Pathogenesis of Fungal Infections and Drug-Resistance Phenomenon

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Abstract

Fungi the primitive eukaryotes are emerging as life-threatening pathogens of public health. Over a decade and ago, the frequency of fungal infections has been enormous, with an increased range of mortality and morbidity in immunocompromised patients. The risk of fungal infections is aggravated by random use of broad-spectrum antibacterial drugs, immunosuppressive agents, and various cancer chemotherapies. Most of the well-known fungal disease and the pathogenic fungi are Aspergillus, Blastomycosis, Candidiasis, Coccidioidomycosis,

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Cryptococcus, and Dermatophytes. The resistance to antifungal medicines might be characteristic, acquired, or clinical. The comprehension of the mechanism of the clinical resistance effect is significant, unlike alternating treatment. In this chapter, after a concise overview of antifungal resistance, the molecular transport mechanism and mechanism of drugs will be detailed. It emerges that the main systems of resistance are necessarily appropriate to the deregulation of antifungal resistance effector genes. This deregulation in transcriptional regulators of the genes is due to the occurrence of point mutations. The study of antifungal its pathogenicity and resistance to drugs is essential for a better understanding of the human pathogenic fungal biology.

Keywords
Drug resistance mutation · PDR gene · Multi-drug resistance · ABC transporters · Antifungal resistance

17.1 Introduction

Fungi are ubiquitous in nature, contain membrane-bound cell organelles and also rigid cell wall encapsulated with a cell membrane. Usually, fungi occur in two basic forms, namely molds (vegetative multicellular organisms) and yeasts (unicellular filamentous organisms). Fungi subsist as a free-living saprobe with no apparent benefits from humans or animals. Characterization of fungi as a pathogen depends merely on the severity of the disease caused. Cause of disease from mild to severe range in the host system. The majority of fungal pathogens in mammals are so-called opportunistic since the disease is caused only when the host immune system lacks the defense response, one such example is the *Aspergillus*, the common mold. The infection of *Aspergillus* is known as aspergillosis with a few varied types present in the environment (Barnes and Marr 2006). Aspergillosis affects the respiratory system that is present in our normal indoor condition cause infections especially in those of weak immune system. Another parasitic fungal disease is blastomycosis, an ailment brought about by the parasite *Blastomyces dermatitidis* infecting the skin. The growth of Blastomyces lives in damp soil and in association with decomposing organic matter such as wooden leaves. The side effects of blastomycosis are frequently like influenza indications. The majority of this blastomycosis is found in midwestern, south-central, and south-eastern states in the USA (Furcolow et al. 1970; Bradsher et al. 2003). An additional example of fungal infection is Candidiasis caused by the organism *Candida* that is inhabitant of mouth, throat, gut, and vagina in the human body. Nearly 20 varieties of candida yeast organisms are reported to cause infections, the most common is *Candida albicans* (Nucci and Anaissie 2001). The other added examples are coccidioidomycosis and cryptococcosis. Coccidioidomycosis known as valley fever is a disease brought about by the growth of Coccidioides, which lives in the dirt of dry low precipitation territories. It is endemic in numerous zones of southwestern USA, Mexico, Central and South

America (Vugia et al. 2013). Cryptococcosis is a fungal infection caused by organisms that belong to the genus *Cryptococcus*, generally acquired by inhalation. The two species *Cryptococcus neoformans* and *Cryptococcus gattii* cause nearly all cryptococcal infections in both humans and animals (Knoke and Schwesinger 2009; Casadevall and Perfect 1998). Dermatophytes are organisms that trigger skin, hair, and nail infections. Diseases brought by these growths are additionally in some cases known as ringworm or tinea. The major recognized classes are Trichophyton rubrum and Trichophyton tonsurans (Hainer 2003).

Histoplasmosis is an infection triggered by the organism *Histoplasma capsulatum*. The fungus survives in surroundings for the most part together with a lot of bat or feathered creature droppings. The signs and symptoms of histoplasmosis are similar to that of pneumonia as the pathogen affects the lungs of human system (Manos et al. 1956). Mucormycosis otherwise called Zygomycosis is an uncommon disease caused by fungi that are related to a group of fungi known as Mucoromycotina in the type Mucorales. These parasites are commonly found in the dirt and along the decomposed biotic matter (Richardson 2009). Pneumocystis pneumonia (PCP) is a severe disease resulting from parasite *Pneumocystis jiroveci*. Pneumocystis pneumonia is one of the most frequent and severe opportunistic infections in people with weakened immune systems, particularly people with HIV and AIDS (Harris et al. 2010).

Sporotrichosis is a disease resulting from an organism called *Sporothrix schenckii*, which is a cutaneous disease and most frequently occurs when in contact with infected plants when the fungus penetrates through the skin (Bastos de Lima-Barros et al. 2011).

Exserohilum is another type of a fungus identified in soil and commonly on plants particularly grasses, and it flourishes in warm and moist atmospheres. It is an extremely uncommon disease in individuals, yet it has been distinguished as one of the dominating pathogens in an ongoing multistate episode of parasitic meningitis and other contagious contaminations related with debased steroid infusions (Revankar and Sutton 2010; Adler et al. 2006). Cladosporium is another uncommon reason for human ailment, yet it has been known to cause a few distinct sorts of diseases including skin, eye, sinus, and mind contaminations (Drabick et al. 1990; Gugnani et al. 2000; Sang et al. 2011). Cladosporium, in the same way as other sorts of organisms, has likewise been related to sensitivities and asthma (Sellart-Altisent et al. 2007).

In contemporary years, fungal infections have acquired significant/substantial prominence due to its enhancement in the immunocompromised population including HIV infected human beings, in which the patients receive immunosuppressive treatment for organ or bone marrow transplantation or cancer patients undergoing cytotoxic agents (Richardson and Lass-Flörl 2008).

A wide range of various treatment strategies are required to address this issue along with triumphing adverse effects and drug resistance. The main objective of this chapter is to review the latest phenomenon of fungi and importance of antifungal agents in clinical trials. Furthermore, countless extracts from various plants have also been demonstrated to combat with diverse fungi.

17.2 Chemical Classes

The treatment mainly depends on the accessibility of antifungal drugs. Numerous antifungal agents illustrate seven different chemical classes such as polyenes, pyrimidine analogs, azoles, candins, allylamines, thiocarbamates, and morpholines.

17.2.1 Polyenes

Polyenes are amphipathic (one hydrophilic charged site and another hydrophobic uncharged site) in nature corresponding to a class of natural compounds. Polyenes target ergosterol in the fungal membrane creating pores and permeating tiny molecules through the membrane causing cell death. Two major polyenes are amphotericin B and nystatin (Canuto and Rodero 2002).

17.2.2 Pyrimidine Analogs

Pyrimidine analogs consist of 5-fluorocytosine (5-FC) only. Susceptible fungi consist of cytosine deaminase that regenerates 5-fluorocytosine into 5-fluorouracil integrating into DNA and RNA, hindering cellular functions. Generally, 5-fluorocytosine has inadequate activity against the majority of filamentous fungi and dermatophytes rendering insufficient cytosine deaminase (Gehrt et al. 1995). Thus most often 5-FC is administered together with polyenes or other antifungal agents (Sanglard 2002).

17.2.3 Azoles

Azoles conjointly with allylamines, thiocarbamates, and morphlines obstruct ergosterol biosynthesis. Azoles hinder cytochrome P450 lanosterol demethylase, Erg11, or Cyp51, which is a fundamental phase in sterol biosynthesis, causing the substitution of ergosterol by methylated sterols in the plasma membrane (Sanglard 2002). Azoles might be responsible for sterol D22-desaturation (Erg5) by impeding cytochrome P450, as in sterol biosynthesis Erg11 takes precedence before Erg5 (Skaggs et al. 1996). Azole drugs are further classified into two classes: (1) imidazoles consisting of ketoconazole, miconazole, and clotrimazole mostly used for skin infections, and (2) triazoles consisting of fluconazole, voriconazole, itraconazole, and posaconazole commonly used for systemic infections (Sheehan et al. 1999).

17.2.4 Candins

Candins are the novel class of antifungal agents. Candins inhibits an enzyme complex b-1-3 glucan synthase, localized in the plasma membrane of fungi. Nowadays, compounds which are chemically related are available in three different types:

caspofungin, micafungin, and anidulafungin. Candins are mainly utilized in treating invasive *Candida* and *Aspergillus* infections (Perlin 2007). Candins repress the biosynthesis of ergosterol at various phases.

17.2.5 Allylamines, Thiocarbamates, and Morpholines

The allylamines (terbinafine) and thiocarbamates (tolnaftate) restrain a similar chemical, squalene epoxidase (Erg1), which illustrates to an early advance in ergosterol biosynthesis. The morpholines (fenpropimorph) hinder two various chemicals, Erg2 and Erg4, catalyzing sterol D14-reductase and D8-D7 isomerase, individually. Even though allylamines, thiocarbamates, and morpholines have an extensive activity spectra in contrast to fungal species, they are typically utilized as topical agents in treating dermatophyte diseases (Niewerth and Korting 2000).

The utilization of antifungal agents, particularly following recurrent or long-term treatments, results in unavoidable advancement of resistance. To establish the occurrence of resistance from these aggravates, the evaluation of antifungal susceptibility has been ordered utilizing various protocols. These protocols, in which fungal development is recorded in the presence of sequential medication dilutions over a limited period, produce a minimum inhibitory concentration (MIC) that is characterized as the least medication fixation bringing about a huge decrease of development. The MIC breakpoint values that are utilized to recognize resistant fungal isolates from susceptible isolates rely on few elements incorporating into in-vitro research facility or clinical perceptions.

17.3 Antifungal Resistance

Antifungal resistance by in vitro susceptibility testing in which MIC is estimated disproportionally in control cells and the organism, but that is yet helpless to drugs has the MIC exceeds the susceptibility breakpoint for that organism. Clinical resistance to fungal infection can be identified in vitro even though there is no microbial resistance from an antifungal agent (Espinel-Ingroff et al. 1997; Rex et al. 1997; Pfaller et al. 2008).

On the other hand, antifungal drug resistance is very critical because of the predetermined number of agents. Therefore, it is essential to comprehend the mechanisms of resistance to antifungal drug agents. In addition to this, the molecular comprehension of resistance mechanisms recognizes fungal genes, which would then be able to be utilized for resistance identification by molecular diagnostic tools. These genes and their related derivatives can encounter definite alternations in the advancement of resistance. Transcriptional administration of drug resistance genes is of remarkable concern since the modification of mechanism can be altered transitorily or constantly in fungal cells. Therefore, considering this, contemporary knowledge of molecular resistance mechanisms to antifungal agents was reviewed, however, by concentrating on transcriptional regulation of genes (Sanglard et al. 2009).

Exclusive therapeutic formulae for obtrusive fungal infections were amphotericin B deoxycholate and 5-fluorocytosine. Initially, the therapeutic substitutions originated with the establishment of itraconazole and fluconazole at the end of the 1980s. Progress in antifungal research over centuries evolved lipid formulation of amphotericin B, broad-spectrum triazoles, and exclusively novel antifungal agents. Adversely, excessive usage of triazoles in prophylactic and empiric treatments attributed drug-resistant pressure in both *Candida* and *Aspergillus* species (Perlin 2009). The consequences led to intrinsically resistant fungi or secondary resistant fungi, but the growth of the acquired fungi was not expedited in AIDS patients (Law et al. 1994). There was no horizontal resistance gene transfer technique acknowledged in fungi (Odds 2010). Presumptions have been made earlier that fungi were typically restricted to vertical gene transfer at a slower pace.

Antibiotic resistance in pathogenic fungi is a remarkable challenge in treating fungal infections triggered by these organisms. The equivalent exceptional preservation of the essential eukaryotic cell biology shown by fungal and animal cells that have enabled these littler eukaryotes to fill in as extraordinary model life form restricts the scope of growth explicit anti-infection agents that have been depicted. Moreover, mutant fungi are promptly isolated, both in the laboratory and in the clinic, that exhibit resistance from a broad scope of antibiotics besides the first utilized treatment. The wide choice of drug resistance is indicated as multidrug fight that shows up in microbes ranging from bacteria to the living beings. The restricted number of antifungal medications builds the phenotype an intense issue in the chemotherapeutic abolition of fungal parasites (Ling 1997). A large amount of multidrug resistance fungi have originated from research studies preferably from the yeast *Saccharomyces cerevisiae*, and the phenotype of this organism is indicated as PDR gene or pleiotropic drug resistance that influence the phenotype of PDR loci. With the advancement of ground-breaking, novel hereditary, and molecular biological procedures, specialists have conferred important understandings of information into the functioning of multidrug resistance from tests executed straightforwardly in infective organisms. This study concentrates on delivering an introduction to the various pathways poignant multidrug resistance in *S. cerevisiae* and by comparison of those pathways to infective growths, for instance, candida, fungus glabrata, and fungus genus fumigates.

The uncomplicated biology of *S. cerevisiae* persuaded the recognizable proof of a cistron arrangement of pleiotropic drug immune modification mapping to a cistron existing body VII that characterizes the PDR1 cistron (Rank et al. 1975). Pdr1p could be an atomic number 30 cluster containing positive transcriptional regulator known with the notable Gal4p interpretation issue (Balzi et al. 1987). Although Pdr1p was the primary multidrug resistance determinant recognized in *S. cerevisiae*, this issue is not an on the spot go-between of drug resistance. Pdr1p associated alternative transcriptional regulators change articulation of an assortment of proteins that demonstrate to counteract the virulent activity of medicine. Considering the proteins initially as an on the spot detoxifier of antifungal agents, we investigate the regulative transcription factors, and finally review the signals that regulate the expression of PDR genes. We are going to review a specific set of genes characterized by their regulation by Pdr1p and its homolog Pdr3p on the full because of the PDR pathway.

17.4 Membrane Transporters

The primarily recognized sequence that satisfied the factors through effector of drug resistance within the Pdr pathway was the PDR5 locus (Balzi et al. 1994; Bissinger and Kuchler 1994; Hirata et al. 1994). This sequence encodes associate degree of ATP-restricting transporter macromolecule that is private from the ABCG category of transporters (Dean and Allikmets 2001). Early investigations indicated that the loss of Pdr5p persuaded theatrical increment in drug sensitivity to a large scope of varied compounds (Leppert et al. 1990; Meyers et al. 1992). Moreover, direct organic chemistry tests showed that pdr5 cells were deficient within the flow of various dyes and radio-labelled probes (Kolaczkowski et al. 1996). Overproduction of Pdr5p by utilization of a high duplicate number of plasmids conveys the existence of hyperactive PDR1 alleles which is related to the PDR phenotype (Dexter et al. 1994; Katzmann et al. 1994; Leonard et al. 1994).

Together, this data firmly bolster the model that raised Pdr5p levels to feature the pleiotropic drug-resistant composition by increasing the movement of this multispecific drug pump. Correlation of cells conveyancing hyperactive PDR1 alleles, and containing or lacking PDR5 contended that, although Pdr5p is a significant determinant within the PDR phenotype, the existence of this factor isn't adequate to clarify the whole range of drug resistance as seems. For example, overactive PDR1–6 mutants square measures soundproof to each cycloheximide and oligomycin. Expulsion of the PDR5 factor kills the enlarged cycloheximide resilience in every PDR1–6 cell, but does not decrease the abnormal state oligomycin opposition (Katzmann et al. 1994).

Screening a high-duplicate range cellular inclusion library for factors that impact oligomycin obstruction allows the convalescence of the YOR1 gene (Cui et al. 1996; Katzmann et al. 1994). YOR1 encrypts Associate in Nursing first principle transporter of the ABCC family that is essential for a normal oligomycin obstruction.

Loss of YOR1 from a PDR1–6 foundation diminishes oligomycin obstruction, but has no impact on the raised cycloheximide resilience given by this Pdr1p subsidiary (Katzmann et al. 1994). Hence, the evacuation of the PDR5 homolog SNQ2 factor from cells conveying a hyperactive gene of PDR1 diminished 4-nitroquinoline- N-oxide obstruction, however, did not impact cycloheximide or oligomycin opposition (Decottignies et al. 1995). This data serves to delineate a remarkable topic within the PDR composition in *S. cerevisiae*, even as contagious multidrug obstruction bushed all. Overrun of assorted first principle transporter proteins is needed for the statement of the complete scope of medication obstruction found in these multidrug-tolerant cells. This unremarkably happens due to Associate in Nursing adjustment within the movement of a translation issue and offers hit likeness with the multidrug obstruction found in class cells. Seclusion of the human MDR1 gene was cultivated by usage of cell lines that tremendously overproduce the multi-drug ABC transporter protein (Riordan et al. 1985; Roninson et al. 1986).

Most multidrug-safe mammalian cells seem to rise by means of enhancement of the gene cryptography of a specific ABC transporter gene (Gottesman et al. 1995 and Roninson 1992), instead of delivering a familiar interpretation factor that may,

regardless of the careful mechanism, the two cells move towards becoming multidrug safe through the peak of ABC transporter articulation.

Alongside the first principle transporter proteins, proteins of the $64,000 assistant taxonomic group (MFS) likewise augment pleiotropic medicate opposition. Contrasted with the first principle transporter-encoding genes, our comprehension of the capability and guideline of the MFS proteins is at a previous stage. At any rate 20 distinctive MFS proteins show basic genes steady with or have simply been presented assume employment in drug resistance (Nelissen et al. 1997; Sá-Correia and Tenreiro 2002).

The large range of those film transporters proposes that their commitments to drug-resistant square measure doubtless unnoticed. The MFS proteins oft supply covering drug limpidity with first principle transporters, which can clarify to some extent why their better-plugged relatives have clouded MFS transporter inclusion in multidrug opposition, for example, the MFS supermolecule Flr1p adds to protection from the antifungal specialist fluconazole, even as cycloheximide (Alarco et al. 1997).

The first principle transporter Pdr5p to boot intervenes resilience to each of those mixes and may be a noteworthy determinant within the obstruction composition to those and completely different medications (Kontoyiannis 1999). Strikingly, whereas a pdr5p strain is utterly touchy to cycloheximide (Leppert et al. 1990), this affectability is often fully smothered if the interpretation issue Yap1p is overproduced (Dexter et al. 1994). This concealment is probably going due to the initiation of FLR1, a Yap1p target factor (Alarco et al. 1997). A lot of stays to be educated for the support of MFS proteins in eukaryotic multidrug opposition.

17.5 PDR Genes Regulated with Sphingolipid Homeostasis

The lipid synthesis of the plasma layer is the focal determinant managing entry of mixes from the outside condition to the inside of the cell. The conveyance of lipid segments in the inward and external handouts of the plasma film is unbalanced and inhibited by Pdr pathway to some extent. Together Pdr5p and Yor1p were discovered to upgrade the outward development (flop) of the phospholipid phosphatidylethanolamine (Decottignies et al. 1998; Pomorski et al. 2003). Phosphatidylethanolamine is regularly kept up at low dimensions in the external flyer by the fast internal development (flip) completed by aminophospholipid translocases, five of which can be found in the *S. cerevisiae* genome (Pomorski 2004).

Enigmatically, two phosphatidylinositol move protein homolog (PDR16 and PDR17) were additionally pragmatic to be the goal genes of the Pdr pathway and to impact phospholipid levels and medication obstruction (van den Hazel et al. 1999). These perceptions foresee that actuation of the Pdr pathway may trigger changes in phospholipid synthesis of the plasma layer, yet the results of these progressions stay dubious.

Eukaryotic film lipids incorporate sterols and sphingolipids into all the same phospholipids. In *S. cerevisiae*, steroid alcohol is the vital steroid within the cell and

is delivered using the activity of work unit pathway (Sturley 2000). An excellent composition of various erg-invalid mutants is outrageous affectability to medication challenges that are reliable with a necessity for steroid alcohol in normal layer work. Examinations of work unit mutant strains demonstrate that Pdr5p transport action is unaffected in these mutants and suggest that loss of steroid alcohol could improve upstage dispersion of mixes over the changed layer (Emter et al. 2002; Kaur and Bachhawat 1999).

The last category of layer lipoid, sphingolipids, is assumed to attach with steroid alcohol to border microdomains known as lipoid rafts that area unit gathered within the external leaflet of the plasma film (Dickson and Lester 2002; Hannun and Obeid 2002). Investigation of the declaration of the IPT1 factor, secret writing of the last advance in sphingolipid synthesis (Dickson et al. 1997), designed up an instantaneous association between the Pdr pathway and synthesis of this category of film lipoid. IPT1 interpretation is unnatural by Pdr1p similarly as Pdr3p and reacts to sign notable to actuate the *S. cerevisiae* Pdr pathway. Strikingly, loss of IPT1 changed medication obstruction of the following mutants and proposes that normal sphingolipid substance is needed for wild-type dimensions of medication resistance (Hallstrom et al. 2001).

Later examinations gave proof that few biosynthetic advances upstream of the Ipt1p-catalyzed response were in addition accessible to increase the PDR pathway-intervened guidelines (Kolaczkowski et al. 2004). The hereditary associations between the Pdr and sphingolipid pathways were reached out by the finding that Pdr1p and Pdr3p manage the RSB1 factor (Kihara and Igarashi 2004; Panwar and Moye-Rowley 2006). Rsb1p is assumed to go about as Associate in the Nursing efflux of ceramide forerunners known as long-chain bases (LCBs) (Kihara and Igarashi 2002). LCBs will be cytotoxic whenever allowable to assemble, and Rsb1p will act to anticipate improper development of those sphingolipid intermediates. Shockingly, loss of Pdr5p and Yor1p from cells without ambiguity raises LCB obstruction (Kihara and Igarashi 2004) in Rsb1p-subordinate style, once more underlining the interconnections between sphingolipid synthesis and also the Pdr pathway. These varied interfaces between pleiotropic medicate opposition and also the equilibrium of layer lipids propose the probability that the physiological job of the Pdr pathway is to help guideline of the capability of the plasma film at the dimension of two lipids and film transporters.

17.6 Pleiotropic Drug Resistance Mutation

A focal determinant in the medication obstruction phenotype of *S. cerevisiae* is given by the guideline of trans-activation ability of a set number of authoritative proteins. Pdr1p and its homolog Pdr3p are Zn2Cys6-containing transcriptional administrative proteins that apply significant effects on the multidrug opposition phenotypes of cells. There are countless Zn2Cys6-containing interpretation factors in *S. cerevisiae* (p50), and a considerable lot of these have been appeared or are accepted to be engaged with pleiotropic drug-resistant (MacPherson et al. 2006).

We will concentrate on Pdr1p and Pdr3p as illustrative of the more significant number of Zn2Cys6-containing factors that add to medicate opposition. Progressively comprehensive contemplations of these and other transcriptional administrative proteins engaged with multidrug obstruction in *S. cerevisiae* are accessible in a few surveys (Fardeau et al. 2007; MacPherson et al. 2006; Moye-Rowley 2003a, b).

As referenced above, hyperactive mutant types of Pdr1p drove the underlying ID of the pleiotropic medicate obstruction phenotype in *S. cerevisiae* (Balzi et al. 1987; Carvajal 1997). Comparable mutant alleles of PDR3 have additionally been portrayed (Nourani et al. 1997). These single amino corrosive substitution types of Pdr1p and Pdr3p produce transcriptional administrative proteins that act as solid, constitutive activators of downstream gene articulation (Carvajal 1997; Nourani et al. 1997). Pdr1p and Pdr3p, both ties to components mentioned to as Pdr1p/Pdr3p reaction components (PDREs), found upstream of target genes (Delahodde et al. 1995; Katzmann et al. 1994). In vivo foot printing trials show that Pdr1p and Pdr3p are probably going to be constitutively bound to significant PDREs (Fardeau et al. 2007; Mamnun et al. 2002), a perception predictable with the constitutive atomic confinement of these proteins (Delahodde et al. 2001). Furthermore, both Pdr1p and Pdr3p can initiate the statement of another zinc bunch interpretation factor-encoding gene called YRR1 (Cui et al. 1998; Zhang et al. 2001). Expanded articulation of Yrr1p can enhance the transcriptional impacts of enactment of either Pdr1p or Pdr3p since this factor perceives a grouping unique about the PDRE (Le Crom et al. 2002).

Even though Pdr1p and Pdr3p share critical similarities, significant disparities are known. To start with, these elements are communicated at significantly various dimensions. Utilization of epitope-tagged types of the two proteins demonstrates that Pdr1p is available at almost multiple times the dimension of Pdr3p (Ghaemmaghami et al. 2003). Second, the guideline of these elements is receptive to various sign. Overproduction of the DnaK protein Ssz1p (Hallstrom et al. 1998) or the DnaJ Zuo1p persuades Pdr1p-subordinate gene interpretation yet has no impact on Pdr3p. Then again, cells coming up short on their mitochondrial genome (p0) enact Pdr3p work, however, have no impact on Pdr1p (Hallstrom and Moye-Rowley 2000a, b). PDR1 articulation levels are steady, though PDR3 is both auto-regulated and highly initiated in p0 cells (Delahodde et al. 2001; Hallstrom and Moye-Rowley 2000a, b). At long last, ongoing work from our research facility shows the Hsp70 protein Ssa1p can adversely direct Pdr3p, however not Pdr1p movement (107a). Even though these two translation elements share greater than 30% personality over their approximately 1000-amino-corrosive lengths (Delaveau et al. 1994), these distinctions show that Pdr1p and Pdr3p have non-identical tasks to carry out in the control of multidrug opposition.

The below-average of translation issue that has been connected with the rule of thumb of multidrug opposition is the basic region-leucine zipper (bZip) group of regulative macromolecules. Albeit a number of these bZip-containing variables are offered in *S. cerevisiae*, we are going to confine our exchange to Yap1p, the primary of those parts incontestable to be related to pleiotropic medicate opposition. Yap1p is healthier glorious for its important job in aerobic pressure resilience

(Moye-Rowley 2003a, b; Paget and Buttner 2003; Rodrigues-Pousada et al. 2004), and its guideline by oxidants has been the subject of escalated research. Quickly, Yap1p typically cycles between the core and the cytoplasm without stress (Kuge 1997).

Upon oxidant challenge, Yap1p quickly gathers in the core, where it actuates cancer prevention agent gene articulation (Coleman et al. 1999; Kuge and Jones 1994; Kuge 1997; Wu and Moye-Rowley 1994). Mutant types of Yap1p have been portrayed that are constitutively situated in the core and hyper-impervious to specific oxidants (Coleman et al. 1999; Kuge 1997; Wemmie et al. 1997).

Less is known about the reaction intervened by Yap1p upon medication challenge, yet the YAP1 gene was segregated as a high-duplicate number middle person of pleiotropic sedate obstruction alongside PDR5 (Leppert et al. 1990). As referenced above, Yap1p characterizes a pathway for drug resistance parallel to that of PDR5. Strikingly, Yap1p is known to initiate the outflow of any rate two unique MFS protein-encoding genes: ATR1 (Coleman et al. 1997) and FLR1 (Alarco et al. 1997). At any rate in *S. cerevisiae*, the control of multidrug opposition gene articulation has all the earmarks of being isolated between zinc group holding factors principally lashing the translation of ABC transporter-encoding genes, while bZip-containing proteins primarily act by controlling mRNA dimensions of MFS proteins. The method of reasoning hidden this division of transcriptional administrative circuits stays to be resolved.

17.6.1 *Candida albicans*

While the incredible hereditary genes related with the utilization of *S. cerevisiae* as a model parasite have permitted the rapid advancement in our comprehension of contagious multidrug opposition, this living being is certainly not a critical reason for human illness. The major parasitic wellspring of circulation system contaminations in people is from the family Candida which has developed in significance until candidemia now speaks to the fourth most regular nosocomial disease (Slavin et al. 2004). The essential *Candida* species related to candidemia is *Candida albicans* (Pfaller et al. 2001), and this life form has been the most seriously contemplated as far as multidrug opposition.

The first multidrug opposition gene from *C. albicans* was recuperated by choice of a section of *C. albicans* genomic DNA that modified medication obstruction in *S. cerevisiae* when carried on a proper plasmid (Ben-Yaacov et al. 1994). The primary gene confined in this style was assigned BENr and is presently cited to as MDR1 (Goldway et al. 1995). The protein encrypted by this particular gene is an individual from the significant facilitator superfamily of film transporters (Marger and Saier 1993). Not long after this discovering, two genes encoding homologs of the *S. cerevisiae* Pdr5p ABC transporter protein were distinguished (Prasad et al. 1995; Sanglard et al. 1997). These proteins were given the abbreviations CDR1 and CDR2 for Candida drug-resistant 1 and 2. Investigations in a few laboratories built up that mutant *C. albicans* strains coming up short on these ABC transporters were

multidrug sensitive (Sanglard et al. 1996, 1997) and that various distinctive safe segregates were found to overproduce CDR1 and CDR2 transcripts (Sanglard et al. 1995; White 1997). Estimations of medication transport in strains designed to overproduce Cdr1p assistance with the possibility that this protein goes about as an ATP-subordinate medication efflux pump (Nakamura et al. 2001). Green fluorescent protein combinations to Cdr1p showed that this protein was fundamentally found in the plasma film, like the area of Pdr5p in *S. cerevisiae* (Shukla 2004).

Later work has concentrated on the control of translation of CDR1 and CDR2. Trials from two distinct research centers gave a portrayal of the advertiser area of CDR1 (de Micheli et al. 2002; Puri et al. 1999). CDR1 transcriptional control was observed to be intricate and the result of different DNA components of either positive or negative nature in the advertiser locale. Investigation of the CDR2 advertiser proposes that this gene is managed in parallel with CDR1 since azole-safe *C. albicans* disconnects regularly display raised mRNA levels relating to both of these ABC transporter-encoding genes (de Micheli et al. 2002).

A few distinctive transcriptional administrative proteins have been involved in the tweak of CDR1 and CDR2 articulation. The best described of these is the Zn2Cys6 group protein Tac1p; this factor ties to a solitary component in the CDR2 advertiser that contains pair rehashes of a CGG succession (Coste et al. 2006). These short trinucleotide rehashes are usually connected with the coupling locales of Zn2Cys6 bunch proteins (MacPherson et al. 2006). Tac1p shows the most noteworthy level of grouping likeness with a protein from *S. cerevisiae* assigned Hal9p, a figure included the control of articulation of the ENA1 sodium-potassium ATPase (Mendizabal et al. 1998).

Strikingly, the existence of a CDR2-lacZ combination in *S. cerevisiae* does not persuade the creation of critical beta-galactosidase action except if Tac1p is heterologous given (Coste et al. 2006), recommending that Hal9p cannot invigorate CDR2 articulation. Even though Pdr1p shares huge grouping similitude with Tac1p, there are clear contrasts between these two Zn2Cys6 bunch proteins at the dimension of DNA restricting particularity and protein arrangement. An intriguing shared characteristic somewhere often caused by gain-of-function mutations in the transcription factors of PDR1 and TAC1 result in profound responsive of target genes that these two significantly control multidrug efflux pumps and sway in their specific life forms.

In *S. cerevisiae*, PDR1 active mutants firmly persuade PDR5 and PDR15, even as another layer super molecule known as Rsb1p that is needed for cover from the long-chain base phytosphingosine (DeRisi et al. 2000). In *C. albicans*, TAC1 active alleles actuate CDR1 (Pdr5p homolog), CDR2 (Pdr15p homolog), and RTA3 (Rsb1p homolog).

A later optimistic controller of CDR1 was seen by viewing a *C. albicans* articulation library in a very *S. cerevisiae* cell conveyance of title a CDR1-lacZ journalist factor for clones that would raise articulation of this heterologous correspondent factor (Chen et al. 2004). This factor was assigned CaNDT80 since it had been found to cypher a homolog of the *S. cerevisiae* Ndt80p translation issue. ScNdt80p serves to enact genes engaged with monogenesis in *S. cerevisiae* (Chu and

Herskowitz 1998). CaNdt80p appears to possess much separated from the work of its *S. cerevisiae* connected super molecule since the *C. albicans* issue is important in the positive guideline of CDR1 throughout vegetative development.

A demonstration involving a significant job for a negative controller of CDR1 articulation has likewise gathered (Gaur et al. 2004). Until this point in time, the character of this factor is as yet dubious, however, its coupling site has been mapped to a component found downstream of the Tac1p acknowledgment component (Gaur et al. 2005). A 55-kDa protein has been demonstrated to be cross-connected to this negative administrative component, and decreases in the dimension of this factor are accepted to cause azole hyper-obstruction in some clinical disconnects. Together, this information proposes that control of articulation of CDR1 in *C. albicans* includes greater unpredictability at the dimension of the translation elements contrasted with the control of ScPDR5 articulation that is reliant on just Pdr1p and Pdr3p (Delaveau et al. 1994; Katzmann et al. 1994).

A few research facilities have additionally analyzed transcriptional control of CaMDR1. Point by point cancellation mapping analyses have been portrayed in a few productions (Harry et al. 2005; Hiller et al. 2006; Riggle and Kumamoto 2006; Rognon et al. 2006). These examinations have distinguished a few unique areas in the CaMDR1 advertiser that are engaged with basal, oxidant- or medication-incited articulation. There are contrasts in the exact jobs of these different components yet unmistakably the CaMDR1 advertiser is a complex transcriptional control district that coordinates various contributions to decide the correct articulation of CaMdr1p.

At any rate, two unique components have been connected to the trans-regulation of CaMDR1 articulation. Detachment of the *C. albicans* Yap1p homolog (Cap1p) demonstrated that CaMDR1 was a possible downstream focus of this translation factor (Alarco and Raymond 1999). This has been upheld by direct mutagenesis of putative Cap1p administrative components present in CaMDR1 (Rognon et al. 2006). Shockingly, different examinations exhibited that loss of CAP1 either had no impact on azole obstruction or contrarily affected resilience to this medication (Alarco and Raymond 1999). In any case, overproduction of a carboxy-terminal truncation mutant of Cap1p persuaded an emotional increment in azole resistance, a perception that corresponds with emphatically raised CaMDR1 translation (Alarco and Raymond 1999). This conduct is likely seen in *S. cerevisiae* when YAP1 is erased as yap1 cells display a humble (twofold) increment while overproduction of Yap1p created a striking increment in the MIC for fluconazole (Chen et al. 2007).

In conjunction with Cap1p, the *C. albicans* homolog of *S. cerevisiae* Mcm1p has additionally been involved responsible for CaMDR1 interpretation (Riggle and Kumamoto 2006; Rognon et al. 2006). Research facility strains of *C. albicans* that were chosen for high azole opposition were observed to be subject to the existences of a useful CaMcm1p restricting site for abnormal state generation of CaMDR1. Cap1p was not required for this impact contending that CaMcm1p is essential if not the sole factor that is upregulated in these azole-safe separates. Azole obstruction has likewise been demonstrated to be affected by changes in articulation of the *C. albicans* IPT1 gene (Prasad et al. 2005), proposing further protection with *S. cerevisiae*. The image that rises out of concentrates in *C. albicans* on the atomic premise

of multidrug opposition is steady with this creature sharing a fundamentally the same as the scope of effector genes with *S. cerevisiae*, however with the guideline of gene articulation showing contrasts. This might be because of the altogether different milieus wherein these life forms ordinarily live. Further investigation of the opposition pathways in these yeasts will explain this thought.

17.6.2 *Candida glabrata*

C. glabrata is a haploid type of Candida that has risen to be mainly the second regular Candida living being related to fungemia (Pfaller et al. 2001). A reasonable contributing element to the quick development (2% during the 1970s to 20% currently) is the strong capacity of *C. glabrata* to get resistance to usually conveyed antifungal operators, for example, azoles. Long haul observing of *C. glabrata* related sickness shows that azole-safe disengages are expanding in recurrence, even from geographic districts in which *C. glabrata* was initially sensitive to these medications (Pfaller and Diekema 2007).

This is not found on account of *C. albicans* since clinical information show that azole medications hold their viability in controlling ailment related to this species (Hazen et al. 2003). A moment muddling factor for *C. glabrata* initiates from the routine multidrug opposition of azole-tolerant separates (Sanguinetti et al. 2005). Not exclusively does *C. glabrata* moderately and effectively convert to an azole-safe structure; however, it adds much of the time seems to turn out to be at the same time multidrug safe.

Protein and DNA progression likeness assessments demonstrate that *C. glabrata* and *S. cerevisiae* are immovably related living things (Wong et al. 2002). This similarity also speaks to this comfortable relationship in the multidrug deterrent pathways in these two yeasts. As depicted above for *S. cerevisiae* and *C. glabrata,* cells are very multidrug safe (Sanglard et al. 2001). This mitochondrial control of multidrug resistance proceeds through the authorization of the CgPdr1p protein (Tsai et al. 2006). An amazing complexity between *S. cerevisiae* and *C. glabrata* is that CgPdr1p addresses indisputably the best homolog of the Pdr1p/Pdr3p, a lot of proteins identified in *S. cerevisiae* (Vermitsky and Edlind 2004). CgPDR1 may contrast with a blend quality between the *S. cerevisiae* PDR1 and PDR3 loci. CgPDR1 shares greater course of action closeness with ScPdr1p; be that as it may, demonstrates the selection seen for ScPDR3 (Tsai et al. 2006).

Single amino destructive substitution freak kinds of CgPdr1p have been found that are associated with irregular state elucidation of both CgPDR1 and CgCDR1, similarly as incredible multidrug block (Vermitsky and Edlind 2004). This lead is clearly for all intents and purposes proportionate to that watched for the hyperactive alleles of ScPDR1 and ScPDR3.

Despite the fact that indisputably *C. glabrata* cells are exceedingly multidrug safe and happen a great part of the time, the activity of these cells in illness is more uncertain. *C. glabrata* clinical segregates that were changed over to petite status by either ethidium bromide or fluconazole treatment were found to have decreased

damaging tendency in a mouse model of infectious pathogenesis (Brun et al. 2005). One stress with these assessments (noted by the makers of that audit) is that the evaluation of ruinous tendency was finished without the association of fluconazole. Since the nonappearance of drug assurance would clear the possible specific good position given by the unusual state verbalization of the CgCDR qualities and related multidrug resistance, the petite cells may be lost due to contention from the strong endogenous microbial verdure. There was proof of modest *C. glabrata* strains isolated from patients (Bouchara et al. 2000); in any case, a greater number of other clinical segregates are not clearly associated with a petite character (Shahi et al. 2007).

Despite the fact that during examination the modest strains of *C. glabrata* and *S. cerevisiae* show a multidrug-safe phenotype demonstrates the similar mitochondrial regulatory reason in these living things, an intriguing complexity has been uncovered by screening a collection of transposon-delivered *C. glabrata* freaks (Kaur et al. 2004). Expansion of a transposon into a couple of qualities was found to raise azole impediment yet, additionally, trigger petite course of action. Exactly when the specific weight was removed, the petite phenotype appeared to die down. Past examinations on both *C. glabrata* and *S. cerevisiae* petite freaks have not uncovered multidrug-safe freaks that show reversible direct (Sanglard et al. 2001; Zhang et al. 2001). One part of the *C. glabrata* petite multidrug-safe freaks that residual parts ill defined is the status of their mitochondrial genome.

The alleged high-repeat azole-safe freaks were displayed to do not have a mitochondrial genome (Sanglard et al. 2001) and eagerly take after the multidrug-safe freaks of *S. cerevisiae*. Three of the transposon-started *C. glabrata* petite freaks were reviewed for mitochondrial genome status (Kaur et al. 2004) and intriguingly found to at present hold cytoplasmic nucleoids. This is a critical potential refinement since different assorted *S. cerevisiae* mutants that are petite notwithstanding to express the multi-drug safe phenotype expression (Zhang et al. 2001).

The petite transposon expansion freaks in *C. glabrata* fuse consideration in the CgSHE9 quality. Aggravation freaks lacking SHE9 also called MDM33 (Messerschmitt et al. 2003) appear to bomb in the mitochondrial genome in neither *S. cerevisiae* nor *C. glabrata*; in any case, multidrug check has quite recently been studied for *C. glabrata* freaks. Further work is required to choose if the related *S. cerevisiae* freaks in like manner demonstrate the reversible multidrug-safe status of the three *C. glabrata* qualities. As suggested previously (Kaur et al. 2004), freaks that show a moderate reducing of mitochondrial work barring all out harm of mitochondrial genome could offer climb to this reversible multidrug.

Freaks of this sort would have clear central focuses in regard to the survival of chemotherapy in a patient since they could join the benefits of the overwhelming multidrug obstacle of a petite cell without always getting the touchy improvement of these mitochondrially inadequate with regard to strains. As depicted above for *S. cerevisiae*, multidrug restriction in *C. glabrata* is furthermore influenced by transcriptional control of MFS protein verbalization. The CgFLR1 quality is convinced by the *C. glabrata* Yap1p homolog (CgAP-1) and gives assurance from an extent of pros, including fluconazole (Chen et al. 2007). *C. glabrata* Cgap-1 freaks

had run of the mill fluconazole obstruction, while Cgpdr1 freaks were unstable to this medicine.

The Yap1p-FLR1 fluconazole restriction pathway seems to serve a subordinate occupation in protection from this antifungal administrator in both *S. cerevisiae* and *C. glabrata*. Somewhat, incredibly, while Cgap-1 freaks are too much sensitive to oxidants, there is no perceptible effect on hurtfulness (Chen et al. 2007). Despite the fact that CgAP-1 is a noteworthy determinant of oxidative weight impediment, this does not appear to affect the limit of *C. glabrata* to colonize a mouse model.

The basic highlights between multidrug-safe separates of *S. cerevisiae* and *C. glabrata* have been extended by assessment of qualities that are transcriptionally open to a hyperactive freak sort of CgPdr1p by microarray (Vermitsky et al. 2006). While different qualities that are affected in *C. glabrata* address homologs that are in like manner brought up in light of *S. cerevisiae* hyperactive Pdr1p, the greatest social event of actuated transcripts contrasts with qualities that are strangely impelled in the pathogenic yeast (Vermitsky et al. 2006). These *C. glabrata* express qualities may address loci that are required for the living form to adequately withstand the troubles of hurtful blends, when revealed in an animal have.

17.6.3 *Aspergillus* Species

The fundamental human pathogen among the filamentous parasites is *Aspergillus fumigatus* (Richardson 2005). Pollutions identified with this living thing have a high distressingness and normally high security from the standard system of antifungal experts (Pfaller and Diekema 2004). As anyone might expect, the utilization of azole-based medications has the irksome consequence of raising the obstruction of ensuing disconnection from the patients. Fortunately, getting off a multidrug deterrent phenotype is commonly remarkable among *Aspergillus* species, nonetheless, this declaration must be qualified by the affirmation that assessment of this phenotype is tangled by specific inconveniences in setting up this phenotype (Moore et al. 2000). Additionally, the nuclear depiction of qualities related to *Aspergillus* multidrug restriction has been demolished by the nonappearance of an absolute genomic progression. This starting has late been developed (Nierman et al. 2005) and will stimulate examination of the loci related to medication opposition in this critical human pathogen.

Past examinations have given a few information concerning multidrug resistance qualities in *Aspergillus*. Degeneration of PCR cloning allowed the disconnection of two different ABC transporter-encoding qualities, and explanation of one of these in *S. cerevisiae* raised security from an antifungal drug of the echinocandin family (Tobin et al. 1997). Azole-safe withdraws picked in-vitro were found to have raised explanation of ABC transporter and MFS-encoding qualities (Nascimento et al. 2003). This data is enduring with similar systems for medicine detoxification existing in *Aspergillus* as have been portrayed in yeasts.

The availability of the genomic course of action of *Aspergillus* has quite recently given interesting bits of information into the comprehensible bit of multidrug

resistance structures in this filamentous parasite. The *A. fumigatus* genome is half greater than that of *S. cerevisiae*, however then predicts the presence of 96 potential MFS multidrug transporters stood out from 24 from growing yeast (Da Silva Ferreira et al. 2005). Though *S. cerevisiae* contains 13 ABC transporter genes, the species look for a multi-drug obstacle, likewise, the Aspergillus is acknowledged to have 35 ABC transporter genes. Assessments of these proteins in *A. fumigatus* are required to avow that these proteins are related with medication obstruction in this living thing, notwithstanding, the presence of such a generally greater number proposes a hardening of the defensive drug limit of this pathogenic animal. It is striking to observe that the extended degree of MFS proteins diverged from ABC transporters found in the *Aspergillus* genome stood out from *S. cerevisiae* takes after the condition in pathogenic microorganisms. At present, there are no cases of ABC transporters in clinically material microorganism pathogens that are noteworthy in drug hindrance, while MFS protein collaboration in the shirking of antibacterial treatment is incredibly typical (Piddock 2006).

17.7 Conclusion

Multidrug restriction is an issue in chemotherapy in the conditions going from bacterial defilements to harmful development. The infectious prescription block is an especially extreme issue on account of the set number of antifungal blends (Kontoyiannis and Lewis 2002). Understanding the rule and limit of multidrug restriction pathways in parasites is still especially work in progression, be that as it may, its hugeness continues creating with the extending number of immunocompromised patients worldwide and their growing reliance on chemotherapy to control infectious maladies (Perlroth et al. 2007; Warnock 2006). A considerable amount of our present appreciation of the sub-nuclear reason for parasitic multidrug restriction springs from work in the ordinarily non-pathogenic yeast *S. cerevisiae*. Regardless, fast advances in the preliminary tractability of pathogenic parasites, for instance, the *Candida* and *Aspergillu*s species will acquire the pathways with clinically huge life structures into center intrigue. This is a critical goal since the systems used for medicine impediment in these pathogens share some equivalence with those in *S. cerevisiae* yet have noteworthy differences that must be uncovered in the neighborhood living being.

References

Adler A, Yaniv I, Samra Z et al (2006) Exserohilum: an emerging human pathogen. Eur J Clin Microbiol Infect Dis 25:247–253. https://doi.org/10.1007/s10096-006-0093-3

Alarco AM, Raymond M (1999) The bZip transcription factor Cap1p is involved in multidrug resistance and oxidative stress response in Candida albicans. J Bacteriol 181:700–708

Alarco A-M, Balan I, Talibi D et al (1997) AP1-mediated multidrug resistance in Saccharomyces cerevisiae requires FLR1 encoding a transporter of the major facilitator superfamily. J Biol Chem 272:19304–19313. https://doi.org/10.1074/jbc.272.31.19304

Balzi E, Chen W, Ulaszewski S et al (1987) The multidrug resistance gene PDR1 from Saccharomyces cerevisiae. J Biol Chem 262:16871–16879
Balzi E, Wang M, Leterme S et al (1994) PDR5, a novel yeast multidrug resistance conferring transporter controlled by the transcription regulator PDR1. J Biol Chem 269:2206–2214
Barnes PD, Marr KA (2006) Aspergillosis: spectrum of disease, diagnosis, and treatment. Infect Dis Clin N Am 20:545–561. https://doi.org/10.1016/j.idc.2006.06.001
Bastos de Lima-Barros M, de Almeida-Paes M, Oliveira-Schubach A (2011) Sporothrix schenckii and Sporotrichosis. Clin Microbiol Rev 24:633–654. https://doi.org/10.1128/CMR.00007-11
Ben-Yaacov R, Knoller S, Caldwell GA et al (1994) Candida albicans gene encoding resistance to benomyl and methotrexate is a multidrug resistance gene. Antimicrob Agents Chemother 38:648–652. https://doi.org/10.1128/aac.38.4.648
Bissinger PH, Kuchler K (1994) Molecular cloning and expression of the *Saccharomyces cerevisiae* STS1 gene product. A yeast ABC transporter conferring mycotoxin resistance. J Biol Chem 269(6):4180–4186
Bouchara J-P, LE Boudouil S, Filmon R et al (2000) In-vivo selection of an azole-resistant petite mutant of Candida glabrata. J Med Microbiol 49:977–984. https://doi.org/10.1099/0022-1317-49-11-977
Bradsher RW, Chapman SW, Pappas PG (2003) Blastomycosis. Infect Dis Clin N Am 17:21–40, vii
Brun S, Dalle F, Saulnier P et al (2005) Biological consequences of petite mutations in Candida glabrata. J Antimicrob Chemother 56:307–314. https://doi.org/10.1093/jac/dki200
Canuto MM, Rodero FG (2002) Antifungal drug resistance to azoles and polyenes. Lancet Infect Dis 2(9):550–563
Carvajal E (1997) Molecular and phenotypic characterization of yeast PDR1 mutants that show hyperactive transcription of various ABC multidrug transporter genes. Mol Gen Genet MGG 256:406–415. https://doi.org/10.1007/s004380050584
Casadevall A, Perfect JR (1998) Cryptococcus neoformans. American Society of Microbiology, Washington
Chen C-G, Yang Y-L, Shih H-I et al (2004) CaNdt80 is involved in drug resistance in Candida albicans by regulating CDR1. Antimicrob Agents Chemother 48:4505–4512. https://doi.org/10.1128/AAC.48.12.4505-4512.2004
Chen K-H, Miyazaki T, Tsai H-F, Bennett JE (2007) The bZip transcription factor Cgap1p is involved in multidrug resistance and required for activation of multidrug transporter gene CgFLR1 in Candida glabrata. Gene 386:63–72. https://doi.org/10.1016/j.gene.2006.08.010
Chu S, Herskowitz I (1998) Gametogenesis in yeast is regulated by a transcriptional cascade dependent on Ndt80. Mol Cell 1:685–696. https://doi.org/10.1016/S1097-2765(00)80068-4
Coleman ST, Tseng E, Moye-Rowley WS (1997) Saccharomyces cerevisiae basic region-leucine zipper protein regulatory networks converge at the ATR1 structural gene. J Biol Chem 272:23224–23230. https://doi.org/10.1074/jbc.272.37.23224
Coleman ST, Epping EA, Steggerda SM, Moye-Rowley WS (1999) Yap1p activates gene transcription in an oxidant-specific fashion. Mol Cell Biol 19:8302–8313. https://doi.org/10.1128/mcb.19.12.8302
Coste A, Turner V, Ischer F et al (2006) A mutation in Tac1p, a transcription factor regulating CDR1 and CDR2, is coupled with loss of heterozygosity at chromosome 5 to mediate antifungal resistance in *Candida albicans*. Genetics 172(4):2139–2156
Cui Z, Hirata D, Tsuchiya E et al (1996) The multidrug resistance-associated protein (MRP) subfamily (Yrs1/Yor1) of Saccharomyces cerevisiae is important for the tolerance to a broad range of organic anions. J Biol Chem 271:14712–14716. https://doi.org/10.1074/jbc.271.25.14712
Cui Z, Shiraki T, Hirata D, Miyakawa T (1998) Yeast gene YRR1, which is required for resistance to 4-nitroquinoline N-oxide, mediates transcriptional activation of the multidrug resistance transporter gene SNQ2. Mol Microbiol 29:1307–1315. https://doi.org/10.1046/j.1365-2958.1998.01027.x

Da Silva Ferreira ME, Colombo AL, Paulsen I et al (2005) The ergosterol biosynthesis pathway, transporter genes, and azole resistance in Aspergillus fumigatus. Med Mycol 43:313–319. https://doi.org/10.1080/13693780400029114

de Micheli M, Bille J, Schueller C, Sanglard D (2002) A common drug-responsive element mediates the upregulation of the Candida albicans ABC transporters CDR1 and CDR2, two genes involved in antifungal drug resistance. Mol Microbiol 43:1197–1214. https://doi.org/10.1046/j.1365-2958.2002.02814.x

Dean M, Allikmets R (2001) Complete characterization of the human ABC gene family. J Bioenerg Biomembr 33(6):475–479

Decottignies A, Lambert L, Catty P et al (1995) Identification and characterization of SNQ2, a new multidrug ATP binding cassette transporter of the yeast plasma membrane. J Biol Chem 270:18150–18157. https://doi.org/10.1074/jbc.270.30.18150

Decottignies A, Grant AM, Nichols JW et al (1998) ATPase and multidrug transport activities of the overexpressed yeast ABC protein Yor1p. J Biol Chem 273:12612–12622. https://doi.org/10.1074/jbc.273.20.12612

Delahodde A, Delaveau T, Jacq C (1995) Positive autoregulation of the yeast transcription factor Pdr3p, which is involved in control of drug resistance. Mol Cell Biol 15:4043–4051. https://doi.org/10.1128/mcb.15.8.4043

Delahodde A, Pandjaitan R, Corral-Debrinski M, Jacq C (2001) Pse1/Kap121-dependent nuclear localization of the major yeast multidrug resistance (MDR) transcription factor Pdr1. Mol Microbiol 39:304–313. https://doi.org/10.1046/j.1365-2958.2001.02182.x

Delaveau T, Delahodde A, Carvajal E et al (1994) PDR3, a new yeast regulatory gene, is homologous toPDR1 and controls the multidrug resistance phenomenon. Mol Gen Genet 244:501–511. https://doi.org/10.1007/BF00583901

DeRisi J, van den Hazel B, Marc P et al (2000) Genome microarray analysis of transcriptional activation in multidrug resistance yeast mutants. FEBS Lett 470:156–160. https://doi.org/10.1016/S0014-5793(00)01294-1

Dexter D, Moye-Rowley WS, Wu AL, Golin J (1994) Mutations in the yeast PDR3, PDR4, PDR7 and PDR9 pleiotropic (multiple) drug resistance loci affect the transcript level of an ATP binding cassette transporter encoding gene, PDR5. Genetics 136:505–515

Dickson RC, Lester RL (2002) Sphingolipid functions in Saccharomyces cerevisiae. Biochim Biophys Acta Mol Cell Biol Lipids 1583:13–25. https://doi.org/10.1016/S1388-1981(02)00210-X

Dickson RC, Nagiec EE, Wells GB et al (1997) Synthesis of mannose-(inositol-P) 2-ceramide, the major sphingolipid in Saccharomyces cerevisiae, requires the IPT1 (YDR072c) gene. J Biol Chem 272:29620–29625. https://doi.org/10.1074/jbc.272.47.29620

Drabick JJ, Gomatos PJ, Solis JB (1990) Cutaneous cladosporiosis as a complication of skin testing in a man positive for human immunodeficiency virus. J Am Acad Dermatol 22:135–136. https://doi.org/10.1016/S0190-9622(08)80019-9

Emter R, Heese-Peck A, Kralli A (2002) ERG6 and PDR5 regulate small lipophilic drug accumulation in yeast cells via distinct mechanisms. FEBS Lett 521(1-3):57–61

Espinel-Ingroff A, Bartlett M, Bowden R et al (1997) Multicenter evaluation of proposed standardized procedure for antifungal susceptibility testing of filamentous fungi. J Clin Microbiol 35(1):139–143

Fardeau V, Lelandais G, Oldfield A et al (2007) The central role of PDR1 in the foundation of yeast drug resistance. J Biol Chem 282:5063–5074. https://doi.org/10.1074/jbc.M610197200

Furcolow ML, Busey JF, Menges RW, Chick EW (1970) Prevalence and incidence studies of human and canine blastomycosis II. Yearly incidence studies in three selected states, 1960–1967. Am J Epidemiol 92:121–131. https://doi.org/10.1093/oxfordjournals.aje.a121184

Gaur N, Puri N, Karnani N et al (2004) Identification of a negative regulatory element which regulates basal transcription of a multidrug resistance gene of. FEMS Yeast Res 4:389–399. https://doi.org/10.1016/S1567-1356(03)00204-6

Gaur NA, Manoharlal R, Saini P et al (2005) Expression of the CDR1 efflux pump in clinical Candida albicans isolates is controlled by a negative regulatory element. Biochem Biophys Res Commun 332:206–214. https://doi.org/10.1016/j.bbrc.2005.04.113

Gehrt A, Peter J, Pizzo PA et al (1995) Effect of increasing inoculum sizes of pathogenic filamentous fungi on MICs of antifungal agents by broth microdilution method. J Clin Microbiol 33(5):1302–1307

Ghaemmaghami S, Huh W-K, Bower K et al (2003) Global analysis of protein expression in yeast. Nature 425:737–741. https://doi.org/10.1038/nature02046

Goldway M, Teff D, Schmidt R et al (1995) Multidrug resistance in Candida albicans: disruption of the BENr gene. Antimicrob Agents Chemother 39:422–426. https://doi.org/10.1128/aac.39.2.422

Gottesman MM, Hrycyna CA, Schoenlein PV et al (1995) Genetic analysis of the multidrug transporter. Annu Rev Genet 29:607–649. https://doi.org/10.1146/annurev.ge.29.120195.003135

Gugnani HC, Sood N, Singh B, Makkar R (2000) Case report. Subcutaneous phaeohyphomycosis due to Cladosporium cladosporioides. Mycoses 43:85–87. https://doi.org/10.1046/j.1439-0507.2000.00545.x

Hainer BL (2003) Dermatophyte infections. Am Fam Physician 67(1):101–110

Hallstrom TC, Moye-Rowley WS (2000a) Hyperactive forms of the Pdr1p transcription factor fail to respond to positive regulation by the Hsp70 protein Pdr13p. Mol Microbiol 36:402–413. https://doi.org/10.1046/j.1365-2958.2000.01858.x

Hallstrom TC, Moye-Rowley WS (2000b) Multiple signals from dysfunctional mitochondria activate the pleiotropic drug resistance pathway in Saccharomyces cerevisiae. J Biol Chem 275:37347–37356. https://doi.org/10.1074/jbc.M007338200

Hallstrom TC, Katzmann DJ, Torres RJ et al (1998) Regulation of transcription factor Pdr1p function by an Hsp70 protein in Saccharomyces cerevisiae. Mol Cell Biol 18:1147–1155. https://doi.org/10.1128/mcb.18.3.1147

Hallstrom TC, Lambert L, Schorling S et al (2001) Coordinate control of sphingolipid biosynthesis and multidrug resistance in Saccharomyces cerevisiae. J Biol Chem 276:23674–23680. https://doi.org/10.1074/jbc.M101568200

Hannun YA, Obeid LM (2002) The Ceramide-centric universe of lipid-mediated cell regulation: stress encounters of the lipid kind. J Biol Chem 277:25847–25850. https://doi.org/10.1074/jbc.R200008200

Harris JR, Balajee SA, Park BJ (2010) Pneumocystis jirovecii pneumonia: current knowledge and outstanding public health issues. Curr Fungal Infect Rep 4:229–237. https://doi.org/10.1007/s12281-010-0029-3

Harry JB, Oliver BG, Song JL et al (2005) Drug-induced regulation of the MDR1 promoter in Candida albicans. Antimicrob Agents Chemother 49:2785–2792. https://doi.org/10.1128/AAC.49.7.2785-2792.2005

Hazen KC, Baron EJ, Colombo AL et al (2003) Comparison of the susceptibilities of Candida spp. to fluconazole and voriconazole in a 4-year global evaluation using disk diffusion. J Clin Microbiol 41:5623–5632. https://doi.org/10.1128/JCM.41.12.5623-5632.2003

Hiller D, Stahl S, Morschhauser J (2006) Multiple cis-acting sequences mediate upregulation of the MDR1 efflux pump in a fluconazole-resistant clinical Candida albicans isolate. Antimicrob Agents Chemother 50:2300–2308. https://doi.org/10.1128/AAC.00196-06

Hirata D, Yano K, Miyahara K, Miyakawa T (1994) Saccharomyces cerevisiae YDR1, which encodes a member of the ATP-binding cassette (ABC) superfamily, is required for multidrug resistance. Curr Genet 26:285–294. https://doi.org/10.1007/BF00310491

Katzmann DJ, Burnett PE, Golin J et al (1994) Transcriptional control of the yeast PDR5 gene by the PDR3 gene product. Mol Cell Biol 14:4653–4661. https://doi.org/10.1128/MCB.14.7.4653

Kaur R, Bachhawat AK (1999) The yeast multidrug resistance pump, Pdr5p, confers reduced drug resistance in erg mutants of Saccharomyces cerevisiae. Microbiology 145:809–818. https://doi.org/10.1099/13500872-145-4-809

Kaur R, Castano I, Cormack BP (2004) Functional genomic analysis of fluconazole susceptibility in the pathogenic yeast Candida glabrata: roles of calcium signaling and mitochondria. Antimicrob Agents Chemother 48:1600–1613. https://doi.org/10.1128/AAC.48.5.1600-1613.2004

Kihara A, Igarashi Y (2002) Identification and characterization of a Saccharomyces cerevisiae gene, RSB1, involved in sphingoid long-chain base release. J Biol Chem 277:30048–30054. https://doi.org/10.1074/jbc.M203385200

Kihara A, Igarashi Y (2004) Cross talk between sphingolipids and glycerophospholipids in the establishment of plasma membrane asymmetry. Mol Biol Cell 15:4949–4959. https://doi.org/10.1091/mbc.e04-06-0458

Knoke M, Schwesinger G (2009) One hundred years ago: the history of crytococcosis in Greifswald. Medical mycology in the nineteenth century. Mycoses 37:229–233. https://doi.org/10.1111/j.1439-0507.1994.tb00418.x

Kolaczkowski M, Michel van der R, Cybularz-Kolaczkowska A et al (1996) Anticancer drugs, ionophoric peptides, and steroids as substrates of the yeast multidrug transporter Pdr5p. J Biol Chem 271:31543–31548. https://doi.org/10.1074/jbc.271.49.31543

Kolaczkowski M, Kolaczkowska A, Gaigg B et al (2004) Differential regulation of Ceramide synthase components LAC1 and LAG1 in Saccharomyces cerevisiae. Eukaryot Cell 3:880–892. https://doi.org/10.1128/EC.3.4.880-892.2004

Kontoyiannis DP (1999) Genetic analysis of azole resistance by transposon mutagenesis in Saccharomyces cerevisiae. Antimicrob Agents Chemother 43:2731–2735. https://doi.org/10.1128/AAC.43.11.2731

Kontoyiannis DP, Lewis RE (2002) Antifungal drug resistance of pathogenic fungi. Lancet 359:1135–1144. https://doi.org/10.1016/S0140-6736(02)08162-X

Kuge S (1997) Regulation of yAP-1 nuclear localization in response to oxidative stress. EMBO J 16:1710–1720. https://doi.org/10.1093/emboj/16.7.1710

Kuge S, Jones N (1994) YAP1 dependent activation of TRX2 is essential for the response of Saccharomyces cerevisiae to oxidative stress by hydroperoxides. EMBO J 13:655–664. https://doi.org/10.1002/j.1460-2075.1994.tb06304.x

Law D, Moore CB, Wardle HM et al (1994) High prevalence of antifungal resistance in Candida spp. from patients with AIDS. J Antimicrob Chemother 34:659–668. https://doi.org/10.1093/jac/34.5.659

Le Crom S, Devaux F, Marc P et al (2002) New insights into the pleiotropic drug resistance network from genome-wide characterization of the YRR1 transcription factor regulation system. Mol Cell Biol 22:2642–2649. https://doi.org/10.1128/MCB.22.8.2642-2649.2002

Leonard PJ, Rathod PK, Golin J (1994) Loss of function mutation in the yeast multiple drug resistance gene PDR5 causes a reduction in chloramphenicol efflux. Antimicrob Agents Chemother 38:2492–2494. https://doi.org/10.1128/AAC.38.10.2492

Leppert G, McDevitt R, Falco SC et al (1990) Cloning by gene amplification of two loci conferring multiple drug resistance in Saccharomyces. Genetics 125:13–20

Ling V (1997) Multidrug resistance: molecular mechanisms and clinical relevance. Cancer Chemother Pharmacol 40:S3–S8. https://doi.org/10.1007/s002800051053

MacPherson S, Larochelle M, Turcotte B (2006) A fungal family of transcriptional regulators: the zinc cluster proteins. Microbiol Mol Biol Rev 70:583–604. https://doi.org/10.1128/MMBR.00015-06

Mamnun YM, Pandjaitan R, Mahé Y et al (2002) The yeast zinc finger regulators Pdr1p and Pdr3p control pleiotropic drug resistance (PDR) as homo- and heterodimers in vivo. Mol Microbiol 46:1429–1440. https://doi.org/10.1046/j.1365-2958.2002.03262.x

Manos NE, Ferebee SH, Kerschbaum WF (1956) Geographic variation in the prevalence of histoplasmin sensitivity. Dis Chest 29:649–668. https://doi.org/10.1378/chest.29.6.649

Marger MD, Saier MH (1993) A major superfamily of transmembrane facilitators that catalyse uniport, symport and antiport. Trends Biochem Sci 18:13–20. https://doi.org/10.1016/0968-0004(93)90081-W

Mendizabal I, Rios G, Mulet JM et al (1998) Yeast putative transcription factors involved in salt tolerance. FEBS Lett 425:323–328. https://doi.org/10.1016/S0014-5793(98)00249-X

Messerschmitt M, Jakobs S, Vogel F et al (2003) The inner membrane protein Mdm33 controls mitochondrial morphology in yeast. J Cell Biol 160:553–564. https://doi.org/10.1083/jcb.200211113

Meyers S, Schauer W, Balzi E et al (1992) Interaction of the yeast pleiotropic drug resistance genes PDR1 and PDR5. Curr Genet 21:431–436. https://doi.org/10.1007/BF00351651

Moore CB, Sayers N, Mosquera J et al (2000) Antifungal drug resistance in Aspergillus. J Infect 41:203–220. https://doi.org/10.1053/jinf.2000.0747

Moye-Rowley WS (2003a) Regulation of the transcriptional response to oxidative stress in fungi: similarities and differences. Eukaryot Cell 2:381–389. https://doi.org/10.1128/EC.2.3.381-389.2003

Moye-Rowley WS (2003b) Transcriptional control of multidrug resistance in the yeast saccharomyces. Prog Nucleic Acid Res Mol Biol 73:251–279

Nakamura K, Niimi M, Niimi K et al (2001) Functional expression of Candida albicans drug efflux pump Cdr1p in a Saccharomyces cerevisiae strain deficient in membrane transporters. Antimicrob Agents Chemother 45:3366–3374. https://doi.org/10.1128/AAC.45.12.3366-3374.2001

Nascimento AM, Goldman GH, Park S et al (2003) Multiple resistance mechanisms among Aspergillus fumigatus mutants with high-level resistance to itraconazole. Antimicrob Agents Chemother 47:1719–1726. https://doi.org/10.1128/AAC.47.5.1719-1726.2003

Nelissen B, Wachter R, Goffeau A (1997) Classification of all putative permeases and other membrane plurispanners of the major facilitator superfamily encoded by the complete genome of Saccharomyces cerevisiae. FEMS Microbiol Rev 21:113–134. https://doi.org/10.1111/j.1574-6976.1997.tb00347.x

Nierman WC, Pain A, Anderson MJ et al (2005) Genomic sequence of the pathogenic and allergenic filamentous fungus Aspergillus fumigatus. Nature 438:1151–1156. https://doi.org/10.1038/nature04332

Niewerth M, Korting HC (2000) The use of systemic antimycotics in dermatotherapy. Eur J Dermatol 10(2):155–160

Nourani A, Papajova D, Delahodde A, Jacq C (1997) Clustered amino acid substitutions in the yeast transcription regulator Pdr3p increase pleiotropic drug resistance and identify a new central regulatory domain. Mol Gen Genet MGG 256:397–405. https://doi.org/10.1007/s004380050583

Nucci M, Anaissie E (2001) Revisiting the source of Candidemia: skin or gut? Clin Infect Dis 33:1959–1967. https://doi.org/10.1086/323759

Odds FC (2010) Editorial: resistance to antifungal agents. Fungal Genet Biol 47:190. https://doi.org/10.1016/j.fgb.2009.12.005

Paget MSB, Buttner MJ (2003) Thiol-based regulatory switches. Annu Rev Genet 37:91–121. https://doi.org/10.1146/annurev.genet.37.110801.142538

Panwar SL, Moye-Rowley WS (2006) Long chain base tolerance in Saccharomyces cerevisiae is induced by retrograde signals from the mitochondria. J Biol Chem 281:6376–6384. https://doi.org/10.1074/jbc.M512115200

Perlin DS (2007) Resistance to echinocandin-class antifungal drugs. Drug Resist Updat 10(3):121–130

Perlin DS (2009) Antifungal drug resistance: do molecular methods provide a way forward? Curr Opin Infect Dis 22:568–573. https://doi.org/10.1097/QCO.0b013e3283321ce5

Perlroth J, Choi B, Spellberg B (2007) Nosocomial fungal infections: epidemiology, diagnosis, and treatment. Med Mycol 45:321–346. https://doi.org/10.1080/13693780701218689

Pfaller MA, Diekema DJ (2004) Rare and emerging opportunistic fungal pathogens: concern for resistance beyond Candida albicans and Aspergillus fumigatus. J Clin Microbiol 42:4419–4431. https://doi.org/10.1128/JCM.42.10.4419-4431.2004

Pfaller MA, Diekema DJ (2007) Epidemiology of invasive candidiasis: a persistent public health problem. Clin Microbiol Rev 20:133–163. https://doi.org/10.1128/CMR.00029-06

Pfaller MA, Diekema DJ, Jones RN et al (2001) International surveillance of bloodstream infections due to *Candida* species: frequency of occurrence and in vitro susceptibilities to fluco-

nazole, ravuconazole, and voriconazole of isolates collected from 1997 through 1999 in the SENTRY antimicrobial surveillance program. J Clin Microbiol 39(9):3254–3259
Pfaller MA, Boyken L, Hollis RJ et al (2008) *In vitro* susceptibility of invasive isolates of Candida spp. to anidulafungin, caspofungin, and micafungin: six years of global surveillance. J Clin Microbiol 46(1):150–156
Piddock LJV (2006) Clinically relevant chromosomally encoded multidrug resistance efflux pumps in bacteria. Clin Microbiol Rev 19:382–402. https://doi.org/10.1128/CMR.19.2.382-402.2006
Pomorski T (2004) Tracking down lipid flippases and their biological functions. J Cell Sci 117:805–813. https://doi.org/10.1242/jcs.01055
Pomorski T, Lombardi R, Riezman H et al (2003) Drs2p-related P-type ATPases Dnf1p and Dnf2p are required for phospholipid translocation across the yeast plasma membrane and serve a role in endocytosis. Mol Biol Cell 14:1240–1254. https://doi.org/10.1091/mbc.e02-08-0501
Prasad R, De Wergifosse P, Goffeau A, Balzi E (1995) Molecular cloning and characterization of a novel gene of Candida albicans, CDR1, conferring multiple resistance to drugs and antifungals. Curr Genet 27:320–329. https://doi.org/10.1007/BF00352101
Prasad T, Saini P, Gaur NA et al (2005) Functional analysis of CaIPT1, a sphingolipid biosynthetic gene involved in multidrug resistance and morphogenesis of Candida albicans. Antimicrob Agents Chemother 49:3442–3452. https://doi.org/10.1128/AAC.49.8.3442-3452.2005
Puri N, Krishnamurthy S, Habib S et al (1999) CDR1, a multidrug resistance gene from Candida albicans, contains multiple regulatory domains in its promoter and the distal AP-1 element mediates its induction by miconazole. FEMS Microbiol Lett 180:213–219. https://doi.org/10.1111/j.1574-6968.1999.tb08798.x
Rank GH, Robertson AJ, Phillips KL (1975) Modification and inheritance of pleiotropic cross resistance and collateral sensitivity in Saccharomyces cerevisiae. Genetics 80:483–493
Revankar SG, Sutton DA (2010) Melanized fungi in human disease. Clin Microbiol Rev 23:884–928. https://doi.org/10.1128/CMR.00019-10
Rex JH, Pfaller MA, Galgiani JN et al (1997) Development of interpretive breakpoints for antifungal susceptibility testing: conceptual framework and analysis of *in vitro - in vivo* correlation data for fluconazole, itraconazole, and Candida infections. Clin Infect Dis 24(2):235–247
Richardson MD (2005) Changing patterns and trends in systemic fungal infections. J Antimicrob Chemother 56:i5–i11. https://doi.org/10.1093/jac/dki218
Richardson M (2009) The ecology of the Zygomycetes and its impact on environmental exposure. Clin Microbiol Infect 15:2–9. https://doi.org/10.1111/j.1469-0691.2009.02972.x
Richardson M, Lass-Flörl C (2008) Changing epidemiology of systemic fungal infections. Clin Microbiol Infect 14:5–24
Riggle PJ, Kumamoto CA (2006) Transcriptional regulation of MDR1, encoding a drug efflux determinant, in fluconazole-resistant Candida albicans strains through an Mcm1p binding site. Eukaryot Cell 5:1957–1968. https://doi.org/10.1128/EC.00243-06
Riordan JR, Deuchars K, Kartner N et al (1985) Amplification of P-glycoprotein genes in multidrug-resistant mammalian cell lines. Nature 316:817–819. https://doi.org/10.1038/316817a0
Rodrigues-Pousada CA, Nevitt T, Menezes R et al (2004) Yeast activator proteins and stress response: an overview. FEBS Lett 567:80–85. https://doi.org/10.1016/j.febslet.2004.03.119
Rognon B, Kozovska Z, Coste AT et al (2006) Identification of promoter elements responsible for the regulation of MDR1 from Candida albicans, a major facilitator transporter involved in azole resistance. Microbiology 152:3701–3722. https://doi.org/10.1099/mic.0.29277-0
Roninson IB (1992) From amplification to function: the case of the MDR1 gene. Mutat Res Genet Toxicol 276:151–161. https://doi.org/10.1016/0165-1110(92)90005-T
Roninson IB, Chin JE, Choi KG et al (1986) Isolation of human mdr DNA sequences amplified in multidrug-resistant KB carcinoma cells. Proc Natl Acad Sci 83:4538–4542. https://doi.org/10.1073/pnas.83.12.4538
Sá-Correia I, Tenreiro S (2002) The multidrug resistance transporters of the major facilitator superfamily, 6 years after disclosure of Saccharomyces cerevisiae genome sequence. J Biotechnol 98:215–226. https://doi.org/10.1016/S0168-1656(02)00133-5

Sang H, Zheng XE, Zhou WQ et al (2011) A case of subcutaneous phaeohyphomycosis caused by Cladosporium cladosporioides and its treatment. Mycoses. https://doi.org/10.1111/j.1439-0507.2011.02057.x

Sanglard D (2002) Resistance of human fungal pathogens to antifungal drugs. Curr Opin Microbiol 5(4):379–385

Sanglard D, Kuchler K, Ischer F et al (1995) Mechanisms of resistance to azole antifungal agents in Candida albicans isolates from AIDS patients involve specific multidrug transporters. Antimicrob Agents Chemother 39:2378–2386. https://doi.org/10.1128/AAC.39.11.2378

Sanglard D, Ischer F, Monod M, Bille J (1996) Susceptibilities of Candida albicans multidrug transporter mutants to various antifungal agents and other metabolic inhibitors. Antimicrob Agents Chemother 40:2300–2305. https://doi.org/10.1128/AAC.40.10.2300

Sanglard D, Ischer F, Monod M, Bille J (1997) Cloning of Candida albicans genes conferring resistance to azole antifungal agents: characterization of CDR2, a new multidrug ABC transporter gene. Microbiology 143:405–416. https://doi.org/10.1099/00221287-143-2-405

Sanglard D, Ischer F, Bille J (2001) Role of ATP-binding-cassette transporter genes in high-frequency acquisition of resistance to azole antifungals in Candida glabrata. Antimicrob Agents Chemother 45:1174–1183. https://doi.org/10.1128/AAC.45.4.1174-1183.2001

Sanglard D, Coste A, Ferrari S (2009) Antifungal drug resistance mechanisms in fungal pathogens from the perspective of transcriptional gene regulation. FEMS Yeast Res 9(7):1029–1050

Sanguinetti M, Posteraro B, Fiori B et al (2005) Mechanisms of azole resistance in clinical isolates of Candida glabrata collected during a hospital survey of antifungal resistance. Antimicrob Agents Chemother 49:668–679. https://doi.org/10.1128/AAC.49.2.668-679.2005

Sellart-Altisent M, Torres-Rodríguez JM, Gómez de Ana S, Alvarado-Ramírez E (2007) Nasal fungal microbiota in allergic and healthy subjects. Rev Iberoam Micol 24:125–130. https://doi.org/10.1016/S1130-1406(07)70027-X

Shahi P, Gulshan K, Moye-Rowley WS (2007) Negative transcriptional regulation of multidrug resistance gene expression by an Hsp70 protein. J Biol Chem 282:26822–26831. https://doi.org/10.1074/jbc.M704772200

Sheehan DJ, Hitchcock CA, Sibley CM (1999) Current and emerging azole antifungal agents. Clin Microbiol Rev 12(1):40–79

Shukla S (2004) Substitution of threonine-1351 in the multidrug transporter Cdr1p of Candida albicans results in hypersusceptibility to antifungal agents and threonine-1351 is essential for synergic effects of calcineurin inhibitor FK520. J Antimicrob Chemother 54:38–45. https://doi.org/10.1093/jac/dkh308

Skaggs BA, Alexander JF, Pierson CA et al (1996) Cloning and characterization of the *Saccharomyces cerevisiae* C-22 sterol desaturase gene, encoding a second cytochrome P-450 involved in ergosterol biosynthesis. Gene 169(1):105–109

Slavin M, Fastenau J, Sukarom I et al (2004) Burden of hospitalization of patients with Candida and Aspergillus infections in Australia. Int J Infect Dis 8:111–120. https://doi.org/10.1016/j.ijid.2003.05.001

Sturley S (2000) Conservation of eukaryotic sterol homeostasis: new insights from studies in budding yeast. Biochim Biophys Acta Mol Cell Biol Lipids 1529:155–163. https://doi.org/10.1016/S1388-1981(00)00145-1

Tobin MB, Peery RB, Skatrud PL (1997) Genes encoding multiple drug resistance-like proteins in Aspergillus fumigatus and Aspergillus flavus. Gene 200:11–23. https://doi.org/10.1016/S0378-1119(97)00281-3

Tsai H-F, Krol AA, Sarti KE, Bennett JE (2006) Candida glabrata PDR1, a transcriptional regulator of a pleiotropic drug resistance network, mediates azole resistance in clinical isolates and petite mutants. Antimicrob Agents Chemother 50:1384–1392. https://doi.org/10.1128/AAC.50.4.1384-1392.2006

van den Hazel HB, Pichler H, Matta MA do V et al (1999) PDR16 and PDR17, two homologous genes of Saccharomyces cerevisiae, affect lipid biosynthesis and resistance to multiple drugs. J Biol Chem 274:1934–1941. https://doi.org/10.1074/jbc.274.4.1934

Vermitsky J-P, Edlind TD (2004) Azole resistance in Candida glabrata: coordinate upregulation of multidrug transporters and evidence for a Pdr1-like transcription factor. Antimicrob Agents Chemother 48:3773–3781. https://doi.org/10.1128/AAC.48.10.3773-3781.2004

Vermitsky J-P, Earhart KD, Smith WL et al (2006) Pdr1 regulates multidrug resistance in Candida glabrata: gene disruption and genome-wide expression studies. Mol Microbiol 61:704–722. https://doi.org/10.1111/j.1365-2958.2006.05235.x

Vugia DJ, Tabnak F, Newton AE et al (2013) Impact of 2003 state regulation on raw oyster-associated Vibrio vulnificus illnesses and deaths, California, USA. Emerg Infect Dis 19:1276–1280. https://doi.org/10.3201/eid1908.121861

Warnock DW (2006) Fungal diseases: an evolving public health challenge. Med Mycol 44:697–705. https://doi.org/10.1080/13693780601009493

Wemmie JA, Steggerda SM, Moye-Rowley WS (1997) The Saccharomyces cerevisiae AP-1 protein discriminates between oxidative stress elicited by the oxidants H2O2 and diamide. J Biol Chem 272:7908–7914. https://doi.org/10.1074/jbc.272.12.7908

White TC (1997) Increased mRNA levels of ERG16, CDR, and MDR1 correlate with increases in azole resistance in Candida albicans isolates from a patient infected with human immunodeficiency virus. Antimicrob Agents Chemother 41:1482–1487. https://doi.org/10.1128/AAC.41.7.1482

Wong S, Butler G, Wolfe KH (2002) Gene order evolution and paleopolyploidy in hemiascomycete yeasts. Proc Natl Acad Sci 99:9272–9277. https://doi.org/10.1073/pnas.142101099

Wu AL, Moye-Rowley WS (1994) GSH1, which encodes gamma-glutamylcysteine synthetase, is a target gene for yAP-1 transcriptional regulation. Mol Cell Biol 14:5832–5839. https://doi.org/10.1128/MCB.14.9.5832

Zhang X, Cui Z, Miyakawa T, Moye-Rowley WS (2001) Cross-talk between transcriptional regulators of multidrug resistance in Saccharomyces cerevisiae. J Biol Chem 276:8812–8819. https://doi.org/10.1074/jbc.M010686200