УДК 616.155.392:612.017

CYTOKINE-MEDIATED SUPPRESSION OF MEGAKARYOCYTOPOIESIS (TNF-A, IL-6, IL-1B)

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ABSTRACT

Megakaryocytopoiesis is a complex, multistep process of megakaryocyte differentiation and maturation in the bone marrow, ensuring physiological platelet production. Disruptions of this process underlie various forms of thrombocytopenia, including inflammatory, autoimmune, and oncohematological disorders. Over the past decades, it has been established that proinflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β), play a crucial role in the pathogenesis of megakaryocytopoietic suppression. These mediators affect both hematopoietic stem cells and committed megakaryocytic progenitors by modulating intracellular signaling pathways such as JAK/STAT, NF-κB, and MAPK, as well as altering the expression of thrombopoietin and its receptor c-Mpl.

This literature review aims to systematize current data on the molecular mechanisms of cytokine-mediated inhibition of megakaryocytopoiesis, its role in the development of thrombocytopenia, and potential therapeutic strategies targeting inflammatory imbalance.

KEY WORDS

Megakaryocytopoiesis, thrombocytopenia, TNF-α, IL-6, IL-1β, cytokines, inflammation, bone marrow, thrombopoietin, NF-κB, JAK/STAT.

INTRODUCTION

Platelets are essential components of the hemostatic system, maintaining vascular integrity and participating in immune responses. Their production occurs in the bone marrow from megakaryocytes—highly specialized cells derived from hematopoietic stem cells (HSCs) through several intermediate stages. This process, known as megakaryocytopoiesis, is regulated by a complex interaction of growth factors, hormones, and cytokines [Kaushansky, 2015, p. 112].

Under physiological conditions, the primary regulator of megakaryocytopoiesis is thrombopoietin (TPO), which interacts with the c-Mpl receptor on megakaryocytes and their progenitors. However, during inflammatory, infectious, autoimmune, and oncological diseases, the bone marrow microenvironment becomes enriched with proinflammatory cytokines, including TNF-α, IL-6, and IL-1β [Metcalf, 2017, p. 94].

These cytokines disrupt the balance between proliferation, differentiation, and apoptosis of megakaryocytes, leading to reduced platelet production and the development of secondary thrombocytopenia [Harker, 2018, p. 301]. Clinically, this manifests as increased bleeding risk, hemorrhagic complications, and deterioration of disease prognosis.

The aim of this review is to analyze the mechanisms of cytokine-mediated suppression of megakaryocytopoiesis, with particular emphasis on the roles of TNF-α, IL-6, and IL-1β.

LITERATURE REVIEW

1. Physiology of Megakaryocytopoiesis

Megakaryocytes originate from HSCs through a megakaryoblast stage followed by endomitosis, resulting in nuclear polyploidy. This process enables high synthetic activity and platelet formation through cytoplasmic fragmentation [Italiano, 2016, p. 44].

Key regulatory factors include:

- Thrombopoietin (TPO)
- Stem cell factor (SCF)
- Interleukins IL-3 and IL-11

TPO activates the JAK2/STAT5 pathway, promoting megakaryocyte survival and maturation [Kaushansky, 2015, p. 118].

2. Inflammatory Cytokines and the Bone Marrow Niche

The bone marrow niche is a dynamic environment where stromal cells, endothelial cells, and immune cells create a cytokine-rich microenvironment. During inflammation, macrophages and T lymphocytes become activated, leading to increased production of TNF-α, IL-6, and IL-1β [Murphy, 2019, p. 210].

These cytokines exert both systemic and local effects on hematopoiesis by altering gene expression related to differentiation and apoptosis.

3. Role of TNF-α in Megakaryocytopoietic Suppression

TNF-α is a key inflammatory mediator that activates the NF-κB pathway. It can:

- Inhibit proliferation of megakaryocytic progenitors
- Induce megakaryocyte apoptosis
- Suppress c-Mpl receptor expression

Elevated TNF-α levels correlate with thrombocytopenia severity in rheumatoid arthritis and systemic lupus erythematosus [Zhou, 2020, p. 87]. Experimental models show that TNF-α reduces cellular responsiveness to TPO by blocking the JAK/STAT signaling pathway [Aggarwal, 2018, p. 152].

4. IL-6 and Megakaryocytic Differentiation

IL-6 exhibits a dual effect: at low concentrations, it may stimulate thrombopoiesis, whereas chronic elevation suppresses it [Scheller, 2014, p. 203].

IL-6 activates the STAT3 pathway, resulting in:

- Disruption of the proliferation–differentiation balance

- Induction of the acute-phase response
- Altered hepatic TPO expression

In chronic infections and malignancies, IL-6 is associated with functional megakaryocyte impairment [Hunter, 2015, p. 77].

5. IL-1β and Inflammatory Regulation of Hematopoiesis

IL-1β is a potent pyrogenic and proinflammatory cytokine that activates NF-κB and MAPK pathways [Dinarello, 2018, p. 61].

In megakaryocytes, IL-1β:

- Inhibits early differentiation stages
- Promotes apoptosis
- Alters interactions with bone marrow stroma

Elevated IL-1β levels are observed in aplastic anemia and myelodysplastic syndromes [Young, 2019, p. 145].

6. Intracellular Signaling Pathways: NF-κB, JAK/STAT, and MAPK

Proinflammatory cytokines activate key intracellular cascades:

Pathway	Biological Effect
NF-κB	Inflammation, apoptosis
JAK/STAT	Altered differentiation
MAPK	Cellular stress response

Activation of these pathways disrupts the normal megakaryocyte cell cycle [O'Shea, 2017, p. 233].

7. Clinical Implications

Cytokine-mediated thrombocytopenia is observed in:

- Sepsis
- Autoimmune diseases
- Malignancies
- Chronic infections

Patients demonstrate reduced platelet counts, impaired platelet function, and increased bleeding risk [Harrison, 2021, p. 412].

RESULTS

Table 1. Effects of Key Cytokines on Megakaryocytopoiesis

Cytokine	**Primary Effect**	**Mechanism**
TNF-α	Suppression	NF-κB activation, apoptosis
IL-6	Dual	STAT3, acute-phase response
IL-1β	Inhibition	MAPK activation, inflammation

Table 2. Diseases Associated with Cytokine-Mediated Thrombocytopenia

Disease	**Main Cytokines**	**Clinical Features**
Rheumatoid arthritis	TNF-α, IL-6	Thrombocytopenia
Sepsis	IL-1β, TNF-α	Bleeding

MDS	IL-1β	Cytopenias

Scheme 1. Mechanism of Megakaryocytopoietic Suppression

Inflammation → ↑ TNF-α / IL-6 / IL-1β
↓
Activation of NF-κB, STAT3, MAPK
↓
Megakaryocyte apoptosis
↓
↓ Platelet production

Scheme 2. Interaction Between Cytokines and TPO

TPO → c-Mpl → JAK2/STAT5 → Megakaryocyte maturation
↑
TNF-α / IL-6 inhibit signaling

DISCUSSION

The reviewed data indicate that proinflammatory cytokines play a central role in the pathogenesis of secondary thrombocytopenia. Their effects are mediated through both direct action on megakaryocytes and modification of the bone marrow niche [Metcalf, 2017, p. 101].

TNF-α appears to exert the strongest inhibitory influence. TNF-α inhibitors such as infliximab and adalimumab have been shown to partially restore thrombopoiesis in patients with autoimmune diseases [Zhou, 2020, p. 92].

IL-6 inhibitors, including tocilizumab, also show promise in correcting cytokine imbalance [Scheller, 2014, p. 211]. However, the risk of immunosuppression and infectious complications must be considered.

CONCLUSION

Cytokine-mediated suppression of megakaryocytopoiesis is a key pathogenic mechanism underlying thrombocytopenia in inflammatory and autoimmune diseases. TNF-α, IL-6, and IL-1β disrupt signaling pathways responsible for megakaryocyte maturation, leading to reduced platelet production.

Understanding these mechanisms provides a foundation for targeted therapeutic strategies aimed at restoring hematopoiesis and improving clinical outcomes.

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