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REVIEW

Exploring the Importance of ZBP1 in Sepsis: A Mini Review on It's Mechanisms and Progress

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Abstract: Sepsis is defined as a severe systemic inflammation, often triggered by an infection, resulting in organ dysfunction and mortality. In recent years, ZBP1 (Z-DNA binding protein 1) has garnered significant attention as a critical immune regulatory factor in the pathogenesis of sepsis. This article aims to comprehensively explore the mechanisms by which ZBP1 operates in sepsis and summarize the relevant research progress. This study will seek to highlight the potential of ZBP1 as a therapeutic target and biomarker in the context of sepsis through an in-depth analysis of its functions in cellular signaling, inflammatory response, and immune response. This review seeks to provide new insights for the clinical management of sepsis.

Keywords: ZBP1, sepsis, immune regulation, inflammatory response, research progress

Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection, which is associated with a high level of morbidity and mortality. It is considered to represent a major global health challenge. The Sepsis-3 definition, which emphasizes the importance of organ dysfunction, has reshaped the clinical approach to managing sepsis in intensive care settings, underscoring the urgency of timely intervention in affected patients.[1,2] Blood cultures are still used clinically as the "gold standard" for diagnosing sepsis by detecting pathogens in the patient's blood, but they are a time-consuming process, usually taking 2–3 days.[3,4] The utilization of certain biomarkers has been demonstrated to play a significant adjunctive role in clinical practice, serving a crucial function in the diagnosis, treatment and prognostic assessment of sepsis. Common biomarkers include C-reactive protein (CRP), procalcitonin (PCT), and interleukin-1 (IL-1).[5] In light of the intricacy of the pathophysiological process of sepsis and the constraints imposed by individual biomarkers in this context, the integration of multiple biomarkers has emerged as a promising approach to enhance the precision and comprehensiveness of the assessment of sepsis patients' condition and prognosis. Here we focus on ZBP1, also known as Z-DNA binding protein 1, is a pivotal component of the innate immune response. It plays a crucial role in the activation of inflammatory pathways. It is involved in the regulation of cellular processes such as apoptosis, autophagy and immune response. Recent research has identified ZBP1 as a potential biomarker for various diseases, including cancer and autoimmune disorders, due to its role in modulating inflammatory responses.[6,7] Recent studies have directed a growing amount of attention to the relationship between ZBP1 and sepsis. ZBP1 has been implicated in the host's response to infections, suggesting that it may serve as a critical mediator in the pathophysiology of sepsis. By influencing the inflammatory response and apoptosis, ZBP1 may contribute to the severity and outcomes of septic patients.[8,9] Although studies have focused on the role of ZBP1 in certain diseases, its specific mechanisms and potential as a biomarker in sepsis have not been fully explored. The review aims to explore and analyze the extant

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literature ZBP1's function in sepsis, with a focus on its potential as a prognostic target and a therapeutic target for the management of this complex syndrome.

Structure and Function of ZBP1

Molecular Structure of ZBP1

ZBP1, also known as Z-DNA binding protein 1, plays a crucial function in the innate immune response and cellular signaling. Structurally, ZBP1 possesses a Z-alpha domain that specifically binds to left-handed Z-DNA and Z-RNA, which are forms of nucleic acids that can arise under certain cellular stress conditions or during viral infections.[10] The ability of ZBP1 to recognize these unusual nucleic acid structures is fundamental for its function as a sensor of viral infections and cellular stress. Recent studies have demonstrated that ZBP1 contains a C-terminal RHIM (RIP homotypic interaction motif) domain, which is vital for mediating necroptosis—a form of programmed cell death associated with inflammation.[11] This structural configuration allows ZBP1 to act as a bridge between nucleic acid sensing and the activation of cell death pathways, highlighting its dual role in recognizing pathogen-associated molecular patterns and orchestrating immune responses.[12]

Functional Role of ZBP1 in Cells

In terms of functionality, ZBP1 serves multiple roles within the cell. Primarily, it acts as a sensor for Z-nucleic acids, triggering inflammatory responses upon detection of these structures. This activation is critical in viral infection, where ZBP1 can induce necroptosis by recruiting RIPK3 and subsequently activating MLKL, leading to cell death and releasing proinflammatory signals.[13] Furthermore, ZBP1 has been implicated in various pathological conditions, including neurodegenerative diseases and cancer. For instance, in Alzheimer's disease, ZBP1 mediates pyroptosis through the regulation of IRF3, thus contributing to neuroinflammation.[14] Additionally, ZBP1 has been shown to promote osteogenic differentiation while inhibiting adipogenic differentiation in mesenchymal stem cells, demonstrating its versatility in cellular differentiation pathways.[11] The multifaceted roles of ZBP1 underscore its importance not only in innate immunity but also in maintaining cellular homeostasis and regulating developmental processes.[15] Overall, ZBP1 is a pivotal molecule that integrates immune signaling with cell death mechanisms, making it a potential target for therapeutic interventions in various diseases.

The Immunoregulatory Role of ZBP1

The Role of ZBP1 in Antimicrobial Immunity

ZBP1, also known as DAI or DLM-1, functions as a crucial sensor in the innate immune response against microbial infections. It recognizes Z-form nucleic acids, which are frequently occur during the course of viral infections, thereby inducing an immune response. The activation of ZBP1 induce the various pro-inflammatory cytokines, which are vital for orchestrating the body's defense against pathogens. Recent research has emphasized the pivotal function of ZBP1 in activating the NLRP3 inflammasome, a key component in the innate immune response that promotes the secretion of interleukin-1β (IL-1β) and IL-18, which are critical for effective antimicrobial immunity.[16] Furthermore, ZBP1 has been implicated in the process of PANoptosis, a form of programmed cell death that integrates apoptosis, necroptosis, and pyroptosis, thus enhancing the host's ability to eliminate infected cells.[17] This multifaceted role of ZBP1 underscores its importance in the immune defense against a variety of pathogens, including viruses and bacteria, making it a potential target for therapeutic interventions in infectious diseases.

The Impact of ZBP1 on Macrophage Function

Macrophages are pivotal players in the immune system, and ZBP1 significantly influences their functionality. Upon activation by pathogens or pro-inflammatory signals, ZBP1 modulates macrophage responses through various signaling pathways. It has been shown that ZBP1 can enhance the necroptotic pathway in macrophages, which is crucial for the elimination of intracellular pathogens.[18] This necroptosis mechanism not only aids in pathogen clearance but also amplifies the inflammatory response, creating a favorable environment for further immune cell recruitment. Recent studies have shown that ZBP1 can have an effect on macrophage function after Borrelia burgdorferi infection in mice by activating two pathways, the type I interferon signalling

pathway and the unfolded protein response (UPR).[19] Additionally, ZBP1's interaction with the NLRP3 inflammasome in macrophages facilitates the production of IL-1β, a cytokine that plays a vital role in the inflammatory response and in driving adaptive immunity.[20] Therefore, the regulation of macrophage function by ZBP1 is essential for both innate and adaptive immunity, stressing its Possible as a therapeutic objective for modulating immune responses in various diseases.

The Function of ZBP1 in T Cell Activation

ZBP1 also plays a significant role in the activation and regulation of T cells, which are crucial for adaptive immunity. It has been reported that ZBP1 is involved in the signaling pathways that lead to T cell activation, particularly through its interaction with various pattern recognition receptors.[21] T-cell proliferation and cytokine production can be increased by activating ZBP1 in T-cells. For example, ZBP1 enhances the innate immune response of T cells by activating IRF3 and ISGs, thus promoting an effective immune response against tumors and infections. Moreover, ZBP1 involved in regulating T cell survival and homeostasis, indicating its broader implications in maintaining immune balance.[22] The role of ZBP1 in T cell responses is further underscored by its involvement in the necroptotic pathways, which can influence T cell fate during inflammatory conditions.[23] These insights into ZBP1's function in T cell activation suggest that it may serve as a potential biomarker for immunotherapy, especially in cancers where T cell responses are critical for therapeutic efficacy.[6]

The Role of ZBP1 in Sepsis Mechanisms

Interaction of ZBP1 with Inflammatory Signaling Pathways

ZBP1 plays a pivotal role in mediating inflammatory responses during sepsis through its interaction with various signaling pathways. It is well-documented that ZBP1 can trigger inflammatory reactions independent of cell death by activating RIPK3 and RIPK1, which are crucial for necroptosis and inflammatory signaling.[24] This mechanism is particularly relevant in the context of sepsis, where the release of pro-inflammatory cytokines is a hallmark of the condition. ZBP1's involvement in the activation of the NLRP3 inflammasome further underscores its significance in the inflammatory cascade, as it facilitates the processing and release of IL-1β and IL-18, key cytokines in the sepsis response.[16] Moreover, ZBP1 has been demonstrated to interact with the NF-κB signaling pathway, thereby enhancing the expression of pro-inflammatory genes, which contributes to the systemic inflammation observed in sepsis.[13] The role of ZBP1 in the TLR (Toll-like receptor) signaling pathway also highlights its importance, as TLRs are critical sensors of pathogen-associated molecular patterns (PAMPs). ZBP1 enhances TLR-mediated signaling, leading to increased expression of inflammatory mediators, thus amplifying the host's immune response to infection.[25] Overall, ZBP1 serves as a crucial mediator in the interplay between various inflammatory pathways, driving the exaggerated immune response characteristic of sepsis. The schematic diagram of the mechanism is shown in Figure 1.

Regulatory Role of ZBP1 in Apoptosis and Autophagy

Apoptosis is a form of programmed cell death accompanied by inflammation, and is characterized by the processes of cellular pyroptosis, apoptosis, and necroptosis. Autophagy is a process in which eukaryotic cells utilize lysosomes to degrade their own cytoplasmic proteins and damaged organelles under the regulation of autophagy related gene (Atg). In addition to its role in inflammation, ZBP1 plays a pivotal role in the intricate regulation of apoptosis and autophagy, processes that are vital for cellular homeostasis and the response to stress during sepsis. Research indicates that ZBP1 can influence cell fate decisions by modulating apoptotic pathways, particularly under conditions of viral infection and stress.[29] The present study has revealed that ZBP1 is stably expressed in the sepsis, a process that is stabilized by the inhibition of TRIM32-mediated autoregulation and that activates the RIPK3 pathway, thereby exacerbating the process of sepsis-induced cell death.[30] Its activation has been linked to both apoptosis and necroptosis, suggesting a complex role in determining cell death modalities during inflammatory responses.[31] Furthermore, ZBP1 has been shown to interact with autophagic machinery, influencing the turnover of RHIM-domain proteins that are essential for the regulation of programmed cell death.[32] This connection between autophagy and cell death pathways highlights the potential of ZBP1 as a therapeutic target, as manipulating its activity could regulating the equilibrium of cell alive and dead in septic conditions. The interplay between ZBP1-mediated autophagy and inflammation also suggests that enhancing autophagic processes may mitigate the detrimental effects of excessive inflammation seen in sepsis.[33] Conversely, ZBP1 inhibits apoptosis when autophagy is impaired. Its accumulation has been demonstrated to serve as

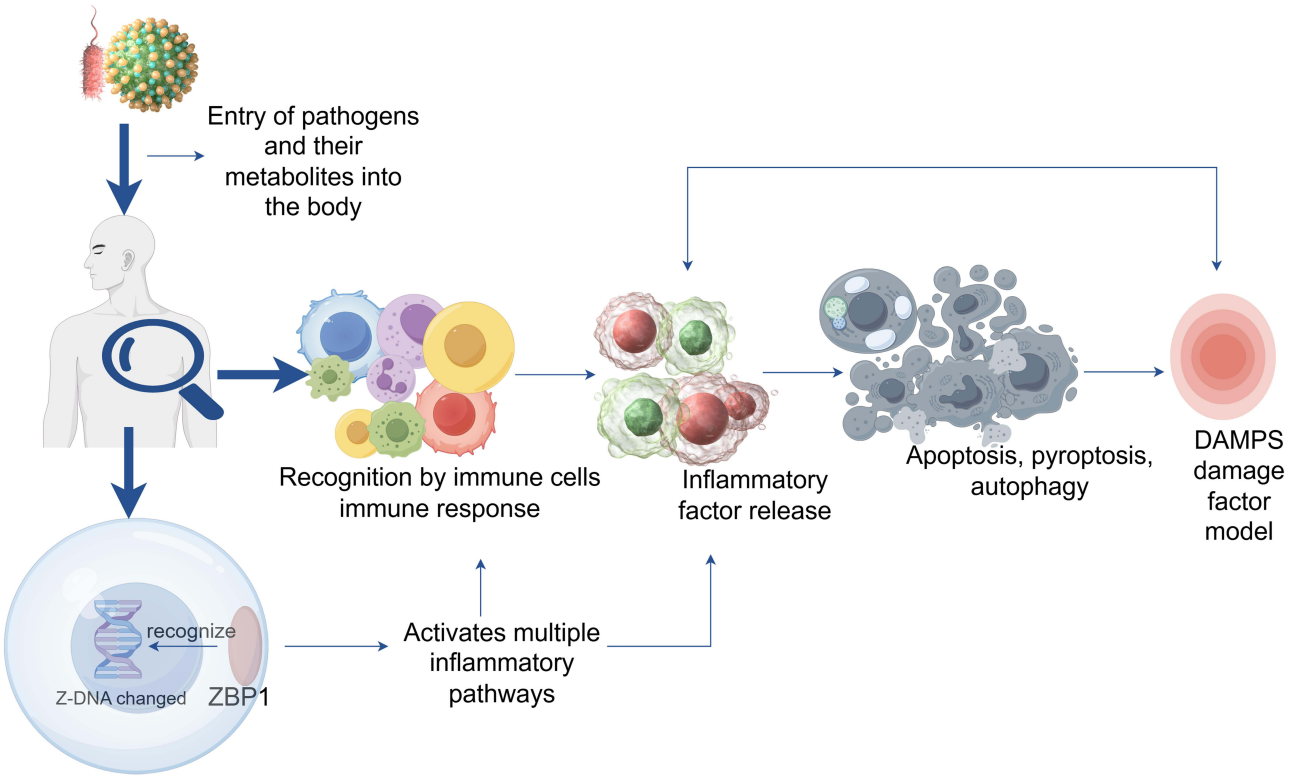

Figure 1 Pathogenesis of sepsis and the role of ZBP1 in sepsis.
Notes: Pathogens and their metabolites enter the body and activate the LPS-TLR4 pathway to be recognized by immune cells, generating an immune response that releases inflammatory factors (including pro-inflammatory and anti-inflammatory factors), causing apoptosis, pyroptosis, and autophagy to form the DAMPS damage factor pattern, which is in turn recognized by immune cells to produce more inflammatory factors; When cells in the body are attacked by pathogens, intracellular Z-DNA/RNA changes occur, which can be recognised by ZBP1 and bind to it, activating inflammatory pathways such as RIPK3/RIPK1, NLRP3, NF-KB, TLR, etc, which further exacerbate inflammation and immune responses, ultimately leading to "inflammatory storms". Data from these studies.[26–28] By figdraw.

a protective measure against excessive apoptosis by impeding the TRIF-RIPK3 signaling pathway.[32] Thus, ZBP1 emerges as a critical regulator not only in the inflammatory response but also in the delicate balance of apoptosis and autophagy during sepsis, with implications for therapeutic strategies aimed at modulating these pathways.

ZBP1 as a Biomarker for Sepsis

Expression Level of ZBP1 in Sepsis Patients

ZBP1 has been proven as a significant biomarker in sepsis, characterized by its role in inflammatory responses and programmed cell death. Recent studies have demonstrated that ZBP1 expression levels are markedly elevated in patients suffering from sepsis compared to healthy individuals. For instance, a study highlighted the upregulation of ZBP1 in various cell types during septic conditions, suggesting its involvement in the pathophysiological processes of sepsis.[34] Furthermore, integrated analyses utilizing single-cell RNA sequencing have identified ZBP1 as a key player among PANoptosis-related genes, which are critical in mediating cell death pathways during sepsis.[35] This elevated expression of ZBP1 correlates with increased inflammatory markers, thus providing a potential indication of its function in the severity and progression of sepsis. The ability of ZBP1 to modulate inflammatory responses positions it as a promising target for therapeutic interventions aimed at mitigating sepsis-related complications. Overall, the expression levels of ZBP1 in sepsis patients underscore its significance as a biological marker that reflects the underlying inflammatory state and cellular dysfunction associated with this critical condition.

Study on the Correlation Between ZBP1 and Prognosis of Sepsis

The prognostic relevance of ZBP1 in sepsis has been the focus of several investigations. Elevated ZBP1 expression has been correlated with worse prognosis in septic patients, as it relates to increased inflammation and cell death pathways

that exacerbate tissue injury. Research has shown that rising levels of ZBP1 correlate with increased mortality rates among sepsis patients, indicating its potential utility in risk stratification.[36] Furthermore, ZBP1 has been shown to play a pivotal role in the mediation of necro-apoptosis and pan-apoptosis, underscoring its significance in the intricate mechanisms of cell death that are integral to the pathogenesis of sepsis.[37] The modulation of ZBP1 signaling pathways could thus represent a novel therapeutic approach to improve outcomes in sepsis. By targeting ZBP1, it may be possible to attenuate the inflammatory response and promote cellular survival, ultimately influencing the prognosis of septic patients. The accumulating evidence positions ZBP1 not only as a biomarker for diagnosis but also as a critical factor in determining the prognosis of sepsis, warranting further investigation into its therapeutic potential.

Potential Therapeutic Targets of ZBP1

Current Status of Drug Development Targeting ZBP1

Recent studies have highlighted ZBP1's role in modulating immune responses and inflammation, making it an valuable target point for drug development. The current landscape of drug development targeting ZBP1 is still in its nascent stages, but promising findings suggest its potential in treating various diseases, particularly those characterized by dysregulated cell death and inflammation. For instance, ZBP1 has been linked to the regulation of the NLRP3 inflammasome, a critical component of the innate immune response, which implicates it in inflammatory diseases and conditions such as sepsis and cancer.[16] Much of the current drug development for ZBP1 has focused on the treatment of cancer, with researchers suggesting that activation of ZBP1 promoted an inflammatory response that stimulating the immune system to attack tumours.[38,39] Furthermore, ZBP1 has been demonstrated to orchestrate necroptotic and apoptotic pathways in response to viral infections, suggesting its potential as a therapeutic target in the treatment of infectious diseases.[40,41] Developing small molecules or biologics that can modulate ZBP1 activity could pave the way for novel treatments for age-related and inflammatory diseases, as ZBP1 is recognized as a modulator of multiple ageing traits.[15] Several studies have also screened the active ingredients of Chinese herbal medicines through in vitro and in vivo experiments and explored their modulation of ZBP1 expression or activity.[42,43] However, challenges remain in translating these findings into clinical applications, and further studies is necessary to explain the precise mechanisms by which ZBP1 affects disease processes and to identify suitable drug candidates.

Prospects of ZBP1 in Sepsis Treatment

The role of ZBP1 in sepsis is increasingly being recognized, particularly in the context of its involvement in inflammatory responses and cell death mechanisms. Sepsis is characterized by a dysregulated immune response to infection, leading to systemic inflammation and organ dysfunction. ZBP1 has been implicated in the activation of pathways that drive both inflammation and cell death, making it a potential therapeutic target in sepsis management. Research suggests that ZBP1 can mediate the inflammatory response through the activation of the RIPK3 pathway, which has been shown to contribute to the pathophysiology of sepsis.[44] Inhibition of ZBP1 or modulation of its activity could, therefore, attenuate the excessive inflammatory response observed in sepsis, potentially improving patient outcomes. Moreover, ZBP1's involvement in PANoptosis highlights its central role in the complex interplay between cell death and inflammation during sepsis.[37] Future studies focusing on the development of ZBP1-targeted therapies could lead to innovative strategies for treating sepsis, addressing both the underlying infections and the resultant inflammatory cascade. Overall, the therapeutic modulation of ZBP1 presents a promising avenue for improving sepsis treatment and warrants further investigation into its mechanisms and potential drug candidates.

Conclusion

In summary, the role of ZBP1 in sepsis has emerged as a significant area of interest, highlighting its critical involvement in the host immune response and inflammatory processes. The accumulating evidence suggests that ZBP1 is not merely a bystander in the pathophysiology of sepsis, but rather a key player that can modulate the severity of the condition through its interaction with various signaling pathways. As a crucial factor, ZBP1 can serve as as an intracellular DNA-sensing protein to sense cytosolic nucleic acids and activate immune responses and as a key target in the early stages of sepsis compared to traditional

sepsis biomarkers. Moreover, ZBP1's potential as a new therapeutic target warrants attention. Given the complexity of sepsis and the need for innovative treatment strategies, ZBP1 could serve as a promising candidate for drug development aimed at enhancing host defense mechanisms or mitigating excessive inflammatory responses. This potential is particularly crucial in light of the growing challenges posed by antibiotic resistance and the limited efficacy of current therapeutic approaches. Targeting ZBP1 may not only provide a means to improve patient outcomes but could also help in developing personalized medicine strategies tailored to individual patient profiles. However, to fully leverage the therapeutic potential of ZBP1, it is imperative that further research is conducted. Animal models (eg, mice) do not fully replicate the complexity and severity of sepsis in humans, and there are also differences between the immune systems of mice and humans. In addition, Cellular experiments are usually performed in vitro, making it more difficult to fully simulate the complex physiological and pathological environment in vivo, potentially leading to inconsistent observation of ZBP1 function in humans. Based on the critical role of ZBP1 in the immune response, its excessive inhibition may lead to impaired immune function and increased risk of infection. Therefore, the potential risks and side effects need to be carefully evaluated when developing therapeutic strategies against ZBP1. Addressing these discrepancies through rigorous and well-designed clinical trials will be vital in establishing a consensus on ZBP1's functions and therapeutic implications. Future studies should focus on illuminating the exact mechanisms by which ZBP1 influences sepsis pathogenesis and to research its clinical applicability in various patient populations. Additionally, balancing the diverse findings from existing studies will be essential in painting a comprehensive picture of ZBP1's role in sepsis.

There are many assays targeting ZBP1 in current experimental studies, such as WB, PCR and so on, which might applied to a wide range of biological samples, including serum, plasma, tissues and more. Despite the expense of a single test, given the potential value of ZBP1 in sepsis management, the cost-benefit ratio of its clinical application may be favorable. Early diagnosis and precise treatment can reduce unnecessary medical interventions, thereby lowering overall healthcare costs. Furthermore, ZBP1 can be used in conjunction with other biomarkers to enhance diagnostic and prognostic accuracy. Although ZBP1 has shown potential in several studies, its application as a clinical biomarker still needs to be validated by large-scale, multicenter clinical trials.

In conclusion, the ongoing exploration of ZBP1 opens new avenues for understanding sepsis and developing targeted interventions. By advancing our knowledge of ZBP1, we can potentially transform the landscape of sepsis management, ultimately improving clinical outcomes for patients suffering from this complex and life-threatening condition.

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Disclosure

The authors declare that they have no competing interests.

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