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Original Article

Dectin-1 participates in β-glucan- or PMA-induced neutrophil extracellular trap formation during antifungal defense

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Abstract: Objectives: The formation of neutrophil extracellular traps (NETs) plays a crucial role in neutrophil-mediated defense against fungal infections and has become a hot topic of immunological research. This study aimed to investigate whether high expression of Dectin-1, a key pattern recognition receptor, contributes to NET formation in response to fungal pathogens. Methods: Human neutrophils were isolated and characterized, then stimulated with cell wall β-glucan to induce NET formation. Phorbol 12-myristate 13-acetate (PMA), a diacylglycerol mimetic, was used as a positive control. Dectin-1 antibody was used to determine the functional significance of Dectin-1 in the formation of NETs. NET formation was detected by Sytox Green staining, myeloperoxidase (MPO) and neutrophil elastase (NE) immunofluorescence staining, and western blot analysis. The relative kits, 2',7'-dichlorodihydrofluorescein diacetate staining and MitoSOX Red staining were used to determine the mechanism of Dectin-1 induced NET formation. Results: Dectin-1 was overexpressed in β-glucan- and PMA-treated neutrophils. Dectin-1 deficiency reduced NET formation, accompanied by decreased Sytox Green fluorescence, lower levels of dsDNA content, and decreased expression of NE, MPO and citrullinated histone H3 (H3Cit). Dectin-1-mediated NET formation was dependent on reactive oxygen species (ROS) produced by NADPH oxidase (NOX), NOX2 protein and mitochondrial superoxide. Moreover, up-regulated Dectin-1 expression activated the extracellular regulated protein kinases (ERK) and p38 MAPK pathways, which were critical for the induction of NETs. Conclusion: Dectin-1 promotes NET formation in neutrophils stimulated by β-glucan or PMA through activation of the ERK and p38 signaling pathways, which might contribute to defense against fungal pathogens.

Keywords: Dectin-1, neutrophil extracellular traps, β-glucan, PMA

Introduction

Fungal infections represent a significant global public health concern, especially among immunosuppressed individuals, often leading to severe complications and high mortality rates [1]. Fungal pathogens such as Candida albicans, Cryptococcus spp., and various Aspergillus species are capable of causing a wide range of diseases from epidermal infections to invasive systemic infections. Neutrophils, the most abundant immune cells, serve as the first line of defense against invading microorganisms [2, 3]. In response to fungal infections, neutrophils exert their protective functions through several mechanisms. They are rapidly recruited to the site of infection, where they engage pathogens through phagocytosis [4], and can further mediate antifungal activity by releasing reactive oxygen species (ROS) and neutrophil extracellular traps (NETs) containing anti-microbial proteins [5, 6].

NETs have emerged as a novel and essential effector mechanism of neutrophil-mediated immunity. These structures are critical components of the innate immune response, deployed by neutrophils to capture and eliminate patho-

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gens. The formation of NETs involves the release of web-like structures composed of DNA, histones, and antimicrobial proteins, such as neutrophil elastase (NE) and myeloperoxidase (MPO), which are capable of immobilizing and killing a broad spectrum of microbes [7, 8]. Beyond their antimicrobial functions, NETs have been increasingly recognized for their dual role in immunopathology. They contribute not only to host defense against bacteria, viruses, and fungi but also to the pathogenesis of sterile inflammatory conditions such as autoimmune diseases, thrombosis, and cancer [9-11]. Thus, elucidating the mechanisms that regulate NET formation is of considerable interest, especially in the context of fungal infections.

Dectin-1, a member of the C-type lectin receptor (CLR) family, is a pattern recognition receptor (PRR) that plays a crucial role in antifungal immunity [12]. It is predominantly expressed on myeloid lineage cells, including dendritic cells, macrophages, neutrophils, and monocytes, which are positioned at mucosal and tissue entry points to detect pathogens [13]. Dectin-1 specifically recognizes β-glucan, a polysaccharide found in the cell walls of fungi and some bacteria, triggering downstream signaling cascades that promote phagocytosis, pro-inflammatory cytokine secretion, and the activation of adaptive immune responses. Since its initial identification in 2000, Dectin-1 has been extensively studied for its indispensable role in mediating resistance to fungal pathogens such as Candida spp. and Aspergillus spp. [14]. Beyond infectious disease contexts, Dectin-1 signaling has also been implicated in a variety of non-infectious inflammatory and immune-mediated disorders, including autoimmune diseases and cancer [15, 16]. Notably, its activation influences macrophage polarization and contributes to disease progression and therapeutic responses [17]. These findings underscore the broad immunological relevance of Dectin-1 and highlight the importance of delineating its regulatory role within neutrophils.

In this study, we investigate the role of Dectin1 in β-glucan- and phorbol 12-myristate 13-acetate (PMA)-induced NETs formation by neutrophils and examine the involvement of key signaling pathways. Our findings aim to provide new mechanistic insights into the Dectin-1-mediated innate immune response and may offer a theoretical foundation for the development of novel therapeutic strategies targeting fungal infections and inflammatory diseases.

Materials and methods

Isolation and identification of neutrophils

Peripheral blood (15 mL) was collected from healthy volunteers into EDTA-coated tubes (final concentration: 0.25%) to prevent coagulation. Neutrophils were isolated by diluting the blood samples with Hanks' solution or phosphate-buffered saline (PBS), followed by density gradient centrifugation using Ficoll. After centrifugation, neutrophils and erythrocytes were located at the bottom layer. Erythrocytes were subsequently lysed using a red blood cell lysis solution. The purity of the isolated neutrophils was assessed via flow cytometry using CD16 and CD66b as surface markers. Only neutrophil preparations with purity greater than 90% were used for subsequent experiments. Written informed consent was obtained from all donors, and the study protocol was approved by the Ethics Committee of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine.

Cell treatment

Purified neutrophils (2×10^5 cells/mL) were seeded in 6-well plates and cultured in serum-free medium for 12 h prior to stimulation. For Dectin-1 inhibition, cells were pre-treated with anti-Dectin-1 antibody (5 μg/mL) for 30 min. Subsequently, cells were stimulated with β-glucan (100 μg/mL; Sigma Aldrich, St. Louis, MO, USA) or PMA (100 ng/mL; Sigma Aldrich, St. Louis, MO, USA) and incubated for an additional 24 h, After treatment, both cells and culture supernatants were collected for further analyses.

SYTOX Green staining

Neutrophils (2×10^5 cells/well) were seeded in 96-well plates and incubated with SYTOX Green dye (1 μM; Thermo Fisher Scientific, Waltham, MA, USA) for 15 min. NET formation was then induced by treatment with β-glucan (100 μg/mL) or PMA (100 ng/mL).

Quantification of serum dsDNA levels

Double-stranded DNA (dsDNA) levels in the supernatant were quantified using the Quant-iT

PicoGreen dsDNA Assay Kit (Invitrogen, Waltham, MA, USA). Samples or neutrophil preparations were incubated with PicoGreen reagent for 5 minutes at ambient temperature in the dark. Fluorescence was then measured using a microplate reader at an excitation wavelength of 485 nm and an emission wavelength of 520 nm.

Measurement of NADP+/NADPH ratio

The activity of NADPH oxidase in neutrophils was assessed using a WST-8-based $NADP^+$/NADPH Assay Kit (Beyotime, Shanghai, China) following the manufacturer's instructions. Each sample was divided equally into two parts. One portion was lysed on ice in the presence of $NADP^+$ for 15 min, while the other was incubated at 60°C for 30 min to degrade NADP+, leaving only NADPH. After centrifugation, 100 µL of G6PDH working solution was added to each well and incubated at 37°C for 10 min. Absorbance was measured at 450 nm using a microplate reader, and the $NADP^+$/NADPH ratio was calculated accordingly.

Immunofluorescence staining

Neutrophils treated with β-glucan or PMA were fixed, permeabilized, and subjected to antigen retrieval, followed by blocking with 10% goat serum for 30 min. Cells were incubated overnight at 4°C with primary antibodies against neutrophil elastase (NE; Abacm, ab131260, 1:100) and MPO (Abcam, ab208670, 1:200). After washing, cells were incubated with Alexa Fluor® 488-conjugated goat anti-mouse IgG (Invitrogen, Carlsbad, CA, USA) for 1 h at room temperature. Nuclear staining was performed using DAPI. Fluorescent images were captured using a fluorescence microscope (Leica Microsystems, Wetzlar, Germany).

Western blot assay

Total protein was extracted from neutrophils using RIPA lysis buffer. Equal amounts (25 µg) of protein, in a volume of 20 µl, were resolved by a 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and transferred onto nitrocellulose membranes. Membranes were blocked with 5% skim milk and incubated with primary antibodies: Dectin-1 (Acam, ab144039, 1:1000), H3cit (Abcam, ab219407, 1:1000), NADPH oxidase 2 (NOX2) (Acam, ab310337, 1:1000), ERK (Acam, ab184699, 1:1000), p-ERK (Acam, ab201015, 1:1000), p38 (Acam, ab170099, 1:2000), p-P38 (Acam, ab178867, 1:1000), and GAPDH (Abcam, ab9485, 1:2500). Membranes were then incubated with HRP-tagged secondary antibodies (Abcam, ab6721, 1:10000). GAPDH was utilized as an internal loading control. Chemiluminescent signals from the immunoreactive bands were captured using the BeyoECL Moon detection kit (Beyotime, Shanghai, China), and band intensities were quantified using ImageJ software (National Institutes of Health, Bethesda, MA, USA).

Detection of ROS and mitochondrial superoxide levels

ROS and mitochondrial superoxide production were assessed using the ROS Assay Kit (Solarbio, Beijing, China), and the MitoSOX Red Mitochondrial Superoxide Indicator (Yeasen, Shanghai, China), respectively. Neutrophils were seeded in 24-well plates pre-coated with poly-L-lysine and washed with PBS. Cells were resuspended in 200 µL of DCFH-DA (10 mM) or MitoSOX Red (5 µM) and incubated at 37°C for 30 minutes. Fluorescence signals, indicating ROS and mitochondrial superoxide levels, were visualized and captured using an Olympus microscope (Olympus, Tokyo, Japan).

Statistical analysis

All experimental data were analyzed using GraphPad Prism 8.0 (GraphPad Software Inc., San Diego, CA, USA) and presented as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) followed by Tukey's post hoc test was adopted for multi-group comparisons. A P-value < 0.05 was considered statistically significant.

Results

Dectin-1 induces NET formation by human peripheral blood neutrophils

Human peripheral blood neutrophils were first isolated and identified by flow cytometry based on CD16 and CD66b expression (**Figure 1A**). To investigate the role of Dectin-1 in NET formation, neutrophils were stimulated with β-glucan or PMA, followed by co-incubation with Dectin-1. Both β-glucan and PMA significantly upregulat-

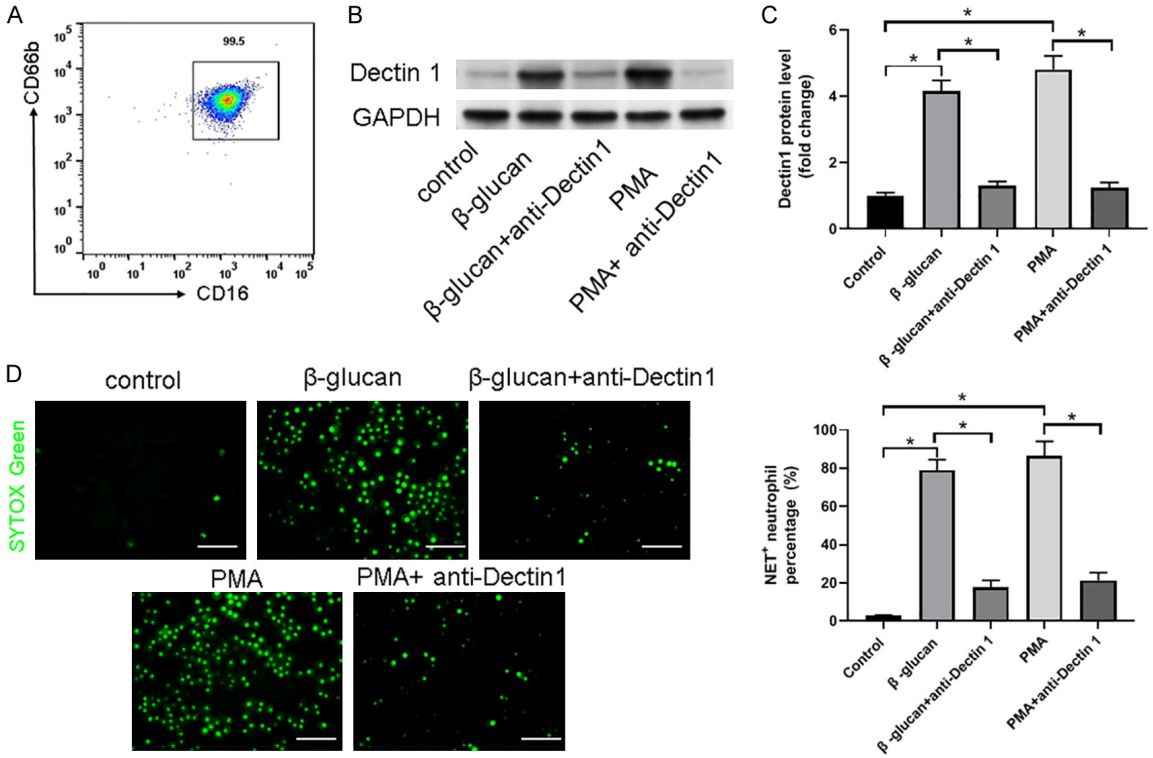

Figure 1. Dectin-1 induces neutrophil extracellular trap (NET) formation in human peripheral blood neutrophils. A: Flow cytometry analysis of $CD16^+$ $CD66b^+$ neutrophils. B, C: Immunoblotting and quantitative analysis of citrullinated histone H3 (H3Cit) levels in β-glucan- or phorbol myristate acetate (PMA)-treated neutrophils. D: Representative images of NET structures stained with SYTOX Green (Scale Bar = 25 μm), with corresponding quantification. *P < 0.05.

ed Dectin-1 protein expression compared with controls, while treatment with the Dectin-1 antibody markedly suppressed this upregulation (**Figure 1B**, **1C**). Confocal microscopy using Sytox Orange staining demonstrated that β-glucan or PMA induced the formation of NETs, whereas blockade of Dectin-1 significantly reduced NET production under both stimulation conditions (**Figure 1D**).

Dectin-1 knockdown inhibits NET formation in stimulated neutrophils

Immunofluorescence analysis revealed that stimulation with β-glucan- or PMA markedly increased the expression of MPO and NE, two key components of NETs. However, Dectin-1 antibody treatment effectively attenuated this increase (**Figure 2A**, **2B**). Besides, Dectin-1 blockade significantly reduced the elevated levels of dsDNA released by β-glucan- or PMA-treated neutrophils (**Figure 3A**). In addition, β-glucan- or PMA stimulation enhanced citrullinated histone H3 (H3Cit) expression-a hallmark of NETosis-which was also reversed by Dectin-1 inhibition (**Figure 3B**, **3C**). The above results demonstrate that Dectin-1 is required for efficient NET formation in response to β-glucan or PMA stimulation.

Dectin-1 facilitates NOX-dependent ROS generation following β-glucan stimulation

ROS are key mediators of NET formation. To determine whether Dectin-1-induced NET formation is dependent on NOX-mediated ROS, we measured ROS production using the DCFH-DA probe. β-glucan and PMA stimulation significantly promoted ROS generation in neutrophils, while Dectin-1 antibody treatment significantly suppressed this effect (**Figure 4A**). Given that both NADPH oxidase and mitochondria contribute to intracellular ROS production, we next used MitoSox Red, a mitochondrial superoxide (MitoSox) indicator, to assess the source of ROS induced by Dectin-1. Results showed a marked reduction in MitoSox Red fluorescence upon Dectin-1 blockade, indicating decreased

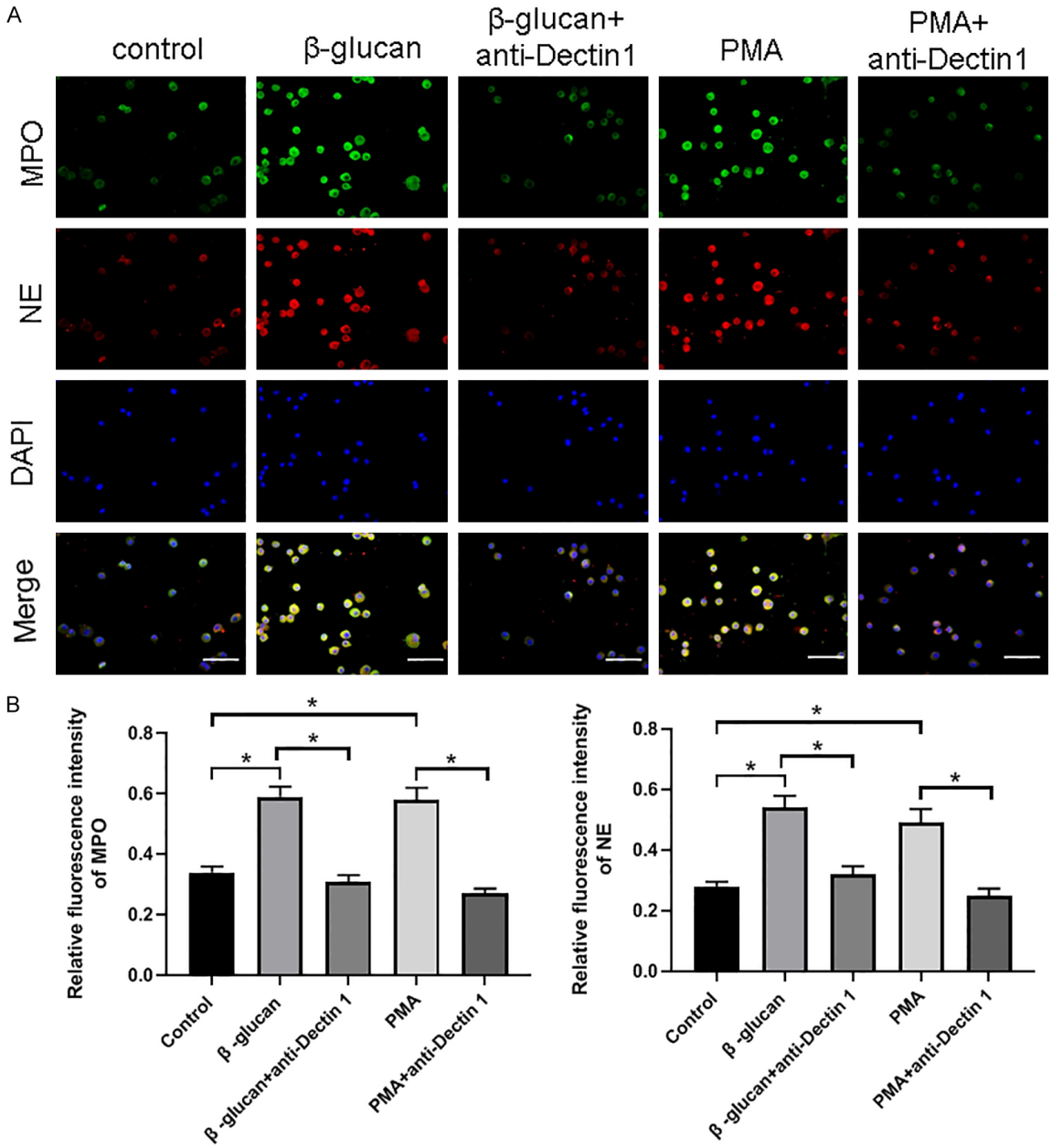

Figure 2. Dectin-1 promotes the formation of neutrophil extracellular traps (NETs) in neutrophils. A: Immunofluorescence (IF) staining of MPO (green), NE (red), and nuclei (blue) in β-glucan- or PMA-treated neutrophils (Scale Bar = 25 μm). B: Quantification of MPO and NE immunofluorescence staining images. *P < 0.05.

mitochondrial ROS generation (**Figure 4B**, **4C**). Furthermore, β-glucan and PMA induced an increase in the NADP+/NADPH ratio, reflecting enhanced NOX activity; this effect was reversed by Dectin-1 inhibition (**Figure 4D**). Western blot analysis showed elevated NOX2 expression following β-glucan or PMA stimulation, which was attenuated upon Dectin-1 antibody treatment (**Figure 4E**, **4F**). These results suggest that Dectin-1 might induce NET formation through a NOX-dependent ROS signaling mechanism.

Dectin-1 activates ERK and p38 MAPK signaling pathways

The mitogen-activated protein kinase (MAPK) signaling pathway, including the ERK and p38 cascades, is known to be activated by ROS and plays a critical role in NET formation [18]. To

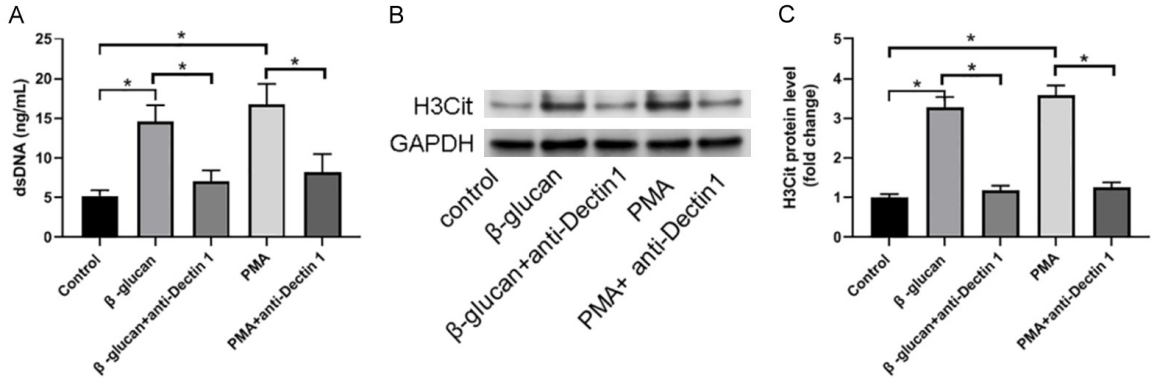

Figure 3. Dectin-1-dependent NET formation requires β-glucan- or PMA stimulation. A: Examination of dsDNA levels in the supernatants of β-glucan- or PMA-treated neutrophils. B, C: Immunoblots and quantification of H3Cit expression in β-glucan- or PMA-treated neutrophils. *P < 0.05.

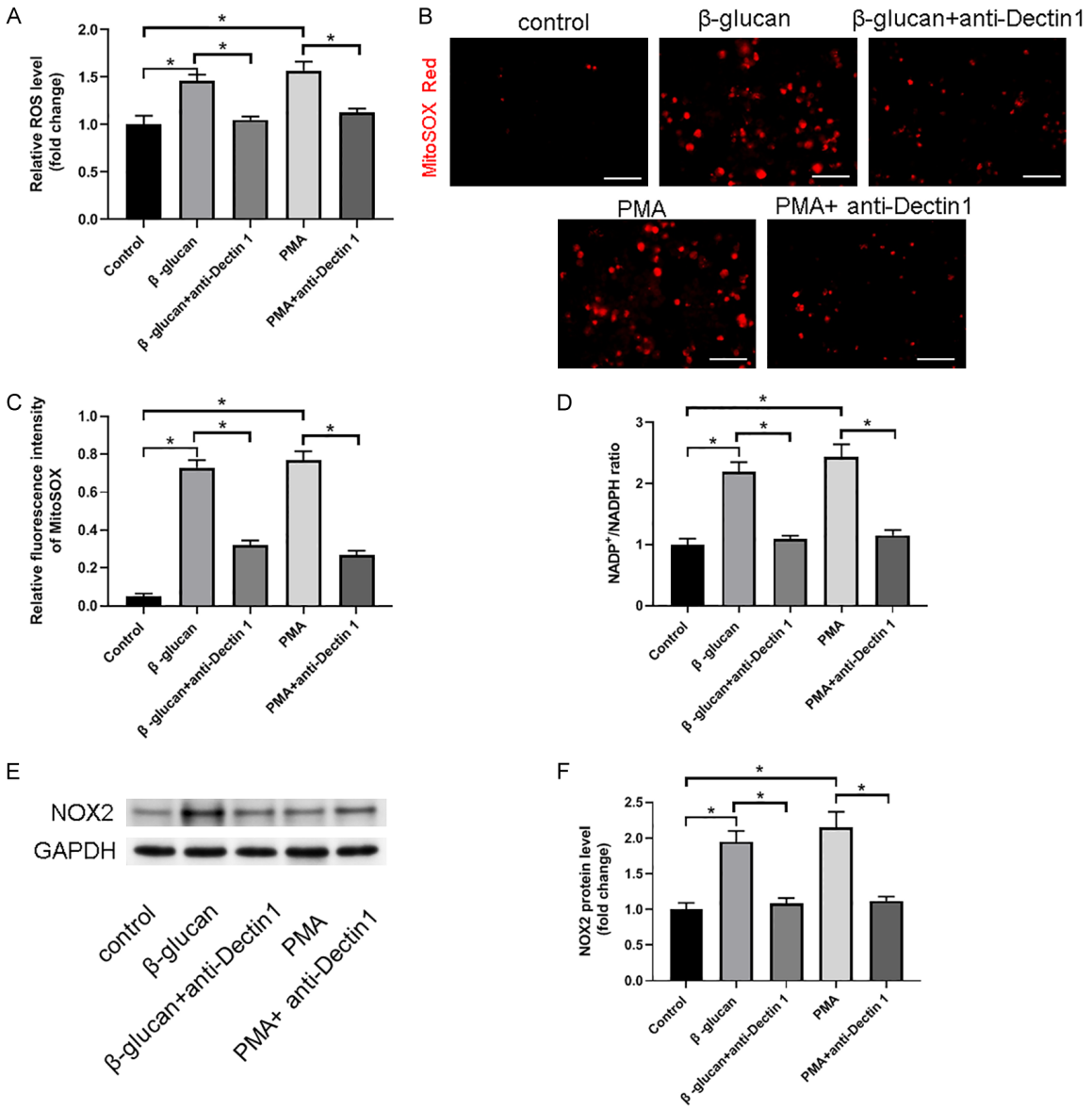

Figure 4. Dectin-1 triggers reactive oxygen species (ROS) production caused by NADPH oxidase (NOX) in neutrophils treated with β-glucan or PMA. A: Quantification of cellular ROS determined by 2',7'-dichlorodihydrofluorescein diacetate (DCFH-DA) probe. B: Representative images of MitoSOX Red staining in neutrophils (Scale Bar = 25 μm). C: Quantification of MPO and NE immunofluorescence staining images. D: Measurement of $NADP^+$/NADPH ratio by NADP+/NADPH detection Kit. E, F: Immunoblots and quantification of western blot results of NOX2. *P < 0.05.

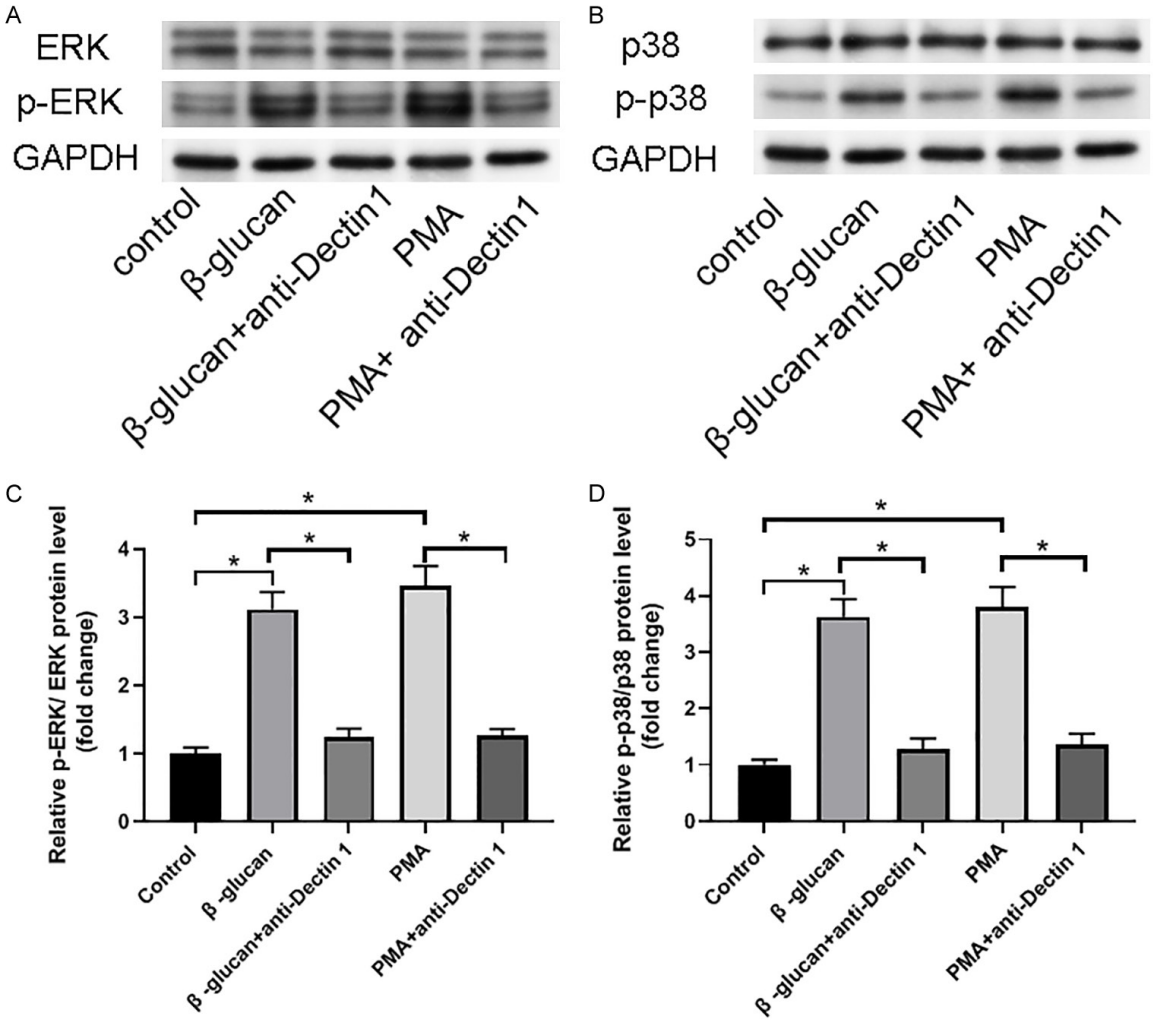

Figure 5. Dectin-1 promotes NET formation via activation of the extracellular regulated protein kinases (ERK) and p38 pathway. A, B: Immunoblots showing phosphorylation of ERK and p38 in neutrophils. C, D: Quantification of ERK and p38 by western blotting. *P < 0.05.

further investigate the downstream mechanisms of Dectin-1, we examined the expression of ERK and p38 signaling pathways. β-glucan or PMA significantly increased the phosphorylation of both ERK and p38, indicating activation of these pathways. However, Dectin-1 antibody treatment resulted in a significant decrease in the phosphorylation levels of ERK and p38 (**Figure 5A-D**). These data indicate that Dectin-1 contributes to NET formation, at least in part, via activation of the ERK and p38 MAPK signaling pathways.

Discussion

In this study, our findings suggested that Dectin-1 expression was increased in neutrophils upon stimulation with β-glucan or PMA, thereby promoting NET formation. Another novel finding is that Dectin-1 reduced NOX activity and ROS production in neutrophils, which in turn affected NET formation. In addition, Dectin-1 increased the activation of ERK and p38 signaling pathways in β-glucan- or PMA-treated neutrophils. These results sug-

gested that Dectin-1 promotes NET formation through a NOX-dependent signaling cascade, which may play a protective role during fungal infections.

Previous studies have shown that NETs play a dual role in fungal infections, either inhibiting or exacerbating disease progression, depending on the context [19]. In murine models, reticulated DNA structures co-localized with NET-associated proteins have been observed at sites of Candida albicans infection, such as subcutaneous abscesses [20]. Likewise, Aspergillus fumigatus infection in the lungs leads to neutrophil-mediated NET formation [21]. NETs contribute to fungal clearance by remodeling the cell wall of Candida albicans and enhancing recognition by Dectin1-expressing immune cells [22]. On one hand, NET-induced damage to fungal cell walls improves Dectin-1 immunorecognition of β-glucan; on the other hand, neutrophil-triggered disruption enhances fungal uptake by macrophages through enhanced cytokine production. Based on these findings, we hypothesized that the Dectin1/β-glucan axis may actively regulate NET formation in the context of fungal infections. Supporting this hypothesis, our in vitro experiments revealed that blockade of Dectin-1 in β-glucan-stimulated neutrophils significantly reduced the expression of NET-associated markers, including NE, MPO and HC3it, suggesting impaired NET formation.

Neutrophils, through a NOX-dependent mechanism, release protein-modified nuclear DNA into the extracellular space [23]. NOX2-derived ROS are critical for initiating chromatin dehistonization, a key event in NET formation. Previous studies have shown that inhibition of NADPH oxidase with DPI effectively suppresses NET generation [24]. The ERK signaling pathway has also been implicated in regulating NOX activity and ROS production, both of which are indispensable for NET release. Similarly, activation of the p38 MAPK pathway may facilitate chromatin decondensation by enhancing histone citrullination via peptidylarginine deiminase 4 (PAD4). ROS can activate the MAPK signaling pathway and its downstream ERK1/2 and p38, thereby promoting the production of NETs [25]. Dectin-1-mediated signaling has been shown to activate key intracellular pathways, including MAPK and nuclear factor-κB (NF-κB), thereby enhancing neutrophil-driven inflammatory responses and promoting ROS generation [26-28]. In this study, blockade of Dectin-1 with a specific antibody led to a significant reduction in NET formation, NOX2 protein expression, and ROS levels. Additionally, inhibition of Dectin-1 attenuated the phosphorylation of ERK and p38, two critical components of the MAPK signaling cascade. These findings provide mechanistic insight into the role of Dectin-1 in bridging fungal recognition and downstream neutrophil effector functions, particularly NET formation.

In conclusion, our study identifies Dectin-1 as a key regulator of NET formation and neutrophil-mediated antifungal immunity. Dectin-1 deficiency led to a reduction in the production of NOX-2-dependent NET production, thereby impairing the ability of neutrophils to trap and eliminate fungal pathogens (**Figure 6**). Our study delineated a novel Dectin-1-ERK/p38-NET signaling axis that serves as a frontline defense against fungal infection. However, whether this pathway exhibits pathogen specificity, such as responsiveness to other Dectin-1 ligands like α-mannan, warrants further investigation. Future studies should aim to validate our findings in animal models and assess their translational relevance in clinical settings. Elucidating the Dectin-1-NET regulatory mechanism may offer promising therapeutic strategies for managing fungal infections, especially in immunocompromised individuals.

Acknowledgements

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Disclosure of conflict of interest

None.

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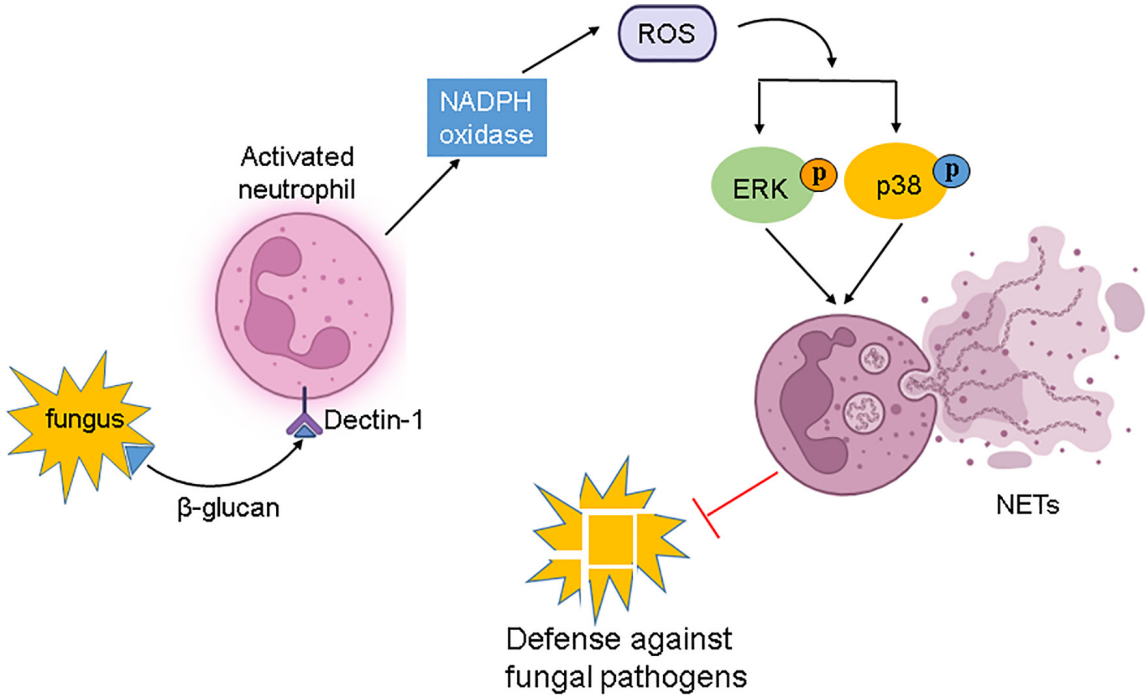

Figure 6. Schematic representation of the mechanism of action of Dectin1/β-glucan modulation of neutrophil extracellular traps in the treatment of fungal infections.

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