Short Communication

Pentraxin-3 (PTX-3): A Potential Marker for Periodontal Disease Activity

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ABSTRACT

Aim: This paper describes the impending part of Pentraxin-3 (PTX-3), an acute-phase protein, as potential marker of periodontal disease activity.

Summary: Pentraxins (PTXs) are classical mediators of inflammation and markers of acute-phase reaction. Pentraxin-3 (PTX-3) is an evolutionarily conserved, multimeric acute-phase inflammatory glycoprotein and is a family member of cardiovascular biomarker C-reactive protein (CRP). The plasma level of PTX3 is raised in inflammation resulting from a wide range of disease states from infection and autoimmune and/or degenerative disorder. Measurements of PTX3 in gingival crevicular fluid (GCF) or plasma may help identify a subset of patients having higher risk patients for destructive disease or those patients undergoing a process of periodontal breakdown. Because of extrahepatic synthesis by vascular endothelium at the site of inflammation, in contrast to (C-reactive protein) CRP, PTX3 levels are believed to be the true independent indicators of periodontal disease activity.

Keywords: Acute-phase protein, chronic periodontitis, disease progression

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Date of Submission : 23-02-2014
Reviews Completed : 24-03-2014
Date of Acceptance : 25-03-2014

INTRODUCTION

Periodontal diseases are infectious/inflammatory diseases involving gram-negative, anaerobic and microaerophilic bacteria that colonize the subgingival area and cause local and systemic elevations of pro-inflammatory prostaglandins and cytokines, resulting in tissue destruction. Immune responses are activated upon stimulation by bacteria or their toxins present in the dental biofilm and eventually play a significant role in alveolar bone destruction observed in periodontitis.[1] In response to the bacterial endotoxins, acute-phase proteins are produced which sequentially activate the inflammatory chute.

Pentraxins (PTXs) are established mediators of inflammation and markers of acute-phase reaction. Pentraxin-3 (PTX3) is the first prototype of the long-pentraxin group that is proposed to play a significant role in innate-immune response against pathogens, regulation of inflammation, and apoptotic cell clearance.[2] Clinical evidence has suggested that the elevated PTX-3 levels might be a valuable early and sensitive indicator for severely ill patients.

LONG ACUTE-PHASE PROTEIN PENTRAXIN-3 (PTX-3)

Pentraxins may be divided into short pentraxins (e.g. CRP and serum amyloid protein), long pentraxins (e.g. PTX-3 and PTX-4) and several neuronal pentraxin. Pentraxin-3 (PTX-3) is an evolutionarily conserved, multimeric acute-phase inflammatory glycoprotein and is a family member of cardiovascular biomarker C-reactive protein (CRP).[3] PTX3 is a 45 kDa protein that assembles to form high molecular weight multimers linked by interchain-disulfide bonds. The C-terminal domain (203 amino acids) of PTX3 shares homology with the classic short pentraxins, however, 178-amino acid N-terminal domain demonstrate no significant homology with other known proteins.[4] Human PTX3 plasma levels are very low (<2 ng/mL) in normal subjects. However, their levels increase rapidly (peak at 6–8 h) and dramatically (200–800 ng/mL) in various pathological conditions including sepsis, acute myocardial infarction, autoimmune and degenerative disorders and small vessel vasculitis.[5,6]

Muller *et al*.[7] reported that PTX-3 correlates with the severity in participants admitted to a medical intensive care unit with clinical conditions ranging from systemic inflammatory response syndrome to septic shock and suggested PTX-3 is a marker of inflammation and infectious disease. PTX-3, in contrast to short PTXs, is made by diverse types of cells, predominantly endothelial cells and macrophages, in response to inflammatory signals.

PTX-3 plays the crucial role in defence mechanism. It activates complement system suggesting its role in the amplification of inflammation and innate immunity. When PTX-3 interacts with the surface immobilized C1q, the classical complement cascade is activated, which is measured as C3 and C4 deposition.[8] Selected bacteria, fungi and viruses are opsonized through PTX-3. Opsonization results in facilitated pathogen recognition (increased phagocytosis and killing) and innate immune cell activation (increased cytokine and nitric oxide production). PTX3 binds fibroblast growth factor-2 and modulate angiogenesis in several physiopathological conditions. PTX3 has been proposed to have the potential to be a new diagnostic marker for several inflammatory and autoimmune diseases.[1] Owing to its extrahepatic synthesis, PTX3 levels are considered to be the independent indicators of disease activity at sites of inflammation and vasculitis. PTX-3 was found to be elevated to its prognostic value in cardiovascular disease, chronic kidney diseases, rheumatoid arthritis, preeclampsia, inflammatory bowel diseases, and severe dengue virus infections and circulating levels of PTX-3 significantly correlated with the severity of infection in critically ill patients.[9]

PTX-3 AND PERIODONTAL DISEASES

The systemic manifestation in periodontitis to many oral bacteria is well known and appears to be increased severity of periodontitis. Thus, the ability to use acute-phase reactants as a measure of inflammation has substantial support. Plasma levels of PTX3 are elevated during inflammation resulting from a wide-spread range of diseased states from infectious disease to autoimmune and/or degenerative disorders. Measurements of PTX3 in GCF or plasma may help identify a subset of patients having higher risk patients for destructive disease or those patients undergoing a process of periodontal breakdown. Pradeep *et al*., [9]Fujita *et al*.[10] and Keles *et al*.[11] assessed PTX-3 levels in GCF and correlated it with different stages of periodontal conditions. Gumus *et al*.[1] suggested that the salivary concentration of PTX-3 may be proposed to be related with periodontal tissue inflammation.

Pradeep *et al*.[9] indicated that the concentration of PTX3 in GCF and plasma increased proportionately with the severity of disease. The mean value was higher in GCF than in plasma. However, the difference in the plasma group was not statistically significant. Further, the proportionate increase in levels from healthy and to gingivitis to periodontitis groups, further confirmed that PTX3 was actively secreted by the predominant cells of periodontal disease activity. Increased PTX3 levels in GCF and plasma in patients with periodontitis indicated an accumulation of neutrophils and monocytes at diseased sites and an amplification of cytokines such as TNF-α and IL-1 and -6. Neutrophils arrive early at sites of injury and infectious disease, which represent a reservoir of pre-stored ready-to-use PTX3 stored in lactoferrin rich specific granules that are translocated to the membrane and are released in response to inflammatory signals.[2,9] Thus representing that PTX-3 deficient neutrophil have defective microbial recognition and phagocytosis.

In a case-control study by Lakshmanan *et al*.,[2] demonstrated higher levels of PTX-3 in the gingival tissue of generalised aggressive patients (AP) as compared to chronic periodontitis (CP) patients. This indicates more severe inflammation in AP than CP, and emphasising on the hyper-responsive character of the neutrophils in AP.[2]

IL-10 and glucocorticoid hormones were shown to co-stimulate PTX3 production induced by inflammatory signals, which is a likely scenario in the late phases of tissue damage. PTX3 concentrations in GCF and plasma increased in periodontitis. Moreover, PTX3 concentrations were high with increasing severity (increase in clinical parameters) of periodontal disease. Thus, PTX3 in GCF could be considered a marker of inflammatory activity in periodontal disease.[9] Keles *et al*.,[11] showed that the concentration of PTX3 in gingival tissue and serum was positively correlated with alveolar bone resorption and inflammatory cells in the epithelium both in healthy controls and experimental periodontitis groups.

Evidence suggests that PTXs (also known as TNF-stimulated gene-14, TSG-14),[9] acts as a non-redundant part of the humoral arm of innate/ inherent immune system, downstream of, and complementary to, cellular recognition, as well as a tuner of inflammation.[12] Although CRP is mainly formed in the liver in response to pro-inflammatory cytokines, PTX3 is produced by the widespread innate immune system cells (e.g., neutrophils, fibroblasts, dendritic cells, epithelial cells, macrophages and vascular endothelial cells) in response to inflammatory intermediaries, such as interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α) and bacterial products, inferring a mechanism for local augmentation of inherent resistance at infectious disease and inflammation site.[2]

Many markers have been used for evaluation of periodontal disease activity e.g., CRP, however, only PTX-3 is considered to be a true marker of inflammatory status, as it is

synthesised mainly from the indigenous vascular endothelial cells. PTX3 is supposed to be the true independent marker of disease activity, thus could have clinical insinuation in diagnosing the "at site" inflammatory status of the periodontal disease.[2] These pentraxins are sensitive and specific in the diagnosis and prognosis of chronic diseases like periodontitis.

CONCLUSION

PTX3 in GCF could be considered a marker of inflammatory activity in periodontal disease, and they also give an understanding into the pathogenesis of the disease, thereby improving the understanding of the course of periodontal diseases. However, molecule is highly non-specific biomarker and scanty literature designates its role as true or independent molecule in periodontal diseases. Long-term multicentre randomised controlled trials are warranted before routine clinical applications of PTX-3 as the prognostic marker for periodontal disease.

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