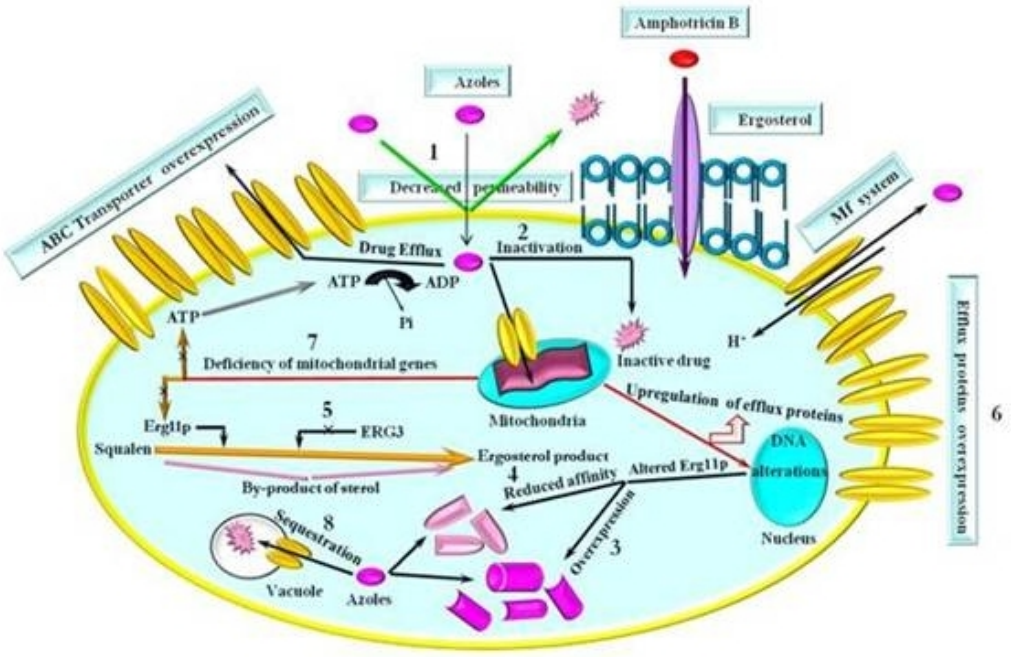
R2598
Abstract (publication only)

Upregulation of the ERG11 gene in Candida krusei by Azoles

M. Tavakoli*, M. Heidari, F. Zaini (Ahvaz, IR)

Background and the purpose of the study: Candida species (spp) are the agents of local and systemic opportunistic infections have become a major cause of morbidity and mortality in the last few decades. Azole resistance in Candida krusei (C.krusei) species appears to be the result of gene alterations in relation to the ergosterol biosynthetic pathway, as well as efflux pumps. The main aim of this study was to examine the RNA expression of ERG11 in C. krusei which had been identified to be resistance to azoles. Method: The ERG11 mRNA expression was investigated in four Iranian clinical isolates of C.krusei, which were resistant to fluconazole and itraconazole by a semiquantitative RT-PCR. Results: The mRNA expression levels were observed in four out of four isolates by this technique. Furthermore, we found the variation in ERG11 expression levels among four representative isolates of C.krusei. Although DNA sequencing revealed no significant genetic alteration in the ERG11 gene, one heterozygous polymorphism was observed in two isolates, but not in others. This polymorphism was found in the third base of codon 313 for Thr (ACT>ACC). Major conclusion: Even though such a polymorphism creates a new Ear1 restriction site, we considered it to have no significant effect on the resistance of C.krusei to azoles. Our results are consistent with previous studies and may provide further evidence for the genetic heterogeneity and complexity of the ergosterol biosynthetic pathway or efflux pumps.



Suggested Mechanisms of Azole Resistance in yeasts. 1- Changes of intra membrane lipid compositions which modify membranous fluidity and control some cell activities such as material transmissions (ABCT-transporters). Also, alteration in membrane-binding properties including reduced uptake of hydrophilic drugs, e.g. fluconazole can change the permeability of amphotricin B **2**- Drug inactivation **3**- amplification or increasing transcription of *ERG11* and subsequently overproduction of the azole target Ergl 1p, a hemoprotein supporting lanosterol 14α-demethylase activity **4**- DNA alterations of *ERG11* gene which leads to reduction of azole affinity to Ergl 1p **5**- loss of other genes which are involved in the ergosterol biosynthetic pathway such as *ERG3*. Moreover, accumulation of a primary substrate or toxic by-products of sterol **6**- Decreasing intracellular drug accumulation by overexpression of efflux pump genes [Efflux pumps are divided into two categories including ATP binding-cassette transporter (ABCT) and major facilitator (MF)] and regulatory networks. **7**- Mitochondria deficiencies as described in the text. **8**- Finally, drug sequestration in vacuole could be involved in the mechanisms of azole resistance in yeast.