International Journal of Infection
ISSN 1972-6945 / 2022 vol. 6, ISSUE N. 1, January-April

IN BACTERIAL INFECTIONS, NEUTROPHIL RECEPTORS DETECT AND RESPOND TO PATHOGENS

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ABSTRACT

Neutrophils are the first immune cells that intervene after bacterial infection. These cells are the first line of defense in combatting infection by responding to and neutralizing pathogens. They have various receptors such as toll-like receptors (TLRs), NOD-like receptors (NLRs), Fc receptors (complement receptors (CRs)), pattern recognition receptors (PRRs), adhesion receptors, scavenger receptors, and chemokine/cytokine receptors, which are important for binding microorganisms. After neutrophil receptor binding, signaling cascades are activated which lead to gene expression changes that produce neutrophil activation. Then, reactive oxygen species (ROS) are produced which are toxic to bacteria. Additionally, neutrophils can produce proteases and antimicrobial peptides which break down bacterial cell walls and membranes, protecting the body from infection.

KEYWORDS: *infection, neutrophil, receptor, bacteria, pathogen, immunity, microbe*

INTRODUCTION

Bacterial infections occur when harmful bacteria invade and multiply within the host body, leading to a range of diseases. These infections can trigger immune responses, including the activation of neutrophils, which are a type of white blood cell and are among the first responders to microbial infection (1). They are part of the innate immune system and play a crucial role in defending against bacterial infections. Neutrophils are the first line of defense against infections and are highly effective at responding to and neutralizing pathogens (2).

DISCUSSION

Neutrophils perform various functions which include phagocytosis (the engulfment and digestion of pathogens and debris) (3), degranulation (the release of antimicrobial peptides and enzymes from granules to destroy pathogens) (4), the creation of neutrophil extracellular traps (NETs) (by expelling a web of DNA and antimicrobial proteins to trap and kill pathogens extracellularly) (4), and the production of cytokines that modulate the immune response and recruit other immune cells (5).

Receptors on the surface of neutrophils and other immune cells recognize and bind to specific molecules (ligands) on bacteria. This recognition is crucial for initiating an immune response. Neutrophils have various receptors on their surface that help them recognize, bind to, and respond to pathogens. Some key receptors that are found on neutrophils include

Received: 04 December, 2021
Accepted: 12 February, 2022

1972-6945 (2022)

toll-like receptors (TLRs), NOD-like receptors (NLRs), Fc receptors (complement receptors (CRs)), pattern recognition receptors (PRRs), adhesion receptors, scavenger receptors, and chemokine/cytokine receptors (6) (Table I).

Table I. *Some key neutrophil receptors that play a role in infection.*

Fcγ Receptors (FcγRs):	Bind IgG antibodies, leading to phagocytosis, antibody-dependent cellular cytotoxicity (ADCC), and release of inflammatory mediators.
Toll-like Receptors (TLRs):	Recognize components of microbial pathogens, such as lipopolysaccharides (TLR4) from Gram-negative bacteria or flagellin (TLR5).
NOD-like Receptors (NLRs):	Detect intracellular bacteria.
CR1 (CD35), CR3 (CD11b/CD18), CR4 (CD11c/CD18):	Bind to complement component C3b.
Fcγ Receptors (FcγRs):	Bind IgG antibodies, leading to phagocytosis, antibody-dependent cellular cytotoxicity (ADCC), and release of inflammatory mediators.
G-protein Coupled Receptors (GPCRs):	respond to chemokines, guiding neutrophils to infection sites.
Selectins:	E-selectin and P-selectin mediate the initial rolling of neutrophils on endothelial cells.
Integrins:	LFA-1 (CD11a/CD18) and Mac-1 (CD11b/CD18) mediate firm adhesion and transmigration.
Scavenger Receptors:	SR-A and CD36 involved in the recognition and phagocytosis of bacteria and apoptotic cells.
Formyl Peptide Receptors (FPRs):	Binds to N-formylmethionine-leucyl-phenylalanine (fMLP), a potent chemoattractant derived from bacteria.
C-type Lectin Receptors (CLRs):	recognize carbohydrate structures on pathogens.
Sialic acid-binding immunoglobulin-like lectins (Siglecs):	recognize sialic acid-containing structures on pathogens and host cells.
P-selectin glycoprotein ligand-1:	interacts with P-selectin and mediates rolling on activated endothelial cells.
CD14:	Acts as a co-receptor with TLR4 for the detection of bacterial lipopolysaccharide (LPS).

TLRs recognize pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharides (LPS) on bacterial surfaces (7). NLRs detect intracellular bacterial components, and Fc receptors bind to antibodies that are attached to bacteria, marking them for destruction (8).

Fc Receptors bind to the Fc region of antibodies that are attached to pathogens, facilitating phagocytosis and antibody-dependent cellular cytotoxicity (9). Fc gamma receptors (FcγR) bind to IgG antibodies and include subtypes like FcγRI, FcγRII, and FcγRIII, while Fc alpha receptors (FcαR) bind to IgA antibodies (10).

CRs recognize complement-coated pathogens, enhancing phagocytosis and inflammatory responses (11). CR1 (CD35) binds to C3b and C4b complement fragments. CR3 (CD11b/CD18, also known as Mac-1) binds to iC3b, a breakdown product of C3b. CR4 (CD11c/CD18) also interacts with iC3b and other complement fragments (12).

PRRs recognize PAMPs and damage-associated molecular patterns (DAMPs). TLRs recognize components of microbial pathogens, such as bacterial LPS (TLR4) and flagellin (TLR5) (13,14). NLRs detect intracellular pathogens and initiate inflammatory responses (7). C-type lectin receptors (CLRs) bind to carbohydrate structures on the surfaces of pathogens (15).

Adhesion receptors mediate the adhesion of neutrophils to the endothelium and their transmigration into tissues (16). Integrins, such as LFA-1 (CD11a/CD18) and Mac-1 (CD11b/CD18), interact with intercellular adhesion molecules (ICAMs) on endothelial cells (17,18). Selectins include L-selectin (CD62L), which mediates initial weak adhesion to the endothelium (19).

Scavenger receptors recognize and bind to a variety of ligands, including modified low-density lipoproteins (LDL) and microbial products. Scavenger receptor-A (SR-A) binds to a variety of polyanionic ligands, while CD36 binds to oxidized LDL and apoptotic cells (20).

Chemokine receptors guide neutrophils to the site of infection or inflammation by detecting chemokines. The receptors CXCR1 and CXCR2 bind to chemokines such as IL-8, which is crucial for neutrophil chemotaxis, and CCR1 and CCR2 respond to other chemokines involved in the recruitment of neutrophils (21).

The interaction between bacterial components and neutrophil receptors involves complex biochemical pathways such as chemotaxis, phagocytosis, degranulation and NETosis. In chemotaxis, neutrophils migrate towards the site of infection in response to chemical signals (chemokines) (22). During phagocytosis, neutrophils engulf and digest bacteria through a process facilitated by receptors such as TLRs and Fc receptors (6). Following phagocytosis there is degranulation, in which antimicrobial substances that destroy bacteria are released from neutrophil granules. During the process of NETosis, NETs are released, which are networks of extracellular fibers composed of DNA and antimicrobial proteins that trap and kill bacteria (23).

Upon receptor binding, signaling cascades are activated (e.g., MAPK, NF-κB) that lead to gene expression changes necessary for neutrophil activation. An oxidative burst follows, with the production of reactive oxygen species (ROS) that are toxic to bacteria. Neutrophils can also produce proteases and antimicrobial peptides, enzymes and peptides that break down bacterial cell walls and membranes.

CONCLUSIONS

Neutrophils are equipped with a diverse array of receptors that enable them to detect and respond to pathogens effectively, thus they play a critical role in the body's defense mechanisms. In bacterial infections, neutrophils use various receptors to detect and respond to pathogens through intricate molecular and biochemical processes. These responses involve a coordinated effort to locate, identify, and destroy bacterial invaders.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Malech HL, DeLeo FR, Quinn MT. The Role of Neutrophils in the Immune System: An Overview. *Methods in Molecular Biology (Clifton, NJ)*. 2014;1124:3-10. doi:https://doi.org/10.1007/978-1-62703-845-4_1
2. Liew PX, Kubes P. The Neutrophil's Role During Health and Disease. *Physiological Reviews*. 2019;99(2):1223-1248. doi:https://doi.org/10.1152/physrev.00012.2018
3. Lee WL, Harrison RE, Grinstein S. Phagocytosis by neutrophils. *Microbes and Infection*. 2003;5(14):1299-1306. doi:https://doi.org/10.1016/j.micinf.2003.09.014
4. Gierlikowska B, Stachura A, Gierlikowski W, Demkow U. Phagocytosis, Degranulation and Extracellular Traps Release by Neutrophils—The Current Knowledge, Pharmacological Modulation and Future Prospects. *Frontiers in Pharmacology*. 2021;12:666732. doi:https://doi.org/10.3389/fphar.2021.666732
5. Tecchio C, Micheletti A, Cassatella MA. Neutrophil-Derived Cytokines: Facts Beyond Expression. *Frontiers in Immunology*. 2014;5. doi:https://doi.org/10.3389/fimmu.2014.00508
6. Futosi K, Fodor S, Mócsai A. Neutrophil cell surface receptors and their intracellular signal transduction pathways. *International Immunopharmacology*. 2013;17(3):638-650. doi:https://doi.org/10.1016/j.intimp.2013.06.034
7. Mogensen TH. Pathogen Recognition and Inflammatory Signaling in Innate Immune Defenses. *Clinical Microbiology Reviews*. 2009;22(2):240-273. doi:https://doi.org/10.1128/cmr.00046-08
8. Franchi L, Warner N, Viani K, Nuñez G. Function of Nod-like receptors in microbial recognition and host defense. *Immunological Reviews*. 2009;227(1):106-128. doi:https://doi.org/10.1111/j.1600-065x.2008.00734.x
9. Tay MZ, Wiehe K, Pollara J. Antibody-Dependent Cellular Phagocytosis in Antiviral Immune Responses. *Frontiers in Immunology*. 2019;10. doi:https://doi.org/10.3389/fimmu.2019.00332
10. Okun E, Mattson MP, Arumugam TV. Involvement of Fc Receptors in Disorders of the Central Nervous System. *Neuromolecular medicine*. 2010;12(2):164-178. doi:https://doi.org/10.1007/s12017-009-8099-5

11. Dunkelberger JR, Song WC. Complement and its role in innate and adaptive immune responses. *Cell Research*. 2009;20(1):34-50. doi:https://doi.org/10.1038/cr.2009.139
12. Lubbers R, van Essen MF, van Kooten C, Trouw LA. Production of complement components by cells of the immune system. *Clinical & Experimental Immunology*. 2017;188(2):183-194. doi:https://doi.org/10.1111/cei.12952
13. Trinchieri G, Sher A. Cooperation of Toll-like receptor signals in innate immune defence. *Nature Reviews Immunology*. 2007;7(3):179-190. doi:https://doi.org/10.1038/nri2038
14. Kawai T, Akira S. TLR signaling. *Cell Death and Differentiation*. 2006;13(5):816-825. doi:https://doi.org/10.1038/sj.cdd.4401850
15. Li TH, Liu L, Hou YY, Shen SN, Wang TT. C-type lectin receptor-mediated immune recognition and response of the microbiota in the gut. *Gastroenterology Report*. 2019;7(5):312-321. doi:https://doi.org/10.1093/gastro/goz028
16. Choi EY, Santoso S, Chavakis T. Mechanisms of neutrophil transendothelial migration. *Frontiers in Bioscience*. 2009;14(5):1596-1605. doi:https://doi.org/10.2741/3327
17. Pflugfelder SC, Stern M, Zhang S, Shojaei A. LFA-1/ICAM-1 Interaction as a Therapeutic Target in Dry Eye Disease. *Journal of Ocular Pharmacology and Therapeutics*. 2017;33(1):5-12. doi:https://doi.org/10.1089/jop.2016.0105
18. Hashimoto M, Shingu M, Ezaki I, et al. Production of soluble ICAM-1 from human endothelial cells induced by IL-1? and TNF-? *Inflammation*. 1994;18(2):163-173. doi:https://doi.org/10.1007/bf01534557
19. Granger DN, Senchenkova E. Leukocyte–Endothelial Cell Adhesion. Nih.gov. Published 2010. https://www.ncbi.nlm.nih.gov/books/NBK53380/
20. Alquraini A, El Khoury J. Scavenger receptors. *Current Biology*. 2020;30(14):R790-R795. doi:https://doi.org/10.1016/j.cub.2020.05.051
21. Smithson A, Sarrias MR, Barceló J, et al. Expression of Interleukin-8 Receptors (CXCR1 and CXCR2) in Premenopausal Women with Recurrent Urinary Tract Infections. *Clinical and Vaccine Immunology*. 2005;12(12):1358-1363. doi:https://doi.org/10.1128/cdli.12.12.1358-1363.2005
22. Petri B, Sanz MJ. Neutrophil chemotaxis. *Cell and Tissue Research*. 2018;371(3):425-436. doi:https://doi.org/10.1007/s00441-017-2776-8
23. Mutua V, Gershwin LJ. A Review of Neutrophil Extracellular Traps (NETs) in Disease: Potential Anti-NETs Therapeutics. *Clinical Reviews in Allergy & Immunology*. 2021;61(2):194-211. doi:https://doi.org/10.1007/s12016-020-08804-7