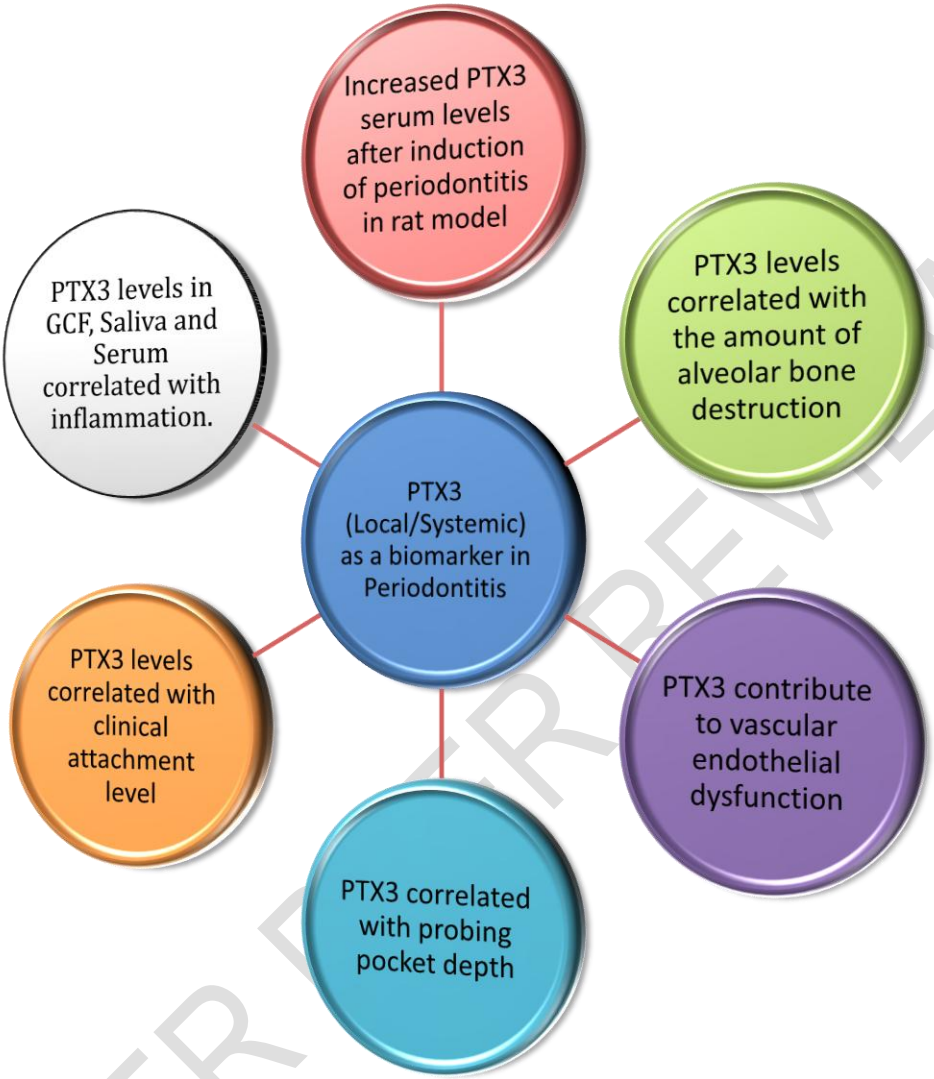
Review Article

ROLE OF PENTRAXIN-3 IN PERIODONTAL INFLAMMATION - A COMPREHENSIVE REVIEW

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



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.

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]

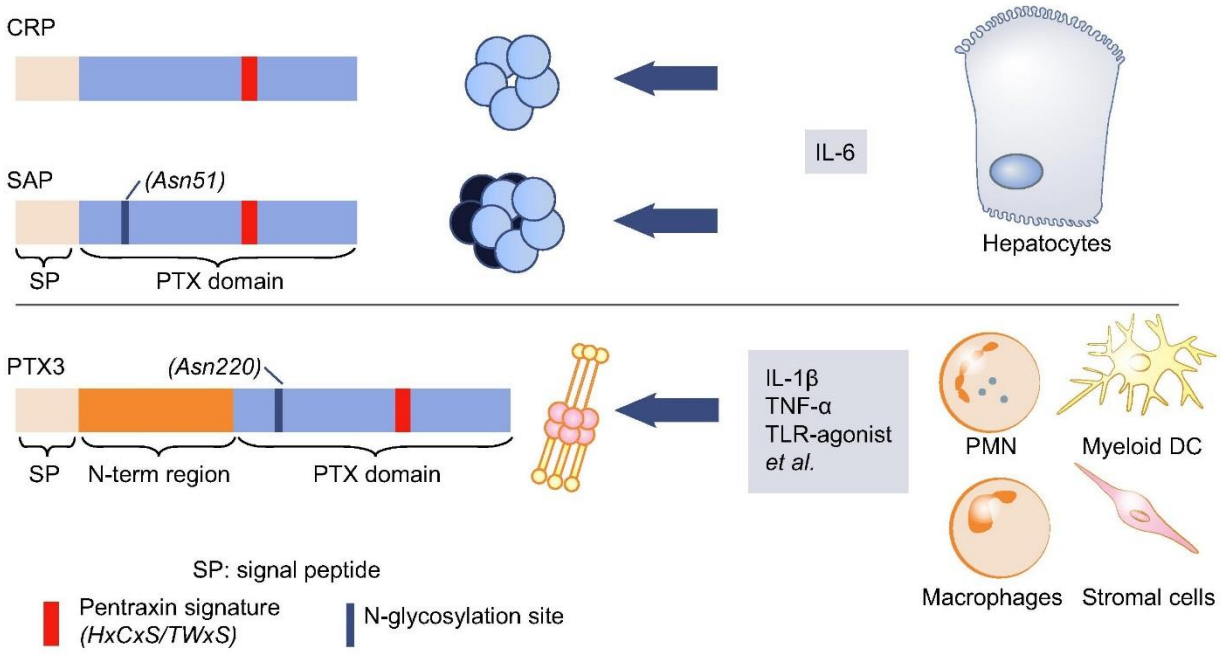


Figure 1 – Schematic representation of Pentraxin (From Bottazi et al [83])

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]

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

Agarwali et al 2009 [1]	soluble 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
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] Mairuhu AT 2005 [24]	Antiviral activity (PTX3 against Influenza Viruses and dengue virus)
Bonavita E et al 2005	PTX3 is a suppressor of complement-dependent inflammation in

[27]	cancer.
Rusnati M et al 2004 [28]	Selective recognition of fibroblast growth factor-2 by the long pentraxin PTX3 inhibits angiogenesis
Rolph MS et al 2002 [29]	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[30] Tong et al 2021[31]	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
Zlibut et al 2019[13], Ching et al 2020[33]	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	GCF and Salivary PTX3 concentrations may have	Periodontal tissue

2012[47], Pradeep et al 2011[48] Gumus et al 2014 [49]	diagnostic potential.	inflammation
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[52]	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 [55] Ctirad et al 2008[56]	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[56]	PTX3 is a reliable prognostic inflammatory disease marker.	Rheumatoid arthritis
Tong et al, 2004[57]	Predictor of all-cause mortality	Chronic Kidney Disease

Muller et al 2001[58]	PTX3 levels increase in critically ill patients. This increase directly correlates with the severity of disease and infection	Critically ill patients

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[58,59,24, 60] Thus the circulating levels of PTX3 is related to the severity of various diseases.[61]

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[62 63]. 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 [64]. 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 [59,64,65].

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.[66]

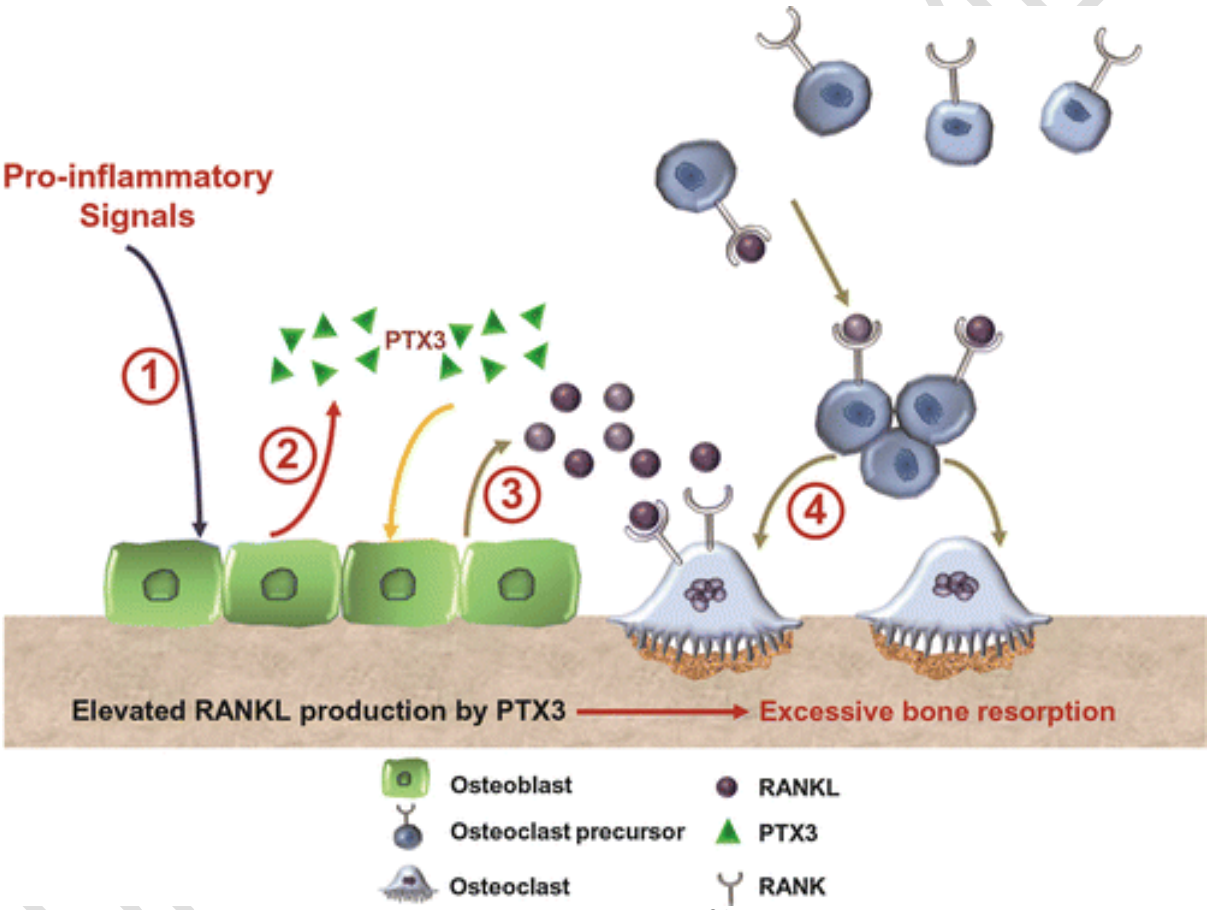


Figure 2 - Role of PTX3 in bone resorption (Choi et al [84])

Table-3: Pentraxin-3 and Periodontal inflammation:

Author/s-Year	Biological sample	Pathogenesis/ Biological effect
Leira et al 2020[67]	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[78]	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[39]	Serum	Increased PTX3 levels as compared to Chronic

		migraine without periodontal disease.
Temelli B et al 2018[71]	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[68]	Serum	PTX3 is independently associated with levels positively correlated with periodontally inflamed surface area in patients with poor prognosis.
Mohan et al 2019[69]	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 [80]	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[82]	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[70]	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[69]	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 2017[72]	GCF	At baseline, PTX3 levels in both groups of patients 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[73]	GCF	PTX-3 is associated with periodontal remodeling under the effect of orthodontic forces.
Rauten et al 2016[74]	GCF	PTX3 has a role in the inflammation and angiogenesis in wound healing in patients with post orthodontic gingivectomy.
Lakshmanan et al 2014[75]	Gingival tissue sample	PTX3 levels correlated positively with clinical parameters in periodontitis.
Gumus et al 2014[49]	Saliva and Serum	PTX3 levels correlate with periodontal tissue inflammation
Elgendy et al 2013[76]	GCF	GCF levels of PTX3 can be used as a marker of periodontal tissue healing.
Surlin et al 2012[77]	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[47]	GCF	A strong correlation between PTX3 and periodontal status was observed.

Pradeep et al 2011[48]	GCF and Serum	PTX3 levels increase during disease progression

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.

REFERENCES:

1. Agrawal A, Singh PP, Bottazzi B, Garlanda C, Mantovani A. Pattern recognition by pentraxins. Adv Exp Med Biol. 2009; 653:98-116.

2. Song T, Wang C, Guo C, Liu Q, Zheng X. Pentraxin 3 overexpression accelerated tumor metastasis and indicated poor prognosis in hepatocellular carcinoma via driving epithelial-mesenchymal transition. J Cancer. 2018;9(15):2650-2658.

3. Yang H, Zhang J, Huan Y, Xu Y, Guo R. Pentraxin-3 Levels Relate to the Wells Score and

Prognosis in Patients with Acute Pulmonary Embolism. Dis Markers. 2019;2019:2324515.

4. Parente R, Sobacchi C, Bottazzi B, Mantovani A, Grčevic D, Inforzato A. The Long Pentraxin PTX3 in Bone Homeostasis and Pathology. Front Immunol. 2019;10:2628.

5. Latini R, Maggioni AP, Peri G, et al. Prognostic significance of the long pentraxin PTX3 in acute myocardial infarction. Circulation. 2004;110(16):2349-2354.

6. Bottazzi B, Bastone A, Doni A, et al. The long pentraxin PTX3 as a link among innate immunity, inflammation, and female fertility. J Leukoc Biol. 2006;79(5):909-912.

7. Pattern Recognition Receptors and the Innate Immune Network. In: Molecular Medical Microbiology. Academic Press; 2015:449-474.

8. Inforzato A, Peri G, Doni A, et al. Structure and function of the long pentraxin PTX3 glycosidic moiety: fine-tuning of the interaction with C1q and complement activation. Biochemistry. 2006;45(38):11540-11551.

9. Ristagno G, Fumagalli F, Bottazzi B, et al. Pentraxin 3 in Cardiovascular Disease. Front Immunol. 2019;10:823.

10. Garlanda C, Bottazzi B, Magrini E, Inforzato A, Mantovani A. PTX3, a Humoral Pattern Recognition Molecule, in Innate Immunity, Tissue Repair, and Cancer. Physiol Rev. 2018;98(2):623-639.

11. Grčević D, Sironi M, Valentino S, et al. The Long Pentraxin 3 Plays a Role in Bone Turnover and Repair. Frontiers in Immunology. 2018; 9: 417.

12. Doni A, Musso T, Morone D, et al. An acidic microenvironment sets the humoral pattern

recognition molecule PTX3 in a tissue repair mode. Journal of Experimental Medicine. 2015;212(6):905-925.

13. Zlibut A, Bocsan IC, Agoston-Coldea L. Pentraxin-3 and endothelial dysfunction. Adv Clin Chem. 2019; 91:163-179.

14. Doni A, Michela M, Bottazzi B, et al. Regulation of PTX3, a key component of humoral innate immunity in human dendritic cells: stimulation by IL-10 and inhibition by IFN-gamma. J Leukoc Biol. 2006;79(4):797-802.

15. Iwasaki A, Medzhitov R. Regulation of adaptive immunity by the innate immune system. Science. 2010;327(5963):291-295.

16. Bonacina F, Baragetti A, Catapano AL, Norata GD. Long pentraxin 3: experimental and clinical relevance in cardiovascular diseases. Mediators Inflamm 2013;2013:725102.

17. Deban L, Bottazzi B, Garlanda C, de la Torre YM, Mantovani A. Pentraxins: multifunctional proteins at the interface of innate immunity and inflammation. Biofactors. 2009;35(2):138-145.

18. Bonacina F, Barbieri SS, Cutuli L, et al. Vascular pentraxin 3 controls arterial thrombosis by targeting collagen and fibrinogen induced platelets aggregation. Biochimica et Biophysica Acta (BBA) Molecular Basis of Disease. 2016;1862(6):1182-1190.

19. Rodriguez-Grande B, Swana M, Nguyen L, et al. The Acute-Phase Protein PTX3 is an Essential Mediator of Glial Scar Formation and Resolution of Brain Edema after Ischemic Injury. Journal of Cerebral Blood Flow & Metabolism. 2014;34(3):480-488.

20. Armstrong-James D, Harrison TS. Immunotherapy for fungal infections. Current Opinion in Microbiology. 2012;15(4):434-439.

21. Garlanda C, Bottazzi B, Moalli F, et al. Pentraxins and atherosclerosis: the role of PTX3. Curr Pharm Des. 2011;17(1):38-46.

22. Maugeri N, Rovere-Querini P, Slavich M, et al. Early and Transient Release of Leukocyte Pentraxin 3 during Acute Myocardial Infarction. The Journal of Immunology. 2011;187(2):970-979.

23. Reading PC, Bozza S, Gilbertson B, et al. Antiviral Activity of the Long Chain Pentraxin PTX3 against Influenza Viruses. The Journal of Immunology. 2008;180(5):3391-3398.

24. Mairuhu ATA, Peri G, Setiati TE, et al. Elevated plasma levels of the long pentraxin, pentraxin 3, in severe dengue virus infections. Journal of Medical Virology. 2005;76(4):547-552.

25. Garlanda C, Bottazzi B, Bastone A, Mantovani A. Pentraxins at the crossroads between innate immunity, inflammation, matrix deposition, and female fertility. Annu Rev Immunol. 2005; 23:337-366.

26. Camozzi M, Zacchigna S, Rusnati M, et al. Pentraxin 3 inhibits fibroblast growth factor 2-dependent activation of smooth muscle cells in vitro and neointima formation in vivo. Arterioscler Thromb Vasc Biol. 2005;25(9):1837-1842.

27. Bonavita E, Gentile S, Rubino M, et al. PTX3 is an extrinsic oncosuppressor regulating complement-dependent inflammation in cancer. Cell. 2015;160(4):700-714.

28. Rusnati M, Camozzi M, Moroni E, et al. Selective recognition of fibroblast growth factor-2 by the long pentraxin PTX3 inhibits angiogenesis. Blood. 2004;104(1):92-99.

29. Rolph MS, Zimmer S, Bottazzi B, Garlanda C, Mantovani A, Hansson GK. Production of the Long Pentraxin PTX3 in Advanced Atherosclerotic Plaques. Arteriosclerosis, Thrombosis, and Vascular Biology, 2002 May 1;22(5): e10-4.

30. Brunetta E, Folci M, Bottazzi B, et al. Macrophage expression and prognostic significance of the long pentraxin PTX3 in COVID-19. Nat Immunol. 2021;22(1):19-24.

31. Tong M, Xiong Y, Zhu C, et al. Elevated Serum Pentraxin-3 Levels is Positively Correlated to Disease Severity and Coagulopathy in COVID-19 Patients. Mediterr J Hematol Infect Dis. 2021;13(1): e2021015.

32. Xiong Z, Wang X, Jiang S, Jin M, Chen W. Association between pentraxin-3 and the risk of preeclampsia: A meta-analysis. Medicine . 2020;99(26): e20744.

33. Ching LL, Nerurkar VR, Lim E, Shohet RV, Melish ME, Bratincsak A. Elevated Levels of Pentraxin 3 Correlate with Neutrophilia and Coronary Artery Dilation During Acute Kawasaki Disease. Front Pediatr. 2020;8: 295.

34. Aygun A, Katipoglu B, Ïmamoglu M, et al. Diagnostic Value of Plasma Pentraxin-3 in Acute Appendicitis. J Invest Surg. 2019;32(2):143-148.

35. Abouhamda A. Pentraxin-3, Interleukin-6, and Acute Appendicitis: Biomarkers That Need Further Exploration. Cureus. 2020;12(8):e9991.

36. Ates U, Bahadir K, Ergun E, et al. Determination of pentraxin 3 levels in diagnosis of

appendicitis in children. Pediatr Int. 2020;62(5):624-628.

37. Gul VO, Destek S. Using pentraxin-3 for diagnosing acute appendicitis and predicting perforation: A prospective comparative methodological study. Ulus Travma Acil Cerrahi Derg. 2020;26(1):21-29.

38. Deng H, Fan X, Wang X, et al. Serum pentraxin 3 as a biomarker of hepatocellular carcinoma in chronic hepatitis B virus infection. Sci Rep. 2020;10(1):20276.

39. Leira Y, Ameijeira P, Domínguez C, et al. Severe periodontitis is linked with increased peripheral levels of sTWEAK and PTX3 in chronic migraineurs. Clin Oral Investig. 2020;24(2):597-606.

40. Zhang D, Ren W-H, Gao Y, Wang N-Y, Wu W-J. Clinical significance and prognostic value of pentraxin-3 as serologic biomarker for lung cancer. Asian Pac J Cancer Prev. 2013;14(7):4215-4221.

41. Dongel I, Gokmen AA, Gonen I, Kaya S. Pentraxin-3 and inflammatory biomarkers related to posterolateral thoracotomy in Thoracic Surgery. Pak J Med Sci Q. 2019;35(2):464-469.

42. Hu T, Qiao L, Li H, et al. Pentraxin 3 (PTX-3) Levels in Bronchoalveolar Lavage Fluid as a Lung Cancer Biomarker. Dis Markers. 2020; 2020:4652483.

43. Ozer Balin S, Sagmak Tartar A, Uğur K, et al. Pentraxin-3: A new parameter in predicting the severity of diabetic foot infection? Int Wound J. 2019;16(3):659-664.

44. Mou P, Chen Z, Jiang L, Cheng J, Wei R. PTX3: A Potential Biomarker in Thyroid Associated Ophthalmopathy. Biomed Res Int. 2018; 2018:5961974.

45. Tatli O, Kurt NBK, Karaca Y, et al. The diagnostic value of serum pentraxin 3 levels in pulmonary contusion. Am J Emerg Med. 2017;35(3):425-428.

46. Liu S, Qu X, Liu F, Wang C. Pentraxin 3 as a prognostic biomarker in patients with systemic inflammation or infection. Mediators Inflamm. 2014; 2014:421429.

47. Fujita Y, Ito H, Sekino S, Numabe Y. Correlations between pentraxin 3 or cytokine levels in gingival crevicular fluid and clinical parameters of chronic periodontitis. Odontology. 2012;100(2):215-221.

48. Pradeep AR, Kathariya R, Raghavendra NM, Sharma A. Levels of pentraxin-3 in gingival crevicular fluid and plasma in periodontal health and disease. J Periodontol. 2011;82(5):734-741.

49. Gümüş P, Nizam N, Nalbantsoy A, Özçaka Ö, Buduneli N. Saliva and serum levels of pentraxin-3 and interleukin-1β in generalized aggressive or chronic periodontitis. J Periodontol. 2014;85(3): e40-e46.

50. Tamura Y, Ono T, Kuwana M, et al. Human pentraxin 3 (PTX3) as a novel biomarker for the diagnosis of pulmonary arterial hypertension. PLoS One. 2012;7(9): e45834.

51. Nebuloni M, Pasqualini F, Zerbi P, et al. PTX3 expression in the heart tissues of patients with myocardial infarction and infectious myocarditis. Cardiovasc Pathol. 2011;20(1): e27-e35.

52. Iwata Y, Yoshizaki A, Ogawa F, et al. Increased serum pentraxin 3 in patients with systemic sclerosis. J Rheumatol. 2009;36(5):976-983.

53. Sprong T, Peri G, Neeleman C, et al. Pentraxin 3 and C-reactive protein in severe meningococcal disease. Shock. 2009;31(1):28-32.

54. Savchenko A, Imamura M, Ohashi R, et al. Expression of pentraxin 3 (PTX3) in human atherosclerotic lesions. J Pathol. 2008;215(1):48-55.

55. Bevelacqua V, Libra M, Mazzarino MC, et al. Long pentraxin 3: a marker of inflammation in untreated psoriatic patients. Int J Mol Med. 2006;18(3):415-423.

56. Ctirad A, Lenka B, David P, et al. Goeckerman's therapy for psoriasis with special reference to serum pentraxin 3 level. Int J Dermatol. 2008;47(10):1011-1014.

57. Tong M, Carrero JJ, Qureshi AR, et al. Plasma pentraxin 3 in patients with chronic kidney disease: associations with renal function, protein-energy wasting, cardiovascular disease, and mortality. Clin J Am Soc Nephrol. 2007;2(5):889-897.

58. Muller B, Peri G, Doni A, et al. Circulating levels of the long pentraxin PTX3 correlate with severity of infection in critically ill patients. Critical Care Medicine. 2001;29(7):1404-1407.

59. Fazzini F, Peri G, Doni A, et al. PTX3 in small-vessel vasculitides: An independent indicator of disease activity produced at sites of inflammation. Arthritis & Rheumatism. 2001;44(12):2841-2850.

60. Azzurri A, Sow OY, Amedei A, et al. IFN-γ-inducible protein 10 and pentraxin 3 plasma levels are tools for monitoring inflammation and disease activity in Mycobacterium tuberculosis infection. Microbes and Infection. 2005;7(1):1-8.

61. Narciso-Schiavon JL, Pereira JG, Silva TE, et al. Circulating levels of pentraxin-3 (PTX3)

in patients with liver cirrhosis. Ann Hepatol. 2017;16(5):780-787.

62. Martinez de la Torre Y, Fabbri M, Jaillon S, et al. Evolution of the pentraxin family: the new entry PTX4. J Immunol. 2010;184(9):5055-5064.

63. Steel DM, Whitehead AS. The major acute phase reactants: C-reactive protein, serum amyloid P component and serum amyloid A protein. Immunology Today. 1994;15(2):81-88.

64. Okutani D. The Role of Long Pentraxin 3, A New Inflammatory Mediator in Inflammatory Responses. Japanese Journal of Clinical Immunology. 2006;29(3):107-113.

65. Johnson NW, Griffiths GS, Wilton JMA, et al. Detection of high-risk groups and individuals for periodontal diseases. Evidence for the existence of high-risk groups and individuals and approaches to their detection. Journal of Clinical Periodontology. 1988;15(5):276-282.

66. Hajishengallis G, Maekawa T, Abe T, Hajishengallis E, Lambris JD. Complement Involvement in Periodontitis: Molecular Mechanisms and Rational Therapeutic Approaches. Adv Exp Med Biol. 2015; 865:57-74.

67. Leira Y, Iglesias-Rey R, Gómez-Lado N, et al. Periodontitis and vascular inflammatory biomarkers: an experimental in vivo study in rats. Odontology. 2020;108(2):202-212.

68. Leira Y, Rodríguez-Yáñez M, Arias S, et al. Periodontitis is associated with systemic inflammation and vascular endothelial dysfunction in patients with lacunar infarct. J Periodontol. 2019;90(5):465-474.

69. Mohan R, Varghese J, Bhat V, Chianeh YR. The effect of nonsurgical periodontal therapy on pentraxin 3 levels in smokers and nonsmokers with chronic periodontitis. Gen Dent. 2019;67(2):e1-e6.

70. Boyapati R, Chinthalapani S, Ramisetti A, Salavadhi SS, Ramachandran R. Association of pentraxin and high-sensitive C-reactive protein as inflammatory biomarkers in patients with chronic periodontitis and peripheral arterial disease. J Indian Soc Periodontol. 2018;22(2):112-115.

71. Temelli B, Yetkin Ay Z, Savaş HB, et al. Circulation levels of acute phase proteins pentraxin 3 and serum amyloid A in atherosclerosis have correlations with periodontal inflamed surface area. J Appl Oral Sci. 2018;26:e20170322.

72. Vijayalakshmi R et al. To estimate the level of Pentraxin–3 in gingival crevicular fluid in patients with Chronic Periodontitis, well controlled diabetes and in uncontrolled Diabetes Mellitus patients. IJAR - Indian Journal of Applied Research. Jul 2017;Volume 7: Issue 7.

73. Thukral R, Mangat S, Ganguly A, Agarkar SS, Bali H, Grover S. Pentraxin-3 Levels in Gingival Crevicular Fluid during Canine Retraction with Nickel-Titanium Coil Spring and Active Tieback. J Contemp Dent Pract. 2017;18(8):710-713.

74. Rauten AM, Silosi I, Stratul SI, et al. Expression of Pentraxin 3 and Thrombospondin 1 in Gingival Crevicular Fluid during Wound Healing after Gingivectomy in Post orthodontic Patients. J Immunol Res. 2016; 2016:4072543.

75. Lakshmanan R, Jayakumar ND, Sankari M, Padmalatha O, Varghese S. Estimation of pentraxin-3 levels in the gingival tissues of chronic and aggressive periodontitis

participants: an in vivo study. J Periodontol. 2014;85(2):290-297.

76. Elgendy EA, Ali SA-M, Zineldeen DH. Effect of local application of tea tree (Melaleuca alternifolia) oil gel on long pentraxin level used as an adjunctive treatment of chronic periodontitis: A randomized controlled clinical study. J Indian Soc Periodontol. 2013;17(4):444-448.

77. Surlin P, Rauten AM, Silosi I, Foia L. Pentraxin-3 levels in gingival crevicular fluid during orthodontic tooth movement in young and adult patients. Angle Orthod. 2012;82(5):833-838.

78. Keles GC, Balli U, Cetinkaya BO, et al. Biochemical analysis of pentraxin 3 and fibrinogen levels in experimental periodontitis model. Mediators Inflamm. 2012; 2012:809801.

79. Fouad AF, Khan AA, Silva RM, Kang MK. Genetic and Epigenetic Characterization of Pulpal and Periapical Inflammation. Front Physiol. 2020;11:21.

80. Wettero J, Jonsson F, von Lohneysen S, Kristenson M, Garvin P, Sjowall C. Pentraxin-3 detected in human saliva shows limited correlation with biomarkers associated with systemic inflammation. APMIS. 2021; 129: 304–313.

81. Gürsoy UK, Könönen E, eds. Use of Saliva in Diagnosis of Periodontitis: Cumulative Use of Bacterial and Host-Derived Biomarkers. Frontiers Media SA; 2017.

82. Gheorghe, D.N.; Popescu, D.M.; Salan, A.; Boldeanu, M.V.; Ionele, C.M.; Pitru, A.; Turcu Stiolica, A.; Camen, A.; Florescu, C.; Rogoveanu, I.; et al. Non-Surgical Periodontal Therapy Could Improve the Periodontal Inflammatory Status in Patients with Periodontitis

and Chronic Hepatitis C. J. Clin. Med. 2021, 10, 5275.

83. Bottazi B et al. The pentraxins PTX3 and SAP in innate immunity, regulation of inflammation and tissue remodeling. Journal of Hepatology 2016 vol. 64: 1416–1427.

84. Choi B., Chang EJ. (2017) Pentraxin 3 (PTX3) as a Biomarker of Bone Disease. In: Patel V., Preedy V. (eds) Biomarkers in Bone Disease. Biomarkers in Disease: Methods, Discoveries and Applications. Springer, Dordrecht.