Peptide gene expression in gastrointestinal mucosal ulceration: ordered sequence or redundancy?

Summary
Many genes, some encoding peptides, are upregulated after mucosal damage in the gastrointestinal mucosa: we have looked for an ordered sequence in the expression of genes such as c-fos, c-jun, egr-1, Sp-1, epidermal growth factor, transforming growth factors α and β, trefoil peptides, epidermal growth factor receptor, hepatocyte growth factor, c-met, fibroblast growth factor, platelet derived growth factor, and vascular endothelial growth factor. All of these gene products play an important reparative role, assisting appropriate healing of the damaged mucosa. There does indeed seem to be a temporal sequence in this gene expression, but there is a certain degree of redundancy within the system, both in terms of receptor binding and the function of the gene products. However, it is probable that the integrated function of these genes and their products safeguard the important healing properties of the gastrointestinal mucosa. Although the function of individual gene products is of course important, it now seems critical to explore the inter-relations between these genes and their encoded products to explain fully mucosal regeneration after damage.

Introduction
The gastrointestinal tract is subjected to a wide variety of mucosal challenges. Helicobacter pylori associated ulcer disease, non-steroidal anti-inflammatory drug (NSAID) associated ulcers, alcohol induced mucosal injury, and a variety of inflammatory conditions, including ulcerative colitis and Crohn’s disease. No matter what the cause of the ulceration, the mucosa usually responds rapidly by triggering off a cascade of repair mechanisms to stimulate repair and restore mucosal integrity. Many genes are induced by the damage: apart from early response genes such as c-fos, c-jun, egr-1, and Sp-1, genes encoding peptides are particularly well represented; there is increasing evidence that at least 30 such genes are involved in the process. In the main, most investigators have pursued the time honoured reductionist approach, singling out individual peptides for detailed attention. However, these peptides are not all expressed at the same time, but follow an apparently ordered sequence. One point which does not seem to have been at all tackled in this field is that many of these peptides have similar actions, prompting the reasonable question—is gene expression after mucosal damage largely redundant, or is there an ordered sequence, with intrinsic interdependency? In this article, we will examine the importance of these peptides in the ulcer healing process, and attempt to identify the sequential gene expression of these peptides after ulceration.

The main players
Trefoil factors (TFF) derive their name from their cysteine rich “three leafed” structure. TFFs are produced rapidly at sites of injury and stimulate the repair process. Three members of this family are present in human gastrointestinal mucosa: TFF1/pS2, TFF2/SP, and TFF3/TF. The production of all three trefoil peptides is upregulated at sites of mucosal injury, and they participate in mucosal repair by stimulating the migration of surviving cells from the edge of the damaged region over the denuded area, a process known as epithelial restitution. Exogenous TFF2/SP increases cell migration in in vitro models of cell wounding and also acts as a cytoprotective agent in rats treated with indomethacin. Thus TFF2/SP has been proposed as a rapid response peptide.

Epidermal growth factor (EGF) is an 53 amino acid peptide found in the salivary glands and the duodenal Brunner’s glands. It is one of the most extensively studied peptides in healing of gastric mucosal lesions, but its exact function in human physiology is not yet fully defined. EGF is a potent stimulant of growth and repair when infused systemically, inhibits gastric acid secretion, and has a cytoprotective effect on the gastrointestinal mucosa. It is also one of the main peptides secreted by repair lineages of the gastrointestinal tract—for example, the ulcer associated cell lineage. The EGF receptor (EGFR) is a single pass transmembrane protein of about 1200 amino acid residues and has a glycosylated extracellular domain that binds EGF, leading to the activation of an intracellular tyrosine kinase domain which causes the phosphorylation of cellular proteins. Apart from EGF, several other ligands also bind to EGFR, such as transforming growth factor (TGF) α, amphiregulin, heparin-binding EGF-like growth factors, and betacellulin. Interestingly, in many studies luminal EGF has very little effect on growth or acid secretion of the non-damaged gastrointestinal mucosa. The reason for this discrepancy may be that the EGFR on gut epithelial cells is restricted to the basolateral surface and is not present on the apical luminal surface in rat or human. Luminal EGF is therefore only able to bind to its receptors when the bowel has been damaged, and thus might be best considered as a luminal surveillance peptide—constantly available but possessing little function unless damage has occurred. The proposal that EGF acts in a surveillance role is supported by the finding that removal of the submandibular glands from rats does not cause spontaneous ulcer development, but does reduce the rate of healing if an ulcerogen is co-administered.

Transforming growth factor α is synthesised as a 160 amino acid precursor molecule that spans the cell membrane. Subsequent exposure of the external domains to specific proteases releases a 50 amino acid residue peptide that shares 35% homology with epidermal growth factor. TGF-α is expressed throughout the gastrointestinal tract in rats and humans and although the biological function of the membrane bound form is unclear, it may function in a juxtacrine manner on adjacent cells. TGF-α is normally trophic to a variety of cell lines in vitro and to the intestine of rats when given systemically. Furthermore,
the administration of TGF-α decreases the extent of gastric damage when rats are exposed to ulcerogens such as ethanol or stress. It has been shown that TGF-α mRNA increases in a dose and time dependent manner in the gastric mucosa of rats after administration of taurocholate. In addition, there was a 68-fold increase in immunoreactive TGF-α in gastric juice within 30 minutes of gastric instillation of hydrochloric acid. The origin of this rapid increase in TGF-α after gastric mucosal injury remains speculative: it may be caused by proteolysis of the transmembrane form or lysis of injured gastric mucosal cells. Recruitment of inflammatory cells into the injured area may also result in increased concentrations of TGF-α, but the paucity of inflammatory cells observed in histological sections taken early after the injury, and the low concentration of TGF-α in the serum, indicates that the TGF-α most likely originates from the gastric mucosa.

These studies support the idea that the predominant role of TGF-α is to maintain normal epithelial integrity, acting predominantly by direct epithelial effects. Thus it may be regarded as a mucosal integrity peptide. Another example of such a mucosal integrity peptide is pancreatic secretory trypsin inhibitor (PSTI) which is secreted into the mucus layer to prevent excessive digestion by refluxed pancreatic proteases and to decrease the rate of mucus digestion by luminal proteases within the stomach and colon. PSTI is found in mucus secreting cells throughout the gastrointestinal tract and also in the kidney, lung and breast, and both increases the proliferation of a variety of cell types and stimulates cell migration, possibly acting via the EGFR. Thus PSTI may also be involved in both the early and late phases of the healing response following injury.

Hepatocyte growth factor (HGF) is secreted from stromal fibroblasts as a single chain, biologically inactive precursor (pro-HGF) and converted to an active heterodimeric protein by a novel serine protease (HGF activator). This proteolytic process is probably essential for HGF to exert its mitogenic activity. Critically, HGF is only converted to its active heterodimeric form in injured tissue, suggesting that selective activation of HGF by HGF activator is a mechanism by which HGF action is localised to damaged tissues. HGF binds to the c-met receptor (HGF receptor) to exert its action and the concentration of c-met receptor is increased in the gastric mucosa after injury. Thus active HGF, when produced in the stomach after a mucosal injury, may stimulate the proliferation of gastric mucosal epithelial cells through increased HGF receptor concentrations. Accompanying increased expression of the HGF gene, increased interleukin (IL) 1α mRNA expression was found in the ulcerated gastric wall. IL-1α may act as the link between the ulcerated tissue and submucosal production of HGF in the indomethacin induced gastric injury model. HGF is also linked to the presence of H pylori and abnormal mucosal growth in patients with large fold gastritis: eradication of H pylori results in a reduction in fold thickness and a parallel fall in HGF concentrations, suggesting that HGF is important in this trophic response. Moreover, a molecular link between H pylori, HGF and abnormal mucosal growth may be mediated by the cytokine IL-1α, as administration of an IL-1α antagonist reduces the production of HGF. Thus this experimental model may provide some insight into the link between the presence of H pylori, cytokine and growth factor production and abnormal mucosal growth, possibly illuminating the relation between H pylori and gastric carcinogenesis.

Transforming growth factor β is another peptide involved in mucosal defence, but in contrast to other growth factors, its function is to turn off the proliferation of epithelial cells once they have left the crypts or glands. It is also a potent stimulant of cell migration. Interestingly, the stimulation of cell migration by TGF-α and EGF, but not trefoil peptides, is dependent on the release of TGF-β. Basic fibroblast growth factor (bFGF) is normally present in the human gastric mucosa, and is a potent stimulant of angiogenesis, accelerating healing of experimental gastric and duodenal ulcers in rats. Administration of recombinant bFGF in patients with NSAID associated gastric ulcers is associated with a reduction in ulcer incidence, with a healing rate of 44% at one month and a mean reduction of 90% in the area of the unhealed ulcer. In ulcerated human gastric mucosa, immunoreactive bFGF is upregulated in the granulation tissue, endothelial cells, mononuclear cells, and epithelial cells at the ulcer rim. However, no increased bFGF mRNA is detectable by in situ hybridisation, suggesting that bFGF mRNA expression may be an early event after mucosal injury, as has been reported in rats.

Platelet derived growth factor (PDGF) was first detected, as its name suggests, in platelets, but it is also synthesised and secreted by activated macrophages. PDGF consists of two disulphide linked polypeptides: chain A (14 kDa) and chain B (17 kDa). Three isoforms exist: PDGF-AA, -AB, and -BB. PDGF is a potent mitogen for fibroblasts, osteoblasts, arterial smooth muscle cells, and glial cells. Both bFGF and PDGF accelerate the healing of cysteamine induced duodenal ulcers in rats by stimulating angiogenesis and granulation tissue formation, and are two million times more potent than cimetidine. Moreover, after experimentally induced duodenal ulcer and colitis in rats, both the duodenal and the colonic concentrations of bFGF and PDGF were reduced, but then increased in the healing phases of both lesions. Thus sequential expression of healing peptides occurs in the foregut and the hindgut.

Vascular endothelial growth factor (VEGF) is a peptide synthesised by vascular endothelial cells. Alternate exon splicing of a single VEGF gene results in four molecular species: 121, 165, 189, and 206 amino acid residues. The 121 and 165 splice variants constitute the secretory form of VEGF, whereas the others are mainly cell associated. VEGF plays a dual role in acute gastroprotection and chronic duodenal ulcer healing. The increased vascular permeability produced by VEGF seems to protect the gastric mucosa by the formation of a perivascular dilutional barrier towards gastrotoxic chemicals. VEGF then stimulates granulation tissue formation and angiogenesis to promote ulcer healing. It has been shown that upregulation of VEGF mRNA expression occurs as early as three hours after ethanol induced gastric mucosal injury.

Patterns of peptide gene expression after mucosal injury

Many genes are upregulated after gastric mucosal injury but are not expressed at the same time. Some genes are initially expressed early, and might be called early response genes, such as EGRF, c-fos, c-jun egr-1, Sp-1, and TFF2/hSP, whereas EGF, TGF-α, bFGF, PDGF, and VEGF appear some time later and might be referred to as intermediate genes. HGF and TFF3/TF are usually expressed late in the process of ulcer healing (fig 1) and in their turn might be termed late genes.

The transcription factors c-fos, c-jun, c-myc, egr-1, and Sp-1 are activated during the process of ulcer healing and are usually called immediate early genes because their rapid and transient transcriptional induction does not require de novo protein synthesis. The fos and jun family protooncogenes are transcription factors which form heterodimers (fos-jun) or homodimers (jun-jun), potent transcription factors which bind to the activator protein-1 site of various target genes, and contribute to the cellular
response to primary stimuli: c-fos and c-myc are thus implicated in the control of cell proliferation in a variety of cell types. The expression of c-myc and c-Ha-ras genes is increased after indomethacin induced mucosal injury of the rat stomach, with c-myc localised to nuclei as early as three hours after injury, whereas c-Ha-ras is localised to the cytoplasm, peaking at six to 12 hours after treatment. Changes in the expression of c-fos and c-myc in stress induced ulcers shows that c-fos mRNA is found in the gastric mucosa as early as two hours and c-myc mRNA at six hours after damage. The change in the expression of c-myc and c-fos precedes the induction of DNA synthesis as measured by [H] thymidine incorporation. Stress induced ornithine decarboxylase (ODC) activity in the gastric mucosa increases mucosal polyamines such as putrescine, spermidine, and spermine. Administration of N-difluoromethylornithine (DFMO), a specific inhibitor of ODC, prevented the notable increase in ODC activity and polyamine concentrations, whereas the expression of c-fos was completely abolished and c-myc mRNA was greatly decreased. Thus c-fos and c-myc are involved in the mechanism of polyamine stimulated healing in gastric mucosal stress ulcers.

In the cysteamine induced duodenal ulcer model in the rat, egr-1 mRNA is expressed as early as 30 minutes after administration. Similarly, Sp-1 expression shifted from the lower to higher molecular weight form at two hours after cysteamine exposure. Both egr-1 and Sp-1 expression precedes the increase in bFGF mRNA at 12–24 hours. Clues on specific transcriptional regulators come from a knowledge of the promoter sequence of bFGF, where GC-rich regions, suggesting that it might play a role in the regulation of bFGF gene transcription. Both Sp-1 and egr-1 seem to be important in the healing of duodenal ulceration, particularly in regulating bFGF and possibly PDGF expression after duodenal ulceration. These data suggest that immediate early genes may start the healing cascade in gastric mucosal lesions.

Most data concerning gene expression after mucosal injury come from animal models of ulceration. Alison et al used the cryoprobe to induce ulcers in rodent stomach and examined the sequential expression of rTFF2/SP, rTFF3/ITF, EGF, and TGF-α. Ribonuclease protection assays showed increased rTFF2/SP mRNA expression very early in the healing process (fig 2). Peak induction occurred between 30 minutes and two hours after damage, but declined thereafter to reach control values after 12 hours of cryoprobe treatment. Thirty minutes after ulcer induction, immunoreactive TFF2/SP was located both in the mucous neck cells of the gastric glands, where it is usually found, and also within the lamina propria and between underlying muscle fibres, suggesting that rTFF2/SP had been released from the mucous neck cells or other storage sites, following tissue injury. In contrast, rTFF3/ITF mRNA was first detected on day 2, peaking at three days after ulcer induction and remained increased at least 10 days after the injury. EGF mRNA was detected after one day, peaking at three days and remained greatly increased at 10 days after cryoprobe application, whereas TGF-α mRNA expression increased greatly only six days after the injury (fig 2).

Interestingly, in a model of 100% glacial acetic induced gastric injury in mice, the concentrations of mTFF2/SP and mTFF3/ITF fell in gastric tissue within 48 hours of ulceration but the concentrations of mTFF2/SP and mTFF3/ITF increased at 42 days and 72 days after injury, suggesting that they may have an ongoing role in the repair process. This late induction of TFF2/SP and TFF3/ITF has a TGF-α dependent component.

A similar time sequence study in experimental ulceration showed that the expression of EGF and TGF-α mRNA precedes the expression of immunoreactive EGF and TGF-α: the expression of EGF and TGF-α mRNA occurred at days 2 and 4 at the ulcer margin, whereas immunohistochemical EGF and TGF-α over-expression occurred later. The expression of EGF and TGF-α was also correlated with the PCNA labelling index, emphasizing the importance of these growth factors as mediators of cell proliferation during ulcer healing. Interestingly, gastric acid secretion was suppressed during ulcer healing, and was accompanied by increased plasma gastrin concentrations. The increase in plasma gastrin concentrations could be secondary to a reduction in gastric acid secretion, which may be mediated by EGF and TGF-α, but alternatively, the presence of an EGF responsive element in the gastrin promoter might explain the stimulation of gastrin gene transcription by this peptide.

There is also over-expression of EGFR in rat gastric mucosa during healing of acetic acid induced ulcers. The EGFR possesses intrinsic tyrosine kinase activity in the intracellular domain, and the tyrosine kinase activity associated with EGFR was greatly (more than 200%) increased within 30 minutes after gastric mucosal injury, suggesting that activation of this enzyme may be an important early event in the initiation of the reparative process. Moreover, 24 hours after gastric mucosal injury produced by hypertonic saline, EGFR concentrations were increased 36-fold, which closely correlated with mucus regeneration; the expression of EGFR mRNA rose gradually throughout the reparative period to 80% above the controls at four hours after 2 M NaCl induced injury. These studies clearly show that the activation of EGFR is an important early event in gastric mucosal regeneration following acute injury.

Hepatocyte growth factor, one of the heparin binding growth factors, is one of the most potent mitogens for gastric cells in vitro, as well as acting as a morphogen. HGF gene expression is augmented at five days after the induction of ulcers by acetic acid, reaching maximal levels on the tenth day. In situ hybridisation with 35S-labelled rat HGF cRNA probes showed that expression of HGF mRNA occurs in the submucosal layer around the ulcer lesions, with no HGF mRNA expression in the non-ulcer regions. Expression of c-met mRNA, the receptor for HGF, was increased six to 48 hours after mucosal injury induced by administration of hydrochloric acid. Furthermore, in a
Gene expression after gastric damage

A model of cryoprobe induced gastric ulcer in rats, in situ hybridisation showed that mRNA of both HGF and c-met is strongly expressed after cryosurgery in the early (day 3) as well as in the late (day 15) remodelling phase of ulcer healing.65 HGF mRNA is located in stromal cells between the regenerative glands and in the arterial vessels in the submucosa, whereas c-met mRNA is located in the epithelial cells of the regenerative glands.

The expression of bFGF and its receptor (FGFR-1 and FGFR-2) in alcohol induced gastric ulcers in rats showed a great increase in bFGF mRNA at eight and 24 hours after injury, followed by an increase in bFGF protein, beginning at 24 hours and lasting until 72 hours after injury. Similar increases in FGFR-1 and FGFR-2 mRNAs and proteins were also detected, and thus gastric mucosal injury. Similar increases in FGFR-1 and FGFR-2 mRNAs beginning at 24 hours and lasting until 72 hours after injury. The hybridisation showed that mRNA of both HGF and c-met is strongly expressed after cryosurgery in the early (day 3) as well as in the late (day 15) remodelling phase of ulcer healing.

Keratinocyte growth factor (KGF), a member of the fibroblast growth factor family (FGF7), is a potent stimulant of keratinocyte proliferation and binds to a splice variant of FGFR-2. It has been shown to ameliorate damage in an experimental model of colitis in rats. But KGF mRNA expression was not increased after indomethacin or acetic acid induced gastric injury in rats, and it is ineffective at reducing indomethacin induced gastric damage. Current data are insufficient to judge whether KGF plays an important role in gastric ulcer healing.

An ordered gene cascade or genetic redundancy after gastric mucosal damage?
It is clear that a wide variety of genes which encode peptides are expressed or upregulated, or both, after gastric mucosal injury. c-jun, c-fos, egr-1, and Sp-1 are activated early in the process, acting as transcription factors, molecular switches triggering the expression of other target genes, but details of the target genes activated by these transcription factors are not known as yet, and further studies are required. A temporal relation may exist between the expression of different peptides: some early response peptides such as TFF2/SP are involved in epithelial restitution which indeed does occur within the first few hours, covering the denuded area, and is not dependent on cell division. Later, the classic healing peptides such as EGF and TGF- 

Figure 2 Changes in the level of mRNA after cryoprobe application in both the ulcerated region and the control region in rats. β-actin concentrations (A) were expressed relative to the corresponding region at time zero; the concentration of rTFF2/SP (B), rTFF3/ITF (C), EGF (D), and TGF-α (E) were expressed as a ratio of the specific mRNA to β-actin mRNA standardised to this ratio at time zero. **p<0.01 versus baseline values.

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syndrome. When the TGF-α gene is knocked out, the healing of acetic acid induced gastric ulcers is the same in knockout and wild-type mice, but the expression of TFF2/SP and TFF3/ITF is suppressed in the TGF-α knockout and wild-type mice, but the expression of healing of acetic acid induced gastric ulcers is the same in late stage of gastric mucosal injury.

Similar redundancy is noticed when we examine the function of these peptides. For example, EGF, TGF-α, and HGF are all powerful mitogens, but they seem to act in a different time frame in the healing process. Moreover, EGF and TGF-α are both secreted by epithelial cells but HGF is secreted by mesenchymal cells. The spatial and temporal expression of peptides by different cells in the damaged mucosa might ensure an appropriate supply of these healing peptides. Similarly, TGF-β, EGF, TGF-α, TFF peptides, and HGF are motogens, involved in epithelial restitution. But EGF and TGF-α act through a TGF-β dependent pathway at the basolateral (serosal) side of the gastrointestinal epithelium whereas TFF peptides are luminal active and are also TGF-β independent.

This redundancy within the system may thus allow different genes or peptides to replace the function of others, possibly in the face of loss of function of other gene products with the same actions. The repertoire of peptides and genes may safeguard the important healing and repair properties of the gastrointestinal mucosa. Furthermore, this complex system of gene interactions might allow the mucosa to use different mechanisms in different circumstances, increasing the plasticity of the response to different environmental insults.

Inter-relations between the players

We have seen that there is some pattern in gene expression after mucosal damage; consequently, it is again reasonable to query the possible interactions between the main players. Some growth factors can induce the expression of intermediate early genes such as c-jun and c-fos in gastrointestinal epithelial cells. For example, TGF-α increases the rate of thymidine incorporation, the activity of mitogen activated protein kinase, S6 kinase, and expression of c-fos, c-jun, and c-myc in the intestinal epithelial cell line IEC-6. EGF also stimulates the proliferation of cells derived from the gastric fundus and induces the expression of c-fos and c-myc. Although the TGF-α and EGF genes are upregulated only late in the response to damage, we should note that upregulation of EGFR occurs quite early, and it is possible that the loss of cells from the surface allows luminal EGF to bind its basolateral receptor on surviving adjacent epithelial cells and induce these early genes.

Besides interaction with the immediate early genes, many of the peptides involved in mucosal repair might act in an integrated fashion. For example, expression of TFF1/pS2 at sites of mucosal damage may be mediated by luminal EGF as TFF1/pS2 has an EGF-responsive enhancer region in the 5' controlling sequence. Thus when ulceration occurs, luminal EGF binds its receptor on the basolateral membranes of the epithelial cell and induces trefoil peptide gene expression, also a result of the TGF-α:EGFR interaction. This enhancer region is also responsive, though not so strongly, to early response gene products such as the c-raf and c-jun. Furthermore, EGF and trefoil peptides can act together in a synergistic manner to stimulate the repair process, but whether this involves a separate trefoil receptor or is mediated wholly via the EGFR is not yet known. We have noted that EGF, a luminal surveillance peptide, and TGF-α, a mucosal integrity peptide, act on the same receptor: the difference in classification relates to their ability to reach the receptor rather than the intrinsic differences in the molecules themselves. Furthermore, a number of peptides, such as EGF, are monomeric in solution yet have been shown to activate their cognate receptors by inducing dimerisation. Thus EGF may signal to the cell through the formation of receptor homodimers (where two EGF or c-erb-B1 receptors link together) or through the formation of heterodimers (where one c-erb-B1 receptor binds to another activated member of the c-erb-B receptor family such as c-erb-B4,
which binds heresulin). This ability to form heterodimers greatly increases the variety and repertoire of ligand-receptor interactions. 

There is also evidence that EGF upregulates the expression of its own intestinal receptor (EGFR) after small bowel resection in rats. Similar mechanisms may operate in the stomach in response to injury, thus forming a positive feedback loop to augment the reparative and healing ability of the injured mucosa.

Epidermal growth factor and TGF-α have a physiologically complementary effects on gastric acid secretion and mucosal growth in the stomach. Both EGF and TGF-α directly stimulate mucosal growth and inhibit gastric acid secretion, but EGF stimulates the transcription of gastrin, a peptide hormone which regulates gastric acid secretion and mucosal growth, mediated by a GC-rich gastrin response element located at −68 to −53 bp upstream from the cap site. The dependence of gastrin gene expression on EGF (TGF-α) stimulation might represent a powerful control mechanism in which the trophic effect of gastrin is switched on while at the same time avoiding excessive acid secretion by the primary action of EGF and TGF-α (fig 3).

Conclusion

It has been clear for a long time that a large variety of genes, cytokines, and peptides are involved in the process of ulcer healing. The reductionist approach has been essential to the initial understanding of the action of the individual players, each with its particular role in the repair and regeneration process. However, we are now in possession of a good deal of information about each player, and have noted a certain degree of redundancy within the system.

Consequently, it is indeed germane to begin to search for the mechanisms which order this gene sequence, and for the initial understanding of the action of the individual genes, switching on while at the same time avoiding excessive acid secretion by the primary action of EGF and TGF-α (fig 3).

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