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Cytokines: The Potential biomarker in Sepsis of Dog

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Abstract

Sepsis is the most important etiological factor for death in dogs throughout the World. Various pathophysiological studies indicated that septic shock is occurred due to an inflammatory reaction that triggers cellular damage, multiorgan failure, and thereby, death. Cytokines have an immense role in causing immunological responses through their pleiotropic activities. Generally, cytokines have both pro- as well as anti-inflammatory actions by maintaining regulatory defences mechanisms through counteracting with invading microorganisms. Cytokines are the important biomarker to unregulate the immunological functions by accelerating inflammation related to cellular damage. In my present study, I correlate the potential role of cytokines in maintaining tissue-damaging activities in tissues in the dog.

Keywords: Cytokines; Biomarker; role; Inflammation; Sepsis; dog

Introduction

Sepsis, the most important danger of death systemic inflammatory response to infection, is a common cause of critical illness and death in dogs, with reported mortality rates ranging from 20% to 68%. Sepsis, the danger of death serious infection, is developed during inflammatory responses towards infection causes serious injury at the cellular system with alteration of the immune system to attack the body (Schulte et al., 2013). Sepsis and septic shock occur as microbial pathogens/organism invades the body and cause a systemic proinflammatory response by triggering changes in the multiple organ systems. It is a highly significant health-related problem with an elevated rate of mortality of dogs (Machado et al., 2014). The epidemiological study revealed that sepsis/septic shock occurs in elder animals, immunocompromised patients, and clinically ill dogs with/or without emerging antibiotic resistance in microorganisms. Multiple organ dysfunction syndromes (MOD), and systemic inflammatory response syndrome (SIRS) are two terms closely associated with sepsis whereas SIRS is characterized by the immunological response of the host system during the pathogenic invasion, toxins, and other non-infectious conditions, such as burns, hypovolemic shock, pancreatitis, trauma, and haemorrhagic conditions and MOD is developed during acute

circulatory failure with constant arterial hypotension (Schulte et al., 2013; (Cabrera-Perez et al., 2014).

Trauma, ischemia, infection, and severe injury may play an immense role in causing sepsis that is indicated an accelerated development of proinflammatory cytokines, such as high-mobility group box (HMGB)-1, tumor necrosis factor (TNF), and interleukin (IL)-1b. Blackwelland and Christman (1996) reported that cytokines are characterized by a cluster of small signaling proteins developed in the cellular metabolism and accelerate host Défense as well as functions of the host system (Schulte et al., 2013). The cytokines help in the tissue by initiating local coagulation to confine tissue damage through its beneficial inflammatory effect. The level or concentrations of cytokines are the indicators to determine the pathological inflammatory disorders in the tissue (Cabrera-Perez et al., 2014). Sepsis plays important role in activating receptor antagonists, anti-inflammatory cytokines, and the soluble cytokine receptors whereas elevated development of pro-inflammatory cytokines causes tissue injury, capillary spillage, and ultimately triggers organ damage (Machado et al., 2014). Interleukin-1 receptor antagonist (IL-1Ra) is attributed to combining IL-1 receptor and thereby hinders IL-1 actions whereas anti-inflammatory cytokine interleukin-10 (IL-10) downregulates the production of various proinflammatory cytokines, such as TNF-α, IL-6, IL-1β, and IL-8 (Schulte et al., 2013). Therefore, anti-inflammatory cytokines play a major role in maintaining and altering responses to inflammatory reactions of sepsis.

Pathophysiology of sepsis with the immunological response

Sepsis is a clinical manifestation characterized by the systemic response of the host to the particular infection. Cytokine responses with inflammatory pathways are the important sequel for the pathogenesis of sepsis. Four major cytokines namely tumor necrosis factor α (TNFα), interleukin 1α(IL-1α), interleukin 8 (IL- 8), and interleukin 6 (IL-6) are attributed to be closely correlated with the septic syndrome (Machado et al, 2014). The immune response of the host's systems is disturbed due to the complex mechanism associated with the activation of the cytokines. The complex mechanisms are correlated with the activation of monocytes as well as neutrophils with an accelerated release of inflammatory mediators. The immune reaction is attributed to developing increased endothelial permeability as well as activation of coagulation pathways (Machado et al, 2014). The immune responses are characterized by the automatic host responses towards infection with the alteration of proinflammatory and anti-inflammatory responses (Schulte et al., 2013). Two types of immune responses depicting

innate and adaptive are important biological values in counteracting the invading microorganism. The first line of cellular defense helps the release of cytokines, chemokines, and inflammatory regulators. alteration of cytokine release can cause endothelial dysfunction, capillary permeability, hypotension, hemoconcentration, macromolecular extravasation, edema, intravascular coagulation, metabolism, neuroendocrine activation, and organ dysfunctions (Cabrera-Perez et al., 2014). The sepsis-inducing damaged innate as well as adaptive immune responses are also closely associated with the systemic proinflammatory reaction with immunosuppression and immunoparalysis that play a pivotal role in the pathogenesis of cell damage, and thereby multiple organ failure, and death in the dog. The immune responses are characterized by alteration of pathogen recognition receptors (PRRs) such as Toll-like receptors (TLRs) with the distinct pathway of pathogen-associated molecular patterns (PaMPs). The responses are generally hampered due to downstream signaling cascades, transcriptional responses, nuclear factor κB (NF-κB), followed by the release of chemokines, cytokines, and nitric oxide (NO) (Machado et al, 2014).

Functions of Cytokines

Cytokines exhibit their functional activities through their autocrine, paracrine, or endocrine activities with considerably lower molecular weights less than 40 kDa. Cytokines are classified as either proinflammatory, anti-inflammatory, chemotactic, or growth-regulating (Bone et al., 1992). It can be assessed genetically, epigenetically, and post-transcriptionally controlled with cytokine signalling cascade between health and diseases. Different cytokines have been regulated through their specific receptors on target cells through relative activation of downstream signalling proteins (Schulte et al., 2013). Cytokines play an integrated major multiple in the immune system against infection and neoplasia in the dog. Cytokines analysis is an important key for assessing the inflammation and pathophysiology of sepsis in both medical and veterinary science. The clinical analysis of cytokines may be the clue of prognostic information to inform clinical decisions for clinical cases of canine with infectious and neoplastic diseases. In addition, proinflammatory cytokines act as an immense capacity in activating innate as well as adaptive immune responses. Proinflammatory cytokines such as tumor necrosis factor (TNF)-α, macrophage migration inhibitory factor (MIF), and interleukin (IL)-1, IL-12, IL-6, and interferon (IFN)-γ (angus et al., 2001; Machado et al, 2014). Proinflammatory cytokines exegeted the delivery of anti-inflammatory cytokines cytokine i.e. transforming growth factor (TGF)-β, IL-10, and IL-4 with the

restoration of immunological equilibrium and activation of signal transduction cascades by exhibiting genome-wide expression (Schulte et al., 2013). As a result, the activities that invaded pathogens may be subsided decrease in tissue-damaging inflammation. The soluble TNF receptors (sTNFRs), IL-1 receptor type II (IL-1R2), and IL-1 receptor antagonist (IL-1Ra), play a vital role in counteracting the inflammatory responses.

Cytokines in sepsis

Cytokines, a cluster of small signaling endogenous immunomodulating, and inflammatory proteins, produced by a significantly big variety of cells play a crucial role in the conservation of cellular defense against systemic inflammatory diseases (Bone et al., 1992). Chemokines, the chemotactic cytokines have a major potentiality in maintaining the innate as well as adaptive immune system by developing the migratory behavior of leukocytes and other cells in the dog. Sepsis triggers excessive production of cytokines with altered homeostatic functions and makes tissue injury by accelerating systemic inflammation with organ dysfunction (angus et al., 2001). Sequential release of cytokines such as cytokine cascade have closely associated with the development and secretion of early or proximal/primary cytokines, that incorporates monocyte-chemotactic protein-1(MCP-1), TNF, and IL-1 (Machado et al, 2014). TNFα actively participates in promoting the of functions lymphocyte with activation of coagulation, as well as induction of synthesis of hepatic acute-phase protein. In addition, the production of IL-6, and IL-8 lead to maintaining inflammatory response as well as repair of tissues. IL-6, a pleiotropic mediator downregulates TNF and IL-1 production decreasing the inflammatory responses (James, 2013).

The most important chemoattractant IL-8 causes mediate neutrophilic tissue inflammation with accelerated tissue damage and organ dysfunction (Schulte et al., 2013). Cytokines, the important predator for assessing regulating proteins are responsible for activating or inhibiting transcription factor binding domains in the promoter location of its gene (Court et al., 2002). On the other hand, nuclear factor B (NF-B) activation and promoter binding maintaining cytokine cascade are activated in many cell types by various stimuli including TNF, IL- 8, IL-6, and IL- 1, and with downregulation of systemic inflammation and acceleration of host inflammatory response (Machado et al, 2014). Soluble cytokine, as well as cytokine receptor antagonists, play a pivotal role in the alteration of signal transduction. Interleukin 10 (IL- 10) and transforming growth factor (TGF)-β, the synergistic, overlapping and antagonist mediator, block the production of TNF, IL- 1, and IL-8 by decreasing systemic

inflammatory responses by modulating the proinflammatory expression of cytokine gene (Martin et al., 2003). The clinical exhibition of sepsis syndrome is associated with the complex interaction between counter-inflammatory cytokines, proinflammatory cytokines, and cytokine neutralizing molecules.

Conclusion

Sepsis is attributed to a crucial factor for tissue degeneration characterized by a critical-dynamic disease process with accelerated inflammatory as well as immune reactions. Various studies in dogs depicted that many different pathophysiologic processes involved in sepsis and pro-and anti-inflammatory cytokines play an immense role in the disease's progress. Pro-inflammatory cytokines and chemokines including tumor necrosis factor (TNF)-α, interferon (INF)-γ, interleukin (IL)-1, IL-2, IL-6, IL-8, IL-12, IL- 18 are necessary for initiating an effective inflammatory response. TNF-α and IL-1β are considered the initiators or proximal cytokines of the pro-inflammatory cytokine cascade in response to infectious disease which results in the production of other cytokines such as IL-6 and IL-8 or distal cytokines. In addition, inflammation-modulating cytokines including IL- 10, and IL-4, modulate cell-mediated inflammatory response by suppressing the gene expression for pro-inflammatory cytokines. Mechanisms associated with pathophysiologic features of sepsis and novel antisepsis strategies could be deployed by implementing immunomodulating treatment.

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