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Editorial Open Access

Point mutations and Antifungal resistance in *Aspergillus fumigatus* and *Candida* spp

Guillermo Garcia-Effron*

Laboratorio de Micología y Diagnóstico Molecular Fac. Bioquímica y Ciencias Biológicas,Universidad Nacional del Litoral,Ciudad Universitaria, Santa Fe, Argentina

***Corresponding author:** Garcia-Effron G, Investigador Independiente CONICET, Profesor Adjunto UNL, Laboratorio de Micología y Diagnóstico Molecular, Fac. Bioquímica y Ciencias Biológicas' Universidad Nacional del Litoral, Ciudad Universitaria, Santa Fe, Argentina, Tel: +54-342-4575209 ext:135; E-mail: guillermo_garciaeffron@yahoo.com.ar

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Editorial

In recent years, the incidence of fungal infections has increased considerably due to the increased number of patients susceptible to opportunistic fungal infections caused both by yeast and filamentous fungi. Treatment options for systemic mycoses are limited due to the existence of only three main antifungal classes: the polyenes, azoles and echinocandins. The first two classes target fungal membrane sterols (ergosterol), while echinocandins inhibit the synthesis of fungal cell wall. Most species of *Candida* and *Aspergillus* are susceptible to all the antifungal classes. However, there are intrinsically resistant fungal species and strains of normally susceptible species that develop antifungal resistance during therapy (secondary resistance).

Aspergillus spp. is intrinsically resistant to fluconazole, while *A. terreus* is also naturally resistant to amphotericin B (the only systemic polyene). Moreover, 5-10% of clinical isolates of *Aspergillus* spp. acquired secondary resistance to triazoles during treatment. Turning to *Candida* spp., *C. krusei* is naturally resistant to fluconazole while *C. glabrata* has high rates of resistance to fluconazole and *C. parapsilosis* sensu lato exhibits reduced susceptibility to echinocandins. In addition, all *Candida* species present in greater or lesser extent secondary resistance to azoles and echinocandin drugs.

Despite its clinical importance, the study of the molecular mechanisms of resistance to antifungal agents have been limited to very few *Candida* spp. and *A. fumigatus* strains that did not respond to therapy with triazoles and echinocandins.

Taking the described facts into account, I decided to focus my research work in Medical Mycology and especially in molecular mechanism of antifungal resistance. During my career I studied the genes and proteins involved in ergosterol and fungal cell wall biosynthesis and the way fungi evade antifungal drugs action. My main objectives were to study the fungal 14 alpha sterol demethylases and the beta 1,3-D glucan synthases, the target of azole and echinocandin agents, respectively. I spent five years (2001-2006) in the Carlos III Institute of Madrid under the direction of Dr. Emilia Mellado studying *A. fumigatus* CYP51 genes and its relationship with the phenotypes of azole antifungal resistance. We published more than 10 journal articles where most of the molecular mechanisms of secondary resistance of *Aspergillus fumigatus* were firstly describe. These studies, along with that of other authors, allowed to establish that the main mechanism of resistance to azoles in filamentous fungi are point mutations in the gene CYP51A while overexpression of efflux pumps (main mechanism azole resistance in yeast) have a marginal or no role in clinical resistance to azoles in filamentous fungi. In addition, we established that each mutation generates a characteristic resistance phenotype. This statement led to the design of molecular diagnostic tools of resistance to azoles that accelerate the correct choice of treatment.

Between 2006 and 2010, I worked at Dr. David Perlin's lab at the Public Health Research Institute (dependent at that time of the University of Medicine and Dentistry of New Jersey and now is part of Rutgers University, USA). During my stay in the US we described the mechanism of intrinsic resistance of *Candida parapsilosis*, *C. metapsilosis* and *C. orthopsilosis* to echinocandin drugs and the secondary resistance mechanisms of *C. albicans*, *C. krusei*, *C. glabrata* and *C. tropicalis* to these antifungals. We also studied the 1,3-β-D glucan synthase complex of these species and showed their common features such as: (i) the presence of mutations in certain areas (hot spots) of the catalytic subunit of the complex 1,3 β-D glucan synthase (FKS1) are responsible for the phenotypes of echinocandin resistance, (ii) the amino acid substitutions in the hot spots reduce the 1,3-β-D glucan synthase complex catalysis speed (lower Vmax) leading to a reduction of the content of 1,3-β-D glucans in these yeasts wall. (Iii) The deficit glucans produced by mutations is compensated by increased expression of FKS2 (FKS1 orthologous) (iv) The heterozygous mutants in FKS1 evidenced the existence of mixed populations when enzymatic complex biochemical properties of 1,3-β-D glucan synthase (two IC50 values, Vmax and Km) were evaluated. In addition, we published two papers that influenced directly on the decision by the CLSI (Clinical and Laboratory Standards Institute) to change the cutoff points for interpretation of the results of Minimum Inhibitory Concentration for echinocandins. These new breakpoints were published in December 2012 in the CLSI document M27S4 and today are used globally in interpreting results in susceptibility to echinocandins *Candida* spp.

In 2010, I have been appointed as CONICET Researcher (Argentinian State Research Agency) and I'm directing the Mycology Laboratory of Molecular Diagnostics at the Litoral University in Santa Fe, Argentina. In these five years, my activities were divided into independent research and cooperative work with other Argentinian and international research groups among which stands out: Dr. Perlin (USA), Dr. Canton (Valencia-Spain), Dr. Arendrup (Denmark), Dr. Mellado (Spain), Dr. Espinell-Ingrof (USA), Malbran Institute (Argentina), etc. We published several research papers on molecular techniques for the detection of echinocandin resistance, epidemiology of *Candida parapsilosis* sensu lato, virulence of echinocandin resistant mutants, etc.