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Review article:

IL-6, TNF-α, IL-1β, and IFN-γ Cytokines as Core Inflammatory Biomarkers: Biological Roles, Diagnostic Utility, and Clinical Applications

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Abstract:

Cytokines are pivotal mediators of intercellular communication in immunity and inflammation, exerting their effects through tightly regulated signaling cascades that shape both innate and adaptive responses. Among them, interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ) represent key biomarkers that orchestrate distinct yet interconnected phases of the inflammatory process. This review synthesizes current evidence on the molecular mechanisms, functional roles, and clinical significance of these four cytokines. IL-1β and TNF-α act as early pro-inflammatory mediators, initiating vascular activation, leukocyte recruitment, and febrile responses. IL-6 sustains acute-phase reactions and bridges innate and adaptive immunity, while IFN-γ enhances antimicrobial defenses and antigen presentation, shaping T-cell polarization. Advances in detection methods—including ELISA, multiplex immunoassays, high-sensitivity biosensors, and IFN-γ release assays—have enabled precise quantification, improving diagnostic accuracy, disease monitoring, and therapeutic decision-making across a broad spectrum of autoimmune, infectious, cardiovascular, and neoplastic disorders. Clinically, elevated cytokine levels serve as diagnostic discriminators, prognostic markers, and guides for targeted therapies such as anti-TNF and anti-IL-6 biologics. Conclusion: IL-1β, IL-6, TNF-α, and IFN-γ emerge as indispensable biomarkers whose measurement provides critical insights into disease pathogenesis and underpins the advancement of personalized medicine in inflammatory conditions.

Keywords: Cytokines, IL-6, TNF-α, IL-1β, IFN-γ.

Introduction

Inflammation is a fundamental biological process that protects the host against infection and tissue injury, but when dysregulated, it contributes to chronic diseases such as autoimmunity, cardiovascular disorders, cancer, and severe infections [1]. Central to the orchestration of inflammation are cytokines, a diverse group of small secreted glycoproteins that regulate intercellular communication, immune activation, and tissue remodeling [2]. Through their binding to cognate receptors and activation of intracellular signaling cascades—including NF-κB, JAK/STAT, and MAPK pathways—cytokines shape both innate and adaptive immune responses [3].

Among the vast cytokine network, **interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis**

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factor-α (TNF-α), and interferon-γ (IFN-γ) play pivotal roles as inflammatory biomarkers. IL-1β, produced mainly by monocytes and macrophages, is a prototypical pro-inflammatory cytokine that induces fever, upregulates endothelial adhesion molecules, and promotes acute-phase reactants [4]. IL-6 is a pleiotropic cytokine that sustains acute-phase responses, promotes B cell differentiation, and bridges innate and adaptive immunity [5,6]. TNF-α, secreted by macrophages and T cells, is a master regulator of inflammation that enhances vascular permeability, induces apoptosis, and drives granuloma formation in infectious diseases [7,8]. IFN-γ, the signature type II interferon, is primarily produced by T cells and natural killer cells, enhancing macrophage antimicrobial activity and antigen presentation [9].

The quantification of these cytokines has become central to both experimental and clinical medicine. Technological advances—including high-sensitivity ELISA, multiplex bead-based immunoassays, electrochemical biosensors, and interferon-γ release assays—allow precise measurement of cytokine levels in biological samples [10]. Clinically, aberrant levels of IL-1β, IL-6, TNF-α, and IFN-γ serve as diagnostic and prognostic biomarkers in a wide range of disorders, including sepsis, autoimmune diseases, cytokine release syndrome, and COVID-19 [11,12]. Furthermore, targeted therapies such as anti-TNF and anti-IL-6 monoclonal antibodies underscore the translational significance of these molecules in modern precision medicine [13].

This review aims to synthesize current evidence on the biological roles, laboratory detection, and clinical applications of IL-1β, IL-6, TNF-α, and IFN-γ as core inflammatory biomarkers. By integrating insights from molecular immunology and clinical practice, and highlights their indispensable roles in advancing diagnostics, prognostication, and personalized therapeutic strategies across a spectrum of inflammatory and immune-mediated diseases.

1. Definition of Cytokines

Cytokines are small (5–25 kDa) glycoproteins secreted by immune and nonimmune cells to orchestrate intercellular communication. Upon binding to their receptors, they activate intracellular signaling cascades—most notably JAK/STAT, MAPK, and NF-κB pathways—modulating gene transcription programs that regulate cell proliferation, differentiation, survival, and effector functions [3].

2. Types of Cytokines

Cytokines are categorized by structure and function:

A. Interleukins (ILs):

- Coordinate leukocyte cross-talk. The IL-1 family mediates fever and endothelial activation, whereas IL-6 regulates acute-phase reactants and adaptive immunity [2].

B. Tumor Necrosis Factors (TNFs):

- TNF-α and TNF-β govern apoptosis, cell survival, and inflammatory gene expression via TRAF-mediated MAPK and NF-κB signaling [14,15].

C. Interferons (IFNs):

- Type I (IFN-α/β) and Type II (IFN-γ) enhance antiviral defense and antigen presentation by inducing STAT1/2 heterodimers [16].

D. Chemokines [17]:

- Small (8–10 kDa) proteins that create chemotactic gradients to recruit leukocytes.

Colony-Stimulating Factors (CSFs)

- Drive hematopoietic lineage proliferation and differentiation.

3. Definition and Mechanism of Inflammation:

Inflammation is a dynamic, tightly regulated response to infection or tissue injury comprising:

A. Initiation

Pattern recognition receptors detect PAMPs/DAMPs, activating NF-κB and inflammasomes [18].

B. Amplification

Cytokine release (IL-1β, TNF-α) increases

vascular permeability and upregulates adhesion molecules (ICAM-1, VCAM-1) [19].

B. Leukocyte Infiltration

Chemokines guide neutrophils and monocytes into the tissue.

C. Elimination & Resolution

Phagocytosis of pathogens and apoptotic cells; switch to anti-inflammatory mediators (IL-10, TGF-β) [20].

D. Chronicity

Persistent stimuli lead to fibrosis, tissue remodeling, and autoimmune pathology.

Temporal cytokine expression orchestrates each phase: **IL-1β** and **TNF-α** in early initiation, **IL-6** sustaining the acute phase, and **IFN-γ** shaping adaptive immunity [4].

4. Synthesis of the Four Markers

IL-1β

- Induced as pro-IL-1β in macrophages/dendritic cells via NF-κB activation.
- NLRP3 inflammasome recruits caspase-1 to cleave pro-IL-1β into its active form [21].

IL-6

- Transcription driven by IL-1β and TNF-α via NF-κB and C/EBPβ in macrophages, endothelial cells, and fibroblasts.
- Signals through the gp130 receptor, activating JAK/STAT3 to induce acute-phase proteins [21].

TNF-α

- Synthesized as a 26 kDa transmembrane precursor by macrophages and T cells; cleaved by TACE/ADAM17 to a 17 kDa soluble form.
- Binds TNFR1/TNFR2, recruiting TRADD and TRAFs to initiate MAPK and NF-κB pathways [22].

IFN-γ

- Secreted by Th1 CD4+ T cells, CD8+ T cells, and NK cells upon antigenic stimulation and IL-12 signaling.

Engages IFN-γ receptor, triggering JAK1/JAK2-mediated phosphorylation of STAT1 homodimers, which induce ISGs [16]. As shown in Table 1 and Figure 1

5. Roles of the Four Markers in Inflammation

As shown in Table 1 and Figure 1:

IL-1β

- Induces fever via hypothalamic prostaglandin E2 production and promotes hepatic synthesis of CRP and serum amyloid A [19,23].
- Upregulates endothelial adhesion molecules, facilitating leukocyte extravasation.

IL-6

- Drives hepatocytes to secrete CRP, fibrinogen, and serum amyloid A.
- Promotes B cell differentiation into plasma cells and skews CD4+ T cells toward Th17 lineage, linking innate and adaptive immunity [21].

TNF-α

- Amplifies vascular permeability and leukocyte recruitment.
- Induces apoptosis in infected or tumor cells via caspase-8 activation.
- Central to granuloma formation in tuberculosis and the pathogenesis of rheumatoid arthritis; TNF inhibitors (e.g., infliximab) significantly improve clinical outcomes[14].

IFN-γ

- Enhances macrophage microbicidal functions by upregulating inducible nitric oxide synthase and promoting phagolysosomal fusion.
- Increases MHC class I and II expression on antigen-presenting cells, bolstering antigen presentation.
- Dysregulated IFN-γ contributes to autoinflammatory syndromes such as hemophagocytic lymphohistiocytosis [24].

6. Laboratory Investigations of the Four Markers Quantitative Assays

- **ELISA:** Gold standard for individual cytokine quantification; sensitivity in pg/mL range.
- **Multiplex Bead-Based Immunoassays (Luminex):** Simultaneous measurement of ≥10 cytokines from minimal sample (25–50 µL), facilitating cytokine profiling in sepsis and autoimmune diseases[21].
- **High-Sensitivity Immunoassays:** Utilize ultrasensitive chemiluminescent detection to measure low-abundance IL-6 and TNF-α for cardiovascular risk stratification.
- **Electrochemical Biosensors:** Noninvasive TNF-α detection in saliva, tears, and urine using portable platforms with rapid turnaround times [25].
- **IFN-γ Release Assays (IGRAs):** Measure antigen-stimulated T cell IFN-γ in whole blood within 24 hours for latent tuberculosis diagnosis; e.g., QuantiFERON-TB Gold [26].

7. Clinical Applications

- **Diagnosis:** Elevated IL-1β and IL-6 distinguish active juvenile idiopathic arthritis from remission [21].
- **Disease Monitoring:** Serial IL-6 levels correlate with cytokine release syndrome severity in CAR-T cell therapy [21].
- **Prognosis:** High baseline TNF-α predicts mortality in septic shock; low IFN-γ responses correlate with severe COVID-19 and hospitalization risk [27].
- **Therapeutic Guidance:**

As shown in Table 1 and Figure 1:

- IL-6 assays inform dosing and tapering of tocilizumab in rheumatoid arthritis.
- TNF-α levels guide anti-TNF therapy adjustments and monitor anti-drug antibodies in RA patients [28].
- IGRAs (Interferon Gamma Release Assay) track TB treatment efficacy and detect latent infection [29].

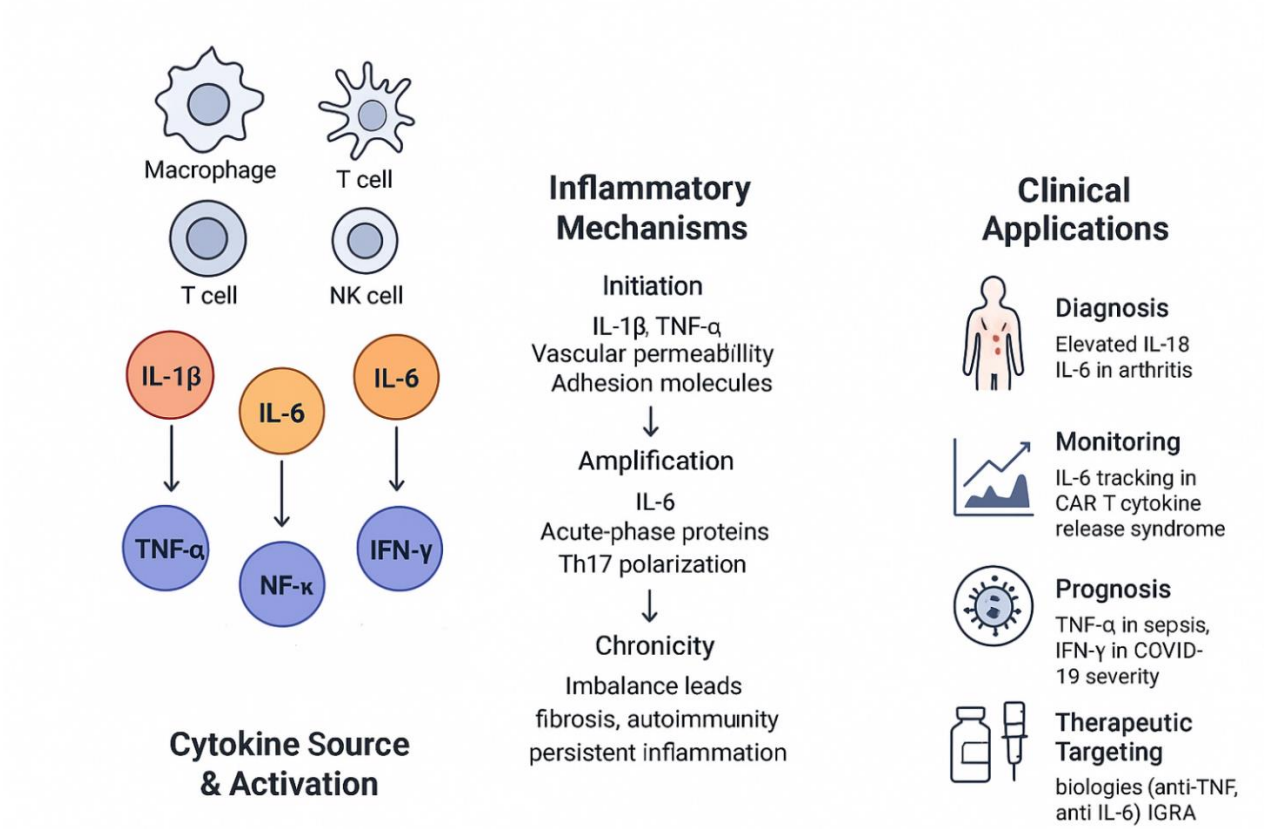

Figure 1: Source and activation of IL-1β, IL-6, TNF-α, and IFN-γ and their roles in the inflammatory mechanism and Clinical Applications.

Table 1: Roles of IL-1β, IL-6, TNF-α, and IFN-γ in Inflammation and Clinical Applications

Stage	Cytokine(s)	Mechanism/Function	Clinical Applications
Cytokine Source & Activation	IL-1β, IL-6, TNF-α, IFN-γ	Secreted by macrophages, dendritic cells, T cells, and NK cells; activate NF-κB, JAK/STAT, and MAPK signaling cascades	Basis for biomarker measurement in serum/plasma
Initiation	IL-1β, TNF-α	Increase vascular permeability; upregulation of adhesion molecules (ICAM-1, VCAM-1); fever induction	Elevated IL-1β and TNF-α help distinguish active inflammation (e.g., juvenile idiopathic arthritis, sepsis)
Amplification	IL-6	Stimulates acute-phase proteins (CRP, fibrinogen, serum amyloid A); promotes Th17 polarization	IL-6 monitoring guides therapy in CAR-T cytokine release syndrome; informs tocilizumab dosing in rheumatoid arthritis
Adaptive Immunity	IFN-γ	Activates macrophages, enhances antigen presentation, increases MHC I & II expression; drives Th1 responses	IFN-γ release assays (IGRAs) for latent TB; IFN-γ deficiency linked to severe COVID-19
Chronicity	Dysregulated cytokine network	Persistent imbalance leads to fibrosis, autoimmunity, and tissue remodeling	Long-term biomarker tracking in chronic inflammatory/autoimmune diseases
Prognosis	TNF-α, IFN-γ	High TNF-α predicts poor outcomes in septic shock; low IFN-γ correlates with severe COVID-19	Cytokine profiling supports risk stratification
Therapeutic Targeting	IL-6, TNF-α	Targeted biologics (anti-TNF, anti-IL-6); monitoring anti-drug antibodies	Improved outcomes in RA, IBD, and other autoimmune disorders

Conclusion:

Precise quantification of IL-1β, IL-6, TNF-α, and IFN-γ provides critical insights into the dynamics of acute and chronic inflammation, enabling improved diagnosis, prognosis, and personalized therapeutic interventions across a spectrum of inflammatory, autoimmune, infectious, and neoplastic disorders.

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