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Acute phase reactants- Diagnostic VS prognostic significance: An overview

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Abstract

Acute phase reaction is a general term attributed to a group of systemic and metabolic changes that occur within hours of an inflammatory stimulus. The most important component of this response is the acute phase proteins, which are a heterogenous group of plasma proteins. If the inflammatory response is self-limiting or treated, level of these proteins returns to normal within days or weeks. A stronger stimulus for inflammation will result in greater change in the concentration of acute phase proteins. The production of these proteins is regulated to a great extent by cytokines and to a lesser extent by glucocorticoid hormones. They bind to bacteria leading to activation of complement proteins that destroy pathogenic organisms.

This article highlights the features, functions, synthesis and types of acute-phase proteins and their associated relation in periodontal disease.

Keywords: Acute phase proteins, cytokines, inflammation, periodontal disease

1. Introduction

The acute-phase reaction represents an early and highly complex reaction of the organism to a variety of injuries such as bacterial, viral or parasitic infection, mechanical or thermal trauma, ischemic necrosis or malignant growth [1]. It refers to physiological and metabolic alterations that ensue immediately after onset of infection or tissue injury. In contrast with the specificity of cellular and humoral immunity, these changes are nonspecific and occur in response to many conditions [2].

2. Features

Characteristic features of the systemic acute-phase response include fever, neutrophilia, changes in lipid metabolism, hypoferrinemia, increased gluconeogenesis, increased protein catabolism and transfer of amino acids from muscle to liver, activation of complement and coagulation pathways, hormonal changes and induction of acute-phase proteins [3].

A prominent aspect of acute-phase response is also the modification of the vasculature with dilation and leakage of blood vessels, particularly at the post-capillary venule. This results in tissue edema, extravasation of red blood cells and associated redness. The alterations are mediated through the release of various inflammatory mediators in the inflamed tissues, including reactive oxygen species, nitrous oxide and arachidonate metabolites.

3. Functions

The acute-phase response is a primary defense reaction and therefore protects against bacterial products such as endotoxins [1]. This systemic response helps to ensure survival during the period immediately following injury and helps to accomplish the same outcomes as the localized inflammatory response, designed to destroy infections or noxious agents, to remove damaged tissue and to repair the affected tissues. An increase in the plasma concentration of acute-phase proteins at the site of injury plays a major role in wound healing. These proteins have an essential role in the inhibition of extracellular proteases, blood clotting, fibrinolysis, modulation of immune cell function and the neutralization and clearance of harmful components from the circulation.

4. Synthesis

The synthesis of acute-phase proteins is regulated by cytokines and to a lesser extent by glucocorticoid hormones. Cytokines related to the acute phase response can be divided into three groups: (i) pro-inflammatory cytokines initiating or enhancing the cascade of events (tumor necrosis factor- α , interleukin (IL) 1, interferon- γ and IL-8); (ii) interleukin-6-type cytokines (IL-6, leukemia inhibitory factor, IL-11, oncostatin M, ciliary neurotrophic factor and cardiotrophin-1), which are responsible for the main systemic features of acute-phase response in a variety of tissues; and (iii) anti-inflammatory cytokines downregulating the acute-phase response (IL-10, IL-4, IL-13 and transforming growth factor- β)^[1].

5. Types

Acute phase proteins can be divided into two groups. Type I proteins include serum amyloid A, C-reactive protein, complement C3 and α_1 acid glycoprotein, which are induced by the pro-inflammatory cytokines (IL-1 and tumor necrosis factor). Type II acute-phase proteins include fibrinogen, haptoglobin, α_1 -antichymotrypsin, α_1 -antitrypsin, α_2 -macroglobulin, which are induced by the IL-6-like cytokines. The α -helical cytokines, IL-6 and oncostatin M are the most potent recognized inducers of acute-phase proteins^[4].

6. Characteristics of the acute-phase reaction response molecules

Acute-phase proteins serve important functions in restoring homeostasis after infection or inflammation. These include homeostatic functions (such as fibrinogen), microbicidal and phagocytic functions (such as complement components or C-reactive protein), antithrombotic properties (such as α_1 -acid glycoprotein) and antiproteolytic properties which are important to contain protease activity at sites of inflammation (such as α_2 -macroglobulin, α_1 -antitrypsin, α_1 -antichymotrypsin)^[3]. The strong acute-phase proteins (C-reactive protein, α_2 -macroglobulin, serum amyloid A) respond rapidly to inflammatory stimuli and serum levels may increase several hundred-fold^[5-7]. Moderate acute-phase proteins (haptoglobin, fibrinogen, α_1 -antitrypsin) can increase 2 to 10 fold^[8]. While weak acute-phase proteins (complement component C3, ceruloplasmin) may increase up to 2 fold^[7].

a. C-reactive protein

C-reactive protein, when bound to bacteria, promotes the binding of complement and facilitates their uptake by phagocytes. This process of protein coating to enhance phagocytosis is similar to opsonisation by antibodies. C-reactive protein may be considered a primitive form of antibody specifically interacting with cell membrane components of microorganisms such as bacteria and fungi as well as damaged mammalian cell membranes. When complexed, C-reactive protein can activate complement to enhance opsonization and clearance of the bacteria prior to the production of specific IgM or IgG. Acute-phase proteins may provide important mechanisms to modulate macrophage function, since macrophages possess C-reactive protein receptors and C-reactive protein can potentially upregulate pro-inflammatory cytokine production^[9]. Thus it induces the synthesis of IL-1, tumor necrosis factor- α and IL-6 in human peripheral blood mononuclear cells and

alveolar macrophages, as one of its physiological roles is the amplification of inflammatory responses; although C-reactive protein probably plays more of an anti-inflammatory role^[10]. The functions of C-reactive protein include reaction with cell surface receptors resulting in opsonization, enhanced phagocytosis and passive protection, activation of the classical complement pathway, scavenger for chromatin fragments, inhibition of growth and/or metastases of tumor cells and modulation of polymorph nuclear leukocyte function.

b. Serum amyloid A

Serum amyloid A protein is also elevated during inflammation and it increases by as much as 1000-fold, particularly during chronic inflammatory responses. It is a precursor of protein amyloid A in secondary amyloidosis and may be deposited in the interstitium of tissues, which can interfere with normal tissue function. Acute-phase serum amyloid A is a chemo attractant for neutrophils, monocytes and T cells.

c. α_2 -Macroglobulin

α_2 -Macroglobulin is one of two principal protease inhibitors in human plasma, the other being α_1 -antitrypsin. Proteolytic enzymes released from damaged tissues as well as from phagocytic cells are partially inhibited after binding to α_2 -macroglobulin. Macrophages and fibroblasts rapidly phagocytose the complexes of proteases and α_2 -macroglobulin. It scavenges proteases by binding excess molecules that are not eliminated by more specific inhibitors. The functions of α_2 -Macroglobulin include hemostasis, coagulation, modulation of the activity of IL-1, IL-6, tumor necrosis factor- α , transforming growth factor- β , and platelet-derived growth factor^[3]. It can also be a carrier protein for IL-6 and modulate its activity as part of the acute-phase response^[11].

d. α_1 -Acid glycoprotein

The acute-phase glycoprotein, α_1 -acid glycoprotein, can be increased by approximately 2- to 4-fold during inflammation. It may also play an immunoregulatory role and binds to a number of diverse drugs^[12].

e. α_1 -Antitrypsin

It is a serine protease inhibitor in human plasma that targets proteases released from leukocytes (such as elastase). α_1 -Antitrypsin is synthesized by the liver and increases 4-fold when stimulated by an inflammatory process. In contrast to complexes of proteases with α_2 -macroglobulin, α_1 -antitrypsin-protease complexes are not taken up efficiently by macrophages. It has a role in several mediator pathways involved in the inflammatory response and in the absence of this protein, the proteases degrade tissue surrounding an inflammatory process and cause damage leading to chronic inflammation.

f. Haptoglobin

It binds to and removes free hemoglobin released by intravascular hemolysis, by forming a complex that is rapidly cleared by hepatocytes. Haptoglobin has the ability to form stable complexes with extra-corporeal hemoglobin and prevent iron loss through urinary excretion^[13]. Following injury, haptoglobin increases 2-to 4-fold and is found in inflammatory exudates.

g. Fibrinogen

Fibrinogen accumulates at the site of injury and in the presence of enzymes released from polymorphonuclear leukocytes and platelets, fibrin is formed. This increases the tensile strength of the wound and stimulates fibroblast proliferation and growth. Fibrinogen synthesis by hepatocytes is increased by approximately 2- to 4-fold and can be stimulated by fibrinogen or fibrin degradation products, indicating a feedback amplification loop that requires macrophages.

h. Complement components

The complement system is a group of serum proteins whose general function is to regulate the inflammatory response. Several of the components are acute phase reactants, as they increase during infection. These components interact with each other and with other elements of the innate and adaptive immune systems. Activation by either the classical or alternative pathway generates various peptides that can attract phagocytes to sites of infection by chemo attractants, increase blood flow to the site, increase vascular permeability for plasma molecules and damage plasma membranes of cells, viruses or microorganisms that have activated the system, producing lysis of the cell. Complement has also been linked to macrophage cytokine release.

i. Ceruloplasmin

It is a glycoprotein that is the major copper-transporting protein in human plasma. Ceruloplasmin and bound copper are essential to collagen formation and the extracellular cross-linking and maturation of collagen and elastin. Ceruloplasmin and copper may also protect the matrix of healing tissue against superoxide ions generated by phagocytes in the course of clearing tissue debris or microorganisms.

j. Albumin and transferrin

Albumin and transferrin, the serum iron transport protein, are decreased during inflammation potentially to starve the micro-organisms of iron required for growth and virulence expression. Cytokines, including IL-1, IL-6 and tumor necrosis factor- α , are important downregulators of the synthesis of these acute-phase reactants.

7. Acute-phase reactants in periodontitis

Pro-inflammatory cytokines and mediators are significantly elevated, with gingival inflammation during the destructive phase of periodontitis [11, 14]. One consequence of these localized gingival inflammatory reactions has been the elevated levels of various acute phase proteins in the gingival crevicular fluid [15]. These have included α_2 -macroglobulin, α_1 -antitrypsin and C-reactive protein, which are altered in the crevicular environment as a result of numerous host-bacterial interactions and may contribute to the defense of the host in this milieu. Increased levels of acute-phase proteins have been noted with gingival inflammation, including during experimental gingivitis and periodontitis, reflecting the locally stressed environment [16]. Thus, measurement of serum acute-phase proteins may help to identify a subset of patients who are at higher risk for destructive disease or disclose the patients who are undergoing a process of periodontal breakdown [17].

8. Conclusion

Oral infections produce a significant increase in systemic inflammatory responses manifested by acute-phase cytokines and acute-phase reactants. Cytokines released from various cells, including neutrophils, modify inflammation and accumulate at its site thereby enhancing the cellular response in an autocrine and paracrine manner. Acute phase response takes place by changes in the acute-phase proteins in response to bacterial infection, trauma, myocardial infarction or collagen tissue disorders [18]. Thus, measurement of acute-phase proteins is a useful marker of inflammation in both dental and medical pathologies. They have and can be used as a clinical guide to diagnosis, prognosis and management.

9. References

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