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MYCOLOGY (B BARKER, SECTION EDITOR)

Germination of a Field: Women in *Candida albicans* Research

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Abstract

Candida albicans is a common human fungal pathogen that was first described in the 1930s and is currently one of the major causes of invasive fungal infections, especially in immunocompromised patients. Since its first identification and association with disease, *C. albicans* has been the subject of intense research investigations. In this review, we focus on the trailblazing women who made instrumental discoveries about some of the key research questions that we are still working on answering today. We highlight five major areas of *C. albicans* research: morphogenesis, drug resistance, polymicrobial interactions, in vivo pathogenesis, and host immune responses. In each section, we discuss early findings by women researchers as well as current, cutting-edge research being performed by women leaders in the field. In many cases, some of the "common knowledge" in *C. albicans* biology was first described by women, and we hope to re-emphasize their contributions to the work that is still being carried out today.

Keywords Candida albicans · History · Female researchers

Introduction

Women have been significant contributors to medical mycology research since the beginning of this field of research. In 1923, **Berkhout** first described the genus *Candida* in her doctoral thesis [1]. In 1931, **Benham's** doctoral thesis described a pathogenic yeast that caused thrush and other diseases in humans, and her work helped to start the field of medical mycology and the study of *Candida albicans* [2]. In the almost 100 years since its discovery, scientists have unraveled many of the complexities of *C. albicans* biology and virulence. *C. albicans* is an opportunistic pathogen, which exists as a benign member of the mucosal microbiota that can cause acute and invasive infections when immune function is compromised or after invasive clinical intervention or trauma [3]. The success of *C. albicans* as a pathogen has been attributed to its arsenal of virulence traits, including its ability to undergo morphogenetic switches and its rapid emergence of drug resistance. Using numerous animal models, scientists have interrogated the host-pathogen interactions of *C. albicans* including the effects on the host immune response, the delicate balance between commensalism and disease, and the interactions with other commensal and pathogenic microbes. Our understanding of *C. albicans* as a pathogen is built off of the many discoveries from countless scientists around the globe, including many instrumental women scientists.

In this review, we intend to introduce the fundamental principles of *C. albicans* biology by featuring some of the women who have contributed to the field throughout history. Through historical PubMed searches, we identified early findings that were instrumental to the field, and we focused on discoveries published with woman first or last authors. To identify women authors, we attempted to confirm their identity through secondary sources such as university profiles, Wikipedia pages, and obituaries. We acknowledge that our methods are flawed as in many cases we assumed the researcher's sex by their given name, which is not indicative of a person's gender identity. These women's names are bolded throughout the review. The women highlighted in this review represent only a fraction of those who have contributed

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to *Candida* research over the years. We would like to acknowledge the numerous contributions by women scientists that we were not able to recognize in this review due to space limitations, language barriers, and inability to identify the authors, full name or sex. Here, we review our understanding of *C. albicans* morphogenesis, drug resistance, polymicrobial interactions, in vivo pathogenesis, and host-immune responses, highlighting the contributions of women scientists.

C. albicans Morphogenesis

One of the most distinguishing features of *C. albicans* is its ability to undergo morphogenetic transitions, from oval single-celled yeasts to morphologies such as elongated, multi-cellular filaments, enlarged chlamydospores and yeast-like cells such as opaque, gray, and gastrointestinally-induced transition (GUT) cells [4]. These transitions are part of an arsenal of *C. albicans* virulence traits that it exploits during infections to colonize, disseminate, evade the immune system, invade organs, and cause systemic damage, as these morphogenetic states impart distinct advantages to *C. albicans* in different host niches and infection states [4]. Additionally, early observations of growth of *C. albicans* (then referred to as *Monilia albicans*) in various morphogenetic states were exploited as a diagnostic tool, as it was a trait that was not conserved in related *Candida* species or more distantly related ascomycete fungi. One of the trailblazing medical mycologists, **Benham**, reported three morphogenetic characteristics distinctive of *C. albicans*: the growth of mycelium or large masses of hyphal and pseudohyphal cells surrounding the fungal colony on solid medium, budding cells from the septa of hyphal cells, and large chlamydospores [2, 5]. Together, this illuminates the utility and importance of morphogenetic transitions, especially chlamydospore production and the yeast-to-hyphal transition, which we will focus on further.

The formation of chlamydospores was long considered to be the most reliable diagnostic test for distinguishing *C. albicans* clinical samples from other non-pathogenic species [2]. Chlamydospores are large, thick-walled *C. albicans* cells often observed at the end of filaments. Early work by the groups of **Benham**, **Taschdjian**, **Stein**, **Carter**, **Grant**, and others characterized the growth medium and conditions to induce chlamydospore production [6–11], demonstrating the influence of carbon source, oxygen levels, inoculation size, age of cells, detergents, and alterations in temperature and pH [12]. Chlamydospore formation is correlated with conditions that favor filamentous growth, which **Hayes** identified is a result of altered distribution of complex polysaccharides and lipids through the cell wall during filamentation that accumulate to produce a thick, dense cell wall [12]. Biochemical and enzymatic studies from **Jansons** were critical in understanding the structure of *C. albicans* chlamydospores, containing a complex cell wall composed of an outer cell wall of mostly β-1,3-glucan and a dense proteinaceous cell wall layer, surrounding a core with high lipid and RNA content [13, 14]. Subsequent electron microscopy studies from **Miller** and colleagues demonstrated that ultrastructural changes occur within chlamydospores, coinciding in a dramatic reduction in metabolic activity [15, 16]. Many questions remain about the biological function of chlamydospores and their structure, and it remains controversial whether these cells have a spore-like function [17]. Without an understanding of their function, it remains unknown why chlamydospores are specific to *C. albicans* and *Candida dubliniensis*, and not shared among related *Candida* species [17], although this specificity proved useful as a diagnostic tool to identify *C. albicans.*

The most well-characterized *C. albicans* morphological transition is the yeast-to-hyphal transition. **Taschdjian** and colleagues were among the first scientists to observe that *C. albicans* induces filamentation within 90 min of being exposed to human or animal serum at 37°C, facilitating the development of a simple and rapid diagnostic test in serum [18]. It is now understood that *C. albicans* transitions from ovoid budding yeasts to elongated filamentous forms, including hyphal and the intermediary pseudohyphal forms, in response to many host-relevant environmental signals including exposure to serum, elevated temperature, nutrient limitation, embedded conditions, and alterations in pH [19]. The yeast-to-hyphal transition can also be induced by the misregulation of morphogenetic regulators through genetic or genotoxic manipulation. Studies from **Pomés, Gil,** and Nomela utilized UV irradiation to generate *C. albicans* mutants that were filamentous in the absence of an inducing cue, indicating the misregulation of an unknown morphogenetic regulator [20, 21].

Though *C. albicans* filamentation has been studied for over 60 years, the complex regulatory circuitry underpinning morphogenesis in response to diverse cues is still being explored. Many groups, including **Sundstrom, Hogan,** and colleagues, have established that the cyclic AMP-protein kinase A (cAMP-PKA) pathway is a critical signaling hub for the induction of filamentous growth in response to diverse cues [22–26]. **Shapiro, Cowen,** and colleagues identified that the essential molecular chaperone, Hsp90, represses morphogenetic signaling through the cAMP-PKA pathway [27]. **Bachewich** and colleagues identified that depletion of critical cell cycle regulators or pharmacological inhibition of the cell cycle induces *C. albicans* filamentation, demonstrating a clear regulatory role of the cell cycle on morphogenesis [28, 29]. Substantial work by **Liu** and colleagues helped map many of the signaling transduction pathways, including mitogen-activated protein kinases, cyclin-dependent kinases, and transcription factors, required for filamentation in response to different cues [30–34]. **Blankenship's** group revealed that the genetic requirements for filamentation in response to diverse inducing cues are mostly affected by the state of the medium

and identified a core transcriptional program associated with, but not required for, filamentation [35]. The expansion of *C. albicans* genetic mutant libraries and the use of high-throughput systematic genetic screens, such as those performed by **O'Meara, Veri, Cowen** and colleagues [36], are expanding our capacity to unveil the complex and interconnected pathways regulating morphogenesis.

In contrast to chlamydospores, the biological importance of *C. albicans* filamentation in virulence has been well explored. Early clinical work found that yeast and filament forms were often observed in clinical samples, including studies of *C. albicans* in newborns by **Taschdjian** [37]**.** This work showed that mostly yeast were observed in the pre-clinical oral smears and the detection of hyphae coincided with the onset of clinical thrush, as hyphae invaded the oral epithelium [37]. Early work from scientists such as **Young** was instrumental in understanding that *C. albicans* yeast cells rapidly convert to filamentous forms when injected intraperitoneally into mice and while the yeast disseminated through the bloodstream, the filaments were observed to invade the pancreas with hyphae penetrating the tissues [38]. **Young** also observed that the yeast cells, but not the larger filaments, could be phagocytosed by immune cells [38]. Findings from **Lo** and colleagues observed that a *C. albicans* mutant deficient in filamentation was avirulent in a mouse model of infection [39]. Work from **Bendel and Wells** demonstrated that a constitutively filamentous strain, incapable of growing as yeast, was deficient in dissemination and was avirulent in oral and intravenous mouse models of infection [40]. These findings were expanded upon by many groups, including work from **Noble** and colleagues, establishing the current paradigm that the majority of mutants that are blocked in the morphogenetic transition are avirulent in mice [41], as both forms play critical and distinct roles in infection [42].

Morphogenesis also has a profound effect on *C. albicans* virulence by influencing the formation of treatment-resistant biofilms on indwelling medical devices such as catheters and pacemakers [43]. Work from **Douglas** was foundational in establishing the first methods to grow and monitor *C. albicans* biofilms, identifying that while yeast cells attach to a surface, biofilms develop into a dense network of yeast, hyphae, and pseudohyphae surrounded by a extracellular matrix [44–46]. *C. albicans* morphogenesis is required for the formation and persistence of biofilms, as the yeast and hyphae form distinct biofilm layers necessary for adherent, properly formed biofilms [47]. **Douglas'** group also performed foundational work establishing that *C. albicans* biofilms are multi-drug-resistant [48, 49]. **Nobile** and colleagues established many factors required for proper *C. albicans* biofilm formation, including adhesins, hyphal wall proteins, and the transcription factor Bcr1 [50–53], many of which also play roles in hyphal development. **Nobile's** work illuminated the master circuit transcriptionally regulating biofilm formation through the connected efforts of six transcription factors [54]. In addition to the threats posed by the drug-resistant biofilms, **Uppuluri** established that yeast cells that disperse from biofilms and disseminate through the bloodstream are more adherent, have enhanced filamentation and biofilm formation, and have increased pathogenicity compared to planktonic yeast cells [55–57]. *C. albicans* biofilms pose a major impediment to the treatment of infections, as well as providing a source for dangerous, subsequent infections.

C. albicans Treatments and Drug Resistance

There are a limited number of classes of antifungals available in the clinic to treat life-threatening *Candida* infections. The first of these classes, the polyenes, were developed in the 1950s, and **Hazen and Brown** discovered and purified the first member of the polyene macrolide group in 1950 and named it Fungicidin (now nystatin) [58]. This was the first antifungal agent approved for use in humans. They demonstrated its effectiveness against *C. albicans* both in vitro and in vivo [59, 60]. **Silva-Hutner**, referred to by some as the "matriarch of mycology," also contributed to the development and characterization of nystatin [61]. Currently, nystatin is not indicated for systemic use, though is still used topically to treat oral candidiasis [62]. The most common member of the polyene class of antifungals is amphotericin B, which is currently used for the treatment of candidiasis, though its use is limited by host toxicity [62]. **Halde** contributed to some of the early characterization of amphotericin B in mice and in humans [63]. The mechanism of action of the polyenes was initially poorly understood. Early work by **Sokol-Anderson** identified a role for oxidative damage in mediating *C. albicans* lethality [64] and identified an association between resistance to amphotericin B and oxidant stress [65]. More recent work has revealed that amphotericin B acts as a "sterol sponge," extracting the critical sterol, ergosterol, from fungal membranes [66]. Thankfully however, fungal resistance to the polyene class of antifungals remains rare. Important work by the **Lindquist** group used whole genome sequencing and laboratory-evolved strains to determine that the acquisition of resistance-conferring mutations results in a large fitness cost [67]. Thus while fungal resistance to amphotericin B remains rare, the use of this antifungal is generally reserved as an alternative therapy for invasive candidiasis due to its toxic effects on the host [62].

The most commonly used antifungal agents in the clinic belong to the class of azole antifungals. The azoles were first introduced in the 1980s, and they function by inhibiting synthesis of ergosterol in fungal cell membranes, thus disrupting the fungal cell membrane [68]. Most first-generation azoles were limited to topical use and suffered from bioavailability challenges. These have been largely replaced with triazoles, of

which fluconazole is the first-line agent [62, 69]). While the triazoles can be used systemically, are orally bioavailable, and have an improved safety profile, the acquisition of resistance to this fungistatic agent is of major concern [68]. A common mechanism of resistance involves mutations in the fungal gene *ERG11*, which encodes the enzyme in the ergosterol biosynthetic cascade targeted by azoles. Work by **Kelly** and others have demonstrated that mutations in *C. albicans ERG11* result in reduced azole binding to the enzyme, thus inhibiting its antifungal activity [70–72], and work by **Flowers** has contributed to the characterization of *ERG11* mutations in *C. albicans* clinical isolates [73]. Furthermore, **Flowers** established that mutations in a key regulator of ergosterol biosynthesis, *UPC2*, contribute to fluconazole resistance in the clinic [74]. Overexpression of drug efflux pumps, such as the ABC transporters Cdr1 and Cdr2, is another common mechanism by which *Candida* species gain resistance to azoles. **Coste** and others identified Tac1 as a transcriptional regulator of *CRD1* and *CDR2* [75] and subsequently identified hyperactive *TAC1* alleles that confer azole resistance [76, 77]. Overexpression of Mdr1, a member of the major facilitator family of drug efflux pumps, also contributes to *C. albicans* fluconazole resistance, as first confirmed by **Wirsching** [78].

In addition to these specific mechanisms conferring azole resistance, stress response pathways play a key role in modulating azole resistance in *Candida* species. Important work by **Cowen and Lindquist** identified the molecular chaperone Hsp90 as a potentiator of the evolution of antifungal drug resistance [79] and found that inhibition of *C. albicans* Hsp90 impairs azole resistance in vivo [80]. Regulators downstream of Hsp90 that mediate azole resistance include the protein phosphatase calcineurin, and work by **Singh, Cowen**, and others established calcineurin as the first client protein of Hsp90 in *C. albicans* [79, 81, 82], and **Cruz** demonstrated that inhibition of calcineurin decreases azole tolerance [83]. Furthermore, Hsp90 regulates circuitry involving the protein kinase C (PKC) mitogen-activated protein kinase pathway to respond to cell wall stress, as shown by **LaFayette** [84]. Together this work reveals inhibition of Hsp90 and downstream stress response regulators as a strategy by which to block the emergence of azole resistance and enhance azole efficacy.

C. albicans is also known for its remarkable genomic plasticity, which contributes to its genetic diversity. **Rustchenko**'s group first reported that *C. albicans* fluconazole resistance can be dependent on chromosomal nondisjunction [85] and had made previous observations connecting *C. albicans* chromosomal copy number alteration to regulation of gene expression [86]. The **Selmecki**, **Forche,** and **Berman** team made further important connections between aneuploidies and azole resistance. They found aneuploidies of multiple chromosomes (most commonly, trisomy of chromosome 5) and the presence of an isochromosome composed of the two left arms of chromosome 5 (i(5L)) were associated with azole resistance [87]. Further work by this group determined that the major mechanism by which i(5L) confers resistance in vivo is by amplifying *ERG11*, encoding the drug target, and *TAC1*, encoding a transcription factor that regulates efflux pump expression [88]. More recently, work by the **Selmecki** group has identified long repeat sequences as drivers of *C. albicans* genome instability and has provided detailed mechanistic insight, highlighting how the remarkable genomic plasticity of this fungus contributes to its evolution of antifungal resistance [89, 90•].

The newest class of antifungal approved for the treatment of invasive fungal infections is the echinocandins, with caspofungin being approved by the Food and Drug Administration (FDA) in 2001 [91]. This semi-synthetic compound shows an excellent safety profile and is the first-line antifungal used for the treatment of invasive candidiasis [62]. Poor oral bioavailability, however, limits the usage of this antifungal class to intravenous administration. Echinocandins impair fungal cell wall synthesis by binding to a subunit of 1,3-β-D-glucan synthase, encoded by *C. albicans FSK1*. *Candida* acquires resistance to this class of antifungals primarily through mutations in hot-spot regions of the drug target [68]. Recent work by the **Rustchenko** group observed that *C. albicans FKS2* and *FKS3* have a role in modulating *FKS1* expression and that their deletion alters echinocandin resistance [92].

As with the azoles, multiple mediators of fungal stress responses have important roles in modulating echinocandin-induced stress. In addition to modulating azole-induced stress, **Singh, Cowen,** and others identified Hsp90 as an important mediator of stress induced by echinocandins, in which depletion of Hsp90 reduced echinocandin resistance in *C. albicans* clinical isolates [82]. As with the azoles, calcineurin is a key Hsp90 client protein that mediates echinocandin resistance [82]. Additional Hsp90 client proteins involved in mediating cell wall stress are those belonging to the protein kinase C (PKC) cell wall integrity pathway, as shown by work in the **Cowen** group [84, 93•, 94]. Pathways governing cell wall synthesis are also key mediators of echinocandin-induced stress. **Blankenship** identified a network of protein kinases governing cell wall integrity and biogenesis [95]. **Walker, Munro,** and others have also made important contributions to our understanding of cell wall biosynthesis and regulation. Cell wall stress results in the compensatory upregulation of chitin synthesis in many species of *Candida*, which is mediated by PKC, HOG, and calcineurin signaling pathways [96–98]. Thus, women have made important contributions to our understanding of response pathways mediating antifungal-induced stress, giving further insight into strategies that can be used to combat resistance to available antifungals.

Polymicrobial Interactions

C. albicans interacts with bacteria that co-colonize similar niches in the host. These fungal-bacterial interactions are diverse in their nature; some bacteria provide a protective effect to the host by antagonizing the pathogenicity of *C. albicans* or preventing fungal overgrowth through competition for resources. Other bacteria can work alongside *C. albicans* to cause life-threatening polymicrobial infections. The importance of fungal-bacterial interactions was first realized following the widespread use of antibacterial antibiotics. An early example is aureomycin, first isolated in 1948; many patients who underwent aureomycin treatment later suffered from acute inflammation of different areas of the body, which was originally attributed to a decrease in bacterial abundance. Work from **Schnall** indicated that *C. albicans* could be isolated from many of these patients and may therefore be the causative agent of inflammatory infections following antibiotic treatment. Furthermore, it was shown that aureomycin stimulates the growth of *C. albicans* [99]. This phenomenon was further investigated by **Sharp**, who demonstrated an increase in *C. albicans* colonization in patients following oxytetracycline treatment, but not sulfadiazine [100]; this highlighted that specific bacteria may limit *C. albicans* growth. This study also indicated that *C. albicans* can colonize multiple body sites commensally, as the fungus was isolated from sputum, throat swabs, and rectal swabs of patients with no clinical indications of disease. **Jarvis** and **Johnston** further demonstrated an increase in oral *C. albicans* colonization in diabetic and leukemia patients, as well as those receiving antibiotics [101].

The life-threatening nature of polymicrobial infections was reported by **Dyess**, who found that polymicrobial blood infections are more fatal than bacteremia or candidemia alone [102]. *Staphylococcus* and *Pseudomonas* are the bacterial genera most commonly isolated from bloodstream infections with *C. albicans*, and investigating the mechanisms behind fungal-bacterial interactions has remained an important topic of research to the present day. **Neely** developed a mouse model to study co-infection with *Pseudomonas aeruginosa* and *C. albicans*, which resulted in significantly higher mortality rates than monoinfection [103]. This group identified a *P. aeruginosa* proteolytic enzyme that significantly contributed to increased mortality during co-infections. In the years since, several *P. aeruginosa* secreted compounds have been identified and characterized based on their effect on *C. albicans* [104–106]. Work from **Hogan** revealed that *P. aeruginosa* attaches to and kills the filamentous form of *C. albicans* and identified a *P. aeruginosa* quorum-sensing molecule that inhibits *Candida* filamentation [104, 105]. **Morales** then determined the killing mechanism behind a *P. aeruginosa* toxin with antifungal properties [106]. Recently, *Enterococcus faecalis* peptides were also shown to inhibit *C. albicans* filamentation; **Graham** also demonstrated that this peptide can inhibit virulence [107].

Douglas, who did extensive work describing *C. albicans* biofilms, was the first to describe mixed species biofilms between *Staphylococcus epidermidis* and *C. albicans* on medical implant devices [108]. The polymicrobial biofilm was found to provide some protection to both microbes against antibiotic and antifungal treatments. In more recent years, the interplay between the pathogen *Staphylococcus aureus* and *C. albicans* has been investigated by **Noverr**, who first characterized mixed biofilms between them [109]. Similar to *C. albicans* and *S. epidermidis* mixed biofilms, formation of a polymicrobial biofilm with *S. aureus* provides the bacteria with increased resistance to the antibacterial vancomycin [109].

As both *C. albicans* and *Lactobacillus* spp. are prominent colonizers of body sites including the mouth and vaginal tract, the influence of these two microbes on one another has been investigated for decades. **Young** and colleagues demonstrated that *C. albicans* growth is delayed in the presence of *Lactobacillus acidophilus* and that direct addition of lactic acid delays *Candida* growth [110]. This group utilized vitamin-deficient conditions to show that *C. albicans* can support the growth of *L. acidophilus*, and imaging of mixed colonies revealed that *L. acidophilus* adheres to *Candida* cells. This work was expanded upon by a group including **Hodges**, **Tribby**, and **Studell**, who similarly manipulated nutritional parameters to test the ability of several *Lactobacillus* spp. to grow in the presence of and antagonize the growth of *C. albicans* [111]. **Strus** used vaginal lactobacilli isolates to demonstrate that hydrogen peroxide production by *Lactobacillus* spp. is partially responsible for the growth inhibition of *C. albicans* [112].

These are only a small number of defined interactions between *C. albicans* and bacteria, and many more interactions are under current investigation. Recent work from **Valentine** indicates that members of the genus *Bacteroides*, many of which have considerable polysaccharide-degrading abilities, can digest *Candida* cell wall components as a carbon source [113]. **Eckstein** demonstrated co-localization of *C. albicans* and *Bacteroides thetaiotaomicron* to the gastrointestinal tract outer mucus layer during colonization [114•]. As our understanding of microbial ecology grows, this early work on polymicrobial interactions will serve as a strong foundation for future research.

In Vivo Pathogenesis Models

Pirofski and Casadevall developed the damage-response framework, which posits that disease comes from damage and that this damage can come from either the microbe or the host immune response [115–117]. To understand the host,

researchers turned to animal models of candidiasis, which allow for study of both the microbe in a complex environment and the host response to the microbe. In the 1950s, **Berg** and colleagues helped establish mouse models of infection, including intraperitoneal, subcutaneous, cerebral, and intracardiac infections [118]. Additional models for examining disseminated candidiasis and fungal virulence have been developed, including an embryonated egg model from **Jacobsen** [119], a zebrafish model described by **Brothers** [120, 121], and a wax worm model from **Fuchs** [122]. While all of these models have utility for studying infections, the mouse model is the standard for the field for examining virulence of different fungal mutant strains due to ease and cost and the availability of knockout strains.

Many of these models focus on disseminated candidiasis, but *C. albicans* also causes oral thrush and vulvovaginal candidiasis, in addition to being a commensal gastrointestinal colonizer. To examine these different modes of interaction with the host, additional animal models were needed. **Yano** helped develop the vaginal model of *C. albicans* vulvovaginal candidiasis that mimics human infection [123, 124]. The oropharyngeal models of *C. albicans* described by **Solis** [125, 126] and **Conti** [127] use immunocompromisation with corticosteroids to model the thrush observed in many HIV/AIDS patients. Denture models are also used for examining oral infections in rats [128] and in mice [129]. For gastrointestinal colonization, many models use antibiotic treatment to establish robust colonization. **Wells** and colleagues showed colonization throughout the gastrointestinal tract and the presence of both yeast and hyphal forms of *C. albicans* in the cecal contents [130]. The team of **Witchely, Pennumetcha,** and **Noble** recently used fluorescence in situ hybridization to show these morphologies during infection and localization in the mucosal layer [131••, 132].

Gnotobiotic animal models provide a useful model to study *Candida*-host interactions without the need to treat with antibiotics to establish fungal colonization and without the influence of resident microbes; as noted above, *Candida* has a variety of interactions with bacteria that alter the fungus as well as host outcomes. For studying colonization, **Kumamoto** first established the gnotobiotic piglet model [133]. **Westwater** used a gnotobiotic mouse model to investigate the differential pathogenicity of *C. albicans* and the related species, *Candida glabrata* [134–136]. Importantly, without the interference of the resident microbiota, *C. albicans* behaves differently in the gastrointestinal tract of gnotobiotic mice. **Böhm** demonstrated that in gnotobiotic mice, *C. albicans* preferentially exists in the yeast form, unlike in conventional, antibiotic-treated mice, where *C. albicans* displays a heterogeneous mixture of yeast and filaments [137]. The germ-free status can also be combined with immunocompromisation. Immunocompromised individuals represent one of the most at-risk populations for candidiasis. **Cantorna** utilized germ-free mice with immunodeficiencies to demonstrate differing levels of lethality of mucosal candidiasis in immunodeficient models and establish an animal model that is naturally susceptible to endogenous mucosal and systemic candidiasis [138]. Additionally, **Cantorna** determined that gastrointestinal colonization with *C. albicans* is not sufficient to confer susceptibility to vaginal candidiasis, even in immunodeficient mice [139].

Host Immune Responses

The innate immune system is the first line of defense against invasive candidiasis. In 1969, **Stanley** and **Hurley** showed that macrophages readily phagocytose *C. albicans* and that the fungi undergo a morphogenetic shift from yeast to hyphae, with eventual macrophage cell death [140]. Recent work from **Hise, Wellington,** and **Uwamahoro** demonstrated that the macrophage cell death is mediated through the NLRP3 inflammasome and pyroptosis [141–143]. The genetic determinants regulating fungal activation of the NLRP3 inflammasome are still being defined, but a recent screen from **O'Meara** identified multiple cell wall components as major contributors [144]; and **Kaspar** identified a role for the fungal secreted peptide toxin candidalysin [145]. **Hise's** lab went on to show that the NLRC4 inflammasome is specifically required for defense against *C. albicans* oral infection [146]. Additionally, **Gringhuis** showed that *C. albicans* can induce a non-canonical caspase-8 inflammasome [147].

The innate immune cells recognize *C. albicans* through conserved pathogen-associated molecular patterns, especially β-glucan [148]. The pattern recognition receptor Dectin-1 plays a key role in recognizing *C. albicans* and enabling phagocytosis by macrophages, though interestingly, its role during systemic candidiasis depends on the fungal and host genetic backgrounds [149]. This was highlighted in joint publications from **Saijo** and Taylor; **Saijo** showed that wild-type and dectin-1-knockout mice were equally susceptible to *C. albicans* infection [150], and Taylor showed increased susceptibility of the dectin-1 knockout mice [151]. On the fungal side, there has been extensive research on fungal genes and environmental cues that influence *C. albicans* β-glucan shielding from recognition, with a resulting decrease in virulence, including work from **Galán-Díez** [152]**, Klippel** [153], **Ene** [154], **Davis** [155]**, Bain** [156]**, Ballou** [157], and **Childers** [158•], among others. In addition to β-glucan, various other *C. albicans* cell wall components can be recognized by additional pattern recognition receptors (PRRs); **Heinsbroek** showed that macrophage C-type lectin receptors (CLRs) coordinate with complement receptors and mannose receptors when phagocytosing *C. albicans* [159], and **Villamon** showed that MyD88, the toll-like receptor (TLR) adaptor protein, is required for immunity to *C. albicans* and

production of proinflammatory cytokines in response to infection [160].

Other cell wall components have also been identified as important antigens [161]. These differences in cell wall composition may underlie some of the variation in virulence observed by the **Goldberg** lab, who demonstrated differences in cell wall between virulent and avirulent strains [162]. **Domer** also showed that cell wall mannoproteins can stimulate CD8+ T cells and that this may be through IL-12p40, a subunit of IL-23 [163]. **Conti** and **Farah** showed that IL-12p40 knockout mice are highly susceptible to oral candidiasis [127, 164], and recent work from the **LeibundGut-Landmann** lab showed that IL-23 is critical for anti-*Candida* defense [165]. The **Gaffen** and **LeibundGut-Landmann** labs have also spearheaded the analyses of the IL-17 cytokine and T_h17 cells in the response to *Candida*. These T_h17 cells are the major determinant of mucosal adaptive immunity to *C. albicans* infections at oral and vaginal sites [166, 167]. **Zelante** in the **Romani** lab showed that IL-17 may directly bind *C. albicans* to induce autophagy, thus inhibiting its growth and pathogenesis [168].

Analysis of the host has also identified pathways that are important for control of fungal infections. **Devesty** [169]**, Carrow** [170], and more recent works by **Tuite** and **Radovanovic** identified genetic loci underlying differences in susceptibility to candidiasis of different inbred mouse backgrounds [171–173]. **Choi** investigated human loci associated with candidiasis in leukemia patients and identified an association with variants in IL-4 [174]. **Puel** identified many human genetic loci that are associated with susceptibility to candidiasis, with errors in IL-17 immunity resulting in chronic mucocutaneous candidiasis [175–177]. This complements the work from the **Gaffen** lab on IL-17 and immunity to mucosal candidiasis [127, 166]. Additionally, the **Puel** lab identified Card9 deficiencies that are associated with increased *C. albicans* disease [178•]. Altogether, these findings illustrate that both fungal factors and variation in host immune responses play key roles in mediating susceptibility to candidiasis.

An ongoing challenge is the development of a vaccine against fungal infections. **Friedman** performed some of the earliest work on immunization of mice against *C. albicans* and showed some protection when mice were vaccinated with sonicated killed yeast [179]. She also trained **Domer,** whose group investigated immune defenses against *Candida* for many years; their work demonstrated that a combination of antibody, cell-mediated immunity, and innate defenses are required for defense against systemic candidiasis [180–182]. One of the earliest protective antibodies against *C. albicans* was against Hsp90, in work from **Matthews** and colleagues, who used a monoclonal antibody against *Ca*Hsp90 to prophylactically protect against systemic *C. albicans* infection [183]. **Moragues** identified roles for anti-*Candida* mannoprotein antibodies in preventing adherence and filamentation, in addition to direct cidal activity [184]. Excitingly, work from **Uppuluri** and colleagues has shown the efficacy of an anti-Als3p antibody against recurrent vulvovaginal candidiasis [185]. This is the only *C. albicans* vaccine that has undergone phase III clinical trials.

Conclusions

This review represents an opportunity to recognize and celebrate the many contributions to *C. albicans* research made by women who helped establish and shape the field of medical mycology. While exploring primary literature relating to *C. albicans*, we were pleasantly surprised to learn that many foundational aspects of *C. albicans* biology that remain heavily investigated to this day were first described by women. The works collected represent nearly a century of *Candida* research by women. It is our intention for this review to serve as a basic introduction to *C. albicans* while also ensuring that the significant contributions from these women are not overlooked as the field expands upon their work. We have focused on five major topics, but women also helped discover other diverse and important aspects of *C. albicans* biology. For example, **Hull** and **Magee** helped decipher *C. albicans* mating [186, 187], **Slutsky** and **Anderson** in the Soll lab investigated white-opaque switching [188, 189], **Hickman** and **Berman** described the first *C. albicans* haploid strain [190], and **Magee** helped map *C. albicans* chromosomal structure [191]. More recently, women have played important roles in identifying and characterizing the emerging species, *Candida auris*. **Chowdhary**, **Litvintseva,** and **Cuomo** have played key roles in tracking the emergence of this fungus around the globe, sequencing its genome, mapping its patterns of antifungal drug resistance, and tracing its evolutionary origins [192–195••].

While this review focused on the contributions made by women mycologists, we do not want to minimize the instrumental work done by other groups of scientists, including individuals who are part of other underrepresented groups like the Black, Indigenous, People of Color, disabled, or LGBTQ2S+ communities, as well as people in the intersections of these groups. We acknowledge their contributions to the field, which we hope will be the focus of future reviews.

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