



THE ROLE OF INTERLEUKIN-1 IN BACTERIAL INFECTIONS

Elena Chiappini^{1*} and Gabriele Bazzocchi²

¹ Department of Health Sciences, Section of Pediatrics, University of Florence, Florence, Italy;

² Montecatone Rehabilitation Institute, University of Bologna, Imola, Italy.

*Correspondence to:

Prof. Elena Chiappini,
Department of Health Sciences,
Section of Pediatrics,
University of Florence,
Florence, Italy.
e-mail: elena.chiappini@unifi.it

ABSTRACT

Cytokines are small, numerous immunoregulatory molecules that play an important role in immune and inflammatory responses. Interleukin-1 (IL-1) is an important cytokine in the body's defense against foreign agents, including bacteria, but when overproduced, it is a highly inflammatory molecule. Targeting IL-1 may be a relevant strategy in many inflammatory diseases including those caused by microorganisms. IL-1 exists in two main forms, IL-1 α and IL-1 β , and both are activated after maturation of their precursors. IL-1 β is produced mainly by macrophage cells and plays an inflammatory role in many diseases, including infectious ones. IL-1 β generates the inactive precursor pro-IL-1 β that is cleaved by the caspase-1 enzyme and then becomes active. IL-1 β binds to the receptor and triggers a signaling cascade involving the adaptor protein MyD88 and leads to activation of nuclear factor kappa B (NF- κ B). Targeting IL-1 in infections reduces inflammation and improves the course of the disease.

KEYWORDS: *Cytokine, IL-1, bacteria, infection, immune response*

INTRODUCTION

Cytokines are small proteins that play crucial roles in cell signaling, particularly in immune responses (1). Among these, Interleukin-1 (IL-1) stands out due to its significant involvement in inflammatory processes and immune defense mechanisms (2). This paper explores the functions of IL-1 in the context of bacterial infections, highlighting its dual roles in promoting and regulating inflammation, as well as its potential as a therapeutic target.

DISCUSSION

Cytokines are a broad category of signaling molecules that mediate and regulate immunity, inflammation, and hematopoiesis (3). They include interleukins (ILs), interferons, tumor necrosis factors, chemokines, and growth factors (4). ILs are a group of cytokines that were first seen to be expressed by leukocytes (5). IL-1 is one of the most studied cytokines within this group and is known for its role in the inflammatory response (6).

IL-1 exists in two primary forms as IL-1 α and IL-1 β , and both are produced after activation of their precursors (7). IL-1 β is particularly significant in bacterial infections due to its potent inflammatory effects (8). It is primarily produced by macrophages, monocytes, and dendritic cells in response to microbial stimuli (9).

IL-1 β is synthesized as an inactive precursor (pro-IL-1 β) that is cleaved by the enzyme caspase-1 to become active (10). This cleavage occurs within a complex known as the inflammasome, which is activated by various pathogen-

Received: 21 February, 2022
Accepted: 08 September, 2022

1972-6945 (2022)

Copyright © by Biolife-Publisher

This publication and/or article is for individual use only and may not be further reproduced without written permission from the copyright holder. Unauthorized reproduction may result in financial and other penalties. Disclosure: all authors report no conflicts of interest relevant to this article.

associated molecular patterns (PAMPs) found on bacteria (10). The most well-characterized inflammasome in this context is the NLRP3 inflammasome, which responds to a variety of bacterial components and stress signals (11).

Once activated, IL-1 β binds to the IL-1 receptor type 1 (IL-1R1) on target cells, initiating a signaling cascade that involves the adaptor protein MyD88 and leads to the activation of nuclear factor-kappa B (NF- κ B) and mitogen-activated protein kinases (MAPKs) which results in the transcription of pro-inflammatory genes and leads to the production of other cytokines, chemokines, and adhesion molecules that recruit and activate additional immune cells (12).

The primary function of IL-1 in bacterial infections is to coordinate the inflammatory response, which is crucial for controlling and eliminating pathogens (13). IL-1 β enhances the migration of neutrophils to the site of infection, promotes phagocytosis, and stimulates the production of antimicrobial peptides (14). Additionally, it induces fever by acting on the hypothalamus, creating an environment less favorable for bacterial growth (15). However, the powerful inflammatory response driven by IL-1 β must be tightly regulated to prevent tissue damage (16). Excessive or prolonged IL-1 β production can lead to chronic inflammation and tissue injury, contributing to diseases such as sepsis, chronic obstructive pulmonary disease (COPD), and inflammatory bowel disease (IBD) (17,18).

IL-1 is important for the immune defense against bacterial infections. *Staphylococcus aureus* is a bacterium that can cause severe infections such as sepsis and endocarditis (19). IL-1 β plays a crucial role in recruiting neutrophils to sites of infection, which is essential for controlling *S. aureus* (20). However, the bacterium can evade immune responses by producing factors that inhibit IL-1 β production or signaling. In *Mycobacterium tuberculosis* infection, IL-1 β is involved in the formation of granulomas, which are structures that contain the infection (21). While beneficial in containing the bacteria, excessive IL-1 β can lead to tissue damage and exacerbate disease symptoms (22). IL-1 β contributes to the inflammatory response that clears the bacteria *Escherichia coli*, responsible for urinary tract infections (UTIs). However, excessive IL-1 β can lead to discomfort and tissue damage in the urinary tract (23).

Given the potent effects of IL-1 β , its activity is subject to multiple levels of regulation. The production of IL-1 β is controlled at the transcriptional level by NF- κ B and other transcription factors (24). Additionally, the activation of pro-IL-1 β by caspase-1 is a tightly regulated process, requiring the assembly of the inflammasome.

Once secreted, IL-1 β activity is further regulated by natural inhibitors such as IL-1 receptor antagonist (IL-1Ra), which binds to IL-1R1 without inducing signaling, thus blocking IL-1 β from exerting its effects (25). Soluble IL-1 receptors can also act as decoys, sequestering IL-1 β and preventing it from binding to cell surface receptors (26).

Given the central role of IL-1 β in inflammation and its contribution to tissue damage in bacterial infections, targeting IL-1 β signaling represents a promising therapeutic strategy (27,28). IL-1Ra (anakinra) is already used in the treatment of various inflammatory diseases such as rheumatoid arthritis. In bacterial infections, modulating IL-1 β activity could help control excessive inflammation and reduce tissue damage (29). For instance, in sepsis, blocking IL-1 β could mitigate the overwhelming inflammatory response that leads to organ failure. However, such interventions must be carefully balanced to avoid impairing the host's ability to control the infection.

CONCLUSIONS

IL-1 β is a pivotal cytokine in the immune response to bacterial infections and helps to orchestrate inflammation and control pathogen spread. Its potent effects on immune cell recruitment and activation are crucial for effective defense against bacteria but also pose risks of excessive inflammation and tissue damage. Understanding the precise mechanisms of IL-1 β regulation and signaling provides valuable insights for developing targeted therapies to manage bacterial infections and their associated inflammatory responses. As research progresses, the potential for therapeutic modulation of IL-1 β activity holds promise for improving outcomes in bacterial diseases.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. *Seminars in Immunopathology*. 2017;39(5):517-528. doi:https://doi.org/10.1007/s00281-017-0639-8
2. Mantovani A, Dinarello CA, Molgora M, Garlanda C. IL-1 and related cytokines in innate and adaptive immunity in health and disease. *Immunity*. 2019;50(4):778-795. doi:https://doi.org/10.1016/j.immuni.2019.03.012

3. Dinarello CA. Overview of the IL-1 family in innate inflammation and acquired immunity. *Immunological Reviews*. 2017;281(1):8-27. doi:<https://doi.org/10.1111/imr.12621>
4. Dinarello CA. Historical insights into cytokines. *European Journal of Immunology*. 2007;37(S1):S34-S45. doi:<https://doi.org/10.1002/eji.200737772>
5. Strober W, James SP. The Interleukins. *Pediatric Research*. 1988;24(5):549-557. doi:<https://doi.org/10.1203/00006450-198811000-00001>
6. Tetè S, Tripodi D, Rosati M, et al. IL-37 (IL-1F7) the Newest Anti-Inflammatory Cytokine Which Suppresses Immune Responses and Inflammation. *International Journal of Immunopathology and Pharmacology*. 2012;25(1):31-38. doi:<https://doi.org/10.1177/039463201202500105>
7. Arend WP, Palmer G, Gabay C. IL-1, IL-18, and IL-33 families of cytokines. *Immunological Reviews*. 2008;223(1):20-38. doi:<https://doi.org/10.1111/j.1600-065x.2008.00624.x>
8. Man SM. Inflammasomes in the gastrointestinal tract: infection, cancer and gut microbiota homeostasis. *Nature Reviews Gastroenterology & Hepatology*. 2018;15(12):721-737. doi:<https://doi.org/10.1038/s41575-018-0054-1>
9. Cho MH, Ahn HJ, Ha HJ, et al. *Bacillus anthracis* Capsule Activates Caspase-1 and Induces Interleukin-1 β Release from Differentiated THP-1 and Human Monocyte-Derived Dendritic Cells. *Infection and Immunity*. 2010;78(1):387-392. doi:<https://doi.org/10.1128/iai.00956-09>
10. van de Veerdonk FL, Joosten LA, Devesa I, et al. Bypassing Pathogen-Induced Inflammasome Activation for the Regulation of Interleukin-1 β Production by the Fungal Pathogen *Candida albicans*. *The Journal of Infectious Diseases*. 2009;199(7):1087-1096. doi:<https://doi.org/10.1086/597274>
11. Paik S, Kim JK, Silwal P, Sasakawa C, Jo EK. An update on the regulatory mechanisms of NLRP3 inflammasome activation. *Cellular & Molecular Immunology*. 2021;18(5):1141-1160. doi:<https://doi.org/10.1038/s41423-021-00670-3>
12. Ge H, Farris CM, Tong M, Maina A, Richards AL. Transcriptional profiles of cytokines and chemokines reveal important pro-inflammatory response from endothelial cells during *Orientia tsutsugamushi* infection. *Microbes and Infection*. 2019;21(7):313-320. doi:<https://doi.org/10.1016/j.micinf.2019.01.002>
13. Slaats J, ten Oever J, van de Veerdonk FL, Netea MG. IL-1 β /IL-6/CRP and IL-18/ferritin: Distinct Inflammatory Programs in Infections. Bliska JB, ed. *PLOS Pathogens*. 2016;12(12):e1005973. doi:<https://doi.org/10.1371/journal.ppat.1005973>
14. Shanmugham LN, Petrarca C, Castellani ML, et al. IL-1 β Induces Alkaline Phosphatase in Human Phagocytes. *Archives of Medical Research*. 2006;38(1):39-44. doi:<https://doi.org/10.1016/j.arcmed.2006.05.016>
15. Alheim K, Chai Z, Fantuzzi G, et al. Hyperresponsive febrile reactions to interleukin (IL) 1 and IL-1, and altered brain cytokine mRNA and serum cytokine levels, in IL-1-deficient mice. *Proceedings of the National Academy of Sciences*. 1997;94(6):2681-2686. doi:<https://doi.org/10.1073/pnas.94.6.2681>
16. Zahid A, Li B, Kombe AJK, Jin T, Tao J. Pharmacological Inhibitors of the NLRP3 Inflammasome. *Frontiers in Immunology*. 2019;10. doi:<https://doi.org/10.3389/fimmu.2019.02538>
17. Lopez-Castejon G, Brough D. Understanding the mechanism of IL-1 β secretion. *Cytokine & Growth Factor Reviews*. 2011;22(4):189-195. doi:<https://doi.org/10.1016/j.cytogfr.2011.10.001>
18. Zhen Y, Zhang H. NLRP3 Inflammasome and Inflammatory Bowel Disease. *Frontiers in Immunology*. 2019;10. doi:<https://doi.org/10.3389/fimmu.2019.00276>
19. Brauweiler AM, Goleva E, Leung DYM. Staphylococcus aureus Lipoteichoic Acid Damages the Skin Barrier through an IL-1-Mediated Pathway. *Journal of Investigative Dermatology*. 2019;139(8):1753-1761.e4. doi:<https://doi.org/10.1016/j.jid.2019.02.006>
20. Constanza Giaì, Gonzalez CD, Sabbione F, et al. *Staphylococcus aureus* Induces Shedding of IL-1RII in Monocytes and Neutrophils. *Journal of Innate Immunity*. 2016;8(3):284-298. doi:<https://doi.org/10.1159/000443663>
21. Moorlag SJCFM, Khan N, Novakovic B, et al. β -Glucan Induces Protective Trained Immunity against Mycobacterium tuberculosis Infection: A Key Role for IL-1. *Cell Reports*. 2020;31(7):107634. doi:<https://doi.org/10.1016/j.celrep.2020.107634>

22. Conti P, Pregliasco FE, Bellomo RG, et al. Mast Cell Cytokines IL-1, IL-33, and IL-36 Mediate Skin Inflammation in Psoriasis: A Novel Therapeutic Approach with the Anti-Inflammatory Cytokines IL-37, IL-38, and IL-1Ra. *International Journal of Molecular Sciences*. 2021;22(15):8076. doi:<https://doi.org/10.3390/ijms22158076>
23. Jung JH, Hong HJ, Aziz Ghaderpour, et al. Differential interleukin-1 β induction by uropathogenic *Escherichia coli* correlates with its phylotype and serum C-reactive protein levels in Korean infants. *Scientific Reports*. 2019;9(1). doi:<https://doi.org/10.1038/s41598-019-52070-3>
24. Karin M, Ben-Neriah Y. Phosphorylation Meets Ubiquitination: The Control of NF- κ B Activity. *Annual Review of Immunology*. 2000;18(1):621-663. doi:<https://doi.org/10.1146/annurev.immunol.18.1.621>
25. Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. *Blood*. 2011;117(14):3720-3732. doi:<https://doi.org/10.1182/blood-2010-07-273417>
26. Kondera-Anasz Z, Sikora J, Mielczarek-Palacz A, Jońca M. Concentrations of interleukin (IL)-1 α , IL-1 soluble receptor type II (IL-1 sRII) and IL-1 receptor antagonist (IL-1 Ra) in the peritoneal fluid and serum of infertile women with endometriosis. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2005;123(2):198-203. doi:<https://doi.org/10.1016/j.ejogrb.2005.04.019>
27. Schauer AE, Klassert TE, Lachner C von, et al. IL-37 Causes Excessive Inflammation and Tissue Damage in Murine Pneumococcal Pneumonia. *Journal of Innate Immunity*. 2017;9(4):403-418. doi:<https://doi.org/10.1159/000469661>
28. Dinarello CA. Anti-cytokine therapeutics and infections. *Vaccine*. 2003;21:S24-S34. doi:[https://doi.org/10.1016/s0264-410x\(03\)00196-8](https://doi.org/10.1016/s0264-410x(03)00196-8)
29. Labzin LI, Lauterbach MAR, Latz E. Interferons and inflammasomes: Cooperation and counterregulation in disease. *Journal of Allergy and Clinical Immunology*. 2016;138(1):37-46. doi:<https://doi.org/10.1016/j.jaci.2016.05.010>