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Review Article

The Immunological Landscape of Sepsis: From Cytokine Storm to Immune Paralysis

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ABSTRACT

Sepsis is a dynamic and heterogeneous syndrome characterized by a dysregulated host response to infection, leading to concurrent hyperinflammation and profound immunosuppression. Early recognition of pathogen- and damage-associated molecular patterns triggers extensive activation of NF-κB, JAK/STAT, and MAPK pathways, resulting in a cytokine storm, metabolic reprogramming, and endothelial dysfunction. Mitochondrial impairment, glycocalyx degradation, and excessive neutrophil activity further propagate organ injury and microcirculatory collapse. Simultaneously, widespread apoptosis and exhaustion of lymphocytes culminate in immune paralysis and increased susceptibility to secondary infections. Advances in transcriptomics, proteomics, metabolomics, and machine-learning–based classification have uncovered distinct immune endotypes of sepsis, providing the foundation for precision medicine. Emerging immunomodulatory therapies—including IL-7, GM-CSF, and immune checkpoint inhibitors—aim to restore immune function in selected subgroups. Ultimately, sepsis must be viewed as a multifaceted immunometabolic disorder requiring individualized diagnosis, monitoring, and treatment approaches.

Introduction

Sepsis represents a vastly complex, dynamic syndrome, which has long represented one of the most challenging tasks in the modern healthcare setting. Sepsis has been defined as life-threatening organ dysfunction elicited by a dysregulated host response to infection [1-2]. While this definition might represent something quite straightforward, it, in reality, masks extremely complex biological processes. Firstly, sepsis should no longer be regarded as a state of exaggerated inflammatory response but, rather, as a polyphasic immunological dysfunction in which the immune, metabolic, and endothelial as well as the neurohormonal systems are simultaneously activated as well as suppressed [3-5]. The rather extreme levels of morbidity as well as mortality that are associated with sepsis, even in the modern setting of sophisticated intensive care, reflect this unpredictably oscillating process of extreme inflammatory overactivation as well as severe immune paralysis [6-7]. This phenomenon also emphasizes the need for individualized and biologically oriented strategies in diagnostic, monitoring, and therapeutic approaches [8].

The initial immune response in sepsis involves the activation of pattern recognition receptors, like Toll-like receptors and NOD-like receptors, following the recognition of microbe-associated molecules or injury-associated molecular patterns [9]. These receptors activate intensive signaling pathways like NF-κB, JAK/STAT, MAPK, and interferons, followed by the massive secretion of inflammatory cytokines like IL-1β, IL-6, TNF-α, IL-8, HMGB1, and interferons [10]. These cytokines cause the inflammatory response syndrome seen in sepsis. The immune cells also undergo a process called the Warburg effect, where there is the metabolic conversion to aerobic glycolysis [11-12]. The process

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increases the secretion of cytokines, but it also results in the reduced efficiency of mitochondria in septic organisms, as seen in the metabolomics and proteomics profiles of septic individuals [13-14].

The dysfunction of the mitochondria also contributes largely to the failure of septic organs, as seen in the metabolomics profiles of septic individuals. The endothelium has a key role in the pathology of sepsis. These inflammatory signals, along with oxidative stress, alter the integrity of the endothelium, causing it to produce leaks, resulting in widespread edema. One of the first, but most calamitous, developments involves the loss of the endothelial glycocalyx, a thin, gelated surface layer composed of proteoglycans and glycosaminoglycans, key in the regulation of the permeability of the vessels, as well as mechanotransduction [15-18]. The loss of the endothelial glycocalyx, as well as the shedding of the proteoglycan syndecan-1, a non-soluble marker in predicting adverse endpoints [19-20], also has a crucial role in the dysfunction in the microcirculatory bed. Endothelial dysfunction is key in the multi-organ dysfunction syndrome, ranging from renal failure, the acute respiratory distress syndrome, and septic shock [21].

Neutrophils play a crucial role in the eradication of pathogens but also show hyperactivation in sepsis conditions. Severe damage to the endothelium can be triggered by the overproduction of reactive oxygen species and proteases along with neutrophil extracellular trap (NET) formation [22-24]. The positive role of NETs in the entrapment of bacteria contributes to thrombosis, but the lack of regulation results in the accumulation of histones and proteases in NETs, triggering cytotoxicity, coagulopathy, and the development of disseminated intravascular coagulation, which represents the severe form of sepsis [25].

Ironically, sepsis also triggers the simultaneous onset of immunosuppression, which is another important contributing factor to the long-term mortality associated with it. The widespread apoptosis of lymphocytes, but more specifically the depletion of CD4+ T, CD8+ T, B, and dendritic lymphocytes, translates into the compromised adaptive immune response as well as antigen presentation [26-27]. The exhaustion of T lymphocytes also occurs early, as there is the overexpression of the inhibitory receptors PD-1, CTLA-4, TIM-3, and LAG-3 [28]. The diminished expression of HLA-DR demonstrates the dysfunction of the monocytes, leading to endotoxin tolerance and an impaired response to cytokines [29]. This phenomenon accounts for the so-called "immunoparalysis." Most importantly, the immune paralysis seen in sepsis-susceptible individuals translates into the predisposition to secondary invasive bacterial sepsis, invasive aspergillosis, and the reactivation of viruses like CMV and EBV, as well as the invasive fungal disease [29]. The simultaneous onset of hyperinflammatory response and the availability of multi-omics technology has unveiled the variability in terms of sepsis in individuals, based upon the heterogeneity that exists in the involved biologies [30].

The immune endotypes in relation to sepsis, based upon the presence of hyperinflammatory, immunoparalytic, and coagulopathic responses, as well as a mixed immune response, can be detected by the use of transcriptomics, involving the utilization of unique molecular pathways [26-28]. The aforesaid classifications also show variability in the response to therapies, which include the use of steroids, vasopressors, and fluid resuscitation, as well as the use of immunotherapies, based upon the immune endotypes [20-22]. The use of proteomics, metabolomics, etc., has also offered important insights in terms of the metabolic pathways, where there has been dysfunction in fatty acid oxidation, amino acid metabolism, and mitochondrial respiration, as well as the use of the kynurenine pathway [11-14]. Epigenetic modifications, such as changes in DNA methylation and histone acetylation, may act as long-term "immunological scars" that sustain immune dysfunction even after initial recovery [15].

Machine learning algorithms, in partnership with AI models, are also increasingly employed to integrate multi-omic, clinical, and demographic data to predict the onset, severity, immune conditions, and mortality associated with sepsis [16-18]. These models also identified the stable gene expression profiles over time, as well as the profiles of biomarkers, which could distinguish between the hyper-inflammatory response and the immunosuppressed response to sepsis [19-21]. These models emphasize the relevance of adopting precision medicine strategies based on the immune phenotype over the standardized approach in sepsis [22-23].

The therapeutic horizon has just begun to change towards targeted immunomodulators. Inflammatory therapeutic targets, like IL-1 inhibitors, TNF-α blockers, and so forth, have demonstrated long-term inefficacy because of non-selective therapy in non-homogenous populations [24].

Selected individuals, rather, harboring hyperinflammatory gene expression profiles might derive maximal benefit from cytokine-targeted therapy. By contrast, immunostimulators like IL-7, GM-CSF, and immune checkpoint inhibitors represent promising therapeutic strategies in the revival of 'immune paralysis' brought upon by restoration of T-cells, as well as restoration of activated monocytes [25-26,29]. IL-7 has proven successful in promoting lymphocytosis survival, heterogeneity, and the like, while GM-CSF has proven effective in the revival of activated monocytes along with

restoration of HLA-DR [27]. PD-1 inhibitors, in particular, might restore exhausted T-cells in individuals [24].

Supportive care in the ICU also has a significant impact on the immune system. Sedative medications like propofol, dexmedetomidine, and ketamine can influence the inflammatory response as well as neuroimmune interactions [6]. Ventilatory management can either decrease the inflammatory response or increase it, depending upon the volumes and pressures. The impact of fluid management in the ICU should not be underestimated in the process of maintaining the integrity of the endothelium, while over- or under-resuscitation can impact the glycocalyx as well as the organ perfusion negatively [15-18].

The use of vasopressors in the ICU has the potential to influence the immune response, but while it increases the inflammatory response, the role of norepinephrine needs consideration, as it has a pro-inflammatory property, whereas the role of vasopressin in the ICU remains relatively neutral [6]. In addition, the management of transfusions and the gut microbiome has drawn increasing attention, as there occurs severe dysbiosis in sepsis [8].

Reduced gut bacterial diversity, along with overgrowth of pathogenic bacteria, has been identified as a factor that compromises gut barriers and leads to bacterial translocation, as well as increased levels of systemic inflammation [11]. The role of therapies aimed at the gut microbiome, such as the use of probiotics and fecal transplantation, has been explored as an adjunct therapeutic approach in sepsis [12].

Briefly, sepsis can be defined as a dynamic syndrome characterized by the interaction of hyperinflammatory, immunosuppressed, endotheliopathic, coagulopathic, and metabolic conditions. The reality of this multifaceted syndrome highlights the impracticality of standardized therapeutic strategies, favoring the use of precision medicine based on sepsis phenotypes and endotypes. Since the development of multi-omics technology, immune monitoring, machine learning algorithms, and modeling systems continues to accelerate, the future management of sepsis will necessitate the use of personalized immunotherapy based on the dynamic host response [23-25,29].

By adopting this reality, sepsisologists, as well as anesthesiologists, can help shape the management strategy aimed at rebalancing the compromised immune response [30].

Conclusion

Sepsis represents a profoundly complex immunological state in which hyperinflammation, immune exhaustion, endothelial injury, and metabolic dysfunction evolve simultaneously and dynamically. The historical concept of sepsis as purely an excessive inflammatory response is insufficient; instead, its pathophysiology reflects a continuum ranging from cytokine storm to deep immunoparalysis. Multi-omics technologies and machine-learning models now allow the identification of biologically meaningful endotypes that predict patient trajectory and therapeutic responsiveness. These insights highlight the limitations of uniform treatment protocols and underscore the necessity of precision medicine. Future management of sepsis will increasingly rely on real-time immune monitoring and targeted immunotherapies aiming to restore immune balance. By embracing this phenotype-based and individualized approach, clinicians can more effectively mitigate organ dysfunction, reduce mortality, and guide the evolution of sepsis care toward personalized immunomodulation.

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