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Genetic Mutations Conferring Resistance to Candida albicans to Antifungal drugs: A Global Perspective and Regional Implications

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Abstract

This article aims to summarize the results of works from January 2013 to December 2017, on the molecular mechanisms of *Candida albicans* resistance to antifungal drugs. It is a prelude to a study on the molecular mechanisms of these resistances in Burkina Faso, with the aim of exploring new therapeutic solutions. Almost all studies have focused on the *ERG11* gene as the most involved in azoles resistance. Mutations have also been demonstrated on other genes conferring resistance to other molecules such as *CDR1* and 2, *MRR1* and 2, TAC1 and ERG for polyenes, allylamines and azoles, *FKS1* for echinocandins, *FCA1* and *FCY1* for pyrimidine analogues. Genetic mutations conferring the resistance of *C. albicans* to antifungals drugs worldwide are regularly reported, but in Burkina Faso we have no data on this subject. As a perspective therefore, a study on the molecular mechanisms of resistance of *C. albicans* to antifungals will be of great help in the fight against the resistance of this frequent yeast to antifungals drugs.

Introduction

In Burkina Faso, candidiosis is a real public health problem. *Candida albicans* is involved in more than 80% of these candidiosis whose spectrum ranges from vaginal, oral, cutaneous candidiosis to deep candidiosis[1](figure 1 and 2). Thus, to combat these infections, antifungals are used, the misuse of which has led to the emergence of *C. albicans* resistance to these molecules[2,3,4,5]. For example, fluconazole used as a preventive treatment for people living with Human immuno-deficiency virus (HIV) in Burkina Faso experienced a 66.5% decrease in susceptibility to *C. albicans*[6]. In the literature, several studies deal with the molecular mechanisms of *C. albicans* resistance to antifungals[3,6,7,8,9,10,11,12,13]. In our context in Burkina Faso, the studies carried out so far are limited to the search for

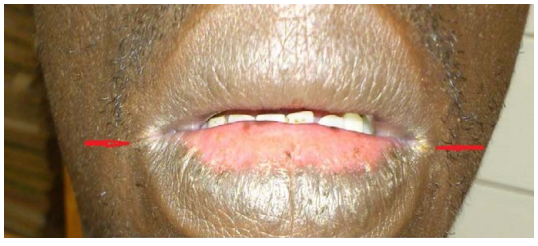

Figure 1: Perleche form of candidiosis *(Department of Parasitology-Mycology, Yalgado Ouedraogo Teaching Hospital, 2017)*

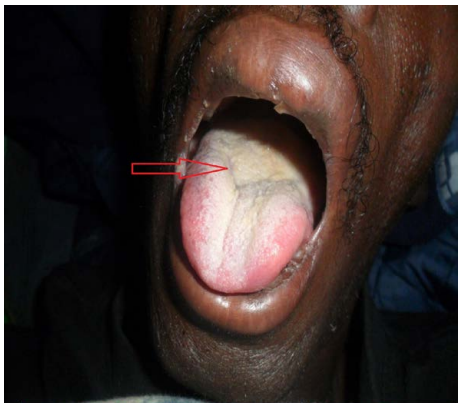

Figure 2: Pseudomembranous form of candidias**is** *(Department of Parasitology-Mycology, CHU Yalgado Ouedraogo, 2016).*

susceptibility profiles of *C. albicans* to antifungals and the identification of the genotypes involved[6]. However, it is necessary to elucidate these molecular mechanisms in our country to explore new therapeutic solutions. This review is therefore a prelude to work on the molecular mechanisms of *C. albicans* resistance to antifungal drugs in Burkina Faso. It allows us to take stock from literature data, studies of the past five years on these resistance mechanisms elsewhere in the world in order to have a clear idea of the importance of the problem.

Data Collecting

This study was conducted in Burkina Faso

This is a review of studies that examined the molecular mechanisms of *C. albicans* resistance to antifungals in the last five years, from 2013 to 2017. The articles were collected from January 2018 to February 2018.

The pubmed database served as a research base. As for the other bases Hinari and google scholar, we consulted them to have access to the full text of some articles.

For the translation of the terms into English, we used the CISMEF website (catalog and index of French-language medical sites: http://www.chu-rouen.fr/cismef/) which allowed us to find the words- key.

The search for the articles was done with great care using the following search terms: Genetic mutations / genomic instability /*Candida albicans* / antifungal drugs resistance. The selection of the studies to be included required the prior establishment of inclusion and non-inclusion criteria. The articles that met the following criteria were used to conduct the review: studies that demonstrated the *C. albicans* strains resistance to antifungal drugs and the molecular mechanisms underlying this resistance; studies written in French or English; studies conducted between 2013 and 2017.

The following articles were not included: articles that focused solely on antifungal susceptibility studies; studies dealing with combinations of antifungals and other molecules; studies that used non-antifungal molecules.

For any selected article, we collected the following data: name of the principal author, date of publication, types of strains (clinical strains, laboratory strains), the molecules used, the resistance genes and their mutations.

A total of 126 articles were included in the review.

Strains of *C. albicans* Used in the Different Studies

The *C. albicans* strains used were essentially clinical strains and incidentally laboratory strains as controls (Table 1)[3,14,15,16,17]. For example, Caban et *al.* in 2016 used three laboratory strains called Ca1r, Ca11r, and Ca12r, as control strains[18].

To better correlate mutations and resistance to antifungal drugs, many authors have used two types of clinical strains in their studies: sensitive strains and resistant strains[19]. And Some authors have preferred to confront three types of strains: sensitive clinical strains, resistant clinical strains and laboratory strains[20].

From a general point of view, we find that most of the strains used in the different studies were clinical strains. The explanation is that these strains would be more available and accessible compared to laboratory strains. Moreover, the results from the manipulation of these strains would be closer to reality, these strains coming directly from sick people in whom the resistances were observed.

In Burkina Faso, studies on the resistance of *C. albicans* to antifungals have so far focused on two aspects of the phenomenon: on the one hand, the phenotypic study of the in vitro sensitivity of clinical strains of *C. albicans* to antifungals and other hand genotypic study of the sensitivity of clinical strains of *C. albicans*[6]. These studies revealed a high frequency of azole-resistant strains, notably fluconazole (resistance observed with 70% of the strains studied)[6]. Of the genotypes A, B and C identified, the genotype A is the most common and most involved in antifungal resistance[6]. However, no studies have yet been conducted on the resistance genes of *C. albicans* in Burkina Faso.

Antifungal Drugs Used in the Different Studies

The majority of authors have focused on resistance to azoles, particularly fluconazole (Table 1)[6,11,14,21,22]. Sometimes other azoles have been associated with fluconazole to demonstrate cross-resistance to azoles. These are voriconazole Iitraconazole, ketoconazole and miconazole[9,16,17,18,19,23,24,25,26]. Indeed, fluconazole is the molecule most used to treat candidosis. The clinical response is generally good, but because of its fungistatic effect, relapses are common. Thus, prolonged and repeated treatment promotes the emergence of resistance to azoles in general and fluconazole in particular[19,27,28].

Table 1: Genes studied, strains used and genetic mutations of *Candida albicans*

Genes or groups of genes studied	Strains used	molecules used	Main mutations of resistance and overexpression of genes or group of genes	sources
ERG11	Clinical	FCZ	E116D F145L I437V	Arati M et *al.* 2016
	Clinical	azoles (FCZ, ITZ et VCZ),	A530C, G622A, G1309A, A1167G, A1230G.	Katarzyna J et *al.* 2013
	clinical + laboratory	azoles (FCZ, KTZ, MCZ, ITR), AMB, 5FC	Q266AspD, L480Q	Caban M et *al.*2016
	Clinical	azoles (FCZ, VCZ)	A114S, Y132H, Y132F, K143R, Y257H K143Q	Xiang MJ et *al.* 2013
	Clinical	FCZ	D225H, K342R, G450E V488I G129A Y132H, A114S, Y257H, V437I, G465S, G448E et K128T	Ying Y et *al*. 2013
	Clinical	FCZ	A61V, D116E, K128T, Y132F, E266D, S279F, L321F, S405F, V488I, S405F	Carvalho VO et *al.* 2014.
	clinical		Y132H et G450E, Y257H G464S,	Lei Z et *al.* 2013
CDR1,CDR2, MDR1,ERG11	clinical	FCZ	overexpression of CD1 gene	Salari S et *al.* 2015
ERG11,CDR1, MDR1, Flu1	clinical + laboratory	FCZ	ERG11p mutations (A114S and Y257H) + overexpression CDR1, MDR1, and Flu1	Xu Y et *al.* 2015
ERG11,CDR1, CRD2, MDR2	clinical	azoles (FCZ, ITZ, VCZ)	overexpression of CDR2, MDR1 and ERG11 + ERG11p mutations (D116E, K128T, V159I and E266D),	Gołąbek K et *al.* 2015
FKS1	Clinical	echinocandins (CFG, MCF)	S645P R1361H S645F	Dudiuk C et *al.* 2015
FKS1, ERG11, ERG2, CDR1 CDR2, TAC1	Clinical	Azoles, and echinocandins	Erg11 mutations (E266D, G307S, G450E and V488I) + Tac1 mutations (R688Q) + Fks1 mutation (S645P) + increased overexpression of ERG11 and CDR2	Jensen RH et *al.* 2015
ERG11, ERG3, MDR1, MRR1	clinical + laboratory	azoles (FCZ , VCZ), polyenes (AMB)	mutation MRR1, ERG11 and ERG3 + overexpression Mdr1, MRR1,	Eddouzi J et *al.* 201
ERG11, MDR1, TAC1, CDR1, CDR2	Clinical	azoles (FCZ et VCZ), allylamines	ERG11 mutations (A114S, Y132H, Y132F, K143Q, K143R, Y257H and G448E) and TAC1 (F964Y)	Liu JY et *al*. 2015
ERG11, ERG4	Clinical	5FC, AMB, FCZ, ITZ, VCZ	2 silent mutations on ERG4 and 10 mutations on ERG11	Feng W et *al.* 2017
TAC1, CDR1, CDR2	Clinical	azoles	Mutations on TAC1 + overexpression of CDR1 and CRR2 genes	Liu Z et *al.* 2017, Popp C 2017
ERG11, *TAC1*, *MRR1*, *UPC2, FKS1*	Clinical	Azoles et echinocandins	126 substitutions: TAC1 (38) ERG11 (20) UPC2 (15) MRR1 (33)	Sitterlé E et *al*. 2017
FUR1, *FCA1, FCY1*			Mutations FUR1 (R101C) + mutations FCA1, FCY1	Arendrup MC et *al.* 2017

FCZ (flconazole), ITZ (itraconazole), VCZ (voriconazole), KTZ (ketoconazole), MCZ (miconazole), AMB (amphtecin B), CFG (caspofungin), MCF (micafungin), 5FC (5flucytosine)

Nevertheless, the literature reports studies on the *C. albicans* resistance to other chemical groups but to a lesser extent: echinocandins[29], polyenes[18,23,24], allylamines candidiosis[23,30].

Mechanisms of Resistance to Antifungals

To azoles

The mechanisms of resistance to azoles are varied and can be divided into four major groups:

Modification of the target (14-alpha-demethylase): The modifications of the 14-alpha-demethylase enzyme correspond to amino acid substitutions in the protein sequence[31,32]. These modifications result in decreased affinity of 14-alpha-demethylase for azoles or conformational changes preventing access of the antifungal agent to the active site[31]. The azoles cannot then play their inhibitor role. These substitutions are the consequence of mutations point in the *ERG11* gene coding for 14-alpha-demethylase[33,34]. Many different mutations have been described.

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According to Carvalho et *al.* in 2014, more than 140 resistant mutations were described on the *C. albicans ERG11* gene[21]. As such, many authors have been interested in this gene in studies of the *C. albicans* resistance to antifungals. The frequencies of the mutant strains in relation to the *ERG11* gene vary from one study to another. Arati et *al.*[14] in 2016 found 34% mutations and 48.1% mutant strains were resistant to fluconazole. Zhang et *al.* in 2013 and Ying et *al.* in 2013 found respectively 41% mutant strains with azoles and 57.9% mutant strains with fluconazole[22,35].

All reported mutations are nucleotide substitutions generating or not (silent mutations) a change of amino acids at a level of the encoded protein (ergosterol). Xiang et *al.* [17] in 2013 showed that ERG11p (14α-demethylase) substitutions A114S, Y132H, Y132F, K143R, Y257H and K143Q were associated with resistance to fluconazole and voriconazole. Arati et *al*. in 2016, found two resistant ERG11p mutations: E116D and F145L[14]. Katarzyna et *al*.[16] in 2013 highlighted the following mutations on the *ERG11* gene: A530C, G622A, G1309A, A1167G, and A1230G. These mutations were observed on resistant strains. But having not obtained any significant association, they then concluded that an isolated mutation on the *ERG11* gene does not necessarily affect the sensitivity of *C. albicans* to azoles, whereas multiple nucleotide substitutions on the *ERG11* gene would affect the sensitivity of *C. albicans* to azoles[16]. Xiang et *al.*[17] in 2013 had reached the same conclusion.

In addition, in this study, a new ERG11p K143Q mutation, which has never been demonstrated by previous studies, has been described in resistant strains[17]. Ying et *al*.[22] in 2013, showed the following ERG11p mutations in fluconazole-resistant strains. Y132H, A114S, Y257H, V437I, G465S, G448E, and K128T: And like the above-mentioned authors they had reached the same conclusion that these multiple amino acid substitutions in Erg11p were frequently found in resistant strains and could be associated resistance to fluconazole[22,36,37]. Carvalho et *al*.[21] in 2014 in a letter to the publisher claimed that the mutation ERG11p S405F would be responsible for an increase of four times the minimum inhibition concentration (MIC) of fluconazole against *C. albicans*. However, mutations of the *ERG11* gene are only one of the mechanisms that may lead to resistance to fluconazole and should not be considered in isolation[21,38].

In conclusion, the authors are unanimous on the following remarks: one substitution observed on the *ERG11* gene in mutant strains of *C. albicans* alone would not be sufficient to confer acquired resistance to azoles, because of the *ERG11* gene polymorphism[23,35]. Thus some mutations are not responsible for resistance azoles[23]. Mutations that cause microbiological resistance are grouped in three very specific regions of the gene azoles[23,35].

Other *ERG* genes such as *ERG1, ERG3, ERG6, ERG24, ERG25* are also involved in the *C. albicans* resistance to azoles[16,23]. However, mutations on these genes have been rarely reported[23].

Overproduction of the target (14-alpha-demethylase): By increasing the production of the target enzyme, *C.albicans* can decrease its sensitivity to the activity of azole antifungals[18,34,39]. Nevertheless, this mechanism must be associated with other mechanisms to achieve resistance in clinical strains[18,34,40]. The overproduction of 14-alpha-demethylase may be the result of two mechanisms. On the one hand, it may be an increase in the expression of the *ERG11* gene, and on the other hand, the overproduction may be the consequence of an increase in the number of copies of the *ERG11* gene[30,40,41]. The regulation of the transcription of the *ERG11* gene in *C. albicans* is complex[40]. The transcription factor *UPC2* makes it possible to control the level of expression of certain genes including *ERG11*. Mutations "gain of function" of *UPC2* can be at the origin of an increase of the activity of this gene, which will result in overexpression of the *ERG11* gene antifungals[20, 32, 36,41]. This type of resistance mechanism has been demonstrated in *C. albicans* strains of clinical origin. Sitterlé et *al*. in a panoramic study of resistance genes on 151 strains of *C. albicans* to antifungal drugs in 2017 made the following conclusion: a total of 126 substitutions identified ,15 concerned *UPC2* gene[11]. Mutations in this gene were associated with resistance to fluconazole[11].

The overproduction of 14-alpha-demethylase may also be related to an increase in the number of copies of the *ERG11* gene occurring as a result of chromosomal rearrangements[9,41,42,43,44].

Phenomena of efflux: To exercise their antifungal activity, azoles must enter the fungal cell and be at an intracellular concentration sufficient to inhibit 14-alpha-demethylase[39]. *C. albicans* has, naturally, at the level of their plasma membrane, multidrug carriers allowing the efflux of different molecules[39]. The *CDR1, CDR2* and *MDR1* genes encode efflux pumps that are membrane transporters that excrete toxic molecules out of the fungal cell. *CDR1* and *CDR2* encode ABC transporters, and the MDR1 gene encodes MFS transporters[24,39].

Increased expression of these transporters (efflux pumps) is an important mechanism of azole resistance in clinical *C. albicans* strains[39]. In recent years, numerous studies have demonstrated the importance of transcriptional regulation of the genes encoding these transporters in the acquisition of azole resistance.

According to Popp et *al*. in 2017 and Zhang et *al*. in 2017, overexpression of these genes could help increase the activity of these pumps and cause resistance to azoles. This increase is the result of mutations in transcription factors such as,

TAC1 and *MRR1* which respectively control the expression of *CDR* and *MDR1* genes[24,40]. In the literature there are cases of resistance to azoles following the overexpression of these genes. Thus, according to Salari et *al*. in 2015, overexpression of the CDR1 gene is strongly correlated with increasing resistance to fluconazole[36]. Other authors such as Gołąbek et *al*. as well as Liu et *al*. reported overexpression of these genes (*CDR1, CDR2* and *MDR2*) that encode efflux pumps was observed in resistant strains of *C. albicans* to azoles confirming the multifactorial character of resistance mechanisms of *C. albicans* already mentioned by some authors[19,25].

In 2015 Jensen et *al*. reported that one or more mutations on the *TAC1* gene would lead to overexpression of the *CDR1*, *CDR2* and *MDR2* genes and thus confer resistance to azoles. Rather in 2013 Eddouzi et *al.* 2013 demonstrated overexpression of the gene superfamily (*CDR1, CDR2, MDR1, MDR2*, and *MRR1*) coding for efflux pumps and strongly associated with resistance of *c. albicans* to azoles[24].

Alterations of the ergosterol synthesis route: In the presence of azoles, the inhibition of 14-alpha-demethylase leads to the accumulation of methylated sterols which are transformed into toxic products by delta-5,6-desaturase, an enzyme which is encoded by the ERG3 gene[19,25]. If the ERG3 gene is mutated, these toxic products are no longer synthesized and the fungal cell can survive and thus become resistant to azoles[19]. This mechanism of resistance, although infrequent, has been demonstrated in some clinical strains of C. albicans[19].

To polyenes

The mechanism involved could be related to a disappearance of ergosterol, the target of the antifungal[45]. This disappearance may be the consequence of a blockage of the ergosterol biosynthesis pathway by mutation of a gene that must be accompanied by the establishment of an accessory metabolic pathway allowing the synthesis of other essential membrane sterols to the survival of the fungal cell[3,12,15,45]. Thus, it has been shown that mutations in delta-5,6-desaturase encoded by the *ERG3* gene were responsible for resistance to amphotericin B in clinically relevant strains of *C. albicans*[45]. In strains with this type of mutation, there is cross-resistance to fluconazole and for some strains a decrease in virulence[45].

To echinocandins

The acquired resistance of *C. albicans* to echinocandins was initially studied in laboratory mutants[11,15]. It is only more recently that cases of resistance have been reported in *C. albicans* strains that cause infections in patients[11,25]. Resistance was initially described for caspofungin but is also present for other echinocandins (micafungin and anidulafungin)[25]. The three echinocandins having the same mechanism of action, it is a class resistance[25].

Currently the only proven mechanism of acquired echinocandin resistance in *C. albicans* is the presence of mutations in the *FKS* genes that encode the target of this antifungal class, beta-1-3-D-glucan synthase[29,30]. At the level of the *FKS* gene, the mutations responsible for resistance are confined to two short sequences that each encode nine amino acids[15]. These regions have been called "hot spot" 1 (HS1) and "hot spot" 2 (HS2) [15]. Mutations are most commonly found in HS1 of *FKS1* for *C. albicans*[20]. For example, The S645P mutation of the Fks1p gene is significantly associated with the resistance of *C. albicans* to echinocandins[15.] Depending on the position of the mutation in the hot spot, the level of resistance may be higher or lower[15]. Biochemical analyzes of beta-1-3-D-glucan synthase extracted from mutated resistant strains showed that the affinity of the enzyme for echinocandins was decreased, confirming the role of mutations in the occurrence of microbiological resistance[15,20,30]. The analysis of a large number of resistant strains shows that the microbiological resistance is therefore undergone by genetic alterations and biochemical modifications at the level of the target enzyme. These resistances have also been confirmed in animal models and are correlated with therapeutic failures in patients[15].

To fluoropyrimidines (5-Fluorocytosine)

The acquired resistance to 5-fluorocytosine can appear rapidly during a treatment of a Candida infection, which does not allow to use this molecule as monotherapy[28]. As a result, 5-fluorocytosine is indicated only in combination with another antifungal agent, most commonly amphotericin B[28]. Different molecular mechanisms can cause resistance to 5-fluorocytosine[28]. Mutations on the *FCA1*, *FCY1* and *FUR1* genes would lead to resistance to 5-fluorocytosine. Indeed, *FCA1* and *FCY1* encode cytosine desaminase, and mutations in these genes therefore inhibit the conversion of flucytosine to 5-F-fluorouridine[28].

FUR1 codes for uracil phosphoribosyltransferase, and mutations in this gene inhibit the conversion of 5-fluorouridine to 5-fluorodeoxyuridylic acid monophosphate[30]. And the substitution R101C on *FUR1* is much associated with this resistance[41,45].

Conclusion

Progresses in molecular biology have allowed researchers to better understand the molecular mechanisms of *C. albicans* resistance to antifungal drugs. The resistance of *C.albicans* to antifungals involves a variety of genes and mechanisms.

In Burkina Faso, resistance to fluconazole is the most observed. But no resistance genes yet studied. To fight against the resistance, we propose two perspectives: - First, identify the resistance genes in order to propose

new molecules with different mechanisms of action. For example, antifungal molecules derived from extracts of *Balanites aegyptiaca* which is a plant of the traditional pharmacopeia used in Burkina Faso to treat superficial candidiosis.

- Secondly, avoid self-medication by prescription of antifungals based on the results of antifungal susceptibility.

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