Molecular mechanisms in septic shock (Review)

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Abstract. Sepsis is a clinical syndrome defined by the presence of infection and systemic inflammatory response to infection and results from a complex interaction between the host and infectious agents. It is characterized by the activation of multiple inflammatory pathways, with an increased risk of mortality. The incidence of sepsis has been on an ever-increasing pathway in recent years. Sepsis can be induced by several clinical situations that predispose to its occurrence: malignant tumors, organ transplantation, AIDS, radiation therapy, burns, sores, polytrauma, diabetes mellitus, hepatic failure, renal failure, malnutrition, catheters or different invasive devices, and urinary catheters. The microorganisms involved in the pathogenesis of sepsis are Gram-positive cocci (*Staphylococci*, *Streptococci*) and Gram-negative bacilli (*Klebsiella, Pseudomonas aeruginosa*, *E. coli*), fungi (*Candida*), parasites, and viruses. Among mechanisms involved in septic shock production, two pathological phenomena appear: the profound decompensation of circulation and metabolic disturbances that evolve towards an irreversible state. The intimate mechanism of shock involves the activation of monocytes, macrophages and neutrophils by lipopolysaccharides of Gram-negative bacteria. The microvascular bed is directly involved in the etiopathogenesis of disorders of acute inflammatory states associated with or without sepsis. A better comprehension of sepsis pathophysiology, especially the molecular mechanisms of septic shock, allows for new therapeutic perspectives.

Contents

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1. Introduction

Sepsis is a systemic inflammatory response developed by an organism following an infection. It is manifested by two or more associated states as a result of infection (1,2). These associated states are infection, bacteremia as well as a systemic inflammatory response to a variety of severe clinical situations [systemic inflammatory response syndrome (SIRS)]. SIRS is manifested by at least 2 of the following clinical signs: temperature (>38˚C or <36˚C, heart rate >90/min, respiratory rate >20/min or $PaCO_2$ <32 mmHg and a leukocyte count of at least 12,000 cells/mm^3 or <4,000 cells/mm^3 or 10% immature cells (3).

Weil and Shubin (4) classified shock into 4 distinct types: Hypovolemic (loss of intravascular volume), cardiogenic, obstructive (heart, arteries and large veins) and distributive. The state of septic shock is represented by the presence of sepsis associated with hypotension although the resuscitation of adequate depletion occurs.

Sepsis can be induced by several clinical situations that predispose to its occurrence: malignant tumors, organ transplantation, AIDS, radiation therapy, burns, sores, polytrauma, diabetes mellitus, hepatic failure, renal failure, malnutrition, catheters or different invasive devices, urinary catheters, and others (5-9). The most common bacterial species that can induce sepsis are Gram-negative bacteria (*E. coli*, *Klebsiella*, *Pseudomonas aeruginosa*) as well as other micro-organisms such as mycobacteria, fungus (*Candida, Histoplasma, Aspergillus*), different types of viruses and protozoa (10). Gram-negative bacteria induce mainly urosepsis while Gram-positive bacteria are responsible for inducing sepsis in about 15% of cases (11). These microbial species have as entry points the genitourinary-urinary tract, gastrointestinal or respiratory tract, various wounds, and others (12,13). In patients with septic shock, the oxygen needs are greatly increased in a situation when its intake and transport to tissues is altered, partly due to the closure of the microvascular shunts (14). The monitoring of patients with septic states may be difficult due to

discrepancies between central (macro-hemodynamic) circulation and microcirculation in internal organs (splanchnic) (15).

2. Mechanisms in septic shock

Sepsis is the systemic response of the body to a severe infection causing a complex of interactions between the host and the pathogenic organism resulting in the response of inflammatory mediators (16). The shock is characterized by a decrease in oxygenated blood tissue flow below the critical level necessary for normal conduct of cellular metabolic processes (17). Septic shock represents hypoxic tissue distress associated with the presence in the blood of pathogenic germs (18).

The incidence of sepsis has been on an ever-increasing pathway in recent years, as a result of longer life expectancy of the population as well as the association of comorbidities, such as cancer, immunosuppression, diabetes mellitus and chronic organ dysfunction (19). The mortality rate in intensive care units (ICUs) is generally 37% and in hospital wards it is approximately 45% (20). It is well known that septic states, and specifically septic shock, associated with various pathologies, significantly increase the mortality rate of these patients. The incidence of septic states is approximately 3 out of 1,000 inhabitants, with a high mortality, ranging from 28 to 80%, depending on the severity of the sepsis, the number of dysfunctions/insufficiencies of organs occurring during clinical evolution, age and pre-existing morbidities (21). Immediate death, within 3 days of admission to the ICU, generally occurs in about 32% of cases, later deaths (about a few days or weeks) occur in around 68% of cases (22-24). Determinants of immediate death include age, malignancy, diabetes mellitus as well as the initial level of severity, but cancer is also a factor with an increased rate of importance (25). For patients that survive for more than 3 days, the factors involved in delayed death include: age, cirrhosis and treatment with previous corticosteroids (21). Moreover, various associations of comorbidities, such as anemia developed in inflammatory bowel disease, may increase significantly the mortality rate (26). Infection with Gram-negative, Gram-positive, rickettsia or viruses produces a septic status characterized by a temperature above 38˚C or below 36˚C, tachycardia, tachypnea (over 20 breaths/min), leukocytosis over 12,000 or below 4,000 cells/mm^3, or the presence of neutrophils in excess of 10% (13).

In septic shock, tissue hypoxia plays a role in reduced oxygen intake and delivery to tissues through the deficient distribution of peripheral blood flow under the action of microbial endotoxins and the increased concentration of mediators released (27). The most studied mechanism is the inflammatory response triggered by the endotoxin released by Gram-negative germs. This is a polysaccharide and has the following three effects: i) Increased permeability with extravasation fluid in interstitial space on endothelial cells results, with the activation of platelets and the coagulation; ii) activation of the XIIth factor (Hageman) which initiates the process of coagulation, and of fibrinolysis; iii) activation of complement, with the release of C_{3a}, C_{4a} and C_{5a} components that stimulate neutrophil aggregation and their fixation on capillary endothelium.

At the pulmonary level, various lesions that could lead to continuous life-long treatment may develop (28). The endotoxin's capacity to induce the release of various cytokines also occurs inside the lungs by producing these mediators by alveolar macrophages (29). The microvascular bed is directly involved in the etiopathogenesis of disorders of acute inflammatory states associated with or without sepsis (systemic inflammatory response syndrome, anti-inflammatory compensatory syndrome) with direct visceral response (multiple organ dysfunction). According to some authors, these mechanisms also appear to be exacerbated by the presence of malignant tumors, such as adenocarcinoma (30-33).

3. The septic syndrome

Systemic inflammatory response syndrome (SIRS) is clinically recognized by a series of objective clinical signs, cardinal, that include tachypnea, fever or hypothermia, tachycardia and leukocytosis or leukopenia with left deviation of the leukocyte formula. SIRS may be the result of infectious or non-infectious causes (19). Non-infectious causes associated with SIRS include trauma, burns, hemorrhagic or hypovolemic shock and, as a major cause, pancreatitis (34).

Sepsis is defined as an SIRS resulting from infections, regardless of the determining agent-bacterial or viral. Its severity is directly proportionate to the intensity of the host body's response. Severe sepsis is defined as sepsis associated with multiple organ dysfunctions (35). Septic shock occurs when systemic hypotension is associated with tissue hypoperfusion and anaerobic metabolism. This simple classification aims to deliver the prognosis of mortality in SIRS (7%), sepsis (16%), severe sepsis (20%) and septic shock (>46%). Grading the septic syndrome reflects the increase in the systemic inflammatory response correlated with worsening of the clinical signs (36). Multiple organic dysfunction syndrome (MODS) is defined by the presence of functional deterioration of at least 2 organs, as an indicator of the impossibility of maintaining homeostasis. In most cases the following organ systems are affected (in order of increased severity): the cardiovascular system (tissue hypoperfusion), pulmonary system (acute pulmonary or ARDS), renal system (acute renal failure), blood (intravascular disseminate coagulation, thrombopenia), nervous system (encephalopathy), vascular endothelium (generalized edema), and the liver (unspecified hepatitis, acute hepatic failure) (37,38).

Microbial species or their endotoxins meet sterile tissues and activate the immune defense mechanisms of host cells. Macrophages engulf bacteria or endotoxins and release several primary mediators. These primary mediators are known to be cytokines, which in turn initiate a cascade of inflammatory reactions. The following inflammatory systems have been shown to be activated in this respect. i) Phospholipase A_2 releases phospholipids that are metabolized through the enzyme system of the cyclooxygenases and lipooxigenesis in prostaglandins and leukotrienes (39). These substances determine fever (especially prostaglandin PGE_1 with effect the hypothalamus), vasodilation with increased cellular permeability (40). ii) The Hageman factor determines the initiation of the coagulation cascade and the activation of the quinine system. iii) The complement system is in turn activated; the result is the production of C_{3a} and C_{5a} (with a destructive bacterial effect), increased vascular

permeability which acts as permeability factor agents for leukocytes (41).

Prostaglandins are synthesized by most cells of the human body. The enzymes involved in the metabolism of arachidonic acid regulate the cellular level of arachidonic acid that remains in an esterification form until its transformation by phospholipase (especially by phospholipase PLA_2) occurs (42,43). In the endoplasmic and the nuclear membranes, the arachidonic acid obtained under PLA_2 action, is subjected to the action of prostaglandin synthase H (PGHS) and then it is metabolized to prostaglandin H_2 (PGH_2). PGHS exists in two forms of isomers: PGHS-1, known as COX-1 (cyclooxygenase) and PGHS-2, known as COX-2. Isoenzyme COX-1 is responsible for PG biosynthesis, in a general mode, while COX-2 is involved in the anti-inflammatory processes (44).

Prostaglandins activate specific receptors that can be cellular-specific or tissue-specific. At least 9 classes of PG receptors are known. Exceptionally, the EP_3 receptor is coupled through the Gi protein and has the effect of diminishing AMPc formation. Prostaglandins that are synthesized in the presence of the COX-2 enzyme located at the level of the nuclear membrane can control nuclear reactions through interactions with receptors activated by peroxisome proliferation (43). This increases the importance of the COX-2 enzyme as a regulating factor in nuclear chemical processes with implications for cell growth and development (45). The activation of leukocytes is achieved by releasing free radicals, proteases and elastases that cause cell injury. The purpose of this inflammatory response is clearly highlighted. Increasing circulating fluid (by vasodilation) and releasing chemotactic factors allow leukocytes and lymphocytes to accumulate in a large number to defend the body (46).

4. Infection and dissemination in septic shock

In the last 25 years, several studies in the field have shown that Gram-negative bacteria are the main cause of sepsis production (47). The most frequently isolated species include *Staphylococcus aureus* (*S. aureus*), *Streptococcus pyogenes* (*S. pyogenes*), *Klebsiella spp.*, *Escherichia coli* (*E. coli*) and *Pseudomonas aeruginosa* (*P. Aeuruginosa*) (48). Each stage of the infectious process involves the development of different factors of virulence, which is based on the stage of infection.

Some of the most important factors of virulence are represented by toxins. These include endotoxin or lipopolysaccharide, which are found in the external membrane layer of Gram-negative bacteria and others are secreted as exotoxins by other bacteria (49-51).

Bacterial toxins are divided into 3 large classes, depending on the mechanisms: i) Type I toxins that destroy the host cell without penetrating it, such as super-antigens produced by *S. aureus* and *S. pyogenes*; ii) type II toxins such as hemolysins and phospholipases that destroy the membrane of the host cell, penetrate it to interfere and inhibit the cellular defense processes of the host cell; iii) type III toxins known as toxins A/B (because of their binary structure) destroy cellular defense processes to allow their dissemination to different organs. Component B of these toxins binds to the surface of the host cell, while component A has enzyme activity of cellular destruction (52).

The endotoxin, a lipopolysaccharide constituent of the bacterial wall, is the trigger factor which determines the inflammatory response. It has 3 components: An oligosaccharide, responsible for the antigen reaction, a co-lipopolysaccharide, responsible for binding and a lipid, responsible for the toxic action. The activation of monocytes, macrophages and neutrophils, succeeded by the release of proinflammatory mediators and the activation of coagulation, plays an important role in the pathogenesis of septic shock. The inflammatory response, which is also a defense against microorganisms, gets out of control, and produces serious hemodynamic disorders. Endotoxin determines the disturbance of the demand-supply balance of oxygen at the cellular level (increases the need with a decreased supply and oxygen extraction capacity by the cells) which leads to disorders in aerobic cell metabolism and eventually leads to cell death (53).

In the mechanism of septic shock, two pathological phenomena develop: the profound decompensation of circulation and metabolic disturbances that evolve towards an irreversible state. These pathological phenomena determine the two phases of shock: the compensated, early shock (hyperdynamic, reversible) and the decompensated, belated shock (hypodynamic, irreversible). Liberated mediators produce, during the hyperdynamic stage, an increase in heart rate and a decrease in peripheral vascular resistance, which ensures increased tissue needs, the result being vasodilation and hypotension. At the same time, it increases pulmonary vascular resistance, with the development of heart failure. Subsequently, the myocardia is depressed by the myocardial depression factor (myocardial depressant substance, MDS), a proinflammatory cytokine. The consequence of these processes is the decrease in cardiac flow and peripheral vasoconstriction, the evolution being towards the hyperdynamic state (decompensated), with the onset of multiorgan deficiency and therefore cellular death (54). Thus, the polymorphic aspect of this multiple organic insufficiency is complete, along with respiratory failure, hypotension, heart failure, disseminated intravascular coagulation, hemorrhage, hepatic and renal failure, lactic acidosis and coma. The intimate mechanism of shock involves the activation of monocytes, macrophages and neutrophils by the lipopolysaccharide of Gram-negative bacteria. This endotoxin represents a bacterial 'signal molecule', which is specifically linked to an LBP acute phase glycoprotein (LPS binding protein), which will transfer it to the level of CD14 and TLR4 receptors (Toll-like receptors) located on the membrane of monocytes, neutrophils and macrophages, the result being the release of the cascade of inflammation mediators, respectively, cytokines (55-58). The soluble CD14 binds this lipopolysaccharide too and transports it to the level of the vascular endothelial cell, which does not have at the membrane level this type of receptor (55).

5. Conclusions

Our analysis of the molecular mechanisms of septic shock has revealed that a better comprehension of sepsis pathophysiology, especially molecular mechanisms of septic shock, will open new therapeutic perspectives.

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Authors' contributions

GG, DC, CM and ER analyzed the data in the literature and prepared and wrote the manuscript. All authors read and approved the final manuscript for publication.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare no competing interests in drafting this manuscript.

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