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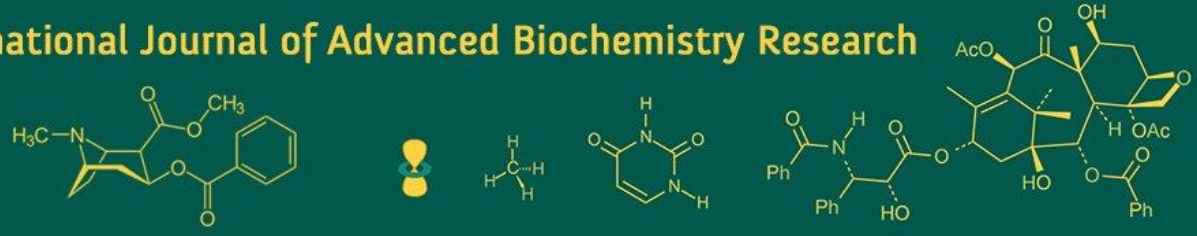

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Inflammation resolution in sepsis: A review

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Abstract
Sepsis is a life-threatening clinical syndrome resulting from a dysregulated host response to infection and remains a major cause of morbidity and mortality worldwide. Despite advances in antimicrobial therapy and critical care, effective disease-modifying treatments remain limited, largely due to an incomplete understanding of the underlying immunopathology. Traditionally, sepsis has been viewed as a condition driven primarily by excessive inflammation; however, increasing evidence indicates that persistent immune dysregulation, rather than inflammation alone, underlies disease progression and poor outcomes.

Inflammation is an essential host defence mechanism, but its timely and active resolution is equally critical for restoring tissue homeostasis. Resolution of inflammation is now recognized as a highly regulated biological process governed by endogenous pathways, including specialized pro-resolving mediators, immune-cell reprogramming, efferocytosis of apoptotic cells, and restoration of tissue integrity. In sepsis, these resolution pathways are frequently impaired or uncoupled from inflammatory responses, resulting in sustained tissue injury, immune suppression, organ dysfunction, and increased susceptibility to secondary infections.

This review synthesizes current knowledge on the mechanisms of inflammation resolution and their relevance to sepsis. We discuss immune dysregulation in sepsis, cellular and molecular defects that impair resolution, and the role of specialized pro-resolving mediators such as lipoxins, resolvins, protectins, and maresins. Emerging evidence supporting the concept of sepsis as a "pro-resolution deficiency disorder" is critically evaluated. Finally, we highlight the therapeutic potential of resolution-based strategies that aim to restore immune balance rather than suppress inflammation. Targeting endogenous resolution pathways may represent a paradigm shift in sepsis management, offering new opportunities for improving outcomes in this complex and devastating condition.

Keywords: Sepsis, inflammation resolution, specialized pro-resolving mediators, immune dysregulation

Introduction
Sepsis remains one of the most formidable challenges in modern medicine and is a leading cause of mortality among critically ill patients worldwide. It is now recognized as a life-threatening condition that arises from a dysregulated host response to infection, resulting in organ dysfunction and, in severe cases, death. Despite advances in antimicrobial therapies, intensive care practices, and supportive interventions, sepsis-related mortality remains unacceptably high, emphasizing the need for improved understanding of its underlying immunopathology [1].

The host immune response to infection is inherently protective, designed to eliminate invading pathogens and restore tissue integrity. Acute inflammation plays a central role in this defence mechanism by promoting pathogen clearance, activating immune effector cells, and initiating tissue repair. Under physiological conditions, inflammation is self-limiting and resolves once the inciting stimulus has been neutralized. However, in sepsis, this finely balanced process becomes profoundly dysregulated. Instead of resolving, inflammation may persist or oscillate alongside immune suppression, leading to tissue injury, organ dysfunction, and vulnerability to secondary infections [2].

Historically, therapeutic strategies in sepsis have focused predominantly on suppressing inflammation, based on the assumption that excessive inflammatory responses drive tissue damage and mortality.

However, clinical trials targeting individual pro-inflammatory mediators have largely failed to improve outcomes. These disappointing results suggest that sepsis cannot be adequately addressed by inhibiting inflammation alone and highlight the need for alternative conceptual frameworks [3].

In recent years, the biology of inflammation resolution has emerged as a critical area of investigation. Resolution is no longer viewed as a passive process that follows the decline of inflammatory signals but rather as an active, highly regulated programme initiated early during the inflammatory response. This programme is mediated by endogenous molecules that actively terminate inflammation, promote clearance of inflammatory cells, and restore tissue homeostasis. Failure of these resolution pathways has been implicated in a range of chronic inflammatory diseases and is increasingly recognized as a key factor in sepsis pathogenesis [4].

This review examines the role of inflammation resolution in sepsis, integrating current understanding of immune dysregulation, cellular and molecular mechanisms of resolution, and the function of specialized pro-resolving mediators. We also explore the hypothesis that sepsis may represent a pro-resolution deficiency disorder and discuss the therapeutic implications of targeting resolution pathways in this complex syndrome.

Sepsis: Evolution of Concept and Definitions

The concept of sepsis has evolved considerably over centuries. The term originates from the Greek word "sepsis," meaning decay or putrefaction, reflecting early observations of infection-associated deterioration. Classical physicians such as Celsus and Galen described inflammation through the cardinal signs of redness, heat, swelling, pain, and loss of function—features that remain relevant to contemporary inflammatory biology [5].

In the late twentieth century, efforts to standardize the definition of sepsis culminated in the introduction of the systemic inflammatory response syndrome (SIRS) criteria. Sepsis was defined as infection accompanied by systemic manifestations such as fever, tachycardia, tachypnoea, and leukocyte abnormalities. While these criteria facilitated early recognition and enrolment of patients into clinical studies, they lacked specificity. Non-infectious conditions such as trauma, burns, pancreatitis, and ischemia-reperfusion injury frequently fulfil SIRS criteria, complicating differentiation between sterile inflammation and infection-driven pathology [5].

Moreover, inflammatory responses are not inherently pathological. Fever, leukocytosis, and increased heart rate may reflect effective host defence rather than disease severity. These limitations led to substantial heterogeneity in sepsis diagnosis, incidence reporting, and outcome assessment [5].

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) addressed these shortcomings by redefining sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction is quantified using the Sequential Organ Failure Assessment (SOFA) score, shifting emphasis from inflammatory markers to functional impairment. Septic shock is defined as a subset of sepsis characterized by profound circulatory, cellular, and metabolic abnormalities associated with increased mortality [5].

This modern definition underscores that sepsis is not merely an exaggerated inflammatory response but a complex syndrome arising from immune dysregulation, in which both excessive inflammation and impaired immune competence coexist.

Immune Dysregulation in Sepsis

Sepsis exerts profound effects on the immune system, disrupting both innate and adaptive immune responses. Early conceptual models proposed a biphasic immune response consisting of an initial hyperinflammatory phase followed by a compensatory anti-inflammatory phase leading to immune suppression. However, accumulating evidence indicates that these processes occur simultaneously rather than sequentially [6].

Innate immune activation is initiated by recognition of pathogen-associated molecular patterns and damage-associated molecular patterns through pattern-recognition receptors, including Toll-like receptors, NOD-like receptors, and C-type lectin receptors. Activation of these receptors triggers intracellular signalling cascades that lead to the production of pro-inflammatory cytokines, chemokines, and acute-phase reactants. While these responses are essential for pathogen elimination, excessive or sustained activation contributes to endothelial dysfunction, capillary leak, coagulation abnormalities, and organ injury [7].

At the same time, adaptive immune responses are markedly impaired. Extensive apoptosis of lymphocytes, reduced antigen presentation by monocytes and dendritic cells, and expansion of regulatory immune cell populations contribute to immune suppression. This state predisposes septic patients to secondary infections, viral reactivation, and poor long-term outcomes. Importantly, inflammatory and anti-inflammatory pathways are activated in parallel, resulting in a persistent state of immune imbalance rather than a simple transition from inflammation to suppression [8].

Recognition of this complex immune landscape has prompted a shift away from therapies that solely inhibit inflammation toward approaches that aim to restore immune homeostasis. In this context, understanding how inflammation is actively resolved has become increasingly relevant to sepsis biology.

Hyperinflammation and Cytokine Storm

Once local containment of infection is lost, microbial components and endogenous danger signals disseminate systemically, exposing the host to pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). These signals are detected by pattern-recognition receptors expressed on immune cells, endothelial cells, and parenchymal tissues, triggering widespread activation of innate immunity. In sepsis, this response frequently becomes excessive and self-amplifying, leading to the phenomenon commonly described as a cytokine storm [2].

The cytokine storm is characterized by rapid and excessive production of pro-inflammatory cytokines, including tumour necrosis factor (TNF), interleukin (IL)-1β, IL-6, and IL-17. These mediators exert pleiotropic effects on vascular tone, endothelial permeability, coagulation, and cellular metabolism. Increased endothelial permeability results in capillary leak and tissue oedema, while dysregulated vasodilation contributes to hypotension and impaired organ perfusion. Concurrent activation of the coagulation cascade

promotes microvascular thrombosis, further compromising tissue oxygen delivery [9].

Complement activation plays a central role in amplifying inflammation during sepsis. Anaphylatoxins such as C3a and C5a recruit and activate leukocytes, enhance vascular permeability, and promote platelet activation. While complement activation is essential for microbial defence, uncontrolled activation contributes to tissue injury and organ failure. The close interaction between inflammation and coagulation, often referred to as immune-thrombosis, exemplifies how protective host mechanisms become maladaptive during sepsis [9].

Importantly, hyperinflammation alone does not fully explain sepsis pathogenesis or mortality. Many patients exhibit persistent inflammation despite declining levels of circulating cytokines, suggesting that additional mechanisms sustain tissue injury. Increasing attention has therefore focused on the failure of endogenous processes that normally terminate inflammation and restore homeostasis.

Biology of Inflammation Resolution

Inflammation resolution is now recognized as an active, highly coordinated biological process rather than a passive decline of inflammatory signals. Early observations of resolving inflammatory exudates revealed that leukocyte clearance and tissue restoration follow defined temporal patterns. Subsequent work established that resolution is governed by endogenous mediators that actively counter-regulate inflammation and promote tissue repair [3].

A defining feature of resolution is lipid mediator class switching. During the initiation phase of acute inflammation, arachidonic acid metabolism predominately generates prostaglandins and leukotrienes that promote vasodilation, leukocyte recruitment, and pain. As inflammation progresses, these same prostaglandins induce the expression of enzymes required for the biosynthesis of specialized pro-resolving mediators (SPMs), including lipoxins, resolvins, protectins, and maresins. This switch marks the transition from inflammation propagation to active resolution [4].

SPMs exert their actions through specific G-protein-coupled receptors expressed on leukocytes, endothelial cells, and tissue-resident cells. Rather than broadly suppressing immune responses, these mediators fine-tune inflammation by inhibiting further neutrophil recruitment, reducing endothelial activation, promoting apoptosis of spent neutrophils, and enhancing their clearance by macrophages. Importantly, these actions occur without impairing host defence, distinguishing resolution from immunosuppression [10].

Resolution also involves profound changes in cellular phenotype and function. Macrophages undergo reprogramming from a classically activated pro-inflammatory state to a pro-resolving phenotype characterized by enhanced efferocytosis and production of anti-inflammatory cytokines such as IL-10 and transforming growth factor-β. This phenotypic shift is critical for clearing inflammatory debris and initiating tissue repair [11].

Resolution: Active or Passive?

For many decades, resolution of inflammation was viewed as a passive process resulting from removal of the inflammatory stimulus, dilution of chemoattractants, and cessation of leukocyte recruitment. According to this model, inflammation subsided simply because pro-inflammatory signals diminished over time. However, accumulating experimental evidence has challenged this view, demonstrating that resolution is an active, regulated programme requiring specific molecular signals [11].

Studies of self-limiting inflammatory responses revealed that resolving exudates contain distinct lipid mediator profiles enriched in SPMs. These mediators actively inhibit further neutrophil infiltration and promote non-phlogistic clearance of apoptotic cells. The identification of lipid mediator class switching provided direct evidence that pro-inflammatory and pro-resolving signals are temporally linked and biologically interdependent [3].

Active resolution also engages specific intracellular signalling pathways. For example, certain SPMs counter-regulate nuclear factor κB signalling, a central pathway in inflammatory gene expression, while others modulate cellular metabolism and cytoskeletal dynamics to enhance phagocytosis. In addition, resolution involves coordinated regulation of extracellular nucleotide metabolism, including adenosine signalling, which further contributes to anti-inflammatory and tissue-protective effects [11].

These findings underscore the concept that inflammation resolution is not simply the absence of inflammation but a distinct phase of the inflammatory response with its own molecular mediators, receptors, and cellular programmes. Failure to initiate or sustain this phase can result in persistent inflammation, tissue injury, and progression to chronic inflammatory states.

Tissue Specificity of Resolution Mechanisms

Although the fundamental principles of inflammation resolution are conserved, the mechanisms involved exhibit significant tissue specificity. Inflammatory responses vary depending on the tissue involved, the nature of the insult, and the resident immune cell populations. Consequently, resolution programmes are shaped by the local cellular environment and mediator milieu [12].

Inflammatory exudates can be broadly classified as purulent, haemorrhagic, or serous, each characterized by distinct cellular and molecular compositions. Purulent exudates are rich in neutrophils and microbial debris, requiring efficient clearance mechanisms to prevent tissue destruction. Haemorrhagic exudates involve vascular injury and coagulation, necessitating coordinated resolution of inflammation and restoration of vascular integrity. Serous exudates, typically associated with mild tissue injury, resolve with minimal leukocyte infiltration and rapid restoration of normal tissue architecture [13].

Tissue-resident macrophages, mast cells, endothelial cells, and epithelial cells play critical roles in shaping local resolution responses. In some tissues, macrophages are the first responders, while in others neutrophils or endothelial cells initiate the inflammatory cascade. The timing and magnitude of SPM production therefore differ between organs, influencing the efficiency of resolution [13].

In sepsis, multiple organs are simultaneously affected, each with distinct inflammatory and resolution requirements. This complexity poses significant challenges for therapeutic intervention and underscores the need for strategies that enhance endogenous resolution pathways across diverse tissues rather than targeting single inflammatory mediators.

Cellular Events in the Resolution of Acute Inflammation

Acute inflammation is characterized by increased blood flow, vascular permeability, leukocyte recruitment, and production of inflammatory mediators. While these events are essential for pathogen elimination, their persistence can result in tissue injury and loss of function. The resolution of acute inflammation therefore requires precise coordination of cellular events that actively terminate inflammatory responses and restore tissue homeostasis [3].

A hallmark of successful resolution is the timely removal of neutrophils from inflamed tissues. Neutrophils are indispensable for host defence, but prolonged neutrophil persistence exacerbates tissue damage through the release of proteases, reactive oxygen species, and inflammatory mediators. Resolution involves inhibition of further neutrophil recruitment, followed by induction of programmed cell death (apoptosis) in senescent neutrophils. Apoptotic neutrophils are subsequently cleared by macrophages through a process known as efferocytosis, which occurs in a non-phlogistic manner and does not provoke further inflammation [11].

Macrophages play a central role in orchestrating resolution. During active inflammation, macrophages exhibit a pro-inflammatory phenotype characterized by production of cytokines such as TNF and IL-1β. As resolution progresses, macrophages undergo functional reprogramming toward a pro-resolving phenotype. This transition is marked by enhanced efferocytosis, increased production of anti-inflammatory cytokines such as IL-10 and transforming growth factor-β, and suppression of pro-inflammatory gene expression. This macrophage reprogramming is critical for clearing inflammatory debris and initiating tissue repair [14].

In addition to neutrophils and macrophages, other immune cells contribute to resolution. Monocytes are recruited in a non-phlogistic manner and differentiate into macrophages that support tissue repair. Dendritic cells modulate adaptive immune responses and promote immune tolerance during the resolution phase. Regulatory T cells further suppress excessive immune activation and contribute to restoration of immune balance. Collectively, these cellular events ensure that inflammation is terminated efficiently without compromising host defence [3].

Pro-Resolving Mediators: Classes and Functions

Resolution of inflammation is governed by a diverse array of endogenous mediators that actively counter-regulate inflammatory processes. Among these, specialized pro-resolving mediators (SPMs) have emerged as central regulators of resolution biology. SPMs are lipid-derived molecules synthesized from polyunsaturated fatty acids, including arachidonic acid, eicosapentaenoic acid, and docosahexaenoic acid [14].

Lipoxins are derived from arachidonic acid and were among the first SPMs identified. Lipoxin A4 inhibits neutrophil chemotaxis, transendothelial migration, and degranulation, while enhancing macrophage-mediated clearance of apoptotic cells. Resolvins are derived from omega-3 fatty acids and are classified into E-series and D-series. These mediators limit leukocyte recruitment, suppress pro-inflammatory cytokine production, and enhance phagocytosis. Protectins and maresins also originate from docosahexaenoic acid and exhibit potent anti-inflammatory and tissue-protective effects [15].

Unlike conventional anti-inflammatory drugs, SPMs do not block inflammation indiscriminately. Instead, they act as agonists that stimulate specific resolution pathways, leading to coordinated termination of inflammation. Importantly, SPMs preserve or even enhance host defence mechanisms, including bacterial clearance by phagocytes. This property distinguishes pro-resolving mediators from immunosuppressive agents and highlights their therapeutic potential in infectious diseases such as sepsis [11].

In addition to lipid mediators, other endogenous molecules contribute to resolution. Proteins and peptides such as annexin A1, galectins, and chemerin-derived peptides exert pro-resolving actions by modulating leukocyte trafficking and phagocytosis. Gaseous mediators such as carbon monoxide and hydrogen sulfide, as well as purinergic signalling molecules such as adenosine, also participate in resolution pathways. Together, these mediators form an integrated network that actively restores tissue homeostasis [10].

Clinical Advantages of Resolution-Based Therapies

For more than a century, pharmacological management of inflammatory diseases has relied predominantly on agents that suppress inflammation by inhibiting cyclooxygenases, cytokines, or immune cell activation. While these therapies can reduce inflammatory symptoms, they often impair host defence and may delay resolution at the tissue level. In the context of sepsis, immunosuppression represents a major concern, as patients are already vulnerable to secondary infections.

Resolution-based therapies offer several conceptual and practical advantages. By activating endogenous resolution pathways, these approaches limit further leukocyte recruitment, promote clearance of inflammatory cells, and facilitate tissue repair without compromising antimicrobial immunity. Experimental studies demonstrate that SPMs not only reduce inflammation but also enhance bacterial clearance by phagocytes, thereby addressing both components of sepsis pathophysiology [16].

Interestingly, several widely used drugs exhibit pro-resolving properties. Aspirin acetylates cyclooxygenase-2, triggering the biosynthesis of aspirin-induced lipoxins and resolvins. Statins promote generation of 15-epi-lipoxin A4 through modification of cyclooxygenase-2 activity, contributing to their anti-inflammatory and vasculoprotective effects. Glucocorticoids induce annexin A1 release, further linking conventional therapies to resolution biology [17].

These observations suggest that enhancing resolution does not necessarily require development of entirely new drugs but may be achieved by repurposing or optimizing existing therapies to favour pro-resolving pathways.

Resolution of Inflammation in Sepsis

In sepsis, resolution of inflammation is initiated early but often fails to proceed effectively. Anti-inflammatory pathways, including production of IL-10 and transforming growth factor-β, are activated shortly after sepsis onset, reflecting an attempt to counterbalance hyperinflammation. Autophagy also contributes to resolution by eliminating intracellular PAMPs and DAMPs, thereby reducing immune activation [6].

Despite activation of these pathways, resolution remains incomplete or dysregulated in many patients. Persistent

neutrophil activation, defective efferocytosis, impaired macrophage reprogramming, and insufficient production of SPMs contribute to ongoing inflammation and tissue injury. Recent clinical studies have demonstrated that resolution circuits are uncoupled in severe sepsis and correlate with disease severity and adverse outcomes [18].

These findings support the notion that sepsis is characterized not only by excessive inflammation but also by a failure of endogenous resolution mechanisms. Restoring these pathways may therefore represent a critical determinant of recovery and survival.

Immune Suppression and Molecular Defects Impairing Resolution

A defining and clinically significant feature of sepsis is the coexistence of persistent inflammation with profound immune suppression. This immunosuppressed state contributes to secondary infections, viral reactivation, prolonged intensive care unit stay, and increased late mortality. Importantly, immune suppression in sepsis is not merely a consequence of inflammation but also reflects defects in pathways that normally coordinate inflammation resolution [1].

At the cellular level, neutrophils exhibit impaired chemotaxis, defective phagocytosis, and altered apoptosis kinetics. Delayed neutrophil apoptosis prolongs tissue exposure to cytotoxic mediators, while impaired clearance of apoptotic cells disrupts efferocytosis and propagates inflammation. Monocytes and macrophages display reduced expression of major histocompatibility complex class II molecules, particularly HLA-DR, leading to defective antigen presentation and diminished activation of adaptive immunity. This state, often termed endotoxin tolerance, is associated with reduced production of pro-inflammatory cytokines in response to secondary challenges [19].

Adaptive immune dysfunction is characterized by extensive apoptosis of $CD4^+$ and $CD8^+$ T lymphocytes and dendritic cells. Regulatory T cells are relatively resistant to apoptosis and become proportionally enriched, further suppressing effector immune responses. Together, these changes compromise immune competence while failing to adequately resolve inflammation [7].

Several molecular pathways contribute to impaired resolution in sepsis. Excessive production of reactive oxygen and nitrogen species leads to oxidative stress, damaging proteins, lipids, and nucleic acids. Oxidative stress interferes with transcription factors such as nuclear factor erythroid-2 related factor-2 and peroxisome proliferator-activated receptors, which are essential for antioxidant defence and regulation of inflammatory gene expression. Dysfunction of these pathways perpetuates redox imbalance and sustains inflammatory signalling [2].

Mitochondrial dysfunction represents another critical mechanism linking immune dysregulation and impaired resolution. In sepsis, mitochondrial respiration is compromised, leading to reduced adenosine triphosphate production and accumulation of reactive oxygen species. Energy depletion induces a state of cellular hibernation, contributing to reversible organ dysfunction. Restoration of mitochondrial bioenergetics has been associated with improved outcomes in experimental sepsis models, highlighting the central role of metabolic regulation in recovery [20].

Sepsis as a Pro-Resolution Deficiency Disorder

The concept that sepsis may represent a pro-resolution deficiency disorder has gained increasing support. This hypothesis proposes that inadequate production, accelerated degradation, or impaired signalling of specialized pro-resolving mediators prevents effective termination of inflammation, leading to persistent immune dysregulation and tissue injury [17].

Experimental studies demonstrate that administration of lipoxins, resolvins, protectins, and maresins attenuates inflammatory responses, enhances bacterial clearance, and improves survival in models of sepsis. These mediators not only suppress excessive cytokine production but also promote macrophage efferocytosis, tissue repair, and restoration of immune balance. Importantly, their actions are distinct from immunosuppression, as host defence mechanisms remain intact or are enhanced [21].

Defective resolution in sepsis may arise from altered lipid metabolism, impaired enzyme activity involved in SPM biosynthesis, or receptor dysfunction on immune cells. Oxidative stress and mitochondrial dysfunction further compromise these pathways. In this context, persistent inflammation is not simply the result of excessive pro-inflammatory signalling but reflects a failure of endogenous mechanisms designed to terminate inflammation and restore homeostasis [17].

Viewing sepsis through the lens of resolution biology provides a unifying framework that integrates hyperinflammation, immune suppression, and organ dysfunction. It also offers a rationale for why therapies targeting single inflammatory mediators have largely failed, as they do not address the underlying deficit in resolution capacity.

Therapeutic Implications and Future Directions

Targeting inflammation resolution represents a promising and fundamentally different approach to sepsis therapy. Rather than inhibiting inflammation indiscriminately, resolution-based strategies aim to restore immune balance by enhancing endogenous pro-resolving pathways. This approach has the potential to limit tissue injury, promote organ recovery, and reduce susceptibility to secondary infections.

Several therapeutic avenues are under investigation. These include direct administration of SPMs or their stable analogues, pharmacological agents that enhance endogenous SPM biosynthesis, and interventions that restore metabolic and mitochondrial function. Commonly used drugs such as aspirin and statins may exert beneficial effects in sepsis partly through their ability to promote resolution pathways, providing opportunities for drug repurposing [21].

Future research should focus on identifying reliable biomarkers of resolution capacity, enabling patient stratification and personalized therapy. Understanding inter-individual variability in resolution responses may explain differences in sepsis outcomes and guide targeted interventions. Translational studies integrating immunology, metabolism, and systems biology will be essential for advancing resolution-based therapies from bench to bedside.

Conclusion

Sepsis is a complex immunological syndrome characterized not only by excessive inflammation but also by a fundamental failure of endogenous inflammation resolution.

Accumulating evidence indicates that impaired resolution pathways contribute to persistent immune dysregulation, organ dysfunction, secondary infections, and mortality. Reframing sepsis as a pro-resolution deficiency disorder provides new insights into its pathogenesis and helps reconcile the coexistence of hyperinflammation and immune suppression.

Specialized pro-resolving mediators and related pathways represent a critical but under-explored component of host defence. Therapeutic strategies that harness or restore these pathways offer the potential to suppress maladaptive inflammation while preserving immune competence and promoting tissue repair. Integrating resolution biology into sepsis research and clinical practice may ultimately transform the management of this devastating condition.

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