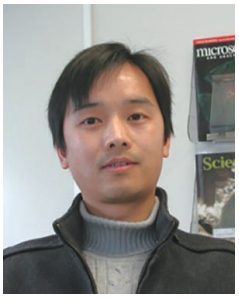
特约综述



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白念珠菌形态转换及其调控机制的研究进展

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摘要 白念珠菌是人体内正常的共生微生物, 也是最常见的机会性致病真菌。该菌最重要的生物学特征是其形态的多样性, 不同形态细胞之间可频繁地相互转换。这种形态的可塑性与白念珠菌在宿主体内的定植能力、侵染性以及有性生殖等方面均有密切关系, 也是该菌对外界环境变化的适应策略。酵母–菌丝相和white-opaque形态转换是白念珠菌中两种典型形态转换系统。宿主相关的环境因子和白念珠菌内源基因共同参与这些形态转换的调控。该文将综述近年来白念珠菌形态转换及其调控机制方面的进展, 重点介绍参与菌丝发育和white-opaque形态转换的关键因子和调控通路。

关键词 白念珠菌, 形态转换; 环境信号; cAMP/PKA信号途径; 有性生殖

Phenotypic Transitions and Their Regulatory Mechanisms in the Human Fungal Pathogen *Candida albicans*

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Abstract *Candida albicans* is a common commensal of healthy people and an opportunistic fungal pathogen. A striking biological feature of this fungus is its morphological plasticity. *C. albicans* can switch among a number of morphological phenotypes. Yeast-filamentous growth and white-opaque transitions are the two typical phenotypic switching systems. As a survival and adaptive strategy of *C. albicans*, phenotypic transitions are involved in the regulation of colonization, virulence, and sexual reproduction. A number of host-related environmental factors and genetic regulators have been proven to be involved in the regulation of phenotypic transitions in *C. albicans*. In this review, we will focus on the regulatory mechanisms of phenotypic transitions in this pathogenic organism.

Keywords *Candida albicans*; phenotypic transitions; environmental cues; cAMP/PKA pathway; sexual reproduction

白念珠菌(*Candida albicans*)是人体内正常的共生微生物, 也是一种重要的机会性致病真菌, 常见于健康人体口腔、上呼吸道、消化道及生殖道等部位。白念珠菌通常不会引起疾病, 但是当人体免疫系统受损或体内正常微生物菌群失衡时, 该菌过度生长引起浅部感染(如鹅口疮和阴道炎), 甚至可能导致致命性的深部器官或系统感染(如败血症)[1]。近年来, 由于新型医疗技术的应用(如免疫抑制剂、器官移植和广谱抗生素的广泛使用)、艾滋病的流行和人口老龄化等因素, 临床上以白念珠菌为主的真菌感染率呈明显上升的趋势, 尤其是深部念珠菌感染问题日益严重[2-3]。

白念珠菌可以感染人体的几乎所有器官。为了适应宿主体内复杂的环境条件, 白念珠菌进化出多种适应机制, 其中白念珠菌形态转换与其环境适应能力关系最为密切。酵母–菌丝相转换和white-opaque形态转换是白念珠菌中研究最多的两种形态转换系统[4-5]。Gray形态是近年来在白念珠菌中发现的一种新形态, gray细胞与white和opaque细胞形成white-gray-opaque三稳态转换系统[6]。外界环境信号和内在的信号通路共同调控白念珠菌的形态转换。宿主相关环境因子[如氮乙酰葡萄糖胺(GlcNAc)、血清、温度、CO_2浓度和pH值等]在菌丝发育和opaque细胞形成过程中均起重要的调控作用; 保守的cAMP/PKA(cAMP-protein kinase A)和MAPK(mitogen-activated protein kinase)等信号通路以及下游转录因子Efg1(enhanced filamentous growth 1)、Flo8(flocculation 8)和Wor1(white-opaque regulator 1)等, 直接参与环境的应答和形态转换的调控[7]。白念珠菌不同形态细胞在基因表达谱、毒性和交配能力等多方面具有明显差异[7]。

1 酵母–菌丝相形态转换

早在1985年, Slutsky等[8]教授的实验室发现, 白念珠菌至少能形成七种不同形态的菌落, 而且不同形态之间可进行高频率的相互转换。从细胞形态上看, 白念珠菌中有酵母型(yeast)、假菌丝型(pseudohyphae)和菌丝型(hyphae)三种不同形态[4,9]。白念珠菌的酵母型细胞呈球形或椭球形, 与二倍体酿酒酵母(*Saccharomyces cerevisiae*)相似。菌丝型细胞是由初期形成的“芽管”不断生长形成的, 呈无隔膜的长管状形态。假菌丝是由一串伸长的酵母态细胞组成, 细胞间有隔膜[10]。本文把假菌丝型和菌丝型的细胞形态统称为菌丝或菌丝型细胞。在宿主相关环境因子的刺激下, 白念珠菌可以在酵母和菌丝形态之间进行转换, 从而更好地适应宿主环境。白念珠菌酵母型细胞定植于黏膜或皮肤的表面, 通常不引起宿主的免疫反应, 但容易通过血液循环系统在宿主体内传播[10]; 其菌丝细胞在侵染宿主组织和穿透上皮细胞方面的能力较强[11], 在逃逸巨噬细胞吞噬方面也具有重要的作用[12-13]。在被感染的宿主组织中, 白念珠菌通常以多种细胞形态(如酵母、菌丝和假菌丝)存在, 说明白念珠菌的酵母–菌丝型形态转换与其毒性有密切关系[1]。

1.1 环境因子调控白念珠菌菌丝生长

多种宿主相关的环境因子(如pH值[14]、温度[4,15]、血清[16]、CO_2[17-18]和GlcNAc[19-20]等)参与调控白念珠菌酵母–菌丝形态转换。人体pH值范围较广, 如阴道的正常pH值为4.5, 人类血液的pH值为7.0, 而消化道pH变化范围更大(pH1.0~pH8.0)[21-22]。白念珠菌适应环境pH变化的能力非常强, 能够在pH2.0~pH10.0的条件下生存[23]。酸性pH值(pH<6.5)抑制酵母型向菌丝型细胞转换, 而中性或碱性pH值(pH>6.5)条件

促进菌丝生长[23-24]。人体血液和组织的pH值为中性或弱碱性, 有利于白念珠菌菌丝的形成, 从而促进其侵染和定植。温度是另一个菌丝发育的调控因子, 人体生理温度37 °C是白念珠菌菌丝生长的最适温度[25]。在低温和常规条件下培养白念珠菌则有利于酵母型细胞的形成, 但在培养基包埋培养条件下, 即使25 °C低温也能促进菌丝形成, 说明物理接触在菌丝发育中有重要作用[15]。

血清和GlcNAc是白念珠菌菌丝生长的两种诱导因子。血清诱导菌丝生长的成分可能是肽聚糖[16], 人体自身不能合成肽聚糖, 血清中的这种成分可能主要来源于肠道共生细菌代谢[16]。GlcNAc是消化道黏膜和细菌细胞壁的组成成分[26-27]。人体肠道和血液中二氧化碳(CO_2)浓度远高于空气中CO_2浓度[26]。GlcNAc和高浓度CO_2能够快速地诱导白念珠菌酵母形态向菌丝形态转换[19,28]。高渗透压和白念珠菌分泌的群体感应分子法尼醇(farnesol)对菌丝生长则起明显的抑制作用[15,29](图1)。

1.2 调控菌丝形成的分子机制

外界环境信号作用于白念珠菌, 激活相应的信号转导途径调控下游基因表达, 进而调控白念珠菌菌丝生长。目前研究较为清楚的信号通路主要有Ras1-cAMP/PKA信号通路、MAPK信号通路、pH信号通路以及Tup1介导的负调控通路等[30](图2)。

1.2.1 Ras1-cAMP/PKA信号途径 Ras-cAMP/PKA信号通路是真核生物中保守的信号传导途径, 在酿酒酵母和白念珠菌的形态转换过程中起关键的调控作用[31]。CO_2[28]、GlcNAc[32]和血清[16,33]等环境因子诱导的白念珠菌菌丝生长主要通过这条途径起作用。Ras1是保守的GTP酶(small GTPase)蛋白, 位于cAMP/PKA通路的上游。敲除*RAS1*基因严重影响白念珠菌的菌丝生长和毒性[33]。Ras1必须结合GTP才有活性, 过表达活性形式的*RAS1*(*RAS1V13*)能够促进菌丝生长[34]。*CYR1*(*CDC35*)是白念珠菌中唯一腺苷酸环化酶编码基因[32]。敲除该基因严重影响细胞生长和毒性, 并抑制菌丝生长[35]。胞外信号分子通过Ras1激活Cyr1, 催化ATP转化为cAMP, 导致胞内cAMP水平升高[31]。cAMP结合PKA复合体的调节亚基Bcy1[36], 使其与催化亚基解离, 从而激活PKA的催化亚基, 磷酸化并激活下游相应的转录因子(如Efg1和Flo8等), 调控白念珠菌的菌丝生长[37]。Efg1和Flo8调控菌丝特异性的G_1期细胞周期相关蛋白Hgc1(hypha-specific G_1 cyclin-related protein)的表达, 进而调控菌丝生长[38]。白念珠菌中含有两种催化亚基Tpk1和Tpk2, 它们对不同环境下的菌丝生长具有不同的调节作用, 敲除*TPK1*的菌株在固体平板上菌丝生长能力受限, 但不影响液体培养条件下的菌丝生长; 而敲除*TPK2*的作用与敲除*TPK1*相反, 只会影响菌株在液体培养条件下的菌丝生长能力[39-40]。高亲和性磷酸二酯酶Pde2主要作用是降解细胞内cAMP, 是Ras-cAMP/PKA信号通路的负调控因子[41-43]。敲除*PDE2*基因导致细胞cAMP水平升高, 从而激活cAMP途径

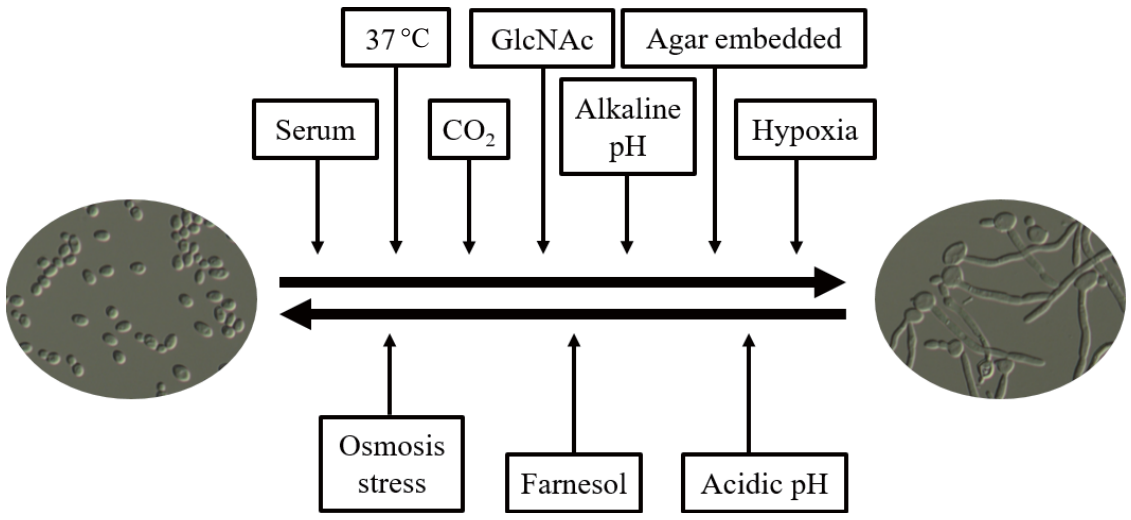


图1 不同环境因子调控白念珠菌菌丝生长

Fig.1 Environmental cues regulate filamentous growth in *C. albicans*

促进白念珠菌菌丝生长[44]。

1.2.2 Ste11-Hst7-Cek1/Cek2介导的MAPK信号途径 Ste11-Hst7-Cek1/Cek2介导的MAPK信号通路是一条高度保守的途径。相应的途径在酿酒酵母中不仅调控交配过程, 也参与菌丝和侵染生长的调控[45]。白念珠菌形态转换和交配中, 该途径同样起重要调控作用[46-50]。MAPK信号通路由三种连续激活的蛋白激酶[MAPKKK(Ste11)、MAPKK(Hst7)和MAPK(Cek1或Cek2)]组成[51-54], 作用于下游的转录因子Cph1(*Candida* pseudo hyphal regulator 1)和Tec1(transposon enhancement control 1)等[55-56]。阻断MAPK信号通路明显影响白念珠菌菌丝生长, 但其影响仍不如阻断cAMP/PKA信号通路强。特别是在血清和GlcNAc等菌丝诱导因子作用下, MAPK信号通路相关突变株仍然能进行菌丝生长。该途径主要参与营养限制(如低氮源培养基)对菌丝生长的调控作用[47,57]。

1.2.3 Rim101(regulator of IME2)介导的pH感应途径 pH变化是所有微生物经常面临的环境压力。白念珠菌中pH的感应主要由转录因子Rim101介导的途径实现[58-60]。环境pH变化影响Rim8、Rim13和Rim20等因子的活性[59-62], 继而调控锌指结构转录因子Rim101活性。*RIM101*的表达本身具有pH值依赖性, 该基因仅在碱性条件下表达[59]。尽管敲除*RIM101*不影响白念珠菌在酸性或碱性条件下的生长, 但会影响菌株在某些培养条件下的菌丝生长能力[63]。激活态的Rim101调控pH感应基因*PHR1*和*PHR2*表达[64-66], 从而调控白念珠菌在不同pH环境中的菌丝生长。*PHR1*和*PHR2*编码两个细胞表面糖苷酶, 可能直接作为pH感应受体起作用[2,59,64]。

1.2.4 菌丝生长负调控因子 目前白念珠菌菌丝发育相关的正调控途径研究的比较多, 少部分的负调控因子[如Tup1(dTMP-UPtake)和Nrg1(negative regulator of glucose-controlled genes 1)]在该过程中的调控作用也有较深入的研究。转录因子Tup1和Nrg1是两个保守的菌丝生长抑制因子[67-68], 白念珠菌*TUP1*和*NRG1*敲除株几乎在所有实验条件下的菌丝生长能力均受到抑制。Tup1与转录因子Nrg1或Rfg1相互作用抑制菌丝相关基因表达[67-69]。在包埋培养条件下, 敲除*EFG1*或*FLO8*也能促进菌丝生长,

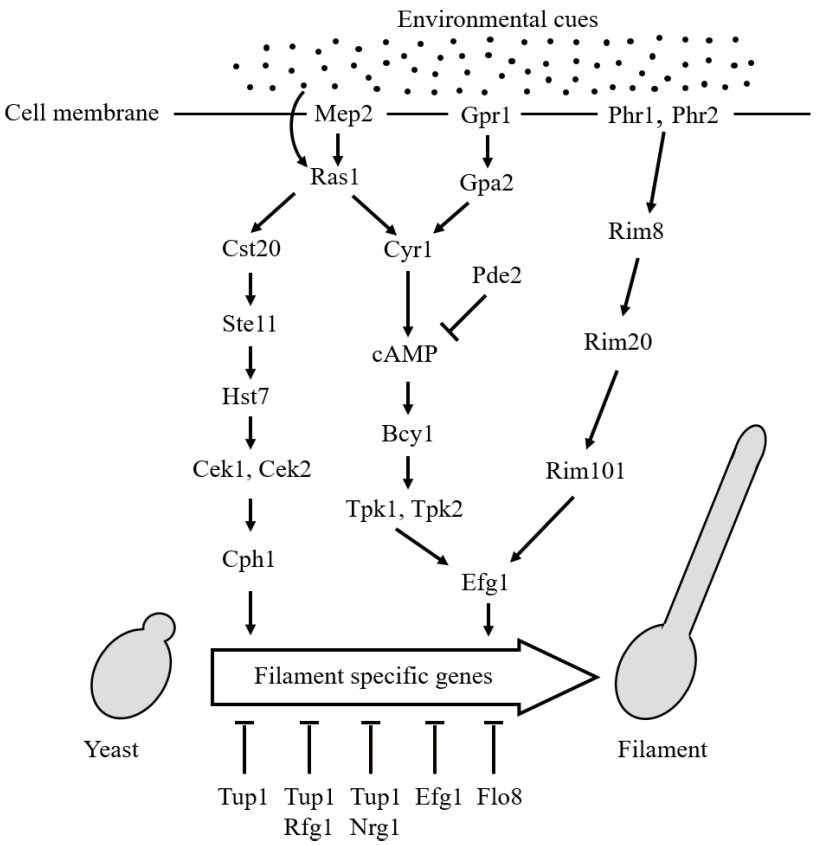


图2 白念珠菌酵母型–菌丝型形态转换的调控机制

Fig.2 Regulatory pathways of yeast-filamentous growth transition in *C. albicans*

说明Efg1和Flo8在某些条件下在菌丝发育中也能起负调控作用[70-71]。

2 白念珠菌white-opaque形态转换

白念珠菌除能进行酵母–菌丝形态转换之外, 还能进行white-opaque双稳态转换[5]。菌丝的生长需要环境因子如37 °C和血清不断地刺激, 才能维持[25]。与菌丝的发育不同, white和opaque两种形态细胞都可以遗传, 两种细胞形态可以相互随机转换; 转换后, 每种细胞都可以稳定维持其原有形态几十代[5]。White细胞呈椭球形, 在固体培养基上形成光滑的半球形菌落; opaque细胞是伸长的、呈圆柱状, 胞内通常含有大液泡, 细胞表面有小突起(pimples), 在固体培养基上opaque细胞形成粗糙、扁平且颜色较暗淡的菌落[72]。White和opaque细胞的细胞壁通透性不同, 在添加红色染料荧光桃红B(phloxine B)的固体平板上, white细胞形成白色菌落, 而opaque细胞形成红色或粉红色菌落[5,72]。

白念珠菌white和opaque细胞的基因组DNA序列完全相同, 因此这种形态的转换主要受表观遗传的调控。White和opaque细胞除细胞形态不同外, 在基因表达谱[73-75]、交配能力[76-77]、对宿主免疫细胞的敏感性以及致病能力[78-80]等方面也存在明显差异。White和opaque细胞各自表达一系列表型特异性基因, *WH11*、*EFG1*和发酵代谢相关基因在white细胞中特异性高表达[73,81-82], 而*OP4*、*SAP4*和氧化代谢相关基因在opaque细胞中特异性表达[73,83-84]。白念珠菌的交配能力与其white-opaque形态转换密切相关, 只有opaque形态细胞才能够进行高效率的交配, white细胞必须先转换成opaque形态后才能交配[77]。White细胞在系统感染中毒性较强; 而opaque细胞在皮肤和其他浅部感染中毒性比white细胞强, 这主要是由于opaque细胞能够分泌胞外天冬氨酸蛋白酶(secreted aspartyl proteinase, Sap), 降解宿主组织[79]。White和opaque细胞对宿主免疫细胞敏感性也不同, 如white细胞更容易被巨噬细胞吞噬[80], 而opaque细胞能有效地逃避宿主免疫细胞的识别。

2.1 环境因子white-opaque形态转换的调控

尽管white和opaque细胞间可以进行自发的转换, 近年来发现, 很多宿主相关的环境因子能促进white向opaque或opaque向white形态转换, 比如温度、CO_2、GlcNAc和环境pH。White和opaque细胞在不同温度下表现出的稳定性不同。室温条件下(如22~25 °C), opaque形态较稳定, 而宿主生理温度(37 °C)或低温度(4 °C)都不利于opaque细胞形态的维持[5,85-86]。研究发现, 宿主皮肤温度较适中(约32 °C), 有利于白念珠菌维持opaque形态, 因此皮肤可能是opaque形态较合适的定植部位[87]。宿主体内重要的环境因子CO_2和GlcNAc不仅影响白念珠菌的菌丝生长, 还参与调控white-opaque形态转换[88-89]。体外实验中, 5% CO_2明显促进white向opaque形态转换, 并且随着CO_2浓度的升高, white向opaque转换的频率也随之提高[88]。我们发现, 转录因子Flo8在白念珠菌感应CO_2过程中起关键的调控作用[90]。白念株菌中保守的cAMP/PKA调控途径和其他的未知途径作用于转录因子Flo8调控CO_2感应[90]。GlcNAc作为唯一碳源培养白念珠菌时, 可显著诱导白念珠菌由white形态向opaque形态转换[89]。CO_2和GlcNAc均可在37 °C时维持白念珠菌的opaque形态, 并且在诱导white-opaque形态转换的过程中具有协同作用[88-89]。环境pH同样对白念珠菌的white-opaque形态转换具有调控作用, 酸性pH促进opaque细胞形成, 但是这种促进作用具有菌株特异性, 对于部分临床菌株的促进作用不明显[91](图3)。

2.2 White-opaque形态转换的分子调控机制

2.2.1 *MTL*基因座对white-opaque形态转换的调控 白念珠菌第5号染色体上存在与酿酒酵母*MAT*(mating-type)基因座相似的*MTL*(mating-type like)基因座, 包含了*MTLa1*、*MTLa2*、*MTLα1*及*MTLα2*四个基因[92]。*MTL*交配基因座不仅控制白念珠菌的交配, 同时还控制white-opaque形态转换[77]。*MTLa/α*杂合型菌株合成Mtla1和Mtlα2形成Mtla1/α2异源复合物, Mtla1/α2结合到white-opaque关键调控因子Wor1的启动子区域抑制*WOR1*表达和opaque细胞形态的形成[93-95]。临床分离的白念珠菌绝大部分是*MTLa/α*杂合型菌株, 这就解释了为什么只有少部分临床菌株能够发生white-opaque转换。近期研究发现, 当GlcNAc作为碳源, 并在5% CO_2中培养时, 部分*MTL*杂合型菌株可被诱导形成opaque形态, 说明*MTL*基因座并不能完全阻断white-opaque形态转换[96]。

临床分离的白念珠菌均为稳定二倍体, 长期以来, 国际上一直认为白念珠菌只能以二倍体状态存在, 不进行减数分裂和交配[97]。直到在白念珠菌中

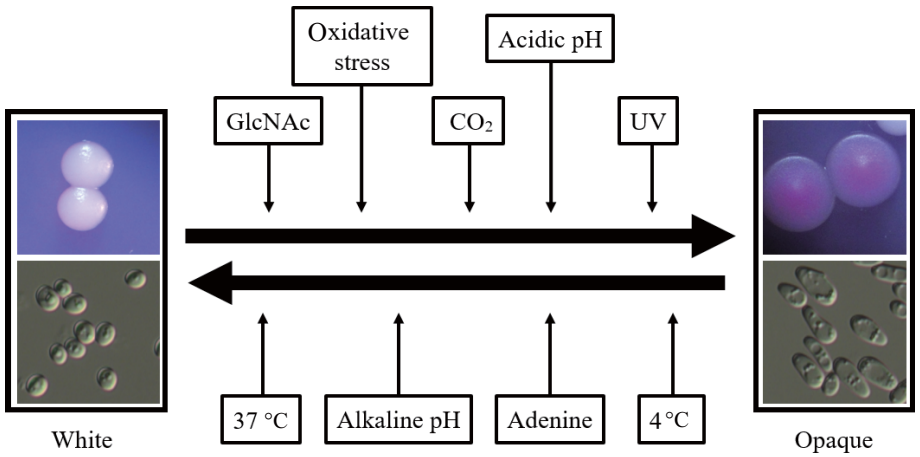


图3 环境因子调控白念珠菌white-opaque形态转换

Fig.3 Enviromental cues involved in the regulation of white-opaque switching in *C. albicans*

发现了*MTL*基因座, 并将杂合的*MTL*位点转换为纯合型基因后, 才在体内和体外实验中发现了白念珠菌的交配现象[98-99], 但是交配效率很低。随后研究发现, 白念珠菌的交配效率与white-opaque形态转换之间存在着密切的关系[77], 即white细胞转换为opaque细胞后才能进行高效率交配。虽然*MTL*杂合菌株也能转换为opaque形态, 但是*MTL*杂合的opaque细胞不能交配[96]。后来发现, 在白念珠菌中敲除*OFR1*基因后, GlcNAc可诱导*MTL*杂合白念珠菌转换为opaque形态, 并且*MTLa/α*的*OFR1*突变株opaque形态可以分别与*MTLa/*Δ型和*MTLa/*Δ型opaque细胞进行交配[100]。

2.2.2 其他基因对white-opaque形态转换的调控 转录因子Wor1在white-opaque形态转换中起到关键的调控作用[93-95]。*WOR1*只在opaque细胞中特异性表达, 并且结合到自身的启动子区域通过正反馈环调控自身表达。敲除*WOR1*使白念珠菌锁定在white细胞状态, 而过表达*WOR1*不仅促进white细胞大量转换为opaque形态, 还可在37 ℃时使opaque细胞处于稳定状态[93-95]。Efg1是white-opaque形态转换的负调控因子, 敲除*EFG1*几乎完全将细胞锁定在opaque形态, 而过表达*EFG1*会促进opaque向white的转换[101]。转录因子Czf1(*C. albicans* zinc finger protein 1)和Wor2在opaque细胞中特异性高表达, 是white-opaque形态转换的正调控因子, 敲除以后均会影响opaque细胞的形成[102-104]。研究发现, Czf1、Wor2和Efg1三个转录因子与Wor1共同组成一个反馈环调控白念珠菌white-opaque形态转换, Wor1处于这个调控网络的中心地位[104]。Wor1不仅能够结合到自身启动子区域调控自身表达, 而还能够结合到*EFG1*、*CZF1*和*WOR2*的启动子区域, 抑制*EFG1*表达, 激活*CZF1*和*WOR2*表达。Czf1抑制*EFG1*的表达, Wor2促进*WOR1*的表达, 而Efg1则对*WOR2*的表达起到抑制作用。因此, 当*WOR1*表达增加时会抑制*EFG1*的表达并促进opaque的状态, 而*WOR1*表达下降时会引起对*EFG1*表达的去抑制作用[104]。

3 White-opaque形态转换与菌丝生长之间的关系

White和opaque两种细胞形态形成菌丝的能力存在明显差异。在常规实验室培养条件下, opaque细胞不容易形成菌丝, 很多能够诱导white细胞菌丝生长的环境因子对opaque细胞菌丝生长不起作用[105]。Opaque细胞和菌丝态细胞存在许多共同点。比如, 两者都有大液泡和相似的细胞表面抗原[72]。许多调节菌丝生长的基因(如*Efg1*、*Efh1*、*Czf1*、*Hda1*和*Tup1*等)同时也调控white-opaque转换[12,101,104,106-108]。CO_2和GlcNAc通过Ras-cAMP/PKA信号通路诱导菌丝生长, 同时也能诱导白念珠菌的opaque形态[88-89]。其他的环境信号(如低氧条件和紫外线)既能诱导菌丝形成, 也能调节white-opaque转换[102,109-111]。cAMP/PKA信号通路及MAPK途径在酵母–菌丝及white-opaque形态转换中都有重要作用[7]。

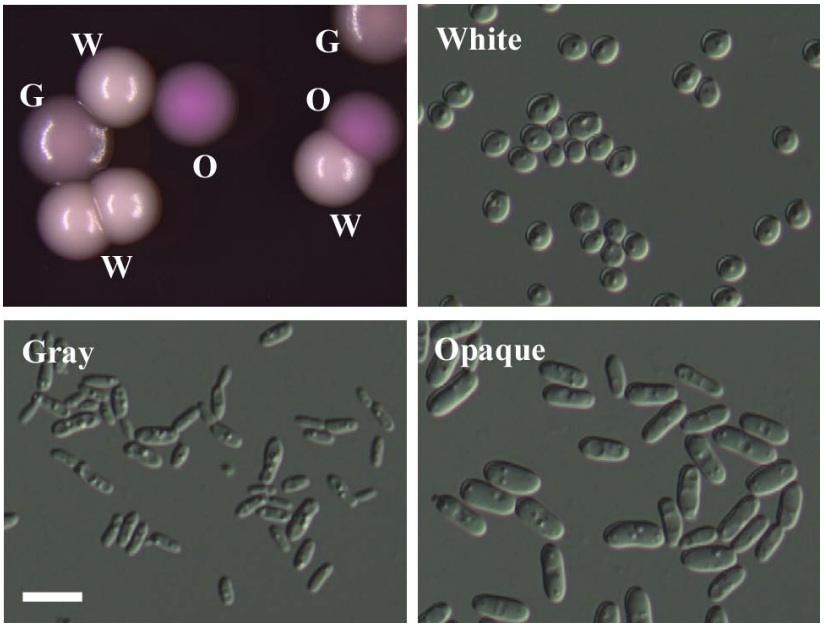
在某些特殊的环境条件下仍然可见opaque细胞菌丝生长现象。当opaque细胞贴壁生长时可以形成菌丝, 悬浮生长的opaque细胞观察不到菌丝生

长[112]。低磷培养基和山梨醇培养基可特异性地诱导opaque细胞形成菌丝, 而对white细胞的菌丝生长不起作用[113]。菌丝生长的关键转录因子Efg1、Ume6(unscheduled meiotic gene expression 6)、Nrg1和Rfg1(repressor of filamentous growth 1)等都参与调控white和opaque细胞菌丝生长[113]。后来研究发现, 常规培养条件下, opaque细胞菌丝生长是受到正调控途径Ras1-cAMP/PKA通路和负调控因子Bcr1(biofilm and cell wall regulator 1)共同调控的, Bcr1及其下游转录因子Cup9、Nrg1和Czf1构成负调控通路特异性的抑制opaque细胞形成菌丝, 而Bcr1调控opaque细胞形成菌丝依赖于cAMP/PKA信号途径[114]。Opaque细胞菌丝生长增强了white-opaque形态转换系统与酵母–菌丝形态转换系统之间的相互联系, 增加了白念珠菌的形态转换多样性及其对宿主环境的适应性。

4 白念珠菌white-gray-opaque三稳态形态转换

白念珠菌中形态的转换形式比以前想象的可能要复杂得多。2014年, 我们实验室报道了白念珠菌中一种全新的形态——gray形态(图4)。Gray细胞形态可稳定遗传, 并能够与white和opaque形态进行相互转换, 形成一种“white-gray-opaque”三稳态转换系统[6]。Gray细胞与opaque细胞相似, 细胞较长、呈圆柱体形, 但细胞体积比较opaque和white细胞都小。在添加红色染料荧光桃红B的固体培养基上, gray细胞形成具有浅红色或粉红色的菌落[6]。Gray细胞能够进行交配, 其交配效率介于white和opaque细胞之间[6]。临床菌株DH1097为*MTL*杂合型菌株, 可进行white-gray-opaque形态转换。当把DH1097转换成*MTL*纯合型菌株时, 仍然能够在white、gray和opaque三种形态之间相互转换, 说明*MTL*基因座不是“white-gray-opaque三稳态”形态转换的主要调控因子。在含有牛血清白蛋白(BSA)的培养基中, gray细胞分泌Sap能力比white和opaque细胞都强, 而在Lee's葡萄糖培养条件下, opaque细胞的Sap活性比gray细胞强, 说明白念珠菌面对不同的宿主环境, 三种不同形态细胞可能表现出不同的毒性特征。在小鼠系统感染模型中, white细胞毒性最强, 其次是opaque细胞, 而gray细胞的毒性最弱[6]。

转录因子Wor1是opaque细胞形成的关键转录因子[6], 在DH1097菌株中敲除*WOR1*后, 导致细胞不能形成opaque形态; 而Efg1是维持white细胞形态的必要转录因子, 敲除*EFG1*后则不能形成white形态。这两个基因单独敲除的菌株都可以形成



标尺=10 μm。

Scale bar=10 μm. W: white; G: gray; O: opaque.

图4 白念珠菌white、gray和opaque的菌落及细胞形态(根据参考文献[6]修改)

Fig.4 Colony and cellular morphologies of white, gray and opaque cells of *C. albicans* (adapted from reference [6])

gray形态, 而白念珠菌中同时敲除*WOR1*和*EFG1*后, 细胞锁定在gray形态, 说明Wor1和Efg1都不是gray细胞形成所必需的转录因子, 但在white-gray-opaque三稳态形态转换的调控中可能具有协同作用[6]。*HXK1*(hexokinase 1)基因编码的GlcNAc激酶在GlcNAc代谢中催化其GlcNAc-6-磷酸的形成, 我们研究发现, 在*MTL*杂合菌株中敲除*HXK1*可以促进gray和opaque细胞的形成, 并且该突变株的三种形态之间可以进行相互转换, 说明Hxk1参与调控白念珠菌white-gray-opaque三稳态形态转换[115]。

5 结语与展望

白念珠菌具有多种多样的形态, 不同形态之间可以相互转换。这种形态的可塑性是白念珠菌重要的生物学特征, 在其适应宿主环境变化以及感染过程中起重要的作用。近年来, 白念珠菌酵母–菌丝相互转换和white-opaque形态转换等方面的研究取得了重要的进展, 尤其是在形态转换的环境因子和遗传调控机制方面进展迅速, 但该领域仍然存在很多问题有待进一步研究。比如, 酵母–菌丝相和white-opaque这两种形态转换系统之间的其他联系是什么? 白念珠菌不同形态细胞与宿主免疫系统的相互作用机制有什么不同? Gray新形态的发现增加了白念珠菌形态的多样性, 诱导该形态形成的环境因子是什么? 其生物学功能有哪些? 这些研究将有利于揭示白念珠菌致病的分子机理, 为白念珠菌感染的预防和新型药物的研发提供新思路。

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