UNIVERSITI PUTRA MALAYSIA

FUNCTIONAL CHARACTERIZATION OF SUPEROXIDE DISMUTASE IN Candida dubliniensis AND EFFECT OF DECYL METHYL CARBINOL

GOH MENG CHUAN

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By
GOH MENG CHUAN

Thesis submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

October 2012

DEDICATION

May my reverends, my parents, my teachers, my sisters, my relatives, my friends and my love one, may you be free from harm and danger, may you be well and happy always.

Abstract of thesis presented to senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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Chairman: Associate Professor Chong Pei Pei, PhD

Faculty: Medicine and Health Sciences

Candida dubliniensis is a *Candida* species that is closely related to *Candida albicans*. Although they share high similarity in both genotypic and phenotypic characteristics including the capability to undergo mycelia transformation from yeast to hypha/pseudohyphae, *C. dubliniensis* is found to be less virulent, more susceptible to antifungal drugs and more sensitive to oxidative stress environment when compared to *C. albicans*. Superoxide dismutase (Sod) is an important enzyme that disproportionates superoxide free radical anions that are generated from oxidative stress. Although *C. dubliniensis* consists of all the *SOD* ortholog sequences which have been found in *C. albicans*, *C. dubliniensis* is unable to sustain significant growth at temperature higher than 40°C when compared to *C. albicans*. Apart from that, quorum sensing molecule (QSM) has been found to be proficient in suppressing morphological switching from yeast to hyphal transition in both *C. albicans* and *C. dubliniensis*. Decyl methyl carbinol (2-dodecanol), a recently identified QSM molecule that has been tested in *C. albicans* is found to have suppressed the yeast to hyphal transformation in hyphal-induced condition. 2-dodecanol also found to suppress certain hyphal-specific genes (HSGs). The current study is focused on the morphological changes of C. *dubliniensis* at different

temperatures. The *SOD* genes in *C. dubliniensis* also have been sequenced and characterized and the expression profile at 37°C and 42°C are studied in comparison to *C. albicans*. The genes expression profiles were quantified using relative quantification real time PCR. Two (2)-dodecanol was used to treat both *C. dubliniensis* and *C. albicans*. The morphological transition, toxicity effect and growth rate in both *C. dubliniensis* & *albicans* were recorded under the effect of 2-dodecanol. *C. dubliniensis* HSGs expression profiles were recorded after exposing 2-dodecanol to *C. dubliniensis* under the hyphal-induced condition. A clinical isolate that is isolated from University Malaya Medical Centre was also molecularly characterized in this study. In the results, *C. dubliniensis* has formed pseudohyphal at 42°C but unable to grow at temperatures higher than 42°C. The *SOD* sequences from *C. dubliniensis* were posted with 85-95% similarity when aligned with the orthologs sequences from *C. albicans*. Despite sharing a certain level of similarities in the *SOD* sequences, a total of 5 *SOD* genes in *C. dubliniensis* were up-regulated in 42°C when compared to *C. albicans* that with only 2 *SOD* genes being up-regulated. This study discovers that, the over-expression of Sod in *C. dubliniensis* could lead to the accumulations of high concentration of hydrogen peroxide and cause *C. dubliniensis* unable to survive in high temperatures. 2-dodecanol, however, showed with the effect to preserve both *C. albicans* and *C. dubliniensis* in round shaped yeast form. Nevertheless, *C. dubliniensis* is significantly more sensitive to high concentration of 2-dodecanol in terms of fungicidal and fungistatic effect. HSGs expression in *C. dubliniensis* under the exposure to 2-dodecanol also vary from what has been seen in *C. albicans* and constant expression of *cdHSP90* can be the main factor that kept *C. dubliniensis* in the yeast form. Interestingly, in this study, we also discovered that the clinical isolate that resembled both *C. dubliniensis* & *C. albicans* are the potential inter-species or intra-species between these two closely related species.

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Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

PENCIRIAN FUNGSI SUPEROXIDE DISMUTASE DALAM *Candida dubliniensis* DAN KESAN DECYL METYL CARBINOL

By

GOH MENG CHUAN

Oktober 2012

Pengerusi: Professor Madya Chong Pei Pei, PhD

Fakulti: Perubatan dan Sains Kesihatan

Candida dubliniensis merupakan species *Candida* yang paling berkait rapat dengan *Candida albicans*. Walaupun mereka berkongsi banyak persamaan dari segi genotip and fenotip yang termasuk keupayaan untuk menjalani transformasi daripada bentuk yis kepada hyphal ataupun pseudohyphal, *C. dubliniensis* didapati kurang berkesan dari segi kebisaan terhadap sel, lebih terjejas kepada ubat-ubatan antikulat dan kekurangan keupayaan untuk hidup dalam persekitaran yang mengandungi tekanan oksidatif yang tinggi berbanding dengan *C. albicans*. Superoxide dismutase (Sod) merupakan enzim yang penting untuk menurunkan atau mengoksidakan ion negatif superoxide redikal yang dijana daripada tekanan oksidatif. Walaupun *C. dubliniensis* mempunyai semua urutan ortholog gen *SOD* daripada *C. albicans*, *C. dubliniensis* tidak dapat menyesuaikan dirinya apabila terdedah kepada suhu yang lebih tinggi ataupun sama dengan 40°C dan akan berhenti mereplikasi atau mati. Selain itu, molekul quorum sensing (QSM) juga didapati berkesan untuk melindungi C. *albicans* dan *C. dubliniensis* daripada menjalankan transformasi yis kepada bentuk hyphal ataupun pseudohyphal. Salah satu QSM yang baru temu dunia, decyl methyl carbinol (2-dodecanol) didapati dapat menghalang pembentukan hyphal atau pseudohyphal daripada bentuk yis. 2-dodecanol

juga dapat menindas ungkapan gen hyphal specifik (HSGs) tertentu. Dalam kajian ini, tumpuan perhatian telah diberi kepada perubahan *C. dubliniensis* dari segi sel morfologi ketika disimpan pada suhu yang berbeza. Kami juga telah mengatur dan membandingkan urutan gen *SOD* dari *C. dubliniensis* dengan urutan gen *SOD* dari *C. albicans*. Ekspresi gen *SOD* daripada *C. dubliniensis* dalam suhu persekitaran 37°C dan 42°C juga dirakamkan dengan mengunakan kaedah kuantifikasi relatif *real time* PCR. Selain itu, 2-dodecanol telah digunakan untuk mengkaji kesannya ke atas peralihan morfologi, ketoksikan dan kadar pertumbuhan dalam *C. dubliniensis* dan *C. albicans*. Ekspresi gen HSGs daripada *C. dubliniensis* juga direkodkan dengan mengunakan kaedah kuantifikasi relatif *real time* PCR. *C. dubliniensis* didapati telah bertumbuh kepada pseudohyphal pada suhu 42°C dan tidak dapat bertumbuh lagi dalam suhu yang lebih tinggi daripada 42°C. Gen *SOD* daripada *C. dubliniensis* juga didapati mempunyai persamaan di antara 85 hingga 95 peratus jika berbanding dengan gen *ortholog* daripada *C. albicans*. Walaubagaimanapun, 5 gen *SOD* dari *C. dubliniensis* telah menunjukkan peningkatan yang jelas dalam suhu 42°C berbanding dengan hanya 2 gen *SOD* dari *C. albicans*. Hipotesis daripada kajian ini telah mencadangkan ungkapan gen *SOD* yang berlebihan di dalam *C. dubliniensis* telah meningkatkan kepekatan *hydrogen peroxide* yang sangat tinggi di dalam *C. dubliniensis* dan menyebabkan ia tidak dapat menyesuaikan dirinya dalam suhu yang tinggi. 2-dodecanol, bagaimanapun, telah menunjukkan kesannya yang mengekalkan *C. dubliniensis* dan *C. albicans* dalam bentuk yis. Tetapi, *C. dubliniensis* lebih sensitif kepada kepekatan 2-dodecanol yang tinggi. Kepekatan 2-dodecanol yang tinggi akan menghalang *C. dubliniensis* daripada menghasilkan generasi yang baru atau akan membunuhkannya. HSGs gen daripada *C. dubliniensis* juga mempunyai cara gen experasi yang berlainan jika berbanding dengan *C. albicans*. Daripada kesimpulan kajian ini, experasi *cdHSP90* yang tinggi mungkin disebabkan oleh perangsangan 2-dodecanol

dan kemungkinan merupakan faktor besar yang mengekalkan *C. dubliniensis* dalam bentuk yis. Kajian ini juga mempunyai pengesanan yang menarik, di mana kemungkinan yang besar species *Candida* daripada hospital Pusat Perubatan Universiti Malaya yang mempunyai ciri-ciri pertengahan diantara *C. dubliniensis* dengan *C. albicans*, adalah species yang baru.

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I certify that a Thesis Examination Committee has met on 17th October 2012 to conduct the final examination of Goh Meng Chuan on his thesis entitled "Functional Characterization of Superoxide Dismutase and Decyl Methyl Carbinol Effect on *Candida dubliniensis*" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the master degree.

Members of the Thesis Examination Committee were as follows:

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

Chong Pei Pei, PhD
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Date:

DECLARATION

I declare that the thesis is my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other institution.

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GOH MENG CHUAN

Date: 17 October 2012

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ALS	Agglutinin-Like Sequence
ATCC	American Type Culture Collection
BLAST	Basic Local Alignment Search Tool
bp	base-pair
cAMP	cyclic adenosine monophosphate
cDNA	complementary Deoxyribonucleic Acid
C.	*Candida*
Ca	*Candida albicans*
Cd	*Candida dubliniensis*
CDK	Cyclin-dependent kinase
cm	centimeter
CO_2	carbon dioxide
CPH	*Candida* PseudoHyphal
C_T	threshold cycle
DEPC	diethyl pyrocarbonate
DNA	Deoxyribonucleic acid
dNTPs	deoxynucleotide triphosphates
E	Amplification Efficiency
EDTA	ethylenediaminetetracetic acid
EFG	Enhanced Filamentous Growth

FBS	Fetal Bovine Serum
g	gram
H_2O_2	Hydrogen Peroxide
HSP	Heat Shock Protein
HWP	Hyphal Wall Protein
ITS	Internal Transcribed Spacer
kb	kilo-base
L	liter
M	Molar
MAP	Mitogen-activated Protein
mb	mega-base
mg	miligram
$MgCl_2$	Magnesium Chloride
MIC	Minimum Inhibitory Concentration
mL	mililiter
mM	milimolar
mm	milimeter
MMLV	Moleney Murine Leukaemia Virus
mRNA	messenger Ribonucleic Acid
NCBI	National Center for Biotechnology Information
NJ	Neighbour-Joining

nm	nanometer
OD	Obtical Density
O_2	Oxygen
$O_2 \cdot^-$	Superoxide anion radical
PBS	phosphate buffer saline
PCR	polymerase chain reaction
pg	picogram
PL	Pospholipase
QSM	Quorum Sensing Molecule
R2	correlation coefficient
RAPD	random amplification of polymorphic DNA
RAS	Rat sarcoma
ROS	Reactive Oxygen Species
RNA	Ribonucleic Acid
rpm	revolution per minute
RPMI	Roswell Park Memorial Institute
RT	reverse transcription
S_{AB}	similarity coefficient
SAP	Secreted Aspartyl Proteinase
SDA	Sabouraud Dextrose Agar
SDB	Sabouraud Dextrose Broth

SIR	Silent Information Regulator
SOD	Superoxide Dismutase
spp.	Species
TAE	Tris acetate EDTA
TBE	Tris Boric EDTA
UMMC	University of Malaya Medical Centre
UV	Ultra Violet
V	volt
v/v	volume/volume
w/v	weight/volume
141	clinical isolate 141
2-dodecanol	decyl methyl carbinol
%	percentage
°C	degree Celsius
µg	microgram
µL	microliter
·OH	hydroxyl radical

CHAPTER 1

INTRODUCTION

Candida species (spp.) are eukaryotic microorganisms that belong to the kingdom of Fungi, phylum of Ascomycota, Subphylum of Saccharomycotina, class of Saccharomycetes, Order of Saccharomycetales and family of Saccharomycetaceae. The capability of some fungal genera to undergo morphological changes had been reported. To date, more than 200 *Candida* spp. have been discovered and described (Kauffman *et al*., 2011). Among them, only a few had been reported to cause medical complications. These include *C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, *C. guiliermondii*, *C. kefyr*, *C. krusei*, *C. lustaniae* and *C. dubliniensis*.

Candida spp. can cause a wide range of infections in humans. Most often, *Candida* spp. are considered as opportunistic pathogens and not true pathogens. *C. albicans* is considered as an inhabitant in human skin and mucosal surfaces and is part of the normal microflora. The spectrum of infections caused by *Candida* spp. includes superficial candidiasis (such as vaginal candidiasis, oral thrush, etc), candidemia and invasive candidiasis (deep-seated organ infections). The importance of *Candida* spp. can be seen in its prevalence in blood stream infections in hospitals, where *Candida* spp. ranked as the fourth most frequently isolated microorganism after bacteria species (Edmond *et al*., 1999). The mortality rates associated with systemic candidiasis is relatively high if left untreated (Pacheco-Rios *et al*., 1997; Friedman *et al*., 2000; Akpan and Morgan, 2002).

The hidden identity of *C. dubliniensis* has been unearthed in the last decade, differentiating it from the most dominant species among pathogenic *Candida* spp., *C.*

albicans. This strange species which has made the oral cavity of immunocompromised patients as their home is often found to be less virulent, more susceptible to antifungal drugs and possess reduced survival rate under stress environment compared to *C. albicans* (Gilfillan *et al*., 1998). Although *C. dubliniensis* rarely causes systemic infection compared to *C. albicans*, antifungal drug resistant *C. dubliniensis* strains had been recovered from infected patients (Moran *et. al*., 1997; Ruhnke *et al*., 2000). Since then, many studies focusing on unravelling additional characteristics of this atypical *Candida* spp. and differentiating it from the most closely related *Candida* spp., *C. albicans* have been published.

Besides *C. dubliniensis*, *C. stellatoidea* and *C. africana* have also been reported to be closely related to *C. albicans* previously and were presumed to be separate species from *C. albicans*. Unlike *C. dubliniensis*, after years of studies, both species have now been classified as two of the sub-strains of *C. albicans* (McCullough *et al*., 1999; Romeo and Criseo, 2009). Scientists believe that more and more subtypes of *Candida* spp. will be revealed in the future and this phenomenon has highlighted the importance to differentiate these species from one another in order to understand this genus better.

From the previous reports, one interesting finding is that *C. dubliniensis* seems to lack the ability to grow at temperatures higher than 40°C when compared to *C. albicans* (Sullivan *et al*., 1995). On another hand, *C. albicans* have been found to consist of 6 different isoforms of superoxide dismutase (Sod), an anti-oxidant enzyme that is well recognized with its function to disproportionate superoxide free radical anions that are generated from the cells themselves when exposed to high temperature (Frealle *et al*., 2005). The *SOD* genes have been identified and characterized in many organisms from

human, animals, plants and microbes. The function of *SOD* genes usually is to protect the host from the reactive oxygen species (ROS). Looking into a newly published genome database of *C. dubliniensis* strain CD36, it is found that *C. dubliniensis* genome library consisted of 8 putative *SOD* genes which may potentially mimic the superoxide dismutase enzymatic functions of *C. albicans*. This has triggered the hypothesis that some of the Sod enzymes in *C. dubliniensis* might possess different expression profiles when compared to *C. albicans* that lead to the disability of *C. dubliniensis* to grow at higher temperature.

Comparing the genetic properties of *C. albicans* and *C. dubliniensis*, the genome size of *C. dubliniensis* is 14.6 Mb while *C. albicans* is varies from 14.3 – 15.6 Mb, depending on the strains (Chibana *et al*., 2005; Butler *et al*., 2009). Both are diploid *Candida* spp., and share more than 98% similarity of the orthologous genes (Magee *et al*., 2008).

Another interesting fact of *C. dubliniensis* is it is capable of undergoing morphological changes to form germ tube to hyphal or pseudohyphal forms and this ability to switch between yeast form and hyphal form has been known as one of the critical virulence factors for pathogenic *C. albicans*. This characteristic also serves as one of the diagnostic tools to distinguish *C. albicans* with other *Candida* spp. in laboratories, although it is no longer the most effective diagnostic method. Studies have pointed out that some of the hypha-specific genes in *C. albicans* are also found in *C. dubliniensis* genome. This suggests that *C. dubliniensis* can also be as pathogenic as *C. albicans*. Recently, cell to cell signalling has been studied intensively in all types of organisms and quorum sensing molecules have been reported to control communication between cells or within the cell itself. The potential of Decylmethyl carbinol (2-dodecanol) as a quorum sensing

molecule has caught the attention of researchers and has been tested in *C. albicans* where it had inhibited *C. albicans* from undergoing morphological transition (Davis-Hanna *et al*., 2008; Lim *et al*., 2009). As *C. dubliniensis* is closely related to *C. albicans*, 2-dodecanol may be able to block *C. dubliniensis* from undergoing phenotypic changes.

Research problems:

Globally, *C. albicans* is still the most predominant species of *Candida* isolated from clinical specimens, although some other *Candida* spp. seem to have survival advantages over this species, such as inherent drug resistance to azole antifungal drugs. *C. krusei* and *C. glabrata* are two species that have inherited reduced-susceptibility to fluconazole, itraconazole and ketoconazole (Koga-Ito *et al*., 2010; Pfaller *et al*., 2004) Unlike *C. dubliniensis*, these 2 species are quite different from *C. albicans* as they are unable to form pseudohypha or true hypha. More importantly, *C. glabrata* is a haploid *Candida* spp. whereas *C. albicans* and *C. dubliniensis* are both diploid *Candida* spp. It is important to conduct more fundamental studies to understand what makes *C. albicans* such a successful opportunistic pathogen, so that potential therapeutic targets or enzymes can be identified as future strategies to eradicate this pathogen. In light of this, *C. dubliniensis* has been chosen as a model organism to study in comparison to *C. albicans*, as *C. dubliniensis* is rarely found to be a causative organism of systemic candidiasis.

Hypothesis:

As *C. dubliniensis* had shown unique differences when compared to *C. albicans*, the hypothesis of this study focused on three parts. The first part of the study described the

growth differences between *C. dubliniensis* and *C. albicans* plus a clinical isolate that possesses close relationship between these two species. The second part of the study mainly aimed to shed light on the effect of 42°C towards the growth pattern, morphological changes and *SOD* gene expression in *C. dubliniensis* and *C. albicans*. The putative *SOD* gene sequences from *C. dubliniensis* were also compared with the sequences of *SOD* genes from *C. albicans*. The third focal point of the study was on the effect of the quorum-sensing molecule, 2-dodecanol towards the growth pattern, morphological changes and the expression of hypha-specific genes in *C. dubliniensis*.

Objectives of the study:

The general objectives of this study were to study the characteristics and behaviour of *C. dubliniensis* in a high temperature environment and when exposed to 2-dodecanol in comparison with *C. albicans*.

The specific aims of this study had been designed to focus on (1) to molecularly identify a clinical isolate that is similar to both *C. dubliniensis* and *C. albicans*, (2) to compare the different morphological and growth profiles between *C. dubliniensis* and *C. albicans* when grown in 37°C and 42°C, (3) to determine the *C. dubliniensis SOD* putative gene expression levels at 37°C and 42°C growth temperatures, (4) to identify the effect of 2-dodecanol in *C. dubliniensis* and (5) to determine the hypha-specific genes (HSGs) expression in *C. dubliniensis* upon exposure to 2-dodecanol.

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