Review Article

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Trefoil Factor 3: A Novel Biomarker in Periodontitis

K. Sai Priyanka[1] Veerendranath Reddy. P[2*] Rajashree. D[3]

[1]PG Student, Department of Periodontology and Oral Implantology, Panineeya Mahavidyalaya Institute of Dental Sciences, Hyderabad, India.
[2]Professor, Department of Periodontology and Oral Implantology, Panineeya Mahavidyalaya Institute of Dental Sciences, Hyderabad, India.
[3]Associate Professor, Department of Periodontology and Oral Implantology, Panineeya Mahavidyalaya Institute of Dental Sciences, Hyderabad, India.

ABSTRACT

Background: The first member of trefoil factor family was discovered about thirty years ago comprises a group of small (12 – 22 kD) peptides which are secreted molecules mostly derived from mucin-producing epithelial cells of the gastrointestinal tract and other tissues, such as salivary glands, parotid ducts, and oral mucosa. The repair of epithelial surfaces is influenced by Trefoil factor 1, 2 & 3. Extensive research is being conducted on their structural and functional properties. The signaling pathways which are involved in cell survival, cell proliferation, and cell migration of oral keratinocytes is modified by the Trefoil factor 3 (TFF3). TFF3 plays an important role in the proper functioning of the epithelium. The data outlined by many studies demonstrated that TFF 3 influence key functional characteristics by regulating cell survival, apoptosis, cell migration and invasion. The conjunction with the periodontal tissues and mammalian trefoil factors have been summarized.

Keywords: Trefoil factor 3, Periodontal disease, Oral mucosa.

INTRODUCTION

Periodontal disease is a chronic microbial infection that triggers inflammation-mediated loss of supporting structures of the teeth. Advances in diagnostic research are moving toward methods where by the periodontal risk can be identified and quantified by objective measures using biomarkers. Trefoil factors (TFFs) are one such secreted molecules that are involved in cytoprotection preventing tissue damage in the immune response. TFFs have been detected in saliva in oral tissues but their clinical significance along with its relation to periodontal therapy in gingivitis and periodontitis should be investigated. Clinical and biochemical analysis of TTF3 reveal its influence on periodontal disease activity and it might serve as an easy to detect and promising biomarker of periodontal disease progression.

Trefoil factors are derived from the epithelial cells of the gastrointestinal tract[1] that produces mucin. They are also secreted from the other tissues such as Oral mucosa[2], small and large intestine, salivary glands[3] and the parotid ducts. Trefoil factor family consists of mainly three peptides Trefoil factor 1 (TFF), TFF 2 and TFF 3.[4] TFF 1 is expressed from gastric mucosal lining. TFF 2 is expressed from Bruner's gland of the duodenum and TFF3 is expressed from the intestinal goblet cells.[5]

The three human TFF genes are clustered on chromosome 21 q22.3.[6] The chromosome is characterized by a trefoil motif or P-Domain. A disulphide bond holds the three leaved structure which resembles a trefoil or clover leaf. A trefoil structure is formed by the composition of 42-43 amino acids, which contain 6-cystein residues, which form di-sulphide bonds that in turn result in a proper trefoil structure. The epithelial surface integrity is maintained and protected by the TFF. TFFs mainly act as mitogens which facilitate the migration of the cells into the lesion, which forms a protective barrier and which is useful for epithelial restitution mainly the mucosal surfaces.[7]

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*Correspondence Dr. Veerendranath Reddy. P.
Department of Periodontology and Oral Implantology, Panineeya Mahavidyalaya Institute of Dental Sciences, Hyderabad, India.
Email: veerureddy@yahoo.com

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The domain of the TFF is a unique cystein rich shuffled model found in certain mosaic patterns and in a cluster of secretory peptides. The TFFs bind to the larger mucins and catalyze the formation of highly viscous stable gel complexes that are resistant to chemical degradation[8] and mechanical forces. TFF3 is the only trefoil peptide that is found in whole saliva. The serous cells in the submandibular gland and the MUC7 mucin secrete the TFF3. TFF3 is also secreted by the mucous cells in the sublingual gland. In the recent studies it was found that TFF3 is also expressed by the epithelium of the parotid duct.[2]

DISCUSSION

EXRESSSION OF TFF 3:

The trefoil factor peptides are secreted along with the mucins for example in the uterus , respiratory tract and the gastrointestinal tract.[5] The trefoil factor expression has also been seen in the pancreas of man and rodents, in human salivary glands, female reproductive organs, prostate glands, lacrimal apparatus and conjunctiva, urino-genital system.[1] Wiede et al studies showed that TFF3 m RNA was accumulated in the human respiratory tract and uterus.[9] Apart from the mucosal epithelia the central nervous system also synthesizes the TFF peptides[5] .The TFF3 m RNA was detected in the different areas of the developing and adult murine and human brain and spinal cord.[10] According to Hinz et al the TFF3 expression was to be restricted to the three regions in the brain first being the cerebellum, second the hippocampus and third the temporal cortex.[10] Among the above three the cerebellum was showing the strongest signal. The synthesis of TFF3 is verified for the neurons in the hypothalamus nuclei, pituitary and the cerebrospinal fluid in the humans. In the recent study Bernstein et al revealed that expression of TFF3 is mainly enriched in mid brain and brain stem nuclei.[11] The TFF3 expression was initially restricted mainly to the neurons and not glial cells. TFF 3 was described as typical neuro peptide which was synthesized by the magno cellular neurons of rat and human hypothalamus.[12] The TFF3 expression was seen in human oligo dendroglia neurons. The mutations of TFF3 was linked to neuro degenerative and neuro psychiatric disorder like schizophrenia, alzheimers and the Parkinson's disease.

TFF3 peptide was very useful in the corneal wound healing.[13] It acted as a therapeutic agent for the patients who had dry eye syndrome. The expression of TFF3 was monitered in the ocular and the central nervous system tissues. In the recent studies only the TFF3 is expressed in the healthy human's retina.[14]

EXPRESSION OF TFF3 IN DISEASE CONDITIONS:

The TFF peptides are unusually seen in fifty percent of the gastric tumors[15] and the TFF genes are inhibited in many cancers such as prostate, pancreatic, liver, gall baldder, intestinal, gastric, breast and oral[16]. In all these conditions the TFF peptides are used as the negative prognostic markers, whereas the salivary TFF 1 and 3 were decreased in patients with chronic periodontitis. Salivary TFF3 expression is negatively related with the embossed periodontopathic pathogens.[17]

FUNCTIONS OF TFF 3:

The trefoil factor peptides have various functions such as accumulation, repair of wounds, antiapoptosis, and interaction of mucin, renewal and regeneration. Epithelial cell restoration is the main fundamental physiological function of the TTFs. It is a way of helping the epithelial cells to migrate to the superficial wounds to reseal them after injury. This process prevents the invasion of the bacterial or foreign material and the loss of electrolytes from plasma. It helps in the mucosal repair that happens before the regeneration to renew the discontinuous mucosal lining.[18]

The monomeric form of TFF3 couldn't produce cell migration whereas the dimerization of TFF3 could initiate the cell migration and further restitution. In an invivo study, TFF 3 showed useful effects on methotrexate-induced enteritis by improving the epithelial restoration on the gastrointestinal epithelial cell layers which were damaged by the methotrexate.[19] Anti-apoptotic is another important property for the epithelial cell restoration. In this process, the anchorage of the epithelial cell is detached and the surface area of the epithelium gets denuded. The TFF3 had anti anoikisis effects on the epithelial cells of the intestine through the

activation of NF-kB signal. Anoiksis means disruption of cell substratum adhesion and loss of anchorage.[18]

Neovascularization is induced by the TFF3 in human gastric carcinoma and also hypoxia-inducing factor 1 angiogenesis.[20] The vascular endothelial growth factor was compared to the pro angiogenic property of all the trefoil factors. TFF3 downregulates the NFkB signal transduction by upregulating the transcription factor TWIST.[21] Hence acting as an anti-inflammatory agent. According to Tebbutt et al[22] TFFs have been elevated when pro inflammatory IL 6 and IL 11 get activated through the SHP2/Erk or the JAK/ STAT signal transduction pathway but according to Granes's suggested that IL-6, IL-1b, and tumor necrosis factor-a decrease the transcription of TFF1 and TFF3 via C/EBPb signal transduction pathway[23]. Pro-inflammatory cytokines and transcription factors, such as NFkB are regulated by the TFFs according to various studies.

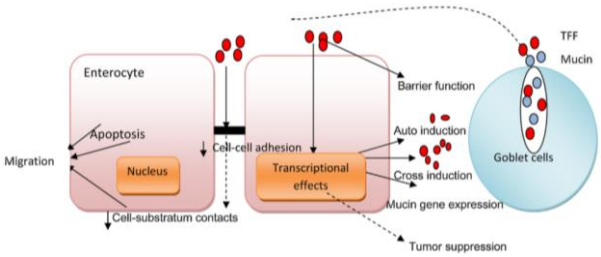

Fig 1: Functions of trefoil factors.[18]

ROLE OF TREFOIL FACTOR 3 IN PERIODONTAL TISSUES:

It is well known that TFF3 peptides are proven to be involved in cell proliferation, and migration of oral keratinocytes. The TFF peptides expressed in the saliva and oral epithelial cells serve as an essential factor in fighting against the oral tissue damage. According to Chaiyarit et al where they have investigated the expression of Trefoil factor 3 in the salivary secretions and in the periodontal tissues of chronic periodontitis (CP) patients. The immunohistochemical study and enzyme linked immunosorbent assay were used to detect the expression of TFFs in saliva and gingival tissues, whereas the real time polymerase chain reaction was used to quantify the pathogenic bacteria where they have concluded that there is a reduced expression of TFF3 in the examined patients, also there is a reduced salivary TFF3 levels during the elevation of pathogenic bacteria like P.gingivalis, T.forsythia in the periodontal tissues, thereby hindering the TFF3 gene expression finally they have advocated that TFF3 may be involved in the pathogenesis of the periodontal diseases.[17]

The TFF peptides provide an outstanding resistance to proteolysis and hydrolysis.[24] The structure of TFF's allow to produce into dimers which play a crucial role of mucin cross linking thereby ultimately producing a protective layers. Thus, additional investigations on immune responses of gingival epithelial cells to these pathogens, signalling transduction that regulates TFF expression and mechanisms at the molecular level in periodontal diseases would be of importance.

TFF3 are also expressed in oral keratinocytes which aids in healing of oral wounds and aid in regulation of cell survival and induces the growth and differentiation, proliferation and migration of oral keratinocytes. The recombinant human TFF3 will express their useful effects on oral epithelial carcinogenic cells.[25] The TFF3 gene expression is inhibited by the infections caused by the periodontopathic pathogens. In the case of patients with chronic periodontitis the TFF3 expression is independent[17] The TFF3 expressions are found to be low in oral squamous cell carcinoma conditions when compared to the normal oral mucosal cells. The expression of TFF was compared using the tissue sample of healthy and oral squamous cell carcinoma (OSCC) patients by immunohistochemistry and ELISA for salivary samples. TFF was negatively co related with OSCC at the end of the result.[16]

Trefoil factor family 3 has been described in vitro to promote several beneficial wound-healing features, such as increased migration, increased angiogenesis, and inhibition of anoikis.[26] A recent clinical trial showed that by use of an oral spray containing TFF3, oral mucositis was significantly reduced in cancer patients.[27] This shows that TFF3 may be of importance for maintaining the homeostasis of the oral mucosa.

CONCLUSION

Trefoil factors (TFF) have been entering an era in the field of dentistry. Its therapeutic and novel use has rejuvenated along with its diagnostic aid for chronic inflammatory diseases. Its importance in the immune response and the physiological interactions with the specific binding proteins is shown. TFF3 can be potentially used as a biomarker to assess periodontal destruction and disease progression. In addition molecular level investigations are needed the mechanisms regulating TFF3 expression in oral tissues and its role in periodontal diseases.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Madsen J, Nielsen O, Tornoe I, Thim L, Holmskov U.(2007) Tissue localization of human trefoil factors 1, 2, and 3. J Histochem Cytochem 2007;55:505-513.

2. Kutta H, May J, Jaehne M, Munnscher A, Paulsen FP.(2006) Antimicrobial defence mechanisms of the human parotid duct. J Anat 2006;208:609-619.

3. Jagla W, Wiede A, Hinz M. (1999) Secretion of TFF peptides by human salivary glands. Cell Tissue Res 1999;298:161-166.

4. Kjellev S. (2009) The trefoil factor family-small peptides with multiple functionalities. Cell Mol Life Sci. 2009;66:1350-1369.

5. Hoffmann W, Jagla W, Wiede A. (2001) Molecular medicine of TFF- peptides: from gut to brain. Histol Histopathol. 2001;16: 319–334.

6. Tomasetto C, Rockel N, Mattei MG, Fujita R, Rio MC (1992). The gene encoding the human spasmolytic protein (SML1/hSP) is in 21q22.3, physically linked to the homologous breast cancer marker gene BCEI/pS2. Genomics 1992; 13: 1328–30.

7. Hoffmann W. (2005) Trefoil factors TFF (trefoil factor family) peptide triggered signals promoting mucosal restitution. Cell Mol Life Sci 2005; 62: 2932–8.

8. Thim L, Madsen F, Poulsen SS. (2002) Effect of trefoil factors on the viscoelastic properties of mucus gels. Eur J Clin Invest 2002; 32: 519–527.

9. Wiede A, Hinz M, Canzler E, Franke K, Quednow C, Hoffmann W.(2001) Synthesis and localization of the mucin-associated TFF-peptides in the human uterus. Cell Tissue Res 2001; 303: 109–15.

10. Hinz M, Schwegler H, Chwieralski CE, Laube G, Linke R, Pohle W, Hoffmann W.(2004) Trefoil factor family (TFF) expression in the mouse brain and pituitary: changes in the developing cerebellum. Peptides 2004; 25: 827–32.

11. Bernstein H, Dobrowolny H, Trubner K, Steiner J, Bogerts B, Hoffmann W. (2015) Differential regional and cellular distribution of TFF3 peptide in the human brain. Amino Acids 2015; 47: 1053–63.

12. Probst JC, Skutella T, Müller-Schmid A, Jirikowski GF, Hoffmann W. (1995) Molecular and cellular analysis of rP1.B in the rat hypothalamus: in situ hybridization and immunohistochemistry of a new P-domain neuropeptide. Brain Res Mol Brain Res 1995; 33: 269–76.

13. Paulsen FP, Woon C, Varoga D, Jansen A, Garreis F, Jager K, Amm M, Podolsky DK, Steven P, Barker NP, Sel S.(2008) Intestinal trefoil factor/TFF3 promotes re-epithelialization of corneal wounds. J Biol Chem 2008; 283: 13418–27.

14. Philippeit C, Busch M, Dunker N. (2014) Epigenetic control of trefoil factor family (TFF) peptide expression in human retinoblastoma cell lines. Cell Physiol Biochem 2014; 34: 1001–14.

15. Park WS, Oh RR, Park JY. (2000) Somatic mutations of the trefoil factor family 1 gene in gastric cancer. Gastroenterology. 2000;119:691–698.

16. Chaiyarit P, Utrawichian A, Leelayuwat C. (2012) Investigation of trefoil factor

expression in saliva and oral mucosal tissues of patients with oral squamous cell carcinoma. Clin Oral Investig. 2012;16:1549–1556.

17. Chaiyarit P, Chayasadom A, Wara-Aswapati N, Hormdee D, Sittisomwong S, Nakaresisoon S.(2012) Trefoil factors in saliva and gingival tissues of patients with chronic periodontitis. J Periodontol. 2012;83:9, Pages 1129-1138.

18. Taupin D, Podolsky DK. (2003) Trefoil factors: initiators of mucosal healing. Nat Rev Mol Cell Biol. 2003;4:721–732.

19. Xian CJ, Howarth GS, Mardell CE. (1999) Temporal changes in TFF3 expression and jejunal morphology during methotrexate-induced damage and repair. Am J Physiol. 1999;277:G785–G795.

20. Furuta GT, Turner JR, Taylor CT. (2001) Hypoxia-inducible factor 1-dependent induction of intestinal trefoil factor protects barrier function during hypoxia. J Exp Med. 2001;193:1027–1034.

21. Zhu YQ, Tan XD. (2005) TFF3 modulates NF-kB and a novel negative regulatory molecule of NF-kB in intestinal epithelial cells via a mechanism distinct from TNF-a. Am J Physiol Cell Physiol. 2005;289:C1085–C1093.

22. Tebbutt NC, Giraud AS, Inglese M. (2002) Reciprocal regulation of gastrointestinal homeostasis by SHP2 and STAT-mediated trefoil gene activation in gp130 mutant mice. Nat Med. 2002;8:1089–1097.

23. Graness A, Chwieralski CE, Reinhold D, Thim L, Hoffmann W. (2002) Protein kinase C and ERK activation are required for TFF-peptide-stimulated bronchial epithelial cell migration and tumor necrosis factor-alpha-induced interleukin-6 (IL-6) and IL-8 secretion. J Biol Chem. 2002;277:18440–18446.

24. Thim L(1994). Trefoil peptides: a new family of gastrointestinal molecules. Digestion 1994;55:35360.

25. Storesund T, Schreurs O, Messelt EB, Kolltveit KM, Schenck K. (2009) Trefoil factor family 3 expression in the oral cavity. Eur J Oral Sci. 2009;117:636–643.

26. Dignass A, Lynch-Devaney K, Kindon H, Thim L, Podolsky DK.(2008) Trefoil peptides promote epithelial migration through a transforming growth factor beta-independent pathway. J Clin Invest 1994; 94: 376–383. Storesund T, Hayashi K, Kolltveit KM, Bryne M, Schenck K. Salivary trefoil factor 3 enhances migration of oral keratinocytes. Eur J Oral Sci 2008; 116: 135–140.

27. Barker NP (2008). ASCO Meeting Abstracts, J Clin Oncol 26; 2008: 9514.