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

IL-1 INDUCES NF-kB IN INFECTIOUS DISEASES

P. Antinolfi*

Department of Surgical and Biomedical Sciences, University of Perugia, Perugia, Italy.

Correspondence to:
Pierluigi Antinolfi,
Department of Surgical and Biomedical Sciences,
University of Perugia,
Perugia, Italy.
e-mail: pantinolfi@gmail.com

ABSTRACT

Cytokines are proteins that mediate the immune response and act as signaling molecules in inflammatory processes. Pathogens activate the immune and inflammatory response which is mediated by cytokines. The most studied cytokines in the inflammatory response are interleukin (IL)-1, tumor necrosis factor (TNF), and interferon (IFN)-γ. These cytokines intervene to attack pathogens but their overexpression causes inflammation. In bacterial infections, IL-1β is secreted and induces nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation with subsequent release of other pro-inflammatory cytokines, such as TNF. This cascade of inflammatory cytokines can be very harmful and can even lead to death. Sepsis is a severe systemic infection with IL-1-mediated NF-kB activation that leads to dysregulation of inflammatory mediators, contributing to the disease. In sepsis, NF-kB activation is crucial for the host defense mechanism, but can also induce a "cytokine storm" that leads to multiorgan failure and death. Viral infection activates NF-kB to control virus replication and spread, but excessive activation can contribute to inflammation and lung damage. In conclusion, understanding the mechanisms of IL-1 in NF-kB activation in infections is important for more effective therapy.

KEYWORDS: *IL-1, NF-kB, infection, cytokine, immunity, inflammation, signal pathway*

INTRODUCTION

Cytokines are small proteins released by cells, particularly those of the immune system, that act as signaling molecules to regulate immunity, inflammation, and hematopoiesis. Infections can trigger a wide range of immune responses, among which the production of cytokines is crucial.

In infections, cytokines are activated after pathogen recognition (1). When a pathogen (such as bacteria, viruses, fungi, or parasites) enters the body, immune cells recognize it through pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) (1). These receptors detect pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) (2).

The recognition of pathogens leads to the activation of immune cells, which then release cytokines. Cytokines, such as interleukins (ILs), interferons (IFNs), tumor necrosis factors (TNFs), and chemokines, play vital roles in orchestrating the immune response and, when they are overexpressed, induce inflammation (3).

Pro-inflammatory cytokines such as IL-1, IL-6, TNF-α, and IFN-γ promote inflammation to help eliminate pathogens (4,5). Anti-inflammatory cytokines, such as IL-10 and TGF-β, regulate and suppress the inflammatory response to prevent excessive damage to the host (6).

Received: 18 February, 2022
Accepted: 13 April, 2022

1972-6945 (2022)

A severe, uncontrolled release of pro-inflammatory cytokines can lead to a "cytokine storm," which can cause systemic inflammation, multi-organ failure, and even death (7,8). This condition is observed in severe infections like COVID-19, influenza, sepsis, and certain autoimmune diseases (9).

Rheumatoid arthritis is mediated by the excessive production of TNF-α and IL-6 which leads to chronic inflammation in the joints (10). In inflammatory bowel disease (IBD), there is dysregulated cytokine production involving TNF, IL-12, and IL-23, which causes chronic inflammation in the gastrointestinal tract (11). In systemic lupus erythematosus (SLE), the overproduction of IFN-α and other cytokines contributes to systemic inflammation and organ damage (12).

Immunodeficiency disorders also involve the dysregulation of cytokines and other immunoproteins, including antibodies. Disorders like Severe Combined Immunodeficiency (SCID) involve deficiencies in cytokine signaling pathways, leading to a severely compromised immune response (13).

Additionally, certain cytokines can promote tumor growth and metastasis. For instance, IL-6 and IL-8 are associated with tumor progression in various cancers (14). Conversely, cytokine-based therapies (like IFN-α and IL-2) are used to treat some cancers by enhancing the immune response against tumor cells (15). However, this treatment is still being investigated and further studies are needed to improve this therapy.

Understanding the role of cytokines in infections and related disorders is critical for developing therapeutic strategies. Targeted therapies that modulate cytokine activity (e.g., monoclonal antibodies against specific cytokines) have been developed to treat various inflammatory and autoimmune diseases, showcasing the importance of cytokines in both health and disease.

DISCUSSION

IL-1 is a key pro-inflammatory cytokine involved in various immune responses and is a potent inducer of inflammation. It exists in two forms: IL-1α and IL-1β, with IL-1β being the most extensively studied due to its role in inflammatory processes. IL-1β is produced primarily by activated macrophages and plays a critical role in host defense against infections (16). It acts by binding to the IL-1 receptor (IL-1R) on target cells, initiating a cascade of signaling events that lead to inflammation and immune activation (17).

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a family of transcription factors that regulate the expression of genes involved in immune and inflammatory responses, cell proliferation, and survival, and it is a central regulator of the immune response (18). NF-κB is activated in response to various stimuli, including cytokines such as IL-1, microbial products, and stress (19). The NF-κB family consists of several proteins, including RelA (p65), RelB, c-Rel, p50, and p52, which can form various dimeric complexes to modulate gene expression (18).

IL-1 induces NF-κB activation by binding to IL-1R, causing the recruitment of adapter proteins and the activation of TAK1 and IκB Kinase (IKK), which leads to NF-κB translocation (20). IL-1β binds to the IL-1 receptor type I (IL-1RI) on the cell surface. This receptor complex also includes the accessory protein IL-1 receptor accessory protein (IL-1RAcP). Upon IL-1 binding, the receptor complex recruits adapter proteins such as myeloid differentiation primary response (88MyD88) and IL-1 receptor-associated kinase (IRAK) (21). These adapters facilitate the downstream signaling cascade. The formation of the receptor complex leads to the activation of transforming growth factor-beta-activated kinase 1 (TAK1). TAK1 plays a crucial role in transmitting signals from the IL-1 receptor to downstream effectors. TAK1 activates the IκB kinase (IKK) complex, which consists of IKKα, IKKβ, and NF-κB essential modulator (NEMO) (22). The IKK complex phosphorylates the inhibitor of NF-κB (IκB), leading to its ubiquitination and subsequent degradation by the proteasome (23). The degradation of IκB releases NF-κB dimers, predominantly the p65/p50 complex, allowing them to translocate into the nucleus (24). Once in the nucleus, NF-κB binds to specific DNA sequences in the promoters of target genes, initiating their transcription.

The role of NF-kB in infection

In bacterial infections, IL-1β-induced NF-κB activation plays a critical role in orchestrating the host immune response (25). For example, during infection with Escherichia coli or Staphylococcus aureus, the activation of NF-κB leads to the production of pro-inflammatory cytokines, chemokines, and adhesion molecules (26). These mediators enhance the recruitment and activation of neutrophils and macrophages to the site of infection, facilitating the clearance of bacteria.

Sepsis is a severe systemic inflammatory response to bacterial infection that is characterized by excessive cytokine production, including IL-1β (27). NF-κB activation in sepsis leads to the upregulation of inflammatory mediators like TNF and IL-6, contributing to the pathophysiology of the disease (27). Dysregulated NF-κB activation can result in a cytokine storm, leading to multi-organ failure and high mortality rates.

In viral infections, NF-κB activation is crucial for the host defense mechanism. Viruses such as influenza and HIV exploit the NF-κB pathway to enhance their replication and evade the immune system (28).

Influenza virus infection activates NF-κB, leading to the production of type I IFNs and pro-inflammatory cytokines (29). While NF-κB activation is essential for controlling viral replication and spreading, excessive activation can contribute to lung inflammation and damage.

HIV-1 utilizes NF-κB to promote its replication. The virus activates NF-κB to enhance the transcription of its genome, integrated into the host cell DNA (30). Persistent NF-κB activation in HIV infection is associated with chronic inflammation and immune activation, contributing to disease progression and co-morbidities (31).

In COVID-19, severe cases are often characterized by the hyperactivation of NF-κB, leading to a cytokine storm (32). Elevated levels of IL-1β, IL-6, and TNF are observed in critically ill patients, contributing to acute respiratory distress syndrome (ARDS) and systemic inflammation (33).

NF-κB activation also plays a role in the immune response to fungal and parasitic infections (34). Infections caused by Candida species trigger NF-κB activation, leading to the production of pro-inflammatory cytokines that are essential for fungal clearance (35). However, excessive inflammation can result in tissue damage and contribute to disease severity.

In malaria, caused by Plasmodium species, NF-κB activation in response to parasitic infection leads to the production of inflammatory cytokines (36). While this response is necessary for controlling parasite replication, dysregulated NF-κB activation can contribute to severe malaria pathology, including cerebral malaria (37).

Targeting the IL-1/NF-κB signaling pathway holds therapeutic potential for managing infectious diseases that are characterized by excessive inflammation. Several strategies are being explored including IL-1 blockade, NF-κB inhibitors, and cytokine modulation.

Agents such as Anakinra (IL-1 receptor antagonist) and Canakinumab (anti-IL-1β monoclonal antibody) have shown efficacy in reducing inflammation in conditions like sepsis and COVID-19. By inhibiting IL-1 signaling, these therapies can attenuate NF-κB activation and its downstream inflammatory effects.

Direct inhibitors of NF-κB signaling are also under investigation. These include small molecules that inhibit IKK activation or NF-κB translocation. However, due to the broad role of NF-κB in immune responses, careful consideration of potential immunosuppressive effects is necessary.

Modulating the balance of pro- and anti-inflammatory cytokines can help control excessive NF-κB activation. For example, enhancing IL-10 production or signaling can provide an anti-inflammatory counterbalance to IL-1β-induced NF-κB activation.

CONCLUSIONS

IL-1-induced NF-κB activation plays a critical role in the immune response to infections. While this pathway is essential for pathogen clearance and immune activation, its dysregulation can lead to excessive inflammation and tissue damage, contributing to the pathology of various infectious diseases. Understanding the intricate mechanisms of IL-1/NF-κB signaling and its impact on infectious diseases opens avenues for targeted therapeutic interventions aimed at modulating inflammation and improving clinical outcomes.

Conflict of interest

The author declares that they have no conflict of interest.

REFERENCES

1. 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
2. Roh JS, Sohn DH. Damage-Associated Molecular Patterns in Inflammatory Diseases. *Immune Network*. 2018;18(4). doi:https://doi.org/10.4110/in.2018.18.e27
3. Steinke J, Borish L. 3. Cytokines and chemokines. *Journal of Allergy and Clinical Immunology*. 2006;117(2):S441-S445. doi:https://doi.org/10.1016/j.jaci.2005.07.001
4. Zhang JM, An J. Cytokines, Inflammation, and Pain. *International Anesthesiology Clinics*. 2007;45(2):27-37. doi:https://doi.org/10.1097/AIA.0b013e318034194e
5. Schroder K, Hertzog PJ, Ravasi T, Hume DA. Interferon-gamma: an Overview of signals, Mechanisms and Functions. *Journal of Leukocyte Biology*. 2004;75(2):163-189. doi:https://doi.org/10.1189/jlb.0603252

6. Sanjabi S, Zenewicz LA, Kamanaka M, Flavell RA. Anti-inflammatory and pro-inflammatory roles of TGF-β, IL-10, and IL-22 in immunity and autoimmunity. *Current Opinion in Pharmacology*. 2009;9(4):447-453. doi:https://doi.org/10.1016/j.coph.2009.04.008
7. Fajgenbaum DC, June CH. Cytokine Storm. Longo DL, ed. *New England Journal of Medicine*. 2020;383(23):2255-2273. doi:https://doi.org/10.1056/nejmra2026131
8. Jaffer U, Wade RG, Gourlay T. Cytokines in the systemic inflammatory response syndrome: a review. *HSR Proceedings in Intensive Care and Cardiovascular Anesthesia*. 2010:2(3);161-175.
9. Oldstone MBA, Rosen H. Cytokine Storm Plays a Direct Role in the Morbidity and Mortality from Influenza Virus Infection and is Chemically Treatable with a Single Sphingosine-1-Phosphate Agonist Molecule. *Current Topics in Microbiology and Immunology*. 2014;378:129-147. doi:https://doi.org/10.1007/978-3-319-05879-5_6
10. Farrugia M, Baron B. The role of TNF-α in rheumatoid arthritis: a focus on regulatory T cells. *Journal of Clinical and Translational Research*. 2016;2(3). doi:https://doi.org/10.18053/jctres.02.201603.005
11. Chang JT. Pathophysiology of Inflammatory Bowel Diseases. Longo DL, ed. *New England Journal of Medicine*. 2020;383(27):2652-2664. doi:https://doi.org/10.1056/nejmra2002697
12. Al Khalili A, Dutz JP. Janus Kinase Inhibition and SLE: Is this a Plausible Treatment Option for SLE? *Current Treatment Options in Rheumatology*. 2020;6(4):406-417. doi:https://doi.org/10.1007/s40674-020-00155-w
13. Leonard WJ. Cytokines and immunodeficiency diseases. *Nature Reviews Immunology*. 2001;1(3):200-208. doi:https://doi.org/10.1038/35105066
14. Kartikasari AER, Huertas CS, Mitchell A, Plebanski M. Tumor-Induced Inflammatory Cytokines and the Emerging Diagnostic Devices for Cancer Detection and Prognosis. *Frontiers in Oncology*. 2021;11. doi:https://doi.org/10.3389/fonc.2021.692142
15. Conlon KC, Miljkovic MD, Waldmann TA. Cytokines in the Treatment of Cancer. *Journal of Interferon & Cytokine Research*. 2019;39(1):6-21. doi:https://doi.org/10.1089/jir.2018.0019
16. Netea MG, Simon A, van de Veerdonk F, Kullberg BJ, Van der Meer JWM, Joosten LAB. IL-1β Processing in Host Defense: Beyond the Inflammasomes. Manchester M, ed. *PLoS Pathogens*. 2010;6(2):e1000661. doi:https://doi.org/10.1371/journal.ppat.1000661
17. 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
18. Oeckinghaus A, Ghosh S. The NF- B Family of Transcription Factors and Its Regulation. *Cold Spring Harbor Perspectives in Biology*. 2009;1(4):a000034-a000034. doi:https://doi.org/10.1101/cshperspect.a000034
19. Liu T, Zhang L, Joo D, Sun SC. NF-κB signaling in inflammation. *Signal transduction and targeted therapy*. 2017;2(17023). doi:https://doi.org/10.1038/sigtrans.2017.23
20. Jiang Z, Ninomiya-Tsuji J, Qian Y, Matsumoto K, Li X. Interleukin-1 (IL-1) Receptor-Associated Kinase-Dependent IL-1-Induced Signaling Complexes Phosphorylate TAK1 and TAB2 at the Plasma Membrane and Activate TAK1 in the Cytosol. *Molecular and Cellular Biology*. 2002;22(20):7158-7167. doi:https://doi.org/10.1128/mcb.22.20.7158-7167.2002
21. Jain A, Kaczanowska S, Davila E. IL-1 Receptor-Associated Kinase Signaling and Its Role in Inflammation, Cancer Progression, and Therapy Resistance. *Frontiers in Immunology*. 2014;5. doi:https://doi.org/10.3389/fimmu.2014.00553
22. Yu H, Lin L, Zhang Z, Zhang H, Hu H. Targeting NF-κB pathway for the therapy of diseases: mechanism and clinical study. *Signal Transduction and Targeted Therapy*. 2020;5(1):1-23. doi:https://doi.org/10.1038/s41392-020-00312-6
23. Kanarek N, London N, Schueler-Furman O, Ben-Neriah Y. Ubiquitination and Degradation of the Inhibitors of NF- B. *Cold Spring Harbor Perspectives in Biology*. 2009;2(2):a000166-a000166. doi:https://doi.org/10.1101/cshperspect.a000166
24. Liang P, Zhang H, Wang G, et al. KPNB1, XPO7 and IPO8 mediate the translocation ofNF-κB/p65 into the nucleus. *Traffic (Copenhagen, Denmark)*. 2013;14(11):1132-1143. doi:https://doi.org/10.1111/tra.12097
25. Rahman MM, McFadden G. Modulation of NF-κB signalling by microbial pathogens. *Nature Reviews Microbiology*. 2011;9(4):291-306. doi:https://doi.org/10.1038/nrmicro2539
26. Günther J, Esch K, Poschadel N, et al. Comparative Kinetics of Escherichia coli- and Staphylococcus aureus-Specific Activation of Key Immune Pathways in Mammary Epithelial Cells Demonstrates That S. aureus Elicits a Delayed Response Dominated by

Interleukin-6 (IL-6) but Not by IL-1A or Tumor Necrosis Factor Alpha. McCormick BA, ed. *Infection and Immunity*. 2010;79(2):695-707. doi:https://doi.org/10.1128/iai.01071-10

27. Chaudhry H, Zhou J, Zhong Y, et al. Role of cytokines as a double-edged sword in sepsis. *In Vivo*. 2013;27(6):669-684.
28. Zhao J, He S, Minassian A, Li J, Feng P. Recent advances on viral manipulation of NF-κB signaling pathway. *Current Opinion in Virology*. 2015;15:103-111. doi:https://doi.org/10.1016/j.coviro.2015.08.013
29. Iwasaki A, Pillai PS. Innate immunity to influenza virus infection. *Nature Reviews Immunology*. 2014;14(5):315-328. doi:https://doi.org/10.1038/nri3665
30. Stroud JC, Oltman A, Han A, Bates DL, Chen L. Structural basis of HIV-1 activation by NF-kappaB - a higher-order complex of p50:RelA bound to the HIV-1 LTR. *Journal of molecular biology*. 2009;393(1):98-112. doi:https://doi.org/10.1016/j.jmb.2009.08.023
31. Lv T, Cao W, Li T. HIV-Related Immune Activation and Inflammation: Current Understanding and Strategies. *Journal of Immunology Research*. 2021;2021:e7316456. doi:https://doi.org/10.1155/2021/7316456
32. Attiq A, Yao LJ, Afzal S, Khan MA. The triumvirate of NF-κB, inflammation and cytokine storm in COVID-19. *International Immunopharmacology*. 2021;101:108255. doi:https://doi.org/10.1016/j.intimp.2021.108255
33. Tripathy AS, Vishwakarma S, Trimbake D, et al. Pro-inflammatory CXCL-10, TNF-α, IL-1β, and IL-6: biomarkers of SARS-CoV-2 infection. *Archives of Virology*. 2021;166(12):3301-3310. doi:https://doi.org/10.1007/s00705-021-05247-z
34. Hayden MS, Ghosh S. NF-κB in immunobiology. *Cell Research*. 2011;21(2):223-244. doi:https://doi.org/10.1038/cr.2011.13
35. Gratacap RL, Rawls JF, Wheeler RT. Mucosal candidiasis elicits NF- B activation, proinflammatory gene expression and localized neutrophilia in zebrafish. *Disease Models & Mechanisms*. 2013;6(5):1260-1270. doi:https://doi.org/10.1242/dmm.012039
36. Wu X, Gowda NM, Kawasawa YI, Gowda DC. A malaria protein factor induces IL-4 production by dendritic cells via PI3K–Akt–NF-κB signaling independent of MyD88/TRIF and promotes Th2 response. *Journal of Biological Chemistry*. 2018;293(27):10425-10434. doi:https://doi.org/10.1074/jbc.ac118.001720
37. Popa GL, Popa MI. Recent Advances in Understanding the Inflammatory Response in Malaria: A Review of the Dual Role of Cytokines. Garcia-Perdomo HA, ed. *Journal of Immunology Research*. 2021;2021:1-9. doi:https://doi.org/10.1155/2021/7785180