Virchows Arch (1997) 431:299–304

REVIEW ARTICLE

G.R. Williams · N.A. Wright

Trefoil factor family domain peptides

Received: 21 July 1997 / Accepted: 21 July 1997

Abstract Within the past 15 years a new family of peptides has been identified, known as trefoil factor family (TFF) domain peptides; they are associated with mucin-secreting epithelial cells and synthesised predominantly in the gastrointestinal tract. They share a highly conserved physical structure, and their role in mucosal defence and healing is becoming increasingly clear; more recently a tumour suppressor function has been postulated. Outside the gastrointestinal tract, members of this group of peptides have also been identified in the normal hypothalamus and pituitary, and in normal breast tissue where it is responsive to oestrogen stimulation. Evidence of peptide expression has been found in a range of urological, gynaecological, gastrointestinal, pulmonary and breast carcinomas, and in the last two it appears to carry prognostic significance. The present review aims to summarise the rapidly expanding data on the role of these peptides in epithelial inflammation, repair and neoplasia.

Key words TFF domain · Trefoil

Introduction

TFF domain peptides are small, stable structures copackaged by the Golgi apparatus of gastrointestinal epithelial cells into mucus granules and secreted with mucins into the protective layer covering the mucosa. The family shares a variable number of conserved motifs based on a compact 3-dimensional trefoil structure of six cysteine residues held together by three pairs of disulphide bonds [9, 12, 60].This structure appears to confer marked proteolytic stability and resistance to acid digestion [24]. There are three known trefoil factors in man: TFF1 and TFF3, which each contain one trefoil motif, and TFF2, with two motifs.

G.R. Williams (✉) · N.A. Wright
ICRF Histopathology Unit, 44, Lincoln's Inn Fields, London, WC2A 3PX, UK
Fax: (44) 171 269 3087

TFF1 was originally discovered in 1982 during searches for oestrogen-inducible mRNAs in breast carcinoma cell lines [34]. The cDNA clone was named pS2, and the corresponding gene locus on chromosome 21q22.3, BCEI (breast cancer estrogen inducible) [36, 48, 63].

TFF2 was identified in 1990 [62] as a human homologue of a peptide isolated from porcine pancreas, pancreatic spasmolytic polypeptide (PSP) [23–25, 61]. The human variant was named spasmolytic polypeptide (SP), since the pancreas did not seem to be a major site of production of the peptide. The gene for SP lies on chromosome 21, within 230 kb of the gene for pS2 [63].

TFF3, originally known as intestinal trefoil factor (ITF), was identified in 1993 [17, 44] as the human homologue of a rat protein identified with oligonucleotide probes based on the peptide sequence of human transformed growth-inhibitory factor (TGIF) [55]. Subsequently there has been no confirmation that TFF3 is related to TGIF. The human TFF3 gene maps to the same cluster on chromosome 21 as TFF1 and TFF2 [8, 52].

Table 1 summarises the known sites of physiological and pathological expression of TFF domain peptides.

Functions

The biological functions of the TFF domain peptides are not completely understood. Investigation of their activity in humans is restricted by the difficulty in purifying large amounts from natural sources, and recombinant DNA techniques are frequently used as the most practicable source of the peptides.

Initial studies on porcine TFF2 in experimental animals suggested they had a role in inhibition of gastrointestinal motility, and on oral administration, in inhibition of pentagastrin-induced acid secretion [25]. However, recent studies on the human and porcine peptides have not supported these findings [35, 42]. The reasons for these discrepancies are not known, but may be due to small differences in study design [35].

Table 1 Sites of expression of TFF domain peptides (*IBD* inflammatory bowel disease, UACL ulcer-associated cell lineage)

Peptide	Site	
Physiological expression		
TFF 1	Stomach	Mucus cells from neck upwards, all regions
	Small intestine	Ductal luminal cells of Brunner's glands
	Large intestine	Goblet cells near surface of crypts
	Pancreas	Focally in duct epithelium
	Gall bladder	Patchy epithelial expression
	Breast	Small proportion of lobular and ductal epithelial cells
	Prostate	Normal tissue adjacent to tumour
TFF2	Stomach	Fundus; mucus neck cells of antrum; mucus cells in base of glands (surface cells mRNA only)
	Small intestine	Brunner's gland acini and distal duct, otherwise luminal mucus only
	Pancreas	Focally in duct epthelium
	Gall bladder	Patchy epithelial expression
TFF3	Small intestine	Brunner's gland acini and ducts, goblet cells
	Large intestine	Superficial goblet cells
	Gall bladder	Patchy epithelial expression
	Hypothalamus	Neurons in periventricular and paraventricular nuclei
	Pituitary	Anterior and posterior
	Female GU tract	Epithelium
Pathologic expression		
TFF1	Oesophagus	Barrett's oesophagus
	Stomach	Intestinal metaplasia: incomplete, goblet and columnar cells; complete, goblet cells only Hyperplastic polyps Carcinoma: diffuse > intestinal
	Small intestine	Gastric metaplasia Chronic ulceration including IBD; UACL upper duct and surface cells, adjacent normal cell lineages (endocrine, goblet and ulcer base)
	Large intestine	UACL Hyperplastic polyps Adenoma Adenocarcinoma
	Gallbladder	UACL and carcinomas of biliary tract, breast, pancreas, endometrium, ovary (mucinous > serous), prostate, bladder, cervix, lung (adenocarcinoma)
TFF2	Oesophagus	Barrett's oesophagus
	Small intestine	Gastric metaplasia Chronic ulceration incl IBD UACL: acinar cells and lower duct adjacent normal cells as TFF1
	Large intestine	UACL Hyperplastic polyps (mRNA only) Adenoma Adenocarcinoma
TFF3	Somach	Glands adjacent to ulceration Goblet cells of intestinal metaplasia
	Small intestine	Chronic ulceration UACL: acini and lower ducts, adjacent normal cells as TFF 1 and 2
	Large intestine	Hyperplastic polyps (mRNA only) Adenoma Adenocarcinoma (particularly those with mucinous histology)

There is now a large body of evidence to show that these peptides play an active role in mucosal defence and, with expression being rapidly up-regulated after mucosal damage, have a further action once inflammation and ulceration have occurred.

Role in mucosal defence

Subcutaneous or oral administration of recombinant human TFF2 and rat TFF3 has been shown, in separate studies, to prevent the development of indomethacin-induced gastric ulceration in the rat [2, 42]. There are two schools of thought as to the mechanisms responsible for this protective function.

The role of TFF domain peptides as a physical barrier at the luminal mucosal surface, protecting the gastric epithelial cells from acid digestion, is suggested by their luminal stability and coexpression with mucin core proteins, leading to very high concentrations of the peptides within the mucus gel layer [13, 14]. TFF1 and TFF2 are expressed specifically with the neutral mucin MUC1, and colon carcinoma cell lines that express MUC2 also secrete TFF2 and 3 [13, 14, 66]. These peptides alter the physical properties of the secreted mucins, leading to an increase in the optical density and viscosity of purified mucin preparations when added in vitro possibly by binding mucus molecules together via oligosaccharide side chains [2].

Other work has indicated that, rather than a lumen-protective function, a receptor-mediated response may be involved. Chloride transport in gastrointestinal epithelial cells is induced by TFF3 application in vitro only when the basolateral surface of the cell is exposed to the peptide [6]. TFF3 has also been found to bind a membrane protein in preparations of colorectal epithelial cells, with associated phosphorylation of tyrosine and β-catenin, cytoplasmic peptides involved in signal transduction and hence highly suggestive of a receptor-mediated response [29].

Role in healing and repair

Expression of TFF domain peptides is increased in inflammatory bowel disease (IBD) and adjacent to peptic ulceration, particularly in epithelial cells migrating across the base of ulcers [10, 45]. Recent transgenic studies support the hypothesis that TFF domain peptides are important in stimulating gastrointestinal repair. Mice that overexpress human TFF2 specifically in jejunal villi show increased resistance to indomethacin-induced jejunal mucosal injury compared with controls, a protection not shared by non-TFF2-expressing ileal regions [43]. Conversely, knockout mice lacking the TFF3 gene have been shown to have impaired mucosal healing and die from extensive colitis after oral administration of dextran sulphate sodium, an agent that causes mild epithelial injury in wild-type mice [33].

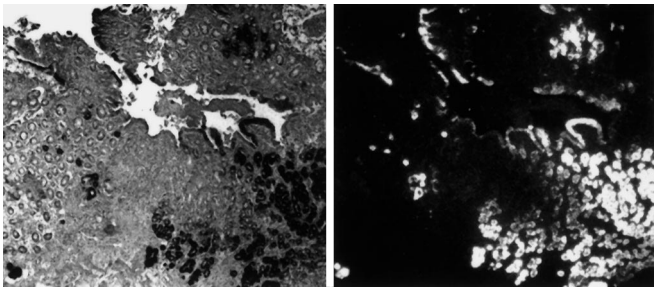

Fig. 1 Light and dark field in situ hybridisation for TFF2 mRNA showing signal in UACL in colonic mucosa

Studies on recombinant peptides have revealed that all are motogens, promoting epithelial cell migration and invasion of collagen gels in vitro, possibly by inducing rapid phosphorylation of β-catenin, and the down-regulation of adhesion molecules, particularly E-cadherin [16, 29]. By stimulating migration of epithelial cells from the wound margin, with associated flattening of immediately adjacent undamaged cells, these peptides therefore contribute to the restoration of mucosal integrity [26, 37, 56].

In both local and diffuse ulcerative conditions of the GI tract, the site of coexpression of the peptides has been shown to be cells of the ulcer-associated cell lineage (UACL), as shown in Fig. 1 [17, 46, 50, 67]. This lineage, budding out from the bases of crypts adjacent to ulcers, plays a key role in the restoration of mucosal integrity, extending through the lamina propria in an acinar network onto the mucosal surface at the sides of the villi and displacing indigenous surface epithelial cells. The sites of expression of TFF-domain peptides in the UACL are shown in Table 1. Normal cell lineages adjacent to the UACL in Crohn's disease also express TFF2 ectopically, as do local neuroendocrine cells [47, 66, 67].

Association with growth factors

Even though TFF3 was initially discovered through its sequence homology with human TGIF, there has been no subsequent confirmation that TFF3 is related in any way to TGIF, and the effects of the peptides on cell migration have been shown to be independent of TGFβ although acting synergistically with epidermal growth factor (EGF) [10, 17, 43, 44]. TFF2 has been shown in one study to have growth factor-like effects, being mitogenic for a colorectal cancer cell line HCT116 and a breast cancer cell line MCF7 [22].

There is some evidence for synergism in intestinal mucosal protection between these peptides and growth factors, including EGF and fibroblast growth factor [57]. In experimental models there appears to be a synergy between rat TFF3 and EGF in increasing prostaglandin-induced fluid and electrolyte secretion by epithelial cells [6] and in protection against indomethacin-induced ulceration [7].

EGF is also involved in the regulation of expression of the TFF1 gene, via a complex enhancer region, along with a wide range of other effectors including oestrogen, insulin-like growth factor-1, basic fibroblast growth factor and the proto-oncogene products c-Ha-ras and c-jun [5, 40]. The regulatory regions of the other TFF peptide genes do not contain an EGF-responsive element [51, 53].

In UACL there is further circumstantial evidence of synergy between TFF domain peptides and growth factors. Immunoreactive EGF/urogastrone (URO) is found in the acinar portions of the UACL corresponding to the sites where TFF1 is found. The growth factor may thus be involved in the expression of the peptide at this site, although immunostaining for the EGF receptor shows positivity only in adjacent normal crypts. TGF-α peptide is expressed abundantly throughout the UACL, and expression of the TGF-α receptor is similarly limited to adjacent normal crypts [1, 66].

Association with neoplasia

TFF1 was originally isolated from human breast carcinoma cell lines. Since this discovery, several series have documented an association between TFF domain peptides and human epithelial neoplasia.

Common epithelial malignancies found to express TFF1 include carcinomas of the breast, stomach, pancreas, lung, endometrium, ovary (particularly mucinous carcinomas), prostate, and (occasionally) bladder and cervix [3, 19]. In gastric, breast and pancreatic tumours the gene appears largely intact [18, 30, 64], although the presence of aberrant TFF1 transcripts in some gastric carcinomas suggests that subtle gene modifications may be occurring in neoplasia [59].

Changes in protein expression, however, are well documented. In breast carcinoma, in which over 50% of tumours express TFF1, expression is significantly associated with oestrogen receptor status, responsiveness to hormone therapy and favourable prognosis [4, 11, 18, 41, 49, 54]. In all other tumours in which TFF1 has been demonstrated, expression appears to be independent of oestrogen receptor status.

TFF1 protein expression is lower in gastric adenomas and carcinomas than in adjacent normal mucosa and hyperplastic polyps [31]. In up to 50% of carcinomas expression is lost completely [19, 30, 32, 38]. Expression has been found to correlate with diffuse morphology, and while some studies have shown no correlation with parameters of tumour prognosis, one series showed a significant relationship between TFF1 expression and tumour stage [32, 38]. TFF3 expression has been reported to occur in enterocytes lacking goblet cell morphology in colonic adenomas and carcinoma, colocalising with neutral mucin production [58]. While complete loss of expression of the protein is rare in colonic carcinomas studied to date, decreased levels have been found to be significantly associated with tumour necrosis and advanced Dukes stage [58].

Nonmalignant lung disease and squamous or small cell bronchial carcinoma are not associated with raised serum levels of TFF1 [21]. However, increased mean serum levels and evidence of immunohistological positivity have been found to correlate with advanced bronchial adenocarcinoma, and specifically the goblet cell subtype of bronchioloalveolar carcinoma [21]. TFF1-positive adenocarcinomas have also been shown to be associated with a poorer prognosis than negative tumours [20].

The biological role of these proteins in tumorigenesis is less clear. Experimental evidence for a role in tumour suppression comes from studies using knockout mice lacking the TFF1 gene [28]. Homozygous animals showed decreased and dysfunctional gastric mucin production with marked antral hyperplasia and dysplasia. All such animals developed antral adenomas and 30% developed multifocal intramucosal carcinomas. Whether the TFF1 gene acts directly in tumour suppression at a genetic level or indirectly via maintenence of normal mucin production remains to be ascertained.

Studies on mouse breast carcinoma cell lines transfected with human TFF1 cDNA have also shown that the peptide has the ability to affect morphogenesis, causing the cells to grow as branched rather than spheroid structures in collagen gels [65]. Recombinant TFF2 has also been shown to modify the pattern of growth of carcinoma cells growing in suspension culture, from spheroidal to multispiked clusters [27]. The actions of TFF domain peptides in morphogenesis and oncogenesis may be mediated by interaction with β-catenin. This protein, as well as being involved with E-cadherin in signal transduction, has been shown to have a role in embryonic developmental patterning in certain species [15]. Furthermore, evidence of a direct interaction between β-catenin and the adenomatous polyposis coli (APC) tumour suppressor protein suggests a role in the regulation of tumour growth [39].

Conclusions

The role of TFF domain peptides has been gradually elucidated since their discovery in 1982. They appear to play a central role in gastric and intestinal mucosal defence, in association with luminal mucins, and they are involved in the healing process following ulceration. Their expression and biological action are closely associated with hormonal control, growth factors and oncogenic stimuli. A potential role in morphogenesis and malignant transformation is suggested by experimental and observational studies.

Much remains to be discovered about their mechanisms of action at the cellular level, in particular their precise interactions with growth factors, adhesion molecules, oncogenes and tumour suppressor proteins. Such studies will be central to the potential use of TFF domain peptides in the clinicopathological assessment of various epithelial malignancies and the realisation of their considerable therapeutic potential in the manage-

ment of ulceroinflammatory disease of the gastrointestinal tract.

Acknowledgements Richard Poulsom and Bill Otto for reviewing the script, and Richard Poulsom for the in-situ photomicrograph.

References

1. Ahnen DA, Gullick W, Wright NA (1991) Multiple growth factor production by the cell lineage induced by mucosal ulceration in Crohn's disease. Gastroenterology 100 (5/2): A512
2. Babyatsky MW, DeBeaumont M, Thim L, Podolsky DK (1996) Oral trefoil peptides protect against ethanol- and indomethacin-induced gastric injury in rats. Gastroenterology 110:489–497
3. Bonkhoff H, Stein U, Welter C, Remberger K (1995) Differential expression of the pS2 protein in the human prostate and prostate cancer: association with premalignant changes and neuroendocrine differentiation. Hum Pathol 26:824–828
4. Cappelletti V, Coradini D, Scanziani E, Benini E, Silvestrini R, Di Fronzo G (1992) Prognostic relevance of pS2 status in association with steroid receptor status and proliferative activity in node-negative breast cancer. Eur J Cancer [A] 28:1315–1318
5. Cavailles V, Garcia M, Rochefort H (1989) Regulation of cathepsin-D and pS2 gene expression by growth factors in MCF7 human breast cancer cells. Mol Endocrinol 3:552–558
6. Chinery R, Cox HM (1995) Modulation of epidermal growth factor effects on epithelial ion transport by intestinal trefoil factor. Br J Pharmacol 115:77–80
7. Chinery R, Playford R (1995) Combined intestinal trefoil factor and epidermal growth factor is prophylactic against indomethacin-induced gastric damage in the rat. Clin Sci 88:401–403
8. Chinery R, Williamson J, Poulsom R (1996) The gene encoding human intestinal trefoil factor (TFF3) is located on chromosome 21q22.3 clustered with other members of the trefoil peptide family. Genomics 32:281–284
9. De A, Brown DG, Gorman MA, Carr M, Sanderson MR, Freemont PS (1994) Crystal structure of a disulfide-linked "trefoil" motif found in a large family of putative growth factors. Proc Natl Acad Sci USA 91:1084–1088
10. Dignass A, Lynch-Devaney K, Kindon H, Thim L, Podolsky DK (1994) Trefoil peptides promote epithelial migration through a transforming growth factor beta-independent pathway. J Clin Invest 94:376–383
11. Foekens JA, Rio M-C, Seguin P, et al (1990) Prediction of relapse and survival in breast cancer patients by pS2 protein status. Cancer Res 50:3832–3837
12. Gajhede M, Petersen TN, Henriksen A, et al (1993) Pancreatic spasmolytic polypeptide: first three-dimensional structure of a member of the mammalian trefoil family of peptides. Structure 1:253–262
13. Gendler SJ, Lancaster CA, Taylor-Papadimitriou J, et al (1990) Molecular cloning and expression of human tumor-associated polymorphic epithelial mucin. J Biol Chem 265: 15286–15293
14. Giraud AS, Parker LM, Whitehead R (1994) Colon cancer cell lines expressing the MUC2 gene also secrete trefoil peptides. Gastroenterology 106:A810
15. Gumbiner BM (1995) Signal transduction by β catenin. Curr Opin Cell Biol 7:634–640
16. Hanby AM, Chinery R, Poulsom R, Playford RJ, Pignatelli M (1996) Downregulation of E-cadherin in the reparative epithelium of the human gastrointestinal tract. Am J Pathol 148:723–729
17. Hauser F, Poulsom R, Chinery R, et al (1993) hP1.B, a human P-domain peptide homologous with rat intestinal trefoil factor, is expressed in the ulcer associated cell lineage and the uterus. Proc Natl Acad Sci USA 90:6961–6965
18. Henry JA, Nicholson S, Hennessy C, Lennard TW, May FE, Westley BR (1989) Expression of the estrogen-regulated pNR-2 mRNA in human breast cancer: relation to estrogen receptor mRNA levels and response to tamoxifen therapy. Br J Cancer 61:32–38
19. Henry JA, Bennett MK, Piggott NH, Levett DL, May FE, Westley BR (1991) Expression of the pNR-2/pS2 protein in diverse human epithelial tumours. Br J Cancer 64:677–682
20. Higashiyama M, Doi O, Kodama K, et al (1994) Prognostic significance of pS2 protein expression in pulmonary adenocarcinoma. Eur J Cancer [A] 30:792–797
21. Higashiyama M, Doi O, Kodama K, Yokuchi H, Inaji H, Tateishi R (1996) Estimation of serum pS2 protein in patients with lung adenocarcinoma. Anticancer Res 16:2351–2356
22. Hoosein NM, Thim L, Jørgensen KH, Brattain MG (1989) Growth stimulatory effect of pancreatic spasmolytic polypeptide on cultured colon and breast tumor cells. FEBS Lett 247:303–306
23. Jeffrey GP, Oates PS, Wang TC, Babyatsky MW, Brand SJ (1994) Spasmolytic polypeptide: a trefoil peptide secreted by rat gastric mucous cells. Gastroenterology 106:336–345
24. Jørgensen KH, Thim L, Jacobsen HE (1982) Pancreatic spasmolytic polypeptide (PSP). I. Preparation and initial chemical characterization of a new polypeptide from porcine pancreas. Regul Pept 3:207–219
25. Jørgensen KD, Diamant B, Jørgensen KH, Thim L (1982) Pancreatic spasmolytic polypeptide (PSP). III. Pharmacology of a new porcine pancreatic polypeptide with spasmolytic and gastric acid secretion inhibitory effects. Regul Pept 3:231–243
26. Lacy ER, Morris GP, Cohen MM (1993) Rapid repair of the surface epithelium in human gastric mucosa after acute superficial injury. J Clin Gastroenterol 17 [Suppl 1]:S125–S135
27. Lalani E-N, Williams R, Jayaram Y, Thim L, Wright NA, Stamp GWH (1995) Effect of hSP on growth and proliferation of MCF-7 cells. J Pathol (Lond) 175 [Suppl]:109A
28. Lefebvre O, Chenard M-P, Masson R, et al (1996) Gastric mucosa abnormalities and tumorigenesis in mice lacking the pS2 trefoil protein. Science 274:259–262
29. Liu D, Chinery R, Wilding J, Gullick WJ, Kmiot W, Pignatelli M (1996) Phosphorylation of beta-catenin and epidermal growth-factor receptor by intestinal trefoil factor. J Pathol (Lond) 179:A10
30. Luqmani Y, Bennett C, Paterson I, et al (1989) Expression of the pS2 gene in normal, benign and neoplastic human stomach. Int J Cancer 44:806–812
31. Machado JC, Carneiro F, Blin N, Sobrinho-Simoes M (1996) Pattern of pS2 protein expression in premalignant and malignant lesions of gastric mucosa. Eur J Cancer Prev 5:169–179
32. Machado JC, Carneiro F, Ribeiro P, Blin N, Sobrinho-Simoes M (1996) pS2 protein expression in gastric carcinoma. An immunohistochemical and immunoradiometric study. Eur J Cancer 32:1585–1590
33. Mashimo H, Wu D-C, Podolsky DK, Fishman MC (1996) Impaired defense of intestinal mucosa in mice lacking intestinal trefoil factor. Science 274:262–265
34. Masiakowski P, Breathnach R, Bloch J, Gannon F, Krust A, Chambon P (1982) Cloning of cDNA sequences of hormone-regulated genes from the MCF-7 human breast cancer cell line. Nucl Acids Res 10:7895–7903
35. McKenzie C, Marchbank T, Playford RJ, Otto W, Thim L, Parsons ME (1997) Pancreatic spasmolytic polypeptide (PSP) protects the gastric mucosa but does not inhibit acid secretion or motility. Am J Physiol (in press) [Gastrointest Liver Physiol] 36:G112–G117
36. Moisan J-P, Mattei M-G, Mandel J-L (1988) Chromosome localization and polymorphism of an oestrogen-inducible gene specifically expressed in some breast cancers. Hum Genet 79:168–171
37. Moore R, Carlson S, Madara JL (1989) Rapid barrier restitution in an in vitro model of intestinal epithelial injury. Lab Invest 60:237–244

38. Muller W, Borchard F (1993) pS2 protein in gastric carcinoma and normal gastric mucosa: association with clinicopathological parameters and patient survival. J Pathol (Lond) 171:263–269
39. Munemitsu S, Albert I, Souza B, Rubinfield B, Polakis P (1995) Regulation of intracellular β catenin levels by the adenomatous polyposis coli (APC) tumour-suppressor protein. Proc Natl Acad Sci USA 92:3046–3050
40. Nunez AM, Berry M, Imler JL, Chambon P (1989) The 5′ flanking region of the pS2 gene contains a complex enhancer region responsive to oestrogens, epidermal growth factor, a tumour promoter (TPA), the c-Ha-ras oncoprotein and the c-jun protein. EMBO J 8:823–829
41. Pallud C, Le Dousal V, Pichon M-F, Prud'homme J-F, Hacene K, Milgrom E (1993) Immunohistochemistry of pS2 in normal human breast and in various histological forms of breast tumours. Histopathology 23:249–256
42. Playford RJ, Marchbank T, Chinery R, et al (1995) Human spasmolytic polypeptide is a cytoprotective agent that stimulates cell migration. Gastroenterology 108:108–116
43. Playford RJ, Marchbank T, Goodlad RA, et al (1996) Transgenic mice that overexpress the human trefoil peptide pS2 have an increased resistance to intestinal damage. Proc Natl Acad Sci USA 93:2137–2142
44. Podolsky DK, Lynch-Devaney K, Stow JL, et al (1993) Identification of human intestinal trefoil factor: goblet cell-specific expression of a peptide targeted for apical secretion. J Biol Chem 268:6694–6702
45. Poulsom R (1997) Molecular aspects of restitution. In: Halter F, Winton D, Wright NA (eds) The gut as a model in cell and molecular biology. Kluwer Falk Symp 94
46. Poulsom R, Wright NA (1993) Trefoil peptides: a newly recognized family of epithelial mucin-associated molecules. Am J Physiol [Gastrointest Liver Physiol] 265[28]:G205–G213
47. Poulsom R, Chinery R, Sarraf C, et al (1992) Trefoil peptide gene expression in intestinal adaptation and renewal. Scand J Gastroenterol 27 [Suppl 192]:17–28
48. Prud'homme JF, Fridlansky F, Le Cunff M, et al (1985) Cloning of a gene expressed in human breast cancer and regulated by estrogen in MCF-7 cells. DNA 4:11–21
49. Rio M-C, Bellocq JP, Gairard B, et al (1987) Specific expression of the pS2 gene in subclasses of breast cancers in comparison with expression of the estrogen and progesterone receptors and the oncogene ERBB2. Proc Natl Acad Sci USA 84:9243–9247
50. Rio M-C, Chenard MP, Wolf C, et al (1991) Induction of pS2 and hSP genes as markers of mucosal ulceration of the digestive tract. Gastroenterology 100:375–379
51. Sands BE, Ogata H, Lynch-Devaney K, deBeaumont M, Ezzell RM, Podolsky DK (1995) Molecular cloning of the rat intestinal trefoil factor gene: characterization of an intestinal goblet cell-associated promoter. J Biol Chem 270:9353–9361
52. Schmitt H, Wundrack I, Beck S, et al (1996) A third P-domain peptide gene (TFF3), human intestinal trefoil factor, maps to 21q22.3. Cytogenet Cell Genet 72:299–302
53. Seib T, Dooley S, Welter C (1995) Characterization of the genomic structure and the promoter region of the human intestinal trefoil factor. Biochem Biophys Res Commun 214:195–199
54. Skilton RA, Luqmani YA, McClelland RA, Coombes RC (1989) Characterisation of a messenger RNA selectively expressed in human breast cancer. Br J Cancer 60:168–175
55. Suemori S, Lynch-Devaney K, Podolsky DK (1991) Identification and characterization of rat intestinal trefoil factor: tissue- and cell-specific member of the trefoil protein family. Proc Natl Acad Sci USA 88:11017–11021
56. Svanes K, Itoh S, Takeuchi K, Silen W (1982) Restitution of the surface epithelium of the in vitro frog gastric mucosa after damage with hypermolar sodium chloride. Gastroenterology 82:1409–1426
57. Szabo S, Folkman J, Vattay P, Morales RE, Pinkus GS, Kato K (1994) Accelerated healing of duodenal ulcers by administration of a mutein of basic fibroblast growth factor in rats. Gastroenterology 106:1106–1111
58. Taupin D, Ooi K, Yeomans N, Giraud A (1996) Conserved expression of intestinal trefoil factor in the human colonic adenoma-carcinoma sequence. Lab Invest 75:25–32.59
59. Theisinger B, Welter C, Seitz G, et al (1991) Expression of the breast cancer associated gene pS2 and the pancreatic spasmolytic polypeptide gene (hSP) in diffuse type of stomach carcinoma. Eur J Cancer 27:770–773
60. Thim L (1989) A new family of growth factor-like peptides. 'Trefoil' disulphide loop structures as a common feature in breast cancer associated peptide (pS2), pancreatic spasmolytic polypeptide (PSP), and frog skin peptides (spasmolysins). FEBS Lett 250:85–90
61. Thim L, Jørgensen KH, Jørgensen KD (1982) Pancreatic spasmolytic polypeptide (PSP). II. Radioimmunological determination of PSP in porcine tissues, plasma and pancreatic juice. Regul Pept 3:221–230
62. Tomasetto C, Rio M-C, Gautier C, et al (1990) hSP, the domain-duplicated homolog of pS2 protein, is co-expressed with pS2 in stomach but not in breast carcinoma. EMBO J 9:407–414
63. Tomasetto C, Rockel N, Mattei MG, Fujita R, Rio M-C (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 13: 1328–1330
64. Welter C, Theisinger B, Seitz G, et al (1992) Association of the human spasmolytic polypeptide and an estrogen-induced breast cancer protein (pS2) with human pancreatic carcinoma. Lab Invest 66:187–192
65. Williams R, Stamp GWH, Gilbert C, Pignatelli M, Lalani E-N (1996) pS2 transfection of murine adenocarcinoma cell line 410.4 enhances dispersed growth pattern in a 3-D collagen gel. J Cell Science 109:63–71
66. Wright NA, Poulsom R, Stamp G, et al (1993) Trefoil peptide gene expression in gastrointestinal epithelial cells in inflammatory bowel disease. Gastroenterology 104:12–20
67. Wright NA, Poulsom R, Stamp GW, et al (1990) Epidermal growth factor (EGF/URO) induces expression of regulatory peptides in damaged human gastrointestinal tissues. J Pathol 162:279–284