International Journal of Pathogen Research

Volume 14, Issue 6, Page 37-48, 2025; Article no.IJPR.146436
ISSN: 2582-3876

Fungal Infections, Immunity and Diagnosis

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/ijpr/2025/v14i6408

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://pr.sdiarticle5.com/review-history/146436

Review Article

Received: 02/08/2025
Published: 27/10/2025

ABSTRACT

Fungal infections (mycosis) have emerged as significant global health concerns, particularly among immunocompromised individuals. This comprehensive review examines the intricate interplay between fungal pathogens and host immunity, emphasizing the crucial roles of both innate and adaptive immune responses. The innate immune system serves as the first line of defense, utilizing physical barriers, pattern recognition receptors, phagocytic cells, the complement system, and cytokines to detect and control fungal pathogens. Dendritic cells play a pivotal role in bridging innate and adaptive immunity by presenting fungal antigens to T cells, guiding specific immune responses. Through the coordinated actions of T helper cells, cytotoxic T cells, B cells, and antibodies, the adaptive immune system offers targeted and long-lasting protection against fungal infections. Despite these robust defense mechanisms, many fungi have evolved sophisticated evasion strategies that complicate immune responses and therapeutic interventions. Advances in diagnostic technologies, including PCR, immunodiagnostic assays, and AI-algorithm have significantly enhanced the early detection and management of fungal infections. Understanding the complex host-fungal interactions and leveraging recent diagnostic innovations are essential for improving outcomes in patients at risk of fungal

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***Cite as:** Marwan Y. Al-Maqtoofi, and Alaa A. Al-Rifaie. 2025. "Fungal Infections, Immunity and Diagnosis". International Journal of Pathogen Research 14 (6):37–48. https://doi.org/10.9734/ijpr/2025/v14i6408.*

diseases. This review highlights the need for ongoing research to develop more effective vaccines, immunotherapies, and diagnostic tools in combating the increasing burden of fungal infections.

Keywords: Adaptive immunity; fungi; immunity; innate immunity; pathogen.

1. INTRODUCTION

Fungi are special microorganisms classified in a separate kingdom. These microorganisms are ubiquitous and eukaryotic by having a membrane surrounding their nucleus, which makes them different and larger than bacterial cells (de Pauw, 2011). Generally, these fungi live as saprophytes as a part of the terrestrial ecosystems by consuming decaying organic materials to participate in recycling nutrients and soil health (Crowther et al., 2012). In addition, fungi play a pivotal role in plant growth promotion, such as endophytic fungi, which participate directly in enhancing agricultural sustainability (Al-Rifaie & Al-Maqtoofi, 2025). Meanwhile, these fungi can be opportunistic fungal pathogens for both plants and humans. Pathogenic fungi are a diverse group of eukaryotic microorganisms capable of causing many types of infections in humans, generally known as mycoses (Angiolella, 2022). These infections can be superficial infections and localized in the skin or nails, and mucous membranes, or can be disseminated diseases in internal organs, causing life-threatening infections. Some of these fungi are supported with critical virulence factors that enable fungal cells to successfully invade, adhere, and colonize for causing infections particularly in susceptible hosts. These factors include the adaptation to human body temperature, dimorphism by switching between yeast and filamentous forms, biofilm formation for increasing drug resistance, mycotoxin production and evading immune defenses (Hernández-Chávez et al., 2017). Collectively, the virulence factors of fungi enhance fungal survival, promoting growth and increasing tissue damage (Casadevall, 2007).

Fungal infections are responsible for over 1.7 million deaths per year globally, almost one-third of the human population, roughly 200,000 more deaths than the bacterial disease tuberculosis, malaria, and breast cancer (Kainz et al., 2020). Fungi are ubiquitous organisms in diverse environmental niches, including soil, air, plants, and water.

The pathogenic fungi are unknown as hidden killers, because they can invade and cause systemic and disseminated infections (Rokas, 2022). For this reason, they are highlighted as a rising threat to human health (Denning, 2024). Interestingly, among the estimation of 5.1 million fungal species, approximately 300 species are responsible for human fungal infections, which are related to four common genera, including *Aspergillus*, *Candida*, *Cryptococcus*, and *Pneumocystis* (Mendonça et al., 2022).

Studies showed that climate change is associated with the rapid rise trend in fungal infections, which leads to an enhancement in the virulence activity of the pathogens (Seidel et al., 2024). For example, temperature increases of the Earth's surface evoke fungal pathogens to quickly adapt to higher temperatures and boost their virulence ability to support their growth and expansion (Nnadi & Carter, 2021). The actual example of this case is *Candida auris,* which has become more tolerant to human temperature, making this fungus a source of human mycosis (Garcia-Bustos et al., 2023).

Antifungal drugs are essential agents for treating fungal infections. There are five main classes of antifungal agents used medically, including azoles, polyenes, echinocandins, allylamines, and pyrimidine analogs (Vanreppelen et al., 2023). These antifungal drugs have different modes of action against fungal propagules with a wide range of effectiveness against yeast pathogens such as *Candida* spp. and other filamentous fungal pathogens. For example, azole antifungal agents such as fluconazole, itraconazole, and ketoconazole are involved in sterol 14α-demethylase inhibition that leads to ergosterol inhibition, which results in loss of fungal cell membrane function and structure (Teixeira et al., 2022). Polyene groups such as amphotericin B and nystatin make pores within the fungal cell membrane due to interaction with sterols, leading to the leakage of cytoplasmic components from the inside to the outside and then cell death (Carolus et al., 2020). Caspofungin, micafungin, anidulafungin, and rezafungin are semisynthetic cyclic lipopeptides, they belong to echinocandins. These antifungals inhibit fungal cell wall formation via inhibiting β-(1,3)-d-glucan synthesis (Szymański et al., 2022). Allylamine drugs such as terbinafine are able to inhibit squalene epoxidase that converts squalene to lanosterol (Hammoudi Halat et al., 2022). 5-fluorocytosine (5-FC) is a typical example of a pyrimidine analogue that interferes with fungal nucleic acid, which includes deoxyribonucleic acid (DNA) and Ribonucleic acid (RNA), replication, and protein synthesis (Billmyre et al., 2020).

Although the vast majority of fungal species are non-pathogenic to humans, a small proportion have evolved mechanisms that enable them to invade and cause disease in susceptible hosts. These diseases, collectively known as mycosis, range from mild superficial infections to severe invasive and systemic illnesses (Seagle et al., 2021). Over the past several decades, there has been a significant increase in the incidence of fungal infections worldwide, primarily driven by the growing population of immunocompromised individuals. Patients with compromised immune systems, whether due to HIV/AIDS, malignancies, organ or hematopoietic stem cell transplantation, immunosuppressive therapies, or autoimmune diseases, are particularly vulnerable to fungal pathogens (Li et al., 2025). The increased use of broad-spectrum antibiotics, corticosteroids, cytotoxic chemotherapy, and biologic immunomodulators has further exacerbated this susceptibility by disrupting normal microbial flora and impairing host immune responses (Airola et al., 2024).

Despite the progress in antifungal treatments, invasive fungal infections remain a cause of high morbidity and mortality due to the lack of accurate and rapid diagnosis. The nonspecific symptoms of fungal infections mimic those of other microbial infections, such as bacterial or viral infections, making this infection seriously challenging. In addition to the time-consuming nature of conventional diagnostic methods, such as culture and microscopy, which require experience and may lack accuracy, particularly during early disease stages of infections. Diseases such as disseminated candidiasis, aspergillosis, cryptococcosis, and mucormycosis require a combination of accurate and rapid laboratory diagnostic tests. To control invasive fungal infections, determine prompt treatment, reduce the rate of morbidity and mortality, and develop fast and sensitive diagnostic techniques is required.

Fungal infections have become a rising concern during the last few years, particularly during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic that caused Coronavirus disease (COVID-19) that emerged in December 2019 in Wuhan city, China (Ashraf et al., 2024). Since this pandemic, scientists have highlighted the risk of invasive fungal infections among infected COVID-19 patients. These co-infections were reported worldwide by researchers, indicating the increasing trend of co-infections in patients with COVID-19 (Baddley et al., 2021). The COVID-19-associated invasive fungal infections have pointed out the concerns about the burden of this infection during a time of missing transportation, difficulties in diagnosing, and isolation. During the COVID-19 pandemic, the only focus was on identifying infected individuals with the virus rather than other microbial infections, such as fungal infections (Jafari et al., 2025). SARS-CoV-2 affects the respiratory tract and usually leads to acute respiratory distress syndrome due to elevated pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, IL-17, and tumor necrosis factor-alpha (TNF-α) levels, which mainly cause cytokine storm (Montazersaheb et al., 2022). Cytokine storm significantly causes severe damage in the epithelium of the lung. For this reason, suppressing the inflammatory response would be a potential strategy to reduce death or severe conditions of viral infections (Riyaz Tramboo et al., 2024). Briefly, the mechanism for damaging alveolar epithelial illustrated by binding SARS-CoV-2 to angiotensin-converting enzyme 2 (ACE2) receptors to facilitate direct viral invasion, resulting in alveolar damage, and necrosis (Erickson et al., 2023). The necrotic tissue provides an ideal condition for invasive fungal propagules and spore germination for biofilm forming of *Aspergillus* and *Mucorales* (Hoenigl et al., 2022). Furthermore, during the immune response suppression status, there is a high chance of fungal spore invasion of the respiratory system, resulting in serious invasive fungal infections (Heung et al., 2023). Many fungal pathogens are associated with co-infections in COVID-19 patients.

COVID-19 COVID-19-associated pulmonary Aspergillosis (CAPA) is emerging as a significant cause of mortality in infected patients residence in intensive care units at hospitals and having mechanical ventilation (Nguyen et al., 2025). The immune system of patients with COVID-19 undergoes immune dysregulation due to the viral infections, leading to suppressed macrophage and neutrophil function, the main innate phagocytic cells, and impairing the role of innate and T-cell-mediated immunity, resulting in *Aspergillus* spores germinating and fungal invasion (Wang et al., 2025).

Candida species were reported in COVID-19 patients due to contamination of mechanical ventilation tools, leading to a greater risk of developing secondary candidemia (Valencia-Ledezma et al., 2025). *Candida* infections, such as candidemia, have emerged as a significant source of mortality in hospitalized COVID-19 patients. These fungal co-infections rise due to the severe COVID-19 infection, which includes causes immune dysregulation, which impairs the host's antifungal immune defense. In addition, a high dose of corticosteroids is needed to control severe symptoms of COVID-19 infections and immunomodulators such as tocilizumab (Burger et al., 2023). Moreover, providing central venous catheters for COVID-19 patients breaches the natural mechanical barrier, such as the skin, which allows *Candida* species to proliferate (Kayaaslan et al., 2022). During these complicated health conditions, multidrug-resistant *Candida* species such as *C. auris* have emerged and caused difficult-to-control outbreaks in intensive care units (Tsai et al., 2022).

Rhizopus spp., *Mucor* spp., and *Rhizomucor* spp. are the most common species that belong to the order *Mucorales*, thesubphylum *Mucoromycotina* (Pham et al., 2023). These species are well-known during the COVID-19 pandemic for causing angioinvasive fungal infection called mucormycosis or black fungus (Pham et al., 2023). These species are opportunistic pathogens that take advantage of immune dysregulation and suppression during infections with SARS-CoV-2 to cause mucormycosis (Chillana & Chilana, 2022).

The immune system contains a complex network of physical, chemical, and cellular barriers that help adaptive immunity for effective fungal pathogens (R. Wang et al., 2024). Neutrophil is one of the professional phagocytic cells and is considered the first cell involved in antifungal immune response for this reason, deficiency in neutrophil function increases fungal invasion and dissemination (Blaize et al., 2024).

This review highlights the role of the immune system response to fungal infections and the recent diagnostic techniques that may be involved in enhancing early detection and management.

2. INNATE IMMUNE RESPONSE TO FUNGAL INFECTIONS

The innate immunity is a rapid and nonspecific response against microbial infections. The innate immune system has barriers, physical, chemical, and cellular barriers, that work collectively to prevent fungal invasion. The mucosal immune system, including antimicrobial peptides, secretory immunoglobulin such as sIgA, and the complement system, is associated with the cellular barrier of the innate immune system, such as macrophages, dendritic cells, and neutrophils, professional phagocytic cells, to control and eliminate fungal elements (Zhou et al., 2025). The skin contains multilayers of tissues, including the epidermis, dermis, cutaneous appendages and subcutaneous tissue. The skin is a part of skin-associated lymphoid tissue (SALT), which comprises both skin cells and professional immune cells (Quaresma, 2019). Around 90% of the epidermis contains keratinocytes, which are able to distinguish between microbiota and microbial pathogens through expression of a class of pattern recognition receptors (PRRs), which are surface toll-like receptors (TLRs), especially TLR2 and TLR4, for detection of pathogens associated molecular patterns (PAMPs) (Fang et al., 2022). In addition to more specific receptors such as NOD-like receptors (NLRs), RIG-I-like receptors (RLRs), and C-type lectin receptors (CLRs) including Dectin-1 and Dectin-2 for the detection of fungal antigens like ß-glucans and mannose (Patin et al., 2019). Detection of fungal antigens by these receptors results in the production of proinflammatory cytokines by activating the NF-κB signaling pathway to produce IL-6, TNF, and IL-8 (Li et al., 2012). Following the recognition step, cytokines and chemokines are released to attract phagocytic cells and initiate an inflammatory response (Hatinguais et al., 2020). Tracking neutrophils (polymorphonuclear leukocytes)**,** macrophages, and dendritic cells (DCs) directly to the site of infection enhances fungal elements clearance via phagocytosis and generates reactive oxygen species (ROS). Releasing neutrophil extracellular traps (NETs), and secreting AMPs effectively kill fungal pathogens (Zhong et al., 2022).

The antimicrobial extracellular traps by neutrophils were first discovered against bacterial cells in 2004 and were then recognized as an effective mechanism for bacterial elimination (Baz et al., 2024). The extracellular traps are released from activated neutrophils.

The NETs contain histones, highly depolymerized chromatin (Wang et al., 2024), myeloperoxidase, and neutrophil elastase (Burn et al., 2025), in addition to antimicrobial peptides such as calprotectin, cathelicidins, and defensin that have microbicidal activity (Biswas et al., 2023). Recently, studies showed that NETs have fungicidal effects against fungal pathogens such as *Candida* spp. and *Aspergillus* spp. (Liang et al., 2022).

A larger population of innate immune cells, such as macrophages, DCs, NKs, and mast cells, in addition to specialized adaptive immune cells such as $CD4^+$ T-cells, lymphocytes γδ T-cells, are localized within the dermis layer (Moyes et al., 2021). For this reason, the skin is the first mechanical barrier to prevent fungal infections. Additionally, antimicrobial peptides (AMPs) exhibit broad-spectrum antimicrobial function that plays an essential role in fungal protection in the human organs, like the skin, respiratory tract, digestive system, and bodily fluids such as mucus, saliva, tears, and breast milk (Abdul-Kareem et al., 2023; Burgess et al., 2022).

DCs have a critical role in evoking the adaptive immunity by capturing fungal antigens and presenting them to naïve T cells in secondary lymphoid tissues (Kulkarni & Nanjappa, 2025). Recent studies showed that monocytes and natural killer (NK) cells can train immunity after exposure to fungal β-glucans (Quintin, 2019).

3. FUNGAL ANTIGEN PRESENTATION AND ADAPTIVE IMMUNITY

Managing fungal antigen detection requires coordinating the host's innate and adaptive immune response to eradicate the pathogen and initiate immunological memory. DCs through their PRRs and antigen presentation to antigen-specific T and B cells link both innate and adaptive immune response through upregulation of co-stimulatory molecules interaction (CD80, CD86 and CD40) and major histocompatibility complex (MHC) molecules class II between DCs and naïve $CD4^+$ T-cells (Fig. 1) (Goughenour et al., 2023). $CD4^+$ T-cells significantly activate host immunity by inducing innate inflammatory immune responses and mediating fungicidal activity. Surface and intracellular PRRs help DCs to recognize fungal antigens such as β-glucans and mannose. Activated $CD4^+$ T-cells lead to differentiation into a T-helper (Th) subset of Th1, Th2, Th17, and Treg (regulatory T cell) (Lee, 2023). Each of these cells are characterized by specific cytokines production, Th1 cells release interferon-γ (IFN-γ), that play a key role in host defense against intracellular pathogens, Th2 cells are characterized by the production of IL-4, and Th17 cells release unique series of cytokine such as IL-17 family, IL-21, and IL-22 that have a

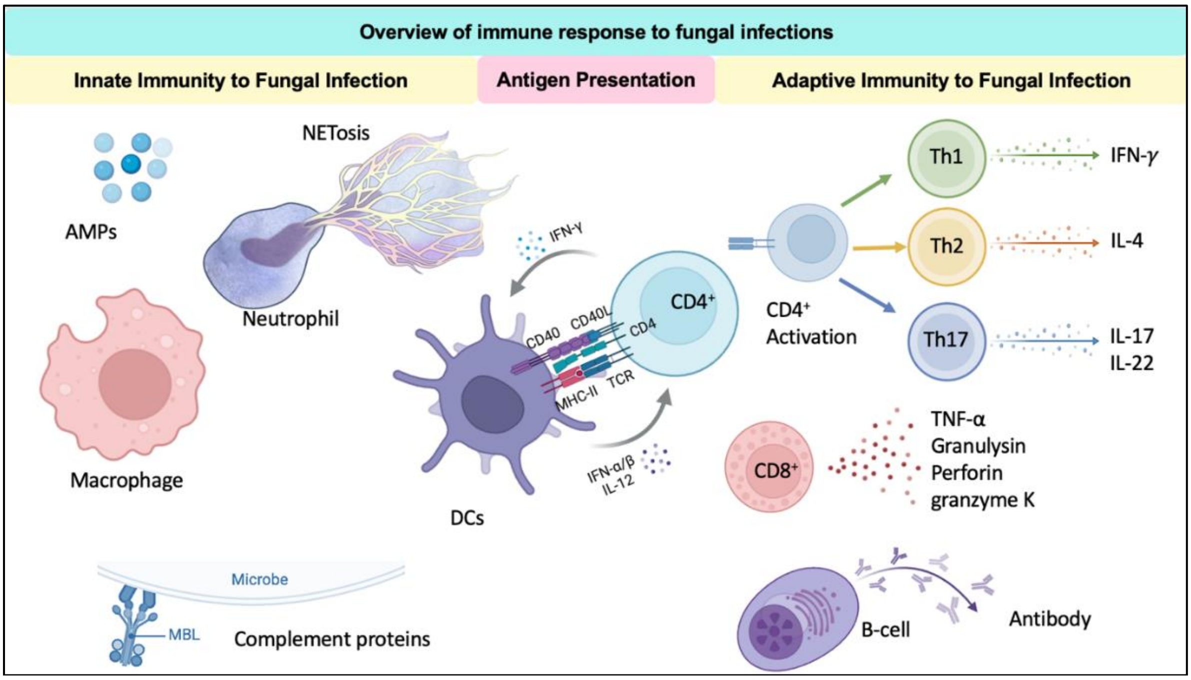

Fig. 1. An overview of the host immune response against fungal infection

crucial task in fungal infections (Aziz et al., 2023; Davidson et al., 2022). $CD8^+$ T cells may participate in fungal clearance through cross-presented via MHC class I molecules (Cruz et al., 2023). Recently, $CD8^+$ T cells were reported to differentiate into Tc1, Tc2 and Tc17 cells upon recognition of fungal peptides presented by antigen-presenting cells (Koh et al., 2023). Tc1 cells involve directly killing of fungal-infected host cells by producing cytotoxic factors such as granulysin, perforin, and granzyme K. To activate antifungal immunity via phagocytic cells, Tc1 produce abundant tumor necrosis factor-α (TNF-α) and interferon-γ (INF-γ) (Sharma et al., 2022).

4. FUNGAL INFECTIONS BETWEEN PUBLIC AWARENESS AND EDUCATION

The awareness about the serious threat from fungal infections to human health is relatively under level globally may lead to delays or misdiagnosis of cases and inadequate treatment. This case facilitates disease transmission and may result in a fungal infection outbreak (Benedict et al., 2020). For this reason, raising awareness through promoting education and improving the diagnosis of fungal infections is a critical factor for effectively preventing severe disease.

5. RECENT ADVANCES IN FUNGAL DIAGNOSIS

Maximizing survival against fungal infections requires rapid and accurate diagnosis and therapeutic strategies. The non-specific clinical symptoms of invasive fungal infections remain a serious challenge regarding clinical diagnosis. For this reason, physicians focus on bacterial or viral infections. The misdiagnosis leads to inaccurate treatment and wasting time and money. Ultimately, the value of human life and health will be at risk of developing disseminated infections. For this reason, there is a need for urgent, accurate, and rapid fungal diagnosis. The molecular techniques using polymerase chain reaction (PCR), a highly sensitive and specific technique diagnosis of invasive fungal disease (Fig. 2). The universal fungal primers are widely used as a broad-range PCR to amplify the primary multi-copy region of the rRNA gene, which is called the internal transcribed spacers 1 and 2 (ITS1 and ITS2) or the D1/D2 regions of the 28S rRNA gene) (Raja et al., 2017). For more specific identification of fungi at species or species complex level, secondary barcoding using specific species primers for protein-coding markers are applied such as RNA polymerase II largest (RPB1), second largest subunit (RPB2) (O'Donnell et al., 2013), translation elongation factor 1-alpha (tef1) (Al-Maqtoofi & Thornton, 2016), and beta-tubulin (tub2) (H. Wang et al., 2019). However, this technique is not yet widely implemented due to concerns regarding limited standardization between assays (Brown et al., 2025).

Immunodiagnostic assays, such as complement fixation and immunodiffusion, to enzyme immunoassays are vital due to their high

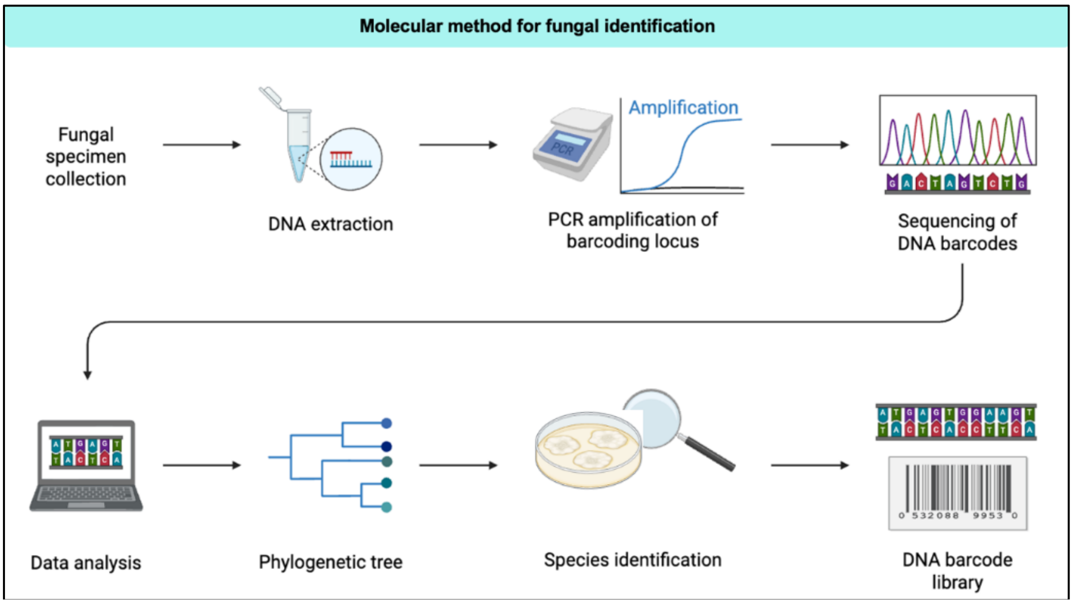

Fig. 2. Molecular technique for diagnosis fungal pathogens. image was created by bioRender

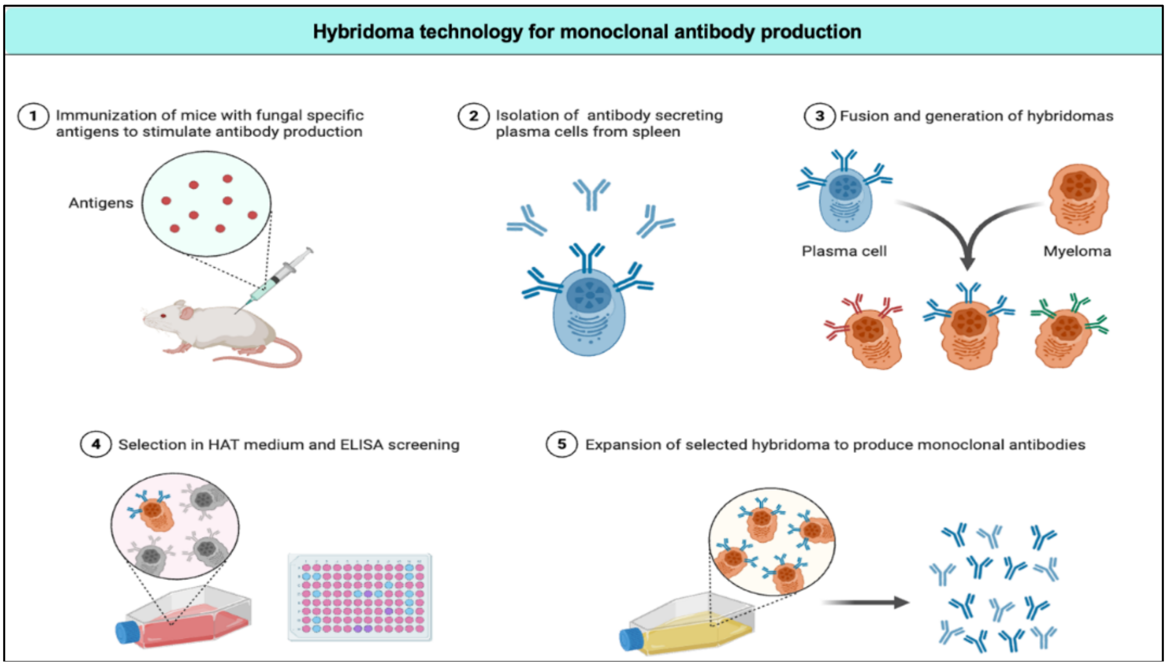

Fig. 3. Developing monoclonal antibody specific for fungal antigen using hybridoma technology. Image was created by bioRender

specificity in diagnosing fungal antigens. Using hybridoma technology and genetic engineering for developing a specific monoclonal antibody is an essential step for a specific immunodiagnostic test that can rely upon for the diagnosis of fungal infections, rather than time-consuming conventional techniques such as culture and histopathology (Fig. 3) (Singh et al., 2023). Many studies showed the accurate, specific, and sensitivity using monoclonal antibodies in the diagnosis of fungal antigens without cross-reactivity with other closely related fungi, as these antibodies have the ability to recognize and bind with a specific fungal epitope. For example, developing a specific immunodiagnostic assay against *Aspergillus* antigens (Thornton, 2010), *Fusarium* (Al-Maqtoofi & Thornton, 2016), and *Trichosporon* (Davies & Thornton, 2014).

The application of artificial intelligence (AI) in the field of fungal diagnosis has emerged recently. AI technologies, particularly machine learning (ML) and deep learning (DL) methods, have significantly enhanced diagnostic accuracy, particularly for less experienced clinicians, by analyzing microscopic images from potassium hydroxide (KOH) examinations, fungal culture tests, and histopathologic slides (Hasan Pour, 2025).

6. CONCLUSION

Fungal pathogens cause many infections, with life-threatening disease, in immunocompetent and immunocompromised individuals. Early recognition of fungal antigens by the host immune system is a pivotal step to trigger a complex network of innate and adaptive responses that synergistically prevent and control infection. Early, rapid, and specific diagnosis for fungal infections, particularly invasive infections, can improve patient outcomes. Future studies should focus on developing novel immunotherapies, antifungal agents, and effective vaccines and refining diagnostic methods to ensure early and precise identification of fungal pathogens.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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