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PENTRAXIN 3 AND ITS ROLE IN PERIODONTITIS

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ABSTRACT

Pentraxin 3 belongs to the family of Pentraxins. It is similar to acute phase proteins like C-reactive proteins (CRP) and Serum Amyloid Proteins (SAP). Pentraxin 3 molecules are produced by various cells like dendritic cells, macrophages, neutrophils, endothelial cells and myeloid cells, other than hepatic tissue in response to inflammation. Periodontitis is caused by gram negative bacteria associated with the biofilm attached to the teeth and the host response elicited by the endotoxins produced by the microorganisms. As a result of these inflammatory reactions there are elevated levels of various acute phase proteins in the plasma. Mediators produced by the host that contribute to tissue destruction include acute phase proteins, prostaglandins and cytokines. Pentraxins are such classical acute phase proteins belonging to a super family of evolutionarily conserved proteins considered as markers of inflammation. Therefore, the use of Pentraxin 3 as a marker to quantify the amount of inflammation and disease state has substantial relevance.

KEY WORDS: Acute Phase Proteins, Periodontitis, Pentraxin-3

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INTRODUCTION

Acute phase reactant (APR) is the generic name given to a group of approximately 30 different biochemically and functionally unrelated proteins. An acute phase protein has been defined as one whose plasma concentrations increases (positive acute phase proteins) or decreases (negative acute phase proteins) by at least 25 percent during inflammatory disorders. Conditions that commonly lead to increase in the acute phase proteins are infection, trauma, surgery, burns, various immunologically mediated and crystal induced inflammatory conditions and advanced cancer. The acute-phase response is a nonspecific process that may occur in the initial host response. Acute phase proteins regulate immune responses, function as mediators and inhibitors of inflammation, act as transport proteins for products generated during the inflammatory process and/or play an active role in tissue repair and tissue remodeling. Some acute phase proteins might constitute an inducible system of factors protecting against cell death by apoptosis.

CLASSIFICATION

The major inducers of acute phase proteins are interleukin-1 (IL-1), IL-6 and tumor necrosis factor (TNF). The two mediators IL-1 and IL-6 have been used to classify acute phase proteins into two subgroups. Type 1 acute phase proteins are those that require the synergistic action of IL-6 and IL-1 for maximum synthesis. Examples of Type 1 proteins are C-reactive protein, serum amyloid A and Alpha-1-acid glycoprotein 1. Type 2 acute phase proteins are those that require IL-6 only for maximal induction. Examples of Type 2 proteins are fibrinogen chains, haptoglobin, and alpha-2-Macroglobulin.

Pentraxin 3 (PTX-3)

Pentraxins (PTX) are a family of phylogenetically conserved, pattern-recognition proteins and a host-defense-related component of the innate immune system. PTX-3 is a member of PTX family and mainly acts as a soluble pattern recognition receptor (PRR) in the innate immune response. PTX-3 was initially isolated from human endothelial cells and fibroblast as they were induced by TNF-α and IL-1β.
Sources
In the immune system, myeloid cells, and dendritic cells are the primary source of PTX-3. Dendritic cells upon stimulation with the Toll like receptor (TLR) ligands, and cytokines like IL-10 and IL-1β leads to production of PTX-3. Other inflammatory cells like macrophages and neutrophils also secrete PTX-3.

Physiological Levels of PTX-3
The normal circulating PTX-3 level is in the range of 2-2.5ng/mL. However, during acute stages of inflammation the level of PTX-3 could reach up to 20 – 200ng/L. During pregnancy, the serum PTX-3 level slightly increases as the pregnancy progresses. A higher PTX-3 level is observed in preeclampsia.

Structure
Mature PTX-3 protein is approximately 40 - 45kDa. Pentraxin molecule has a pentagonal structure, which consists of five subunits. Human PTX-3 is a multimeric glycoprotein, whose composing subunits are made of 381 amino acids, including a 17-residue signal peptide. Its C-terminal(carboxy terminal) domain consists of 203 amino acids and the unique N-terminal domain consists of 178 amino acids.

Functions
Role in Immunity and Inflammation
Similar to other pentraxins, PTX-3 also plays a role in Pathogen recognition. Pathogen associated molecular patterns (PAMPs) are recognized by receptors known as Pathogen Recognition Molecules (PRM’s). PRMs are mainly of two types; they are either tissue associated (eg. Toll like receptors) or fluid associated. The fluid associated PRMs consist of 3 clearly defined subgroups – Collectins, Ficolins and Pentaxins.

Interaction with Complement
PTX-3 induces the activation of the classical complement pathway, whereby it binds to the surface of apoptotic cells along with the complement fractions and helps in tissue debris clearance. PTX-3 has also been described to interact with factor H, thus enhancing factor H and iC3b deposition on apoptotic cells. Factor H is the main soluble regulator of the alternate complement pathway. Interaction with PTX-3 molecules results in increased deposition of factor H on the PTX-3 coated surface. PTX-3 binds to plastic immobilized C1q of the complement system. The binding of fluid phase PTX-3 to C1q may inhibit complement activation by competitive blocking of relevant interaction sites. Thus PTX-3 has a dual role and contrasting effects of complement activation as it helps in the clearance of material that are able to bind PTX-3 or it may protect against unwanted complement activation. Complement activation and interaction is modulated by the extent of PTX-3 glycosylation. Factor H is the main soluble regulator of the alternative pathway of compliment. PTX-3 has also been described to interact with factor H, thus enhancing factor H and iC3b deposition on apoptotic cells. Mannose binding lectin (MBL) is a component of the lectin pathway. The mannose binding lectin (MBL) binds PTX-3 via its collagen-like domain. MBL/PTX-3 complexes recruit C1q and elicit C3 and C4 deposition on target cell surfaces, such as those of Candida albicans. Phagocytosis thereof is mightily enhanced. PTX-3 also triggers Ficolin; which is a pattern recognition molecule and leads to activation of the lectin complement pathway. The binding of P selectin with PTX-3 dampens the neutrophil recruitment at the sites of inflammation.

PTX-3 and Neutrophil extracellular traps (NETs)
Neutrophil extracellular traps (NETs) are a chromatin material assembled with nuclear proteins which are set free concomitantly with apoptosis of neutrophils. The components of NETs include Azurocidin 1 (AZU1) and myeloperoxidase (MPO). AZU1 and MPO directly bind to PTX-3 and exert bactericidal activity. Localization of PTX-3 in neutrophil extracellular traps contributes to the generation of an antimicrobial microenvironment which
augments local capacity to trap and kill microbes. At the same time, neutrophil-derived PTX-3 accounts for another feedback mechanism which restricts excess transmigration of activated neutrophils into the host’s tissues, thus dampening unwanted dissemination of inflammatory reactions.

Figure 2 elucidates the role of PTX-3 in the pathogenesis of periodontal diseases. The antigenic peptides of the microbes are recognized by toll like receptors in the epithelium leading to the production of interleukins and tumor necrosis factor-α (TNF-α). These cytokines act on the macrophages leading to the secretion of PTX-3. PTX-3 is also secreted by fibroblasts, endothelial cells and by inflammatory cells like dendritic cells and neutrophils. This leads to the activation of classical pathway of complement activation. PTX-3 binds with the neutrophil extracellular traps (NETs) which proves to be bactericidal. It also binds with macrophages aids in the process of phagocytosis.

PTX-3 and Periodontitis
Pradeep AR et al in 2011 carried out a study on 40 subjects divided into 3 groups; healthy (n=10), gingivitis (n=15) and periodontitis(n=15). GCF and plasma samples were collected from each subject and quantified using ELISA. In tandem with the disease progression from healthy to gingivitis to periodontitis, mean PTX-3 concentration increased both in GCF and plasma. However, it was found that GCF value were higher than plasma values. The PTX-3 values were highest in the periodontitis group and least in the healthy group. Thus it was observed that PTX-3 correlated positively with the periodontal parameters. Pradeep AR et al in 2011 also carried out a study and examined
60 subjects and divided them into 3 groups based on glomerular filtration rate and periodontal parameters into healthy group, Chronic kidney disease group or Chronic kidney disease with periodontitis. Plasma samples were obtained and quantified using ELISA. It was found that both patient groups with CKD had higher PTX-3 values than control group but there was no significant difference between the two CKD groups. Group 3 patients had higher concentration of PTX-3 (6.338ng/ml) than group 2 (5.41ng/ml) and group 1(1.835ng/ml). In all groups, plasma PTX-3 correlated positively with the periodontal parameters. Yuzo F et al in 2011 determined the levels of IL-1β, IL-6, IL-8, TNF-α, IL-10 and PTX3 in GCF from diseased and healthy sites in patients with Chronic periodontitis. Cross sectional clinical data were obtained from one healthy site and one disease site per subject. PTX-3 levels were measured by ELISA whereas the rest of the markers were assayed by multiplexed beaded immunoassay. Mean clinical parameters were significantly higher in diseased sites as compared to healthy sites. And the mean levels of PTX-3, IL-1β, IL-6, IL-8, IL-10 and TNF-α were higher in diseased sites than in healthy sites. The results suggest that GCF PTX-3 is useful diagnostic marker for periodontal disease. Reema Lakshmanan et al in 2014 assessed tissue biopsy specimen of healthy, aggressive and chronic periodontitis showed that PTX-3 levels were the highest in generalized aggressive periodontitis followed by generalized chronic periodontitis and the least in healthy group. The mean differences between the groups were also statistically significant. In chronic periodontitis group there was significant positive correlation of PTX-3 values were found with individual plaque index and individual probing depth. In aggressive periodontitis group significant positive correlation of PTX-3 was found with individual gingival index (p=0.024), full mouth gingival index (p=0.001), full mouth probing depth (p=0.005) and full mouth clinical attachment level (p=0.026). Gumus et al in 2014 reported that significantly higher salivary concentration of PTX-3 was found in the Aggressive (AgP) and Chronic (CP) periodontitis group than the healthy control groups. Saliva levels of IL-1β were also significantly higher in AgP and CP groups than the healthy controls in this study. Enas Ahmed Elgendy et al in 2014 evaluated the effectiveness of adjunctive treatment of tea tree oil (TTO) on the clinical parameters and the level of PTX-3 in chronic periodontitis. A total of 40 patients with moderate to severe chronic periodontitis were divided into two groups, Group I received scaling and root planing (SRP) only, Group II received SRP and TTO gel. Clinical parameters were recorded and gingival crevicular fluid (GCF) samples were collected from each subject for measuring PTX-3 levels at baseline, 1, 3 and 6 months after treatment. There was statistically significant reduction in each of the studied clinical parameters and PTX3 level in Group II as compared with Group . The results from these studies done in periodontitis have found an increase in the level of PTX-3 during active stage of the disease and the levels were lower in health. The level of PTX-3 was found to reduce from diseased state to health after regression of periodontitis in the study by Elegendy et al. These evidences suggest the significant role of PTX-3 in the pathogenesis of a periodontitis. As majority of the studies suggest a strong association between periodontitis and various systemic chronic disease it is important to identify significant inflammatory markers for these conditions. PTX-3 are produced by the local inflammatory cells unlike CRP(C-Reactive Protein); their levels from localized specimens are more reflective of the inflammatory status at the site. Thus the results from these studies highlights the usage of PTX-3 as an inflammatory marker for the diagnosis of periodontitis in its early stages.

**CONCLUSION**

PTX3 is an acute phase protein that is produced by local cells in the process of inflammatory response and since there are only few biomarkers that are produced by the local inflammatory cells they can be used as a diagnostic marker in various inflammatory disorders. Moreover in conditions like periodontitis, PTX3 levels have been found to be higher so their use as an inflammatory marker might be justified. However further longitudinal
case control studies in which PTX 3 levels before after treatment of conditions like periodontitis is
needed to determine their role as an prognostic marker for periodontitis.

REFERENCES


