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REVIEW ARTICLE

Pathophysiology, Diagnosis, and Therapeutic Strategies of Cytokine Storms in Autoimmune Diseases

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ABSTRACT: Autoimmune diseases are caused by the immune system mistakenly attacking its healthy cells and tissues. Sometimes, the body's production of the protein cytokine becomes dysregulated, generating an imbalance in proinflammatory and anti-inflammatory cytokines. Excessive release of proinflammatory cytokines causes a cytokine storm, characterized by unregulated inflammation that leads to impaired organ functions, damaged tissues, and increased mortality rate. Cytokine storms are associated with various conditions, including sepsis, COVID-19, and influenza. Strategies for the treatment of cytokine storms are still developing, with a particular focus on the inhibition of cytokine secretion. Despite the advancements, challenges in early detection and diagnosis remain, and further research to understand cytokine storms is taking place to discover personalized medicine and novel therapeutic methods for the future. This review discusses the mechanisms and consequences of cytokine storms and their interplay with autoimmune diseases and provides potential therapeutic strategies and future research directions to restore balance in the immune system.

KEYWORDS: Biomedical and Health Sciences, Pathophysiology, Cytokine Storm, Autoimmune Diseases, Hyperinflammation.

Introduction

Autoimmunity is when adaptive immune molecules are directed against the body components,[1] often due to the interaction between one's genetic predisposition and environmental factors. Autoimmune diseases are an array of conditions caused by autoimmunity, particularly the response of aberrant B cells and T cells towards host constituents. These diseases are widespread and affect all individuals, although they tend to be the most prevalent in women. It is frequently triggered by infection and microbiota-induced pathogenesis.[2]

A pathological reaction that autoimmune diseases can lead to is cytokine storm (CS), a set of medical symptoms and pathological responses resulting from an overstimulated immune response.[3] In 1993, the term was first used to describe the effects of an uncontrolled inflammatory response for graft-versus-host disease (GvHD).[4] However, it is now commonly seen as a condition in which the excessive production of cytokines prompts rampant, systemic inflammation, bringing about multi-organ failure and, in severe cases, death.[5] Cytokines are essentially small soluble proteins facilitating communication between cells and their surrounding environment and modulating immune responses vital for regulating immune homeostasis. Interleukins, interferons, and tumor necrosis factor (TNF) are all types of cytokines, and their dysregulation is prone to detrimental consequences.[6] Table 1 summarizes the sources and functions of common biomarkers affected in a CS.

Table 1: The sources and functions of common biomarkers affected during the cytokine storm. IL, interleukin; IFN, interferon; TGF, transforming growth factor; CCL, chemokine ligand; CXCL, CXC motif chemokine ligand; CRP, C-reactive protein.

Biomarker (abbreviation)	Source	Function
Cytokines		
IL-1	macrophages, pyroptotic cells, epithelial cells	Proinflammatory; pyrogenic function; activation of macrophage and Th17 cells
IL-4	Th2 cells, basophils, eosinophils, mast cells, NK cells	Anti-inflammatory; Th2 differentiation; adhesion; chemotaxis
IL-6	T cells, macrophages, endothelial cells	Proinflammatory; pleiotropic; pyrogenic function; acute phase response; lymphoid differentiation; increased antibody production
IL-10	regulatory T cells, Th9 cells	Anti-inflammatory; inhibition of macrophage activation; inhibition of Th1 cells and cytokine release
IL-13	Th2 cells	Anti-inflammatory; differentiation of B cells; mediator of humoral immunity
IL-17	Th17 cells, NK cells, group 3 innate lymphoid cells	Protection from bacterial and fungal infections; promotion of neutrophilic inflammation
IFN-γ	Th1 cells, cytotoxic T cells, group 1 innate lymphoid cells, NK cells	Proinflammatory; activation of monocytes and macrophages
TGF-β	Treg cells, monocytes, macrophages, fibroblasts, epithelial cells, cancer cells	Immunosuppressive; regulation of proliferation, differentiation, apoptosis, and adhesion; inhibition of hematopoiesis
TNF	T cells, NK cells, mast cells, macrophages	Pyrogenic; increasing vascular permeability
Chemokines		
CCL2	macrophages, dendritic cells, cardiac myocytes	Pyrogenic; recruitment of TH1 cells, NK cells, macrophages, eosinophils, and dendritic cells
CCL3	monocytes, neutrophils, dendritic cells, NK cells, mast cells	Recruitment of Th1 cells, NK cells, macrophages, and dendritic cells

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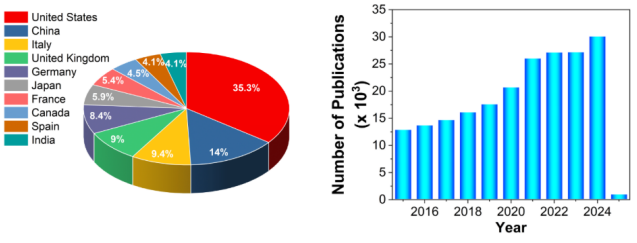
CXCL10	monocytes, endothelial cells, keratinocytes	Interferon-inducible chemokine; recruitment of TH1 cells, NK cells, and macrophages
CXCL13	B cells, follicular dendritic cells	Recruitment of TH1 cells, monocytes, dendritic cells, and basophils
Plasma proteins		
CRP	hepatocytes	Interleukin-6 increases CRP expression, interleukin-8 and MCP-1 secretion

The concept of CS has recently gained significant attention due to the COVID-19 pandemic, as its severe cases have medical features similar to a cytokine storm.[7] Early detection of CS is crucial in choosing appropriate treatment methods, as well as in the prediction of its progression and outcome. Sepsis pathology is complicated, with the dynamic nature of cytokines and the presence of anti-inflammatory intermediaries (molecules that aid in regulating and reducing inflammation) such as interleukin-4 (IL-4), IL-10, IL-13, and anti-IL-1ra at the starting point of inflammation. The initial proinflammatory phase may be absent in patients with pre-existing immunological impairments from chronic diseases or iatrogenesis (adverse health effects resulting from medical treatment). Nonetheless, the concentrations of pro- and anti-inflammatory cytokines are mutually dependent. When the pro-inflammatory response is heavily expressed, the production of anti-inflammatory cytokines increases to counteract the effect. The excess production of anti-inflammatory mediators can lead to immunosuppression,[8] a state of weakened immune system that increases risks of conditions such as cardiovascular diseases and cancer, in addition to heightened susceptibility to other infections.[9]

$CD4^+$ T cells that produce IL-17 (Th17 cells) generate tissue inflammation and autoimmunity because they recognize self-antigens as targets in dysfunction and are crucial in inducing autoimmune diseases.[10] When Th1 cells are exposed to innate inflammatory cytokines, they transform into pathogenic effector cells and cannot produce IL-10. They instead release IL-22 and IFN-γ, which contribute to hyperinflammation.[11] Similarly, large amounts of proinflammatory cytokines (TNF-α, IL-6, and IL-1β) are released during sepsis, triggered by the excited Toll-like receptor 4 (TLR4) by the microbial component lipopolysaccharides (LPS). Together, the cytokines cause vascular dysfunction, increasing their permeability extensively and lowering blood pressure, tissue necrosis, dysregulation of metabolic activities, and ultimately, systemic organ failure.[7]



(a) (b)

Figure 1: (a) Statistics illustrating the countries actively researching autoimmune diseases. (b) The graph depicts the surge in publications related to autoimmune disease research from 2015 to 2025 (Data courtesy: Scopus, February 2025).

Table 2: List of abbreviations used in the article..

Abbreviation	Full Form
CS	Cytokine Storm
IL	Interleukin
TNF	Tumor necrosis factor
TLR	Toll-like receptor
IIR	Inflammatory immune response
iNOS	Inducible nitric oxide synthase
TGF	Transforming growth factor
CAR	Chimeric antigen receptor
IFN	Interferon
TCZ	Tocilizumab
CRS	Cytokine release syndrome
HLH	Hemophagocytic lymphohistiocytosis
ELISA	Enzyme-linked immunosorbent assay
POC	Point-of-care
FET	Field-effect transistor
LoC	Lab-on-a-chip

Discussion

1. Pathophysiology of Cytokine Storms in Autoimmune Diseases:

Inflammation, immune protection, and immune suppression are the three functional categories of immune responses. In particular, inflammatory immune responses (IIRs), the ability of immune cells to adapt to changes in the external and internal environment, play a role in cytokine release. While moderate, IIR defends the body against diseases, overstimulation can cause harm.[12] During a viral infection or a disease, homeostasis in the immune system due to the balance between pro- and anti-inflammatory cytokines is thrown off, leading to the hyperactivation of diverse immune cells, such as macrophages, T and B lymphocytes, dendritic cells, and natural killer cells. This results in the production of an abundance of proinflammatory cytokines and chemokines that would generate a positive feedback loop to promote the immune response in the body, which can damage the body through a CS, for example.[13]

Interleukin-1β (IL-1β) plays an essential role in cytokine storms associated with COVID-19. It synthesizes enzymes like cyclooxygenase and inducible nitric oxide synthase (iNOS), with the nitric oxide from iNOS contributing to tissue impairment during airway inflammation. Moreover, it increases the expression of chemokines and adhesion molecules and stimulates the formation of interleukin-6 (IL-6).[13] IL-6 is a versatile cytokine with pro- and anti-inflammatory activity based on the circumstances. It assists B cells to mature into memory B cells and plasma cells. When IL-6 binds to its receptors, the JAK/STAT pathway is activated, which causes further production of inflammatory cytokines. Because IL-6, along with transforming growth factor β (TGF-β), prompts the differentiation of naïve T cells to Th17 cells, dysregulated IL-6 production is crucial to autoimmune diseases. IL-6 is the

primary cytokine responsible for the cytokine storm observed in some patients who underwent chimeric antigen receptor (CAR) T-cell therapy.[14] Interferon-gamma (IFN-γ) is another key mediator of excessive immune activation in inducing a CS. It links innate and adaptive immune responses and is vital in the body's defense against intracellular pathogens and tumor control. Combining IFN-γ and tumor necrosis factor (TNF-α) can induce pyroptosis, simply an inflammatory cell death. Together, they activate the JAK/STAT1/JRF1 pathway and produce nitric oxide, which triggers caspase-8/FADD-interceded inflammatory cell death, a process termed PANoptosis.[13]

Endothelial cells (ECs) are activated and produce tissue factors that stir up the extrinsic coagulation pathway, resulting in a hypercoagulable state. In the case of a CS, the ECs are likely to become impaired and dysfunctional. The dysfunction of the ECs can cause unregulated platelet aggregation and thrombosis from the abnormal production of ADP. It also activates the proinflammatory peptide C5a, triggering a coagulation cascade and the production of thromboxane A2, which contributes to platelet aggregation. Systemic multiorgan ischemia can be aroused by inappropriate pro-inflammatory mediators that provoke microvascular congestion and the coagulation cascade.[15]

Chemokines, such as CCL2, CCL3, CXCL10, and CXCL13, also significantly initiate a CS. Chemokines are chemoattractant cytokines or small proteins that bind to cell surface receptors and guide cells' movement around the body. They dictate the positioning of cells, steering stem cells and ECs through their route, and controlling leukocytes in extra- or intravasation.[16] Along with cytokines, they modulate the tumor microenvironment (TME) by activating signaling pathways, including nuclear factor kappa-B (NF-κB), which is crucial in enhancing activating B cells and driving inflammatory responses, and vascular endothelial growth factor (VEGF) that instigates epithelial-mesenchymal transition (EMT), and hence contributing to the resistance of therapeutic and promoting aggressive metastatic colorectal cancer (CRC) development.[17] Elevated levels of proinflammatory cytokines and chemokines are usually found in cases of SARS-CoV-2 infections. Bronchoalveolar lavage fluid (BALF) from critically ill patients shows high levels of inflammatory macrophages and chemokines in the lungs.[18] Viral infection, such as influenza, triggers excessive immune system activation to produce increased cytokine levels and chemokine levels. The amplification of the CS can cause severe inflammation and tissue damage in organs like the lungs **(Figure 2)**.

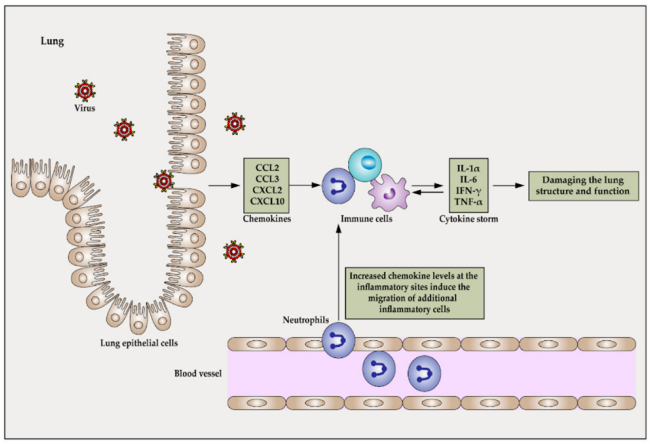


Figure 2: Influenza-induced cytokine storm in the lungs leads to amplified inflammation and lung tissue damage. Due to the viral infection, the immune response is triggered, and excess cytokines are released (Reproduced with permission,[19] Copyright 2021, MDPI).

2. Therapeutic Strategies:

Various therapeutic strategies are involved in treating CS in autoimmune diseases, such as suppressing the release of cytokines or reducing the inflammation already present in the body. Systemic corticosteroids are one method that is widely used for mechanically ventilated patients, ICU patients, and especially COVID-19 patients in grave conditions. It is an immunomodulatory agent and was used in a retrospective study involving 107 patients suffering from SARS. The study showed that 89% fully recovered, with 95 patients treated with high doses of methylprednisolone and hydrocortisone exhibiting signs of clinical improvement in their condition.[20] However, corticosteroids have a broad spectrum of adverse effects associated with them as well, divided into twelve categories: cardiovascular system, dermatological complications, endocrine glands, fluids and electrolytes balance, gastrointestinal tract, renal system, metabolism, musculoskeletal system, nervous system, ophthalmic complications, reproductive system, and allergic reactions.[21] Although its short course treatments (for example, up to 10 days) are clearly shown to provide benefits for those with severe ARDS, there is no evidence for positive outcomes in the case of extended corticosteroid therapy, and it may even have a higher mortality rate than those who are not treated with corticosteroids. It is essential to consider the risk-benefit ratio for each patient before its use and to avoid long-term treatments.[22]

Targeting proinflammatory cytokines like IL-1β, IL-6, and TNF-α is another therapy frequently adopted by patients suffering from CS. This type of therapeutics aims to inhibit the production of cytokines in an attempt to lessen hyperinflammatory conditions in the body.[23] Antagonists for IL-1β include anakinra and canakinumab. Anakinra, which blocks the receptor of IL-1β, was investigated in over 20 clinical trials of cytokine-induced multiorgan failures with a particular focus on the lungs. In an earlier study of anakinra by Cavalli et al., when combined with 4-aminoquinoline, the antagonist showed impressive results by decreasing the mortality rate while improving respiratory functions. However, since the results of extended studies have not been confirmed, regulatory

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use for anakinra in treatment has yet to be decided, unlike canakinumab, which is approved for treating autoimmune diseases.[24] Canakinumab is a monoclonal antibody that targets to neutralize IL-1β, reducing inflammation and hence treating various inflammatory diseases, namely adult-onset Still's disease (AOSD).[25] Tocilizumab (TCZ) is a recombinant humanized monoclonal antibody that interferes with immune responses by targeting IL-6 receptors. A case study evinced a notable decline in CRP levels (from 225 to 3 mg/L) in a COVID-19 patient after treatment with TCZ for four days. Other studies also found quick recovery and rapid TCZ reduction as well, but multiple administrations of medication may be required for some patients who are acutely ill.26 Siltuximab works similarly to TCZ in the way it binds to IL-6 directly to inhibit its effect. A 77-year-old patient with relapsed/refractory multiple myeloma (RRMM) developed cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). After 1 hour of siltuximab administration, CRS was cured, and within 7 hours of treatment, the patient recovered from ICANS as well, demonstrating the effectiveness of siltuximab in relieving CRS.[27]

High levels of TNF-α facilitate the pathway that allows virus penetration into host cells, or the TNF-α-converting enzyme (TACE)-dependent alteration of ACE-2, which can be stopped by TNF-α blockers.[28] TNF-α inhibitors tend to be monoclonal antibodies, such as adalimumab, certolizumab pegol (CDP87), and golimumab. New anti-TNF-α agents that address the limitations of the current inhibitors are also in the development process. For instance, ozoralizumab has nanobody characteristics, and ZINC09609430 has the potential to be used as a novel inhibitor for TNF-α in evaluating *in vitro* and *in vivo*.[29]

3. Challenges and Future Directions:

Symptoms of CS are nonspecific and resemble septic shock and other systemic diseases, making its diagnosis difficult. Diagnostic tools evolved from HLH-1991, based on five easily determined markers to identify CS, but lacked universality, to HLH-2004 by the International Histiocyte Society. These are diagnostic guidelines for hemophagocytic lymphohistiocytosis (HLH), a severe cytokine-driven inflammatory disorder. HLH-2004 was further refined by research into immunopathophysiology and advanced diagnostic techniques and is now the most widely accepted diagnostic criterion.[30] Studying biomarkers in laboratory settings is one method for their comprehensive evaluation. For example, procalcitonin and neutrophil-to-lymphocyte ratio, along with T cells and cytokines, and endothelial dysfunction markers, predict the severity of the inflammation and, hence, the disease. Depending on the different causes of CS, cytokine levels differ, with CS associated with CAR T cell therapy having an increased amount of IFN-γ compared to others, and IL-1β and markers of endothelial damage being reported in high levels for systemic infection-associated CS. Accurate measurement of cytokines is challenging due to biological factors, including fluctuating secretion patterns, low concentrations in body fluid, and barriers to accessibility, as the equipment required is costly and has limitations in implementing continuous monitoring of cytokine levels.[31]

Developed in 1971, enzyme-linked immunosorbent assay (ELISA) is a relatively versatile test using specific antibodies to locate a single analyte. It is sensitive to not only high but also low concentrations of body fluids, as well, and has a high accuracy rate with quick turnabout time for results, but it faces hardships in making it more efficient for multiplexing or the detection of multiple analytes at the same time.[32] Point-of-care (POC) testing allows on-site diagnosis of patients, making it a quick and affordable detection method and an attractive choice during the COVID-19 pandemic. It holds an advantage over ELISA because no specialized equipment is needed. POC can be paper-based, more lightweight, cost-effective, or transistor-based. In field-effect transistors (FET), an underlying semiconducting material covered by non-metalized gate dielectrics in contact with an electrolyte solution converts biological binding activities into quantifiable signals. This allows FET-based POCs to be highly sensitive to cytokines and track them in time.[33] Lab-on-a-chip (LoC) devices and biosensors are now utilized to overcome diagnostic limitations. The microfluidic structure of LoC devices permits biochemical reactions to occur faster by their small channels' high surface area to volume ratio, careful control from minimized reagent use, and multiplexed analysis. Moreover, by integrating nanotechnology and biosensors, biomarkers of lower quantity in the human body can be detected. Multiple methods exist to observe cytokines, such as fluorescence signals, electrochemical transduction, and color changes.[34]

Negative regulators of TLR signaling play a key role in recognizing pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) to activate pathways that induce a pro-inflammatory immune response. The effectiveness of their inflammatory response has been tested in animal studies and clinical trials. While it showed potency in animal models, organ damage and mortality rates did not reduce in sepsis patients. Seeking to solve this problem, researchers proposed targeting specific pathways, like the Wnt/β-catenin signaling pathway, which may be able to act as negative regulators. Therapeutic approaches considering the genetic variants in individuals, considering the patient's age and genetic background, is also a potential approach in developing personalized treatments for sepsis and CS.[35] Continuous research is taking place to analyze the cellular and molecular contributors of CS, and other anti-inflammatory strategies, including TLR4 antagonists, cyclooxygenase (COX) inhibitors, sphingosine-1-phosphate modulators, and protease-activated receptor (PAR) 2 agonists, are being tested in animal models, making advancements toward the progression of effective therapy for CS in various autoimmune diseases.[36]

■ Conclusion

In conclusion, cytokine storms are a critical factor in the pathogenesis of autoimmune diseases, driving excessive inflammation and contributing to disease severity. By identifying the key cytokines and signaling pathways involved, researchers have made significant strides in understanding how dysregulated immune responses lead to tissue damage and systemic

complications. Establishing a deeper connection between cytokine storm mechanisms, their harmful effects on the body, and their role in disease progression is essential for developing targeted treatments. Advancing this knowledge can pave the way for novel therapeutic strategies that mitigate the impact of cytokine storms and improve overall disease management, ultimately enhancing patient outcomes.

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