Growth factors in inflammatory bowel disease

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N WRIGHT. Growth factors in inflammatory bowel disease**. Can J Gastroenterol 1996;10(3):191-198.** Growth factors have many influences on the gastrointestinal tract, not just modulating cell proliferation, but also acting on other aspects of physiology. Several of these functions are incriminated in the pathogenetic and healing phenomena that accompany inflammatory bowel disease (IBD). A review of growth regulation in the intestine is presented. Topics include growth phenomena in IBD, sources of growth factors, growth factors in gut growth responses, trefoil peptides, other growth factors and role of growth factors in IBD.

Key Words: *Growth factors, Inflammatory bowel disease, Review*

Facteurs de croissance dans la maladie inflammatoire de l'intestin

RÉSUMÉ : Les facteurs de croissance exercent de nombreuses influences sur les voies digestives et ne font pas que moduler la prolifération cellulaire, puisqu'ils agissent sur d'autres aspects de la physiologie. Plusieurs autres de ces fonctions sont incriminées dans les phénomènes pathogéniques et cicatriciels qui accompagnent la maladie inflammatoire de l'intestin (MII). Un survol de la régulation de la croissance dans l'intestin est présenté ici. Les thèmes abordés sont entre autres : les phénomènes de croissance dans la MII, les sources des facteurs de croissance, les facteurs de croissance dans la réponse de croissance de l'intestin, les peptides «trefoil», autres facteurs de croissance et rôle des facteurs de croissance dans les MII.

Several morphological changes can be discerned in the spectrum of inflammatory bowel disease (IBD), encompassed by the general processes of cell proliferation and differentiation. Examples are the mucosal hyperplasia that accompanies ulcerative colitis, where colonic crypts lengthen and undergo increased crypt fission, the mucin cell depletion also found in ulcerative colitis and the several metaplasias, such as pyloric metaplasia in Crohn's disease, and Paneth's cell metaplasia, most common in ulcerative colitis. It is therefore relatively easy to manufacture a slot for the study of growth control in understanding the pathogenesis of IBD.

Knowledge of growth regulation in the intestine is at an interesting stage – we have come a long way in our understanding of how the intestinal renewal system is organized. However, the molecular processes that control this integrated proliferative system have only now begun to be identified, and while we are able to write a list of molecules that we believe are involved in growth control, we are not able to appreciate how these molecules interplay to produce an organized and responsive proliferative system.

The organization of crypt systems in the gut is relatively well known (1) (Figure 1). Each small intestinal or colonic crypt is a clonal population derived, ultimately at least, from a single stem cell. This 'unitarian hypothesis' of intestinal cytogenesis, which states that all cell lineages emanate from a

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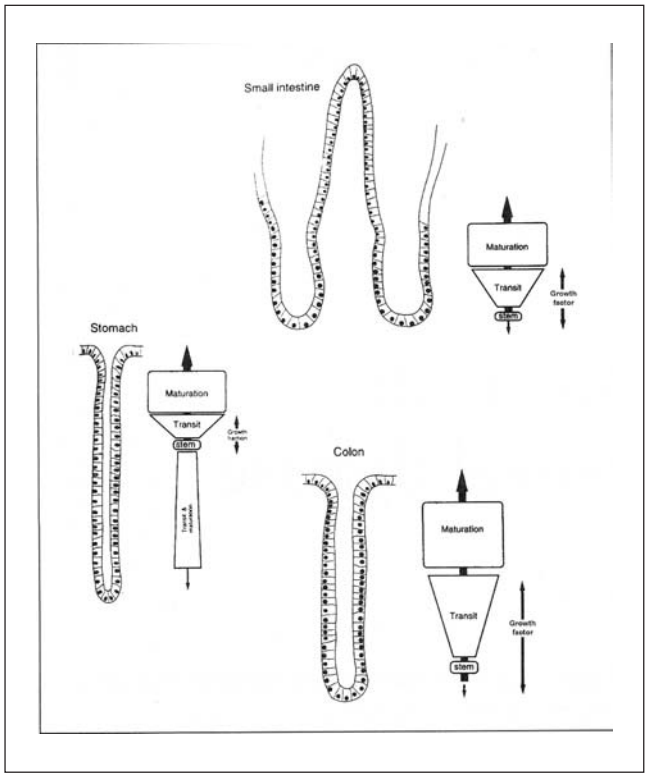


Figure 1) *Classical concept of the organization of cell proliferation in the crypt systems of the gut*

single stem cell, was conceived long ago by Cheng and Leblond (2) for the small bowel and by Chang and Leblond (3) for the colon, but definitive proof was lacking until studies involving tetraparental allophenic chimeric mice (4) and associated crypt-restricted lectin binding, and mice heterozygous for an X-chromosome-linked enzyme defect (glucose-6-phosphate dehydrogenase) (5). Such crypt-restricted markers in these models show that Paneth, columnar and goblet cell lineages are clonal, but that the clonality of gut endocrine cells is only shown by using male:female allophenic chimeric mice (6), in effect the final nail in the neural crest component of the all-encompassing amine precursor uptake and decarboxylation cell hypothesis (7).

The crypt stem cell feeds the proliferative compartment of the crypt, where the stem cell efflux is amplified, and subsequently cells cease division and migrate onto the surface to coat the villi in the small intestine and the surface of the colon as functional enterocytes and colonocytes.

Intestinal cells are well known for their rapid rate of proliferation, one of the highest in the human body. Nevertheless, the system remains adaptive, undergoing circadian variation (1) and responding to different physiological and, of course, pathological conditions. Intestinal adaptation has perhaps been best studied by partial resection, after which the remnant undergoes considerable hyperplasia (1). As well as exhibiting hyperplastic phenomena, the intestine also adapts to decreased workload during starvation or total parenteral nutrition (TPN) by reducing its rate of cell production.

GROWTH PHENOMENA IN IBD

In ulcerative colitis there is an increase in the rate of crypt cell proliferation, not only in the mucosa surrounding the ulcers, but also in the mucosa between the ulcers (8). This results in lengthening of the colonic crypts. There is also an increase in the rate of crypt fission, which can result in as many as 30% of crypts dividing in ulcerative colitis. There are also changes in the cytology of the crypts, with a reduction in the numbers of mucin-secreting goblet cells. While there is an increased rate of production of goblet cells in experimental colitis with goblet cell depletion, there is also an increased rate of mucin discharge so that goblet cells cannot be recognized in tissue sections (8). In the later stages of both ulcerative colitis and Crohn's disease there is also an increased risk of dysplasia and carcinoma (9).

Other changes in crypt cytology include Paneth cell 'metaplasia' which is found in the colon, especially in ulcerative colitis. Also, in ulcerative colitis, but especially in Crohn's disease and particularly in the small bowel, cells resembling pyloric cells appear in the mucosa ('pyloric' or 'pseudopyloric' metaplasia). The life history and function of these cells have recently been traced, and they are a source of several modulating peptides that have considerable trophic effects in the regenerating mucosa (10) (see below).

In IBD there is a considerable infiltrate of both mononuclear and polymorphonuclear cells in the lamina propria and associated hyperplasia of mucosal lymphoid tissue.

SOURCES OF GROWTH FACTORS

Circulating hormones: Circulating hormones can modulate growth responses in the gut. Older literature documents effects of 'classical' hormones such as corticosteroids, thyroxine, growth hormone and insulin on cell proliferation in the intestine; however, their importance in the pathogenesis of IBD is difficult to discern, apart from the obvious reduction in proliferative rate induced by corticosteroids which may be important therapeutically (11). But there is a considerable body of evidence that supports the hypothesis that circulating hormones, probably of intestinal origin, are important in inducing adaptive responses in the gut. The minutiae of this complex field is summarized by Williamson (12,13), but the critical experiments are probably:

- that partial intestinal resection of one animal in a pair of rats joined in cross-circulation (not parabiosis) results in induced cell proliferation in the intestine of the unoperated partner (14);
- that Thirty-Vella loops, isolated from the normal fecal stream, show proliferative responses when the animals are fed orally but not when fed by TPN (15), and show proliferative responses after resection of the intestine in continuity (16), and;
- that infusion of hypertonic glucose into the rectum of rats leads to the induction of cell proliferation in the small intestine (17).

The identity of the circulating hormone and its source is not clear; suspicion has fallen on enteroglucagon as the candidate hormone (18), but definitive proof is lacking.

Luminal factors: Food in the gut lumen is a potent stimulus of cell proliferation. The exact nature of this so-called 'luminal nutrition' has defied explanation for some time – whether the epithelial cells need a constant supply of absorbed nutrients for sustained proliferation (19), whether some nutrients (for example, polyamines, glutamine and short chain fatty acids [SCFA], the fermentation products of soluble fibre, which also influence growth, see below) are responsible, whether the induction of a 'functional demand' in the form of increased mucosal workload by absorption/secretion (19) is operative or whether luminal contents evoke trophic gut hormone or growth factor release is unclear.

Certainly absence of food in the lumen leads to prominent mucosal atrophy; this is not due to overall calorie malnutrition because such atrophy still occurs when animals are fed intravenously (20). There is also evidence that individual nutrients infused into isolated loops or Thirty-Vella fistulas induce local cell proliferation, namely elemental diets, glucose, disaccharides and amino acids. Such induction may be independent of substrate, and thus transport alone may be the inducer of cell proliferation (19).

Specific luminal molecules may act as growth factors for the epithelium. Polyamines have a potent effect on the growth of the intestinal mucosa (21,22). The production of polyamines is rate-limited by the enzyme ornithine decarboxylase (ODC), and inhibition of ODC leads to abrogation of epidermal growth factor (EGF)-induced cell proliferation in the small intestine (23) and to hypoplasia, as well as to a reduction in the proliferative response to other hyperplastic stimuli (23,24). Polyamines in the lumen may increase expression of ODC, increasing the production of spermine and spermidine which stimulate cell proliferation (24). Epithelial cells in the small intestine can use polyamines (25), and infusion of putrescine, a further polyamine, increases rat mucosal growth (26). Other molecules with designated trophic actions include SCFA and glutamine. The well known stimulation of cell proliferation in the rat colon caused by dietary fibre has been shown to be due to its fermentation, which produces SCFA (27), and to direct luminal infusion of SCFA (27).

Hormones/growth factors induced by luminal contents: The presence of food in the lumen may induce secretion of gut hormones and/or growth factors, which stimulates growth and, hence, maintains mucosal mass. There is no doubt, for example, that feeding induces secretion of enteroglucagon, the candidate enterotrophin, and other candidate hormones in both animals and humans (28). The direct trophic action of these hormones is yet to be determined.

Perhaps more reliable is the report that luminal contents can induce the expression of genes that encode for growth factors known to stimulate cell proliferation in the gut (29). Dietary fibre has been shown to stimulate rat colonic cell proliferation (27); Figure 2 shows the relationship between dietary fibre type and cell proliferation in the rat colon, and

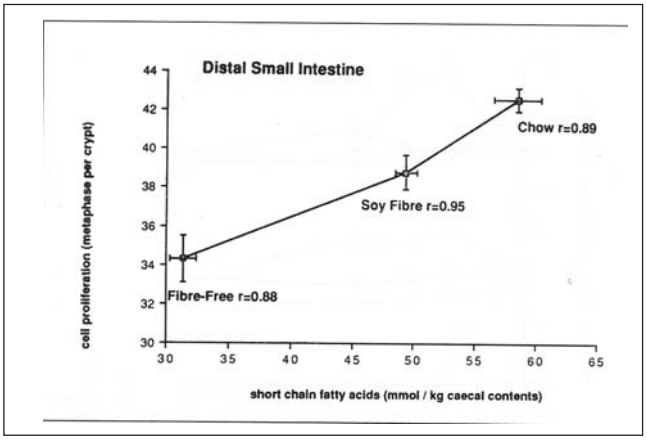


Figure 2) *Relationship between the rate of crypt cell production in the rat colon, here represented by the crypt cell production rate, and the ingestion of different types of dietary fibre*

Figure 3 shows that this induction of cell proliferation is associated with increased EGF and transforming growth factor-alpha (TGFα) gene expression. It is thus clear that luminary-directed growth responses in the gut are associated with growth factor gene expression.

A consideration of these growth factors in gut growth responses follows.

GROWTH FACTORS IN GUT GROWTH RESPONSES – EGF/TGFα

EGF and TGFα are members of a growing group of molecules that include EGF, TGFα, amphiregulin and heparin-binding EGF; there are other homologues such as cripto. Their commonality lies in the possession of six cysteine residues that form three disulphide bonds, resulting in highly stable molecules. Both EGF and TGFα are initially elaborated as membrane-bound molecules; pro-proEGF has a 24 amino acid signal peptide on its amino terminal, and a membrane-bound 25 residue hydrophobic domain on the C-terminal end. TGFα also has this membrane-spanning domain, and it is clear that both EGF and TGFα have to be enzymatically released from the membrane-bound state to be secreted. However, TGFα can act in a juxtacrine manner when still attached to the membrane, although the evidence for EGF acting in this manner is scant. There is little known about the regulation of EGF gene expression, but the upstream elements of the TGFα gene show SP1 and AF2 binding sites.

Both EGF and TGFα bind the EGF receptor (EGFR), a 150,000 kDa membrane-spanning molecule with a ligand-binding extracellular domain, a hydrophobic transmembrane domain and an intracellular domain with tyrosine kinase activity. Ligand-receptor binding results in autophosphorylation and possible nuclear translocation. While there are some differences between EGF and TGFα in affinity for the EGFR, their functional effects are remarkably similar.

EGF, a secreted molecule in the gastrointestinal tract, is found in upper gastrointestinal secretions and can be localized to the salivary glands, the mucous neck cells of the gas-

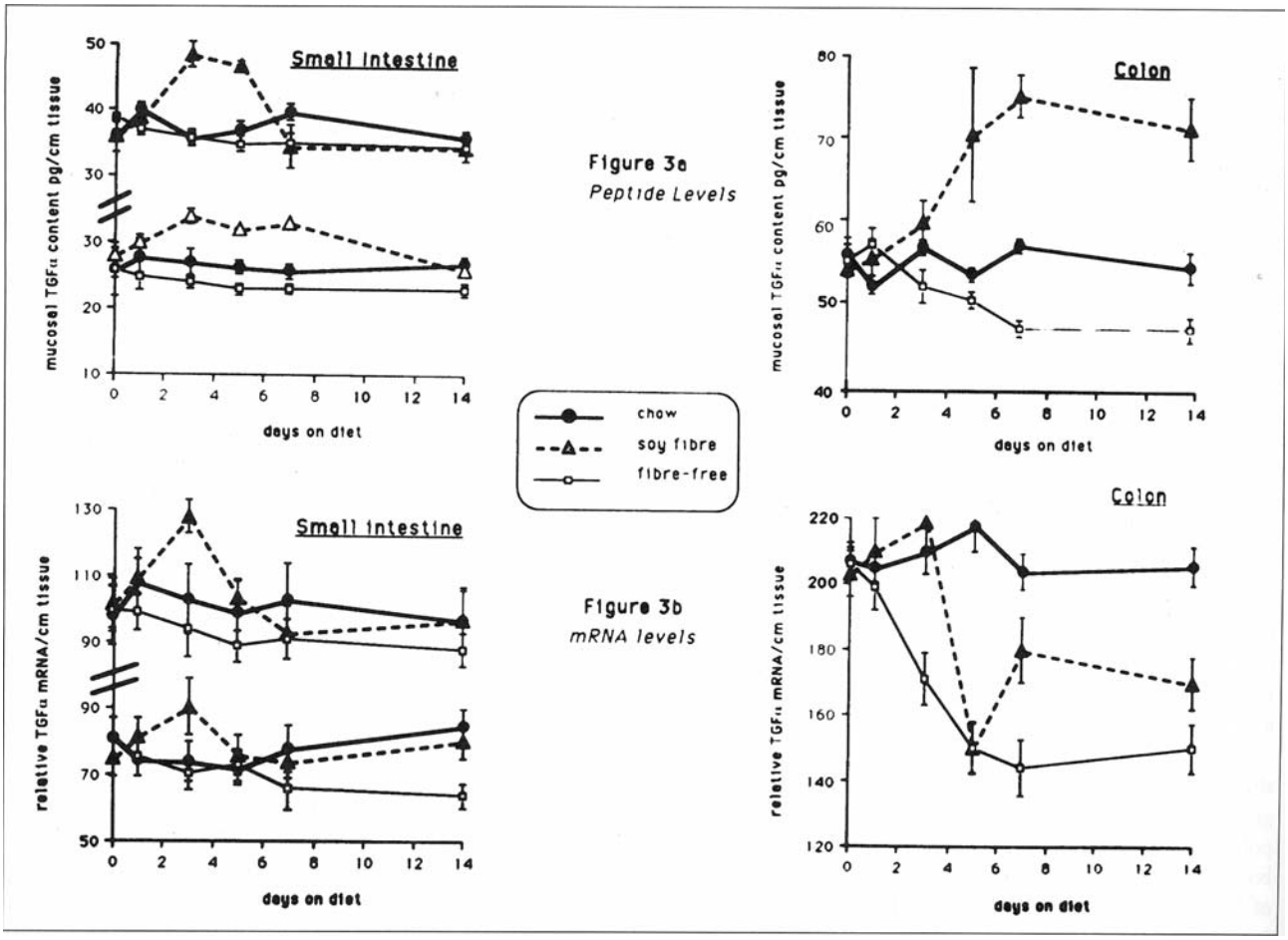


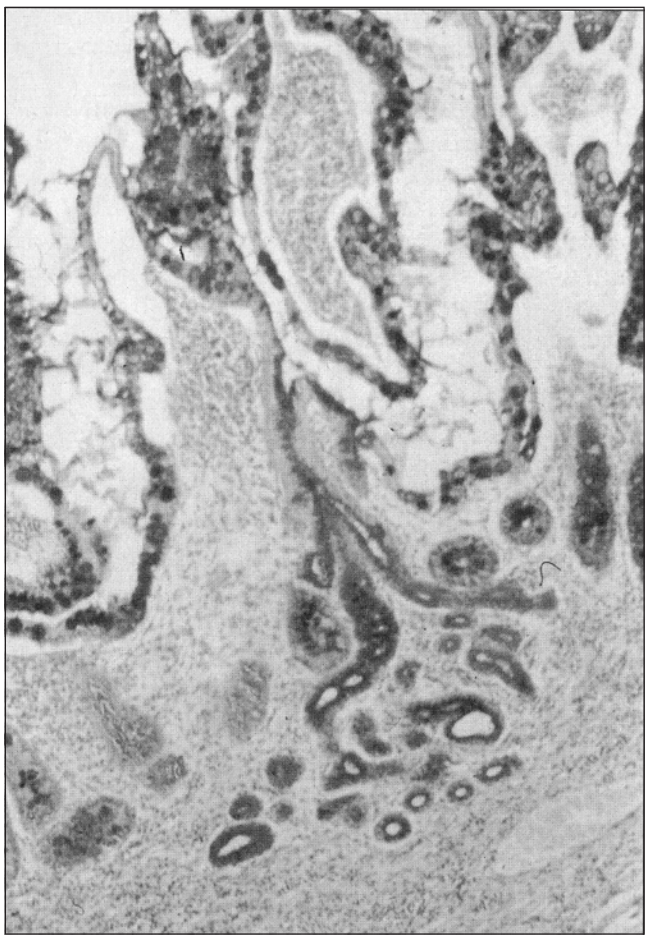
Figure 3) *Effects of different types of fibre on epidermal growth factor and transforming growth factor-alpha (TGFα) mRNA and peptide levels in the small intestine and colon of the rat*

tric mucosa and the mucus-secreting acini of Brunner's glands; there is little evidence for EGF secretion elsewhere in the gut (but refer to Figure 3). EGF is also present in maternal milk (30). It is therefore important to ask whether EGF acts luminally. EGF receptors are found both on the apical enterocyte surface and on the basolateral surface. In the neonate, there are EGF-modulated effects evoked by luminally administered EGF (31). In the calf there is evidence that the apical EGFR is not phosphorylated by EGF ligand-receptor binding, although the basolateral receptors are, but Thompson (32) has recently shown that luminal EGF binds EGFR and neu on the apical surface in neonatal rat intestine, resulting in phosphorylation of both these receptors. Nevertheless, certainly in the adult animal (33) and possibly in the neonate (31), EGFRs are concentrated on the basolateral surface. This distribution implies that EGF must be transported intact across the mucosa to have an effect. While there is limited evidence for intact EGF being taken up by the neonatal rat ileum (34), in that study (34) most EGF is degraded. It has also been anticipated that EGF would be degraded in the mature intestine (35), but it has been suggested that the pancreatic secretory trypsin inhibitor, secreted not only by the pancreas but also by the mucous neck cell lineage in the stomach, and evoked by luminal contents, protects EGF in the intestinal lumen.

The evidence for luminal activity of EGF in mature animals, however, is mixed – certainly infusion into defunctionalized colonic segments also stimulates cell proliferation (36). Goodlad and colleagues (37) failed to show any action of luminal EGF in animals maintained on TPN, even at high doses, whereas when lower doses given intravenously were used, the authors were able to replicate levels of cell proliferation seen in intact, fed, control animals. Moreover, the acid-inhibitory action of EGF seen after intravenous infusion is not evoked by intragastric or intrajejunal infusion (38).

These studies suggest that EGF may need mucosal damage to bind its receptor; certainly orally administered iodinated EGF does not bind to intact rat gastrointestinal mucosa, but does bind locally around areas of mucosal damage. In IBD, especially Crohn's disease, EGF can be produced by a cell lineage, the so-called 'ulcer-associated cell lineage' (UACL), which grows adjacent to the chronic ulcers (Figure 4) (10).

TGFα, on the other hand, is found throughout the gastro-



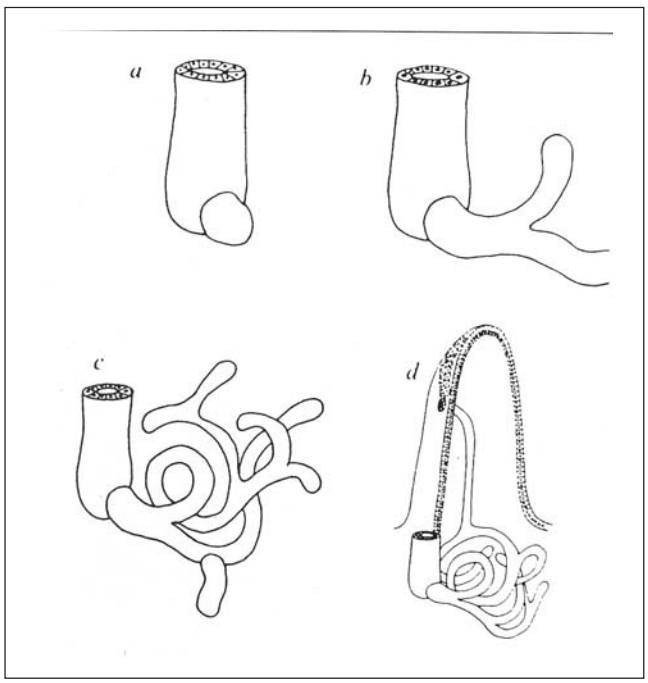


Figure 4) Above *Diagrammatic representation of the histogenesis of the ulcer-associated cell lineage (UACL).* ***Left*** *Photomicrograph of the mature UACL system. The condition is Crohn's disease. Note the acini, the duct and the cells emerging onto the villus surface replacing the indigenous cell lineages*

intestinal mucosa (39) and occupies the differentiated cell compartment in the small intestine and villus epithelium. Nevertheless, there is evidence that TGFα stimulates gut epithelial cell proliferation. There is little information on how TGFα localizes to and binds the EGFR.

While many studies concentrate on the growth-promoting properties of EGF/TGFα, it should be stressed that noncell cycle-related genes are also regulated. For example, EGF stimulates electrolyte and nutrient transport in the gut (40), up-regulating brush border enzyme activity (31), and enhances pS2 (a trefoil peptide, see below) gene expression (41).

GROWTH FACTORS IN GUT GROWTH RESPONSES – TRANSFORMING GROWTH FACTOR-BETA

The transforming growth factor-beta (TGFβ) family, whose actions were first described as a 'transforming activity' that induced anchorage-independent growth in a nonneoplastic cell line (42,43), is a series of related molecules, TGFβ 1-5. In mammals the main classes of TGFβ are TGFβ 1-3. These are synthesized as large precursor molecules and processed to yield 12.5 kDa mature monomers. However, the sequence of events that leads to homodimeric peptide secretion has not yet been fully worked out. There are at least three classes of TGFβ receptor.

TGFβ has several functions that make it potentially a very important molecule in IBD: it inhibits epithelial cell proliferation (44); it affects differentiation of colorectal carcinoma cells (45,46); and it has important actions on the synthesis of extracellular matrix proteins, increasing synthesis of the collagens (fibronectin, tenascin and elastin), decreasing synthesis of collagenases, stromelysin and plasminogen activators, and increasing synthesis of protease inhibitors such as tissue inhibitor of metalloproteinase and plasminogen activator inhibitor (47). Thus, in a very complex manner, TGFβ induces formation of extracellular matrix and affects its composition. Moreover, TGFβ can act as an 'indirect mitogen' for mesenchymal cells, possibly up-regulating platelet-derived growth factor expression (48).

TGFβ also acts on immune function, inhibiting both T and B cell growth, reducing immunoglobulin production and natural killer cell activity, and modulating cytokine production, reducing the synthesis of interleukin 1, 2 and 3 (47). TGFβ is also a powerful attractant for monocytes, fibroblasts and neutrophils (47) in femtomolar concentrations. In this manner TGFβ also stimulates cell migration in IEC-6 cells (an intestinal cell line) after 'wounding' a monolayer of these cells in vitro while cell proliferation was inhibited (49); this action was inhibited by anti-TGFβ antiserum. This suggests a role for TGFβ in promoting epithelial restitution after mucosal damage.

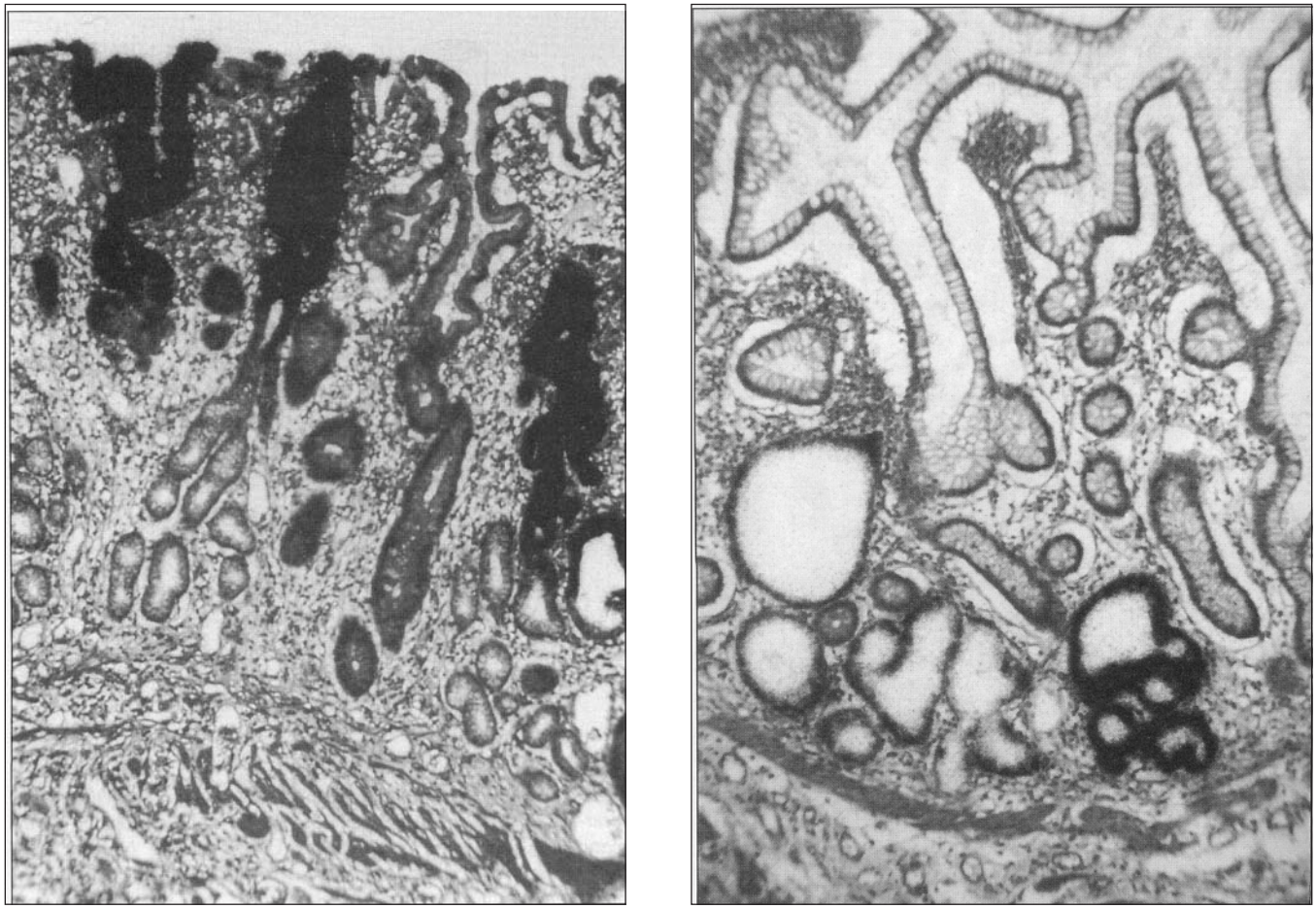


Figure 5) *Distribution of (**left**) pS2 mRNA and (**right**) hSP mRNA in the ulcer-associated cell lineage as demonstrated by in situ hybridization using 35S riboprobes*

TGFβ 1-3 are found in the intestine, both in crypt epithelial cells and in the lamina proprial cell populations. Thus these molecules have a potentially important role in IBD.

TREFOIL PEPTIDES

Trefoil peptides are a series of related molecules that are characteristically secreted by mucus-secreting cells. Their common characteristic is a three-looped structure strongly held by disulphide bonds based on six intramolecular cysteine residues. The three-dimensional structure of these molecules has recently been worked out using a combination of x-ray crystallographic and nuclear magnetic resonance methods (50,51). Trefoil peptides exist in mammalian tissues as single trefoil domain peptides, such as pS2 which is found in the gastric epithelium, and as intestinal trefoil factor (ITF) which is usually localized to the intestinal goblet cells. These peptides also exist as two-domain molecules, such as spasmolytic polypeptide (SP), first described by Thim et al (52) in pig pancreas, but which has also been localized in humans in mucous neck and foveolar cells of the gastric mucosa, antral mucus-secreting glands, and Brunner's gland acini and ducts.

The functions of these peptides is not yet clear. pSP has been reported to inhibit gastric acid secretion and intestinal muscular activity (53). However, recent results have not confirmed this latter action (personal communication). There have been reports that pSP stimulates the growth of colorectal carcinoma cells in vitro, but this action is singular in being glutathione-dependent (personal communication), and there does not appear to be any effect when infused into rats maintained on TPN (personal communication). However, ITF appears to have an action on electrogenic chloride transport in the rat small intestine and to be a powerful stimulant of cell migration in epithelial monolayers 'wounded' in vitro (personal communication). Moreover, hSP has been shown to stimulate epithelial restitution after indomethacin-induced damage in the rat stomach (personal communication). These molecules may be involved in the organization of the viscoelastic mucus layer. These molecules are abundant and very resistant to degradation, and their function in the gut is therefore important to resolve.

OTHER GROWTH FACTORS

There are several other growth factor families produced in the gut whose role in homeostasis control is less well known. Thus, insulin-like growth factors (IGFs) have a minor proliferative effect on the intestine and the fibroblast growth fac-

tor family has major effects on angiogenesis (its actions may be very important in the healing of ulcers).

ROLE OF GROWTH FACTORS IN IBD

It is unknown which growth factors are responsible for the several growth phenomena noted in IBD; contenders have been listed above. Certainly the EGF/TGFα molecules are very likely involved in the mucosal hyperplasia that accompanies ulcerative colitis. However, direct evidence of this is lacking. On the other hand, IGF-1 expression is upregulated in fibroblast-like cells of granulation tissue in an animal model of enterocolitis, pointing to a potential role for IGF-1 in the fibrogenic complications associated with IBD (54). A preliminary report describing TGFβ mRNA levels in patients with varying levels of IBD activity did not find statistically significant differences (55).

However, one phenomenon that does give some insight into the potential role of growth factors in the repair of ulcerative intestinal disease is UACL formation (10). In the crypts surrounding chronic ulcers in the gastrointestinal tract, small buds of cells appear with a distinctive phenotype, mucus-secreting cells that elaborate D/periodic acid-Schiff-positive neutral mucin rather than the alcianophilic acid mucin usually found in indigenous goblet cells. These buds grow into tubules, which ramify in the lamina propria and form new glandular complexes. A duct then grows upwards through the lamina propria to make contact with the surface via a pore. A photomicrograph of the mature UACL, together with a diagram of the proposed histogenesis, is shown in Figure 4. The system is presumably fed by cells from the parent crypt(s), but in the mature UACL a proliferative zone develops in the duct, which probably feeds cells upwards towards the surface and downwards into the acinar area (56).

The range of regulatory peptides elaborated by the UACL is really quite extensive. The basal acini contain quantities of immunoreactive EGF, while the whole lineage contains immunoreactive TGFα. The acini and the lower duct contain hSP protein and mRNA (Figure 5), while pS2 mRNA and peptide are concentrated in considerable amounts in the upper duct and surface cells (Figure 5), and hITF is present throughout the UACL (53). Lysozyme is also present in the acini, and the UACL is singular in the intestine for expressing MUC 1, as shown by HMFG1 and HMFG2 staining (10).

It has been proposed that this lineage grows adjacent to intestinal and gastric ulcers, and once access to the mucosal surface has been gained, pours its cocktail of growth factors into the local milieu. Because of the mucosal defect, EGF and TGFα at least can bind their receptors on the basolateral side of the surrounding enterocytes or colonocytes.

CONCLUSIONS

Growth factors have many and manifold influences on the gastrointestinal tract, not just modulating cell proliferation, but also acting on other aspects of physiology. Several of these functions are incriminated in the pathogenetic and healing phenomena that accompany IBD. Now that we can recognize the molecules and know at least their potential functions, we can study their genetic regulation and how their expression and functions contribute to IBD phenomena. Thereby, perhaps, lies the avenue to future therapeutic intervention.

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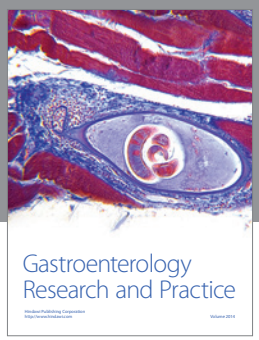

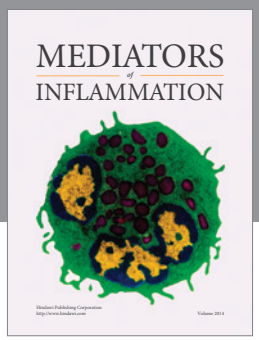

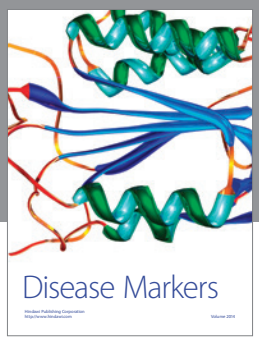

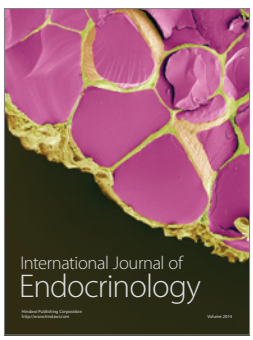

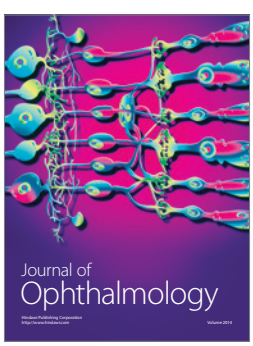

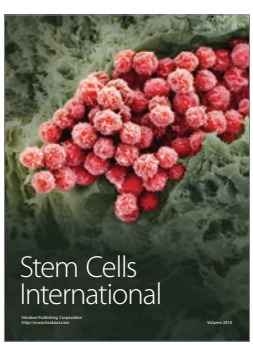

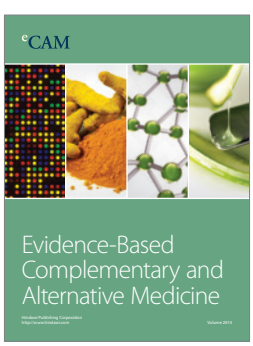

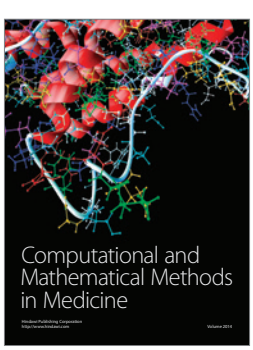

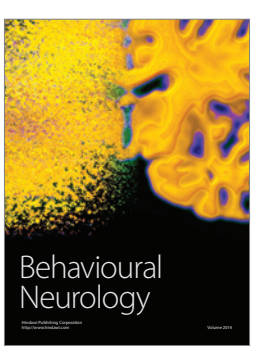

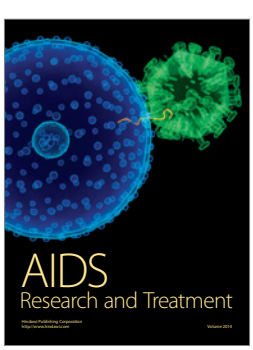

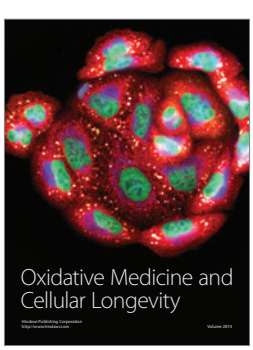

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