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Precision immunotherapy for sepsis: Harnessing passive IgE to Activate M2 macrophages

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Abstract

Sepsis is a rapidly progressing and often fatal medical emergency caused by uncontrolled immune activation in response to infection. The ensuing cytokine storm drives systemic inflammation, leading to multiple organ dysfunction and high mortality rates worldwide. Recent advances highlight the critical role of M2 macrophages, which counteract excessive inflammation, facilitate tissue repair, and help reestablish immune homeostasis. This review explores a novel immunotherapeutic strategy: the use of passive immunoglobulin E/allergen complexes (IgE-ACs) to selectively engage CD23 receptors on M2 macrophages. By promoting anti-inflammatory cytokine release and limiting tissue injury, this targeted approach has the potential to restore immune balance and improve clinical outcomes in sepsis. The current evidence, mechanisms of action, and a prophetic example is discussed to illustrate the promise and challenges of this emerging therapy.

Keywords: Sepsis; M2 macrophage (M2); CD23; Cytokines; Immunoglobulin E/allergen Complex (IgE-AC); Superallergen

1. Introduction

Every three seconds, sepsis claims a life somewhere in the world—a sobering testament to its speed, severity, and the urgent medical challenge it presents. Sepsis arises when the body's immune system spirals out of control in response to infection, unleashing a cytokine storm that causes widespread inflammation, rapid organ dysfunction, and frequently, death. While advances in critical care have improved survival rates, sepsis remains a leading global cause of mortality, and current therapies often fall short of restoring the intricate immune balance essential for recovery. Novel, targeted immunotherapies are urgently needed to address this therapeutic gap.

Current medical management of sepsis relies heavily on broad immunosuppression and general immunomodulation to counteract hyperinflammation. Therapeutic strategies include corticosteroids to dampen immune responses, monoclonal antibodies (such as tocilizumab) to block key inflammatory mediators, and JAK inhibitors to disrupt cytokine signaling pathways. Additionally, blood purification techniques—such as plasmapheresis or cytokine adsorption columns—are employed to physically remove excess cytokines from circulation [1].

Despite these approaches, immunomodulatory therapy remains an area of active research for its potential to restore immune balance and mitigate excessive inflammation [2]. Innovative strategies, such as hyper-allergenic skin cream therapy, have been explored to stimulate IgE-based humoral immunity as a prophylactic measure—aiming to prevent severe innate immune overreactions during viral infections. Such approaches seek to harmonize the rapid activation of innate immunity with pre-primed adaptive responses, ultimately reducing the risk of dangerous inflammation [3].

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Recent studies suggest that stage-specific interventions, tailored to modulate macrophage phenotype at distinct phases of sepsis, may help suppress runaway M1-driven toxicity while avoiding the risks of immune paralysis [4].

In this context, the review examines the emerging role of IgE-allergen complexes (IgE-ACs) that engage CD23 receptors on M2 macrophages, thereby stimulating targeted anti-inflammatory cytokine release via forced vesicular exocytosis.

2. Discussion

2.1. Overview and Rationale

Sepsis remains a leading cause of death worldwide due to the overwhelming, dysregulated immune response it triggers. The search for targeted immunotherapies has led to interest in modulating macrophage phenotypes—particularly the transition from pro-inflammatory M1 to anti-inflammatory M2—to restore immune equilibrium and promote recovery.

2.2. Role of M2 in Sepsis

M2 macrophages are instrumental in counteracting the pathophysiology of sepsis. They suppress excessive inflammation, clear cellular debris, and promote tissue repair—key factors in resolving the cytokine storm and limiting organ dysfunction. Through the release of anti-inflammatory mediators such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), M2 macrophages mitigate the damaging effects of unchecked M1 activity [5].

2.3. Therapeutic Potential of M2 Vesicular Exocytosis

Therapeutically inducing vesicular exocytosis in M2 macrophages during the early stages of sepsis could reduce tissue damage and dampen excessive inflammation. **In the later resolution phase**, M2 activity becomes essential for tissue repair, restoration of homeostasis, and full recovery [6]. The timing and specificity of these interventions are critical, emphasizing the need for stage-adapted approaches to macrophage modulation.

2.4. CD23 Receptor Targeting

Among M2 subtypes, M2a macrophages express particularly high levels of the CD23 receptor compared to M1 macrophages [7]. This receptor serves as a promising therapeutic target: engaging CD23 on M2 could selectively amplify anti-inflammatory responses, offering a new avenue for suppressing the cytokine storm and improving patient outcomes.

2.5. Mechanism of IgE-Allergen Complexes (IgE-AC)

Macrophages express both high-affinity IgE receptors (Fc\epsilonRI) and low-affinity CD23 receptors (Fc\epsilonRII). CD23 is central to the mechanism of IgE-allergen complexes (IgE-ACs), which are engineered for dual specificity: their complementary-determining regions (CDRs) bind allergens with high affinity, while framework regions (FRs) interact with superallergens. This dual binding produces a stable macromolecule, optimized for selective CD23 engagement and minimal off-target effects [8].

Upon binding to CD23 on M2 macrophages, IgE-ACs generally promote non-inflammatory, homeostatic clearance mechanisms rather than acute inflammatory responses. Notably, the engineered conformation of these complexes reduces their affinity for mast cells, basophils, and eosinophils, thereby minimizing the risk of IgE-mediated hypersensitivity and off-target inflammation.

2.6. Implications for Immunotherapy

Harnessing the unique binding profile of IgE-ACs enables selective stimulation of M2 vesicular exocytosis. This targeted, precision immunotherapy approach has the potential to rebalance the immune response in sepsis, curbing pathological inflammation while supporting tissue repair. Such strategies may profoundly improve clinical outcomes and reduce sepsis-associated mortality.

2.7. Prophetic Clinical Application Example

For instance, the lab-generated human IgE monoclonal antibody MOv18 IgE [9] can be combined with a defined quantity of an FRα allergen [10] and the superallergen Protein A (derived from *Staphylococcus aureus)* [11]. Consider a patient in the early phase of sepsis admitted to the intensive care unit: in addition to standard care (antibiotics, fluids, and organ support), the patient receives an intravenous infusion of this engineered IgE-AC as part of a clinical trial. The complex

is specifically designed to minimize allergic risks and to preferentially engage CD23 receptors on M2 macrophages. Following infusion, the IgE-AC circulates in the patient's bloodstream and binds to CD23 receptors on circulating and tissue-resident M2 macrophages. This targeted engagement stimulates vesicular exocytosis of anti-inflammatory cytokines (such as IL-10 and TGF-β), enhances phagocytic clearance of cellular debris, and promotes tissue repair. Collectively, these actions counterbalance the patient's hyperinflammatory response and support organ recovery.

Through therapy, clinicians closely monitor the patient's inflammatory biomarkers, organ function, and clinical status. The therapeutic goal is to mitigate the severity and duration of the cytokine storm, minimize tissue injury, and accelerate recovery—without compromising the body's ability to clear the underlying infection.

This hypothetical scenario demonstrates the potential for integrating precision immunotherapy into standard sepsis care, providing a targeted strategy to restore immune balance, limit collateral tissue damage, and improve patient outcomes.

3. Conclusion

The targeted activation of M2 macrophages using IgE-allergen complexes represents a novel and promising direction for precision immunotherapy in sepsis. This approach addresses the fundamental challenge of sepsis—restoring immune balance by curbing excessive inflammation and supporting tissue repair—without compromising host defense. While the prophetic model highlights significant therapeutic potential, rigorous clinical studies are essential to establish efficacy, safety, and optimal administration strategies. Advancing this innovative therapy could transform sepsis management and reduce the global burden of this devastating condition.

Compliance with ethical standards

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Grammarly was used for grammar, spelling, and punctuation throughout the preparation of the review article. The tool (Grammarly, version 14.1271.0, Grammarly Inc., San Francisco, CA) was used to review and edit the entire article for grammatical accuracy, clarity, and readability. Grammarly's AI-powered writing assistant provided suggestions on sentence structure, word choice, and tone consistency, which the author reviewed and selectively incorporated. The tool was not used to generate original scientific content, data analysis, or research conclusions. The author takes full responsibility for the integrity of all content generated and presented in this review article.

Disclosure of conflict of interest

The author claims no conflict of interest.

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