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Research Article

Role of IL-22 and TNF-α in pulmonary candidiasis and its effects as immunomodulation through Dectin-2 receptor mediation

Milad A. Mezher
Department of Biology, College of Education for Pure Sciences, Tikrit University, Salah-Al-Din, Iraq
Ahmed H. M. Shugran
Department of Biology, College of Education for Pure Sciences, Tikrit University, Salah-Al-Din, Iraq
Maysam A. Mezher
Department of Clinical Laboratory Sciences, College of Pharmacy, Tikrit University, Salah Al-Din, Iraq
Khaled H. Abu-Elteen*
Department of Biology and Biotechnology, Faculty of Science, The Hashemite University, Zarqa 13133, Jordan
Khalil I. Altaif
Faculty of Pharmacy, Middle East University, Amman, Jordan
Hassan Yahaya
Department of Medical Laboratory Sciences, Faculty of Applied Health Sciences, Bayero University, Kano, Nigeria
Batol I. Dheeb
Department of Pathological Analysis, College of Applied Science, Samaraa University, Salah Al-Din, Iraq

*Corresponding author. E-mail: salma@hu.edu.jo

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Abstract
Pulmonary fungal infections are severe and potentially fatal conditions caused by various fungi, with varying levels of seriousness. The present study aimed to determine the immunomodulatory role of IL-22 and TNF-α in patients with pulmonary candidiasis. Sputum specimens from 106 (Male/Female) outpatients were collected at the Consultation Clinic for Chest and Respiratory Diseases in Salah Al-Din Governorate in Tikrit – Iraq, from June 2022 to December 2022. The age groups ranged from 20 - 75 years. Phenotypic identification of isolates was performed based on Gram reaction, direct wet preparation (10% KOH), and HiCrome™ candida differential agar. Complete species identification was confirmed using the Vitek2® compact system. The study patients' stimulation of IL-22 and TNF-α production through the 4Dectin-2 (CLEC6A) receptor was also examined. The results revealed that 40 of the collected specimens (37.7%) were confirmed as *Candida. albicans*. Dectin-2 (CLEC6A) expression indicates the concurrent release of TNF-α and IL-22 cytokines in response to *C. albicans*. The study determined that *C. albicans* was the main cause of pulmonary candidiasis. These findings can provide valuable insights to optimize the treatment strategies, ultimately enhancing the patient's quality of life.

Keywords: *Candida albicans;* Dectin-2, IL-22, Pulmonary fungal infections, Tumor Necrosis Factor-α

INTRODUCTION

Humans are constantly exposed to fungal particles through various means. However, this exposure may only aggravate respiratory illnesses in individuals with pre-existing health conditions or specific genetic predispositions (Vacher *et al.,* 2015). Immunocompromised personnel are most susceptible to the life-threatening respiratory fungal infection *Candida* and other pathogenic species, which are significant pulmonary fungal pathogens responsible for life-threatening fungal invasive illnesses (Tanwar *et al.,* 2023). *Candida* species cause candidiasis in various clinical forms, such as cutaneous, mucosal, and systemic infections. Approximately 20 species are implicated in candidiasis, but the most prevalent and important of which is *C. albicans*

(Dadar *et al.,* 2018 ; Bhattacharya *et al.,* 2020 ; Nett and Andes, 2020 ; Wang *et al.,* 2022 ; Yahaya and Sule, 2023). *Candida* species exhibit distinct pathological characteristics, including invasiveness, virulence, and antifungal susceptibility patterns, which distinguish them from one another (Hassan *et al.*, 2021). The mannosylated proteins of the cell wall act as pathogen-associated molecular patterns (PAMPs), which are recognized by the host immune system as signals of infection.

The recognition of *C. albicans* is primarily mediated by two classes of pattern recognition receptors (PRRs): C-type lectin receptors (CLRs) and Toll-like receptors (TLRs). CLRs are a crucial component of antifungal immunity. Dectin-1 and dectin-2, are two key CLR members, which play a pivotal role in orchestrating the immune response against fungal infections by triggering a cascade of events that lead to the activation of innate immune cells and can also extend to activate the adaptive immunity by promoting the differentiation of Th17 cells. TLR4 specifically recognizes O-linked mannans, while CLRs like macrophage mannose receptor (MR) and dendritic cell (DC)-specific-ICAM3-grabbing non-integrin (DC-sign) recognize N-linked mannans. Dectin-1, another CLR, specifically recognizes β-glucans, and TLR2 recognizes phospholipomannans (PLMs) (Davidson *et al.,* 2018). Dectin-1 is a type II transmembrane receptor expressed on many antigen-presenting cells (APCs) of myeloid origin, including mast cells, dendritic cells, neutrophils, macrophages, monophagous cells, and in the pulmonary epithelium (Goyal *et al.,* 2018). Dectin-1 is responsible for detecting β- glucans on the cell wall of *C. albicans*, while other CLRs recognize different mannose-containing structures (Wang, 2015). Fungal hyphae are thought to be invisible to dectin-1. By using bud scars with a mannoprotein layer, *C. albicans* protects its cell structure by further limiting the accessibility of β-glucan, thereby reducing recognition by innate immune cells (de Jong *et al.,* 2010). In addition to its role in modifying T helper 17 (Th17) cell responses, Dectin-2 (encoded by CLEC6A) has been linked to the production of reactive oxygen species (ROS), as well as the phagocytosis and elimination of *Candida glabrata*, the second most prevalent strain of *Candida* after *C. albicans* (Netea *et al.,* 2015). Interleukin (IL)-22 is a member of the IL-10 family cytokines with various immunologic functions. IL-22 is produced by T helper (Th)22, a newly identified subset of $CD4^+$ T, γδT, natural killer (NK), and NK T cells. IL-22 stimulates antimicrobial immunity, inflammation, and tissue repair at cellular surface barriers, including the skin, intestine, pancreas, liver, lung, and kidney (Sato *et al.,* 2020; Shohan *et al.,* 2020). It also plays many pathological roles such as in autoimmunity, cancer development, and allergic diseases (Shohan *et al.,* 2020). For this, IL-22 is considered a natural defender against chronic candidiasis (Ma *et al.,* 2022). The receptors of the innate immune system, particularly PRRs, swiftly recognize the invasion of *Candida* yeast into the human system and initiate an efficient immune response. Antigens from the *Candida* species, especially those found on the surface of *C. albicans*, have superantigen-like characteristics that activate T lymphocytes without the need for antigen presentation and result in an excessive release of pro-inflammatory cytokines (Pietrzak *et al.,* 2018). Receptors from diverse types of PRRs, such as TLRs and CLRs can detect numerous fungal structures, including the cell wall components β-glucans, mannans, and PLMs. The PRRs that contribute to host defense against species of *Candida* are, however, tissue-specific and dependent on fungal morphological structure (Kühbacher *et al.,* 2017). IL-1 stimulates the production of IL-17 and IL-22 by Th17 cells. Neutrophils and macrophage's fungicidal activity is significantly influenced by interferon (IFN). Antifungal β-defensins are released when IL-17 and IL-22 activate neutrophils, recruit neutrophils, and recruit epithelial cells. They contribute to *Candida* species clearance through the release of direct phagocytosis, large quantities of antimicrobial peptides (AMPs), and the formation of neutrophil extracellular traps (Davidson *et al.,* 2018; de Jong *et al.,* 2010). The present study aimed to investigate the influence of dectin-2 (CLEC6A) on the evaluation of pulmonary candidiasis by measuring the production of cytokines (IL-22 and tumor necrosis factor-α (TNF-α) in response to six *Candida* species isolates.

MATERIALS AND METHODS

Specimen collection

A total of 106 sputum specimens were collected from outpatients who visited the chest and respiratory diseases clinic at Tikrit Teaching Hospital, Salah al-Din Governorate, Iraq, between June 2022 and December 2022. Patient information was collected using a standardized questionnaire during this period.

Ethical approval

Ethical approval was obtained from the Ethical Committee of Scientific Research (ECSR), Faculty of Pure Sciences, Tikrit University, Tikrit (Ethical Approval number: 2022.3 at 14-3-2022).

Yeast control strain preparation

Candida albicans (ATCC 14053) was used as a control strain. It was obtained from the culture repository of the biology department at Tikrit University, Tikrit, Salah al-Din, Iraq. The control strain was cultured on yeast dextrose agar (YPD) at 25°C for three days before sub culturing on Sabouraud dextrose broth (SDB) and incubated at 25°C in a shaker water bath for another three

days. The strain was washed in phosphate-buffered saline (PBS), and standardized by MacFarland at a concentration of 5 x 10^8 per ml. It was prepared and stored at -20°C until needed (Dheeb *et al*.,2023).

Sputum culture and identification

Sputum samples and deep throat swabs for the patients who could not produce sputum were collected 106 samples were promptly transported to the Microbiology Laboratory at Tikrit University. These samples were immediately cultured on Sabouraud dextrose agar (SDA) plates with chloramphenicol (SDAC) (Difco, USA) and chromogenic agar *Candida* plates (Oxoid Ltd, UK) to isolate yeast and ensure the purity of the isolates. Suspected yeast species were cultured from three consecutive early morning sputum samples using SDA as standard culture media which was supplemented with 0.04 mg/ml chloramphenicol (Merck, Germany). All sputum specimens and *C. albicans* (ATCC 14053) strains were treated as previously described (Smith *et al*., 1999). To ensure reproducibility, each sample was used in triplicate. Phenotypic identification of isolates was performed based on Gram reaction, direct wet preparation (10% KOH), and HiCrome™ candida differential media (HiMedia Laboratories, India). Following the manufacturer's instructions, the isolates and control strains were incubated at 37°C for 48 hours. The Vitek® compact 2 systems (bioMérieux, France) were used to verify the species status of each isolate compared to the control strains.

Blood samples

For serological analysis, five ml of blood samples were withdrawn from the veins of forty patients suffering from pulmonary candidiasis. Forty blood samples were collected from healthy individuals serving as the control group. The age range of patients and healthy individuals was 20 to 75 years.

Cytokines quantification assays

The measurement of human TNF-α, IL-22, and dectin-2 in the collected serum samples was performed using the Enzyme-linked immunosorbent assay (ELISA) sandwich technique. The human Douset sandwich ELISA kit (Cat No. DY782, Sigma) for human IL-22, the human Douset sandwich ELISA kit (Cat No. DY210, Sigma) for human TNF-α, and the human CLEC6A ELISA kit (Cat No. MBS9324720, MyBioSource) for dectin-2 (R&D Systems, London, UK) were used. The results were expressed in pg/mL. All ELISA assays were conducted following the manufacturer's instructions.

Statistical analysis

Data were collected and analyzed using SPSS version 26.0. All data were presented as means using Two-way ANOVA for multiple groups. *P*-values less than 0.05 were considered statistically significant: *$*p < 0.05$, **$p < 0.005$, ***$p < 0.001$.*

RESULTS

In this study, a total of 106 sputum specimens (88 sputa and 18 deep throat swabs) were collected from 402 outpatients. The ATCC controls and clinical isolates were accurately confirmed using the Vitek® compact 2 systems for speciation and categorization. *C. albicans* was the most prevalent *Candida* sp.

Distribution of *Candida albicans* with gender and age

Among the 106 sputum samples collected, only 40 *C. albicans* isolates were positive for respiratory infections, while 66 were negative. The gender and age group data of patients with positive cultures of *C. albicans* are illustrated in Table 1. Gender distribution of *C. albicans* isolation revealed a minor increase in the prevalence rate among males, 21(52.5%) in comparison to females, 19 (47.5%). The prevalence of *C. albicans* among age groups showed that the age ranges of 62–67, 58–61, and 38–41 years exhibited a high prevalence with 18 (*P*-value < 0.0001),13, and 11 (*P*-value < 0.05), respectively among other age groups (Fig. 1).

Detection of TNF-α, IL-22 and CLEC6A

The distribution of TNF-α, IL-22, and CLEC6A cytokine levels in pulmonary patients' cells was assessed. Determination of Dectin-2 (CLEC6A) signifies the corre-

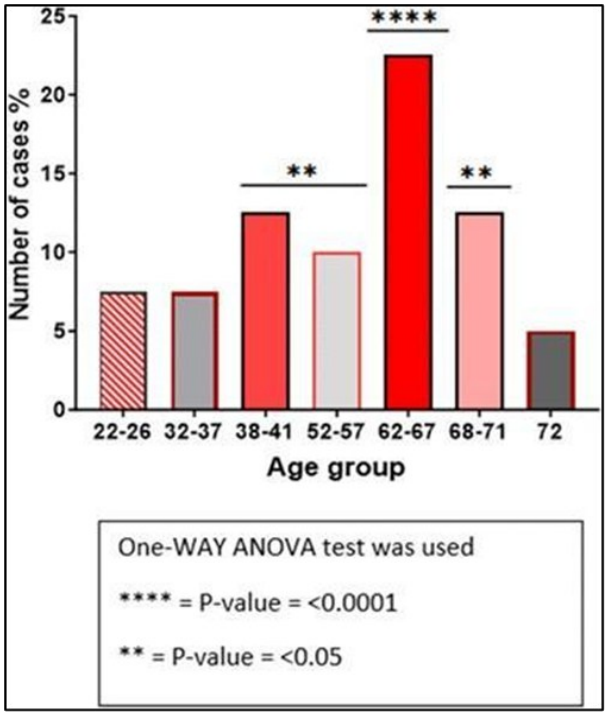

Fig. 1. *Distribution of C. albicans isolates based on age group*

Table 1. Frequency of *C. albicans* isolated from 40 positive samples based on age groups

	Gender		
Age groups	***C. albicans***	**Male**	**Female**
22-26	3	2	1
32-37	3	3	0
38-41	5	2	3
52-57	4	1	4
58-61	9	6	3
62-67	9	5	4
68-71	5	1	4
≥72	2	2	0
Total	40	21(52.5%)	19(47.5%)

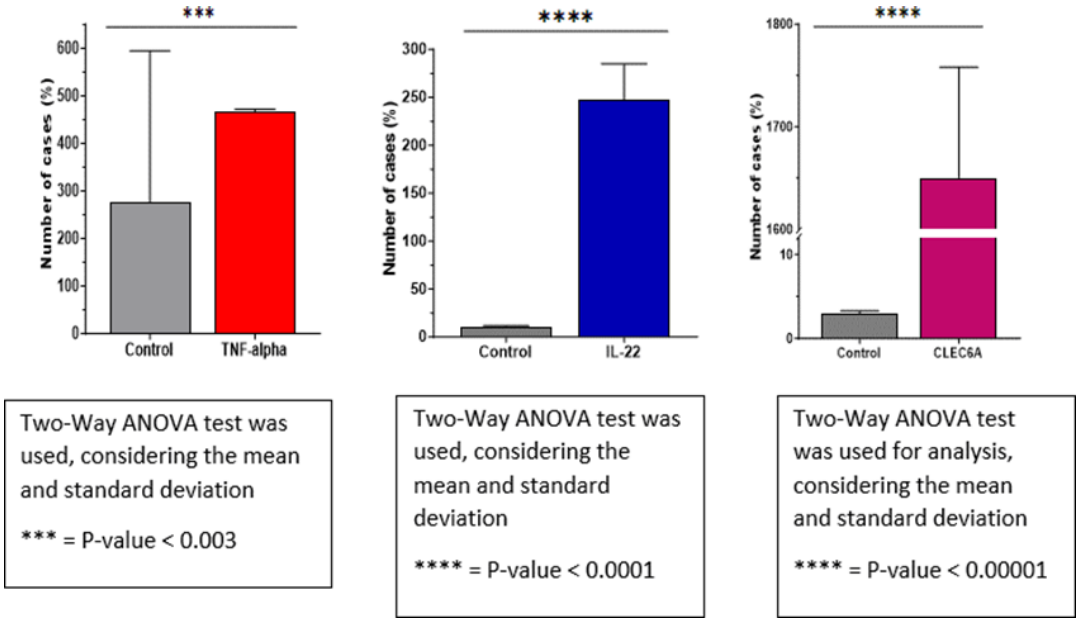

Fig. 2. *Showing* ***c****ytokine production stimulated by TNF-α, IL-22, and CLEC6A; Each column representing the mean ± SD of triplicate cultures; Error bars signifying the standard deviation (SD). Two-way ANOVA was performed to determine the statistical significance. The 95% confidence intervals of the mean are indicated by error bars based on analyses of the same ELISA assays*

sponding production of TNF-α and IL-22 cytokines as an immune response to *C. albicans*. The levels were determined and compared between the neutralizing antibodies and their corresponding isotype controls based on the ELISA technique. The mean doubling time and standard deviation error were calculated using two independent technical replicates and two to three independent biological replicates. Error bars were included to demonstrate the data's reproducibility. One-way and two-way ANOVA tests indicate that the results obtained were statistically significant ($p < 0.05$) (Fig. 2).

DISCUSSION

The present results may be related to protection that was only obtained with a 100-fold higher dose of dead *C. albicans*. The protective effect may be due to complex host-pathogen interactions, as LPS and independently isolated *Candida* cell wall components or their interactions failed to reduce mortality (Abdulateef *et al.,* 2024). These results showed that just activating one or more pathogen recognition receptors did not result in this protective effect and stimulate immune system(Abdullah *et al.*,2019, Abdulateef *et al.,* 2024,). The present study revealed that among many species of *Candida, C. albicans* was the most prevalent species in Tikrit, Salah Al-Din Governorate, Iraq. This finding is similar to that reported by many authors from different countries: United states, Pakistan, England UK, and Jordan(Dadar *et al.,* 2018; Bhattacharya *et al.,* 2020; Wang *et al.,* 2022; Yahaya and Sule, 2023). Changes in the pro- to anti-inflammatory cytokines ratio favor infectious diseases by weakening the host's defenses (Li *et al*. 2019). The current findings confirm the results of cytokines IL-22 and TNF-α acting as immune stimulants and possess control of *Candida* infection (Nett and Andes, 2020, Abed *et al*., 2022). Previous studies explained the mechanism of antigen presentation, the secretion of pro inflammatory cytokines and the phagocytosis and destruction of invasive microorganisms to

protect against fungal infections (Johnson *et al*., 2012). *C. auris* stimulates the innate immune system by detecting CLRs, primarily triggered by structurally distinct mannoproteins. According to other research, spleen tyrosine (Bruno *et al.,* 2020, Wang *et al*. 2022). Dectin-1/2, and MR (mannose receptor) were all linked to fungal recognition. Furthermore, the present results of TNF-α showed the highest expression with a mean of 468.2 and IL-22 was observed in sputum samples but not in the serum (Li *et al*. 2019). Among those studies IL-22 cytokine modulates epithelial function, stimulating host defense and repair mechanisms in the airways (Albrecht *et al*., 2022; Galocha *et al.,* 2019). A study by Thompson *et al.* (2021) concluded that Dectin-1 retraction significantly raised mortality in experimental mice during systemic candidiasis induced by *C. albicans* but had no impact on mortality rates after infection with *C. glabrata*, *C. tropicalis*, or *C. parapsilosis* (Li *et al*. 2019). On the other hand, some evidence showed that Dectin-1 is species-dependent for particular immune responses to *Candida* and Th1 and Th17 cellular responses predominate in the host adaptive immune response to *C. albicans*, which includes T-cells (De Luca *et al.,* 2010). In addition, earlier results demonstrated that IL-17, attracts and activates neutrophils, and IL-22, stimulates B-defensin secretion (Jaszczura *et al.,* 2019; Al Zaher *et al.,* 2024). Netea *et al*. (2015) concluded that the 17 cell responses play a significant role in mucosal host defenses against *Candida*. However, concerning present results, the pro-inflammatory marker IL -22 showed a significant difference (*P*-value = 0.0001) with a mean count of 247.1. β -glucan is developed by *C. albicans* and regulated by a signaling pathway. This pathway seems to reduce macrophage uptake and decrease the inflammatory response (TNF-α and MIP1α) and neutrophil recruitment and is associated with the transcription factor Crz1 and the G-protein coupled receptor Gpr1. The increased TNF-α secretion increases the efficacy of macrophages in pathogen killing. According to Galocha *et al.* (2019) the *Pra1* gene plays a main role in adaptive immune response due to its binding to $CD4^+$ T cells of the mouse, causing a high reduction in the secretion of cytokine (IFN-γ and TNF) and antigen stimulation. Furthermore, Galocha *et al.* (2019) noted that *Candida* infection resulted in the generation of modest levels of proinflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8, and IFN-γ). Conversely, Wang *et al*. (2022) research on mice with systemic infection from *C. albicans* showed a significant increase in the levels of chemokines (CXCL1 and CXCL2) and proinflammatory cytokines (IL-1β, IL-6, and TNF-α) in the serum. As a primary source of cytokine production, *C. albicans* primes the recruitment of ILCs to the lungs through attracting phagocytic cells to the lungs, these cytokines enable the respiratory epithelium to produce antimicrobial peptides (Al-Sarraj *et al.,* 2024; Hashim *et al.,*2023). By means of these pathways, exposure to *C. albicans* priming the alveolar innate immune response provides protection against infection model. Strategies to stimulate the Th17 pathway in the innate immune system have already been investigated, and they may offer an intriguing avenue for Candidiasis infections (Hatem and Dheeb,2024; Hussain *et al.,*2020).

Conclusion

The present study showed the possibility of immunization against candidiasis infections through TNF-α and IL-22, to enhance immune responses against *C. albicans* infections. Additionally, suggesting immunotherapies for airway infections and cytokine profiling in clinical settings could improve treatment strategies for *Candida* infections. Dectin-2-mediated signalling pathways stimulate the production of these pro-inflammatory cytokines, enhancing pathogen clearance and infection control. It is recommended that more in-depth studies be performed to analyze the precise mechanisms that contribute to the therapeutic potential of targeting Dectin-2 and cytokine pathways.

Conflict of interest

The authors declare that they have no conflict of interest.

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