In contrast, *S. gordonii* lightly increased the *C. albicans* hyphae formation (Figure 3C). To our knowledge, this is the first report of *S. aureus* strain inhibiting the hyphae formation of *C. albicans in vitro.*

Discussion

Growth suppression of *C. albicans* by oral flora has been well documented in literature. The aim of this study was to investigate the effect of clinical isolated oral bacterial species on the growth and hyphae formation of *C. albicans* isolated from the oral cavity. Our findings indicate that some bacterial species isolated from saliva could suppress yeast growth to some extent, and one isolated *S. aureus* strain showed the strongest inhibitive effect on the growth and pseudohyphae/hyphae formation of all clinically isolated *C. albicans* strains.

Candida infections rely on the organism's ability to switch morphology between yeast cells and hyphae forms in order to adhere to surfaces, form biofilms, and penetrate tissues [7,24]. Hyphae are believed to be the invasive and pathogenic form of Candida species while yeast is the commensal nonpathogenic form [4]. Some molecules generated by Gram-negative bacteria were reported to inhibit the formation of hyphae in *C. albicans*, e.g. 3-oxo-C12 homoserine lactone or cis-2-dodecenoic acid (BDSF) produced by *Pseudomonas aeruginosa* or *Burkholderia cenocepacia*, respectively [25,26]. Gram-positive bacterium *Streptococcus mutans* also produces Competence Stimulating Peptide (CSP), trans-2-decenoic acid and secondary metabolites to suppress filamentation in *C. albicans* [27-29]. However, there is no report about hyphal repression of *C. albicans* by *S. aureus*, since it is well known that these two microbes usually form mixed fungal-bacterial biofilms, and this structure confers them extreme resistance to antimicrobial compounds or host clearance forces [30, 31]. Furthermore, *C. albicans* hyphal protein agglutinin-like sequence 3 (Als3p) can regulate *S. aureus* binding to *C. albicans* hyphae, thus, *C. albicans* establishes the biofilm base and facilitates the development of *S. aureus* biofilm [32-34]. In this study, we found one *S. aureus* strain, isolated from the mouth of a healthy people, apparently suppressed the formation of *C. albicans* pseudohyphae and hyphae in semi-CDM, which was often utilized to mimic human oral condition [21]. In contrast, similar to the report [15], *S. gordonii* did not affect *C. albicans* hyphae formation. Thus, this result provides a great evidence to prove the complexity of interspecies interaction in human oral cavity. The inhibitory effect of various bacteria on the development of *C. albicans* hyphae should play a crucial role for its pathogenicity.

Although most studies depicted both *C. albicans* and *S. aureus* exist in a cooperative relationship, quorum sensing molecule farnesol generated by *C. albicans* was found to interrupt *S. aureus* cell membrane integrity and then inhibit its biofilm formation and viability [35,36]. Thus far, the inhibitory effect of *S. aureus* on *C. albicans* has not been reported. In this study, *S. aureus*, *S. salivarius*, and *E. aerogenes* were determined to be effective in inhibiting yeast growth, and *S. aureus* was the most effective species. Using qPCR assay, 2 strains in all 7 strains of *C. albicans* were identified as being strongest inhibited on the growth by *S. aureus*, and the rest five *C. albicans* strains showed reduced growth to some extent in the presence of *S. aureus* (Figure 3). In a study exploring the antagonistic fungal-bacterial interaction between *C. albicans* and *P. aeruginosa*, Hogan and Kolter determined that *P. aeruginosa* was unable to bind or kill the yeast form of *C. albicans*, but it could form a dense biofilm on *C. albicans* hyphae, which killed the fungus [37]. Surprisingly, in this study, this *S. aureus* strain apparently suppressed the pseudohyphae/hyphae formation of all isolated *C. albicans* strains, but displayed the obviously inhibitory effects on their growth. Thus, further studies are required to figure out the mechanism(s) of repression of *S. aureus* on *C. albicans*.

Acknowledgements

This research was supported by the J. Dean Robertson Society, and NIH/NIDCR R15 DE019940-01 to FQ.

References

1. Smith AJ, Jackson MS, Bagg J. The ecology of Staphylococcus species in the oral cavity. J Med Microbiol. 2001; 50: 940-946.
2. Kolenbrander PE, Palmer RJ Jr., Periasamy S, Jakubovics NS. Oral multispecies biofilm development and the key role of cell-cell distance. Nat Rev Microbiol. 2010; 8: 471-480.
3. Kreth J, Zhang Y, Herzberg MC. Streptococcal antagonism in oral biofilms: Streptococcus sanguinis and Streptococcus gordonii interference with Streptococcus mutans. J Bacteriol. 2008; 190: 4632-4640.
4. Cannon RD, Holmes AR, Mason AB, Monk BC. Oral Candida: clearance, colonization, or candidiasis? J Dent Res. 1995; 74: 1152-1161.
5. Thein ZM, Samaranayake YH, Samaranayake LP. Effect of oral bacteria on growth and survival of Candida albicans biofilms. Arch Oral Biol. 2006; 51: 672-680.
6. Douglas LJ. Medical importance of biofilms in Candida infections. Rev Iberoam Micol. 2002; 19: 139-143.
7. Shirtliff ME, Peters BM, Jabra-Rizk MA. Cross-kingdom interactions: Candida albicans and bacteria. FEMS Microbiol Lett. 2009; 299: 1-8.
8. Cannon RD, Chaffin WL. Oral colonization by Candida albicans. Crit Rev Oral Biol Med. 1999; 10: 359-383.
9. Liljemark WF, Gibbons RJ. Suppression of Candida albicans by human oral streptococci in gnotobiotic mice. Infect Immun. 1973; 8: 846-849.
10. de Miranda CM, van Wyk CW, Basson NJ. Growth interaction between Candida albicans and Streptococcus salivarius: in vitro and in vivo studies. J Dent Assoc S Afr. 1992; 47: 253-256.
11. Zhou P, Liu J, Merritt J, Qi F. A YadA-like autotransporter, Hag1 in Veillonella atypica is a multivalent hemagglutinin involved in adherence to oral streptococci, Porphyromonas gingivalis, and human oral buccal cells. Mol Oral Microbiol. 2015; 30: 269-279.
12. Zhou P, Liu J, Li X, Takahashi Y, Qi F. The Sialic Acid Binding Protein, Hsa, in Streptococcus gordonii DL1 also Mediates Intergeneric Coaggregation with Veillonella Species. PLoS One. 2015; 10: e0143898.
13. Jenkinson HF. Beyond the oral microbiome. Environ Microbiol. 2011; 13: 3077-3087.
14. Jenkinson HF, Lala HC, Shepherd MG. Coaggregation of Streptococcus sanguis and other streptococci with Candida albicans. Infect Immun. 1990; 58: 1429-1436.
15. Dutton LC, Nobbs AH, Jepson K, Jepson MA, Vickerman MM, Aqeel Alawfi S, et al. O-mannosylation in Candida albicans enables development of interkingdom biofilm communities. MBio. 2014; 5: e00911.
16. Harriott MM, Noverr MC. Candida albicans and Staphylococcus aureus form polymicrobial biofilms: effects on antimicrobial resistance. Antimicrob Agents Chemother. 2009; 53: 3914-3922.
17. Peters BM, Noverr MC. Candida albicans-Staphylococcus aureus polymicrobial peritonitis modulates host innate immunity. Infect Immun. 2013; 81: 2178-2189.
18. Nash EE, Peters BM, Fidel PL, Noverr MC. Morphology-Independent Virulence of Candida Species during Polymicrobial Intra-abdominal Infections with Staphylococcus aureus. Infect Immun. 2015; 84: 90-98.
19. Moretro T, Hermansen L, Holck AL, Sidhu MS, Rudi K, Langsrud S. Biofilm formation and the presence of the intercellular adhesion locus ica among staphylococci from food and food processing environments. Appl Environ Microbiol. 2003; 69: 5648-5655.
20. Nishida H, Sugiyama J. Phylogenetic relationships among Taphrina, Saitoella, and other higher fungi. Mol Biol Evol. 1993; 10: 431-436.
21. He X, Wu C, Yarbrough D, Sim L, Niu G, Merritt J, et al. The cia operon of Streptococcus mutans encodes a unique component required for calcium-mediated autoregulation. Mol Microbiol. 2008; 70: 112-126.
22. Embong Z, Wan Hitam WH, Yean CY, Rashid NH, Kamarudin B, Abidin SK, et al. Specific detection of fungal pathogens by 18S rRNA gene PCR in microbial keratitis. BMC Ophthalmol. 2008; 8: 7.

23. Dutton LC, Paszkiewicz KH, Silverman RJ, Splatt PR, Shaw S, Nobbs AH, et al. 2015. Transcriptional landscape of trans-kingdom communication between Candida albicans and Streptococcus gordonii. Mol Oral Microbiol. 2016; 31: 136-161.

24. ten Cate JM, Klis FM, Pereira-Cenci T, Crielaard W, de Groot PW. Molecular and cellular mechanisms that lead to Candida biofilm formation. J Dent Res. 2009; 88: 105-115.

25. Boon C, Deng Y, Wang LH, He Y, Xu JL, Fan Y, et al. A novel DSF-like signal from Burkholderia cenocepacia interferes with Candida albicans morphological transition. ISME J. 2008; 2: 27-36.

26. Hogan DA, Vik A, Kolter R. A Pseudomonas aeruginosa quorum-sensing molecule influences Candida albicans morphology. Mol Microbiol. 2004; 54: 1212-1223.

27. Vílchez R, Lemme A, Ballhausen B, Thiel V, Schulz S, Jansen R, et al. Streptococcus mutans inhibits Candida albicans hyphal formation by the fatty acid signaling molecule trans-2-decenoic acid (SDSF). Chembiochem. 2010; 11: 1552-1562.

28. Jarosz LM, Deng DM, van der Mei HC, Crielaard W, Krom BP. Streptococcus mutans competence-stimulating peptide inhibits Candida albicans hypha formation. Eukaryot Cell. 2009; 8: 1658-1664.

29. Joyner PM, Liu J, Zhang Z, Merritt J, Qi F, Cichewicz RH. Mutanobactin A from the human oral pathogen Streptococcus mutans is a cross-kingdom regulator of the yeast-mycelium transition. Org Biomol Chem. 2010; 8: 5486-5489.

30. Nair N, Biswas R, Gotz F, Biswas L. Impact of Staphylococcus aureus on pathogenesis in polymicrobial infections. Infect Immun. 2014; 82: 2162-2169.

31. Kojic EM, Darouiche RO. Candida infections of medical devices. Clin Microbiol Rev. 2004; 17: 255-267.

32. Klotz SA, Chasin BS, Powell B, Gaur NK, Lipke PN. Polymicrobial bloodstream infections involving Candida species: analysis of patients and review of the literature. Diagn Microbiol Infect Dis. 2007; 59: 401-406.

33. Peters BM, Jabra-Rizk MA, Scheper MA, Leid JG, Costerton JW, Shirtliff ME. Microbial interactions and differential protein expression in Staphylococcus aureus -Candida albicans dual-species biofilms. FEMS Immunol Med Microbiol. 2010; 59: 493-503.

34. Peters BM, Ovchinnikova ES, Krom BP, Schlecht LM, Zhou H, Hoyer LL, et al. Staphylococcus aureus adherence to Candida albicans hyphae is mediated by the hyphal adhesin Als3p. Microbiology. 2012; 158: 2975-2986.

35. Jabra-Rizk MA, Meiller TF, James CE, Shirtliff ME. Effect of farnesol on Staphylococcus aureus biofilm formation and antimicrobial susceptibility. Antimicrob Agents Chemother. 2006; 50: 1463-1469.

36. Hornby JM, Jensen EC, Lisec AD, Tasto JJ, Jahnke B, Shoemaker R, et al. Quorum sensing in the dimorphic fungus Candida albicans is mediated by farnesol. Appl Environ Microbiol. 2001; 67: 2982-2992.

37. Hogan DA, Kolter R. Pseudomonas-Candida interactions: an ecological role for virulence factors. Science. 2002; 296: 2229-2232.