Immunomodulatory Mechanisms of Secondary Hemophagocytic Lymphohistiocytosis

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Abstract: This study aims to comprehensively investigate the immunomodulatory mechanisms of secondary hemophagocytic lymphohistiocytosis (sHLH), focusing on cytokine and immune cell alterations to enhance diagnostic and treatment strategies. Through a systematic review of existing literature and clinical case analyses, we explored the roles of cytokines like IL-6, TNF-α, and IFN-γ, and immune cell changes in macrophages, T cells, and NK cells. We also examined the impact of genomic and epigenetic factors on sHLH pathogenesis. The results indicate that abnormal cytokine expression and immune cell dysfunction are central to sHLH development. Targeted therapies against specific cytokines show promise in managing sHLH. In conclusion, understanding these complex immunomodulatory mechanisms is crucial for developing more effective, personalized treatment plans to improve patient outcomes and survival rates. Future research should focus on standardized, multi-center studies to further elucidate these mechanisms and refine therapeutic approaches.

***Keywords*:** secondary hemophagocytic lymphohistiocytosis; immunomodulation; cytokines; immune cells

1. Introduction

Secondary hemophagocytic lymphohistiocytosis (sHLH) is a life - threatening disorder marked by over - activation of the immune system. This leads to macrophage and lymphocyte proliferation, causing multi - organ damage. Its etiology is complex, often induced by infections, malignant tumors, or autoimmune diseases. Current research shows sHLH pathogenesis is closely linked to immune system dysregulation, especially abnormal macrophage activation and excessive cytokine release [1]. Understanding these mechanisms is vital for improving sHLH diagnosis and treatment.

2. The Role of Cytokines

2.1 Cytokines are crucial in sHLH pathogenesis

Interleukin - 6 (IL - 6), a multifunctional cytokine, has excessive production related to sHLH severity and prognosis [2]. It heightens the immune system's reactivity by promoting the acute inflammatory response and regulating T and B cell functions. In sHLH patients, IL - 6 levels are significantly elevated, often with increased C - reactive protein (CRP) and serum ferritin. These marker increases are linked to multi - organ dysfunction [3]. IL - 6 activates the JAK/STAT signaling pathway, promoting the acute - phase response and immune cell activation [4]. Anti - IL - 6 monoclonal antibodies (e.g., tocilizumab) show some efficacy in sHLH, especially in infection - related cases [2]. Tumor necrosis factor - α (TNF - α), secreted mainly by activated macrophages and T cells, is important in sHLH. It activates the NF - κB and MAPK signaling pathways, promoting the inflammatory response and immune cell activation. In sHLH, excessive TNF - α can cause tissue damage and multi - organ dysfunction. Studies show TNF - α promotes inflammatory cell infiltration and other cytokine production, forming a vicious cycle and worsening the inflammatory response [5]. TNF - α inhibitors may benefit sHLH patients. Interferon - γ (IFN - γ), secreted by activated T cells and natural killer (NK) cells, is central to immunomodulation. It enhances the body's infection resistance by boosting macrophage antimicrobial activity and promoting T cell proliferation and differentiation. In sHLH patients, IFN - γ levels are usually high, indicating a strong immune response to infections. However, excessive IFN - γ can lead to immunodysregulation and cytokine storms [6]. Targeting the IFN - γ signaling pathway may offer new treatment ideas.

3. Changes in Immune Cells

Immune cell changes in sHLH are mainly in macrophages, T cells, and NK cells: Macrophages in sHLH patients are overly activated, disrupting the immune system and causing tissue damage. Their abnormal functions in sHLH involve cytokine secretion and reduced pathogen - clearing ability. Normally, macrophages regulate the immune response by

secreting cytokines like TNF - α and IL - 6. But in sHLH, these functions are enhanced, leading to systemic inflammation and multi - organ dysfunction [7]. Regulating macrophage functions may be a new treatment strategy. T cells play a key role in sHLH immunomodulation. CD8+ T cells in sHLH patients show activation and exhaustion. Their abnormal activation disrupts the immune response balance and may attack normal cells, worsening tissue damage [4]. In sHLH patients, Th1 and Th17 cell proportions increase, while regulatory T cell (Treg) numbers decrease [5]. Also, CD4+ and CD8+ T cell functions in the peripheral blood are inhibited, with reduced cytokine production and cytotoxicity. Restoring T cell subset balance may be key to improving sHLH prognosis. Natural killer (NK) cells are important in sHLH immune response. Their functions in sHLH patients are inhibited, with decreased activation marker expression and cytokine secretion. Normally, NK cells perform immune surveillance by eliminating tumor or infected cells. But in sHLH, these functions are impaired, reducing the ability to clear such cells [1]. NK cell dysfunction is related to macrophage and T cell abnormalities, forming a complex immune network. Regulating NK cell activation and functions may offer new treatment ideas [6].

4. Genomic and Epigenetic Factors

4.1 Genomic Factors

sHLH is closely related to various gene mutations. Patients often have mutations in genes like PRF1, UNC13D, and STXBP2, which are related to immune system functions. PRF1 mutations can cause cytotoxic T cell and NK cell function defects, triggering excessive immune and inflammatory responses, leading to sHLH. UNC13D and STXBP2 mutations are related to intracellular signal transduction and cell fusion, affecting immune cell activation and cytokine release. These mutations affect the body's response to infections and result in diverse sHLH clinical manifestations.

4.2 Epigenetic Factors

Epigenetic changes are important in sHLH pathogenesis. DNA methylation patterns in sHLH patients differ from healthy people, which may cause abnormal expression of key immune genes, worsening inflammation and immune activation. For example, methylation levels of specific genes in sHLH patients' immune cells are decreased, leading to gene overexpression, abnormal cytokine secretion, and excessive immune cell activation. Epigenetic changes can also affect intracellular signaling pathways, like the abnormal activation of the JAK/STAT pathway in sHLH [4], which may be epigenetically regulated.

5. Clinical Manifestations and Immunological Monitoring

The clinical manifestations of sHLH include high fever, hepatosplenomegaly, lymphadenopathy, and other symptoms. Laboratory tests typically reveal elevated ferritin levels, anemia, and thrombocytopenia [8] Fever is a common symptom in sHLH patients, with nearly all presenting with an initial body temperature greater than 38.5°C. Hepatosplenomegaly and lymphadenopathy are also important features, with approximately 59% of patients experiencing hepatosplenomegaly . In terms of laboratory findings, sHLH patients usually have ferritin levels higher than 500 ng/mL, and in some cases, levels exceed 10,000 ng/mL, which is related to disease severity. Hematological examinations often show anemia, thrombocytopenia, and leukopenia. About 72% of patients have anemia, and 73% have thrombocytopenia. These laboratory indicators are crucial for aiding in the diagnosis of sHLH and are associated with prognosis. Immunological monitoring is essential for the diagnosis and management of sHLH. Quantifying immune cells helps evaluate the patient’s immune status, with flow cytometry being able to detect the numbers and functions of T cells, B cells, and NK cells. Monitoring cytokine levels is also important for sHLH diagnosis. For example, elevated levels of IL-6 and TNF-α are associated with sHLH and can be used as markers of inflammatory response to determine disease severity and progression. During the COVID-19 pandemic, the importance of immunological monitoring increased, as COVID-19 patients may experience sHLH-like immunodysregulation, leading to cytokine storms and multi-organ damage .

6. Conclusion

The immunomodulatory mechanisms of sHLH are complex, involving interactions of cytokines and immune cells. Although current research lacks a unified framework, cytokine - targeted therapies show good results. Future research should focus on standardized design and multi - center cooperation to better understand sHLH and develop treatment strategies, providing more effective options. In - depth study of sHLH immune mechanisms and clinical manifestations can help create personalized treatment plans, improving patients' quality of life and survival rate.

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