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HOST IMMUNE RESPONSE TO FUNGAL SEPSIS: NEUTROPHIL EXTRACELLULAR TRAPS AND CIRCULATING IMMUNE COMPLEX FORMATION

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Background. Sepsis is a major global health problem, with fungal pathogens such as *Candida albicans* emerging as a significant cause of invasive infection. Fungal sepsis has a higher mortality rate than bacterial sepsis and is complicated by antifungal resistance. Although neutrophil extracellular traps (NETs) help to contain fungi, excessive NETs can contribute to inflammation and tissue injury. Understanding these mechanisms could reveal markers of disease activity and new therapeutic targets.

Materials and Methods. Fungal sepsis was induced in twelve male BALB/c mice via an intraperitoneal injection of *Meyerozyma guilliermondii* (10^7 cells per mouse). Blood was collected at the beginning of the study and then on days 1–3, 7–9, and 13–15. Serum was analyzed for IgG, IgM, circulating immune complexes (ELISA), and extracellular DNA (fluorescence assay).

Results and Discussion. In mice with fungal sepsis, IgG levels remained stable while IgM levels increased significantly between days 7 and 9, before declining from day 13. IgG–IgM immune complexes peaked around days 8–9, reflecting active antigen-antibody responses. Free DNA levels, which indicate NETs formation, increased by day 7 and then declined, showing early neutrophil activation followed by humoral control. Together, these findings suggest a coordinated immune response in which NETs and immune complexes contribute to both pathogen control and inflammation.

Conclusion. Fungal sepsis induced by *Meyerozyma guilliermondii* resulted in early NETosis and an increase in IgM and immune complexes. IgM levels peaked on days 7–9 before declining. Unlike *Candida albicans*, this strain does not cause rapid lethality,

enabling detailed tracking of disease progression over time. After day 9, immune parameters began to normalize, indicating the resolution of the acute phase and supporting the usefulness of this model for studying host immune dynamics in fungal sepsis.

Keywords: fungal sepsis, *Meyerozyma guilliermondii*, acute inflammation, immune defense, circulating immune complexes, neutrophil extracellular traps (NETs)

INTRODUCTION

Sepsis remains one of the most critical health challenges worldwide, with both severe sepsis and septic shock ranking among the leading causes of mortality and long-term illness (Guarino *et al.*, 2023). While bacterial infections are traditionally recognized as the main culprits, fungal pathogens, particularly *Candida albicans* (*C. albicans*) and related Candida species, have emerged as significant contributors to sepsis over the past decades (Lass-Flörl *et al.*, 2024). The incidence of fungal sepsis has steadily risen, posing not only a major clinical burden but also escalating healthcare costs. Alarmingly, fungal sepsis is often associated with higher mortality rates compared to bacterial cases (Manika *et al.*, 2025).

Among fungal bloodstream infections, *Candida* species dominate, typically arising from gastrointestinal translocation or colonization of medical devices such as intravenous catheters. This underscores the complexity of fungal pathogenesis and highlights the limitations of current antifungal therapies, especially in the face of increasing drug tolerance and resistance. Understanding host immune defenses against these infections is therefore crucial (Soriano *et al.*, 2023).

Neutrophils, as central players in innate immunity, are particularly important in combating invasive fungal pathogens (Desai & Lionakis, 2018). Beyond their traditional roles in phagocytosis, oxidative burst, and degranulation, neutrophils deploy an additional antimicrobial strategy: the release of neutrophil extracellular traps (NETs) (Rosales, 2018). Since their discovery in 2004 (Brinkmann *et al.*, 2004), NETs have been recognized as a key mechanism for immobilizing and killing pathogens too large to be engulfed, such as fungal hyphae (Liang *et al.*, 2022). This process, known as NETosis, represents a unique form of immune response that can occur with or without neutrophil cell death (Retter *et al.*, 2025).

Experimental studies have shown that proteolytic enzymes released during NET formation, especially neutrophil elastase (NE), facilitate the degradation of IgG–IgM immune complexes. The temporal dynamics of these complexes reveal an initial rise in early inflammation, followed by a decline correlated with increased elastase activity, suggesting a regulatory role in the host defense response. Nevertheless, inadequate clearance of highly immunogenic NET components and circulating immune complexes perpetuates systemic inflammation and tissue damage (Yancey & Lawley, 1984). Such insights have spurred interest in therapeutic strategies aimed at modulating NET activity, including inhibition of key enzymes or degradation of extracellular DNA using DNase. These approaches have shown promise in reducing thrombosis, enhancing microvascular perfusion, and limiting organ injury (Kimball *et al.*, 2016).

The aim of this study was to investigate the dynamics of IgG, IgM, and circulating immune complexes in a mouse model of fungal sepsis, and to evaluate the formation of neutrophil extracellular traps (NETs) as a potential marker of disease activity and progression.

MATERIALS AND METHODS

Animals. Twelve male BALB/c mice (6–8 weeks old, 25±3 g) were used. Fungal sepsis was induced by intraperitoneal injection of *Meyerozyma guilliermondii* ($1 \cdot 10^7$ cells/mouse). Mice were maintained in filter-covered cages under controlled temperature and an automated 12 h light/dark cycle, with free access to standard chow and water. All animal procedures were approved by the Bioethics Committee of the Institute of Cell Biology, NAS of Ukraine (Protocol No. 2025-4).

Blood collection. Blood was collected from the orbital sinus under anesthesia (Parasuraman *et al.*, 2010) at baseline (day -3) and on days 1–3, 7–9, and 13–15 post-sepsis induction. Mice were divided into three groups (n = 4 each) to limit sampling to once every six days. Serum was isolated and stored at -20 °C.

Enzyme-linked immunosorbent assay (ELISA). Total serum IgG and IgM, as well as IgG–IgM circulating immune complexes, were measured by ELISA. Maxibinding plates (SPL Life Sciences, Korea) were coated with 50 µL of $F(ab')_2$ Goat Anti-Mouse IgG or IgM (2 µg/mL) in 0.1 M carbonate-bicarbonate buffer (pH 9.6) and incubated overnight at 4 °C. After blocking with 100 µL of 4% BSA, serum samples in wash buffer were added. Bound antibodies were detected with 50 µL of HRP-conjugated goat anti-mouse IgG (Jackson ImmunoResearch, #115-035-003) or goat anti-mouse IgM (Jackson ImmunoResearch, #115-035-020), both diluted 1:20,000. Plates were developed with 50 µL of TMB/H_2O_2 substrate (Carl Roth GmbH, #6834), stopped with 1 N H_2SO_4, and absorbance was measured at 450 nm with 620 nm reference using a BioTek ELx800 microplate reader (BioTek, USA).

Fluorescence-based quantification of DNA in serum samples. Genomic DNA levels were determined with the DNA Quantification Kit, Fluorescence Assay (Sigma-Aldrich, DNAQF-1KT). Briefly, DNA standards from calf thymus DNA, and samples (10 µL) were incubated with a fluorogenic dye, Hoechst 33342 (bis-benzamide, 3.75 mM), a DNA-specific fluorescent dye, in assay buffer (2 mL). Fluorescence was measured using a Shimadzu RF-600 spectrofluorometer (Ex: 360 nm, Em: 460 nm), and DNA concentrations were calculated from a standard curve.

Statistical analysis. Data were analyzed using Excel 2016 (Microsoft, Redmond, WA, USA) and GraphPad Prism 8.0 (GraphPad Software, San Diego, CA, USA). Results are expressed as mean ± SD. Statistical differences were assessed using GraphPad Prism 8.0 with a non-parametric Kruskal-Wallis ANOVA and Dunn's post-hoc test. A p-value <0.05 was considered significant, with three levels of significance: *p <0.05, **p <0.01, ***p <0.001.

RESULTS AND DISCUSSION

To investigate the roles of immunoglobulins, circulating immune complexes, and NETs in fungal sepsis, we established an experimental murine model. Considering that sepsis caused by *C. albicans* often leads to rapid and fatal outcomes, which would prevent the study of disease progression and immune dynamics, we selected *Meyerozyma guilliermondii* (syn. *Pichia guilliermondii, Candida guilliermondii*), a less pathogenic fungal species. Although less virulent, this organism is capable of inducing sepsis under controlled laboratory conditions, thereby providing an opportunity to monitor the temporal development of the immune response, including changes in IgG and IgM levels, the formation of circulating immune complexes, and the release of NETs.

An immunoenzymatic analysis was performed to determine the levels of total IgG and IgM immunoglobulins, as well as IgG–IgM immune complexes, in the blood serum of mice that underwent experimental fungal sepsis. The results showed that total IgG levels remained stable during the study (**Fig. 1*A***). In contrast, dynamic changes were shown in the content of total IgM immunoglobulins. A statistically significant increase in IgM levels was observed from days 7 to 9 after sepsis induction (**Fig. 1*B***). From day 13 of the experiment, a gradual decrease in the IgM concentration was detected. These results are consistent with the role of IgM as the first immunoglobulin to respond to acute infection by providing early protection before IgG-mediated immunity develops (Sathe & Cusick, 2025).

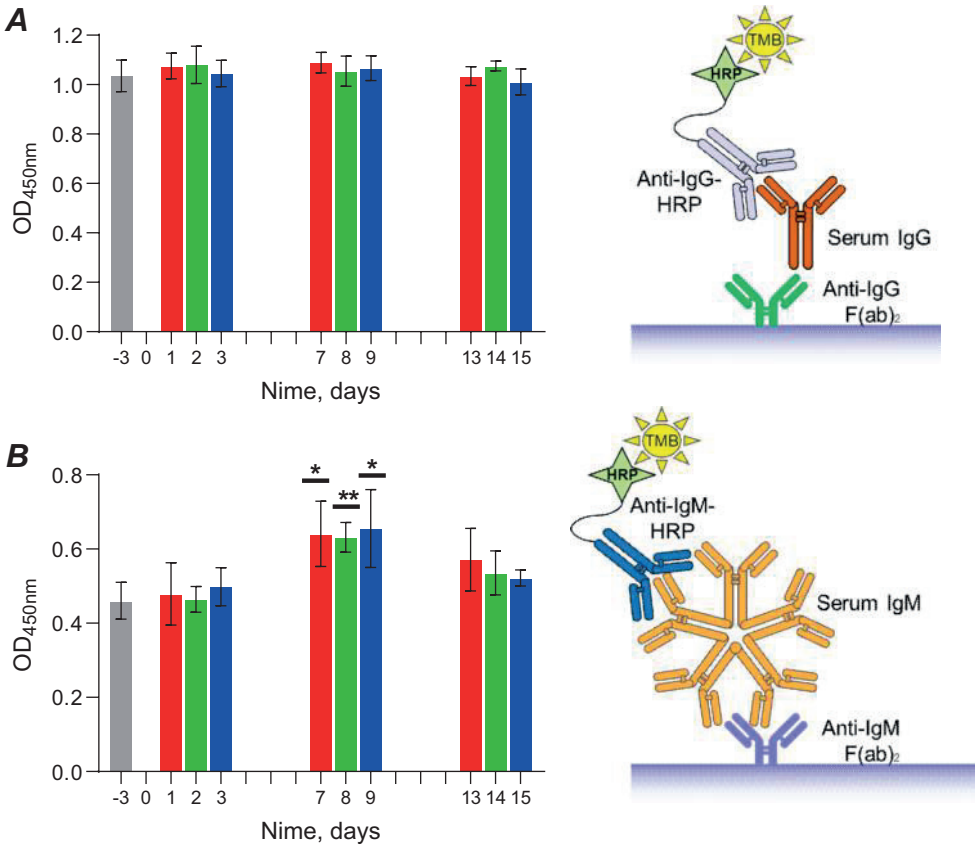

Fig. 1. The serum levels of total IgG (***A***) and IgM (***B***) immunoglobulins in laboratory mice before (day -3, grey column) and after the induction of fungal sepsis. Sepsis was induced on day 0. The color columns represent groups of animals from which blood samples were taken sequentially. * p <0.05, ** p <0.01

A similar trend was observed for IgG–IgM immune complexes (**Fig. 2**). Their levels increased significantly on days 8-9, reflecting active antigen-antibody interactions and the formation of circulating immune complexes. This increase is likely a response to the high antigenic load during the progression of fungal sepsis. Similar data have been reported for bacterial sepsis (Dumych *et al.*, 2019). Like bacteria, fungi are foreign pathogens, so the body tries to overcome the progressive infection.

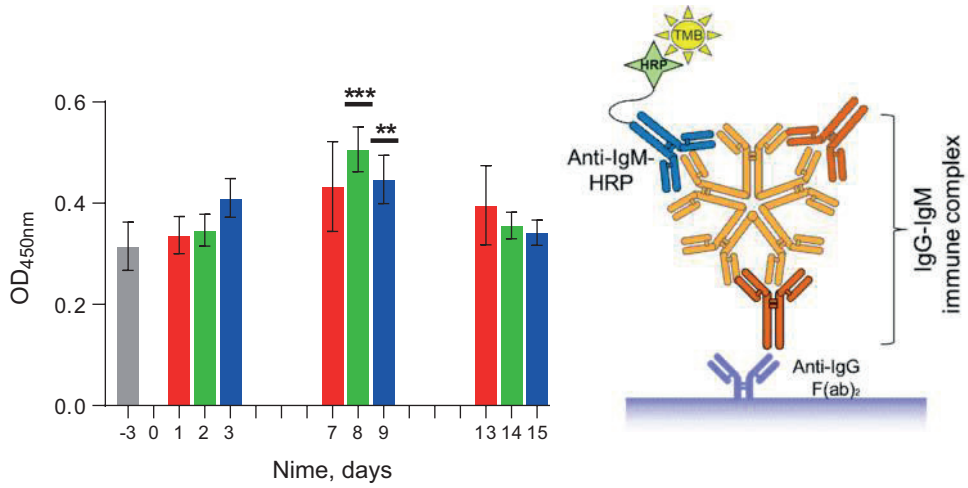

Fig. 2. The serum levels of IgG–IgM immune complexes in laboratory mice before (day -3, grey column) and after the induction of fungal sepsis. Sepsis was induced on day 0. The color columns represent groups of animals from which blood samples were taken sequentially. ** p <0.01, *** p <0.001

Neutrophils are the first line of defense against foreign agents entering the body. During severe infections, neutrophils form NETs, which are webs of DNA, histones, and granular proteins that immobilize pathogens and limit their dissemination (Delgado-Rizo *et al*., 2017). Because these traps contain DNA, we measured the level of free circulating DNA as an indirect marker of NET formation.

NET detection can be carried out using different methods that generally focus on NET-associated proteins such as myeloperoxidase (MPO), citrullinated histone H3 (citH3), and NE rather than directly on extracellular DNA. Standard techniques, like ELISA or Western blot, require significant time, while faster options, such as flow cytometry, are costly, highlighting the need for a quicker and more affordable approach, especially in clinical use. For this reason, NETs detection was performed using a spectrofluorometer and the chromatin-staining dye Hoechst 33342.

The concentration of free circulating DNA in serum began to rise on the third day after sepsis induction (**Fig. 3**). According to published studies, the spleen and liver of mice recruit large numbers of neutrophils during the first few days after infection to control fungal growth and prevent systemic spread (Desai & Lionakis, 2018; Lopes & Lionakis, 2022). On day 7, free DNA levels were significantly higher than baseline, indicating increased NETosis activity in response to fungal invasion. On day 9, the concentration of DNA began to decrease, accompanied by a further decrease in levels of IgM and immune complexes. This temporal relationship indicates a coordinated immune response in which early neutrophil activation is followed by humoral mechanisms that control persistent infection.

Accumulating evidence demonstrates the importance of NETs in controlling fungal infections, particularly those caused by *C. albicans*. However, excessive NET formation has been increasingly implicated in the pathogenesis of both acute and chronic inflammation, including sepsis (Dumych *et al*., 2019; Paryzhak *et al*., 2018). The antifungal activity of neutrophils depends on both oxidative mechanisms driven by NADPH

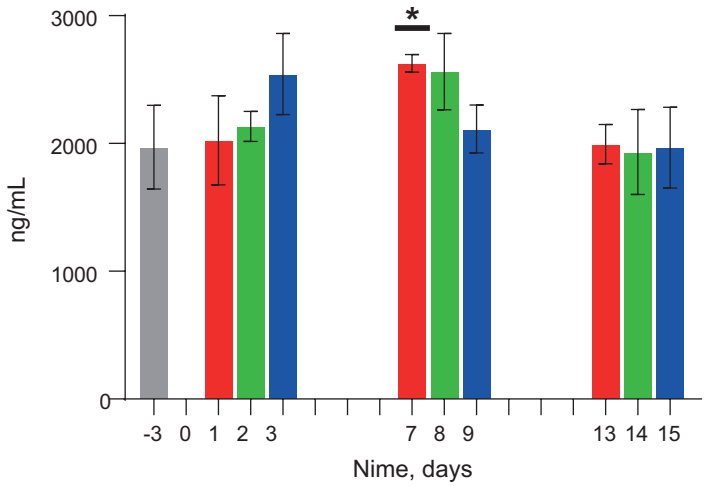

Fig. 3. The serum levels of free circulating DNA in laboratory mice before (day -3, grey column) and after the induction of fungal sepsis. Sepsis was induced on day 0. The color columns represent groups of animals from which blood samples were taken sequentially. * p <0.05

oxidase and myeloperoxidase, as well as non-oxidative pathways involving antimicrobial peptides, hydrolases, and receptors such as DECTIN-1 and CR3 (Lopes & Lionakis, 2022). While NETs restrict microbial dissemination, their overproduction can induce widespread tissue and organ damage. This emphasizes the need for balanced modulation of NETs and targeted regulation of neutrophil responses in therapeutic strategies for fungal sepsis. In sepsis, the intense antigenic burden drives NET release beyond the clearance capacity of phagocytes, resulting in pathological consequences such as the accumulation of IgG–IgM circulating immune complexes. When NETs are present, they can act as both a scaffold and an antigen source for immune complex formation, further amplifying systemic inflammation and immune dysregulation (Lehman & Segal, 2020). Regarding the heterogeneous patterns of fungal disease, restoration of NADPH oxidase activity in *Aspergillus nidulans* infection reinstates NET formation and suppresses fungal growth, while sub-inhibitory echinocandin treatment enhances NET release against *C. albicans* biofilms (Liang *et al.*, 2022). However, excessive NET formation, as observed in invasive aspergillosis, contributes to tissue damage (Alflen *et al.*, 2020). Therefore, a balanced modulation of NET activity, using DNase I or histone/MPO inhibitors to block cytotoxic NET components, may offer a promising yet challenging antifungal strategy (Block & Zarbock, 2021).

CONCLUSION

Fungal sepsis caused by *Meyerozyma guilliermondii* in mice provokes a time-dependent immune response. The initial surge in free DNA suggests the activation of neutrophils and the initiation of NETosis. An increase in immune complexes indicates the involvement of adaptive immune mechanisms in fighting fungal infections. These time frames for evaluating the interactions between NETs and immune complexes during fungal sepsis confirm their potential as disease activity biomarkers. This research used the *Meyerozyma guilliermondii* strain, which does not cause the rapid and lethal effects seen

with *Candida albicans*. The study parameters began to return to normal after the ninth day from the start of the sepsis induction.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest: the authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Human Rights: this article does not contain any studies with human subjects performed by any of the authors.

Animal Studies: all international, national, and institutional guidelines for the care and use of laboratory animals were followed.

AUTHOR CONTRIBUTIONS

Conceptualization, [S.P.; T.D.]; methodology, [S.P.; T.D.]; validation, [S.P.; T.D.]; formal analysis, [S.P.; T.D.]; investigation, [S.P.; T.D.]; resources, [S.P.; T.D.]; data curation, [S.P.; T.D.]; writing – review and editing, [S.P.; T.D.]; visualization, [S.P.; T.D.] supervision, [S.P.; T.D.]; project administration, [S.P.; T.D.]; funding acquisition, [S.P.; T.D.]. Both authors have read and agreed to the published version of the manuscript.

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ІМУННА РЕАКЦІЯ ОРГАНІЗМУ ХАЗЯЇНА НА ГРИБКОВИЙ СЕПСИС: НЕЙТРОФІЛЬНІ ПОЗАКЛІТИННІ ПАСТКИ ТА ФОРМУВАННЯ ЦИРКУЛЮЮЧИХ ІМУННИХ КОМПЛЕКСІВ

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Вступ. Сепсис є серйозною глобальною проблемою охорони здоров'я, а грибкові патогени, такі як *Candida albicans*, стають однією з основних причин інвазивних інфекцій. Грибковий сепсис має вищий рівень летальності, ніж бактеріальний, і ускладнюється резистентністю до протигрибкових препаратів. Хоча нейтрофільні позаклітинні пастки (НПП) допомагають локалізувати грибки, надмірна кількість НПП може сприяти запаленню й ушкодженню тканин. Розуміння цих механізмів може допомогти виявити маркери активності захворювання та нові терапевтичні мішені.

Матеріали та методи. Грибковий сепсис було індуковано у 12 самців мишей BALB/c внутрішньочеревним введенням *Meyerozyma guilliermondii* (10^7 клітин на мишу). Кров відбирали на початку дослідження, а також на 1–3, 7–9 і 13–15-й дні. Сироватку аналізували на вміст IgG, IgM, циркулюючих імунних комплексів (ELISA) та позаклітинної ДНК (флуоресцентний аналіз).

Результати. У мишей із грибковим сепсисом вміст IgG залишався стабільним, тоді як рівні IgM значно зросли між 7-м і 9-м днями, а потім знизилися з 13-го дня. Імунні комплекси IgG–IgM досягали піку приблизно на 8–9-й день, що відображає активну реакцію антиген–антитіло. Рівень вільної ДНК, який вказував на утворення НПП, зростав до 7-го дня, а потім знижувався, що свідчить про ранню активацію нейтрофілів із подальшим гуморальним контролем. Загалом ці результати вказують на скоординовану імунну відповідь, у якій НПП та імунні комплекси беруть участь як у контролі патогенів, так і у підтриманні запалення.

Висновки. Грибковий сепсис, індукований *Meyerozyma guilliermondii*, супроводжувався раннім нетозом і підвищенням вмісту IgM та імунних комплексів. Рівень IgM досягав піку на 7–9-й день, після чого знижувався. На відміну від *Candida albicans*, цей штам не спричиняє швидкої летальності, що дає змогу

детально відстежувати прогресування хвороби з часом. Після 9-го дня імунні показники почали нормалізуватися, що свідчить про завершення гострої фази та підтверджує корисність цієї моделі для вивчення імунної динаміки хазяїна із грибковим сепсисом.

Ключові слова: грибковий сепсис, *Meyerozyma guilliermondii*, гостре запалення, імунний захист, циркулюючі імунні комплекси, нейтрофільні позаклітинні пастки (НПП)

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