Antifungal Resistance and its Evolution: An Increasing Concern

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Abstract

This work describes different mechanism of drug resistance and some aspects of evolution of fungi in order to evade antifungal effects. Fungal infections are an issue of concern, and it is necessary to develop new strategies in order to mitigate mortality rates caused by these types of pathogens. However, fungi exhibit different resistance mechanisms, ranging from genetic mutations to metabolic adaptations to the action of several antifungal compounds available for clinical treatments. However, some antifungal resistance are no-evident and need to be studied in order to avoid rising of new resistant fungal strains. Moreover, it is well known that drug resistance is linked to fungal evolution. For this reason, it is important to understand adaptation mechanisms carried out by fungi to resist antibiotic action, such as aminoacid mutations or different metabolic responses of fungal species to several antifungal drugs, in order to, design both new antifungal compounds or strategies for treating fungal infections.

Keywords: Antifungal resistance; Antifungals; Evolution; Fungal infections; Drugs; Pathogens; metabolic Adaptations; Aspergillus species; C. guillermondii; C. lusitaniae; C. parapsilosis; Fluconazole; Fusarium; Enzyme; Toxicity; Phenomenon; C. glabrata; Candida species; Biofilms; Multi drug resistant microorganisms; Inhibitory

Abbreviations: MDR: Multi Drug Resistant Microorganisms; MIC: Minimum Inhibitory Concentration

Mini Review

Antifungal resistance

Over the past 30 years, the importance of antifungal drugs to the practice of modern medicine has increased dramatically. Antifungal drugs used for therapy of fungal diseases can lead to antifungal resistance. Based on a study conducted by National Institute of Health, in the United States during 1980-1997, mortality rates due to invasive mycoses have been increased by 3.2 fold [1,2]. In addition, high both mortality and morbidity caused by poor diagnosis, emergence of drug-resistance and lack of effective antifungal therapy are commonly produced [2]. Nevertheless, antifungal resistance has been described for all virtually antifungal agents in several pathogens, including Candida and Aspergillus species. Additionally, azole resistance in A. fumigatus is widespread with high geographic variance since the first report of itraconazole resistance in 1997 [3]. Moreover, Candida genera exhibit resistance against almost all antifungals available, especially against Fluconazole [4-7]. For instance, C. lusitaniae and C. guillermondii are intrinsically resistant to amphotericin B [8], while other ones such as C. glabrata or C. parapsilosis are more resistant to echinocandins [3,9]. More alarming are the recent global epidemics of C. auris, which displays high resistance to all classes of antifungal drugs,

eliminating effective therapeutic options [10,11]. Similarly, resistance in molds against antifungals available in the market has been demonstrated by Aspergillus fumigatus and other Aspergillus species, and even genera as Scedosporium and Fusarium [12]. For example, A. flavus and A. terreus are able to tolerate higher concentrations of amphotericin B compared to other Aspergillus species, due to different response to oxidative stress [13,14].

In addition, some species of Cryptococcus, which are responsible for more than 1 million infections at high mortality rates (620 thousand deaths per year in sub-Saharan Africa), are resistant to echinocandins, limiting the options of treatment of polyenes that target ergosterol or its biosynthesis [15,16]. Mechanisms of antifungal resistance have been elucidated at molecular level for most of antifungal agents and fungal pathogens. However, molecular mechanisms that lead to antifungal resistance are very complex. These mechanisms include: decrease in effective drug concentration, alteration of drug targets, and metabolic "by pass" [3, 7, 17-20].

Decreasing of effective drug concentrations can be achieved by: Modification of diffusion mechanisms, mediated by the activity of several efflux transport, and, overexpression of the

targeted protein by modification of the promoter region of the gene, which increases drug resistance, offering a pathway for adaptive evolution and a tool for target identification. Overexpression of ERG11 has also been reported for azole-resistant in isolates of C. glabrata, Candida parapsilosis, Candida tropicalis, and Candida krusei. However, the mechanism for this overexpression or its contribution to azole resistance in these species remains largely unknown [19]. Another mechanism of resistance, generally involved in the reducing of drug uptake, is the biofilm formation, associated with resistance to several drugs, including azoles, polyenes, and pyrimidine analogs [7].

These different mechanisms, which may be responsible for the intrinsic resistance of Candida species biofilms, include high density of sessile cells, growth and nutrient limitation, effects of the biofilm matrix, presence of persistent cells, antifungal resistance gene expression and increase of sterols on the membrane of biofilm cells [21-23]. Recent data showed that the cell matrix is involved in this process due to its ability to capture and store antifungal agents. This process has been clearly documented for fluconazole [22,24] and suggested for AmB in C. albicans [25].

Genetic modification of the drug target resulting in reduced affinity for drug is one of the most prominent mechanisms for antifungal resistance [3,20]. Several studies describe point mutations in the ERG11 (CYP51) gene, which encodes 14-α-demethylase; and these amino acid substitutions alter protein structure, decreasing enzyme affinity for azole with the consequent impact of fungal susceptibility to fluconazole. A single instance of an ERG11 mutation has been reported in C. glabrata; a clinical isolate containing a missense mutation produced a cell membrane with no-ergosterol and displayed high resistance to fluconazole [26]. Alteration drug target has been reported for at least two classes of antifungal agents, including azoles and echinocandins. The targets of these two drugs are 14-alpha-demethyliase and Beta-1,3-glucan synthase, respectively. Lanosterol demethylase is encoded by ERG11 in C. albicans and Cyp51A in A. fumigatus. Mutations in ERG11 producing non-synonymous substitutions of amino acids that are present in isolates of C. albicans resistant to azoles. These are numerous and show decrease in affinity of the target to antifungal azoles [27].

Metabolic By-pass occurs when the metabolic pathways are disturbed by loss or sharp decrease in specific cell functions. The metabolic by-pass can be compared with compensatory mechanisms in which the cells by-pass toxic effects exerted by some antifungal agents. For example, azole resistance can be measured by loss of function mutations in the ERG3 gene encoding a sterol Δ5,6-desaturase. If this gene is activated, the enzyme expressed converts 14-alpha-methylated sterols that arise from exposure to azoles into a toxic 3,6-diol derivative [28]. Fungi that are unable to produce this metabolite have azole resistance. Several studies have been reported of mutations that produce the loss of function of ERG3 and exhibit azole resistance [29-32]. However, due to a deficiency in ergosterol biosynthesis, these isolates may be less competitive than wild-type isolates under conditions found in the host. As a result of the loss of function of ERG3 in specific mutants, ergosterol is absent from cell membranes. In this way, mutants evade the toxic effect of AmB, which normally acts as a "sponge" for ergosterol to rapidly destabilize membrane functions [33]. Other mutations in the ergosterol biosynthesis pathway (ERG6, ERG24, and ERG2) lead to the same effect and also have a compensatory effect [34-36]. A mutation in the FUR1 gene that uracil phosphoribosyl transferase decreases the conversion of 5-Fluoro-Uracil (5-FU), which is produced from the deamination of 5-Fluoro-Cytosyne(5-FC), in a toxic metabolite (5-FC- monophosphate). In this way, the toxic effect of 5-FC cannot be exerted [37].

Evolution of antifungal resistance

Evolution of resistance to antifungal drugs is of particular interest due to the increasing incidence of fungal infections that threaten health of patients and limited number of antifungal drugs with different targets [38]. During this transformation, microorganisms have adapted to compete and survive in their natural environments [39, 40]. At the species level, fungi may differ in their inherent ability to proliferate during stress induced by drug exposure, regardless of the acquisition of specific adaptive mutations, which is often referred to as tolerance [38,41,42]. At the population level, fungi can acquire specific mutations that reduce the inhibitory effects of a drug, creating resistance.

Frequency of which resistance is acquired varies dramatically depending on the type of antifungal used. In the case of resistance to azoles, this is the most prevalent, due to both fungistatic nature and strong selection pressure exerted on the survivor populations [42,43]. For echinocandins, a specific type of tolerance denominated paradoxical effect is observed, so that the fungal growth is restored at drug concentrations substantially that are higher than the Minimum Inhibitory Concentration (MIC) [44,45]. This mechanism is due in part to the transcriptional overregulation of the chitin synthases in A. fumigatus and C. albicans, once they are exposed to the echinocandins [44], facilitating mutations that confer fungal resistance.

Variations of susceptibility to antifungals occur also among closely related fungal species. Up to 20% of the strains of Candida glabrata are intrinsically resistant to azoles and even susceptible strains can quickly acquire resistance, leading doctors to recommend echinocandins as a first line therapy to treat a range of candidiasis [46,47]. Furthermore, it is not understood exactly how Cryptococcus neoformas can tolerate echinocandin concentrations that are generally inhibitory, given that the enzyme target (1,3) -Beta-D-Glucan synthase is highly inhibited by echinocandins in vitro, suggesting that the resistance mechanism would not be linked to the enzyme [48].

The phenomenon of hetero-resistance is another example of variation in drug susceptibility within a population. For example, individual cells of Cryptococcus and Candida albicans are able of developing a progeny with phenotypes of heterogeneous resistance, with a small subset of the progeny with azole resistance [49-51]. This phenomenon allows to populations adapt to increasing concentrations of azoles in a gradual manner, restoring the original susceptibility after fungal cells are no exposed to antifungal drugs [50]. The molecular mechanism that governs this response in C. neoformans involves the acquisition of a disomy on chromosome 1, which shares the genes for the azole target ERG11 and the efflux transporter AFR1 [52]. Such phenomena have been observed in clinical and laboratory settings [50,53], which represents an intrinsic adaptive mechanism for survival during azole stress.

On the other hand, antifungal resistance has become a significant concern for clinicians who are responsible for caring for patients at high risk of suffering from invasive fungal infections. Resistance to current antifungal agents may develop secondary mechanisms of resistance acquisition once patients are exposed to these drugs. Recent trends in acquired antifungal resistance include increased resistance to azoles between non-Candida albicans and Aspergillus fumigatus isolates, and resistance to echinocandins in C. glabrata [54-58]. In contrast, some fungal species are intrinsically resistant to certain antifungal drugs (eg C. kuresi to fluconazole, or C. lusitaniae to amphotericin B), while others have demonstrated microbial resistance to all clinically available antifungal drugs (eg Lomentospora prolificans and Fusarium solani) [59-61]. However, new species of fungi resistant to multiple available drugs (eg C.

Conclusion

In this review, we exposed some aspects about antifungal resistance mechanisms and role of evolution in acquisition of resistance. Although the prevalence of antifungal resistance does not occur at the levels observed for some bacteria against different antibiotics, treatment options for invasive fungal infections are limited, and high-risk patients often have multiple co-morbidities, among which are included immunosuppression, which may limit the effectiveness of the therapy, even in the absence of resistance to antifungal drugs. In consequence, new treatment strategies are required to mitigate these resistances, and also overcome the adverse effects and toxicity, as well as drug interactions that are associated with current available antifungals, which may limit the effectiveness of the therapy.

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