Trends in Immunology

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Forum

Dual effects and balanced regulation of cytokines in sepsis

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Sepsis, a life-threatening condition triggered by infection, disrupts the body's immune balance and remains a major global health challenge. This forum explores the dual roles of cytokines in sepsis: their overactivation drives 'cytokine storms,' and dysregulation leads to immunosuppression. It also discusses regulatory mechanisms for developing targeted therapies.

Proinflammatory signals: the 'vanguard force' of molecular immunity

Sepsis, a life-threatening syndrome from the body's dysregulated infection response, is a leading cause of intensive care unit mortality. Clinically, it progresses through an initial 'cytokine storm' hyperinflammatory phase to prolonged immunosuppression. This dynamic imbalance highlights cytokines' dual roles as inflammation drivers and immune suppressors. In the hyperinflammatory phase of sepsis, damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) can activate multiple signaling pathways, such as nuclear factor-κB, mitogen-activated protein kinase, and Janus kinase/signal transducer and activator of transcription, thereby triggering a cytokine storm and causing a systemic inflammatory response, vascular endothelial injury, and activation of the coagulation cascade [1]. The relationship between cytokine storms and programmed cell death (PCD) is quite complex. For instance, pyroptosis is a proinflammatory form of PCD driven by inflammasomes. This process activates gasdermin D, which forms pores in the cell membrane, leading to the release of IL-1β, IL-18, and DAMPs. In contrast, apoptosis is characterized by the gradual disintegration of cells and typically does not elicit a strong inflammatory response. However, in the context of sepsis, apoptosis can induce immune cell exhaustion, thereby leading to the release of DAMPs. Ferroptosis, driven by lipid peroxide and free iron accumulation, triggers unique inflammatory signaling pathways that prompt the secretion of proinflammatory cytokines [2]. This PCD can both initiate the release of proinflammatory cytokines and release DAMPs to amplify the inflammatory response. Dissecting their integrative roles in sepsis can provide a crucial theoretical basis for targeted inflammation-modulating therapies. Additionally, individual clinical variations in sepsis hinder the accurate assessment of cytokine storms. As biomarkers, cytokines exhibit dynamic limitations. Current research on proinflammatory signaling mechanisms focuses on individual differences and biomarker dynamics, which are crucial for the diagnosis and treatment of sepsis.

Immunosuppression: the 'truce order' of molecular immunity

Severe sepsis is associated with immunosuppression, which is one of the main causes of secondary infections and high mortality. These include immune cell dysfunctions such as T-cell exhaustion, B-cell dysfunction, and monocyte/macrophage dysregulation [3]. Different cytokines can exert opposing effects. Thus, if the cytokine storm is constant, it might result in exhaustion, apoptosis, or inactivation of immune cells. The release of anti-inflammatory cytokines, including IL-10 and transforming growth factor-β (TGF-β), reduces antigen presentation and the release of proinflammatory mediators [4]. IL-10 reduces the production of proinflammatory cytokines, hampers antigen-presenting capacity, and regulates T cell differentiation. TGF-β inhibits the activation of T cells and B cells, induces Treg differentiation, and limits macrophage activity. These mechanisms ultimately result in an imbalance within the anti-inflammatory and proinflammatory cytokine network, significantly inhibiting the activation and effector functions of immune cells. Given the central role of cytokines in sepsis-induced immunosuppression, immune intervention strategies targeting these molecules have become a prominent research focus. Current studies primarily focus on regulating cytokine levels, blocking signaling pathways, and promoting the recovery of immune functions. As our understanding of the immunopathogenic mechanisms underlying sepsis deepens, the immune subtyping of patients using multiomics technologies and the implementation of cytokine-targeted precision therapies have become increasingly prevalent. This approach involves selecting antagonists or activators based on the patient's immune status and cytokine profile; however, these strategies still necessitate large-scale clinical studies to validate their efficacy and safety [5].

Triggering factors of cytokine network imbalance

The imbalance of the cytokine network in sepsis is a complex, multifactorial process driven by various interrelated mechanisms. Following pathogen invasion, immune cells recognize PAMPs, leading to massive release of proinflammatory cytokines. Concurrently, DAMPs released from injured or dead cells amplify proinflammatory secretion and create a vicious cycle of inflammation, exacerbating the imbalance [6]. As illustrated in Figure 1, PAMPs and DAMPs collectively disrupt the dynamic equilibrium of inflammatory mediators through interactions with immune cell surface receptors and downstream signaling pathways.

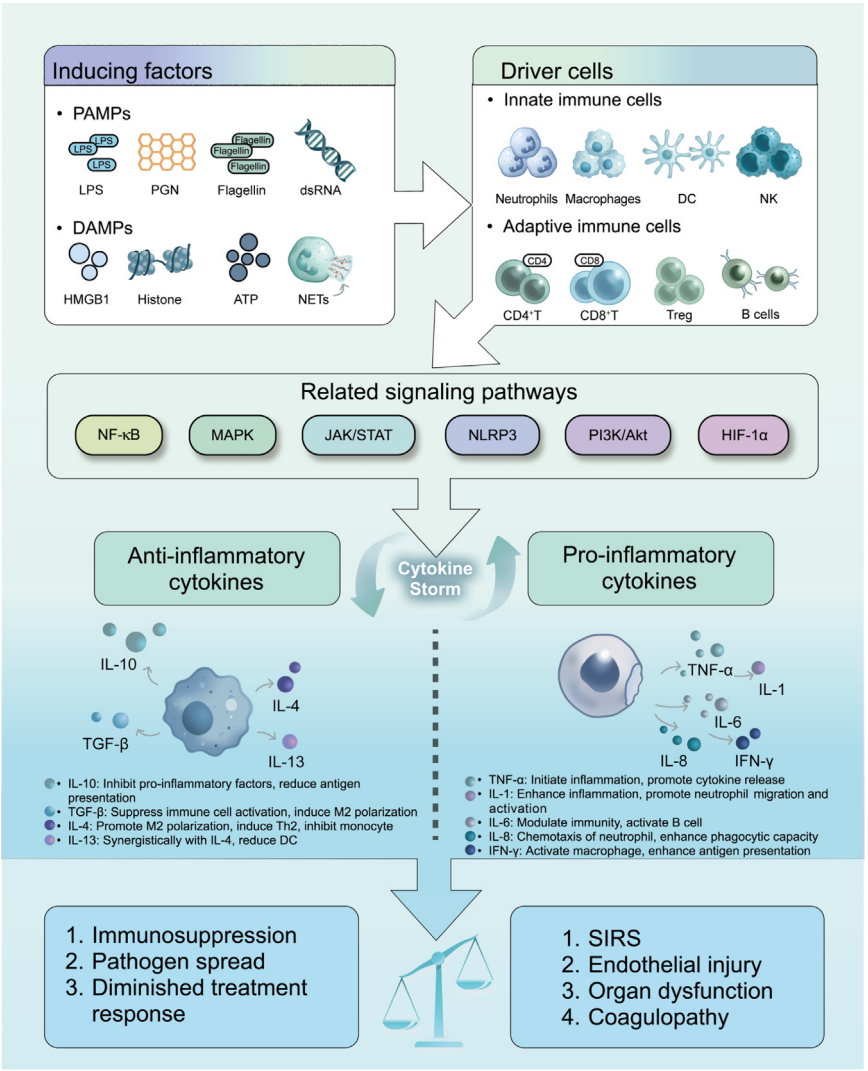

Figure 1. Schematic diagrams of inflammatory response and immune dysregulation in sepsis. During the development and progression of sepsis, a variety of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) are released. PAMPs include lipopolysaccharide (LPS), peptidoglycan (PGN), and flagellin, and DAMPs include high-mobility group box 1 (HMGB1), histones, and ATP. These molecules bind to pattern recognition receptors on immune cells, activating both innate immune cells (e.g., macrophages, neutrophils, dendritic cells, natural killer cells) and adaptive immune cells (e.g., T lymphocytes, B lymphocytes). The activated cells then initiate multiple signaling pathways, such as nuclear factor (NF)-κB, mitogen-activated protein kinase (MAPK), and Janus kinase/signal transducer and activator of transcription (JAK/STAT). Through their synergistic actions, immune cells release numerous inflammatory mediators. When these mediators are excessively secreted, they can trigger an inflammatory storm, causing a loss of control over local and systemic inflammatory responses. An imbalance between proinflammatory and anti-inflammatory factors may either amplify the inflammatory response, leading to systemic inflammatory response syndrome (SIRS), endothelial injury, coagulation dysfunction, and multiple organ damage, or promote immune suppression, reducing pathogen clearance, facilitating pathogen spread, and diminishing responsiveness to treatment, ultimately impairing sepsis prognosis.

Dysfunctions of immune cells play a critical role in the imbalance of the cytokine network. For instance, disordered macrophage phenotype switching is marked by early M1-type polarization, which induces cytokine storms, whereas late M2-type polarization inhibits pathogen clearance. T-cell exhaustion results in a diminished proinflammatory function, whereas excessive proliferation of Tregs promotes immunosuppression through the secretion of anti-inflammatory cytokines such as IL-10 and TGF-β [7]. Additionally, mitochondrial dysfunction contributes to network regulation through metabolic reprogramming and the burst release of reactive oxygen species. Intestinal barrier dysfunction–induced bacterial translocation directly activates systemic inflammatory responses and disrupts the proinflammatory/anti-inflammatory balance [8]. In combination, they create a complicated regulatory network of interactions that jointly induce the pathological dysregulation of the cytokine network in sepsis.

Regulatory strategies for cytokine network balance

The strategy to regulate cytokines appears to be a promising approach to sepsis therapy, but most clinical trials targeting single cytokines have failed [9]. First, cytokines have short half-lives and narrow therapeutic windows. This limits the effective duration of therapeutic agents *in vivo* and complicates the accurate determination of doses. Moreover, the intricacy of cytokine targeting renders cures that target a single cytokine insufficient to halt disease progression. The complexity of sepsis diminishes the significance of any single-target treatment as the patient's pathology can differ substantially. Furthermore, it complicates the modulation of immune responses through single-target strategies because of the many different immune cell types and feedback mechanisms involved in immunoregulation.

Given these challenges, multiomics technology has potential in optimizing treatment strategies for sepsis. Genomics, transcriptomics, proteomics, and metabolomics systematically identify stage-specific and patient-specific biomarkers in

sepsis to provide a basis for the implementation of personalized medicine [10]. For example, through joint multiomics analysis, patients can be accurately classified into immune phenotypic subtypes such as 'hyperinflammatory type,' 'immunosuppressive type,' and 'mixed type,' and differentiated intervention strategies can be formulated accordingly. Furthermore, by integrating multiomics data such as transcriptomic immune profiles and proteomic cytokine dynamic maps with clinical indicators such as Acute Physiology and Chronic Health Evaluation II score and lactate level through artificial intelligence models, a real-time updated individualized treatment decision-making system can be constructed to achieve precise regulation of the whole-course management of sepsis. In addition, therapies that control several cell components or mediators at once may overcome the limitations of a single-target flaw. The modulation of macrophage polarization, reversal of T-cell exhaustion, and regulation of immune cell metabolism, moreover, have provided avenues for restoring cytokine balance. These strategies, which target multiple pathways together, can precisely regulate the cytokine network at different stages of sepsis and provide important guidance for clinical application [11].

Concluding remarks

Cytokine storm immunotherapies in sepsis antagonize and/or regulate the cytokine network to restore immune homeostasis using a multidimensional intervention strategy. For instance, monoclonal antibodies neutralize proinflammatory factors, immune cell function modulation enhances the expression of anti-inflammatory cytokines, and blood purification techniques eliminate circulating cytokines [12]. The cytokine storm observed in early sepsis and the subsequent immunosuppression in later stages represent a continuous dynamic process. Consequently, phased and dynamically coordinated multitarget intervention strategies are essential for overcoming existing therapeutic bottlenecks. During the hyperinflammatory phase, interventions should prioritize the inhibition of proinflammatory signals, whereas the immunosuppressive phase necessitates a focus on restoring immune cell functionality. Future studies should develop personalized stage-specific models that integrate information on molecular markers and clinical features to continuously optimize therapeutic targets [13].

The fundamental scientific question for sepsis is how an acute-phase cytokine storm transitions to late-stage immunosuppression. Immune cells can initiate mechanisms of negative feedback to mitigate tissue damage caused by excess inflammation. Despite this, with a sustained stimulus, these activated immune cells will likely become passively exhausted. The transition may also be controlled by crucial molecular switches at different regulatory nodes, including receptors that sense metabolic status (e.g., AMPK, mechanistic target of rapamycin) and immune checkpoint molecules (e.g., PD-1/PD-L1, CTLA-4) [14]. A deeper understanding of the molecular mechanisms by which this transition is regulated will provide a stronger theoretical basis.

It is clinically controversial to target cytokines and to inhibit immune checkpoints. Cytokines serve as both protective factors and disease markers while also acting as reactive mediators that cause direct organ injury. A challenge is the timing and selection of patients for treatment with immune checkpoint inhibitors [15]. In addition, both therapies carry the risk of complications and immune-mediated adverse reactions, and the significant heterogeneity in clinical trial results further restricts their clinical application. The clinical challenges and potential solutions are systematically summarized in the Clinician's corner, which outlines the key obstacles of single-target therapies and the future directions for immunotherapeutic interventions in sepsis.

Clinician's corner

This box systematically summarizes the key obstacles faced by single-target cytokine therapies in clinical practice and outlines potential strategies for advancing sepsis immunotherapy, integrating mechanistic insights with translational perspectives.

Clinical challenges of single-target cytokine therapies

- Limited efficacy: the complexity and dynamic characteristics of the cytokine network render single-target therapies insufficient for comprehensive regulation of the inflammatory cascade.
- Patient heterogeneity: patients with sepsis exhibit significant variations in clinical manifestations and immune responses, rendering standardized treatment protocols ineffective.
- Timing dilemma: early intervention may interfere with the body's innate defense mechanisms, whereas late intervention fails to reverse established immunosuppression.
- Safety concerns: targeting specific cytokines may increase the risk of secondary infections or exacerbate inflammatory responses, necessitating a balance between therapeutic benefits and risks.

Multidimensional explorations in immunotherapy

- Personalized medicine: tailoring treatment protocols on the basis of patients' genetic profiles, immune status, and infectious etiologies.
- Multitarget interventions: simultaneously regulating multiple components of the immune response to restore cytokine network balance and improve prognosis.
- Dynamic therapeutic strategies: adjusting treatment regimens in real time according to disease progression and patient responses, requiring continuous monitoring of clinical conditions.
- Biomarker-guided therapies: developing reliable biomarkers to predict treatment responses and monitor disease progression, enabling precision medicine.
- Early detection and prevention: optimizing diagnostic tools and implementing preventive measures for high-risk populations, with emphasis on early identification of sepsis.

The dynamic evolution of cytokines, transitioning from an early storm to late immunosuppression in sepsis, represents a fundamental biological event that determines patient outcomes. Future research

could focus on several directions: first, leveraging advanced technologies such as single-cell spatiotemporal transcriptomics to elucidate the key molecular mechanisms driving transitions in immune states; second, integrating multiomics data with clinical features to construct stage-specific molecular marker systems for precise patient stratification; and third, exploring the optimal timing and synergistic effects of multitarget combined interventions. Furthermore, investigating key critical scientific questions, including the interactive mechanisms of mitochondrial metabolic reprogramming and immune cell function, the signaling amplification pathways of intestinal microbiota–systemic inflammation, and the pathogen-specific cytokine dynamics, will lay a theoretical foundation for the development of phased precision treatment strategies in sepsis.

Author contributions

C.W., X.D., and C.Z. contributed to the manuscript writing and figure preparation. W.Z. and C.W. designed the work. C.W. and W.Z. supervised the work. All authors have read and approved the article. All authors read and approved the final manuscript.

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Declaration of interests

The authors have no interests to declare.

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