REVIEW ARTICLE

Antifungal Drug Resistance in *Candida albicans:* Identifying Novel Targets for the Development of Effective Antifungal Agents

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ABSTRACT

Candidiasis, a fungal infection initiated primarily through *Candida albicans*, affects various portions of the human body and is particularly prevalent in immunocompromised individuals. The pathogenicity of *C. albicans* is facilitated by numerous virulence causes, including adhesins, morphogenesis, and phenotypic switching. The organism's capability in the direction of switching between yeast and hyphal forms contributes to the severity of infections. The appearance of resistant strains has rendered current treatments less effective, necessitating the exploration of new drug targets and the progress of novel antifungal agents. Antifungal drug resistance is a multifaceted phenomenon involving genetic mutations, overexpression of efflux pumps, epigenetic changes, and biofilm formation, all regulated by complex genetic and transcriptional networks. These resistance mechanisms can cause treatment failures, highlighting the need for new antifungal agents and improved diagnostic tools. The identification of potential drug targets in *C. albicans* is critical due to increasing resistance to existing antifungal agents. Recent studies have identified promising targets, for example the riboflavin metabolic pathway and unique protein kinases involved in regulating virulence and pathogenicity. Developing new antifungals is difficult due to *C. albicans'* eukaryotic nature and resistance. Ongoing research is essential to find novel targets and strategies, especially with the limited antifungal drug classes available.

Keywords: Candidiasis, *Candida albicans*, Antifungal drug resistance, Antifungal drug targets.

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INTRODUCTION

Candidiasis, mainly caused by *Candida albicans*, can affect mucous membranes, skin, systemic organs, and the gastrointestinal, urinary tracts, and bloodstream, potentially becoming life-threatening if untreated.[1] The infection is particularly prevalent in immunocompromised individuals, and a number of virulence factors facilitate its pathogenicity for example adhesins, morphogenesis, and phenotypic switching.[2] The incidence of candidiasis is significant, with a noted increase in more virulent forms of the infection. Contradictorily, while *C. albicans* is a common member of the human microflora. It can become pathogenic under certain conditions, leading to candidiasis.[3] The organism's capability in the direction of switching between yeast and hyphal forms contributes to its pathogenicity and the severity of infections.[4] Moreover, the emergence of resistant strains has rendered current treatments less effective, necessitating the exploration of new drug targets and the development of novel antifungal agents.[5-9] Additionally, the complete genome sequence of *C. albicans* has been instrumental in understanding its pathogenesis and host interactions, providing insights for potential therapeutic interventions.[10] It is a dimorphic fungus that exists as a portion of the common human flora but can cause candidiasis under opportunistic conditions. The infection's prevalence and the advent of resistant strains focus on the prerequisite for continued research into its pathogenic mechanisms and the development of new treatments. Understanding the biological processes of pathogenicity and immune evasion by *C. albicans* is crucial for the advancement of antifungal therapies and, potentially, a vaccine to reduce the incidence of candidiasis.[11-14] Figure 1 shows the Schematic representation of *C. albicans* antifungal drug targets.

Antifungal Therapy and Drug Resistance

Antifungal drug therapy is essential for treating fungal infections, which can range from superficial to life-threatening invasive mycoses.[15,16] However, the effectiveness of these therapies is increasingly compromised by the emergence of antifungal drug resistance, which is an emergent apprehension in clinical settings. Resistance mechanisms include alterations

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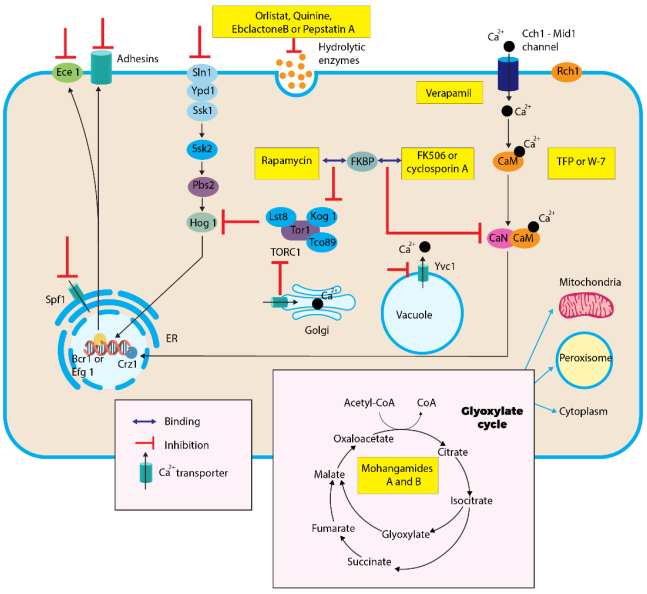

Figure 1: Schematic representation of *C. albicans* antifungal drug targets

in drug targets, increased efflux pump activity, biofilm formation, and genetic and epigenetic changes that enhance fungal survival under antifungal stress.[17-22] Interestingly, the development of resistance is not only an outcome of genetic mutations but also involves complex regulatory networks and epigenetic modifications. This multifaceted nature of resistance mechanisms presents both challenges and opportunities for the development of innovative diagnostic tools as well as therapeutic approaches.[23] Additionally, the economic burden of fungal infections and the cost associated with resistance are significant, underscoring the need for effective management strategies.[24-27] Fungal properties, host factors, antifungal use, and drug pressure influence resistance development.[28-30] Increased antifungal use has led to a "pathogen shift," with non-albicans *Candida* species, less susceptible to fluconazole, becoming more common.[31,32]

Possible Drug Targets in *Candida albicans*

Identifying drug targets in *C. albicans* is crucial due to rising antifungal resistance.[33] The complexity of the pathogen's resistance mechanisms, including alterations in ergosterol biosynthesis and drug efflux, necessitates novel therapeutic strategies. Additionally, the limited number of unique molecular targets available for antifungal development due to the eukaryotic nature of fungi, further complicates the finding of new drugs.[34] Interestingly, recent studies have identified several promising targets.[35] For instance, riboflavin (RF) has been revealed in the direction of disrupting membrane and cell wall integrity in *C. albicans*, indicating that the RF metabolic pathway could be a potential drug target.[36,37] Furthermore, in-silico studies have identified unique protein kinases in *Candida* spp. that are involved in regulating virulence and pathogenicity, which could serve as novel drug targets.[38,39] These kinases are not homologous to human proteins, reducing the potential for host toxicity. Developing new antifungals is challenging due to *C. albicans* eukaryotic nature and resistance, but recent research has identified potential drug targets. These include the RF metabolic pathway and unique protein kinases. These findings are key to developing new treatments for *C. albicans* infections.[40-42]

Glyoxylate Cycle

The glyoxylate cycle is crucial for pathogen survival and fungal virulence, enabling carbon utilization and supporting gluconeogenesis inside the host.[43,44] In the context of antifungal pathways, the glyoxylate cycle's relevance is highlighted by the finding that *Candida albicans* mutants lacking the key enzyme isocitrate lyase (ICL1) are markedly less virulent, indicating the cycle's importance in microbial pathogenesis.[45,46] Interestingly, while the cycle is a well-established metabolic pathway in bacteria, fungi, and plants, its presence in mammalian tissues has been debated.[47] However, recent evidence suggests that mammalian chondrocytes may possess the capacity for gluconeogenesis *via* the glyoxylate pathway, which was previously thought to be absent in vertebrate tissues.[48] This finding could have implications for understanding metabolic flexibility in mammalian cells and their potential role in antifungal defense mechanisms. The cycle is key to fungal virulence and a potential target for antifungal therapies. The cycle's enzymes, for example, ICL and malate synthase (MS), are upregulated during pathogen infection and are essential for the existence of pathogens like *C. albicans* within the host. The discovery of the glyoxylate cycle in mammalian chondrocytes opens new avenues for research into its potential functions in vertebrate biology and disease resistance.

High Osmolarity Glycerol Pathway

The high osmolarity glycerol (HOG) pathway is a well-documented antifungal response mechanism in various yeast and fungal species.[49] It is activated under conditions of osmotic stress and contributes to the regulation of adaptive responses to a range of environmental stressors.[50] In Saccharomyces cerevisiae, mutations in the pathway genes, for example, PBS2 and HOG1, confer resistance to calcofluor, an antifungal agent that binds to cell wall chitin.[51-54] This resistance is attributed to the altered functionality of the HOG pathway, which also affects cell wall architecture and basal salt tolerance. Similarly, in *Scedosporium apiospermum*, the HOG pathway is activated by various stressors, including antifungal agents, suggesting its role as a general stress regulator.[55-57] Interestingly, while the HOG pathway's role in osmoadaptation and stress response is well-established, its direct involvement in antifungal resistance is more nuanced.[58] For instance, in *Talaromyces marneffei*, the response regulator SskA, which acts upstream of the HOG pathway, is essential for osmotic adaptation and morphogenesis, indicating a complex regulatory network where the HOG pathway intersects with other signaling systems.[59] Additionally, the HOG pathway's interaction with other cellular processes, for example, sphingolipid and sterol biosynthesis, further illustrates its multifaceted role in stress

response.[60] The HOG pathway is a critical constituent of the antifungal reply in yeast and fungi, mediating adaptation to environmental stresses, including exposure to antifungal agents. Its functionality is interconnected with various cellular processes, and mutations or alterations in this pathway can lead to antifungal resistance. However, the pathway's role extends beyond mere resistance, as it is also elaborated in maintaining cell integrity and regulating other stress responses.[61]

Target of Rapamycin Signaling Pathway

The TOR signaling pathway regulates growth and metabolism in eukaryotic cells. TOR inhibition, such as with rapamycin, affects fungal growth and pathogenicity in species like *Phanerochaete chrysosporium* and *Verticillium dahliae*.[62-68] These findings suggest that the TOR pathway could be a potential target for antifungal strategies, as its inhibition appears to impair fungal growth and virulence. Interestingly, while the papers do not explicitly discuss the TOR pathway as an antifungal target, they do provide insights into the broad role of TOR signaling in fungal biology. For example, in *Aspergillus flavus*, TOR signaling is implicated in various processes including aflatoxin production, stress responses, and growth.[69] Additionally, the TOR pathway's regulation of mRNA turnover in *Saccharomyces cerevisiae* and its involvement in cellular proliferation and transcriptional repression in yeast further underscore its central role in fungal cell physiology.[70-71] The TOR signaling pathway as an antifungal pathway collectively demonstrates that TOR inhibition affects fungal growth and development across different species. This suggests that the TOR pathway could be explored as a target for antifungal interventions. The impact of TOR inhibition on fungal growth, development, and pathogenicity indicates its potential relevance in antifungal research, warranting further investigation into its mechanisms and applications in antifungal therapy.[72]

Cellular Homeostasis

Cellular calcium homeostasis appears to be a critical factor in various cellular processes, including responses to antifungal drugs. The Spf1 null mutant in *C. albicans* exhibited hypersensitivity to antifungal drugs, suggesting a link between calcium homeostasis and antifungal drug sensitivity.[73,74] This mutant also showed defects in hyphal development and attenuated virulence, which are important factors in the pathogenicity and the response to antifungal treatments in fungal organisms.[75,76] Interestingly, while the primary focus of the papers is not on the antifungal pathway, several studies highlight the importance of calcium homeostasis in cellular stress responses and pathogenesis, which could be relevant to antifungal resistance or sensitivity.[77-79] Mattson and Chan (2001) explore calcium's role in Alzheimer's disease, while Clark *et al*. (2017) suggest that regulating calcium homeostasis could reduce beta cell death in type 1 diabetes.[80,81] These findings suggest that targeting calcium homeostasis could aid in developing antifungal strategies and understanding resistance mechanisms, highlighting a potential area for further research.

Innate Antifungal Immunity

The antifungal pathway involves a complex interplay between host defense mechanisms and the invasive strategies of fungal pathogens, with hydrolytic enzymes playing a critical role in this interaction.[82] In *Drosophila*, the Toll receptor pathway activates the Rel family of transcription factors, comprising DIF, which is essential for the expression of the antifungal peptide drosomycin in response to fungal infections.[83] Similarly, the host cellular immune response to fungal invasion includes the upregulation of hydrolytic enzymes, which are part of the defense strategy against entomopathogenic fungi like *Beauveria bassiana*.[84] Hydrolytic enzymes are also produced by microbial communities in the rhizosphere, contributing to the degradation of fungal pathogens and serving as a biological control mechanism in plant disease management.[85] These enzymes, including chitinase, glucanase, protease, and cellulase, target the cell wall of fungal pathogens, leading to their breakdown and cell death.[86] In *C. albicans* infections, protein-protein interaction networks regulate morphogenesis, hyphal growth, and immune responses. Insect fungi use hydrolytic enzymes for colonization, while hosts produce antifungal lipids. For keratitis, the immune system alters tear protein glycosylation and activates defenses. Research continues on innate immunity and drug resistance in fungal infections.[87-90] Hydrolytic enzymes is integral to both fungal invasion strategies and host antifungal defenses. The host's immune system responds to fungal pathogens by upregulating hydrolytic enzymes and other defense factors, while fungi have developed mechanisms to evade these defenses and establish infection. Understanding these interactions is crucial for developing effective antifungal therapies and managing fungal diseases.

***Candida albicans*: Transcription Factors that Regulate Biofilm Formation**

In *C. albicans*, transcription factors regulate biofilm formation and antifungal resistance. Flo8 binds to the ERG6 promoter, affecting ergosterol biosynthesis and biofilm formation.[91] Additionally, biofilm formation is regulated by transcriptional regulators for example, Bcr1 and Tec1, which are involved in the genetic regulatory mechanisms of biofilm development.[92] A computational framework identified 23 transcription factors potentially related to biofilm formation, with 10 previously reported in literature, highlighting the complexity of the gene regulatory networks involved.[93,94] Interestingly, while Flo8's role in ergosterol biosynthesis and biofilm formation is well-established, other studies emphasize the multifactorial nature of biofilm-related antifungal resistance, including extracellular matrix production, efflux pumps, and genetic changes.[91-94] The antifungal pathway in *C. albicans* is regulated by a network of transcription factors that control biofilm formation and ergosterol biosynthesis, contributing to antifungal resistance. The identification of additional transcription factors through computational approaches provides a broader understanding of the regulatory mechanisms and potential targets for

combating biofilm-associated antifungal resistance. The identification of transcription factors through computational models underscores the potential for discovering novel targets for therapeutic intervention.[95-98]

Nontraditional Targets for Antifungal Therapy

The exploration of physiological processes beyond the traditional targets of antifungal therapy has revealed several potential antifungal targets.[99-104] The metabolism of glucose in *C. albicans* is intricately associated with the direction of its virulence, and enzymes involved in glucose metabolism pathways present novel targets for antifungal agents.[105] Similarly, the understanding of growth and virulence mechanisms in *C. albicans* has highlighted potential targets for new antifungal drugs.[106] Contradictorily, while the identification of novel targets is promising, the complexity of fungal physiology and the similarity to host cells pose challenges. Heat shock proteins (Hsps) in *C. albicans*, which are involved in various physiological activities and virulence, have been identified as potential targets, but their similarity to human Hsps could limit the specificity of potential drugs.[107] Furthermore, amino acid transport and metabolism have been proposed as drug targets, but the translation of these targets into clinical practice faces hurdles.[108] The identification of novel physiological processes as potential antifungal targets is a critical area of research. The stress response mechanisms, glucose metabolism pathways, and virulence factors in fungi offer promising targets. However, the challenges associated with the eukaryotic nature of fungal cells and the potential for host toxicity must be carefully considered. Continued research into these physiological processes is needed for the development of effective and specific antifungal therapies.

Challenges for Novel Antifungal Therapies

The rise in invasive fungal infections highlights the need for new antifungals due to current treatments' toxicity, limited efficacy, and resistance. Despite identifying fungal-specific targets, few new compounds are in development. Repurposing off-patent drugs and advancing technologies like structural biology and virtual imaging could boost drug discovery.[109] Interestingly, while the search for new antifungal agents is imperative, there is a contradiction in the approach; the focus has shifted from solely targeting fungal growth to also targeting virulence and fungal-specific pathways, for example, the glyoxylate cycle and trehalose biosynthetic pathway.[110] Moreover, the use of combinational therapies and the exploration of natural products, for example antifungal peptides and secondary metabolites, offer promising avenues for new treatments. The incorporation of modern omics methods, bioinformatics, and micro- and nanoscale approaches, including microfluidic platforms and nanosensors, is revolutionizing the field and enabling rapid and personalized antifungal drug screening.[111] Antifungal drug resistance is a multifaceted phenomenon involving various molecular mechanisms. These mechanisms include alterations in drug targets, increased efflux pump activity, and epigenetic changes that affect gene expression.[112-115] Specifically, mutations in drug targets, overexpression of these targets, and upregulation of efflux transporters are common strategies fungi employ to resist antifungal agents. Additionally, epigenetic modifications, for example histone acetylation and methylation, contribute to the increased resistance. Contradictions are not evident in the literature; however, interestingly, the molecular mechanisms of resistance are often shared between strains with inherent reduced susceptibility and those that acquire resistance during treatment. This suggests a complex interplay between genetic predisposition and adaptive responses. Furthermore, the transcriptional regulation of drug resistance genes, for example, those controlled by Tac1p, Upc2p, and Mrr1p, has been recognized as a crucial element in the emergence of resistance.[116,117] The role of biofilms and genetic factors for example, aneuploidy in resistance, also provides insight into the complexity of this issue. Antifungal drug resistance is governed by a range of molecular mechanisms, including targ*et al*terations, efflux pump activity, and epigenetic changes. The shared mechanisms between inherently resistant strains and those acquiring resistance during therapy highlight the need for a comprehensive understanding of these processes. This knowledge is crucial for developing new antifungal therapies and improving the efficacy of existing treatments. The current literature underscores the pressing need for novel antifungals in clinical settings due to the rise in antifungal resistance and the limited number of effective drugs available. The existing antifungal agents, which include polyenes, azoles, echinocandins, and flucytosine, are hindered by issues for example, toxicity, drug-drug interactions, and the emergence of resistance, the advancement of innovative pharmaceuticals with unique modes of operation.[118-121] Interestingly, despite the recognized need for new antifungals, the development of such drugs has been relatively stagnant since the 1990s.[122] This stagnation is juxtaposed with the increasing use and cost of antifungals in clinical settings, as evidenced by the high proportion of antifungal drug costs relative to other antimicrobials in hospitals.[123] The development of new antifungal therapies is a multifaceted challenge that requires a concerted effort to identify novel drug targets, minimize drug toxicity, and improve delivery methods.[124] The integration of advanced technologies and the exploration of natural products and combinational therapies are key strategies in this endeavor.[125] The literature indicates a critical demand for novel antifungal agents in clinical practice to address the challenges posed by antifungal resistance and the limitations of current drugs.[126-130] Developing new antifungals with unique mechanisms is crucial for better patient outcomes and managing therapy costs.

CONCLUSION

Candidiasis, a fungal infection caused primarily by *C. albicans*, affects various portions of the human body and is prevalent in immunocompromised individuals. The pathogenicity of *C. albicans* is facilitated by virulence factors, and its capability in the direction of switching between yeast and hyphal forms contributes to the severity of infections. The emergence of

resistant strains has rendered current treatments less effective, necessitating the exploration of new drug targets and novel antifungal agents. Antifungal drug resistance is a multifaceted phenomenon concerning genetic mutations, overexpression of efflux pumps, epigenetic changes, and biofilm formation, all regulated by complex genetic and transcriptional networks. The identification of potential drug targets in *C. albicans* is critical due to increasing resistance, with recent studies identifying promising targets for example, the riboflavin metabolic pathway and unique protein kinases involved in regulating virulence and pathogenicity.

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