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Pitout JDD, Church DL, Gregson DB, Chow BL, McCracken M, Mulvey M, Laupland KB (2007). Molecular epidemiology of CTXM-producing Escherichia coli in the Calgary Health Region: emergence of CTX-M-15-producing isolates. Antimicrob. Agents Chemother. 51: 1281-1286.

Pelczar JR, Harley JP, Klein DA (1993). Microbiology: Concepts and Applications. McGraw-Hill Inc., New York, pp. 591-603.

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Full Length Research Paper

Clinico-mycological profile of superficial mycosis and the relationship Of ABO blood grouping with superficial mycosis

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A total of 456 clinically diagnosed cases (170 male and 286 female) of superficial mycosis was conducted. Highest incidence of cutaneous candidiasis followed by pityriasis versicolor was found. The maximum incidence of superficial mycosis was found in adult females with cutaneous candidiasis then pityriasis versicolor in both sexes (females 83 and males 80). In this study, the most common isolate was *Trichophyton mentagrophytes* (24.3%) of all dermatophyte infections, and 8.5% of the total cases of superficial mycosis. The authors investigated the relationships between cutaneous mycosis and ABO blood groups, through blood typing, clinical and mycological diagnosis with identification of isolated dermatophytes. They concluded that *T. mentagrophytes* was isolated from 53.8% of the patients belonging to blood group A, 33.8% to group O and 15.3% to group B. *Epidermophyton floccosum* was seen in 23.4% group A, 65.3% group O and 14.2% group B. *Trichophyton tonsurans* was found in 41% belonging to group A, 43.7% to group O and 13.2% group B. *Trichophyton rubrum* was found in 40% for each patient with blood group A and O, while 20% for patients with blood group B. The relationship of cutaneous candidiasis with blood group O was found to be 45.8%, group A 34.1%, group B 18.9% and only 1.2% for blood group AB, while in pityriasis versicolor, blood group O was found in 74% of the cases, group A in 13.9%, group B in 10.7% and group AB was found in only 1.4% of the cases of pityriasis versicolor. The main age group affected was 21-30 years (59 cases) (male 28 cases and females 31 cases) out of 136 total cases of pityriasis versicolor. Even though the authors have found a higher number of patients belonging to blood group O infected with *E. floccosum,* these results suggested that there is statistical evidence (P > 0.001) that these individuals are more susceptible to superficial mycosis.

Key words: Blood groups, dermatophytes, superficial mycosis.

INTRODUCTION

Superficial mycosis refers to the diseases of the skin that are caused by fungi and exclusively invasive of the integumentary tissue. Among this group, dermatophytosis, pityriasis versicolor and candidiasis occur most frequently.

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They possess the affinity for parasitizing the horny layerof the skin as well as other structures rich in keratin, such as hair and nails (Hainer, 2003; Padhye and Summerbell, 2005; Decorby et al., 2009; Ameen, 2010; Grumbtand et al., 2011; Sahai and Mishra, 2011). They produce a dermal inflammatory response with intense itching and also cause cosmetic disfiguration. Dermatophyte infections are caused by three genus: Trichophyton, Microsporum and Epidermophyton with morphological, physiological and antigenic characteristics that relate them to each other (Azulay, 1985).

Studies involving cell wall of dermatophytes have demonstrated that the fungus *Trichophyton mentagrophytes, Trichophyton rubrum* and *Epidermophyton floccosum* have glycoproteins that are antigenically similar to human erythrocyte isoantigen A (Young and Roth, 1979). According to the authors, individuals that have these erythrocytic antigens would be more susceptible to development of generalized dermatophytosis and resistant to treatment than the individuals devoid of these antigens.

Upon investigation of this premise (Balajee et al., 1996) high incidence of dermatophytosis infected individuals belonging to blood group A, and from those 89.9% presented chronic dermatophytosis with persistent lesions for more than five years was found. Similarly Gamborg-Nielsen (1994) verified higher incidence of individuals belonging to this blood group and infected with the fungus *Trichophyton mentagrophytes.* Contrary to this data, Neering (1979) could not demonstrate any relationship between blood group and dermatophytes infection.

In the face of these results and considering the lack of studies on this subject in our country, the aim of the present work was to identify the clinical pattern of superficial mycosis and to identify the most common pathogens responsible for superficial mycosis in patients attending dermatological clinic with the possible relationship through the identification of the dermatophyte isolated, cutaneous candidiasis and pityriasis versicolor cases and blood groups.

MATERIALS AND METHODS

This study was conducted in the Department of Dermatology and Venereology in Mirjan Teaching Hospital during the period of January 2012 to December 2013 on 456 patients: 170 male, 286 female with all age groups. Hair and all scrapings were taken for KOH examination, nail clipping in KOH solution overnight then examination was performed under the microscope. KOH positive specimen was proceeded for culture. Pityriasis versicolour cases were subjected to KOH examination only as pityrosporum is a normal skin flora so culture was not done. If any growth was found on Sabouraud's dextrose agar medium, colonial morphology (grossly and microscopically), pigment production were further observed. Blood samples were sent to hospital laboratory for typing of blood groups. Qi square test was used in statistical analysis for determination of the significance differences between ABO blood group of normal people and patients with cutaneous mycoses.

RESULTS

Among the 456 cases observed, 170 were males and 286 females. Most of the clinically diagnosed cases were KOH positive and some scrapings failed to grow in culture even when they were KOH positive. The highest incidence of superficial mycosis was found in the month of August (85 cases) and the lowest incidence in April (13 cases) in the age group of 15-35 years. The maximum incidence among superficial mycosis was pityriasis versicolor, 163 cases (females 83, males 80) followed by cutaneous candidiasis, 133 cases (106 female and 27 male). Chronic wide spread skin rash of pityriasis versicolor was found in 39 males and 30 females. The main age group affected was 21-30 years, 59 cases (male 28 cases and females 31 cases). The maximum incidence of cutaneous candidiasis (especially candidal intertrigo) was found in adult females (72 female) with candidiasis of external genetalia and groin (36 females and 2 males), candidal vulvovaginitis was found in 6 pregnant females, candidal napkin rash in 22 children and candidal intertrigo of the neck was found in only 12 infants. 9 cases of oral thrush was reported and candidiasis involving skin under breast and axilla was also reported in 19 females (Table 1).

It was noticed that the most common presentation was cutaneous candidiasis which is accounted by 39.2% of the total cases, the second most common presentation was pityriasis versicolor with over all incidence of 35.7% of the total cases. Tinea corporis occupied the third position, 23.75% of the dermatophytes infections, and 8.3% of the total cases, then Tinea cruris accounted for 21.25% of the dermatophytes infections and 7.3% of the total cases (Table 2). Infections occurring in multiple sites simultaneously were also very common (20%).

In the present study, the most common isolates was *T. mentagrophytes* which accounted for 24.3% of the dermatophyte infections, and 8.5% of the total cases of the superficial mycosis (Table 2). The relationship between blood groups and isolated dermatophytes is reported in (Table 3). The fungus *T. mentagrophytes* was isolated from 53.8% of the patients belonging to blood group A, and 33.8% to group O and 15.3% to group B; in *E. floccosum*, 23.4% group A, 65.3% group O and 14.2% group B. *Trichophyton tonsurans* was found in 41% of the patients belonging to group A and 43.7% to group O and 13.2% group B. While *T. rubrum* was found in 40% of the patients belonging to blood group A, 40% belonging to blood group O and 20% to group B.*(*Table 4*)*

The incidence of blood groups in the normal healthy population studied in 600 individuals is as follows: group A seen in 22.8% (137), group O 27% (162), group AB 24.5% (147) and group B 25.7% (154). There is a significant statistical difference between the cases of *T. mentagrophytes*, cutaneous candidiasis ($P < 0.001$) and *T. tonsurans* ($P < 0.01$) with the normal healthy people. In *T. rubrum*, *Trichophyton verrocosum* and *Microsporum canis*, there was no significant statistical difference

Table 1. Incidence of superficial mycoses in relation to the gender.

Candidal infections (total no.133)	Female (total no.106)	Male (total no. 27)
Candidal intertrigo	17	7
Candidiasis under breast, axilla	19	0
Candidiasis (groin, genitalia)	36	2
Canididal intertrigo of neck (infants)	8	4
Candidal vulvovaginitis (pregnant)	6	0
Canididal napkin rash	14	11
Oral thrush	6	3
Other superficial Mycosis	Female (no. 83)	Male (no. 80)
Pityriasis versicolor (No.163)	39	30

Table 2. Distribution of the patients with dermatophytes infection according to the area affected with relation to the gender.

Types of dermatophytes	Male no. 63	Female no. 97	Total no. 160	%
Tinea corporis	32	6	38	23.75
Tinea capitis	5	7	12	7.5
Tinea pedis	6	3	9	5.6
Tinea unguium	1	12	13	8.1
Tinea manuum	2	14	16	10
Tinea cruris	16	18	34	21.25
Tinea faciei	1	5	6	3.75
Combination of more than one type	14	18	32	20

Table 3. Total frequency of dermatophyte species isolated from cultures of clinical samples based on the patients' sex.

Type	N (%)	Female (%)	Male (%)
T . mentagrophytes	59(36.8)	43(44.3)	16(25.4%)
T. tonsurans	39(24.3)	17(17.5)	22(34.9)
T. rubrum	5(3.1)	3(3.1)	2(3.2)
T. verrucosum	7(4.3)	4(4.1)	3(4.8)
E. floccosum	49(30.0)	29(29.9)	20(31.7)
M. canis	1(0.6)	1(1.0)	-
Total	160(100)	97(100)	63(100)

between these cases and the normal control (P>0.05). In *E. floccosum* there was a significant statistical difference between the cases of normal people (P > 0.001).

The relation of cutaneous candidiasis with blood grouping (No. 86), group O was found in 61/86 (70.9%), group A in 24/86(27.9%), group B in 9/86 (10.4%) and blood group AB was found in only 1/86 (1.1%) while in pityriasis versicolor (No. 119), blood group O was found in 77/ 119 (64.7%) of the cases, group A in 23/119 (19.3%), group B in 17/119 (14.2%) and group AB was found in only 2/119 (1.6%).

DISCUSSION

Several researchers have studied the relationship between blood group and infectious diseases. In Hansen's

Table 4. Blood group results according to species of isolated dermatophytes.

Type	Group A no. (%)	Group O no. (%)	Group B no. (%)
T. mentagrophytes	30(53.8%)	20(33.8%)	9(15.3%)
T. tonsurans	16(41%)	19(43.7%)	4(13.2%)
T. rubrum	2((40%)	2(40%)	1(20%)
T. verrucosum	3((42.8%)	4(57.1%)	0
E. floccosum	10(23.4%)	32(65.3%)	7(14.2%)
M. canis	0	1(100%)	0

disease, Beiguelman (1963) verified that the frequency of individuals of blood group O was higher in patients with tubercloid clinical form when compared with the lepromatous form. In coccidioidomycosis, Deresinski (1979) observed higher prevalence of the disease in individuals from group B. In a way, their studies suggested that individuals belonging to this blood group, present Gram negative infections with higher frequency than individuals belonging to the remaining blood groups (Foster and Lobrum, 1976; Robinson et al., 1971; Socha and Kaczera, 1969). 40.9% of the patients with recurrent furunclosis (caused by *S. aureus*) had blood group O followed by 22.7% having blood group B (Al-Khafajii, 2014).

In dermatophytosis Young and Roth (1979) observed antigenic similarities between *T. rubrum, T. mentegrophyte* and *E. floccosum* cell wall glycoprotein and A1 and A2 human erythrocyte isoantigens, suggested that possible cross reactivity would turn individual belonging to blood group A more susceptible to chronic dermatophyte infections.

In the present work we found that comparison with the incidence of blood groups in the normal population studied in 600 individuals is as follows: group A seen in 22.8% (137), group O 27% (162), group AB 24.5% (147), and group B 25.7% (154). There is a significant statistical difference between the cases of *T. mentagrophytes* and cutaneous candidiasis in comparison with healthy population ($P< 0.001$), in *T. tonsurans* the P value was $P< 0.01$. This suggests that there is a higher susceptibility of individuals with group O and A to different dermatophyte infections including *T. mentagrophytes, T. tonsurans, E. floccosum*, cutaneous candidiasis and pityriasis versicolor. So this result is similar to the study of Young and Roth (1979) that demonstrated that blood group active glycoprotein is found in *T. mentagrophytes* and *E. floccosum* which are commonly the cause of chronic infection in human while *M. canis* which does not appear to possess this antigen is seldomly so involved. In *T. rubrum*, *T. verrocosum* and *M. canis*, there is no significant statistical difference between these cases and the normal control ($P>0.05$), which supports the findings of Neering (1979) that reported no difference in susceptibility of individuals from blood group A to dermatophytosis.

Conclusion

This study concluded that there is statistical evidence indicating that individuals with blood groop O and A are more susceptible to superficial mycosis.

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Full Length Research Paper

Expression of neuronal protein Tau in *Candida albicans*

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***Candida albicans* is a dimorphic, opportunist fungal pathogen in which cell adhesion and filamentation contribute to host tissue invasiveness and fungal pathogenicity. Morphogenesis in *C. albicans* which involves yeast to hyphae transition is dependent on temperature, the growth media composition, and is regulated by quorum sensing. In yeasts, filament formation and polarized growth are associated with the actin cytoskeletal network and microtubule interactions. The microtubule associated protein (MAP), Tau (tau), is a neuronal protein in mammals that participates in microtubule binding, microtubule assembly, bundling and stabilization. In the current study, we generated an electroporated tau derivative of a strain of *C. albicans*. We have observed that tau expression accelerates and increases the extent of medium dependent filamentation. We have also noted tau interacts mainly with actin filaments and to some extent, microtubules. We believe that these interactions are involved in the temporal control of filament formation in tau-containing cells.**

Key words: *Candida albicans*, tau, pathogenicity, morphogenesis.

INTRODUCTION

Candida albicans is a dimorphic yeast that has the ability to invade host tissue and initiate superficial and systemic infections through a process which is initiated by cell adhesion and involves filamentation and biofilm formation. Biofilms provide a protective environment for microorganisms, facilitate intercellular communication and allow organisms to remain in a favorable niche with respect to nutrients (Harris et al., 2004). Adherence of yeast cells of *C. albicans* to host tissues and abiotic surfaces is mediated by agglutinin-like sequence proteins (ALS) (Otoo et al., 2008). The ability to transition from yeast to a filamentous state occurs in response to a variety of environmental cues including carbon or nitrogen source depletion, serum addition, pH, temperatures, CO2 levels and phosphate concentration (Chandra et al., 2001). The three pathways that have been described for the regulation of hyphal development which are mediated by specific activation of transcriptional factors include: (i) the Mitogen-Activated Protein Kinase pathway (MAPK), (ii) the cAMP-PKA pathway and (iii) the pH-responsive pathway (Whiteway et al., 2007). In *C.albicans*, cells grown in 2% glucose containing minimal medium do not filament due to the production of quorum sensing molecule, farnesol (Sabine et al., 2009). Although N-acetyl glucosamine and galactose-proline minimal media support filament formation, filamentation

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in both is delayed. In *C. albicans* filamentous growth is associated with two types of filaments pseudohyphae and hyphae.

Pseudohyphae, are chains of elongated cells with constrictions at septal sites whereas, true hyphae are elongated continuous, segmented, germ tubes (Liu et al., 2001; Shapiro et al., 2012). Hyphal extension in *C. albicans* is mediated by actin and microtubules with their corresponding motor proteins, kinesin, dynein and myosin (Finley et al., 2005; Fischer et al., 2008; Steinberg, 2007). Actin plays a significant role in apical growth, septation and elongation of hyphal filaments and in the localization of vesicles during cell wall extension (Fischer, 2007). Microtubules function in nuclei positioning and regulation of hyphal morphogenesis through the delivery of landmark proteins for the control of growth directionality, the polarization of the actin cytoskeleton (Finley et al., 2005; Fischer, 2007; Fischer et al., 2008; Whiteway et al., 2007) and are associated with virulence in this yeast (Sanchez-Martinez et al., 2001).

The MAP protein tau found mainly in mammalian neuronal cells is a hydrophilic, phosphoprotein, that is reported to play a major role in microtubule assembly, stabilization and bundling (Brandt, 1996; Oyama et al., 2004). Tau is coded for by a single gene located on chromosome 17. In the central nervous system, there are six different isoforms of tau that are generated by alternative splicing of its mRNA. Each isoform differs with respect to amino terminal inserts (0N-2N) and carboxyl terminal repeats (3R or 4R); which affects the protein's length, interactions with cytoskeletal elements, signal transduction and microtubule polymerization and stabilization (Buée et al., 2000; Wang et al., 2008). In microtubule assembly, tau participates in the nucleation of tubulin. Tau also modulates the dynamic instability of tubulin assembly by affecting the rates of polymerization, and the proper formation of microtubules (Brandt, 1996; Weingarten et al., 1975). Phosphorylation of tau protein is developmentally regulated. Normal tau protein contains one to three moles of phosphate per mole of tau protein whereas, in various tauopathies such as Alzheimer's disease (AD), the level of phosphorylation has been reported be three to four times higher than the normal tau protein (Buée et al., 2000; Iqbal et al., 2009; Kopke et al., 1993). The level of tau phosphorylation controls the normal interactions with microtubules. When tau is in a hyperphosphorylated state, it disassociates from microtubules and self assembles into filaments and tangles, as it has been observed in AD and related tauopathies (Alonso et al., 2001; Alonso et al., 2008; Wang et al., 2008).

As for the role of tau-actin interactions in neuronal cells, the literature on it is limited. Fulga et al. (2007) have shown that tau-induced neurodegeneration results in the accumulation of F-actin and the formation of actin-rich rods in *Drosophila* and mouse models. Buée et al. (2000) reported that the N-terminal region of tau binds to actin, and permits microtubules to interconnect with other cytoskeletal elements. Tau flexibility, which is important for neuronal stability in mammalian systems is restricted (Buée et al., 2000; Fulga et al., 2007). These authors also noted that colocalization of tau and the actin cytoskeletal was observed only when tau interacted with src-family kinase, fyn, which activates the tyrosine signaling pathway. This pathway may influence cell shape through interactions with the submembranous actin cytoskeleton (Buée et al., 2000).

The model yeast *Saccharomyces cerevisiae,* does not contain an isoform of tau, however it has been *humanized* to express both 3R and 4R tau isoforms (Braun et al., 2009; Vandebroek et al., 2005). Vandebroek et al. (2005) reported that *S. cerevisiae* has similar mechanisms for phosphorylation of tau. The yeast orthologues of the cyclin dependent kinase 5 (cdk5) and glycogen synthase kinase-3 β (GSK-3 β), Pho85 and Mds-1, can be activated by mammalian cyclins and vice versa in mammalian cells. In yeast cells deficient in Mds-1 and Pho85, hyperphosphorylation of tau was evident (Vandebroek et al., 2005). Tau protein expressed in *S. cerevisiae* does not "*appreciably*" bind yeast microtubules and it is reasonable to assume that the lack of tau binding would exclude this cell system in the analysis of the effects of aberrant tau on the microtubule cytoskeleton (Braun et al., 2009; Vandebroek et al., 2005).

In the current study, *C. albicans* strain CC504, was electroporated with plasmid vector containing the promoter region of CMV and the full length tau (2N, 4R) gene. *C. albicans* was selected as a model organism because of the importance of filamentation in biofilm formation and virulence. We proposed that if tau could be expressed in *C. albicans,* effects on the filamentation capabilities of this yeast might be demonstrable. In this study, we observed filamentation in tau containing cells of *C. albicans* CC504 after 24 h incubation at 37°C whereas the parental CC504 strain and the derivative containing the CMV plasmid required 96 h for filament formation. We also demonstrated that tau interacts with actin filaments as well as microtubules in these cells and have shown that tau interactions with actin were more pronounced in comparison with tau- tubulin interactions. We believe these findings promote the use of *C. albicans* as a model system to investigate tau interactions with cytoskeletal proteins and the influence of the tau-like proteins on the yeast filamentation process.

MATERIALS AND METHODS

Strain and growth conditions

For each experiment, starter cultures of *C. albicans* strain CC504, a clinical isolate (Quality Technologies, Newbury Park, CA) and its derivatives, CC504-CMV (CMV-plasmid), CC504-CMV-Tau (tau-containing) were grown overnight in YEP (1% yeast extract, 2% peptone, 2% glucose) complete medium at 37°C. Overnight culture

cell counts for CC504, CC504-CMV and CC504-CMV-Tau were 10^7-10^8 colony forming units (CFUs). The cells were routinely harvested by centrifugation, resuspended in galactose-proline (gal-pro) minimal medium (0.67% Difco Yeast Nitrogen Base, 2% galactose, 0.02% proline, (Fisher Scientific, Suwanee, GA)). For well plating, 10^{-2} dilutions of the cells were made and resuspended in the same medium and checked daily under stationary conditions, cell counts were performed at 24 h for determination of cell viability. Samples were imaged using the inverted light compound microscope every 24 -72 h to determine aggregation and filament formation. All images were taken with a 20x objective. For immunocytochemistry, cell cultures were prepared in the same manner except that longer time intervals were required to demonstrate filamentation (48-120 h).

Tau expression vector for *C. albicans*

The vector of choice was pFA-CMV (cytomegalovirus vector, Invitrogen, Van Allen Way, Carlsbad, CA), the microtubule associated protein tau (tau) gene was subcloned from pEGFP-N1 plasmid (Alonso et al., 2004).

pFA-CMV was restriction digested with restriction enzymes: xbaI and bgl II and incubated at 37°C overnight, 20 ng/µl was recovered (Promega, Madison, WI). After, it was gel-purified and processed with the Wizard SV gel and PCR clean-up system kits according to manufactures directions.

The tau gene insert (1.3 Kb) was obtained with PCR using infusion primers that matched the cut vector: infusion1: 5'GGGCTGGAATTCTAGAATGGCTGAGCCCCGCCAGGAGTTCG AAGTG-3'; infusion2: 5'TACTTATTCAAGATCTTCACAAACCCTGCTTGGCCAGGGAGG -3' (black sequence, is the original primer and red sequence, for the vector-specific). PCR conditions included 30 cycles of 94°C for 30 s, 62°C for 30 s, 72°C for 45 s with a final 72°C extension phase for 10 min, as described (Duff et al., 2000). The PCR product was gel-purified and processed with the Wizard SV gel and PCR clean up system kit.

The plasmid vector, pFA-CMV and PCR-tau, were then ligated using the Infusion-2.0 Dry Down kit following the manufactures guidelines (Clontech, Mountain View, CA) and transformed into *E. coli* DH-5α. For selection of transformed cells, LB-kanamycin plates were prepared at 0.1 mg/ml of kanamycin. Isolated resistant colonies were isolated and re-purified (lysed) with PureYield Plasmid Miniprep system kit (DNA purification) according to manufactures protocols, (Promega, Madison, WI), DNA concentrations were checked with a UV-double beam spectrometry, 3.95 µg/ul of DNA was recovered.

Electroporation of Tau into *C. albicans*

The purified plasmid was electroporated by a modified electroporation method (BIO-RAD Cat.No.165-2100): Cell cultures were grown overnight in YEP, harvested by centrifugation, diluted in the same medium and allowed to grow for 2 h. When cultures were between 0.5 and 1.0 at A600, cells were harvested by centrifugation, washed in ice-cold 1M sorbitol for 15 min, then centrifuged, three times. 200 µl of sorbitol was added to the cell pellets and these were transferred into microcentrifuge tubes on ice with purified vector with and without tau for 5 min. Following the incubation, the cells were pipetted into cold electroporation cuvettes, and electroporated with BioRad *Escherichia coli* Pulser at 1.5 kV for 1 s (BIO-RAD, Hercules, CA). Following electroporation, 450 µl of 1 M sorbitol was added to cuvettes then transferred to microcentrifuge tubes. Yeast cells containing plasmids with and without the tau gene were selected on antibiotic plates with 1000 µg/ml of G418. For practical purposes, the stable electroporated, CC504, *C. albicans* with the empty CMV-vector was called CC504-CMV and with CMV vector containing tau gene, CC504-CMV-Tau.

Immunocytochemistry and confocal scanning

Determination of tau

For analysis of tau protein expression, the cells were harvested by centrifugation for 6 min and resuspended in 1 mM phosphate-buffered saline, pH 7.0. The cells were re-centrifuged, the supernatants decanted and the pellets were fixed in 4% formaldehyde in 1 mM PBS for 60 min at room temperature (RT). The fixed preparations were harvested by centrifugation and blocked for 1 h with blocking buffer composed of 4% Donkey serum and 0.05% Tween-20 in 1 mM PBS. Then the samples were centrifuged and an antibody dilution buffer composed of 2% Donkey serum in 1 mM PBS was added. The primary antibody, DA9 (mouse monoclonal antibody, generous gift of Dr. Peter Davies) was added at the final concentration of 1:200 for 24 h at 4°C. Following the primary antibody exposure, the samples were washed 3 times, for 15 min each, in the antibody dilution buffer and harvested. For secondary antibody labeling, donkey anti-mouse conjugated with a fluorescent (CY5, red, Invitrogen, Carlsbad, CA) was added (1:200 dilution) and incubated at 37°C for 1.5 h in the dark. The samples were centrifuged, resuspended in 1 mM PBS, washed 3 times for 15 min each. After the last wash, 2-3 drops of Slowfade with DAPI was added to each antibody treated sample. 10 µl of each sample was added to a slide and cover slips were used to seal the slides. All samples were imaged with the Leica Confocal Laser Scanning Microscope (CLSM) with Leica software.

For determination of tau distribution with tubulin or actin, the same immunocytochemical protocol was used with some modifications. After 60 min of fixation with 4% formaldehyde, cells are harvested by centrifugation then 100% cold methanol was added to cell preparations for 4.5 min, harvested, then blocked for 1 h with blocking buffer. For primary antibody anti-tubulin, antibody T-3526 (Sigma, St. Louis, MO) was used according to the manufacturer's guidelines (1:80 dilution). Primary labeling of tau was the same as previously noted. For secondary antibody labeling anti-rabbit conjugated with a fluorescent was used according to the manufacturer's guidelines (1:100 dilution, Invitrogen, Carlsbad, CA), or rhodamine-phalloidin stain was added for F-actin labeling (1:100 dilution). Samples were imaged with Leica Confocal Laser Scanning Microscope with Leica Software. All images were taken with 60x objective. All hardware settings were the same for each cell type.

RESULTS

Tau is expressed in *C. albicans*

Tau is a microtubule associated protein that is important in both binding and bundling of microtubules. Tau protein is not normally present in yeast cells. Therefore, we decided to study the effect of tau expression in *C. albicans.* Plasmid vector pFA-CMV, was the chosen vector since, it has the yeast DNA binding domain GAL4. The tau gene was subcloned, into the pfa-CMV vector and was electroporated into *C. albicans,* and electroporated cells were selected for resistant to G418 as described in the material and methods. Tau expression in *C. albicans* was confirmed by immunocytochemistry (Figure 1). In CC504-CMV-Tau,

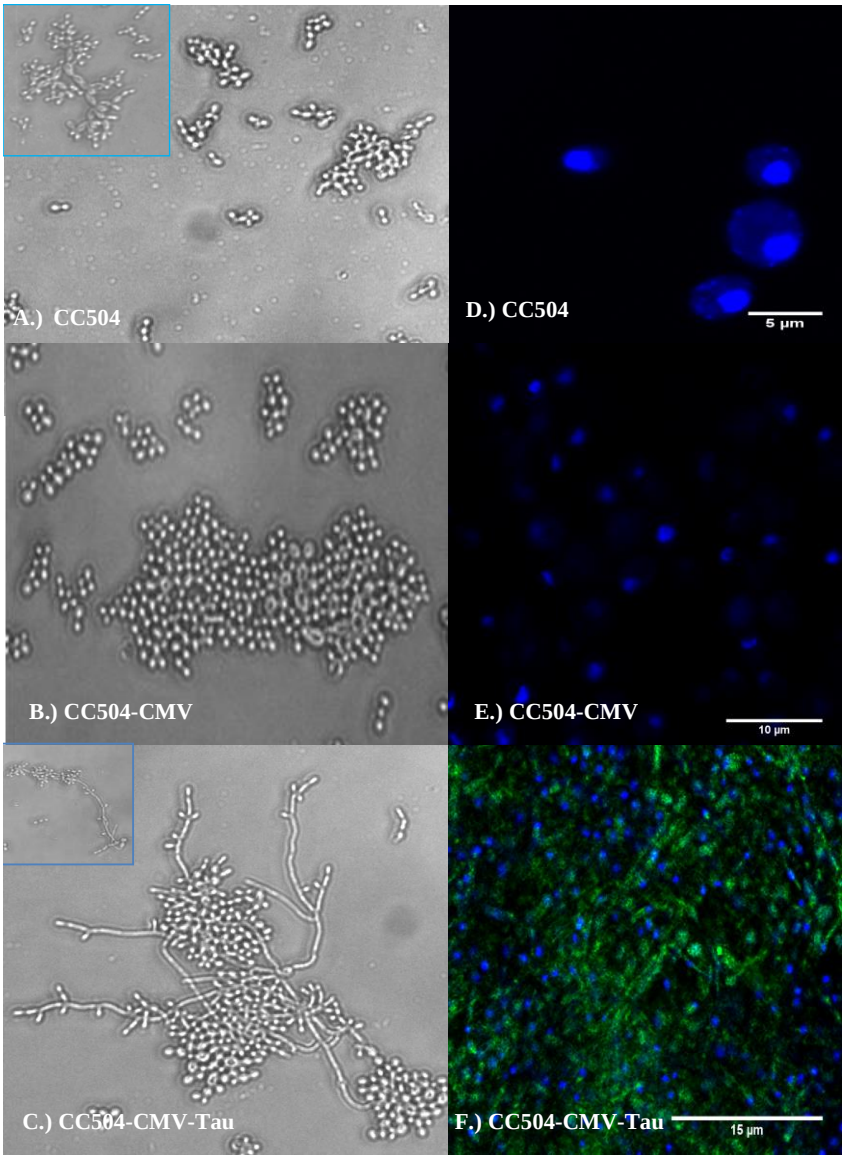

Figure 1. Tau expressing *C. albicans* exhibits filamentation: CC504, CC504-CMV and CC504-CMV-Tau were observed under compound light microscopy between 24-72 h period. Only *C. albicans* cells containing tau exhibited filamentation (C) whereas, without tau expression only yeast cells and aggregation can be noted (Images A, B, C, 200x/20x objective). Tau-expression was verified by immunocytochemistry, cells were fixed, blocked and immunolabeled with anti-tau primary and FITC-conjugated secondary antibody as described in the material and methods, then imaged with confocal laser scanning microscopy (Images D, E, F). CC504 control (D), and CC504-CMV (E) exhibited no tau labeling, and as expected CC504-CMV-Tau (F), exhibited tau expression. The nuclei of the *C. albicans* was stained with DAPI (blue) and tau was stained with green (FITC).

tau expression was observed in the cytoplasm and along the hyphae (Figure 1).

Tau affects filamentation in *C. albicans*

Adhesion and filament formation is important in the ability of *C. albicans* to invade host tissue and to initiate infection (Chandra et al., 2001; Otoo et al., 2008). To determine the effects of tau expression, *C. albicans* cells were grown in gal-pro minimal medium for 24-72 h period in well-plates under stationary conditions and checked daily for adhesion and filament formation. At 24 h, cell counts in gal-pro minimal medium for CC504, CC504-

CMV and CC504-CMV-Tau were 10^6-10^7 CFUs for determination of cell viability. As early as 24 h incubation, CC504-CMV-Tau showed filament formation, whereas the parental strain, CC504 and CC504-CMV did not even after 72 h incubation (Figure 1). This result suggests that tau expression induces early filamentation.

Tau and microtubules in *C. albicans*

Actin and microtubule interactions are important in polarized growth. In polarized growth in *C. albicans*, the delivery of nutrients to the hyphal tip is guided by microtubules, and is essential in hyphal development (Fischer, 2007; Fischer et al., 2008). Microtubule formation in *C. albicans* affects stabilization of hyphae and the polarity of actin. Tau and tubulin distributions were analyzed in CC504-CMV-Tau by immunocytochemistry using anti-tau and anti-tubulin antibodies as described in the materials and methods. It can be noted that tubulin immunoreactivity in yeast cells is more pronounced as compared to filamentous hyphae (Figure 2D). Contrary to our expectations, only a modest co-localization of tau and tubulin was observed (Figure 2F).

Tau and actin in *C. albicans*

F-actin is important in the myosin-based transport processes that participate in membrane trafficking to the growing hyphal tip (Fischer, 2007). Actin is known to be important in polarized growth in filamentous fungi. CC504-CMV-Tau were co-stained for tau and actin (Figure 2). It can be noted that the tau co-localized tightly with actin (Figure 2C). Tau co-localization with actin was observed both in yeast cells and in the hyphae (Figure 2C).

DISCUSSION

The introduction of human tau into strains of *S.cerevisiae* has been performed to study molecular mechanisms associated with tau hyperphosphorylation and aggregation in a eukaryotic cell culture system that is well-defined but less complex than mammalian culture systems (Braun et al., 2009; Vandebroek et al., 2005). In *S. cerevisiae*, the ability to study tau-microtubule interactions has been significantly affected by the lack of sufficient binding of human tau protein to yeast microtubules (Braun et al., 2009). However, studies designed to elucidate the cellular mechanisms that trigger toxicity and cell death have been reported in this yeast system (Braun et al., 2009). In the current investigation, we chose *C. albicans* strain CC504 as a test organism since in previous studies strains of *C. albicans* appeared to be more resistance to oxidative stress induced by different chemicals tested and hyphal filaments were readily demonstrable under defined growth conditions (Chandra et al., 2001; Whiteway et al., 2007; Nikoloau et al., 2009; Jamieson et al., 1996). We have demonstrated in control experiments, that parental cells and the CC504-CMV derivative strain did not exhibit immunolabeling with anti-tau antibody, which suggests that *C. albicans* does not contain a protein with epitopes similar to the human tau protein. However, structural similarities with the yeast cell-wall ALS proteins, and amyloid-forming protein have been described (Otoo et al., 2008). In our studies, CC504-CMV-Tau cells exhibited accelerated and increased filamentation as compared to the control strains. Strong interaction with actin and weak association with microtubules were also noted. There was no evidence of cellular toxicity in *C. albicans* CC504-CMV or CC504-CMV-tau.

The yeast to hyphal transition involves polarized extension of germ tubes and is associated with extensive cell wall remodeling. Actin plays an important role in the maintenance of hyphal polarity in filamentous fungi. Microtubules also function in the morphogenetic transition through protein delivery and polarization of the actin cytoskeleton (Finley et al., 2005; Fischer, 2007; Fischer et al., 2008; Whiteway et al., 2007). In neuronal cells, the formation and stabilization of microtubules and interactions with actin depend on the tau protein and are regulated by tau phosphorylation (Fulga et al., 2007). Although, the role of actin has been well documented in fungi (Harris et al., 2004), actin involvement in various neuronal tauopathies is poorly understood (Fulga et al., 2007).

The initial phases of biofilm formation which requires cell-to-cell contact and adherence are dependent on the expression of ALS proteins in the yeast cell wall. The ALS proteins constitute a family of cell wall bound adhesins with broad binding specificity for mammalian peptide ligands as well as bacterial cells (Otoo et al., 2008). Otoo et al (2008) reported that ALS proteins contain a conserved amyloid- forming T-region with protein aggregation sequences similar to those found in the tau protein of neuronal cells. In a BLAST search, 41% homology between ALS 3 and the tau protein was found (http://blast.ncbi.nlm.gov/Blast.cgi) which does not reflect identity. However, it is possible that ALS proteins and tau may have similar functions, since they have a level of structural similarity. Phosphorylation, the tau modification in mammalian cells that has been extensively studied, has been shown to be involved in the regulation of the C-terminal microtubule binding domains (Vandebroek et al., 2005). *C. albicans* contains a cyclin- dependent kinase, PHO85, an orthologue of the neuronal kinase, cdk5. PHO85 is involved in the regulation of filamentation (Shapiro et al., 2012). Vanhelmont et al. (2010) reported that serine-409 phosphorylation in the proline rich C-terminal domain of tau reduced the binding of tau protein

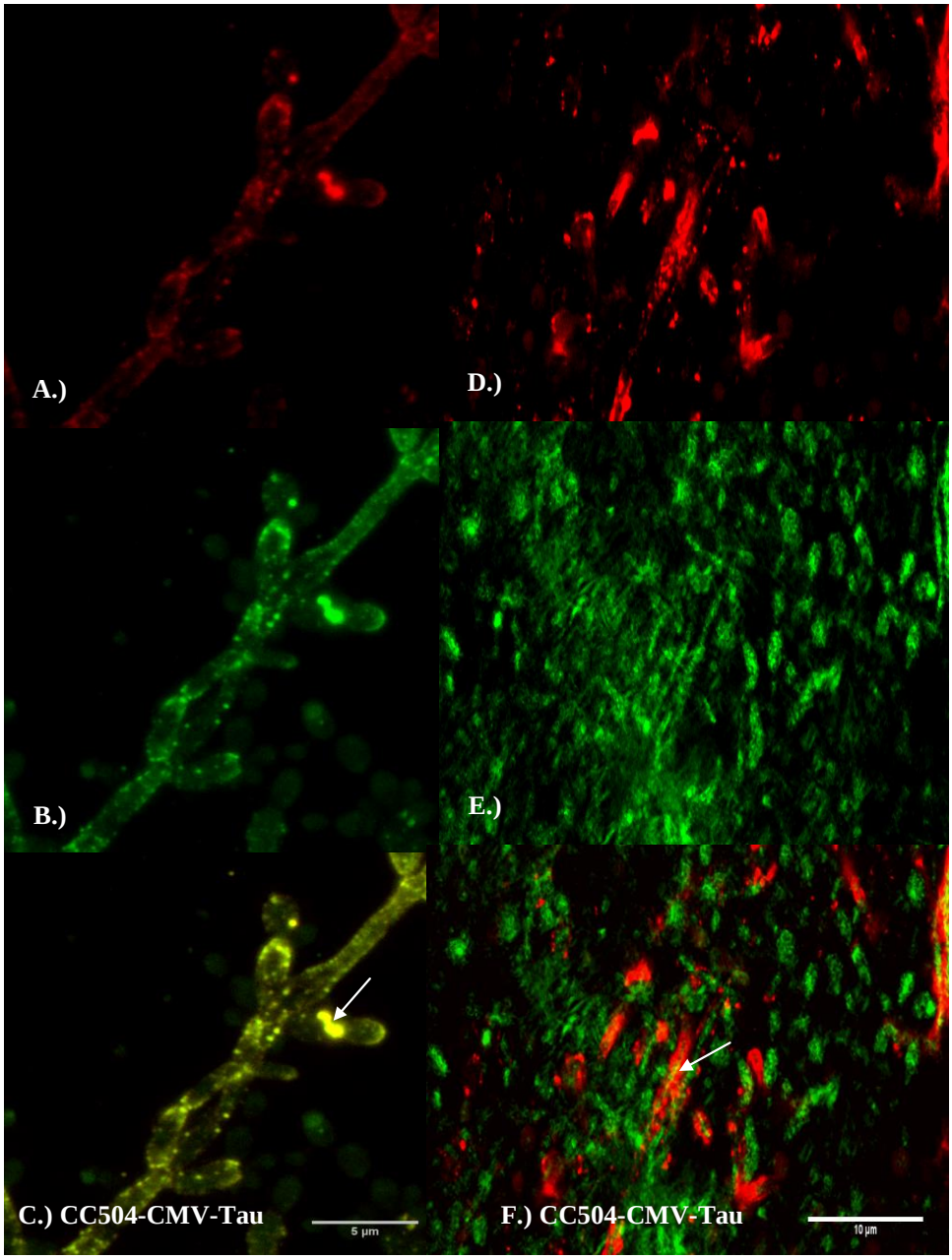

Figure 2. Tau interacts with actin and microtubules in Gal-Pro minimal medium: CC504-CMV-Tau were grown for 72 h in Gal-Pro minimal medium. For determination of tau interaction with actin or microtubules, cells were fixed, blocked and immunolabeled with anti-tau (B, C, E and F, FITC, green), anti-tubulin antibody (D and F, CY3, red) and rhodamine-phalloidin staining for polymerized actin (A and C; red) as described in materials and methods, the regions that are yellow (white arrows) are presumed to be where tau and actin co-localize or tubulin co-localized, scale bars are 5 and 10 µm.

to preformed microtubules in tau expressing yeast cells. Studies on the effect of tau modification which could account for the weak microtubule interaction and the use of an additional tau-containing *C. albicans* laboratory strain which is less efficient in biofilm formation under these growth conditions are currently in progress.

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Conflict of Interests

The author(s) have not declared any conflict of interests.

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