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Commentary

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On page 204, Hull and colleagues examine the benefit of using basic fibroblast growth factor to decrease aspirin induced gastric and duodenal injury. Administration of recombinantly produced, acid stable basic fibroblast growth factor (bFGF, CS-23) decreased the amount of duodenal, but not gastric, injury (erosions) induced by co-administration of aspirin. In the second component of the study, they gave indomethacin to the same subjects after cessation of treatment with bFGF. Subjects who had received bFGF in the first part of the study were found to have a reduced susceptibility to indomethacin induced relapse of artificially induced mini-ulcers. This suggests that the mucosa was somehow 'stronger' in subjects who had been treated with bFGF when compared with those who had received placebo. This paper therefore highlights two areas of interest; (1) the use of recombinant peptides for the treatment of gastrointestinal disease and (2) the concept of 'quality' of ulcer healing.

The most widely prescribed bioactive peptide used in clinical practice is insulin and has been of undoubted benefit to many thousands of patients. Peptides purified from biological material (for example, porcine pancreas) have usually been the initial source of peptides for clinical usage. The risks of contamination with infectious agents (as seen in patients treated with growth hormone developing Creutzfeldt-Jakob disease) and the development of antibodies to the administered peptide, however, have encouraged the development of recombinant peptide technology.

The most widely prescribed recombinant peptide used by gastroenterologists is probably interferon α for the treatment of infective liver disease. Treatment results in a long term 'cure' in only about 25% of patients with hepatitis C and this must be borne in mind when one considers the cost of a treatment course on a 'per patient' basis (about £2000 per patient). The economic implications of using this drug are particularly relevant to less well developed countries with high prevalence rates of hepatitis C.

One of the most extensively studied peptides for the treatment of gastrointestinal damage is epidermal growth factor (EGF). EGF is a potent mitogenic factor normally secreted into the intestinal lumen by the human salivary glands and Brunners glands of the duodenum. It was suggested many years ago that EGF may be a useful treatment for gastrointestinal ulceration. Despite hundreds of papers showing mitogenic activity and healing responses in various animals models, it has failed to find a place in clinical practice.

One of the major areas of concern of using peptides such as EGF in the clinical setting is the worry that systemic administration of growth factors may act to promote tumour growth elsewhere in the body. It is partly for this reason that there is increasing interest in the potential value of trefoil peptides to treat human gastrointestinal disease, as they seem to stimulate repair without increasing proliferation.[1]

Oral, as opposed to systemic, administration of growth factors provides one possible approach to this problem. However, for EGF and the trefoil peptides, the oral doses required to treat gastrointestinal damage may be up to a thousand times greater than when the peptide is given systematically, making oral therapy economically unrealistic.

One possible explanation for this is that the peptides (like any other ingested food product) come into contact with luminal proteases and may be digested into inactive forms.[2] In the paper by Hull, a recombinant modified form of bFGF has been used to decrease the susceptibility to acid and pepsin degradation. Stabilising against digestion in the small intestine will probably be more difficult because of the many different proteolytic enzymes produced by the pancreas. The peptide may have to be co-administered with non-specific serine protease inhibitors or in a site specific release formulation to overcome these problems.

Most studies examining the potential value of recombinant growth factors to treat gastrointestinal disease have examined their effects on gastric models of injury. Their clinical value in peptic ulcer disease is, however, likely to be small because of the high rate of success of ulcer healing using acid suppressants and *Helicobacter pylori* eradication regimens. It is also relevant that the third group studied by Hull and coworkers were treated with cimetidine, an extremely cheap drug.

This group showed a similar protective effect against aspirin induced duodenal injury and, like the bFGF treated subjects, resulted in a reduced susceptibility to subsequent indomethacin induced injury compared with placebo treated subjects. Although many peptides have been shown to decrease injury when given before the ulcerogen, there is much less evidence that these peptides have a major effect on the rate of healing when administered after the damaging agent. These studies would obviously be of more relevance to the clinical setting.

Two human studies that have shown a beneficial effect of oral peptide therapy involved the use of basic fibroblast growth factor therapy to treat patients with NSAID associated gastric ulcers[3] and using oral EGF to treat patients with duodenal ulcer, where the healing efficacy was similar to that of using cimetidine.[4] Other peptides that are presently under investigation include insulin-like growth factor 1[5] and keratinocyte growth factor.[6]

Instead of administering exogenous peptide healing factors, an alternative approach is to inhibit endogenous peptide factors which may be exacerbating the injury. Baert *et al*, for example, have recently shown that administration of a tumour necrosis factor α neutralising antibody to patients with Crohn's disease considerably reduces inflammatory activity.[7] Tumour necrosis factor α is

thought to be an important mediator of the inflammatory process.

The concept that ulcers may heal with different 'quality' (that is, differences in the amount of residual submucosal abnormalities seen on histological examination) is comparatively new and will probably be an important area of further research.[8] Patients who have taken NSAIDs have impaired ulcer healing with a tendency to recurrence. The mechanisms by which this occurs are unclear, although areas of previous ulceration usually contain scar tissue and disrupted histology despite appearing endoscopically normal. Administration of peptides that stimulate repair, such as bFGF which promotes angiogenesis, may result in the scarred area having an improved vascular supply, increasing its resilience to further injury.

In summary, recombinant peptides are (comparatively) cheap and easy to produce and have the potential to treat gastrointestinal damage in clinical diseases where treatment is presently suboptimal. Problems to be overcome include decreasing their susceptibility to luminal digestion and finding peptides that are capable of stimulating healing when given after ulceration has occurred. In the next few years we will probably see an increasing number of peptide therapy studies being extended from the laboratory environment into the clinics.

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