Vol 1,2,3,4, Dec, 2018 P 25- 35
DOI, 10.15562/tcp.70

CANCER PRESS
www.imaqpress.com

Review Article

Trefoil Factor Family in Pre-neoplastic Lesions and Gastric Cancer

Behrooznia Z[1], Ghaderi p[1], Jafarzadeh N[2], Izanloo A[2], Sima H.R[3], Mansoori Majoofardi S[1], Rahimi Kakhki R[1], Nabi-pour M[1], Farzanehfar M.R[4], Goshayeshi L[4], Bary A.R[5], Sima A.R[6], Sharifian Razavi M[4], Saber afsharian S[7], Lary S[1], Ghaffarzadehgan K[2*]

Author Information

1. Gastric Cancer Research Group, Mashhad, Iran./ Medical Student, Student Research Committee, Faculty of Medicine, Mashhad Islamic Azad University, Mashhad, Iran
2. Razavi Cancer Research Center, Razavi Hospital, Imam Reza International University, Mashhad, Iran
3. Ivision of Gastroenterology, Department of Medicine, Mount Sinai Beth Israel, St. Luke's and West Hospital Centers, Icahn School of Medicine at Mount Sinai.
4. Department of Internal Medicine, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran.
5. Department of Hematology and Oncology, Ghaem Hospital, Mashhad University of Medical Sciences, Mash-had, Iran.
6. Digestive Diseases Research Institute,Tehran University of Medical Sciences,Tehran,Iran
7. Islamic Azad University, Faculty of Medicine, Mashhad branch, Mashhad, Iran

Submitted: 16.12.2018
Accepted: 29.12.2018
Published : 30.12.2018

Abstract

Gastric cancer is the fourth most common cancer and the second leading cause of cancer death worldwide. Although the global incidence of gastric cancer has been decreased dramatically in recent decades, north and northwest of Iran have the highest incidence rate of gastric cancer. Whilst the surgical procedures for gastric cancer have been improved, there is no cure for that. The intestinal type of GC results from pre-neoplastic conditions including atrophic gastritis, intestinal metaplasia and dysplasia. Trefoil Factors Family proteins (TFFs) are small and stable molecules secreted by the mammalian gastrointestinal tract. TFFs constitute a family of three peptides (TFF1, TFF2and TFF3) that are widely expressed in a tissue specific manner in the gastrointestinal tract. Variable TFFs expression in gastric cancer and pre-neoplastic lesions has been found. TFF1 has a tumor suppressor activity and inhibits tumorogenesis in gastric cancer. Its expression decreases in gastritis, gastric atrophy, dysplasia, intestinal metaplasia and gastric cancer.TFF2 has a protective effect on gastrointestinal epithelium. As a prognostic factor, TFF2 expression decreases in gastric ulcer, chronic atrophic gastritis and gastric cancer TFF3 is considered as an oncogenic factor in gastric

tissues. Whilst the normal gastric tissues don't express TFF3, it increases in intestinal metaplasia. Therefore, more studies are necessary to clarify the role of TFFs in GC and pre-neoplastic conditions. This review has focused on elucidating the important role of TFFs in gastric cancer and pre-neoplastic lesions.

Key words: *TFF, Gastric cancer, Intestinal metaplasia, Pre-neoplastic lesion*

Introduction

Gastric Cancer (GC) remains the major health problem being fourth common cancer in the world and the second cause related to cancers. Almost one million new cases of GC are reported annually worldwide (1). Although there is declining trend of gastric cancer in the worldwide, new cases of GC are increasing in some Asian countries (2). In Iran, gastric cancer is the most common cause of mortality related to cancers in both genders(3).

The most prevalent of gastric cancer is Adenocarcinoma. According to Lauren's histological classification, it is subdivided into diffuse and intestinal pathologic subtypes(4). The intestinal type of GC results from multistep inflammatory process. H-Pylori infection has been considered as an initiatory lesion. It can also progress to pre-neoplastic conditions including multifocal chronic atrophic gastritis, intestinal metaplasia and dysplasia (5). These pre-neoplastic lesions are frequent and increase the risk of GC (6). Although diagnostic and therapeutic approaches of GC have been improved, the mortality of GC is still high (7). Efficacious screening and early stage treatment can reduce mortality of gastric cancer (8). Until now there is no standard biomarker for early diagnosis and no consensus on screening programs(9). Thus, the valuable diagnostic biomarker seems to be helpful. Some classical biomarkers in early diagnosis of gastric cancer include CEA and CA19-9 that low specificity and sensitivity are their limitations. MicroRNAs (miR/miRNA) have been introduced as novel biomarkers in early diagnosis of GC. Several classical prognostic

References

4. Ghaffarzadehgan K, Jafarzadeh M, Raziee HR, Sima HR, Esmaili-Shandiz E, Hosseinnezhad H, et al. Expression of cell adhesion molecule CD44 in gastric adenocarcinoma and its prognostic importance. 2008;14(41):6376.
5. Gonzalez CA, Pardo ML, Liso JM, Alonso P, Bonet C, Garcia RM, et al. Gastric cancer occurrence in preneoplastic lesions: a long-term follow-up in a high-risk area in Spain. International journal of cancer. 2010;127(11):2654-60.
6. Dinis-Ribeiro M, Areia M, de Vries AC, Marcos-Pinto R, Monteiro-Soares M, O'Connor A, et al. Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED). Endoscopy. 2012;44(1):74-94.

markers including growth factors, cytokines, cell cycle regulators and apoptosis-associated factors have been studied, but extensive clinical trials is necessary prior to clinical application(10).

Trefoil Factor Family proteins consist of three subtypes (TFF1, TFF2 and TFF3). They are thermo stable and protease-resistant proteins (1) being expressed and secreted in the mucous cells of the mammalian gastrointestinal tract (11). They are clustered in 50-kb on human chromosome 21q22.3 region characterized by the presence of at least one 40-amino acids protein domain with three conserved disulfide bonds (12). The integrity of the gastrointestinal mucosa is maintained by numbers of secreted factors including Trefoil Factor Family (12). TFF1 and TFF2 are predominantly secreted in gastric mucosa, while TFF3 is expressed in goblet cell of the human intestine.TFF1 plays important roles in protection and repairing of mucosal barrier(13-15). Protection is done through the interaction of TFF1 and cysteine-rich domain of mucin protein to stabilize gastric epithelium gel layers (16-18) . Gastric hormone, gastrin, is positive regulator of TFF1. Promoter of TFF1 has gastrin responsiveness element which can be activated by this hormone (19). It has been suggested that loss of TFF1 leads to development of neoplastic lesions and also gastric adenocarcinoma (7, 20, 21) . TFF2 is mainly expressed in stomach, duodenum and pancreas (15, 22). High levels of TFF2 would observe 30 minutes after ulceration and last for 10 days (23).TFF2 up-regulates in chronic inflammation and has a protective effect on mucus and intestinal ulcers (24). On the other hand, TFF3 mainly expresses in goblet cells of small and large intestines.TFF3 is positive in goblet cells of intestinal metaplasia, but the normal gastric mucosa is negative for TFF3 . This TFF protein subtype is necessary for promoting normal cells migration and preserving gastrointestinal (GI) mucosal integrity (7). Many studies believe that TFF3 hasa correlation between inflammation and occurrence of GI tumors (7, 25, 26). Moreover, some studies implied overexpression of TFF3 has

References

7. Xiao P, Ling H, Lan G, Liu J, Hu H, Yang R. Trefoil factors: Gastrointestinal-specific proteins associated with gastric cancer. Clinica chimica acta; international journal of clinical chemistry. 2015;450:127-34.
8. Kaise M, Miwa J, Tashiro J, Ohmoto Y, Morimoto S, Kato M, et al. The combination of serum trefoil factor 3 and pepsinogen testing is a valid non-endoscopic biomarker for predicting the presence of gastric cancer: a new marker for gastric cancer risk. J Gastroenterol. 2011;46(6):736-45.
9. Boroumand-Noughabi S, Sima HR, Ghaffarzadehgan K, Jafarzadeh M, Raziee HR, Hosseinnezhad H, et al. Soluble Fas might serve as a diagnostic tool for gastric adenocarcinoma. 2010;10(1):275.
10. Jin Z, Jiang W, Wang L. Biomarkers for gastric cancer: Progression in early diagnosis and prognosis (Review). Oncology letters. 2015;9(4):1502-8.

has just a significant correlation with patient's age and has no substantial association with other factors such as gender in general population (12).

TFFs have been known as acute phase reactant. They seem to have an important role in repairing of gastrointestinal tract (27). While TFF1 and TFF2 are gastric tumor suppressor genes, TFF3 can promote gastric cancer (7).Different studies have reported variable changes of TFFs expression in gastric cancer and pre-neoplastic conditions(28-30). This review aims to overview the precise role of TFFs in gastric cancer and pre-neoplastic lesions..

TFFs and H.pylori infection:

There is a significant correlation between H. Pylori infection and TFFs peptides.Soutto M. demonstrated that TFF1 has an important role in suppressing helicobacter pylori inflammation in gastric carcinogenesis. Thus, loss of TFF1 expression has a significant function in H.pylori-mediated gastric cancer (31). Another study in 2015 indicated that TFF1 can activate H. *pylori*-mediated oncogenic activation of β-catenin and induces carcinogenesis (21).

It has been proposed that H.pylori infection would decrease the antral expression of TFF2, affected by promoter hypermethylation, which can lead to pre-neoplastic events progression (32, 33). However, Xai et al. reported that H. pylori infection induces expression of TFF2 in gastric epithelium (34).Literatures indicated that there was no correlation between TFF3 expression and influence of H.pylori infection or inflammation in non-malignant gastric tissues [34]. In the evaluation of long time influence of H.pylori infection, it was found that this infection could markedly elevate TFF1，TFF2 and TFF3 serum levels. After treating and eradicating of H.pylori, TFF1 and TFF2 levels decreased but TFF3 serum level was not significantly affected by H.pylori eradication. Hence, high serum level of TFF3 can be proposed as a stable biomarker for early diagnosis of gastric cancer because , serum level of TFF3 remains high even in eradication therapy of H.pyloriinfection (

References

11.Jin EH, Lee SI, Kim J, Seo EY, Lee SY, Hur GM, et al. Association between Promoter Polymorphisms of TFF1, TFF2, and TFF3 and the Risk of Gastric and Diffuse Gastric Cancers in a Korean Population. Journal of Korean medical science. 2015;30(8):1035-41.

12. Dhar DK, Wang TC, Tabara H, Tonomoto Y, Maruyama R, Tachibana M, et al. Expression of trefoil factor family members correlates with patient prognosis and neoangiogenesis. Clin Cancer Res. 2005;11(18):6472-8.

13. Taupin D, Podolsky DK. Trefoil factors: initiators of mucosal healing. Nature reviews Molecular cell biology. 2003;4 (9):721.

14. Hoffmann W. Trefoil factors. Cellular and molecular life sciences. 2005;62(24):2932-8.

15. Katoh M. Trefoil factors and human gastric cancer (review). International journal of molecular medicine. 2003;12 (1):3-9.

(35).

TFFs and gastric pre-neoplastic/cancer conditions:

A) TFF1:

In immunohistochemical study of gastric specimens including 35 chronic superficial gastritis samples (CSG), 35 gastric ulcers (GU), and 35 chronic atrophic gastritis samples (CAG) results showed tendency decreasing of TFF1 expression in CSG, GU and CAG(36).There are strong evidence indicating that TFFs have pivotal role in oncogenic transformation, proliferation, migration, invasion and angiogenesis of human gastric cancer (37).Song JY presented down regulation of TFF1 expression during progression of IM type I to type III, and proposed this result might be associated with carcinogenesis (38). (38). Moreover, decreasing in TFF1 expression in low-grade dysplasia and high-grade dysplasia has been documented (39).TFF1 activates P53 tumor suppressor gene by down regulation of miR-504. Overexpression of miR-504 prevents the activity of P53 and decreases the p53-induced apoptosis. Also, it implicates in tumorigenesisprocess (20). The other study reported expression of TFF1 is increased in gastric ulcers but, showed reduced expression in gastric ulcerocancer. Then, it might be important to tell that it can be considered as a marker to differentiate malignant gastric ulcerocancer from gastric ulcer(40) A publication in 2015 implied that expression of TFF1 and its polymorphisms had protective effects in lymph node metastasis negative GC and diffuse-type GC (11). One of the important signaling pathways in gastric cancer development is JAK/STAT. It has been suggested JAK/STAT suppresses TFF1 expression by the epigenetic silencing of GATA6transcription factor which is regulatory factor of TFF1 transcription and via this pathway attributes to cancer development (41) . Furthermore, reduced expression of TFF1 playsa significant role in gastric cancer carcinogenesis and it can be used as a marker of poor prognostic for patients with early stage gastric cancer (35) .

References

16. Wright N. Interaction of trefoil family factors with mucins: clues to their mechanism of action? Gut. 2001;48(3):293-4.
17. Tomasetto C, Masson R, Linares JL, Wendling C, Lefebvre O, Chenard MP, et al. pS2/TFF1 interacts directly with the VWFC cysteine-rich domains of mucins. Gastroenterology. 2000;118(1):70-80.
18.Machado JC, Nogueira AM, Carneiro F, Reis CA, Sobrinho-Simões M. Gastric carcinoma exhibits distinct types of cell differentiation: an immunohistochemical study of trefoil peptides (TFF1 and TFF2) and mucins (MUC1, MUC2, 19. MUC5AC, and MUC6). The Journal of pathology. 2000;190(4):437-43.
19. Baus-Loncar M, Giraud AS. Multiple regulatory pathways for trefoil factor (TFF) genes. Cellular and molecular life sciences: CMLS. 2005;62(24):2921-31.

Noticeably, down-regulation of TFF1 expression in gastric cells decreases cell apoptosis and facilitates proliferation of gastric cells. Hence, over expression of TFF1 increases the apoptosis of gastric cells and inhibits their proliferation (42).On the other hand, hypermethylation of TFF1 promoter which is one of the main cause of TFF1 silencing,down-regulates TFF1 levels and involves in tumor formation at early stage of gastric tumorigenesis.In 2006, it was reported that loss of TFF1 is associated with intestinaltype ofgastric cancer (43).In support of tumor suppressor function of TFF1, it reduces gastrointestinal cell proliferation through delaying G1-S phase transition(44).TFF1 covalently bounds with TFIZ1 as a heterodimer in normal human gastric mucosa and forms heterodimer protein. Disruption of this formation has deleterious effects in gastric cancer and it has been reported that TFF1 peptide in the absence of TFIZ1 is correlated with more migration and invasion phenotype (45).

B) TFF2:

A study in 2004, evaluated trefoil factor family proteins expression by immunohistochemistry method in dyspepsia biopsy samples. According to this study, TFF2 mainly expresses in columnar cells in intestinal metaplasia. As the intestinal metaplasia progresses from type 1 to type 3, the expression of TFF2 protein would increase (46).In 2004 Shi SQ and colleaguesconfirmed that TFF2 expression would decrease in precancerous conditions and gastric cancer (47). He also showed decrease of TFF2 expression in gastric ulcer, chronic atrophic gastritis and gastric cancer in 2006(29). TFF2 as a tumor suppressor gene has shown reduction in expression during gastric carcinogenesis(48). Studiesof TFF2 correlation and prognosis of gastric cancer suggest that TFF2 is positive in diffuse and large tumors which invaded to lymph nodes, so it can be considered as a predictor for a worse disease free survival(12, 49). Therefore, it could be a possible explanation for gastric protective role of low dose aspirin against GI carcinogenesis (50). TFF1 and TFF2 have a noticeable correlation in non-cancer tissue and gas-

References

20. Soutto M, Chen Z, Saleh MA, Katsha A, Zhu S, Zaika A, et al. TFF1 activates p53 through down-regulation of miR-504 in gastric cancer. Oncotarget. 2014;5(14):5663-73.
21. Soutto M, Romero-Gallo J, Krishna U, Piazuelo MB, Washington MK, Belkhiri A, et al. Loss of TFF1 promotes Helicobacter pylori-induced beta-catenin activation and gastric tumorigenesis. Oncotarget. 2015;6(20):17911-22.
22. Thim L. Trefoil peptides: from structure to function. Cellular and Molecular Life Sciences. 1997;53(11):888-903.
23. Dubeykovskaya Z, Dubeykovskiy A, Solal-Cohen J, Wang TC. Secreted trefoil factor 2 activates the CXCR4 receptor in epithelial and lymphocytic cancer cell lines. Journal of Biological Chemistry. 2009;284(6):3650-62.
24. Shi S-Q, Cai J-T, Yang J-M. Expression of trefoil factors 1 and 2 in precancerous condition and gastric cancer. World journal of gastroenterology. 2006;12(19):3119.

Tric cancer (51). In 2016, Cai established that activity of TFF2 against gastric cancer is impressed by its interaction with Sp3 protein in cancerous cells (52). Otto and colleagues identified blottin as TFF2 binding protein (54). It is produced by gastric epithelium and seems to have a protective effect on gastrointestinal mucus (15, 53). However, exact molecular and cellular mechanism is still unknown. So, further studies are required for clarifying the exact mechanism of TFF2 during pre-cancerous and cancerous conditions which might be a target for therapeutic purposes.

C) TFF3:

TFF3 mRNA expression is significant in gastric biopsy with intestinal metaplasia compared to normal gastric biopsy (51).TFF3 expression is decreased in the progression of intestinal metaplasia from type I to type III (46). Reduced expression of TFF3 in intestinal metaplasia is significant(54).High expression of TFF3 in early stage of gastric cancer has been reported, and it has been suggested that perhaps this peptide is an independent marker of poor prognosis (35).Otherwise, Leung reported there was no significant difference in expression of TFF3 between gastric cancer and normal gastric tissues. This controversy with other studies might be related to small sample size in study (39).

Genetic alteration of TFFs:

Several genetic and epigenetic alternations have been proposed to play important roles in the carcinogenesis pathway(55). It has been documented that genetic alteration of TFF1 contributes to gastric cancer pathogenesis. Deletion, and/or mutations of the TFF1 gene have been found in human gastric carcinomas.Somatic mutations in exon 1 and 2 of TFF1 has been reported in 16.3% of gastric carcinomas in Korean population (56). These mutations may alter the structure and function of TFF1 which can result in interruption of gastric mucosal barrier. Furthermore, site-directed mutagenesis experiments were performed to determine the fu-

References

25. Durer U, Hartig R, Bang S, Thim L, Hoffmann W. TFF3 and EGF induce different migration patterns of intestinal epithelial cells in vitro and trigger increased internalization of E-cadherin. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology. 2007;20(5):329-46.
26. Meng JR, Tang HZ, Zhou KZ, Shen WH, Guo HY. TFF3 and survivin expressions associate with a lower survival rate in gastric cancer. Clinical and experimental medicine. 2013;13(4):297-303.
27. Dossinger V, Kayademir T, Blin N, Gott P. Down-regulation of TFF expression in gastrointestinal cell lines by cytokines and nuclear factors. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology. 2002;12(4):197-206.
28. Emami S, Rodrigues S, Rodrigue CM, Le Floch N, Rivat C, Attoub S, et al. Trefoil factor family (TFF) peptides and cancer progression. Peptides. 2004;25(5):885-98.

-nctional role of TFF1 mutations, and suggested that TFF1 mutations contribute to malignant behavior of gastric cancer cells including invasion and loss of tumor-suppressor activity(57).

Otherwise, the research claimed that no mutation identified in ninety gastric carcinoma tissues and concluded that point mutation of TFF1 is a rare event in gastric carcinogenesis (58). Hence, a large patient population study is essential to clarify the role of TFF1 somatic missense mutations in gastric carcinogenesis. The loss of TFF1 expression by Loss of Heterozygosity (LOH) of 21q23.3 region and DNA methylation of TFF1 promoterhas been identified in gastric tumors (58-60). Inactivation of TFF1 by these two mechanisms confirms the function of TFF1 as a gastric-specific tumor suppressor.However, the accurate role of TFF1 in gastric carcinoma pathway remains to be elucidated. **Serum level of TFFs and screening test:**

Inevaluation of TFF1 and TFF2 serum levels in gastric cancer patients undergoing gastrectomy operation, it was found that serum levels of these peptides would dramatically decrease after the surgery which confirms the origin of TFF1 and TFF2 (54). It seems that the serum level of TFF2 is lower in well-differentiated gastric cancer than undifferentiated types (54).TFF3 serum level is significantly related to grade of intestinal metaplasia stomach and can predict the grade of intestinal metaplasia (8). Susumu Aikou found that serum level of TFFsin gastric cancer was significantly higher than control group (54).Moreover, Zhigang Huang reported serum level of TFF3 in intestinal type was significantly lower than that of diffuse type(1). On the other hand, Ping Xiao study showed that TFF3 expression in normal gastric tissue is negative, but serum level of TFF3in lung,pancreatic and prostate cancer upregulates(61). Thus, further evaluation is required to clarifywhetherincreasing TFF3 serum level is specific for GC or not .

Serum levels evaluation of TFFs, pepsinogen test, and anti-*H. pylori* IgG can be used for detecting

References

29. Shi SQ, Cai JT, Yang JM. Expression of trefoil factors 1 and 2 in precancerous condition and gastric cancer. World journal of gastroenterology. 2006;12(19):3119-22.
30. Ren JL, Luo JY, Lu YP, Wang L, Shi HX. Relationship between trefoil factor 1 expression and gastric mucosa injuries and gastric cancer. World journal of gastroenterology. 2005;11(17):2674-7.
31. Soutto M, Chen Z, Katsha AM, Romero-Gallo J, Krishna US, Piazuelo MB, et al. Trefoil factor 1 expression suppresses Helicobacter pylori-induced inflammation in gastric carcinogenesis. Cancer. 2015;121(24):4348-58.
32. Peterson AJ, Menheniott TR, O'Connor L, Walduck AK, Fox JG, Kawakami K, et al. Helicobacter pylori infection promotes methylation and silencing of trefoil factor 2, leading to gastric tumor development in mice and humans. Gastroenterology. 2010;139(6):2005-17.

-gastric cancer that Aiko's study showed TFF1 and TFF3 have significantly higher odds ratio than pepsinogen test (54). (Table1).

Besides, studies established that combining TFF3 and pepsinogen test has more sensitivity and specificity than test for pepsinogen (PG) lonely. This test may improve early diagnosis of gastric cancer(8, 54). (Table2)

Table 1: Sensitivity and specificity of serum level of TFFs, pepsinogen test and anti-H. pylori IgG for detectinggastric cancer (56).

	Sensitivity	Specificity
TFF1 Cutoff: 1.0ng/ml	89.6	67.7
TFF2 Cutoff: 4.0ng/ml	77.6	71.4
TFF3 Cutoff:3.6ng/ml	80.9	81.0
Pepsinogen test	44.8	87.4
Anti-HP IgG	62.3	65.1

Table 2: Combining test of TFF3 with PG sensitivity increases the sensitivity to 75% but specificity will be decreased(51).

Criteria	Sensitivity	Specificity	Odds ratio
PG test (+)	37.50%	81.08%	2.57
TFF3 (≥42ng/ml)	66.67%	83.78%	10.33

33. Michelis R, Sela S, Sbeit W, Cohen HI, Reshef R. Decreased TFF2 expression in the gastric antrum in patients infected with CagA-positive Helicobacter pylori. Isr Med Assoc J. 2009;11(1):11-5.

Conclusions:

Although the exact molecular mechanisms of TFFs are not well-understood, many studies have been implied the key role of TFFs in Gastric cancer. HypermethylatedCPG islands of TFF1 and TFF2 in DNA of tumor tissues might be useful in GC diagnosis.TFF1 can be used as therapeutic target of gastric cancer, since its involvement in cell migration and metastasis through TFF1 binding has been demonstrated. Otherwise, correlation between TFF3 and tumor invasion has been reported. Thus,TFF3 as a stable biomarker might be considered for early diagnosis of GC.Further investigation can improve the prospective of molecular mechanisms and clinical applications of TFFs (7, 15).

References:

34. Xia HH, Yang Y, Lam SK, Wong WM, Leung SY, Yuen ST, et al. Aberrant epithelial expression of trefoil family factor 2 and mucin 6 in Helicobacter pylori infected gastric antrum, incisura, and body and its association with antralisation. J Clin Pathol. 2004;57(8):861-6.
35. Im S, Yoo C, Jung JH, Choi HJ, Yoo J, Kang CS. Reduced expression of TFF1 and increased expression of TFF3 in gastric cancer: correlation with clinicopathological parameters and prognosis. International journal of medical sciences. 2013;10(2):133-40.
36. Shi S, Cai J. The expression of trefoil factor 1 and trefoil factor 2 in gastric cancer and precancer. Zhonghua nei ke za zhi. 2004;43(3):195-7.
37. Perry JK, Kannan N, Grandison PM, Mitchell MD, Lobie PE. Are trefoil factors oncogenic? Trends in Endocrinology & Metabolism. 2008;19(2):74-81.
38. Song JY, Kim BW, Lee AW, Lee KY, Chung IS, Lee BI, et al. Expression of MUC5AC and Trefoil Peptide 1 (TFF1) in the Subtypes of Intestinal Metaplasia. Clinical endoscopy. 2012;45(2):151-4.
39. Chen Z, Soutto M, Rahman B, Fazili MW, Peng D, Blanca Piazuelo M, et al. Integrated expression analysis identifies transcription networks in mouse and human gastric neoplasia. 2017;56(7):535-47.
40. Yang J, Li CX, Dai YY, Peng F, Weng XM, Ji MX. [Expression and significance of trefoil factor 1 protein and 40. serum pepsinogen in benign and malignant gastric ulcers]. Zhonghua yi xue za zhi. 2012;92(22):1540-3.
41. Wu CS, Wei KL, Chou JL, Lu CK, Hsieh CC, Lin JM, et al. Aberrant JAK/STAT Signaling Suppresses TFF1 and .41 TFF2 through Epigenetic Silencing of GATA6 in Gastric Cancer. International journal of molecular sciences. 2016;17 (9).
42. Ge Y, Zhang J, Cao J, Wu Q, Sun L, Guo L, et al. TFF1 inhibits proliferation and induces apoptosis of gastric cancer cells in vitro. Bosnian journal of basic medical sciences. 2012;12(2):74-81.
43. Milne AN, Carvalho R, Morsink FM, Musler AR, De Leng WW, Ristimäki A, et al. Early-onset gastric cancers have a different molecular expression profile than conventional gastric cancers. Modern Pathology. 2006;19(4):564.
44. Bossenmeyer-Pourié C, Kannan R, Ribieras S, Wendling C, Stoll I, Thim L, et al. The trefoil factor 1 participates in gastrointestinal cell differentiation by delaying G1-S phase transition and reducing apoptosis. The Journal of cell biology. 2002;157(5):761-70.

References:

45. May FE, Griffin SM, Westley BR. The trefoil factor interacting protein TFIZ1 binds the trefoil protein TFF1 preferentially in normal gastric mucosal cells but the co-expression of these proteins is deregulated in gastric cancer. The international journal of biochemistry & cell biology. 2009;41(3):632-40.
46. Kim BW, Kim KM, Lee BI, Maeng LS, Choi H, Cho SH, et al. Expression of trefoil peptides in the subtypes of intestinal metaplasia. Peptides. 2004;25(5):779-83.
47. Shi SQ, Cai JT. [The expression of trefoil factor 1 and trefoil factor 2 in gastric cancer and precancer]. Zhonghua Nei Ke Za Zhi. 2004;43(3):195-7.
48. Kirikoshi H, Katoh M. Expression of TFF1, TFF2 and TFF3 in gastric cancer. International journal of oncology. 2002;21(3):655-9.
49. Dhar DK, Wang TC, Maruyama R, Udagawa J, Kubota H, Fuji T, et al. Expression of cytoplasmic TFF2 is a marker of tumor metastasis and negative prognostic factor in gastric cancer. Laboratory investigation. 2003;83(9):1343-52.
50. Azarschab P, Al-Azzeh E, Kornberger W, Gott P. Aspirin promotes TFF2 gene activation in human gastric cancer cell lines. FEBS Lett. 2001;488(3):206-10.
51. Leung WK, Yu J, Chan FK, To KF, Chan MW, Ebert MP, et al. Expression of trefoil peptides (TFF1, TFF2, and TFF3) in gastric carcinomas, intestinal metaplasia, and non-neoplastic gastric tissues. J Pathol. 2002;197(5):582-8.
52. Cai Y, Yi M, Chen D, Liu J, Guleng B, Ren J, et al. Trefoil factor family 2 expression inhibits gastric cancer cell growth and invasion in vitro via interactions with the transcription factor Sp3. International journal of molecular medicine. 2016;38(5):1474-80.
53.Otto WR, Patel K, McKinnell I, Evans MD, Lee CY, Frith D, et al. Identification of blottin: a novel gastric trefoil factor family-2 binding protein. Proteomics. 2006;6(15):4235-45.
54.Aikou S, Ohmoto Y, Gunji T, Matsuhashi N, Ohtsu H, Miura H, et al. Tests for serum levels of trefoil factor family proteins can improve gastric cancer screening. Gastroenterology. 2011;141(3):837-45.e1-7.
55.Abbaszadegan MR, Moaven O, Sima HR, Ghafarzadegan K, A'rabi A, Forghani MN, et al. p16 promoter hypermethylation: a useful serum marker for early detection of gastric cancer. 2008;14(13):2055.
56. Park WS, Oh RR, Park JY, Lee JH, Shin MS, Kim HS, et al. Somatic mutations of the trefoil factor family 1 gene in gastric cancer. Gastroenterology. 2000;119(3):691-8.
57. Yio X, Diamond M, Zhang JY, Weinstein H, Wang LH, Werther L, et al. Trefoil factor family-1 mutations enhance gastric cancer cell invasion through distinct signaling pathways. Gastroenterology. 2006;130(6):1696-706.
58. Carvalho R, Kayademir T, Soares P, Canedo P, Sousa S, Oliveira C, et al. Loss of heterozygosity and promoter methylation, but not mutation, may underlie loss of TFF1 in gastric carcinoma. Laboratory investigation. 2002;82 (10):1319.
59. Nishizuka S, Tamura G, Terashima M, Satodate R. Loss of heterozygosity during the development and progression of differentiated adenocarcinoma of the stomach. The Journal of pathology. 1998;185(1):38-43.
60. Sakata K, Tamura G, Nishizuka S, Maesawa C, Suzuki Y, Iwaya T, et al. Commonly deleted regions on the long arm of chromosome 21 in differentiated adenocarcinoma of the stomach. Genes, Chromosomes and Cancer. 1997;18(4):318-21.
61. Xiao P, Ling H, Lan G, Liu J, Hu H, Yang R. Trefoil factors: Gastrointestinal-specific proteins associated with gastric cancer. Clinica Chimica Acta. 2015;450:127-34.