中国真菌学杂志 2011, 6(4) 193-198 DOI: ISSN: 1673-3827 CN: 31-1960/R

专家论坛

念珠菌的耐药机制及应对策略研究

姜远英, 刘伟, 曹永兵

中国人民解放军第二军医大学新药研究中心, 上海200433

摘要： 念珠菌是临床上深部真菌感染的主要致病菌,致死率高,耐药性严重,耐药机制主要包括:药物作用靶标结构变异;靶标表达增加;靶标缺失;影响药物外排;改变细胞膜甾醇成分;形成生物被膜;钙调神经磷酸酶通路激活等。针对真菌耐药性问题,首要的应对策略应是研究发现新的药靶,开发全新结构和作用方式的新药。同时,筛选研究能降低真菌耐药性的新药,通过与现有的抗真菌药物联合使用,也可作为临床克服真菌耐药,防治真菌感染的有效策略。

关键词： 念珠菌 耐药机制 新药靶 对策

Abstract:

Keywords:

收稿日期 2011-03-04 修回日期 网络版发布日期

DOI:

基金项目:

国家高技术研究发展计划(863计划,2008AA02Z128);上海市基础研究重点项目(08JC1405900)

通讯作者:

作者简介: 姜远英,男(汉族),教授,博士研究生导师.E-mail:jiangyy@smmu.edu.cn

作者Email:

参考文献：

[1] 王红,叶嗣颖.深部真菌感染临床特点分析[J].中国微生态学杂志,2010,22(8):734-737.
[2] Feng LJ,WanZ,Wang XH,et al.Relationship between antifungal resistance of fluconazole resistant Candida albicans and mutations in ERG11 gene[J].Chin Med J,2010,123 (5):544-548.
[3] Brian G,Oliver JL,Song JH,et al.Cis-Acting elements within the Candida albicans ERG11 promoter mediate the azole response through transcription factor Upc2p[J].Eukayotic Cell,2007,6(12):2231-2239.
[4] Nico D,Teresa TL,Katherine SB,et al.A gain-of-gunction mutation in the transcription factor Upc2p causes upregulation of ergosterol biosynthesis genes and increased fluconazole resistance in a clinical Candida albicans isolate[J]. Eukayotic Cell,2008,7(7):1180-1190.
[5] Clemens JH,Sabrina S,Katherine SB,et al.An A643T mutation in the transcription factor Upc2p causes constitutive ERG11 upregulation and increased fluconazole resistance in Candida albicans

[J].Antimicrobial Agents and Chemotherapy,2010,54(1):353-359.
[6] Zheng H,Jiang YY,Wang Y,et al.TOP2 gene disruption reduces drug susceptibility by increasing intracellular ergosterol biosynthesis in Candida albicans[J].J Med Microbiol,2010,59(7):797-803.
[7] Luiz RB,Charles E G,Yu XM,et al.Fluconazole transport into Candida albicanss ecretory vesicles by the membrane proteins Cdr1p,Cdr2p,and Mdr1p[J].Eukayotic Cell,2010,9(6):960-970.
[8] Ann R H,Ya HL,Kyoko N,et al.ABC transporter Cdrl p contributes more than Cdr2p does to fluconazole efflux in fluconazole-resistant Candida albicansclinical isolates[J].Antimicrobial Agents and Chemotherapy,2008,52 (11):3851-3862.
[9] Sarah T,Fariba R,Martine R.Relative contributions of the Candida albicans ABC transporters Cdr1p and Cdr2p to clinical azole resistance[J].Antimicrobial Agents and Chemotherapy,2009,53(4):1344-1352.
[10] Shen H,An MM,Wang D J,et al.Fcr1p inhibits development of fluconszole resistance in Candida albicans by abolishing CDR1 induction[J].Biol Pharm Bull,2007,30(1):68-73.
[11] Maurizio S,Brunella P,Barbara F,et al.Mechanisms of azole resistance in clinical isolates of candida glabrata collected during a hospital survey of antifungal resistance[J].Antimicrobial Agents and Chemotherapy,2005,49 (2):668-679.
[12] Bryce EM,HannaNO,Brian GO,et al.Azole drugs are imported by facilitated diffusion in Candida albicans and other pathogenic fungi[J].PLoS Pathogens,2010,6(9):1-11.
[13] Mukherjee PK,Zhou G,Mohamed S,et al.Candida albicans biofilm:isolation and composition of extracellular matrix:abstracts of the seventh ASM conference on eandida and candidiasis,Austin,TX,2004 [C].
[14] Mukherjee PK,Chandra J,Kuhn DM,et al.Mechanism of azole resistance in Candida albicans biofilms:phase specific role of efflux pumps and membrane sterols[J].Infect Immun,2003,71:4333-4340.
[15] Jeniel Nett,Leslie Lincoln,Karen Marchillo,et al.Putative role of β-1,3 glucans in Candida albicans biofilm resistance[J].Antimicrobial Agents and Chemotherapy,2007,51 (2):510-520.
[16] Jeniel EN,Kyler C,Karen M,et al.Role of Fks1p and matrix glucan in Candida albicans biofilm resistance to an echinocandin,pyrimidine,and polyene[J].Antimicrobial Agents and Chemotherapy,2010,54(8):3505-3508.
[17] Sheena DS,Nicole R,AimeeKZ,et al.Hsp90 governs echinocandin resistance in the pathogenic yeast Candida albicans via calcineurin[J].Plos Pathogens,2009,5(7):1-14.
[18] Cowen LE,Carpenter AE,Matangkasombut O.Genetic architecture of Hsp90-dependent drug resistance[J].Eukaryot Cell,2006,5:2184-2188.
[19] Jennifer LR,Scott GF,Joseph H.Elucidating the Candida albicans calcineurin signaling cascade controlling stress response and virulence[J].Fungal Genetics and Biology,2010,47:107-116.
[20] Jia XM,Ma ZP,Jia Y,et al.RTA2,a novel gene involved in azole resistance in Candida albicans [J].Biochemical and Biophysical Research Communications,2008,373:631-636.
[21] Jia XM,Wang Y,Jia Y,et al.RTA2 is involved in calcineurinmediated azole resistance and sphingoid long-chain base release in Candida albicans[J].Cell Mol Life Sci,2009,66:122-134.
[22] Martel CM,Parker JE,Bader O,et al.Identification and characterization of four azole-resistant erg3 mutants of Candida albicans[J].Antimicrob Agents Chemother,2010,54 (11):4527-4533.
[23] Miyazaki T,Yoshitsugu M,Koichi I,et al.Fluconazole treatment is effective against a Candida albicans erg3/erg3 mutant in vivo despite in vitro resistance[J].Antimicrobial Agents and Chemotherapy,2006,50 (2):580-586.
[24] Peyron F,Favel A,Calaf R,et al.Sterol and fatty acid composition of Candida lusitaniae clinical isolates[J].Antimicrob Agents Chemother,2002,46 (2):531-533.
[25] Laura YY,Christina MH,Joseph H.Disruption of ergosterol biosynthesis confers resistance to amphotericin B in candida lusitaniae[J].Antimicrobial Agents and Chemotherapy,2003,47(9):2717-2724.
[26] Martel CM,Parker JE,Bader O,et al.A clinical isolate of Candida albicans with mutations in ERG11 (encoding sterol 14alpha-demethylase) and ERG5 (encoding C22 desaturase) is cross resistant to azoles and amphotericin B[J].Antimicrob Agents Chemother,2010,54 (9):3578-3583.
[27] Prasanna DK,Peter AS,Miller RL,et al.A Small subpopulation of blastospores in Candida albicans biofilms exhibit resistance to amphotericin B associated with differential regulation of ergosterol and β-1,6-glucan pathway genes[J].Antimicrobial Agents and Chemotherapy,2006,50(11):3708-3716.
[28] Park S,Kelly R,Kahn JN,et al.Specific substitutions in the echinocandin target Fks1p account for reduced susceptibility of rare laboratory and clinical Candida sp.isolates[J].Antimicrob Agents Chemother,2005,49:3264-3273.
[29] Desnos OM,Bretagne S,Raoux D,et al.Mutations in the fks1 gene in Candida albicans,C.tropicalis,and C.krusei correlate with elevated caspofungin MICs uncovered in AM3 medium using the method of the European committee on antibiotic susceptibility testing[J].Antimicrob Agents Chemother,2008,52(9):3092-3098.
[30] Zimbeck AJ,Iqbal N,Ahlquist AM,et al.FKS mutations and elevated echinocandin MIC values among Candida glabrata isolates from U.S.population-based surveillance[J].Antimicrob Agents Chemother,2010,54(12):5042-5047.
[31] Warn PA,SharpA,MorrisseyG,et al.Activity of aminocandin (IP960 ; HMR3270) compared with amphotericin B,itraconazole,caspofungin and micafungin in neutropenic murine models of disseminated infection caused by itraconazole-susceptible and-resistant strains ofAspergillusfumigatus[J].Int J

Antimicrob Agents,2010,35(2):146-151.
[32] Sandeep S,Rohit KS,Rahul J.Current advances in antifungal targets and drug development [J].Current Medicinal Chemistry,2006,13:1321-1335.
[33] Gonzólez IJ,Milewski S,Villagómez CJC,et al.Sporothrix schenckii:purification and partial biochemical characterization of glucosamine-6-phosphate synthase,a potential antifungal target[J].Med Mycol,2010,48(1):110-121.
[34] Pasqualotto AC,Thiele KO,Goldani LZ.Novel triazole antifungal drugs:focus on isavuconazole,ravuconazole and albaconazole[J].Curr Opin Investig Drugs,2010,11 (2):165-174.
[35] Kakeya H,Miyazaki Y,Senda H,et al.Efficacy of SPK-843,a novel polyene antifungal,in comparison with amphotericin B,liposomal amphotericin B,and micafungin against murine pulmonary aspergillesis [J].Antimicrob Agents Chemother,2008,52 (5):1868-1870.
[36] Nafsika HG.Antifungals targeted to sphingolipid synthesis:focus on inositol phosphorylceramide synthase[J].Expert Opinion on Investigational Drugs,2000,9 (8):1787-1796.
[37] Mandala SM,Thomton RA,Milligan J,et al.Rustmicin,a potent antifungal agent,inhibits sphingolipid synthesis at inositol phosphoceramide synthase[J].J Biol Chem,1998,273 (24):14942-14949.
[38] Wen YZ,Matthew WJ,Nafsika H.Geergopapodakou.Inhibition of inesitol phesphorylceramide synthase by aureobnsidin a in candida and aspergillus species[J].Antimicrobial Agents and Chemotherapy,2000,44 (3):651-653.
[39] Aoyagi A,Yano T,Kozuma S,et al.Pleofungins,novel inositol phosphorylceramide synthase inhibitors,from Phona sp.SANK 13899 Ⅱ Structural elucidation[J].J Antibiot,2007,60 (2):143-152.
[40] Sandbaken MG,Lupisella JA,DiDomenico B,et al.Protein synthesis in yeast.Structural and functional analysis of the gene encoding elongation factor 3[J].J Biol Chem,1990,265 (26):15838-15844.
[41] Prasad KK,Toraskar MP,Kadam VJ.N-myristoyltransferase:a novel target[J].Mini Rev Med Chem,2008,8(2):142-149.
[42] Sheng C,Zhu J,Zhang W,et al.3D-QSAR and molecular docking studies on benzothiazole derivatives as Candida albicans Nmyristoyltransfernse inhibitors[J].Eur J Med Chem,2007,42(4):477-486.
[43] Melissa DJ,John RP.Use of antifungal combination therapy:agents order and timing[J].Curt Fungal Infect Rep,2010,4(2):87-95.
[44] Sun L,Sun S,Cheng A,et al.In vitro activities of retigeric acid B alone and in combination with azole antifungal agents against Candida albicans[J].Antimicrob Agents Chemother,2009,53(4):1586-1591.
[45] Guo XL,Leng P,Yang Y,et al.Plagiochin E,a botanic-derived phenolic compound,reverses fungal resistance to fluconazole relating to the efflux pump[J].J Appl Microbio1,2008,104 (3):831-838.
[46] Jin J,Guo N,Zhang J,et al.The synergy of honokiol and fluconazole against clinical isolates of azole-resistant Candida albicans[J].Lett Appl Microbiol,2010,51 (3):357-361.
[47] Quan H,Cao YY,Xu Z,et al.Potent in vitro synergism of fluconazole and berberine chloride against clinical isolates of Candida albicans resistant to fluconazole[J].Antimicrob Agents Chemother,2006,50 (3):1096-1099.
[48] Huang S,Cao YY,Dai BD,et al.In vitro synergism of fluconazole and baicalein against clinical isolates of Candida albicans resistant to fluconazole[J].Biol Pharm Bull,2008,31 (12):2234-2236.
[49] An M,Shen H,Cno Y,et al.Allicin enhamces the oxidative damage effect of amphotericin B against Candida albicans[J].Int J Antimicrob Agents,2009,33(3):258-263.
[50] Xu Y,Wang Y,YanL,et al.Proteomic analysis reveals a synergistic mechanism of fluconazole and berberine against fluconazole-resistant Candida albicans:endogenous ROS augmentation[J].J Proteome Res,2009,8(11):5296-5304.
[51] Cao Y,Dai BD,Wang Y,et al.In vitro activity of baicalein against Candida albicans biofilms[J].Int J Antimierob Agents,2008,32(1):73-77.

本刊中的类似文章

1．季雅娟, 王爱平, 刘伟, 万喆, 李若瑜.特比萘芬与其他抗真菌药物对外阴阴道念珠菌病病原菌的体外相互作用研究[J]. 中国真菌学杂志, 2012,(2): 73-76,81
2．阳隽, 张天托, 朱家馨.荧光定量PCR检测不同状态下白念珠菌CPH1、EFG1基因的表达[J]. 中国真菌学杂志, 2012,(2): 77-81
3．江爱萍, 黄剑清, 卢万丁, 徐明, 吴建华.PCR指纹图谱分析在念珠菌性阴道炎、龟头炎流行病学研究中的应用[J]. 中国真菌学杂志, 2012,(2): 82-84,115
4．郎涤非, 李文, 孙宁霞.氟康唑联合克霉唑阴道片治疗复发性外阴阴道念珠菌病临床观察[J]. 中国真菌学杂志, 2012,(2): 104-105,108
5．吴启富.硝酸舍他康唑乳膏治疗儿童皮肤念珠菌病50例[J]. 中国真菌学杂志, 2012,(2): 106-108
6．商庆华, 曹颖瑛, 苗浩, 姜远英.白念珠菌生物被膜的基因表达及相关基因研究进展[J]. 中国真菌学杂志, 2012,(2): 125-128
7．朴英兰, 沈亮亮, 叶元康, 潘胜利, 武济民.五环三萜类柴胡皂苷单体对白念珠菌伊曲康唑耐药株活性研究[J]. 中国真菌学杂志, 2012,7(1): 8-11
8．周万青, 沈瀚, 张之烽, 张葵.白念珠菌临床分离调查及基因分型研究[J]. 中国真菌学杂志, 2012,7(1): 20-23
9．蔡晴, 刘维达.先天性皮肤念珠菌病[J]. 中国真菌学杂志, 2012,7(1): 43-46
10．仇萌, 邹先彪.Sap2与侵袭性白念珠菌感染相关性研究进展[J]. 中国真菌学杂志, 2012,7(1): 52-54

11. 乔祖莎, 冯文莉.克柔念珠菌对抗真菌药物耐药机制的研究进展[J]. 中国真菌学杂志, 2012,7(1): 55-58
12. 林莉, 王莉, 周洋洋, 陈耀华, 孟新丽, 康健.大鼠白念珠菌支气管肺感染时肺组织Toll样受体2的表达及意义[J]. 中国真菌学杂志, 2011,6(6): 337-340
13. 王爱平, 万喆, 涂平, 陈伟, 李若瑜.慢性皮肤黏膜念珠菌病1例[J]. 中国真菌学杂志, 2011,6(6): 352-354,357
14. 曾荣, 李岷, 陈青, 王乐, 吕桂霞, 沈永年, 蔡晴, 李彩霞, 唐荣才, 刘维达.卡泊芬净、米卡芬净对念珠菌体外药物敏感性的动态研究[J]. 中国真菌学杂志, 2011,6(5): 276-280
15. 帕丽达·阿布利孜, 哈木拉提·吾甫尔, Takashi Yaguchi, Kayoko Takizawa, 李若瑜.新疆地区白念珠菌基因型分析及其体外药物敏感性研究[J]. 中国真菌学杂志, 2011,6(1): 10-14
