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Innate immunosenescence and sepsis in the elderly: mechanisms and innate immune modulation strategies

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Abstract

This study aimed to investigate the mechanisms of innate immunosenescence in elderly patients with sepsis and to evaluate the potential application of innate immune modulation strategies in clinical management. Through a literature review, the characteristics of sepsis in the elderly, the aging mechanisms of the innate immune system, the impact of immunosenescence on susceptibility to sepsis, and clinical management strategies for sepsis in the elderly were analyzed. The incidence and mortality rates of sepsis in the elderly increase significantly with age, closely related to the severity of infection, the high prevalence of comorbidities, atypical symptoms, and a greater risk of multi-organ failure. Innate immunosenescence, including the decline in function of neutrophils, monocytes/macrophages, natural killer cells, and dendritic cells, is a key factor in the increased susceptibility to sepsis in the elderly. Immunomodulatory treatments, such as granulocyte colony-stimulating factor (G-CSF), interferon γ (IFN-γ), and granulocyte-macrophage colony-stimulating factor (GM-CSF), show potential in improving the prognosis of elderly patients with sepsis and reducing mortality rates. The management of sepsis in the elderly requires a comprehensive approach that takes into account age-related physiological and pathological changes, as well as early diagnosis and proactive intervention measures. Immunomodulatory strategies targeting the unique characteristics of immunosenescence in the elderly offer new avenues for improving survival rates and treatment outcomes in elderly patients with sepsis.

Key words: *elderly, sepsis, innate immunosenescence, immunomodulation strategies, clinical management.*

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Introduction

Sepsis is a life-threatening condition characterized by a dysregulated host response to infection, leading to organ dysfunction [1]. It accounts for 20% of global deaths [2], posing a significant public health issue, particularly in adults aged 70 and above. The pathogenesis of sepsis involves complex interactions between immune and adaptive responses, endothelial dysfunction, and autophagy [3]. Age is typically considered an independent risk factor for both mortality and morbidity, with the incidence and death rates increasing significantly with age [4, 5]. A nationwide study on sepsis in Taiwan revealed that the incidence of sepsis in the oldest elderly (≥ 85 years) was 31 times higher than in adults (18-64 years) and three times higher than in the elderly (65-84 years) [6].

The high mortality rate in elderly sepsis patients is linked not only to infection severity but also to comorbidities, atypical symptoms, and a higher risk of multi-organ failure [7]. Immunosenescence, the age-related decline in immune function, is a critical factor in immune system impairment and a key risk factor for sepsis severity in the elderly [8]. Understanding innate immunosenescence mechanisms can inform more effective clinical strategies for elderly sepsis patients.

Characteristics of sepsis in the elderly

Infections are common in the elderly, leading to increased hospitalization and mortality, especially in those aged 85 and older. Lower respiratory tract infections and urinary tract infections (UTIs) are predominant [9]. A retrospective study indicated that among 308 elderly patients, respiratory tract infections accounted for 49.7%, UTIs for 33.8%, bloodstream infections for 21.1%, and surgical site infections for 4.9% [10]. Due to the presence of comorbidities, impaired immune function, sarcopenia, reduced physiological reserve associated with aging, malnutrition,

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and polypharmacy, infections in the elderly are particularly prone to progress to sepsis [11].

The diagnosis of sepsis in the elderly is challenging due to atypical symptoms, age-related changes, and comorbidities. Additionally, aging increases the risk of sudden deterioration into septic shock, necessitating rapid treatment, which further complicates diagnosis and management [12]. Typical clinical markers of infection, such as C-reactive protein (CRP) and procalcitonin, lack sensitivity and specificity in this age group, leading to delays in treatment [13-15].

Immunosenescence impairs both cell-mediated and humoral immune responses, worsening prognosis and increasing mortality in elderly sepsis patients [16]. Immunosenescence contributes to post-sepsis organ damage [17]. Specific pathophysiological changes during aging, including immunosenescence, lead to higher mortality rates in elderly sepsis patients [18]. Moreover, a reduction in immunocompetent B cells and impaired humoral immunity are critical changes in elderly sepsis patients, increasing their susceptibility to secondary infections [19]. Differences in immune responses to sepsis between neonates and the elderly, particularly at the leukocyte transcriptome level, further contribute to the increased mortality in these groups [20]. Additionally, the decline in immune function in elderly patients, including defects in T and B cell functions, alterations in cytokine and chemokine signaling networks, and a more pronounced pro-coagulant state, play significant roles in their increased susceptibility to severe diseases.

Innate immune system and its aging mechanisms

The aging of the innate immune system is characterized by a decrease in certain immune cells, changes in cytokine activity, and an imbalance between pro-inflammatory and anti-inflammatory responses [21]. Although the clinical significance of immune aging is still debated [22], it is clear that it significantly impacts the health of the elderly, leading to higher infection risks and reduced responses to vaccinations [23].

Mechanisms of neutrophil aging and their impact

Neutrophils, the most abundant white blood cells, defend against bacterial and fungal infections. Although aging does not affect the total number of circulating neutrophils, their functional aspects decline with age [24].

In the elderly, neutrophil responsiveness to chemotactic factors decreases, reducing migration efficiency to infection sites and increasing infection spread risk [25, 26]. Neutrophils release neutrophil extracellular traps (NETs) to capture and immobilize pathogens, but NETs from elderly individuals have larger DNA fiber sizes, resulting in lower bactericidal activity and reduced stimulation of HaCaT cell proliferation. Additionally, neutrophils from elderly patients show an increased mitochondrial response, enhancing NET formation, which contributes to vascular endothelial damage and thrombosis [27]. Elderly patients' neutrophils also display a deficient response to TREM1, leading to reduced cytokine, chemokine, and reactive oxygen species (ROS) production, which increases susceptibility to microbial infections [28].

Mechanisms and effects of aging on monocytes/macrophages

Monocytes differentiate into macrophages, crucial for immune defense and tissue repair. With aging, the functions of monocytes and macrophages undergo significant changes:

In elderly individuals, the number of macrophages remains relatively stable, but their initial response to microorganisms and other inflammatory stimuli decreases. Van Duin *et al*. observed that macrophages isolated from aged mice showed a reduced response to TLR-1, TLR-2, and TLR-4 stimulation, with decreased activation of pro-inflammatory signaling pathways such as NF-κB, p38, and JNK, leading to reduced production of tumor necrosis factor α (TNF-α), interleukin (IL)-1β, and IL-6 [29-31]. Additionally, Li *et al*. found that alveolar macrophages isolated from aged mice exhibited decreased Rac1 mRNA expression, resulting in lower levels of Rac1 GTP and Arp2/3 activation, reduced downstream F-actin polymerization, impaired filopodia formation, and decreased MARCO surface expression, severely affecting macrophage phagocytosis [32]. Furthermore, reduced HLA-DR expression during aging diminishes the ability of macrophages to present antigens to $CD4^+$ T cells [33], and their ability to clear apoptotic cells also declines with age. This not only weakens their effectiveness in eliminating infections but also leads to excessive inflammation and tissue damage [34, 35].

Interferon γ (IFN-γ) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are major activators of monocytes and macrophages [36]. In sepsis patients, recombinant IFN-γ or GM-CSF treatment has been shown to enhance phagocytosis and HLA-DR expression in monocytes and macrophages, improving survival rates [37, 38]. Since aging and sepsis both reduce HLA-DR expression, and phagocytic function, they may have a cumulative inhibitory effect in elderly sepsis patients. Therefore, IFN-γ and GM-CSF could be potential therapeutic alternatives to reverse monocyte or macrophage dysfunction in elderly sepsis patients, thereby improving survival rates.

Mechanisms and effects of aging on natural killer cells

Most studies indicate that the number of natural killer (NK) cells, crucial for innate immune defense, remains

stable or slightly elevated during aging [39, 40]. However, with age, there is a decrease in the subset of cytotoxic NK cells ($CD56^{dim}$ NK cells) and an increase in the subset of regulatory NK cells ($CD56^{bright}$ NK cells). This shift can negatively impact immune responses against infections and malignancies [41, 42].

Functionally, NK cells in the elderly exhibit normal or increased production of IFN-γ but have reduced cytotoxicity [39, 43]. This reduction in cytotoxicity may be due to the impaired secretion of perforin in the immune synapse, which is critical for the granule exocytosis (perforin/granzyme) pathway that NK cells use to induce apoptosis in target cells [44]. The defect in perforin secretion contributes to the decrease in NK cell cytotoxicity (NKCC) observed with physiological aging [43]. Additionally, studies have shown that the reduced cytotoxicity in elderly NK cells is associated with significantly decreased activity of acid phosphatase, an enzyme crucial for the maintenance of NK cell cytotoxic function by regulating signal transduction pathways originating from killer cell immunoglobulin-like receptors (KIRs) [45-47].

Aging mechanisms and effects on dendritic cells

Dendritic cells (DCs) initiate and regulate adaptive immune responses. With aging, the number of DCs slightly increases [48]. However, aged DCs exhibit impairments in migration, antigen uptake, pinocytosis, and phagocytosis [49].

CCR7 and CXCR4 are key regulators of DC migration, and their expression and function decline with age [50]. Additionally, the CXCL12-CXCR4 axis, another critical pathway for DC migration, is affected by aging [51]. Agrawal *et al*. observed that monocyte-derived DCs (MODCs) in elderly individuals have reduced antigen capture capacity, potentially due to impaired AKT kinase activation [52]. Aged DCs exhibit a pro-inflammatory phenotype characterized by increased basal secretion of pro-inflammatory cytokines such as IL-6 and TNF-α, which may be linked to the senescence-associated secretory phenotype, a hallmark of immunosenescence [53-55]. Furthermore, Li *et al*. found that $CD8\alpha^{+}$ DCs in elderly mice show poor upregulation of co-stimulatory molecules for MHC-II and CD40, leading to a less effective T-cell priming environment [56].

Immunosenescence and susceptibility to sepsis

Immunosenescence involves the functional decline and altered signaling pathways of various immune cells. These changes increase susceptibility to infections in the elderly and impair the initiation and maintenance of effective immune responses during infections, leading to higher incidence and mortality of sepsis. A thorough understanding of these mechanisms is crucial for developing effective clinical management strategies to improve outcomes for elderly sepsis patients.

Neutrophil aging and susceptibility to sepsis

Neutrophil aging significantly impacts their function, making elderly individuals more susceptible to sepsis [57]. The role of neutrophils in sepsis is complex. Nacionales *et al*. observed that aged septic mice exhibit impaired neutrophil migration and antibacterial activity, leading to an inadequate response to infection [58]. This is likely due to reduced expression of the surface receptors CXCR1 and CXCR2 [59]. Additionally, aged mice show an ineffective bone marrow response to sepsis, further increasing susceptibility [60].

Elderly individuals often have an excess of NETs with compromised functionality, resulting in organ dysfunction and severe tissue damage associated with sepsis [61]. The reduced accuracy of neutrophil migration and increased formation of NETs prolong the immunosuppressive phase, contributing to higher susceptibility and mortality in elderly patients and septic animals [62].

Neutrophils can also act as antigen-presenting cells, bridging innate and adaptive immune responses by activating T cells [19]. However, in elderly septic patients, an immunosuppressive subset of neutrophils emerges, characterized by the production of large amounts of IL-10, which further suppresses T cell proliferation and function [63, 64].

Monocyte/macrophage aging and susceptibility to sepsis

Increased susceptibility to sepsis in aged mice can be partly attributed to reduced phagocytic activity and immune resolution of monocytes and macrophages, along with increased expression of aging-related markers and elevated production of inflammatory cytokines [65]. This heightened susceptibility is exacerbated by local inflammatory responses in aged mice [66].

Rondina *et al*. observed that elderly septic patients exhibited enhanced platelet-monocyte aggregate (PMA) formation, along with increased production of the pro-inflammatory cytokines IL-6 and IL-8 by monocytes, both significantly correlated with 28-day mortality [67]. Enhanced PMA formation has been shown to amplify inflammatory and thrombotic responses in elderly septic patients, potentially leading to an impaired immune response, organ failure, disability, and death [68]. Furthermore, aging impairs the phagocytic ability of alveolar macrophages, increasing the susceptibility of elderly individuals to sepsis [32]. During sepsis, reduced expression of HLA-DR isoforms in bone marrow diminishes the antigen-presenting

capacity of monocytes, further exacerbating immunosuppression and reducing pathogen-fighting ability [69].

NK cell aging and susceptibility to sepsis

Research indicates that NK cells undergo significant functional and phenotypic changes during aging, which may affect the susceptibility of elderly individuals to infections, particularly sepsis [70].

Aged NK cells exhibit reduced efficacy in combating bacterial and viral infections, mainly due to decreased expression of activating receptors such as NKp30 and NKp46, leading to diminished cytotoxicity at the single cell level [71]. Furthermore, IL-2-triggered signaling pathways are impaired in aged NK cells, along with decreased mitochondrial function and metabolic flexibility. These changes result in reduced NK cell effector functions and increased production of IFN-γ, which exacerbates tissue damage, potentially explaining the higher incidence of sepsis in the elderly [39, 43].

Activated NK cells require a transition from oxidative phosphorylation (OXPHOS) to aerobic glycolysis to maintain their effector functions [72, 73]. However, aged NK cells exhibit defects in this metabolic transition, leading to a higher incidence of sepsis in elderly patients [74]. This metabolic shift is also crucial for T cell effector functions [75]. The age-related decline in the ability to adapt to stress, including reduced reactive oxygen species production, may further increase the susceptibility of elderly individuals to sepsis [76].

Dendritic cell aging and susceptibility to sepsis

Studies comparing monocyte-derived myeloid dendritic cells (MDDCs) in elderly individuals to DCs in younger people have shown that although their phenotypes are similar, aged DCs exhibit reduced AKT phosphorylation. This suggests decreased activation of the PI3K pathway, which is crucial for phagocytosis and migration, and functions as a negative regulator of TLR signaling through p38 MAPK activation. This may explain the impaired innate immune function in elderly DCs [53].

Additionally, aged DCs display reduced capacity for antigen uptake through phagocytosis and endocytosis. The decreased expression and function of HLA-DR further impair antigen presentation, reducing the efficacy of adaptive immune responses and increasing susceptibility to secondary hospital infections [77].

The significant increase in TNF-α and IL-6 secretion induced by lipopolysaccharide (LPS) and single-stranded RNA in aged DCs affects T and B cell activities. This can lead to inappropriate immune activation or suppression, with excessive inflammatory responses causing systemic inflammatory response syndrome (SIRS), thus exacerbating sepsis progression.

Clinical management strategies

Managing sepsis in the elderly is challenging due to age-related changes, comorbidities, and institutionalization, often resulting in atypical infection presentations such as confusion, decreased appetite, and gait instability [78]. These atypical presentations lead to significant delays in the diagnosis and treatment of sepsis [68]. Therefore, management strategies must focus on early recognition and intervention [79]. Recent studies emphasize the importance of immunomodulatory treatments to improve prognosis and reduce mortality.

For neutrophil dysfunction, granulocyte colony-stimulating factor (G-CSF) can enhance neutrophil numbers and function, improving infection clearance and survival rates in elderly sepsis patients [80]. Targeting neutrophils through strategies such as A2A adenosine receptor activation can prevent their senescence and promote polarization from the N1 to N2 phenotype, thereby improving their function [81].

Another study indicated that statins can modulate age-related neutrophil function, enhancing their response to infections. A randomized, double-blind, placebo-controlled pilot study showed that high-dose simvastatin improved systemic neutrophil function (NETosis and chemotaxis), reduced systemic neutrophil elastase load, and improved Sequential Organ Failure Assessment (SOFA) scores in elderly patients with community-acquired pneumonia and sepsis (CAP+S) [82].

Regarding macrophages, GM-CSF can mediate high phagocytic capacity by regulating glycolysis and lipid metabolism and produce IL-10 under LPS stimulation [83]. GM-CSF also enhances mitochondrial turnover in macrophages by regulating fatty acid β-oxidation, tricarboxylic acid cycle activity, and ATP production [84]. Interferon γ-treated macrophages show increased colocalization with the autophagy molecule p62, increased autophagosome formation, and increased lysosomal transport, significantly reducing the bacterial burden compared to untreated macrophages [85].

Additionally, IL-15 and FLT3 ligand (FLT3L) have shown potential applications. Interleukin 15 can enhance the immunostimulatory properties of DCs, inducing strong CD8 T cell responses and higher NK cell proliferation [86]. It also effectively recruits immune effector cells such as $CD8^+$ T cells, NK cells, and γδ T cells [87]. Interleukin 15 can enhance NK cell cytotoxicity by upregulating NKG2D and cytotoxic effector molecule expression and phosphorylating STAT1 and ERK1/2, contributing to effective anti-infection responses [88]. FLT3L, a DC growth factor, has been shown in mouse models to prevent the decline in post-sepsis T cell numbers and improve T cell function

Table 1. Immune cell aging and modulation strategies in elderly patients with sepsis

Type of immune cell	Modulators	Functions	Future prospects
Neutrophils	TREM1, G-CSF	Decreased responsiveness to chemotactic factors, reduced efficiency in migrating to infection sites	Development of new NET modulators to enhance bacterial clearance
Monocytes/ macrophages	IFN-γ, GM-CSF	Reduced initial response to microbes, decreased activation of pro-inflammatory signaling pathways	Use of IFN-γ and GM-CSF treatments to improve macrophage function and survival rates
Natural killer (NK) cells	Perforin, interleukin 2	Reduced cytotoxicity, decreased perforin secretion	Enhancement of NK cell cytotoxicity and anti-infection capabilities
Dendritic cells	CCR7, CXCR4, CXCL12	Impairment in migration, antigen uptake, pinocytosis, and phagocytosis	Improvement of DCs' antigen presentation ability, enhancement of T-cell priming efficiency

[89], suggesting potential for ameliorating sepsis-induced immunosuppression.

Strategies targeting immune cell functional changes, including enhancing metabolic activity and adjusting immune signaling pathways, can significantly improve monocyte function and infection response in elderly patients [90].

The intricate relationship between aging, immune function, and sepsis susceptibility is further elucidated in the following summary table (Table 1).

Conclusions

This review explores the key mechanisms of innate immune aging in elderly sepsis and its impact on disease management. With aging, the functions of immune cells such as neutrophils, macrophages, NK cells, and dendritic cells decline, increasing susceptibility to sepsis and worsening disease severity and prognosis. These cellular senescence processes include reduced chemotaxis, impaired bactericidal activity, and altered cytokine and chemokine production, which collectively weaken the immune response to infections in the elderly.

Diminished innate immune function poses specific challenges in the clinical management of sepsis in the elderly, necessitating adjustments and optimizations to existing treatment protocols. Immunomodulatory strategies targeting the unique characteristics of immune aging in the elderly show promising potential for improving outcomes.

Future research must delve deeper into the detailed mechanisms of innate immune aging related to elderly sepsis and develop new diagnostic and therapeutic tools to better understand and manage this complex clinical issue. Particularly, validating these new immunomodulatory strategies in clinical trials will provide critical guidance for managing elderly sepsis patients. Through these efforts, we aim to offer more effective, personalized treatment plans for elderly sepsis patients, ultimately improving their prognosis and quality of life.

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