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Review Article

Mycology Research in India in the Last Ten Years (2008-2018)

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With the rise in the incidence of fungal infections in India due to the unique environmental and socioeconomic reasons, the research activities on fungal infections and fungi causing human infections have increased manifold. The major areas of clinical research on fungal infections include (i) epidemiology fungal infections, (ii) antifungal resistance detection, surveillance and its mechanism, (iii) molecular diagnosis and pathogenesis, (iv) outbreak investigations, (v) development of management guidelines, and (vi) clinical trials. The basic scientists' research areas include (i) understanding different molecular mechanisms on the evolution of fungi, (ii) computational models that is operating at different cellular levels of pathogenic fungi, (iii) understanding molecular details on the biosynthesis, signalling pathways involved in fungal virulence, (iv) identifying potential new antifungal drug targets, (v) basis of antifungal resistance mechanisms. The major centres in India carrying out advanced research in this field are Department of Medical Microbiology, PGIMER, Chandigarh, which also houses the National Reference Centre and WHO Collaborating Centre; Department of Pulmonary Medicine (PGIMER, Chandigarh), which focusses clinical research on respiratory mycoses; VP Chest Institute (New Delhi), JNCASR (Bengaluru), School of Life Science (JNU, New Delhi), CCMB (Hyderabad), and AIIMS (New Delhi). The two national organizations, Fungal Infection Study Forum (FISF) and Society for Indian Human and Animal Mycology (SIHAM) have conducted multicentric epidemiological studies. The fungal diseases that have been studied in India in the last decade include invasive candidiasis (due to *Candida tropicalis*, *Candida glabrata*, *Candida albicans*, *Candida auris*), mucormycosis (caused by *Rhizopus arrhizus*, *Apophysomyces variabilis*), invasive asperillosis (*A. flavus* and *A. fumigatus*), allergic bronchopulmonary aspergillosis (*A. flavus* and *A. fumigatus*), fungal rhinosinusitis (*A. flavus*), cryptococcosis (*C. neoformans* and *C. gattii*), histoplasmosis, sprorotrichosis, sebrohhoeic dermatitis/dandruff (*Malassezia* sp.), dermatophytosis (*T. mentagrophytes*, *T. rubrum*), mycetoma, fungal keratitis/endophthalmitis, phaeohyphomycosis (*Cladophialophora bantiana*).

Keywords: Mycology; Epidemiology; Candidiasis; Mycosis

Introduction

India has distinct position in the research on medical mycology, as the epidemiology of fungal infection is unique. Fungal infection rate is very high in India due to tropical region, too many patients in the hospital, and compromise in healthcare. Endemicity of certain fungi and emergence new species of fungi causing human infection has raised formidable challenge for researchers in India. The research in this field in India can be grossly classified in three areas, *viz.,* epidemiology research – multiple multicentre studies sponsored by national societies, clinical research from certain medical centres of excellence, and basic mycology research related to human infection by certain non-medical Institutes. The need of mycology research has gained importance as a result of recent developments in the form of societies which provides a common forum for exchange of ideas between researchers that subsequently helps in strengthening this branch of medical research. Two such societies namely Indian Human and Animal Mycologists (SIHAM), and Fungal Infection Study Forum (FISF, a non-profit trust of clinicians) dedicated to clinical research bring active researchers together. Further, various working groups are developed under International Society for Human and Animal Mycology and proposed to conduct research in specific areas like 'Fungal Sinusitis', 'Allergic bronchopulmonary aspergillosis in Asthma', 'Zygomycosis' etc.

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Epidemiological Research

A number of studies have been conducted on epidemiology, treatment and outcome of various fungal infections across India by various organisations.

Invasive Candidiasis

SIHAM conducted a prospective epidemiological study on the ICU acquired candidemia in CU covering 27 ICUs across India. The study highlighted a high burden, early onset after ICU admission, higher risk despite less severe physiology score at admission and a vast spectrum of agents causing candidemia in Indian ICUs with predominance of *C. tropicalis* (Chakrabarti *et al.,* 2015).

Mucormycosis

FISF conducted a Multi-centre (17 Centres) Observational Study on Epidemiology, Treatment, and Outcome of Mucormycosis in India –The study identified high incidence; rhino-orbital-cerebral mucormycosis in uncontrolled diabetics as common presentation. *Rhizopus arrhizus* followed by *Apophhysomyces variabilis* are common species isolated from those patients and *Rhizopus homothallicus* as emerging agent of mucormycosis in India. Due to financial constraints clinicians failed to provide antifungal treatment of choice and nearly 25% patients left the hospital when cost of therapy explained to them (Patel *et al.,* 2018).

Another study, 'A prospective multicentre study on mucormycosis in India: Epidemiology, diagnosis, and treatment' was conducted at four major tertiary care centres of India (two in north and two in south India) during 2013-2015 to compare the epidemiology, treatment strategies and outcome of mucormycosis between the two regions. A total of 388 proven/ probable mucormycosis cases were reported during the study period with overall mortality at 46.7%. Uncontrolled diabetes (n = 172, 56.8%) and trauma (n = 31, 10.2%) were the common risk factors. Overall, *R. arrhizus* (n = 124, 51.9%) was the predominant agent identified, followed by *R. microsporus* (n = 30, 12.6%), *A. variabilis* (n = 22, 9.2%) and *R. homothallicus* (n = 6, 2.5%). While comparing the two regions, majority (82.7%) cases were recorded from north India; uncontrolled diabetes (n = 157, P = .0001) and post-tubercular mucormycosis (n = 21, P = .006) were significantly associated with north Indian cases, and north Indian patients have higher mortality compared to South India *(Prakash et al., 2018).*

Invasive Mould Infections

FISF conducted another study 'Epidemiology and clinical outcomes of invasive mould infections (IMIs) in Indian intensive care units" - The study was conducted over 11 ICUs across India. A total of 398 patients with IMIs (96 proven, 302 probable) were identified over 15-month period, amounting to a prevalence of 9.5 cases/1000 ICU admissions (Chakrabarti *et al.,* 2018). The study highlighted high disease burden, new susceptible patient groups, comparatively younger patients with less morbidity acquire infection early. Though *Aspergillus flavus* and *A. fumigatus* were common mould isolated, considerable number of mucormycosis cases were also identified.

Antifungal Resistance Surveillance

Indian Council of Medical Research initiated Antimicrobial Resistance Surveillance and Research Network (AMRSN) since 2013. The AMRSN currently includes six nodal centres (NCs) that are located in four tertiary care medical institutions and 15 regional centres (RC). For antifungal resistance surveillance, PGIMER, Chandigarh is the nodal center. The NC focuses on the identified resistant organisms, confirm the resistance and preserve all the resistant isolates to build the fungal bank on the resistance fungi. The NC also performs the research to identify the mechanism of resistance in different group of fungi. It also helps in identifying the outbreaks caused by the fungi and provides the logistic support to other centres to control the outbreak and manage the patients. *Candida tropicalis* and *A. flavus* were the most commonly isolated yeast and mould respectively. *Wickerhamomyces anomalous* (13.1%) was recognized as emerging yeast in paediatric patients. Resistance in *C. tropicalis* against fluconazole and caspofungin is a serious concern. Heterogeneous over expression of efflux pumps was noticed in resistant *C. tropicalis* isolates (Paul *et al.,* 2018a; Paul *et al.,* 2015).

Research in Medical Mycology Reference Laboratories

National Mycology Reference Centre at Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh

The only WHO Collaborating Centre on Reference and Research on Fungi of Medical Importance in the world. National Culture Collection of Pathogenic Fungi (NCCPF) is also housed at the same centre. Major activities conducted by the center in the last 10 years are highlighted in specific categories:

Epidemiology

It provided the leadership of multi-centre studies on mucormycosis, candidemia in Indian ICU settings, and invasive mould infections in ICU settings. The centre also conducted epidemiological studies on allergic bronchopulmonary aspergillosis (Agarwal *et al.,* 2013), fungal sinusitis (Chakrabarti *et al.,* 2009), fungal keratitis (Ghosh *et al.,* 2016), *Malassezia* infections (Rudramurthy *et al.,* 2014), mucormycosis (Prakash *et al.,* 2018), candidemia (Chakrabarti *et al.,* 2015), trichosporonosis (Rastogi *et al.,* 2016) and *Cladophialophora* infections (Chakrabarti *et al.,* 2016).

Antifungal Resistance

Candida auris infection and antifungal resistance in various ICUs across India, mutation in squalene epioxidase gene imparting resistance to allylamines in *Trichophyton* spp., Novel mutations responsible for the voriconazole resistance in *Aspergillus flavus*, higher MIC to amphotericin B in *Apophysomyces* species were identified. (Prakash *et al.,* 2016; Paul *et al.,* 2015). MALDI for identification and antifungal drug resistance detection: Studies included expanding the data base on MALDI platform and identification of yeasts, Hyalohyphomycetes, dematiaceous fungi and *Malassezia* species, detection of azole resistance using MALDI-TOF etc, (Paul *et al.,* 2017; Paul *et al.,* 2018b; Honnavar *et al.,* 2018).

Molecular Diagnosis and Pathogenesis

Developed molecular techniques for the diagnosis of *Pneumocystis* pneumonia from respiratory specimen (Ruduramurthy *et al.,* 2018a), *Mucorales* from fresh tissue and formalin fixed paraffin embedded blocks. (Zaman *et al.,* 2017). Also, pathogenesis of fungal sinusitis (Kale *et al.,* 2015), *Malassezia* infections (Honnavar *et al.,* 2017) and mucormycosis were studied.

Clinical Trials

Utility of voriconazole and prednisolone and itraconazole and prednisolone for ABPA patients complicated with asthma (Agarwal *et al.,* 2018a, 2018b).

Outbreaks

Investigation and control of outbreaks such as *C. auris* and *Candida viswanathii*, *Pichia anomala*, *Kodamaea ohmeri* infections, and *Saccharomyces cerevisiae* fungemia after probiotic use etc. Used or standardized molecular typing techniques like AFLP, MLMT, MLST to investigate those outbreaks (Chakrabarti *et al.,* 2014; Roy *et al.,* 2017; Biswal *et al.,* 2017; Shankarnarayan *et al.,* 2018).

Management Guidelines

Participated in European and World guideline initiatives for management of fungal infections due to dematiaceous fungi, and mucormycosis, aspergillosis. Also participated in management guidelines for treating of dermatophytosis in India (Rajagopalan *et al.,* 2018; Ullmann *et al.,* 2018).

Disease Classification

The ISHAM working group on Fungal sinusitis, resolved the confusion that exists in the classification of fungal sinusitis and established the new classification. (Chakrabarti *et al.,* 2009a). Further, the members of 'ABPA complicating asthma' working group of ISHAM, a new diagnosis and staging criteria for ABPA was established (Agarwal *et al.,* 2013).

Basic Research

Characterization of biofilm formed by *Mucorales* (Singh *et al.,* 2011), description of new species of *Malassezia* (Honnavar *et al.,* 2016), stress response in *Mucorales* (Singh *et al.,* 2016), detailed description on phenotypic characterization on *Malassezia japonica* (Honnavar *et al.,* 2015) many rare fungi causing human infection.

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Their primary area of research is allergic bronchopulmonary aspergillosis (ABPA). The group first described their large experience of screening patients with asthma for allergic bronchopulmonary aspergillosis (ABPA) wherein it was demonstrated that the prevalence of *Aspergillus* hypersensitivity and ABPA were substantial (27.2%) in outpatients with bronchial asthma and even higher (38.6%) in patients with severe acute asthma. They have also calculated the burden of allergic aspergillosis at 1.4 million cases in India (Agarwal *et al.,* 2014). They showed that asthmatic patients with *Aspergillus* sensitization but without ABPA also demonstrate poorer control of asthma than those without. They delineated certain markers of poor prognosis associated with the disease such as high-attenuation mucoid impaction and aspergilloma. *Aspergillus* sensitization can complicate the course of other adult airway disorders such as chronic obstructive pulmonary disease, pulmonary tuberculosis related fibro-cavitary diseases and even after bidi consumption. Their work proposed a new radiological classification of ABPA and demonstrated the utility of several of the components of the currently followed diagnostic criteria including peripheral blood eosinophils, total IgE, *A. fumigatus* specific IgE, *A. fumigatus* specific IgG and serum galactomannan. Further, they have proposed a new diagnostic criterion and published the diagnostic performance of the individual components of the criteria (Agarwal *et al.,* 2013) and found an overlap in immune response between allergic bronchopulmonary and chronic pulmonary aspergillosis opening new avenues of research. Regarding management, they showed the futility of inhaled steroids in ABPA, evaluated the efficacy of two different glucocorticoid doses in ABPA (Agarwal *et al.,* 2016) and the effectiveness of nebulized amphotericin B in patients with ABPA who experience recurrent exacerbations. Recently, in two different RCTs, they have also shown that the antifungal triazoles including itraconazole (Agarwal *et al.,* 2018b) and voriconazole are also effective as monotherapy in the management of treatment-naïve ABPA (Agarwal *et al.,* 2018a). In another RCT, the group found the lack of benefit of adjunctive vitamin D therapy in ABPA.

VP Chest Institute, New Delhi

It is recognized as a National Reference Centre for Respiratory Mycoses - the major contribution of the centre is in the field of cryptococcosis, endemic mycoses of the country and allergic respiratory fungal diseases. The centre worked on the ecology of cryptococcosis and different molecular types of *Cryptococcus*, and prevalence of azole resistant *Aspergillus fumigatus*. Their laboratory has generated comprehensive data on molecular types and antifungal susceptibility profiles of indigenous fungal isolates such as *C. neoformans*, *C. gattii*, *Aspergillus* spp., *Schizophyllum commune* and *Mucorales*. The centre also has identified multi-azole resistant clinical isolates of *A. fumigatus* in India and new clonal strains of multi-drug resistant *Candida auris* in India. (Chowdhary *et al.,* 2011; Chowdhary *et al.,* 2014; Chowdhary *et al.,* 2015; Chowdhary *et al.,* 2017; Chowdhary *et al.,* 2018; Sharma *et al.,* 2018).

All India Institute of Medical Science, New Delhi

The centre studied the epidemiology of candidemia, azole resistant *A. fumigatus*, and molecular identification and resistance with *Trichophyton* species (Dabas *et al.,* 2017; Dabas *et al.,* 2018)

Research in Specific Areas

Candida auris

Candida auris has emerged as a challenge in diagnosis, and therapy. ICU based observational study showed the prevalence of *C. auris* was 5.3% (74 out of 1400 patients) in India (Chakrabarti et al., 2015). In case-control analysis, the infection is found to be common in those patients staying long time in ICU and have multiple interventions especially in public-sector hospitals. The resistance to fluconazole has rose to 90%, voriconazole 50%, polyenes 15-30%. Multidrug resistance was noted in 16.2% isolates. To control the spread of *C. auris* in Indian hospitals chlorhexidine washing of patients and decontamination of environmental surfaces with stabilized hydrogen peroxide disinfectant were found to be useful. The frequently used disinfectants in hospital and current hand hygiene practices were efficient against *C. auris* if proper contact time and procedures were followed. Evaluation of possible persistence of *C. auris* on dry fabrics showed that they can persist

for up to seven days. (Rudramurthy *et al.,* 2017; Biswal *et al.* 2017).

Candida tropicalis

In India, many studies have reported an increase in C. *tropicalis* blood stream infections (Chakrabarti *et al.,* 2009b; Kothari *et al.,* 2009; Kothavade *et al.,* 2010; Chakrabarti *et al.,* 2015). The reason of such high prevalence of *C. tropicalis* in India is still unknown. Certain reports from western countries and few Asian countries have suggested that the extensive use of antifungal drugs can cause higher prevalence of *C. tropicalis*.

Apophysomyces variabilis

A maiden attempt was made to sequence and analyze the genomic structure of *A. variabilis*, the *Mucorales* species commonly isolated in India. The total size of genome assembly of *A. variabilis* was 39.38 Mb with 12,764 protein-coding genes. The transposable elements (TEs) were low in *Apophysomyces* genome and the retrotransposon Ty3-gypsy was the common TE. Phylogenetically, *Apophysomyces* species were grouped closely with *Phycomyces blakesleeanus*. OrthoMCL analysis revealed 3025 orthologues proteins, which were common in those three pathogenic *Apophysomyces* species. Expansion of multiple gene families/duplication was observed in *Apophysomyces* genomes. Approximately 6% of *Apophysomyces* genes were predicted to be associated with virulence on PHIbase analysis. The virulence determinants included the protein families of CotH proteins (invasins), proteases, iron utilization pathways, siderophores and signal transduction pathways. Serine proteases were the major group of proteases found in all *Apophysomyces* genomes. The carbohydrate active enzymes (CAZymes) constitute the majority of the secretory proteins. The presence of unique CAZymes in cell wall might be exploited in future for antifungal drug development. (Prakash *et al.,* 2017).

Dermatophytes

A changing pattern in infections due to dermatophytes with increasing treatment failures and the emergence of recalcitrant dermatophytosis in India has been seen. Resistance was rarely reported to allylamines and azoles antifungals. From PGIMER, Chandigarh reported for the first time the increase in allylamine and azole resistance and mutation in squalene epoxidase gene responsible for allylamine resistance from the *T. interdigitale* and *T. rubrum* isolated from relapse/ recurrent cases. A T1189C mutation was observed in *T. interdigitale* and *T. rubrum* isolates that exhibited high MIC's to allylamines (Rudramurthy *et al.,* 2018b).ÿþ Later other study from India reported similar findings (Singh *et al.,* 2018).

Malassezia Infection

Studies related to pityriasis versicolor (PV), seborrheic dermatitis/dandruff (SD/D), psoriasis (PS) and atopic dermatitis (AD) have focused mainly on *Malassezia* species. In India, Rudramurthy *et al.* showed *M. restricta* and *M. globosa* as the most prevalent species among dandruff patients. (Rudramurthy *et al.,* 2014a). A new species, *M. arunalokei* was isolated from patients with either mild or moderate SD/D and from healthy controls (Honnavar *et al.,* 2016). In pityriasis versicolor, *M. globosa* is the most frequently isolated species (Kaur *et al.,* 2013). Rudramurthy et al. reported that no strong association of *Malassezia* species was formed with psoriatic lesion in general; the fungi may play a role in exacerbation of scalp psoriasis (Rudramurthy *et al.,* 2014b). In pathogenesis of *Malassezia* infection, Honnavar *et al.* found that the phospholipase activity significantly increased after exposure to *â*-endorphin (in isolates from patients; *M. globosa, M. restricta*), which did not occur in isolates from healthy controls (Honnavar *et al.,* 2017).

Mycetoma

A study reveals that mycetoma is endemic in western Rajasthan, and the maximum density of mycetoma has been recorded at Jodhpur, northwest Rajasthan. *Maduromycotic mycetoma* is more frequently encountered at western Rajasthan than is actinomycotic mycetoma as compared to the southeastern parts of Rajasthan. However, the incidence of actinomycotic mycetoma has increased during the last five years, probably due to increased irrigation by Rajasthan Canal, changing pattern of rainfall, urbanization of villages, and modification in agriculture, all of which has converted desert climate to humid climate. (Bakshi *et al.,* 2008).

Sporotrichosis

Studies have been done to elucidate the epidemiology of sporotrichosis in the sub –Himalayan region. A steady rise in number of cases was seen. Seasonal trends showed most cases in between March- April (Verma *et al.,* 2012). Cases are also now reported from non-Himalayan belt where the index of suspicion is low e.g.: Mysore and North Karnataka in South India. (Suchitha *et al.,* 2008).

Histoplasmosis

A rise in the cases of histoplasmosis has been noted after the advent of HIV infection. In the setting of disseminated disease, oral lesions are present in 30-50% of the patients and may occur in almost every part of the oral mucosa. The most common sites are the tongue, palate and buccal mucosa. In some cases, oral lesions appear to be the primary or only manifestation of the disease. (Bhagwat *et al.,* 2009; Koley *et al.,* 2014).

Fungal keratitis

The spectrum of fugal keratitis has been evaluated in many recent Indian studies. Of the 23,897 corneal ulcer patients who had their corneal smear examined during this period, a fungal pathogen organism was identified in 34.3%, a bacterial organism in 24.7% and no organism in 38.3%. (Vengayil *et al.* 2009; Chidambaram *et al.,* 2016; Ghosh AK *et al.,* 2016; Prajna *et al.,* 2017).

Allergic Bronchopulmonary Aspergillosis (ABPA) Complicating Asthma

This working group formed under ISHAM studied, epidemiology, genetic susceptibility factors, diagnosis, and treatment.

Basic Research in Mycology from Various Centres

Jawaharlal National Center for Advanced Scientific Research (JNCASR), Bengaluru

The group under the leadership of Dr. Kaustuv Sanyal working in fungal infections helped in understanding the mechanism of chromsosome segregation, kinetochore assembly, and centromere evolution in two classes of pathogenic fungi that cause majority of deaths of immunocompromised patients by fungal infections. These major discoveries led to the foundation of quick and accurate identification of species from the patient samples, and identification of targets for developing antifungal drugs:

- Identification of centromeres in a related strain of *Candida albicans*, *Candida dubliniensis* that revealed centromeres of these two species are most rapidly diverging DNA sequence in their genomes (Padmanabhan *et al.,* 2008). Unique centromere DNA sequences can be used as a target to identify these two species (Sanyal *et al.,* US patent 2016).
- Kinetochore assembly in *C. albicans* is unique as unlike other known yeast species, an interdependent circuitry of proteins stabilizes the centromeric chromatin and the kinetochore integrity in *C. albicans* (Roy *et al.,* 2011; Thakur and Sanyal, 2011; Thakur and Sanyal, 2012).
- Centromere assembly in unique DNA sequence of *C. albicans* on each chromosome is epigenetically regulated. These epigenetic factors include the spatial location of the centromere on the chromosome as revealed by mapping the neocentromere loci (Thakur and Sanyal, 2013) and the interplay between the replication origin, replication-repair proteins and the kinetochore assembly. The replication forks originating from the centromere-adjacent origins stall at the kinetochore that activates Rad51 and Rad52, which in turn bring centromeric histone to recruit at the centromere in a DNA sequence independent manner (Mitra *et al.,* 2014).
- A rapid transition of centromere structure and function occurred in a closely related *Candida* species, *C. tropicalis*. Unlike *C. albicans* and *C. dubliniensis*, centromeres in *C. tropicalis* are repeat associated and share a high degree of sequence conservation (Chatterjee *et al.,* 2016).
- *C. neoformans* cells undergo semi-open mitosis as opposed to closed mitosis in other budding yeasts, the nuclear division takes place in the daughter cell as opposed to the mother cell and the kinetochore assembly is step-wise but not interdependent as in *C. albicans* (Kozubowski

et al., 2013). The RNAi-proficient *Cryptococcus* species maintain full length retrotransposons at the centromeres which are longer than those of the RNAi-deficient species that lost all full-length retrotransposons at the centromere. This has been further evidenced by an experimental evolution experiment using a RNAi-mutant of the RNAi-proficient species (Yadav *et al.,* 2018).

- A computational model has been developed to simulate the process of chromosome segregation in *Candida* and *Cryptococcus* species to identify the factors that are responsible for the difference observed in the process in these two organisms. This led to identification of two determinants: a) number of cytoplasmic microtubules and b) the concentration of dynein motor proteins (Sutradhar *et al.,* 2015).

School of Life Sciences, JNU, New Delhi

One of the most important aspect deals with understanding the molecular details of glycosyl-phosphatidylinositol (GPI) anchor biosynthesis in the human pathogenic fungus, *C. albicans*. It was showed that the enzyme complex, involved in the first step of GPI anchor biosynthesis in *C. albicans* is mutually co-regulated with ergosterol biosynthesis in the organism and is closely linked to Ras signalling/hyphal morphogenesis. While controlling hyphal morphogenesis is seen as a key step towards controlling virulence in this pathogen, ergosterol and the sterol biosynthetic pathway are the most important current targets for therapeutic intervention in controlling *Candida* infections. The enzyme involved in the de-*N*-acetylation of GlcNAc-PI (the second step of the pathway) was studies and showed that the *C. albicans* homologue shows metal-dependent activity in cell-free systems unlike the *E. histolytica* de-*N*-acetylase which exhibits a unique metal-independent general acid-base pair catalytic mechanism. (Yadav *et al.,* 2014; Komath *et al.,* 2018; Jain *et al.,* 2018).

Another aspects focusses on cellular homeostasis and chromatin regulation of *Candida albicans* virulence which led to the discovery of two novel genes- a critical transcription factor and a key transcriptional coregulator that control stress responses and survival in *C. albicans*. The transcription factor *CAP2/HAP43* gene is essential for survival under poor iron environments and functions as a dual regulator of iron homeostasis (Singh *et al.,* 2011; Srivastav *et al.,* 2018). Deletion of *CAP2* impaired virulence in a mouse model of *C. albicans* virulence. It was recently identified that the transcriptional coregulator TAF12L is a subunit of the SAGA complex, a multifunctional chromatin modifying complex (Sinha *et al.,* 2017). TAF12L is required for oxidative stress response and cell survival, iron starvation response and deletion led to aberrant filamentation and also abrogated virulence in a mouse infection model of *C. albicans* virulence. (Singh *et al.,* 2011; Sinha *et al.,* 2017; Srivastav *et al.,* 2018).

Further, research led by Panwar and coworkers focuses on identifying potential drug targets for the development of new antifungals for treating *Candida* infections. In this context, various roles of mitochondria in this pathogenic fungus were deciphered and reported that mitochondria are indispensable for *C. albicans* and it not only affects drug susceptibility but also serves as a control point for virulence. Altering mitochondrial functions renders this pathogen avirulent in a mouse model of candidiasis. Additionally, the role of 7-transmembrane receptor proteins (regulatory proteins) such as Rta2 and Rta3 in ER stress resistance and biofilm formation in this pathogenic fungus, respectively were identified. Interestingly, Rta3 affects biofilm development in *C. albicans* by perturbing the asymmetric distribution of phosphatidylcholine across the plasma membrane thereby forging a link between membrane biogenesis and biofilm formation. These 7-transmembrane receptor proteins are exclusively present in the fungal kingdom and thus may have therapeutic implications. (Thomas *et al.,* 2013; Thomas *et al.,* 2015; Srivastava *et al.,* 2017).

Center for Cellular and Molecular Biology, Hyderabad

Research group here led by Kaur and co-workers is focused on delineating the virulence and antifungal drug resistance mechanisms in the pathogenic yeast *Candida glabrata*. Through large-scale mutant screens, they have identified many novel antifungal targets as well as factors that act synergistically with azole antifungals (Borah *et al.,* 2011; Bhakt *et al.,* 2018). Recently, work with clinical isolates have

shown that the actin network polymerization inhibition partially reverses the drug resistance in azole-resistant isolates of *C. glabrata* (Bhakt *et al*., 2018). Additionally, an in-depth characterization of interaction of *C. glabrata* with macrophages was carried out and it was found that *C. glabrata* is able to replicate intracellularly, prevent acidification of the phagolysosome and suppress production of the pro-inflammatory cytokine IL-1b (Rai *et al.,* 2012). Using the THP-1 macrophage culture model, through the signature-tagged mutagenesis approach, phosphoinositide 3-kinase and chromatin remodelers as pivotal determinants of intracellular survival and proliferation were identified (Rasheed *et al.,* 2018). Currently, the research group is focussing on identification of yeast and mammalian substrates for cell surface-associated aspartyl proteases (Yapsins), that are essential for intracellular survival and virulence of *C. glabrata* (Rasheed *et al.,* 2018). The research over last one decade has implicated CgYapsins in many patho-biological processes including intracellular pH and vacuole homeostasis, cell wall organization and activation of macrophages, and the group, currently, is engaged in establishing epithelial, endothelial and neutrophil culture model systems to study the role of aspartyl proteases in fungal virulence (Rai *et al.,* 2015).

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