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Role of Pentraxin-3 in Periodontal Inflammation - A Comprehensive Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Acute phase reactants like C-reactive protein (CRP), and pentraxin 3 (PTX3) are increased with inflammation and tissue injury. PTX3 is an acute phase protein and a member of the long pentraxin family. CRP is synthesized in the liver but PTX3 is generated locally at the inflammatory site. It is a fluid-phase pattern-recognition molecule that regulates antimicrobial immunity and inflammation by interfering with selectin-dependent neutrophil recruitment and regulating the complement cascade. Hence, PTX3 could be used as a potential biomarker to identify inflammatory response in both acute and chronic diseases. In this review, we discuss the role of PTX3 in periodontal inflammation.

Keywords: Acute phase reactants; pentraxins; PTX3; periodontitis; inflammation.

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1. INTRODUCTION

Pentraxins are a superfamily of ancient evolutionarily conserved versatile pattern-recognition proteins made up of five identical subunits. The pentraxins are divided into two groups based on the subunit's primary structure: short pentraxins and long pentraxins. The C-reactive protein (CRP) and serum amyloid P-component (SAP) comprise the two short pentraxins, while Pentraxin-3(PTX-3) is the long pentraxin prototype protein group. In the case of acute inflammation, CRP and SAP, are produced primarily in the liver, whereas PTX3 is produced in a variety of tissues [1]. PTX-3 is the most studied protein among the superfamily of Pentraxins. Hence in this review, the authors aim to brief the role played by PTX-3 in inflammation with an emphasis on its role in periodontal inflammation.

1.1 Pentraxin-3: Structure and Functions

PTX-3 is also called tumor necrosis factor-stimulated gene 14. It is a prototypic soluble long pentameric structural protein-containing of 381 amino acids [2,3,4]. PTX3 is produced mainly by dendritic cells, endothelial cells and macrophages in response to primary inflammatory stimuli [5]. PTX3 plays complex, non-redundant functions in vivo. It interacts with several ligands and acts as a predecessor of antibodies, recognizes microbes, activates complement, facilitate certain pathogen recognition and protective responses by phagocytes [6,7]. Hence, PTX3 has an essential role between innate immunity, various inflammatory processes, tissue repair, female fertility and cancer biology [2,8].

Structurally, the long pentraxin 3 (PTX3) is a member of a complex superfamily of multifunctional proteins characterized by a cyclic multimeric structure [6]. PTX3 is a long pentraxin with a cyclic multimeric structure with an unrelated N- terminal domain linked to a pentraxin-like C-terminal domain which is required for c1q recognition and complement activation [2,8].

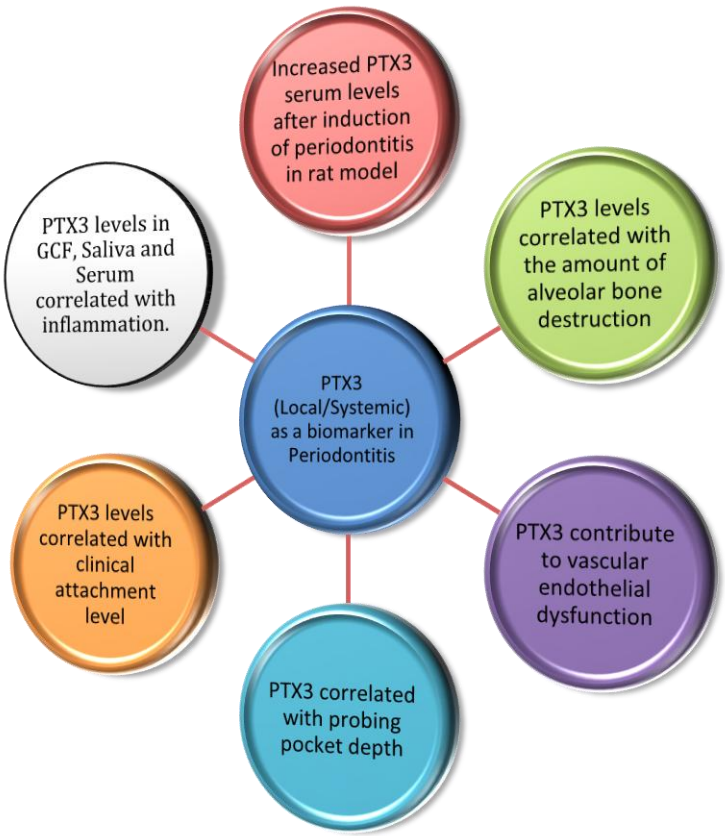

Fig. 1. PTX3 as biomarker in Periodontitis

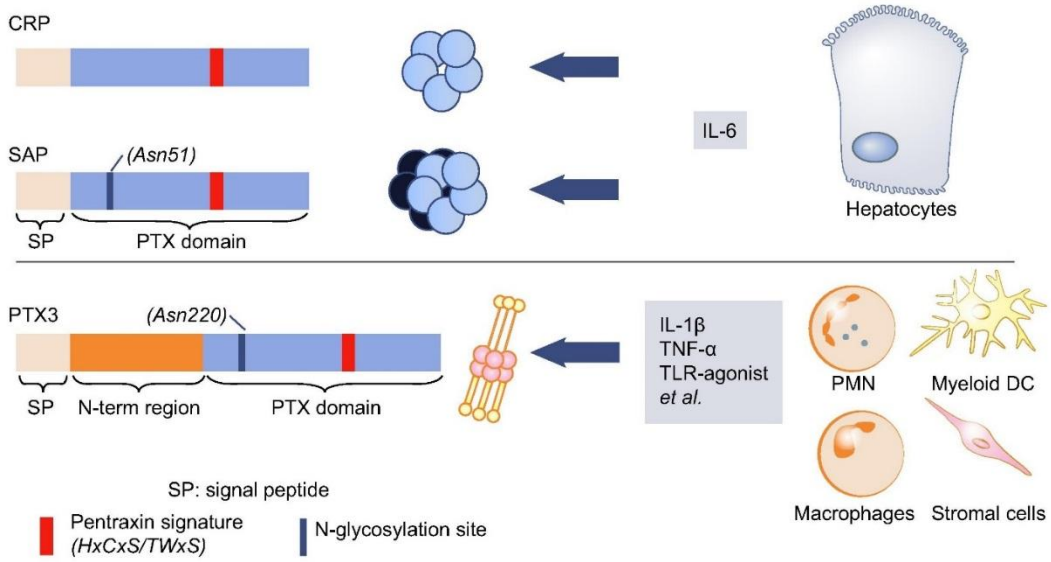

Fig. 2. Schematic representation of Pentraxin (From Bottazi et al [9])

Table 1. Functions of Pentraxins

Author/s	Role of Pentraxins
Tissue Repair	
Ristagno et al 2019 [9]	Tissue repair, resolution and fibrinolysis.
Garlanda C, et al 2018 [10].	It shows complex regulatory roles in inflammation and extracellular matrix organization and remodeling.
Grcevic D et al 2018 [11].	Pentraxin 3 plays a role in bone turnover and repair
Doni A, Musso et al 2015 [12].	Promote migration of remodeling cells.
Zlibut et al 2009 [13].	PTX3 increases the matrix metalloproteinases synthesis. It increases the MMP synthesis directly or by blocking NO synthesis.
Doni et al 2006 [14].	PTX3 is a component of extracellular matrix and models the tissue in chronic inflammation.
Innate immunity	
Ristagno et al 2019 [9]	Innate immunity - Resistance to selected microbes, Opsonization of certain pathogens.
Iwasaki and Medzhitov 2010 [15], Bonacina et al 2013 [16]	PTX3 recognizes and binds to various ligands including microbial moieties, complement components, and P-selectin. It recognizes the pathogen-associated molecular patterns (PAMPs) expressed by microorganisms and binds a number of bacteria, fungi, and viruses.
Doni et al 2006 [14]	PTX3 plays a vital role in Humoral Immunity.
Inflammation	
Ristagno et al 2019 [9]	Inflammation: Regulation of complement activity & neutrophils recruitment.
Deban et al [17]	PTX3 is an essential tuner of inflammation. It has multifunction soluble
Agarwali et al 2009 [1]	pattern recognition property. It works in tandem with other components of inflammation.
Other Functions	
Parente et al. 2019 [4]	PTX3 is a mediator of bone homeostasis.
Bonacina F et al 2016 [18]	PTX3 controls arterial thrombosis by targeting collagen and fibrinogen induced platelets aggregation
Rodriguez-Grande B et al 2014 [19]	PTX3 is an essential mediator of glial scar formation and resolution of brain oedema after ischemic injury

Author/s	Role of Pentraxins
Armstrong-James and Harrison, 2012 [20]	PTX3 is protective against invasive aspergillosis
Garlanda 2011 [21]	PTX3 plays a cardiovascular protective effect.
Maugeri N et al 2011 [22]	PTX 3 leads to release of leukocytes during acute myocardial infarction.
Bonacina F 2013 [16]	Deficiency of the long pentraxin PTX3 promotes vascular inflammation and atherosclerosis.
Reading PC et al 2008 [23]	Antiviral activity (PTX3 against Influenza Viruses and dengue virus)
Mairuhu AT 2005 [24]	
Bonavita E et al 2005 [25]	PTX3 is a suppressor of complement-dependent inflammation in cancer.
Rusnati M et al 2004 [26]	Selective recognition of fibroblast growth factor-2 by the long pentraxin PTX3 inhibits angiogenesis
Rolph MS et al 2002 [27]	Atherosclerotic lesions in humans showed strong expression of PTX3

Table 2. Pentraxin-3: Its association with various diseases and possible use as a disease biomarker

Author/s: Year	Pathogenesis	Disease
Brunetta et al 2021 [28]	High levels of PTX3 are expressed by myelomonocytic cells and endothelial cells in patients with COVID-19. Independent strong prognostic indicator of short-term mortality. PTX3 Serum level is positively correlated with COVID-19 disease severity and coagulopathy.	COVID-19
Tong et al 2021 [29]		
Zlibut et al 2019 [13], Ching et al 2020 [30]	PTX 3 stimulates vascular inflammation by modulating inflammatory cells.It is involved in endothelial dysfunction via several pathogenetic pathways.	Vascular inflammation & Vascular endothelial Dysfunction
Fujita et al 2012 [31],	GCF and Salivary PTX3 concentrations may have diagnostic potential.	Periodontal tissue inflammation
Pradeep et al 2011 [32]		
Gumus et al 2014 [33]		
Garlanda et al 2011 [21]	It is a biomarker for vascular pathology. It correlates with events that have the risk of developing vascular events.	Vascular pathology
Iwata Y 2009 [34]	PTX3 expression in skin from Systemic sclerosis was more intense relative to skin of healthy individuals. Serum PTX3 levels increase with the disease severity in systemic sclerosis.	Systemic Sclerosis
Bevelacqua et al.2006 [35]	Disease activity of psoriasis positively correlates with PTX3. PTX3 is a reliable prognostic inflammatory disease marker in untreated psoriatic patients.	Psoriasis
Ctirad et al 2008 [36]		
Ctirad et al 2008 [36]	PTX3 is a reliable prognostic inflammatory disease marker.	Rheumatoid arthritis
Tong et al, 2004 [37]	Predictor of all-cause mortality	Chronic Kidney Disease
Muller et al 2001 [38]	PTX3 levels increase in critically ill patients. This increase directly correlates with the severity of disease and infection	Critically ill patients

1.2 Circulating Pentraxins Concentrations

PTX3 is an acute phase response protein. The blood levels of PTX3 is low in normal conditions and is < 2 ng/mL in humans, increase rapidly (peaking at 6–8 h after induction) and dramatically high (200–800 ng/mL) during certain conditions like endotoxic shock, sepsis and other inflammatory and infectious conditions mentioned in table 1, correlating with the severity of the disease. PTX3 is a rapid marker for primary local activation of innate immunity and inflammation [38, 39, 24, 40, 69, 71] Thus the circulating levels of PTX3 is related to the severity of various diseases [41]. PTX3 could be identified in serum of patients with lung cancer, thoracic surgery, diabetes, pulmonary contusion, pulmonary artery hypertension, myocardial infarction [65, 66, 67,68, 70, 72-78]

1.3 Pentraxins in Periodontal Inflammation

PTX3 is expressed in response to inflammatory stimuli, including TNF α, IL-1β and LPS by a variety of cell types in periodontal tissue like neutrophils, fibroblasts, monocytes/macrophages, dendritic cells, epithelial cells, endothelial cells and vascular smooth muscle cells, adiposities, dendritic cells [42,43]. The plasma levels of PTX3 as mentioned above are very low in normal subjects and are raised in inflammatory conditions resulting from a wide range of disease states from infections to autoimmune and/or degenerative disorders [44]. Its levels may directly reflect the inflammatory status because PTX3 is produced from vascular endothelial cells and macrophages, not as CRP which is produced in the liver. In addition; short pentraxins are conserved during phylogenesis. This possibly indicates that PTXs confer a survival advantage. For the above reasons; the measurements of PTX3 in GCF or plasma may help identify patients who are at a higher risk for destructive disease, or those patients who are undergoing a process of periodontal breakdown [59,44,45].

Furthermore, infectious diseases of the bone, like periodontitis and osteomyelitis, set the scene for even tighter cooperation between bone and immune components, as exemplified by the involvement of the complement system in the onset and progression of periodontitis [46].

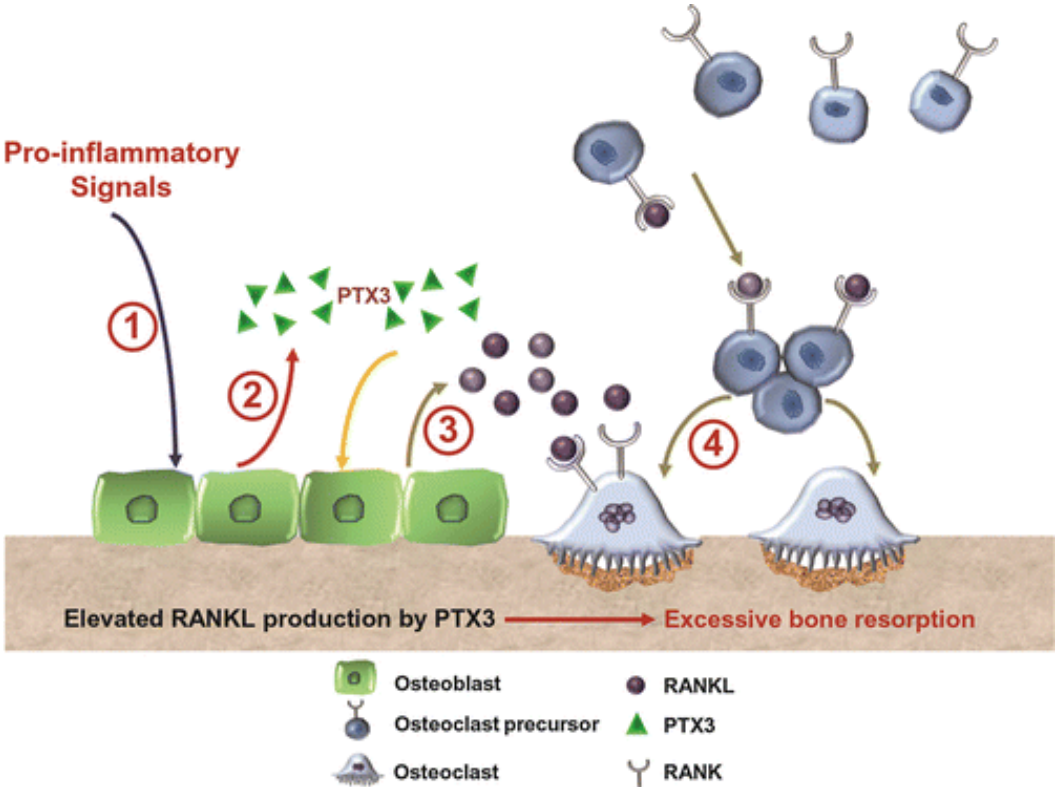

Fig. 3. Role of PTX3 in bone resorption (Choi et al [47])

Table 3. Pentraxin-3 and Periodontal inflammation

Author/s-Year	Biological sample	Pathogenesis/ Biological effect
Leira et al 2020 [48]	Experimental Periodontitis in rats-Serum	Increase in serum PTX3 levels post-induction. Periodontitis is associated with increased systemic inflammation. Gingival tissues of periodontal patients showed increased levels of PTX3 and sTWEAK compared to non-periodontally affected tissues.
Keles et al 2012 [49]	Gingival and serum PTX3 levels in Experimental Periodontitis - Rats	PTX3 seems to be associated with tissue destruction in earlier periods of inflammatory periodontal disease, contrary to the fibrinogen findings. Alveolar bone resorption and periodontal inflammation were evident in periodontitis groups. Levels of PTX3 in gingival tissue were statistically higher in Group 1 than those in groups 2 and 3. Plasma fibrinogen levels were significantly increased in the experimental periodontitis groups.
Leira et al 2020 [50]	Serum	Increased PTX3 levels as compared to Chronic migraine without periodontal disease.
Temelli B et al 2018 [51]	Serum levels of PTX3	PTX3 levels positively correlate with periodontal inflamed surface area in Coronary artery disease (-) groups. Patients aged from 30 to 75 years who underwent coronary angiography with coronary artery disease CAD suspicion were included. One of the plausible mechanisms in the relationship between periodontitis and CAD is the systemic inflammatory burden comprised of circulating cytokines/mediators related to periodontitis.
Leira et al 2019 [52]	Serum	PTX3 is independently associated with levels positively correlated with periodontally inflamed surface area in patients with poor prognosis.
Mohan et al 2019 [53]	GCF and Saliva	Scaling and root planing led to a reduction in PTX3 levels. This reduction was greater in periodontitis patients who smoked than those who were nonsmokers.
Wettero et al 2021 [54]	Saliva	PTX3 was detectable in saliva, and it reflected the local inflammation. PTX3 concentrations varied over the day with higher morning concentrations, but the PTX3 relative protein levels (percentage of total protein) were significantly higher in the evening. Smoking showed lower PTX3 levels.
Gheorghe et al 2021 [55]	GCF	CRP and PTX3 correlated with levels of periodontal inflammation. It reduced with non-surgical periodontal therapy. In chronic hepatitis C patients with periodontitis, the gingival fluid levels of pro-inflammatory markers reduced significantly.
Boyapati et al 2018 [56]	Serum	PTX3 is significantly correlated with clinical periodontal parameters such as pocket depth, clinical attachment loss and periodontal inflamed surface area. Higher levels of PTX3 correlated with peripheral arterial disease and periodontal disease.
Mohan et al 2019 [53]	GCF and Serum	Non-surgical periodontal therapy consisting of scaling and root planing led to a statistically significant reduction of PTX3 levels.
Vijayalakshmi et al	GCF	At baseline, PTX3 levels in both groups of patients

Author/s-Year	Biological sample	Pathogenesis/ Biological effect
2017 [57]		with chronic periodontitis were found to be significantly higher. Scaling and root planing led to an improvement in the clinical parameters and a statistically significant reduction of PTX3 levels. PTX3 in the gingival crevicular fluid increases with an increase in inflammation, irrespective of the presence or absence of systemic diseases.
Thukral et al 2017 [58]	GCF	PTX-3 is associated with periodontal remodeling under the effect of orthodontic forces.
Rauten et al 2016 [59]	GCF	PTX3 has a role in the inflammation and angiogenesis in wound healing in patients with post orthodontic gingivectomy.
Lakshmanan et al 2014 [60]	Gingival tissue sample	PTX3 levels correlated positively with clinical parameters in periodontitis.
Gumus et al 2014 [61]	Saliva and Serum	PTX3 levels correlate with periodontal tissue inflammation
Elgendy et al 2013 [62]	GCF	GCF levels of PTX3 can be used as a marker of periodontal tissue healing.
Surlin et al 2012 [63]	GCF	PTX-3 involvement in periodontal orthodontic remodeling and the aseptic inflammation induced by the orthodontic forces. PTX3 levels increase at early time points.
Fujita et al 2012 [31]	GCF	A strong correlation between PTX3 and periodontal status was observed.
Pradeep et al 2011 [32]	GCF and Serum	PTX3 levels increase during disease progression

2. CONCLUSION

PTX3 is generated locally at the site of inflammation in response to chemokines and bacterial components. It may play an important role in modulating the cross-talk between inflammatory cells and endothelium in various diseases. It can act as a biomarker to estimate the disease activity in inflammation and help in patient management, follow-up and clinical trial designing. Mucosal immunity and possible clinical use of salivary biomarkers are being in focus for the past few years. Limited number of studies have previously described PTX3 in saliva or in gingival crevicular fluid (GCF). Many studies correlate the levels of PTX3 with increased periodontal destruction. Reported literature shows differences between the PTX3 levels in serum when compared to Saliva\GCF. Hence, large studies are needed to assess the diagnostic and prognostic value of PTX3 as a clinical biomarker.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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