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Septic Shock in Older People

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Abstract

Sepsis is a complex condition that is initiated by infection. The incidence of sepsis and its severity are higher at an older age (mean age of approximately 65 years). Clinical manifestations of sepsis are derived from systemic inflammatory response syndrome. Age-related defects in immunity are shown by changes in cellular and humoral immunity. Recent studies have shown significant changes in the innate response (e.g., changes in toll-like receptor expression, abnormal activation of mitogen-activated protein kinases, and production of reactive oxygen species) in older people. Transcriptomic analysis on a large scale has provided interesting information showing that specific groups of patients actually have singular profiles for inflammatory responses. Findings from our research group have identified major molecular pathways that are particularly affected in older people during sepsis. Oxidative phosphorylation pathways and mitochondrial dysfunction are altered the most in older people with sepsis compared with younger patients with sepsis. These pathways might have a pivotal role in worsening clinical outcomes compared with younger people with sepsis. The mechanisms leading to specific dysfunction of several signaling pathways in the immune response of older people are complex and appear to involve multiple factors, including environmental factors, microRNAs, and epigenetic changes.

Keywords: sepsis, aging, inflammation, transcriptomics

1. Introduction

Sepsis is a complex disease that is triggered by infection and characterized by massive deregulation of the immune system [1]. Clinical manifestations of sepsis, such as fever, a hypercoagulable

state, and peripheral hypotension, are derived from systemic inflammatory response syndrome (SIRS). Clinically, SIRS can be classified according to the nature of the symptoms manifested by the individual, such as (1) hypothermia or fever, (2) tachycardia, (3) tachypnea, and (4) leukocytosis or leucopenia [2]. Infection is probably the most common cause of SIRS, associated with the action of cytokines that are derived from cells of the immune system acting in organs and systems with specific receptors [3]. **Figure 1** illustrates the stages of evolution of sepsis using SIRS as the standard diagnosis.

Recently, the Journal of the American Medical Association (JAMA) published the “Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).” This is the most recent international consensus on diagnostic criteria for sepsis and septic shock. According to the new criteria for the diagnosis of sepsis, organ dysfunction promoted by the disease must be considered [4]. In this regard, SIRS is no longer used as a diagnostic criterion for sepsis, and organ dysfunction is represented by an increase of two or more points in the Sequential Organ Failure Assessment (SOFA) score. The SOFA score is obtained by using a scoring scheme that assigns one to four points. The SOFA score uses variables, such as the platelet count, bilirubin, and oxygenation index, using variables as scoring of platelet, bilirubin, oxygenation index, use of vasoactive drugs, the Glasgow Coma Scale, and creatinine.

Septic patients have an average age of approximately 65 years [5], and the incidence of sepsis and its severity are significantly increased at an older age [6, 7]. Factors that contribute to this increase include defects in the integrity of epithelial barriers, dysfunction in the cough reflex, changes in level of consciousness, immobility, comorbidities, presence of invasive medical devices, a decrease in physiological reserves, endocrine disorders, and malnutrition [8, 9].

Immune defects associated with age are shown by changes in cellular and humoral immunity [10]. Aging is associated with an increase in memory T-cell [9] repertoire and in the responses of types 1 and 2 [11, 12]. B cells gradually decrease with age, while the production of immunoglobulin increases [13].

Initial reports described preservation of the innate immune response in older people [14], but recent studies have shown significant changes in these components [9]. Studies have

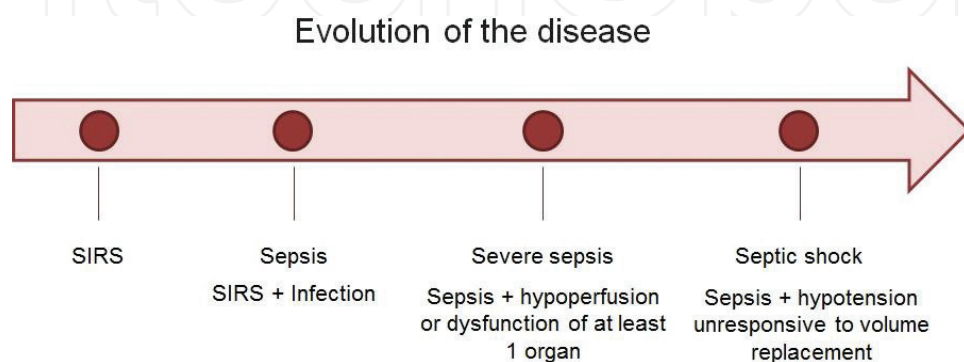


Figure 1. Evolution of sepsis.

suggested changes in expression and toll-like receptor (TLR) function as age advances and that this affects the response to pathogens [15]. An increase in the basal levels of inflammatory mediators [16, 17], aberrant activation of mitogen-activated protein kinases [18], an increased number of apoptotic cells [19], defects in the process of phagocytosis, production of reactive oxygen species (ROS), and deregulation in expression of accessory molecules have been reported [20]. Indeed, evidence indicates that older people produce higher levels of pro-inflammatory cytokines, coagulation factors, and acute phase proteins in the absence of infection [21–23].

However, the inflammatory response of older people in the presence of a serious infectious process remains controversial. Because of the increasing aging population, this issue has received great attention from the scientific community (Figure 2). Studies have identified a higher mortality, inflammatory response, hypothermia, disseminated intravascular coagulation, and apoptosis in aged animals undergoing experimental models of sepsis [24]. Aspects

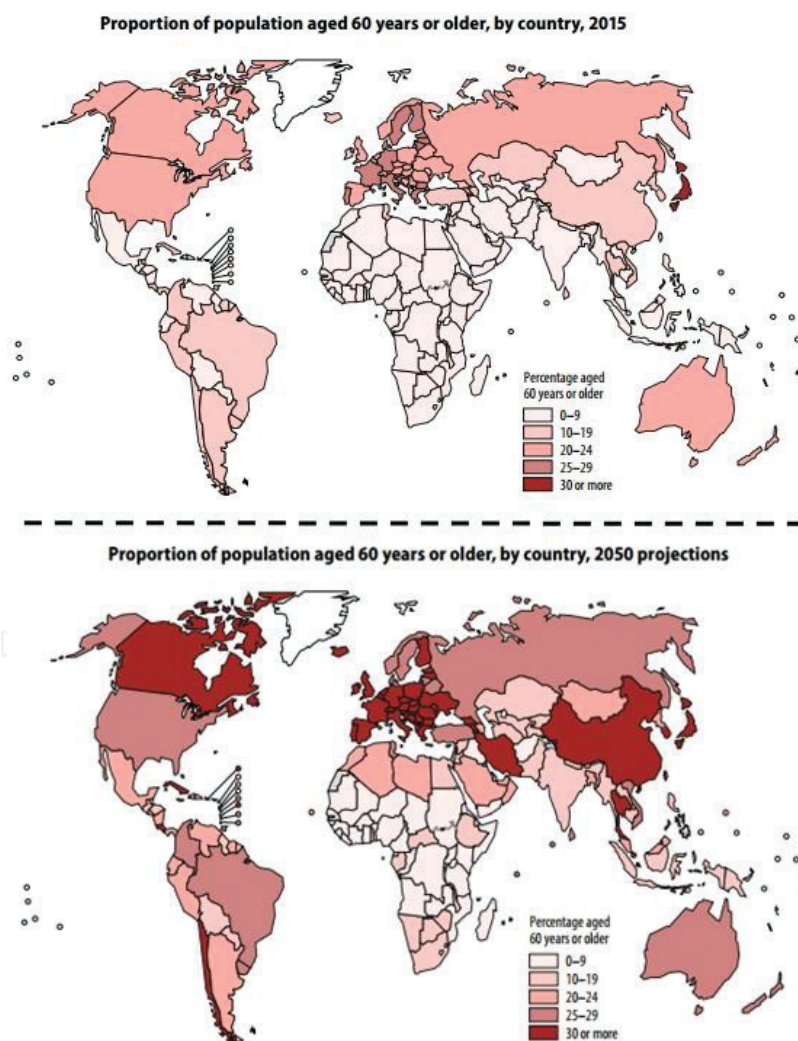


Figure 2. Population aging around the world. Source: World Health Organization—World report on Ageing and Health—2015.

of immunosenescence and a more intense inflammatory response in aged rodents with sepsis have been well characterized [25, 26]. However, intriguingly, clinical studies (including our own research group) have detected a similar immune response profile when comparing older patients with sepsis with younger patients [27–30].

2. Transcriptomics in sepsis

Transcriptomics is a powerful technique, which can be used for detecting new therapeutic biomarkers and targets in the field of infectious diseases [31, 32]. Several studies of gene expression in sepsis on a large scale have been performed. These studies have shown persistent repression of genes of adaptive immunity and massive activation of pathways of innate immunity in septic shock [33]. Using RNA obtained from total blood, Wong and colleagues [34] identified activation of oxidative phosphorylation, signaling by interleukin (IL)-10, TLRs, TREM, NF- κ B, the protein ubiquitination pathway, and IL-6 in macrophages. These authors also described suppression of specific pathways of T lymphocytes and signaling by chemokines (CCR5). Similarly, Cvijanovich and colleagues [35] detected activation of TLRs, IL-10, IL-6, and NF- κ B with concomitant suppression of T lymphocytes. Additionally, they detected activation of protein in the acute phase, p38, the complement system, and some nuclear receptors (LXR and PPAR) in association with repression of antigenic presentation pathways.

Shanley et al. [36] used total blood RNA from septic patients and performed global gene expression experiments. Their results agree with those studies described above in many aspects, except that they also identified integrin activation, IGF-1, GM-CSF, and insulin receptor. Tang et al. [37] described activation of apoptosis genes, including *CARD12*, *APAF1*, and *ELMOD2*, in mononuclear cells of septic patients. Moreover, a recent study in patients with severe blunt trauma described surprisingly similar results with activation of a large number of genes involved in inflammation, pattern recognition, and antimicrobial function [38]. This study also showed simultaneous repression of genes involved in antigenic presentation and proliferation of T cells, suggesting that severe physiological stress, regardless of the cause, has similar genetic signatures.

3. Sepsis: a heterogeneous disease

Sepsis affects different groups of patients (e.g., those with an older age, diabetes, nephropathy, multiple trauma, surgery, and obesity). Historically, each specific group of patients is thought to be present with a characteristic inflammatory response. In the course of sepsis, transition of the inflammatory response to standard immunosuppression has been suggested to explain the disappointing results obtained by clinical studies that investigated the use of anti-inflammatory drugs in this population of patients [39–41]. Transcriptomic analysis on a large scale has provided interesting information in this regard, showing that specific groups of patients actually have singular profiles [42–44]. However, a recently published systematic review was

unable to detect distinct pro-inflammatory and anti-inflammatory phases in sepsis or differences in gene expression when analyzing different sub-populations [45]. Therefore, this issue remains extremely controversial.

To the best of our knowledge, our research group was the first to study characteristics of sepsis in older people through transcriptomics analysis on a large scale [46]. We detected 388 genes that were differentially expressed between older and younger people with sepsis and 442 genes among older and healthy younger subjects.

Interestingly, oxidative phosphorylation pathways and mitochondrial dysfunction were the most altered in older people with sepsis compared with younger patients with sepsis. Other relevant pathways were signaling by TGF- β , Wnt/ β -catenin, and calcium, as well as pathways that have been less studied in this disease, such as those involved in nerve growth factor and bone morphogenic protein.

Initially, our results confirmed that, regarding the production of TNF- α , IL-6, IL-1 β , TLRs, and other classical markers of cell activation, younger and older people respond similarly to a severe infectious insult. Some other pathways, as described above, appear to be more affected in older patients in a critical condition than in younger patients. We consider that defects of mitochondrial function and oxidative phosphorylation, and signaling by TGF- β , Wnt/ β -catenin, bone morphogenic protein, nerve growth factor, and calcium are different in older patients with sepsis than in younger patients with sepsis.

Confirming our hypothesis, we observed a notable decrease in gene expression of the mitochondrial respiratory chain in older patients with sepsis [46]. Mitochondrial dysfunction is known for contributing to multiple organ failure in sepsis. Physiologically, small amounts of reactive species of oxygen are produced by complex I and III of the respiratory chain. Sepsis is characterized by an increase in oxidative stress due to increased production of neutrophils, an increase in xanthine oxidase activity, increased plasma levels of nitric oxide, and decreased antioxidant capacity of plasma [47]. Pro-inflammatory mediators and oxidative stress deregulate the function of respiratory chain enzymes and lead to structural damage of lipids, proteins, and mitochondrial DNA [48, 49], promoting failure of multiple organs [50]. Mitochondrial damage and secondary dysfunction to oxidative stress are also characteristic of the aging process [6, 51, 52]. Mice that have defective function of mitochondrial DNA polymerase enzyme have a shorter life and show many signs of premature aging, such as alopecia, decreased physical activity, and early loss of reproductive function [53].

The mechanisms that lead to specific dysfunction of several signaling pathways in the immune response of older people are complex and involve multiple factors. We propose that environmental factors [54, 55], microRNAs [56], and epigenetic changes [57] play a major role in modulating the immune response cascades that are particularly affected in older patients.

Our data confirm previous reports that aging is accompanied by changes in gene expression of immune system pathways [58]. Another important result of our research group shows that noncoding long RNA subgroups are deregulated in sepsis and during the aging process.

Therefore, extensive studies are required to investigate the biological role played by this class of transcripts in septic shock in older individuals.

4. Conclusion

There is great expectation that studying biological systems can provide a better understanding of several complex diseases. Further information could be used to identify new therapeutic targets and groups of patients who should benefit from such interventions.

Using this strategy, we have identified the main pathways that are altered in older people with sepsis. Our findings highlight that the systemic inflammatory response differs depending on the population that is studied. Oxidative stress appears to play a central role, inducing various types of dysfunction, in older patients with sepsis. Moreover, we have identified several other genes and signaling pathways that are altered in these patients. This information will facilitate understanding of the nature of the immune response in this situation.

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